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Chemoembolization for the Treatment of Large Hepatocellular Carcinoma

Shiro Miyayama, MD, Masashi Yamashiro, MD, Miho Okuda, MD, Yuichi Yoshie, MD, Natsuki Sugimori, MD, Saya Igarashi, MD, Yoshiko Nakashima, MD, Kazuo Notsumata, MD, Daisyu Toya, MD, Nobuyoshi Tanaka, MD, Takeshi Mitsui, MD, and Osamu Matsui, MD

PURPOSE: To retrospectively evaluate the efficacy of chemoembolization for inoperable hepatocellular carcinoma (HCC) tumors larger than 5 cm in diameter.

MATERIALS AND METHODS: Chemoembolization was performed in 30 patients with HCCs with a largest diameter of more than 5 cm with three or fewer lesions and no portal vein tumor thrombus. The mean maximum tumor diameter was 7.7 cm ± 2.4. When the tumor was extremely large and had multiple feeding arteries, stepwise chemoembolization sessions at intervals of 3–10 weeks were performed. In addition, extrahepatic collateral supply was identified and embolized. Local therapeutic effects, survival rates, and complications were analyzed.

RESULTS: The mean follow-up period was 33.8 months ± 24.1. One to 13 chemoembolization sessions (mean, 4.0 sessions ± 3.0) were performed in each patient. Additionally, 62 collateral vessels were embolized in 21 patients, including 22 vessels in 14 patients at the initial procedure. Early tumor response rate 2–3 months after treatment was 43.3% by Response Evaluation Criteria In Solid Tumors. Complete radiologic response was achieved in 19 patients. Eleven patients died between 4 and 61 months after treatment (mean, 27.2 months ± 21.8), including four deaths unrelated to hepatic causes. Nineteen patients have survived for 6–103 months (mean, 37.5 months ± 25.2). Overall and progression free-survival rates at 1, 3, and 6 years were 82.3% and 66.0%, 73.9% and 57.6%, and 32.9% and 34.2%, respectively. Three infectious complications developed and were managed by interventions.

CONCLUSIONS: Chemoembolization was effective for large HCCs, although there is a risk of infectious complications after the procedure.

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Abbreviations: HCC = hepatocellular carcinoma, IPA = inferior phrenic artery, RF = radiofrequency

WITH advances in imaging modalities and screening of high-risk groups, it has become possible to detect small hepatocellular carcinoma (HCC). However, HCC may still be discovered in advanced stages because its clinical symptoms are infrequent. Surgical resection has been considered the most effective therapy for HCC tumors larger than 5 cm in diameter (ie, "large HCC"). However, only 41% of patients with HCC are candidates for hepatectomy in Japan because of the associated liver cirrhosis and occasional multicentricity (1). Liver transplantation is another surgical treatment option (2), but it is performed in a limited number of patients because of the lack of donors and high costs.

Recently, local therapeutic options, such as radiofrequency (RF) ablation, have been developed and play an important role in the treatment of unresectable HCC (3–5). However, the local control of tumors 3–5 cm in diameter (ie, "medium-sized HCC") by RF ablation is usually limited because of the limited area of coagulation necrosis compared with that for HCCs smaller than 3 cm in diameter (ie, "small HCC") (4,5). Additionally, RF ablation is typically contraindicated for large HCCs because of the difficulty in completely ablating such tumors (4).

Since the first report by Yamada et al (6), chemoembolization has been performed for inoperable HCCs worldwide. Although the local recurrence rates after chemoembolization have been higher than those after RF ablation (7,8), it can be performed in almost all patients with HCC regardless of the size or number of tumors. However, the prognosis of patients

Departments of Diagnostic Radiology (S.M., M.Y., M.O., Y.Y., N.S. S.I., Y.N.); Internal Medicine (K.N., D.T., N.T.), and Surgery (T.M.), Fukuiken Saiseikai Hospital, 7-1 Funabashi, Wadanakacho, Fukui 918-8503, Japan; and Department of Radiology (O.M.), Kanazawa University Graduate School of Medical Science, Kanazawa, Japan. Received February 11, 2009; final revision received March 8, 2010; accepted April 5, 2010. **Address correspondence to** S.M.; E-mail: s-miyayama@fukui.saiseikai.or.jp

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with large HCC treated by chemoembolization is limited (2,9). Large tumors are usually fed by multiple feeding arteries—not only hepatic arterial branches but also extrahepatic collaterals—and this may make it difficult to achieve complete necrosis of large tumors by chemoembolization (10,11). In a report by Chung et al (11), the prevalence of extrahepatic blood supply at the initial chemoembolization session in a tumor less than 4 cm in diameter was less than 3%; this increased to 63% when the tumor was larger than 6 cm in diameter. For transcatheter management of HCC to be effective, not only the hepatic arterial branches but also these collateral vessels should be adequately embolized (10–13).

We have introduced tumor-targeting chemoembolization for HCC to improve the local control effects and to reduce adverse effects (7,8). In this report, we describe the local therapeutic effects, survival rates, and complications of chemoembolization in the treatment of HCCs larger than 5 cm in diameter.

MATERIALS AND METHODS

We performed a retrospective study to evaluate the therapeutic effects of chemoembolization for large HCC lesions. This was a retrospective study that used imaging data and clinical records with no change in patient care; institutional review board approval is not required at our institution for this type of study. Written informed consent was obtained from each patient before the chemoembolization procedure.

Patients

The selection criteria required patients to have (i) HCCs larger than 5 cm in largest diameter, with three or fewer tumors and no portal vein tumor thrombus; and (ii) newly detected HCC without any previous treatment. We excluded patients with more than four lesions or with tumors extending into the portal vein because it was expected to be difficult to perform tumor-targeting chemoembolization in these cases. We also excluded patients with a history of HCC treatment because blood supply to the tumor may have been influenced by the previous treatment. The following conditions were also considered contraindications to chemoembolization: severe thrombocytopenia (platelet count < 30,000/mL), hyperbilirubinemia (serum total bilirubin > 3 mg/dL), and severe hepatic dysfunction (ie, Child-Pugh class C disease). Between March 2000 and July 2008, 30 patients met the listed criteria. There were 23 men and seven women, and the mean patient age (± SD) was 70.4 years ± 8.1 (range, 52–83 y). Patient profiles are summarized in **Table 1**. All patients had chronic hepatitis (n = 2) or liver cirrhosis (n = 28). This was related to hepatitis C virus in 17 patients (56.7%) and hepatitis B virus in three patients (10.0%). The etiology was unknown in 10 patients (33.3%). Twenty-five patients (83.3%) were classed as having Child-Pugh class A disease and five (16.7%) had Child-Pugh class B disease. Twenty-five patients (83.3%) had a solitary tumor and five (16.7%) had two or three tumors. The mean diameter of the largest tumor was 7.7 cm ± 2.4 (range, 5.1–14 cm). Diagnosis was established by imaging findings of computed tomography (CT) and/or magnetic resonance (MR) imaging: characteristic nodular enhancement on the arterial phase and washout on the delayed-phase images. Serum levels of α-fetoprotein were more than 21 ng/mL in 12 patients (21–100 ng/mL, n = 6; 101–400 ng/mL; n = 3; and > 401 ng/mL, n = 3). Serum levels of protein induced in vitamin K absence II (14) were more than 41 mAU/mL in 26 patients (41–100 mAU/mL, n = 2; 101–400 mAU/mL, n = 6; > 401 mAU/mL, n = 18). Serum levels of protein induced in vitamin K absence II were not measured in one patient. In 10 patients, serum levels of both tumor markers were increased. In three patients, serum levels of both tumor markers were within the normal ranges. Histologic confirmation was not obtained in any patient. None of the tumors were candidates for surgical resection because of tumor distribution extending to the bilateral lobes or beyond the hepatic hilum (n = 9), poor hepatic function reserve (ie, Child-Pugh class B disease; n = 5), cardiopulmonary dysfunction (n = 4), other underlying diseases (n = 7), or patient refusal (n = 5).

Four patients (13.3%) presented with hemoperitoneum resulting from tumor rupture. Two patients presented with massive bleeding and emergent chemoembolization was performed. In the remaining two patients with minor bleeding, chemoembolization was electively performed. In another patient (3.3%) with a tumor measuring 14 cm in diameter, serum total bilirubin level was increased to 12.8 mg/dL as a result of bile duct compression at the hepatic hilus by the tumor. Chemoembolization was performed after normalization of serum bilirubin level after percutaneous transhepatic biliary drainage.

Table 1
Patient and Disease Profile (N = 30)

Characteristic	Value
Sex	
Male	23
Female	7
Mean age (y)	70 ± 8.1
Liver cirrhosis	28 (93.3)
Chronic hepatitis	2 (6.7)
Hepatitis C virus–related	17 (56.7)
Hepatitis B virus–related	3 (10.0)
Etiology unknown	10 (33.3)
Mean maximum HCC size (cm)	7.7 ± 2.4
Intrahepatic multiplicity	
Single	25 (83.3)
Multiple (≤ 3)	5 (16.7)
Tumor rupture	4 (13.3)
Obstructive jaundice	1 (3.3)

Note.—Values in parentheses are percentages. Values presented as means ± SD where applicable.

Chemoembolization Technique

A 2-F–tip (Progreat-α; Terumo, Tokyo, Japan) or 2.4-F–tip (Microferret; Cook, Bloomington, Indiana) microcatheter was used for all chemoembolization procedures through a 4-F catheter placed in the celiac artery, superior mesenteric artery, or common hepatic artery. To navigate the microcatheter, a 0.016-inch guide wire (GT-wire; Terumo) was used. The microcatheter was advanced into the tumor-feeding branch as selectively as possible to minimize the embolized area in each patient.

After the microcatheter was inserted into the target branch, 0.5 mL of 2% lidocaine (Xylocaine; Fujisawa,

Osaka, Japan) was intraarterially injected to prevent pain and vasospasm. First, a mixture of iodized oil (Lipiodol; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) and anticancer drugs was injected and injection of gelatin sponge particles followed. The total amount of iodized oil in the single procedure was determined based on the tumor size (almost equal to the diameter of the tumor, eg, a 6-cm tumor received 6 mL of iodized oil), but did not exceed 10 mL. In total, 6–10 mL of iodized oil, 30 mg of epirubicin (Farmorbicin; Kyowa Hakko, Tokyo, Japan), and 6 mg of mitomycin C (Kyowa Hakko) were used in a single procedure. After injecting the mixture of iodized oil and anticancer drugs, the target branch was embolized by gelatin sponge particles until the blood flow was stopped. Until December 2006, gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Michigan) that had been cut into approximately 1-mm cubes were injected to block the target vessel. Since January 2007, commercially available gelatin sponge particles (Gelpart; Nippon Kayaku, Tokyo, Japan) 1 mm in diameter were used. When the tumor was extremely large or had multiple feeding arteries, stepwise chemoembolization sessions were performed at 3–10-week intervals to avoid complications. In addition, extrahepatic collateral vessels supplying the tumor were identified and embolized if necessary. Arteriograms of the right inferior phrenic artery (IPA) and right renal capsular artery were routinely obtained in almost all patients. Other extrahepatic collateral vessels, such as the left IPA, right intercostal and lumbar arteries, right adrenal arteries, and bilateral internal mammary arteries, were examined according to the tumor location. Aortography was not performed in any patient in this series.

Follow-up

Unenhanced CT was performed 1 week after the procedure in all patients to check for iodized oil accumulation in the target tumor. All patients were followed by dynamic CT and/or MR imaging every 2–3 months after chemoembolization to screen for any tumor recurrence. In patients who underwent stepwise chemoembolization sessions, follow-up dynamic CT and/or MR imaging studies were obtained every 2–3 months after the last session of the sequential treatment. When tumor recurrence and/or newly developed tumors at other sites were detected, additional chemoembolization was performed if possible. Intraarterial infusion chemotherapy was indicated for patients when intrahepatic disseminated lesions became uncontrollable by chemoembolization. Distant metastases that developed in patients with controlled HCC in the liver were treated by combined chemoembolization and radiation therapy.

Assessments

Early tumor response was assessed by dynamic CT or MR imaging obtained 2–3 months after the initial treatment based on the change in the maximum diameter of the whole tumor, according to the criteria of Response Evaluation Criteria In Solid Tumors (15). Overall survival rates and progression-free survival rates were calculated by the Kaplan-Meier method.

Major complications were assessed based on the previously described guideline for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy (16).

RESULTS

Treatment

In 20 patients (66.7%) with a mean maximum tumor diameter of 6.6 cm ± 1.5 (range, 5.1–10 cm), including four who had a ruptured tumor, the tumor was embolized in a single chemoembolization procedure. In the remaining 10 patients (33.3%) with a mean maximum tumor diameter of 10 cm ± 2.2 (range, 7.2–14 cm), two– to four–stepwise chemoembolization sessions (mean, 2.7 sessions ± 0.8) were performed per patient.

In 24 patients (80.0%), multiple chemoembolization procedures were performed during the subsequent treatment course. The total number of mean chemoembolization sessions in each patient was 4.0 sessions ± 3.0 (range, 1–13 sessions).

Three patients underwent another treatment in addition to chemoembolization. Two patients underwent implantation of an arterial infusion port system because of uncontrollable intrahepatic metastases and underwent infusion of 2,500 mg of 5-fluorouracil (Kyowa Hakko) on day 1. Interferon (12 million IU; Advaferon; Astellas, Tokyo, Japan) was also subcutaneously administered on days 1, 3, and 7. This treatment schedule was repeated twice in one patient and four times in another at 1-week intervals; however, it was not effective. Bone metastasis to the left seventh rib developed in another patient with well controlled HCC in the liver, and the metastatic lesion was treated by a combination of chemoembolization with 20 mg of epirubicin and gelatin sponge particles followed by 50 Gy of radiation therapy. However, bone metastases at other sites rapidly developed in this patient.

Chemoembolization through Extrahepatic Collateral Vessels

Extrahepatic blood supply to the largest tumor was observed in 21 patients (70.0%) during the treatment course. In particular, this finding was observed in 14 patients (46.7%) at the initial chemoembolization (**Fig 1**). In total, 62 collateral vessels that fed the tumor were demonstrated during the observation period, including 22 vessels at the initial procedure. All vessels were successfully embolized with use of a mixture of iodized oil and anticancer drugs and gelatin sponge particles (**Table 2**).

Local Tumor Control

Table 3 shows local tumor control of each tumor after chemoembolization. In 28 patients (93.3%), the entire tumor could be completely embolized as shown on arteriograms, including those treated by intentional stepwise chemoembolization. In all four patients with ruptured tumor, hemostasis was achieved by chemoembolization. Concerning early tumor response 2–3 months after treatment as assessed by Response Evaluation Criteria In Solid Tumors, 13 patients (43.3%) were classified as having a partial response, 16 patients (53.3%) were classified as having stable disease, and one patient (3.3%) was classified as having progressive disease. Complete response was not achieved in any patient (0%),

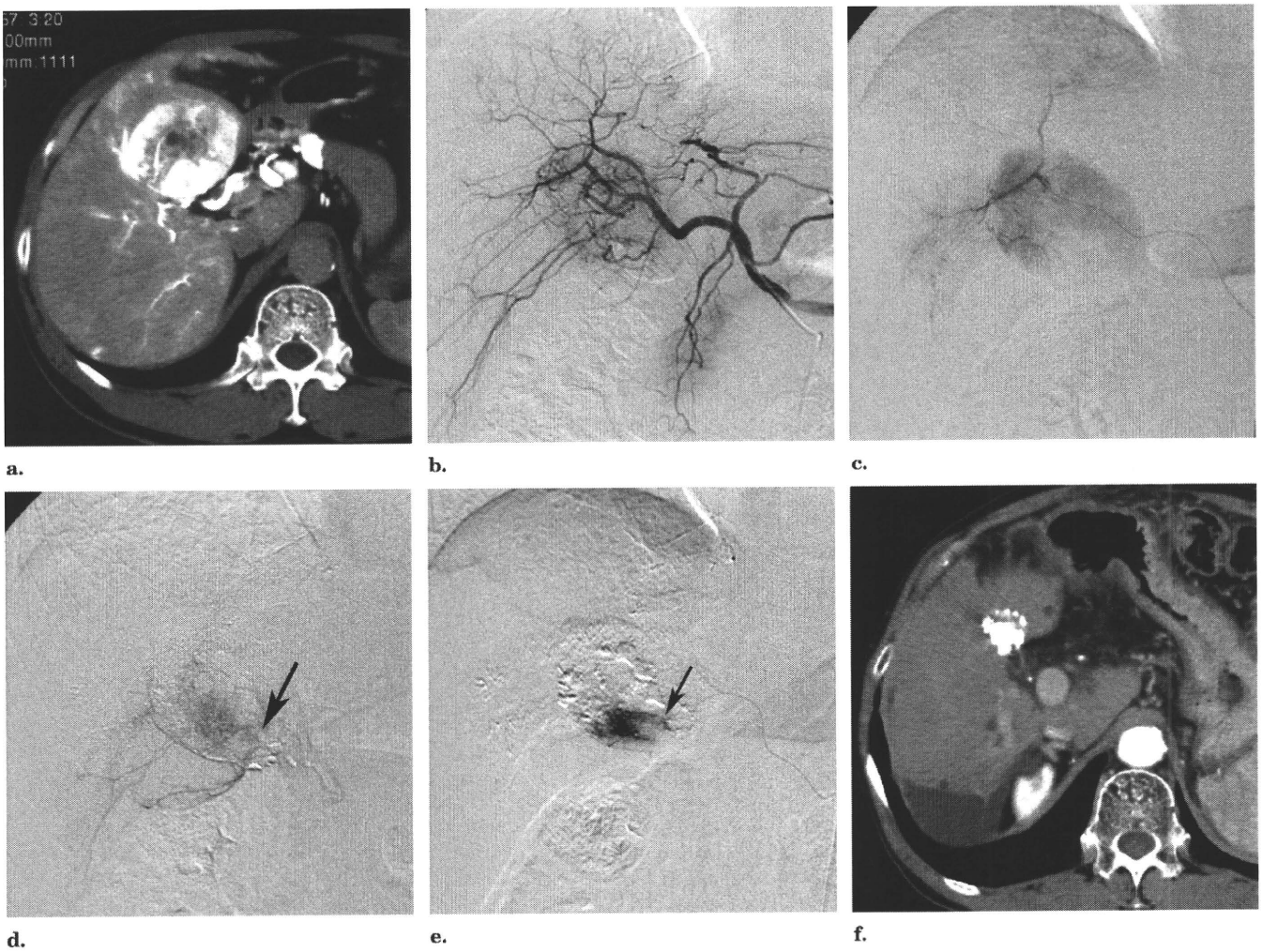

Figure 1. Images from a 66-year-old man with HCC 7.6 cm in diameter. **(a)** Axial CT during hepatic arteriography showed a large hypervascular tumor in segments IV and V of the liver. **(b)** Celiac arteriogram showed a large tumor stain. **(c)** First, the anterior segmental artery of the liver was selected and chemoembolization was performed. **(d)** Arteriogram of the cystic artery obtained after chemoembolization of the anterior segmental artery showed a partial tumor stain. The arrow indicates the tumor-feeding branch. **(e)** The tumor-feeding branch was selected and chemoembolization was performed. The arrow indicates the catheter tip. Seven weeks later, chemoembolization through the medial segmental artery of the liver was performed (not shown). The tumor recurred after 6 and 77 months and was treated by chemoembolization. A new lesion that developed after 63 months was also treated by chemoembolization (not shown). **(f)** Axial CT scan obtained 102 months after the initial chemoembolization shows that tumor size is markedly reduced. There are no viable tumors detected in the liver.

Therefore, the early response rate was 43.3%.

In 11 of 28 patients, complete radiologic response was achieved during the follow-up period of 6–103 months (mean, 32.6 months ± 22.3; **Figs 1, 2**). In one patient, a 6-cm-diameter tumor disappeared 11 months after a single chemoembolization (**Fig 2**).

In 17 of 28 patients, local tumor progression was observed within 2–77 months (mean, 12.9 months ± 17.9) and additional chemoembolization was performed. In this group, complete radiologic response was achieved in eight of 17 patients. In nine patients, the tumor progressed despite repeat chemoembolization (**Fig 3**).

In the remaining two patients, who had maximum tumor diameters of 9.3 cm and 14 cm, respectively, the entire tumor could not be completely embolized despite stepwise chemoembolization. In both patients, residual tumor stain was observed through the left hepatic artery at the end of the fourth and final chemoembolization procedure performed through the right hepatic artery. Additional chemoembolization could not be performed in either patient because of poor general condition.

Tumor recurrence at other sites in the liver was also observed in 16 patients (53.3%), and was treated by chemoembolization if possible.

Outcomes

All patients were followed up for 4–103 months (mean, 33.8 months ± 24.1). Eleven patients (36.7%) died during a follow-up of 4–61 months (mean, 27.2 months ± 21.8). Seven patients (23.3%) died of tumor progres-

Table 2
Incidences of Blood Supply to HCC from Extrahepatic Collateral Vessels

Artery	During Follow-up (n = 21; 70.0%)	At Initial Treatment (n = 14; 46.7%)
Right inferior phrenic	14	6
Cystic	6	3*
Right renal capsular	6	2
Left inferior phrenic	6	1
Right posterior intercostal	4	1
Right omental	4	2
Right middle adrenal	4	—
Left gastric	4	1
Right internal mammary	3	2
Bile duct	2	1
Right colic	2	—
Dorsal pancreatic	2	1
Right gastric	1	1
Right inferior adrenal	1	—
Middle colic	1	—
Right lumbar	1	—
Left gastroepiploic	1	1
Total	62	22

* Cholecystitis occurred as a result of the development of a fistula between the tumor and the gallbladder after chemoembolization through the cystic artery in one patient.

Table 3
Outcomes on a Per-tumor and Per-patient Basis

Outcome	Incidence
Per tumor (N = 30)	
Successful treatment of entire tumor(s)	28 (93.3)
Complete remission after initial treatment	11 (33.3)
Local tumor recurrence	17 (56.7)
Complete remission after additional procedure(s)	8 (26.7)
Local recurrence despite additional procedure(s)	9 (30.0)
Unsuccessful treatment of entire tumor(s)	2 (15.0)
Newly developed tumor(s) at other site(s)	16 (53.3)
Per patient (N = 30)	
Dead	11 (36.7)
Mean survival (mo)	27.2 ± 21.8
Tumor progression	7 (23.3)
Causes unrelated to liver	4 (13.3)
Alive	19 (63.3)
Mean survival (mo)	37.5 ± 25.2
Without viable tumor	14 (46.7)
With viable tumor	5 (16.7)

Note.—Values in parentheses are percentages. Values presented as means ± SD where applicable.

sion, including distant metastases (lung, n = 2; bone, n = 2). Four deaths (13.3%) were unrelated to hepatic causes: arrhythmia after 4 months, pneumonia after 7 months, infectious endocarditis after 54 months, and massive bleeding from a gastric ulcer after 61 months. Two of these patients (one with a tumor measuring 8.6 cm in diameter who died 4 months later, and another with a tumor measuring 10 cm in diameter who died 61 months later) had no viable HCC at the time of death. One patient who died after 7 months had a small viable portion in the tumor measuring 14 cm in diameter, and the remaining patient who died after 54 months had a new small tumor without local progression of the initial tumor measuring 10 cm in diameter. Nineteen patients (63.3%) survived for 6–103 months (mean, 37.5 months ± 25.2). Sixteen patients did not exhibit any viable tumors on the last follow-up CT images obtained 6–102 months after treatment (mean, 40.5 months ± 6.6). Three patients had viable HCC on the last follow-up CT study obtained 15, 19, and 27 months after treatment, respectively. Two of three patients had a locally progressed tumor (**Fig 3**). The remaining patient had intraperitoneal seeding masses in addition to a locally progressed tumor and intrahepatic metastases because this patient had presented with tumor rupture before chemoembolization. The cumulative overall survival rates at 1, 2, 3, 4, 5, and 6 years were 82.3% (95% CI, 82.6%–96.4%), 78.5% (95% CI, 63.2%–93.8%), 73.9% (95% CI, 57.0%–90.8%), 73.9% (95% CI, 57%–90.8%), 49.3% (95% CI, 23.4%–75.2%), and 32.9% (95% CI, 1.5%–64.3%), respectively. The progression-free survival rates at 1, 2, 3, 4, 5, and 6 years were 66.0% (95% CI, 48.8%–83.3%), 57.6% (95% CI, 39.0%–76.2%), 57.6% (95% CI, 39.0%–76.2%), 51.2% (95% CI, 30.8%–71.6%), 51.2% (95% CI, 30.8%–71.6%), and 34.2% (95% CI, 3.6%–64.8%), respectively (**Fig 4**). The median survival was 4.5 years ± 0.5.

Complications

There were three major complications (10%) that were successfully managed by percutaneous drainage. In one patient who underwent percutaneous transhepatic biliary drainage before chemoembolization, infection to the necrotic tumor and fistula between the tumor and bile duct developed. The biliary drain was left in place after removal of the drainage tube in the necrotic tumor cavity until the patient died of pneumonia 7 months after the initial chemoembolization procedure. In another patient with a tumor that invaded the gallbladder, cholecystitis occurred as a result of the development of a fistula between the tumor and gallbladder. In this patient, the tumor was initially fed by the cystic artery and the feeding branch derived from the cystic artery was embolized. Percutaneous transhepatic gallbladder drainage was performed and the drainage tube was removed after cholecystitis was resolved. In the remaining patient, who

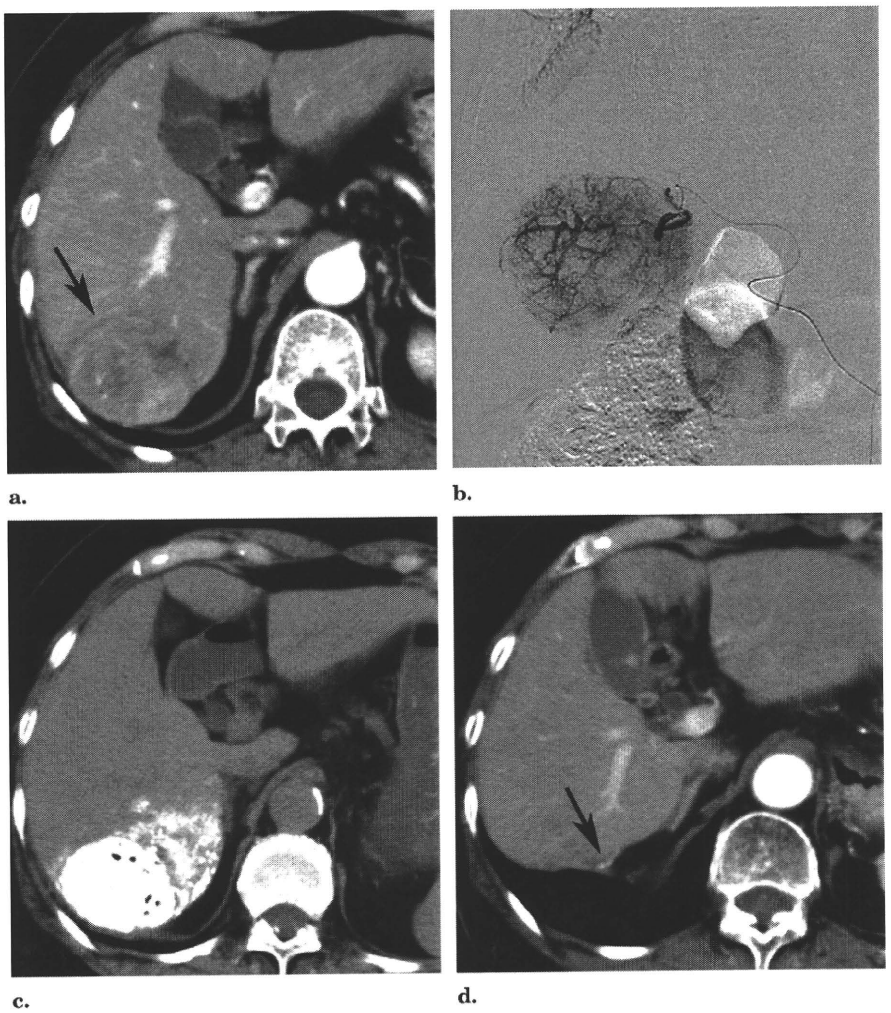

Figure 2. Images from an 81-year-old woman with HCC 6 cm in diameter. **(a)** Axial arterial-phase CT showed a tumor in segments XI and XII (arrow). **(b)** The tumor-feeding branch was selected and chemoembolization was performed. **(c)** Axial CT image obtained 1 week after chemoembolization showed dense iodized oil accumulation in the tumor. **(d)** The tumor disappeared 11 months after chemoembolization. Axial CT image obtained 3 years and 7 months after chemoembolization shows that the tumor disappeared, and a small amount of iodized oil is still retained in the liver parenchyma (arrow).

presented with dilation of the intrahepatic bile duct caused by compression of the tumor before chemoembolization, a large biloma developed after three chemoembolization sessions including embolization of the caudate arterial branches of the liver, and it was treated by percutaneous drainage. After healing of the biloma, obstructive jaundice caused by the bile duct stricture at the hepatic hilus also developed. Percutaneous transhepatic biliary drainage was performed and the bile duct stricture was managed by placement of two metallic stents (Zilver stent; Cook; **Fig 3**). There were no toxic complications as a result of injection of anticancer drugs in any patient.

DISCUSSION

Treatment for large HCCs is challenging. For small unresectable HCCs less than 3 cm in diameter, several local therapeutic options are available, such as RF ablation (3–5), microwave coagulation (17), ethanol injection (18), or acetic acid injection (19), in addition to chemoembolization (6–9). However, local therapies may have limited effects on medium and large HCCs (4,5).

Tumor size is one of the most important predictive factors for long-term prognosis after hepatectomy (20). According to the report from the Liver Cancer Study Group of Japan (1), the survival rates for patients with a maximum tumor diameter greater than 5 cm but less than 10 cm treated by surgical resection were 81%, 56%, and 42% at 1, 3, and 5 years, respectively, and those in patients with a maximum tumor diameter greater than 10 cm treated by surgical resection were 67%, 43%, and 32% at 1, 3, and 5 years, respectively. Shuto et al (21) reported that the 1-, 5-, and 10-year tumor-free survival rates in patients with tumors larger than 5 cm in diameter treated by hepatic resection were 48%, 18%, and 16%, respectively.

There are a few reports concerning nonsurgical treatment of large HCCs. Livraghi et al (5) reported the usefulness of RF ablation for HCCs larger than 5 cm in diameter, indicating that 100% tumor necrosis was achieved in 25% of noninfiltrating tumors and 23% of infiltrating tumors, and 90% or more necrosis was achieved in 71% of noninfiltrating tumors and 59% of infiltrating tumors. However, in a report by Obara et al (22), insufficient treatment of HCC by RF ablation, which allows the survival of some tumor cells, might induce further malignant transformation in vivo. Osuga et al (23) reported bland embolization with the use of superabsorbent polymer microspheres for large HCCs with a mean diameter of 8.1 cm, and complete necrosis was achieved in three of nine tumors, nearly complete necrosis (90%–99%) was achieved in three, and partial necrosis (50%–90%) was achieved in three. Takaki et al (24) reported RF ablation combined with chemoembolization for 20 patients with 32 HCCs larger than 5 cm in diameter (mean maximal tumor diameter of 6.2 cm) who each had fewer than three lesions. Their estimated overall survival rates were 100%, 62%, and 41% at 1, 3, and 5 years, respectively. In the present study, overall and progression-free survival rates at 1, 3, and 6 years were 82.3% and 66.0%, 73.9% and 57.6%, and 32.9% and 34.2%, respectively. This suggests that chemoembolization for large HCCs may also be an effective therapeutic option, although multiple procedures are required.

Severe complications after chemoem-

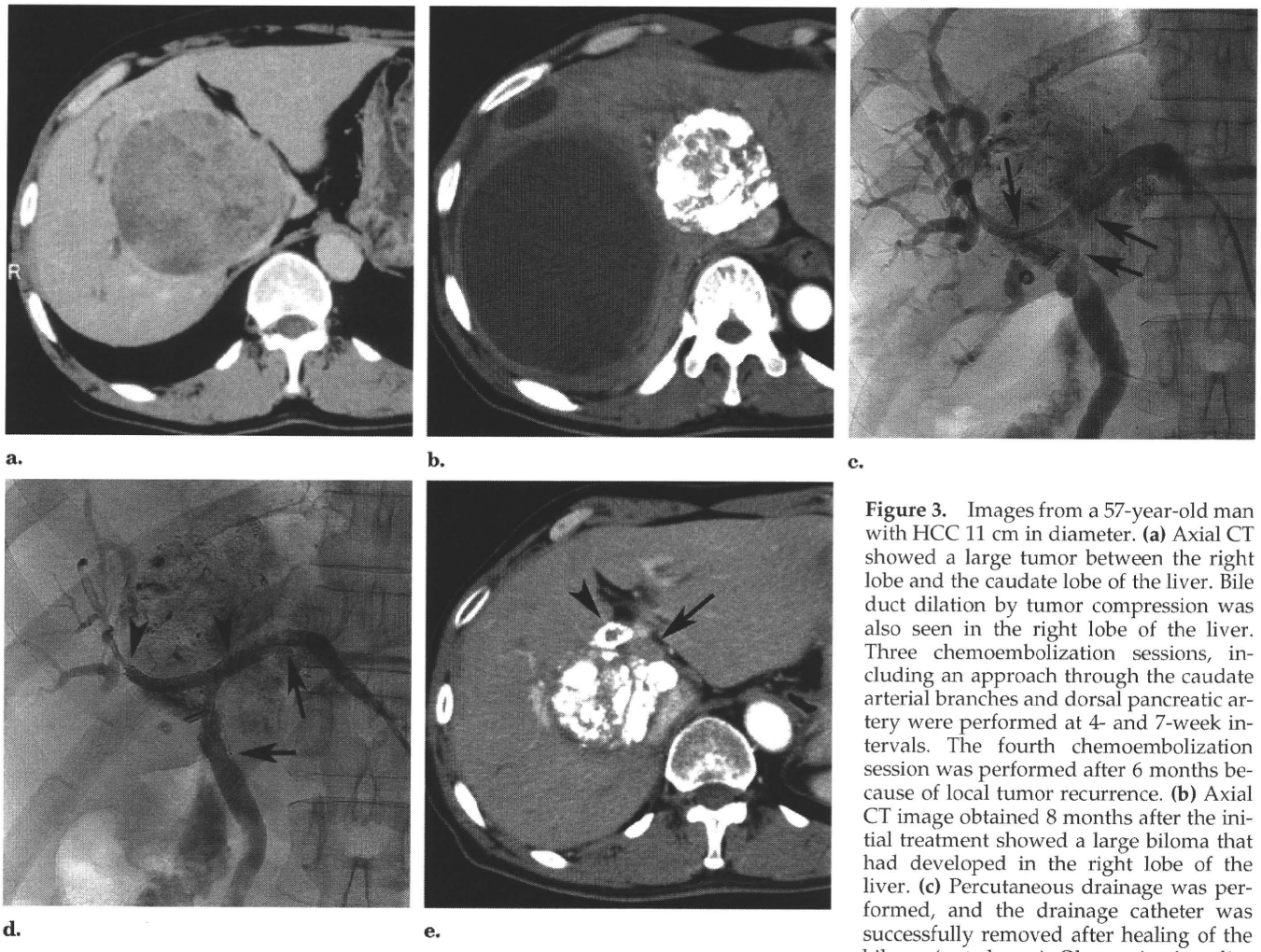

Figure 3. Images from a 57-year-old man with HCC 11 cm in diameter. **(a)** Axial CT showed a large tumor between the right lobe and the caudate lobe of the liver. Bile duct dilation by tumor compression was also seen in the right lobe of the liver. Three chemoembolization sessions, including an approach through the caudate arterial branches and dorsal pancreatic artery were performed at 4- and 7-week intervals. The fourth chemoembolization session was performed after 6 months because of local tumor recurrence. **(b)** Axial CT image obtained 8 months after the initial treatment showed a large biloma that had developed in the right lobe of the liver. **(c)** Percutaneous drainage was performed, and the drainage catheter was successfully removed after healing of the biloma (not shown). Obstructive jaundice developed 10 months after the initial treatment. Percutaneous transhepatic biliary drainage demonstrated a bile duct stricture at the hepatic hilus (arrows). **(d)** The bile duct stricture was successfully treated by placement of two metallic stents: one stent extended from the left hepatic duct to the common bile duct (arrows) and the other from the left hepatic duct to the right hepatic duct through the stented lumen (arrowheads). **(e)** The tumor recurred 11 months after the initial treatment, and a fifth chemoembolization procedure was performed. However, axial CT obtained 15 months after the initial treatment shows a small viable tumor (arrow) despite tumor reduction. The arrowhead indicates the metallic stent.

bolization of large HCCs have been reported (16,25–30). Acute tumor lysis syndrome is one of the most catastrophic complications (25). After treatment, tumor cells are lysed, thereby releasing a significant amount of intracellular potassium and phosphate into the extracellular circulation. As a result, severe hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure occur. Pulmonary oil embolism has also been reported and mainly develops in patients who receive more than 20 mL of iodized oil during the chemoembolization procedure (26,27). In the present study, stepwise chemoembolization was attempted to prevent severe complications in cases of tumors with a mean diameter of 10 cm. In addition, the total amount of iodized oil in the single session was limited to less than 10 mL. We consider stepwise chemoembolization key to the safe treatment of large tumors. Acute tumor lysis syndrome and pulmonary oil embolization did not occur in any patient in the present series.

Development of abscess and biloma after chemoembolization is another well-known major complication (16,27–29). The incidence of abscess formation or bile duct injury in patients with larger HCCs may be higher than that in patients with small HCCs. Song et al (28) reported that biliary invasion or extrinsic compression of the bile duct by tumor plus a decrease in portal venous inflow might be risk factors for abscess formation. As a large tumor is more likely to invade or compress the bile duct and portal vein, the risk of abscess formation may increase. In fact, all three of our patients who presented with infectious complications had bile duct dilation or tumor invasion to the gallbladder before chemoembolization. Bile duct necrosis also causes biloma or bile duct stenosis (29,30). This is likely to develop when small particles (< 250 μm) are used (30).

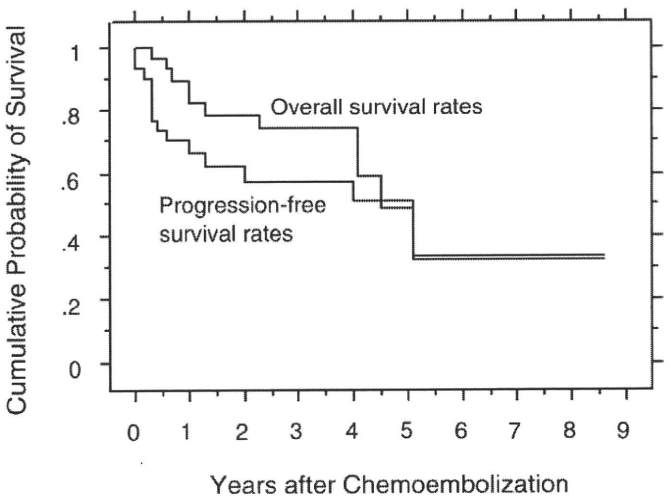

Figure 4. Survival rates of patients who received chemoembolization. Overall survival rates calculated by the Kaplan-Meier method at 1, 2, 3, 4, 5, and 6 years were 82.3%, 78.5%, 73.9%, 73.9%, 49.3%, and 32.9%, respectively. The progression-free survival rates at 1, 2, 3, 4, 5, and 6 years were 66.0% (95% CI, 48.8%–83.3%), 57.6% (95% CI, 39.0%–76.2%), 57.6% (95% CI, 39.0%–76.2%), 51.2% (95% CI, 30.8%–71.6%), 51.2% (95% CI, 30.8%–71.6%), and 34.2% (95% CI, 3.6%–64.8%), respectively.

However, in our case, it developed with the use of particles approximately 1 mm in diameter. We speculate that chemoembolization of the caudate arterial branch carries the potential risk of bile duct stricture at the hepatic hilus (31).

Large HCCs generally have multiple feeding vessels, not only through hepatic branches but also through extrahepatic collateral vessels (10–13). Chung et al (10) reported that right IPA parasitization was retrospectively suspected at the initial chemoembolization in 37 of 50 medium and large tumors (> 3 cm but < 5 cm, $n = 18$; > 5 cm, $n = 32$), with blood supply to tumors from the right IPA demonstrated on follow-up angiography. They also reported that the prevalence of extrahepatic blood supply at the initial chemoembolization session in a tumor smaller than 4 cm in diameter was less than 3%; this increased to 63% when the tumor was larger than 6 cm in diameter (11). In the present study, extrahepatic collateral supply was demonstrated in 70% of patients during the subsequent course of treatment, mainly through the right IPA. In addition, it was demonstrated in 47% of patients at the initial treatment. We consider successful embolization through extrahepatic collateral vessels to be another key to the control of large tumors. Physicians should develop sufficient knowledge of the spectrum of extrahepatic collateral vessels that supply HCC, and should be familiar with procedures for chemoembolization through these vessels.

There are several limitations to the present study. First, we selected patients with three or fewer tumors. Large HCCs generally produce intrahepatic metastases and/or portal vein tumor thrombus. Therefore, we evaluated the efficacy of chemoembolization in only a minority of patients with large HCCs. In addition, the number of patients who were treated in the present study was small and 83% of patients had a solitary tumor. Second, we investigated several extrahepatic vessels to evaluate tumor feeding. However, in elderly patients with atherosclerosis, screening of small branches directly arising from the aorta, such as the middle adrenal artery or right renal capsular artery, may have been incomplete (13). For these reasons, there is a possibility that some small tumor-feeding vessels might have been missed. Third, arterial infusion chemotherapy or irradiation was performed in a few patients in addition to chemoembolization. However, clinically, these treatments were ineffective and did not improve patient prognosis. Therefore, it is thought that our results might directly reflect the efficacy of chemoembolization for large HCCs.

In conclusion, chemoembolization was an effective treatment for large HCCs, as well as surgical resection or combination therapy with chemoembolization and RF ablation. However, there is also a risk of severe complications after chemoembolization for large HCCs, and prompt treatment is necessary to manage such complications.

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Interventional oncology: new options for interstitial treatments and intravascular approaches

Superselective TACE using iodized oil for HCC: rationale, technique and outcome

Osamu Matsui · Shiro Miyayama · Jyun-ichiro Sanada · Satoshi Kobayashi · Wataru Khoda · Tetsuya Minami · Kazuto Kozaka · Toshifumi Gabata

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Abstract Superselective TACE is defined as TACE from the distal portion of the feeding subsegmental hepatic artery to evoke strong ischemic effects on a small area of the liver, thus avoiding damage to liver function. Lipiodol (iodized oil) is semi-fluid, and it can flow into the surrounding portal venules and hepatic sinusoids through peribiliary plexus (PBP) and the drainage route from the hypervascular HCC. Therefore, the reversed flow from the hepatic sinusoids and portal venules to the peripheral portion of the tumor and daughter nodules can be blocked by Lipiodol injected before a particulate embolus (such as gelatin sponge particles). Common complications of superselective TACE are mild local pain and fever and temporary minimal changes of liver function. Reported CR ratio of definitely hypervascular HCC are around 30–60% by superselective TACE with Lipiodol for hypervascular HCC less than 5 cm. According to a nationwide survey by the Liver Cancer Study Group of Japan (LCSGJ), overall 5-year survival rate was 26% in patients with HCCs not indicated for surgery or RFA (PEI), mainly treated by segmental or subsegmental TACE using Lipiodol. Therefore, this TACE technique should be widely introduced as the first line technique for TACE therapy of HCC.

Keywords Hepatocellular carcinoma · TACE · Iodized oil (Lipiodol)

Introduction

Hepatocellular carcinoma (HCC) shows frequent multicentricity even at the time of the first diagnosis, and frequent recurrence following surgery or local ablation, especially in HCV related liver cirrhosis. In addition, it is usually associated with liver cirrhosis, and often shows intrahepatic dissemination without extrahepatic metastasis. For these multiple HCC lesions in the liver, transcatheter arterial chemoembolization (TACE) is the most important treatment method. In a 2002–2003 survey conducted by the Liver Cancer Study Group of Japan, TACE was employed in around 30% of the patients, local ablation in 31%, surgical resection in 34%, and chemotherapy in 5%, as the first line treatment for newly diagnosed HCC [1]. In addition, TACE is performed for almost all recurrent multiple HCCs. Therefore, in Japan, TACE is the most commonly performed treatment method for HCC, and an even less invasive and more effective procedure for its accomplishment would be welcomed in clinical practice.

Rationale

Superselective TACE is defined as TACE from the distal portion of the feeding subsegmental hepatic artery to evoke strong ischemic effects on a small area of the liver, thus avoiding damage to liver function ("transcatheter medical subsegmentectomy" or "transcatheter ablation" [2]).

To induce this "subsegmentectomy-like" effect, the role of Lipiodol is important. Because Lipiodol is semi-fluid, it

O. Matsui (✉) · J. Sanada · S. Kobayashi · W. Khoda · T. Minami · K. Kozaka · T. Gabata
Department of Imaging Diagnosis and Interventional Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
e-mail: matsuio@med.kanazawa-u.ac.jp

S. Miyayama
Department of Radiology, Fukui-saiseikai Hospital, Fukui, Japan

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can flow into the surrounding portal venules and hepatic sinusoids through the peribiliary plexus (PBP) and the drainage route from the hypervascular HCC [3, 4]. According to our previous analysis, in cirrhotic livers, the PBP is markedly dilated as compared with normal liver [5]. Therefore, more Lipiodol can flow into the portal veins and hepatic sinusoids through PBP after intra-arterial injection, especially in cirrhotic livers. One of the important technical problems of TACE only with particulate embolus in HCC was the suspected reversal of flow from the surrounding hepatic sinusoids and portal venules into the peripheral portion of the tumor following TACE. Because of this flow reversal, viable cancer cells frequently remained at the tumor margin and in satellite lesions after particulate TACE without Lipiodol. On the other hand, reversed flow from the hepatic sinusoids and portal venules to the peripheral portion of the tumor and daughter nodules can be blocked by Lipiodol injected before the particulate embolus. As we reported recently [6], the strong correlation between portal vein visualization during superselective TACE and local recurrence ratio of HCC may strongly support this hypothesis.

Technique

The first indispensable step of subsegmental TACE is superselective insertion of a microcatheter into the tumoral feeding artery to treat the tumor and at least 1 cm of peritumoral safety margin of liver parenchyma. Epirubicin (EPR) is the most common anticancer drug: it is usually dissolved in non-ionic contrast medium, and then mixed with Lipiodol by pumping through a three way stopcock to make a water in oil emulsion which is stable for long hours and works as the drug carrier. The total amount of Lipiodol used is almost equal to the diameter of the tumor. The gelatin sponge sheet is cut into small cubes approximately 0.5 mm in diameter. After the administration of pentazocine, a mixture of Lipiodol and anticancer drugs is injected gradually until the abundant visualization of the surrounding portal vein and/or marked retardation of arterial flow is seen. Subsequently, gelatin sponge particles are injected until a complete stoppage of the arterial flow is achieved. In the case of multiple HCC nodules, superselective TACE is performed for each nodule.

Complications

Commonly reported complications of superselective TACE are local pain (usually mild), fever (usually mild) and temporary minimal changes of liver function. Liver failure, cholecystitis, biloma, abscess and bile duct necrosis are rare, especially if the superselective catheterization is carefully carried out [2].

Outcome

Reported CR ratios of definitely hypervascular HCC are around 30–60% by superselective TACE with Lipiodol for hypervascular HCC less than 5 cm [2, 6–8]. On the other hand, according to the reports from European RCT studies, a 15–55% of PR ratio with conventional TACE is described by Llovet et al. [9]: the discrepancy seems enormous.

Our old study showed that the overall 5- and 10-year survival rates in 172 patients with hypervascular HCC less than 4 cm in diameter and less than 3 in number treated only by superselective TACE were 50.2, and 18.5%, respectively [10]. Similar results had been reported by Matsuo et al. [11] and Takayasu et al. [8]. According to a nationwide survey by the Liver Cancer Study Group of Japan (LCSGJ) analyzing 8510 patients during 8 years [1, 12], median survival time (MST) was 34 months, and overall 5-year survival rate was 26%. 5-year survival rate increased to 52% when restricted to a subgroup with Stage I of tumor extension and liver damage A. Multivariate analysis revealed that liver damage degree, TNM stage and serum AFP value were significant prognostic factors. Although various techniques were used in this population, the majority of patients analysed were treated by superselective TACE, and procedure-related mortality was only 0.5%. These results may partly reflect the high level of confidence using TACE achieved in Japan.

Conclusions

Absolute indications of TACE are multiple HCCs, more than 3 lesions without major portal venous extension and Child-Pugh A or B, and unresectable single HCC larger than 3 cm. Relative indications are reserved for unresectable and small HCCs not amenable to thermal ablation with less than 2 lesions less than 3 cm in diameter and those patients having HCC in Child-Pugh C class cirrhosis, for whom superselective TACE is possible without significant danger.

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CASE REPORT

Sloughing of Intraductal Tumor Thrombus of Hepatocellular Carcinoma After Transcatheter Arterial Chemoembolization

Miho Okuda · Shiro Miyayama · Masashi Yamashiro · Yuichi Yoshie · Natsuki Sugimori · Saya Igarashi · Yoshiko Nakashima · Taku Sanada · Shotaro Kosaka · Daishu Toya · Osamu Matsui

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Abstract Transcatheter arterial chemoembolization (TA CE) is effective for hepatocellular carcinoma (HCC) with intrabile duct thrombus. After TACE, intraductal tumor thrombi occasionally detach from the intrahepatic tumor and drop into the bottom of the common bile duct, causing clinical symptoms similar to the impaction of choledocholithiasis. The investigators describe three cases of sloughing of HCC intraductal tumor thrombi after selective TACE. In each of the three cases, the necrotic tumor cast was successfully removed endoscopically, and the patient's symptoms were dramatically improved. Two patients survived without recurrence of the intraductal tumor thrombus for 8 and 11 months after TACE, respectively.

Keywords Hepatocellular carcinoma · Intraductal tumor thrombus · Transcatheter arterial chemoembolization · Sloughing of tumor thrombus

M. Okuda (✉) · S. Miyayama · M. Yamashiro · Y. Yoshie · N. Sugimori · S. Igarashi · Y. Nakashima
Department of Radiology, Fukuiken Saiseikai Hospital, 7-1 Funabashi, Wadanaka-cho, Fukui 918-8503, Japan
e-mail: kusanagi_miho@mbr.nifty.com

T. Sanada · S. Kosaka · D. Toya
Department of Internal Medicine, Fukuiken Saiseikai Hospital, 7-1 Funabashi, Wadanaka-cho, Fukui 918-8503, Japan

O. Matsui
Department of Radiology, Kanazawa University Graduate School of Medical Science, 13-1 Takaramachi, Kanazawa 920-8641, Japan

Introduction

Although invasion into the portal vein is a common feature in hepatocellular carcinoma (HCC), intraductal tumor thrombus is considered to be rare [1, 2]. Transcatheter arterial chemoembolization (TACE) is one of the most effective therapeutic options for unresectable HCC, and it is also accepted procedure for tumor thrombi in the bile duct [3]. In this report, we describe three patients presenting with biliary obstruction caused by sloughing of an HCC intraductal tumor thrombus after TACE.

Case Reports

Case No. 1

A 61-year-old woman with HCC associated with liver cirrhosis secondary to hepatitis C and alcohol use was admitted to our hospital. She had previously undergone two TACE sessions for HCC in the past 30 months. Computed axial tomography (CAT) showed a recurrent tumor, 1.5 cm in diameter, with an intraductal tumor thrombus in segment IV and dilatation of the left bile duct system (Fig. 1A). She was not a suitable candidate for surgical resection because of her limited hepatic function. On admission, her serum bilirubin level was 3.2 mg/dl. It gradually increased to 7.4 mg/dl; however, it then spontaneously decreased to 3.1 mg/dl after 1 month. TACE was selectively performed in both hepatic arterial branches in segments IV and VIII without serious complications. Seven days after TACE, she presented with epigastric pain and fever. Her serum bilirubin level increased from 2.7 to 13.8 mg/dl. CAT showed dense iodized oil accumulation in the tumor and disappearance of the intraductal tumor thrombus (Fig. 1B). A

hyperattenuating mass was seen at the bottom of the common bile duct, and the entire biliary system was dilated (Fig. 1C). We decided that the necrotic tumor thrombus had detached from the main tumor and dropped into the common bile duct, causing biliary obstruction. Two days later, the necrotic thrombus was removed endoscopically (Fig. D). After removal of the necrotic tissue, she was free of symptoms, and her serum bilirubin level returned to normal. The tumor in segment IV recurred 5 months later and was successfully treated by additional TACE. There has been no recurrence of the intraductal tumor thrombus for 8 months.

Case No. 2

An 82-year-old woman with HCC associated with liver cirrhosis caused by unknown etiology was admitted because of abdominal pain and jaundice. She had previously been treated with three TACE sessions during the course of 22 months. CAT showed multiple HCC in both lobes of the liver. The main tumor was 1.8 cm in diameter and was located in the hepatic hilum; however, it had invaded into the right hepatic duct and caused dilatation of the biliary system (Fig. 2A). Magnetic resonance imaging (MRI) demonstrated blood degradation products in the common bile duct in addition to an intraductal tumor thrombus (Fig. 2B). Because of her poor hepatic function reserve, she was assessed as being inoperable. On admission, her serum bilirubin level was 9.1 mg/dl. It gradually increased to 16.1 mg/dl; however, it then spontaneously decreased to 2.8 mg/dl after 1 month. TACE was selectively performed through the right hepatic arterial branches without serious complications. CAT obtained 7 days after TACE showed dense iodized oil accumulation in the main tumor and intraductal tumor thrombus. The intraductal tumor thrombus had shrunk slightly and migrated distally (Fig. 2C). Ten days after TACE, she presented with epigastric pain, fever, and jaundice. Her serum bilirubin level increased from 2.3 to 4.5 mg/dl. Sloughing of the intraductal thrombus into the bottom of the common duct and dilatation of the bile duct were confirmed on CAT (Figs. 2D and 2E). The necrotic tissue was removed endoscopically, and her symptoms improved. During the 11 month follow-up period, local recurrent tumors and newly developed tumors at other sites were treated by two additional TACE sessions. The bile duct tumor thrombus has not recurred for 15 months.

Case No. 3

A 71-old-woman with HCC associated with liver cirrhosis secondary to hepatitis C was admitted. She had undergone

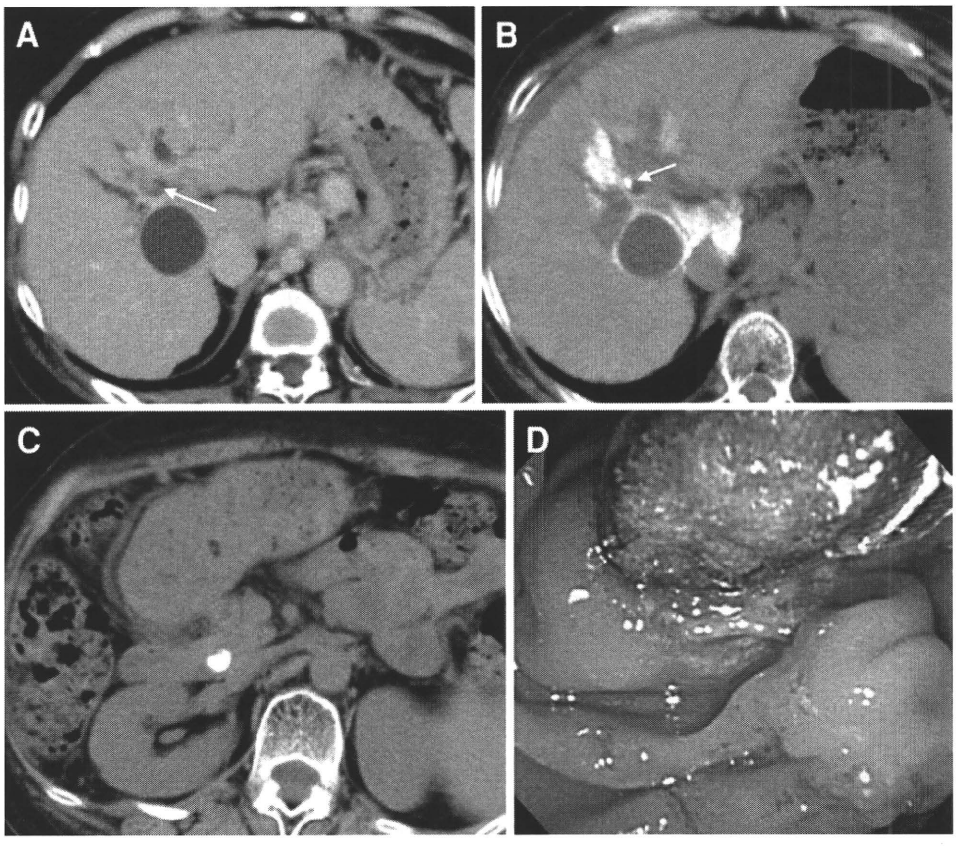

Fig. 1 Case no. 1. **A** Contrast-enhanced CAT image before TACE shows a recurrent tumor with an intraductal tumor thrombus (*arrow*) in segment IV and dilatation of the left bile duct system. **B** Unenhanced CAT 7 days after TACE shows dense iodized oil accumulation in the hepatic tumor and disappearance of the intraductal tumor thrombus (*arrow*). **C** On the CAT image at the bottom of (**B**), a hyperattenuating mass is seen at the bottom of the common bile duct, indicating a sloughed tumor with iodized oil accumulation. **D** The necrotic tissue was endoscopically removed, and the patient's symptoms improved dramatically

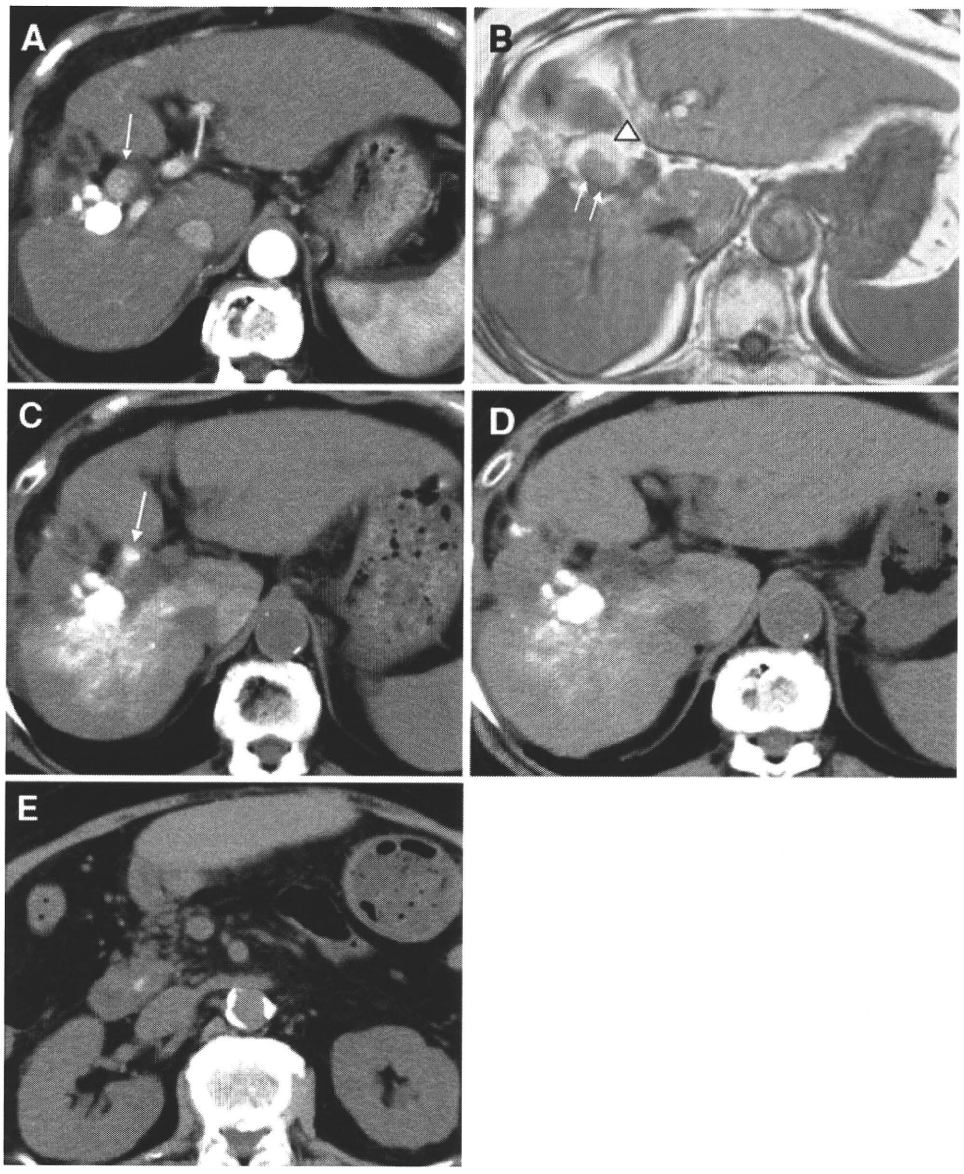

Fig. 2 Case no. 2. **A** Arterial-phase CAT shows an intraductal tumor thrombus in the right hepatic duct (*arrow*). **B** Axial T1-weighted MRI demonstrates the intraductal tumor (*arrows*) and hemobilia (*arrowhead*). **C** Unenhanced CAT 7 days after TACE shows dense iodized oil accumulation in the tumor and intraductal tumor thrombus (*arrow*). The tumor thrombus has shrunk slightly and migrated distally. **D** Unenhanced CAT 10 days after TACE shows the disappearance of the intraductal tumor thrombus. **E** At the bottom of the CAT image shown in (**D**), the tumor thrombus has sloughed into the common bile duct

seven TACE sessions for HCC during the course of 3 years. CAT showed multiple HCC in both lobes of the liver and tumor thrombi in the right hepatic and common bile ducts. She was not a suitable candidate for surgical resection because of her poor general condition. TACE was performed through the right hepatic artery without serious complications. Seven days after TACE, she presented with epigastric pain, and sloughing of the intraductal tumor thrombus and dilatation of the bile duct were confirmed on CAT. Her serum bilirubin level increased from 2.6 to 15.3 mg/dl. The necrotic tissue was removed endoscopically, and her symptoms improved. Her serum bilirubin level decreased after removal of the detached tumor thrombus; however, she died of intrahepatic tumor progression 38 days after TACE.

Discussion

HCC with intrabile duct invasion is less common than invasion into the portal vein. Intraductal tumor thrombi cause hemobilia and/or jaundice and rapid deterioration of hepatic function. Lin [1] classified such cases as "icteric hepatoma." Kojiro et al. [2] described the features of 24 cases of HCC with prominent intrabile duct tumor growth among 238 autopsy and 21 surgical cases, with a prevalence of approximately 9%. In their series, the survival time of patients with intraductal tumor growth was significantly shorter than that of patients without bile duct invasion in their series [2]. In contrast, it has also been reported that not all patients with HCC intrabile duct invasion are terminally ill, and good

palliation and occasional cure may be possible with proper management [4].

The ideal treatment for patients with intraductal tumor thrombus is surgical resection [5, 6]. However, most tumors with bile duct invasion are generally large and located near the hepatic hilum. Such patients usually have poor hepatic function reserve; therefore, most patients are not candidates for surgery. Kitagawa et al. [3] reported the efficacy of TACE for controlling hemobilia caused by advanced HCC rupturing into the biliary system. In their series, hemobilia was temporarily stopped by TACE in all three patients. They stated that selective TACE was safe and effective for managing hemobilia in the selected patients with even far-advanced HCC.

Hiraki et al. [7] reported a case of sloughing of intraductal tumor thrombus who presented with jaundice and severe back pain 18 days after TACE. The clinical symptoms were improved after endoscopic removal of the tumor cast in the bile duct. Tumor thrombi in the bile duct are usually histologically similar to the main tumor; however, they generally become more necrotic and hemorrhagic. In addition, tumors growing into the bile duct usually do not attach tightly to the bile duct wall [2]. In a report by Yamamoto et al. [8], an intraductal tumor thrombus was removed by endoscopic catheter insertion alone. In our three cases, as in a case reported by Hiraki et al. [7], the bile duct tumor thrombus was easily detached and dropped into the common bile duct after TACE. This suggests that TACE has a strong therapeutic effect and achieves complete necrosis of the intraductal tumor thrombus. Therefore, physicians should recognize the risk of obstructive jaundice and acute pancreatitis caused by sloughing of the intraductal tumor thrombus after TACE [7].

The clinical symptoms and management of dropped intraductal tumors are similar to those of the impaction of choledocholithiasis. In our three cases, the necrotic tumor cast was successfully removed endoscopically. We believe that endoscopic removal is the most desirable and effective treatment. To remove the necrotic tissue, however, endoscopic sphincterectomy (EST) may be necessary. Most patients with liver cirrhosis have hypersplenism-related thrombocytopenia; therefore, platelet transfusion may frequently be required to perform EST. Endoscopic tube stent insertion into the common bile duct may also be useful to relieve jaundice in patients with poor general condition. There have not been enough reports discussing the usefulness of prophylactic biliary drainage in such patients. We believe endoscopic intervention should be considered when a symptomatic sloughed tumor develops because not all intraductal tumor thrombi may drop after TACE.

In the present two cases (case nos. 1 and 2), a relatively small tumor located near the hepatic hilum progressed into the bile duct. In such cases, TACE may provide sufficient effects not only on the main tumor but also against the intraductal tumor thrombus. In our two patients, the intraductal tumor thrombus disappeared and has not recurred for > 8 and 11 months, respectively. In addition, the recurrent tumor and newly developed tumors were well controlled by TACE in both patients. Therefore, we conclude that intraductal tumor thrombus may not be a terminal illness and rather can be successfully managed by selective TACE in certain patients, especially when the main tumor is relatively small.

TACE is generally contraindicated for patients with hyperbilirubinemia. Okazaki et al. [9] performed TACE in 38 patients with intraperitoneal hemorrhage secondary to HCC, and there was a significant difference in the survival period between 24 patients without hyperbilirubinemia and 14 patients with hyperbilirubinemia > 3 mg/dl. Considering hepatic function, it is preferable that TACE is performed in patients with a low bilirubin level. Although in the present two cases (case nos. 1 and 2), the patients' bilirubin levels were high on admission, they decreased to approximately 3 mg/dl after 1 month of medical therapy; therefore, we were able to perform effective TACE without severe complications. However, we would not hesitate to perform TACE even in patients with hyperbilirubinemia when uncontrolled massive hemobilia from an intraductal tumor occurs [6]. In such conditions, the embolized arterial branches should be minimized so as not to deteriorate hepatic function further.

There is a limitation to the present study. Histopatologic confirmation of the dropped tumor thrombus was not obtained in all three cases because the mass was released into the duodenum after removal from the common bile duct. However, we believe that the removed mass was a completely necrotic intraductal tumor thrombus on the basis of serial CAT findings.

In conclusion, intraductal tumor thrombi may easily drop into the common bile duct after TACE and cause obstructive jaundice and acute pancreatitis, symptoms similar to choledocholithiasis. An endoscopic procedure may be required if clinical symptoms develop. TACE is effective for treating intraductal tumor thrombi and achieves sufficient results, especially if the main tumor is relatively small.

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CLINICAL INVESTIGATION

The March of Extrahepatic Collaterals: Analysis of Blood Supply to Hepatocellular Carcinoma Located in the Bare Area of the Liver After Chemoembolization

Shiro Miyayama · Masashi Yamashiro · Miho Okuda · Yuichi Yoshie · Yoshiko Nakashima · Hiroshi Ikeno · Nobuaki Orito · Osamu Matsui

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Abstract The purpose of this study was to evaluate changes in vascular supply to hepatocellular carcinoma (HCC) located in the bare area of the liver in patients who were mainly treated with chemoembolization. Twenty-six patients with HCC showing a mean diameter of 3.1 ± 1.4 cm (mean ± standard deviation) were mainly treated with chemoembolization. All patients underwent 2.7 ± 2.3 chemoembolization sessions over 40.1 ± 25.2 months. Tumor feeding branches demonstrated in each chemoembolization session were retrospectively evaluated. Initially, 18 tumors (59.2%) were supplied by the hepatic artery (H) and 8 (30.8%) by both the hepatic and the extrahepatic arteries (H + C). Fourteen tumors (53.8%) recurred at the posterior aspect of the tumor and were supplied by H ($n = 4$), H + C ($n = 5$), and extrahepatic collaterals (C) ($n = 5$). Several tumors recurred despite repeated chemoembolization, and these were supplied by H ($n = 1$), H + C ($n = 7$), and C ($n = 2$) at the second recurrence, by H ($n = 1$), H + C ($n = 2$), and C ($n = 3$) at the third, by H + C ($n = 2$) and C ($n = 2$) at the fourth, by H + C ($n = 2$) and C ($n = 2$) at the fifth, and by H ($n = 1$) and C ($n = 1$) at the sixth. One tumor was supplied by H at the seventh and by H + C at the eighth recurrence. As the number of local recurrences increased, the feeding vessel shifted from H to C. Especially, the right inferior phrenic artery (IPA) and renal capsular artery (RCA) supplied the tumor early, while the small right RCAs, adrenal arteries, and intercostal and lumbar artery supplied late recurrences in turns. In conclusion, HCCs located in the bare area are frequently supplied by extrahepatic vessels initially, while recurrence after chemoembolization is mainly due to extrahepatic blood supply. The right IPA and RCA are common feeding vessels demonstrated early, while other extrahepatic collateral supply from the retroperitoneal circulation occurs in turns during the later course.

Keywords Hepatocellular carcinoma · Chemoembolization · Bare area of the liver · Extrahepatic blood supply

S. Miyayama (✉) · M. Yamashiro · M. Okuda · Y. Yoshie · Y. Nakashima · H. Ikeno · N. Orito
Department of Diagnostic Radiology, Fukuiken Saiseikai Hospital, 7-1, Funabashi, Wadanaka-cho, Fukui 918-8503, Japan
e-mail: s-miyayama@fukui.saiseikai.or.jp

O. Matsui
Department of Radiology, Kanazawa University Graduate School of Medical Science, 13-1, Takara-machi, Kanazawa 920-8641, Japan

Introduction

Hepatocellular carcinoma (HCC) frequently recurs after chemoembolization and development of extrahepatic collateral pathways is one of the causes of local tumor recurrence. Several extrahepatic collateral pathways supplying HCC have been reported [1–14].

At the level of the bare area of the liver, branches of the inferior phrenic arteries (IPAs) are in direct contact with the liver [3, 4]. In the event of hepatic artery damage, or even with a patent hepatic artery, these branches contribute substantially to the hepatic tumor vascular supply. In addition, IPAs usually anastomose with several arteries, such as the internal mammary artery and intercostal arteries [5, 6, 15]. Therefore, a tumor located in the bare area of the liver has the potential to receive collateral blood flow through several individual sources. Extrahepatic collateral supplies can inhibit the effectiveness of chemoembolization. For transcatheter management of HCC to be effective, these collaterals should be adequately embolized [1–14].

Therefore, interventional radiologists should have sufficient knowledge of extrahepatic blood supply to HCCs.

In this report, we retrospectively analyzed changes in vascular supply to HCCs located in the bare area of the liver during the subsequent clinical course of patients who were mainly treated by chemoembolization.

Materials and Methods

Patients

In the present study, we define "the bare area of the liver" as the posterior surface of Segment 7 demarcated by the right hepatic vein. Although we are well aware that "the bare area of the liver" also includes a part of lateral surface of Segment 8, the right-side margin is not anatomically outlined clearly. Between August 1999 and August 2008, we treated 26 consecutive HCC lesions in the bare area of the liver by chemoembolization. The patient profiles are summarized in Table 1. There were 14 men and 12 women and the mean patient age was 68.9 ± 7.5 years (mean ± standard deviation; range, 51 to 81 years). All patients had liver cirrhosis, which was associated with hepatitis C in 19 patients and hepatitis B in 6 patients, while in the remaining patient, the etiology was unknown. All patients had a single HCC lesion at the bare area, including 6 patients with 1 other HCC in addition to the tumor in the bare area and 2 patients with multiple HCCs but fewer than 5 lesions at other sites. The mean diameter of tumors in the bare area was 3.1 ± 1.4 cm (range, 1–6 cm). Diagnosis was established by imaging findings on computed tomography (CT) and/or magnetic resonance (MR) imaging, characteristic nodular enhancement during the arterial phase, and washout during the delayed phase images in all patients.

Table 1 Patent profiles

Patient characteristic	
Gender	
Male	14
Female	12
Mean age (yr)	68.9 ± 7.5
Liver cirrhosis	26 (100%)
HCV related	19 (73.1%)
HB related	6 (23.1%)
Etiology unknown	1 (3.8%)
Tumor size in the bare area (cm)	3.1 ± 1.4
Intrahepatic multiplicity	
Single	18 (69.2%)
Two	6 (23.1%)
Three-5 lesions	2 (7.7%)
Treatment	
Chemoembolization alone	22 (84.6%)
Combination of chemoembolization & RFA	4 (15.4%)

RFA radiofrequency ablation

Initially, 22 tumors were treated by chemoembolization alone and 4 were treated by a combination of chemoembolization and radiofrequency ablation (RFA).

Chemoembolization Procedure

Written informed consent was obtained from each patient before the chemoembolization and RFA procedures. Institutional review board approval was not required at our institution for this retrospective study.

A 2-Fr tip (Progreat α; Terumo, Tokyo, Japan) was mainly used for all chemoembolization procedures. To navigate the microcatheter, a 0.016-in. guidewire (GT-wire; Terumo) was used. After the microcatheter was inserted into the feeding branch, 0.5 ml of 2% lidocaine (Xylocaine; Fujisawa, Osaka, Japan) was intra-arterially injected to prevent pain and vasospasm. First, a mixture of iodized oil (Lipiodol; Andre Guerbet, Aulnaysous-Bois, France) and anticancer drugs (epirubicin [Farmorbicin], Kyowa Hakko, Tokyo, Japan; mitomycin C [Mitomycin], Kyowa Hakko) was injected, and injection of gelatin sponge particles followed. Until December 2006, gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, MI, USA) cut into approximately 1-mm cubes were used. Since January 2007, 1-mm-diameter commercially available gelatin sponge particles (Gelpart; Nippon Kayaku, Tokyo, Japan) were used.

The embolized branches of the hepatic artery were minimized as selectively as possible in each patient. Extrahepatic collaterals were searched for with the use of a 4-Fr shepherd-hook catheter (Terumo) or cobra-shaped catheter (Hanako Medical, Kobe, Japan). When tumor stain was demonstrated through the extrahepatic vessel on angiography, the tumor-feeding branch was selected by the microcatheter. In total, 1–6 ml of iodized oil, 10–30 mg of epirubicin, and 2–6 mg of mitomycin C were used in a single chemoembolization session, depending on the size of each tumor.

RFA Procedure

RFA was performed 1–2 weeks after chemoembolization in the first 4 consecutive tumors (2.5–5 cm in diameter; mean, 3.3 ± 1.4 cm) in 4 patients. The procedure was performed using an expandable electrode (LeVeen; Radiotherapeutics, Sunnyvale, CA, USA) under ultrasonographic (US) guidance without injection of saline into the pleural cavity. However, RFA was not performed after the fifth patient because we were able to obtain a complete ablative margin in only 1 of the previous 4 tumors.