Angiographic Subsegmentectomy for the Treatment of Patients with Small Hepatocellular Carcinoma

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BACKGROUND. The therapeutic results of nonsurgical treatment for patients with hepatocellular carcinoma (HCC) have been poor, and improved treatments are needed. The authors recently developed a new technique called *angiographic subsegmentectomy* for the treatment of patients with small HCC.

METHODS. The technique includes confirming the diagnosis of small HCC using a helical computed tomography (CT) scan combined with an angiography system for identifying the tumor-feeding subsegmental hepatic artery, injecting lipiodol containing farmorubicin until it enters the portal vein in sufficient amounts, and injecting sponge particles into the hepatic artery for embolization. Occlusion of the hepatic artery with gel particles and occlusion of the portal vein by lipiodol induce infarction necrosis, which encompasses the entire tumor and the surrounding liver parenchyma.

RESULTS. The treatment was given to 23 patients with 30 HCC tumors that measured < 20 mm in greatest dimension. It was successful in all 23 patients. Serum alanine aminotransferase levels were elevated to a significant level in the majority of patients after treatment, mild ascites developed in three patients, and the patients complained of pain and fever posttreatment that were controlled readily. No patients developed hepatic failure. Only one patient developed recurrent disease posttreatment at 1.5 years, for a recurrence rate of 5% at 1 year and 6.6% at 1.5 years, a rate that has never been achieved with other treatment modalities.

CONCLUSIONS. Angiographic subsegmentectomy is a novel treatment for patients with small HCC. The results indicated that it is equivalent to undergoing small resection and is superior to conventional arterial chemoembolization. ***Cancer* 2003;97:1051–6.** *© 2003 American Cancer Society.*

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Hepatocellular carcinoma (HCC) is a common malignancy throughout the world and has high morbidity and mortality rates. Although an early detection program with modern imaging techniques now permits the diagnosis of small HCC,[1] treatment is difficult, and the prognosis for these patients remains poor.[2] Because patients with HCC often have coexisting cirrhosis, hepatic resection frequently is contraindicated. Nonsurgical treatment modalities now include chemotherapy,[3] intraarterial chemoembolization,[4] radiation,[5] immunotherapy,[6] local ablation therapy[7] (such as percutaneous ethanol injection[8]), and interstitial thermal ablation therapy[9] (such as radiofrequency coagulation[10]). However, the therapeutic results of these nonsurgical treatments are unsatisfactory due to incomplete destruction of the tumor and frequent recurrence after the treatment.

For these reasons, improvement of the current therapy or development of new therapeutic modalities is required urgently.

Lipiodol, which is a lymphographic contrast agent, was used first by Konno et al.[11] for the treatment of patients with HCC. In 1983, those authors mixed a lipophilic derivative of neocarzinostatin (stylene malei anhydride neocarzinostain [SMANSC])[12] with lipiodol and injected the mixture into the hepatic artery to accompany local chemotherapy: Lipiodol droplets trapped in tumor tissues slowly release the antitumor agent. Lipiodol also proved to be diagnostic for small HCC, because it remains in the tumor almost indefinitely and provides clear tumor contrast on computed tomography (CT) scans.[13] Early in the 1980s, Yamada et al.[14] began using arterial embolization for the treatment of patients with HCC. In their technique, which obtained good results, gel-foam particles were injected into the hepatic artery to embolize the tumor-feeding arteries. Thus, intraarterial chemotherapy using lipiodol as a drug-delivery vehicle and gel-particle embolization came to be combined for better therapeutic effects in Japan. This lipiodol chemoembolization technique soon was adopted by other countries. Because SMANCS was not available immediately, other chemotherapeutic agents were used that do not mix with lipiodol, including the use of angiographic agents with the same specific gravity as lipiodol to produce a fine emulsion.[15] Although lipiodol droplets are trapped within capillaries of the tumor, acting as microemboli, embolization itself without an antitumor drug has no therapeutic effect.[16] Lipiodol chemoembolization is now used widely around the world, although the results have not been very satisfactory.[4,17]

In 1988, Nakamura et al.[18] observed that, after embolization using lipiodol and doxorubicin hydrochloride with or without gelatin particles, lipiodol was seen in the portal vein, and the amount of lipiodol seen was correlated with the amount that was injected despite a lack of arterioportal shunting. Those authors postulated that lipiodol entered the portal vein through arterioportal communications after pooling in the sinusoids. They warned that the use of high doses of lipiodol will increase adverse reactions and suggested that lipiodol doses that show the third-order portal vein fairly well would suffice for the purpose.[19] Of six patients who were treated by those investigators, necrosis was incomplete in two tumors, both of which measured > 5 cm.

With the system of combining helical CT with angiography, we are able to identify the exact feeding artery at the subsegment level; and, with the use of a thin catheter, we developed a technique in which the subsegmental artery that is feeding a small HCC is catheterized, and excess lipiodol mixed with an antitumor agent is injected. Lipiodol regurgitates into the portal vein and occludes it. Occlusion of both the artery and the portal vein induces infarction or necrosis of that particular subsegment. Although nontumorous liver tissue surrounding the tumor is undergoes necrosis with elevation of serum aminotransferase levels, the amount of necrotic tissue produced is not enough to induce hepatic failure. By limiting tumor size to 3 cm, we have been successful in inducing complete necrosis in the majority of tumors with very infrequent recurrence.

MATERIALS AND METHODS

We followed about 300 patients with chronic liver disease mainly due to hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. These are patients who are at high risk for HCC, and we conduct abdominal ultrasound (US) examinations, serum α-fetoprotein (AFP) screening, and des-γ-carboxy prothrombin (PIVKA-II) measurement for these patients every 3 months. Whenever a suspicion of HCC arises, helical CT-angiography is carried out for diagnosis.

In the past 2 years, we identified HCC tumors measuring < 20 mm in 23 patients, with the number of tumors ranging from 1 to 3 in individual patients. Clinical diagnosis of these patients was chronic hepatitis B in 3 patients, chronic hepatitis C in 10 patients, B-viral cirrhosis in 2 patients, and C-viral cirrhosis in 8 patients (Table 1). Follow-up from the time of diagnosis to the time HCC was detected ranged from 1 month to 17 years (average, 4.7 years). The diagnosis of cirrhosis was mainly clinical and was based on US examination, CT scan, endoscopy, and biopsy. Findings indicative of cirrhosis included ascites, splenomegaly, liver surface irregularity, dilated left gastric vein, dilated paraumbilical vein, obtuse liver edge, enlarged caudate and left lobes, and esophageal varices seen by endoscopy.

For imaging diagnoses, a Shimazu SCT 6800 TX angio-CT system was used. The imaging techniques that were used for diagnosis and treatment consisted of digital subtraction hepatic arteriography (DSA) using 40 mL of iomeprol (350 mgI/mL) followed by helical CT during hepatic arteriography (CTA) with 5-mm slices and 5-mm collimation at 5-mm reconstruction intervals. CTA was followed by CTA in which the superior mesenteric artery was catheterized, and 20 μg of prostaglandin E_1 were injected immediately before the injection of 90 mL of Iomeprol at a rate of 3 mL per second using a power injector (CTAP). Prostaglandin is used in CTAP to increase the blood flow of

TABLE 1
Patients who Underwent Angiographic Subsegmentectomy

Age (yrs)	Gender	FU post-Dx (months)	Virus	Dx	AFP (ng/mL)	PIVKA-II (mAU/mL)[a]	No. of tumors	Size (mm)[b]	FU after Tx (months)
62	M	7.0	B	LC	1786/40[c]	58/25[c]	3	15	12
55	M	5.0	C	CH	6/7	25/14	2	15	24
72	F	15.0	C	LC	594/15	297/24	2	20	18
85	F	6.0	C	CH	6/6	34/22	3	20	18
52	M	17.0	B	CH	15/37	21/32	1	15	18
71	F	4.0	C	CH	10/30	16/25	1	10	18
64	M	0.5	C	LC	79/43	10/9	1	8	24
59	F	4.0	C	LC	31/151	56/195	1	10	24
76	M	7.5	C	CH	14/14	38/29	1	19	24
69	M	2.0	C	CH	91/282	26/54	1	12	18
47	M	4.5	B	LC	12/13	32/16	1	20	18
66	F	2.0	C	LC	106/68	12/13	1	20	18
79	F	1.0	C	CH	9/8	26/51	1	20	18[d]
58	M	1.0	C	LC	182/72	29/20	1	10	12
67	M	1.0	C	CH	109/41	72/28	1	15	24
68	M	5.0	C	CH	258/34	18/17	1	10	12
69	F	2.0	C	LC	26/189	946/1082	1	18	12
47	M	8.0	B	CH	4/4	26/20	1	20	24
70	M	11.0	C	CH	10/7	146/74	1	15	6
48	F	6.0	B	CH	107/12	25/19	1	20	2
69	M	11.0	C	LC	125/69	23/20	1	17	1
71	M	15.0	C	CH	4/4	20/14	1	15	1
55	M	9.0	C	LC	161/34	20/25	2	20	18

FU: follow-up; Dx: diagnosis; AFP: α-fetoprotein; PIVKA-II: des-γ-carboxy prothrombin II; Tx: treatment: M: male; LC: cirrhosis; CH: chronic hepatitis; F: female.

[a] Normal: < 40 mAU/mL.

[b] Size of the greatest mass.

[c] At the time of diagnosis/follow-up.

[d] This patient developed recurrent disease 18 months after treatment.

the superior mesenteric artery. Informed written consent was obtained from each patient.

When a small HCC was identified from the CTAP and CTA findings (Fig. 1A), a 2.7-French or 3.0-French microcatheter was advanced into the subsegmental artery, usually the fourth-order artery, that is feeding the mass. After confirming that the catheterized artery is feeding the tumor, a mixture of farmorubicin (5 mg) and 5–8 mL of lipiodol is injected until the portal vein branches are opacified retrogradely (Fig. 1B). Gel foam cut into 1-mm particles and soaked in 6 mg of mitomycin C are then injected to embolize the artery. The reason for mixing farmorubicin with lipiodol is that it produces a good emulsion, whereas mitomycin C does not. The targeted lesion receives lipiodol, and lipiodol delineates the lesion clearly. The area containing the HCC lesion undergoes necrosis, and the whole area shrinks (Fig. 1C). Three of the treated lesions subsequently were biopsied, and complete necrosis was confirmed. After embolization, serum alanine aminotransferase (ALT) levels are elevated, and the patient complains of fever and pain, which are controllable with medication. Elevated ALT levels return to normal in 1 week. All patients were discharged in 2 weeks. For the diagnosis of possible recurrent disease, US examinations were carried out every 3 months, and plain and enhanced CT scans were taken every 6 months.

RESULTS

A total of 30 lesions measuring < 20 mm were identified in 23 patients (Table l) and were treated with our angiographic subsegmentectomy. Liver function tests in these patients varied: Serum bilirubin levels were in the range of 1.0–1.6 mg/dL, albumin levels were 2.5–3.6 g/dL, and indocyanin green clearance at 15 minutes was 1.6–51.6%. The amount of lipiodol injected was adjusted according to the liver function reserve of the patient, but it never exceeded 10 mL. Lipiodol was deposited into the targeted lesion and into some of the surrounding liver tissue, and the treatment was success in all patients. Serum ALT levels were elevated to > 500 IU/L in 8 patients, and mild ascites developed in 3 patients and were controlled with diuretics. Several patients required 200 mg of Solu-Cortef (Upjohn)

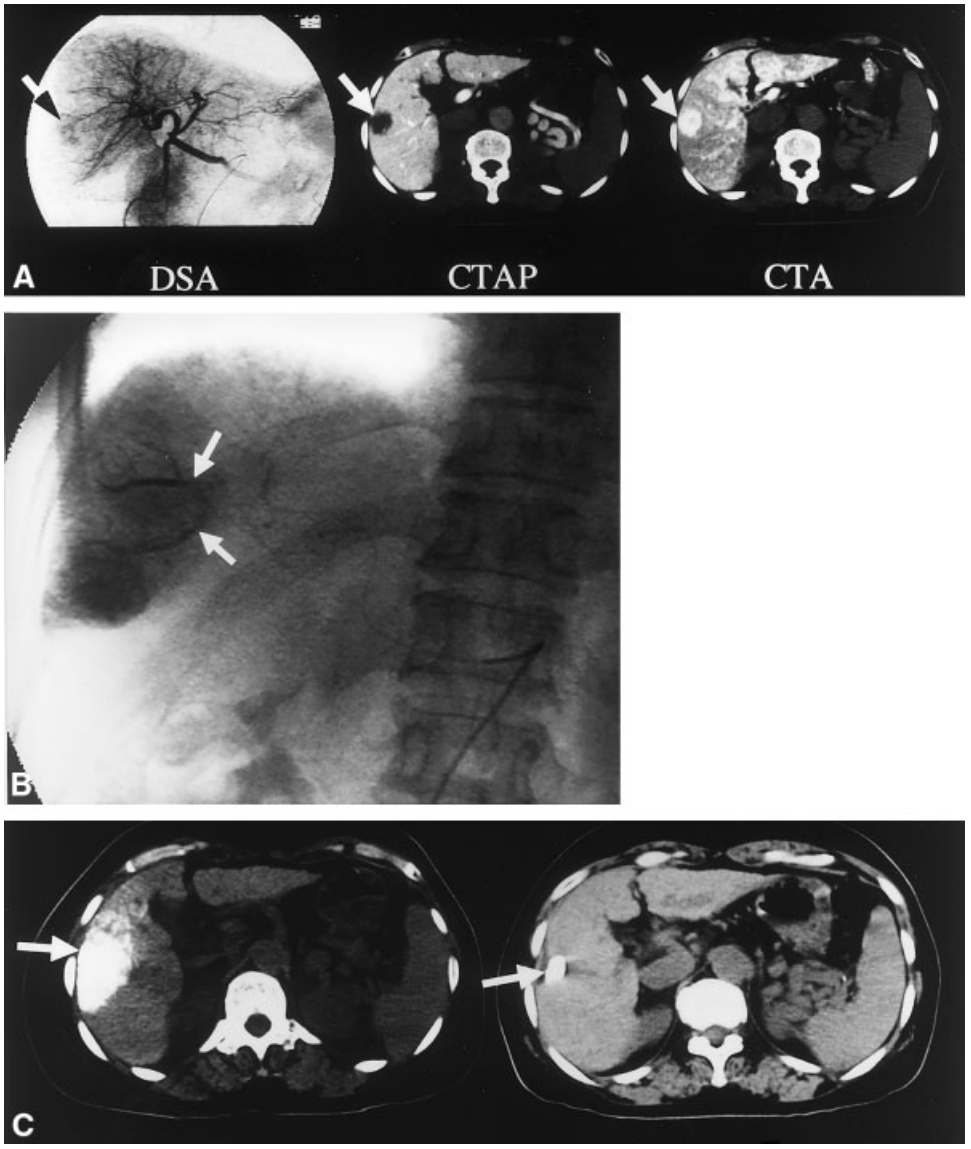

FIGURE 1. In this 66-year-old woman with C-viral cirrhosis, a 20-mm lesion, typical of hepatocellular carcinoma (HCC) was found in the fifth liver segment in March, 200l. (A) Digital subtraction arteriography (DSA), helical computed tomography (CT) scan during hepatic arteriography and catheterization of the mesenteric artery with 20 μg of prostaglandin E_1 (CTAP), and helical CT during hepatic arteriography (CTA) all showed a typical small HCC (arrows). (B) During embolization, portal vein branches were opacified retrogradely (lower arrow) and antegradely (upper arrow). (C) Left: CT scan showing deposition of lipiodol in and around the lesion (arrow) immediately after embolization. Right: CT scan 8 months later. The lipiodolized lesion (arrow) has shrunk along with the surrounding liver parenchyma.

for fever and pain that lasted for a few days. No patients developed hepatic failure, and all patients were discharged within 2 weeks.

Figure 2 illustrates another patient who was treated with our angiographic subsegmentectomy: Regurgitation of lipiodol into the portal vein and deposition of lipiodol in the tumor and the surrounding tissue is seen clearly. Figure 3 illustrates the disappearance of liver parenchyma around the targeted lesion. Although the posttreatment follow-up is still $\leq$ 2 years (Table 1), to date, recurrent disease developed in only 1 of 19 patients who were followed for $>$ 1 year (5%) or in only 1 of 15 patients who were followed for $>$ l.5 years (6.6%). Posttreatment serum levels of AFP and PIVKA-II are shown in Table 1. Of 27 patients, 16 or 17 patients had AFP and PIVKA-II levels that were unchanged or reduced, and 6 or 7 patients had elevated levels.

DISCUSSION

The nonsurgical management of patients with HCC has various problems, and the results have been far from satisfactory. The most commonly used procedure worldwide is arterial chemoembolization; however, as discussed above, the results from this procedure generally are poor.[4,17] Our procedure was designed to improve the therapeutic efficacy of chemoembolization by necrotizing the tumor and some surrounding liver parenchyma to be certain that the tumor is necrotized completely. The overall effect is something like nonsurgical subsegmentectomy. It is known that liver parenchyma does not undergo ne-

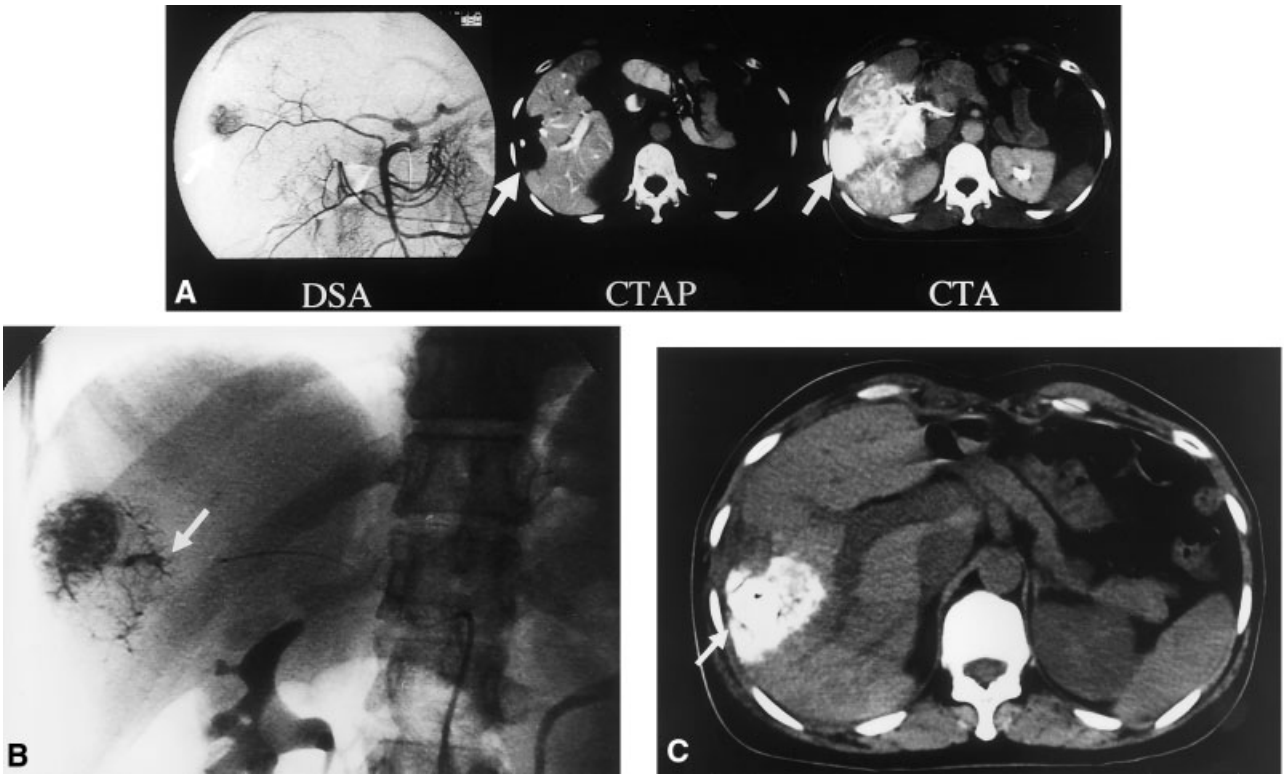

FIGURE 2. (A) In this 48-year-old woman with B-viral cirrhosis who underwent hepatic resection three times in the past and underwent radiofrequency ablation most recently (February, 2001), a 20-mm lesion was found by digital subtraction arteriography (DSA; arrow), helical computed tomography (CT) scan during hepatic arteriography and catheterization of the mesenteric artery with 20 μg of prostaglandin E_1 (CTAP; arrow), and helical CT during hepatic arteriography (CTA; arrow) in the fifth liver segment in February, 2002. The lesion was immediately caudal to the ablated region, suggesting that this was a marginal recurrence. (B) The lesion was embolized by superselective catheterization, and lipiodol was injected until it regurgitated back into the portal vein (arrow). (C) CT scan immediately after embolization showing lipiodol deposition in and around the lesion (arrow). Serum α-fetoprotein levels dropped from 597 ng/mL to 22 ng/mL.

crosis if only the artery or the portal vein is occluded: It causes atrophy called *Zahn infarct*.[20] Tissue is killed only when both the artery and the portal vein are occluded. This is what occurs with our technique. Although the patient's reaction to induced necrosis is rather severe and requires careful assessment of liver function, we have not yet encountered hepatic failure.

We do not know how large an HCC can be treated with our method, but it is clear that, the smaller the tumor, the better the results. Our results showing that only 1 of 23 tumors recurred at 1.5 years posttreatment is remarkable. Takayasu et al.[21] first emphasized the utility of the unified helical CT and angiography system in 2001. Those authors treated 54 patients with HCC

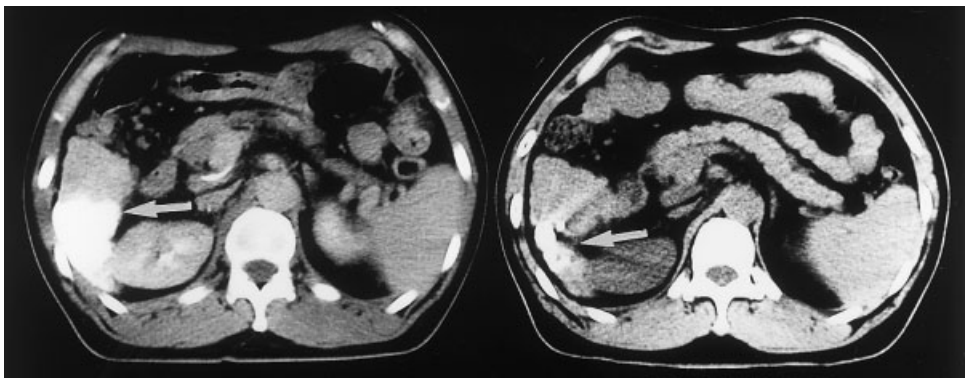

FIGURE 3. In this 47-year-old man with B-viral cirrhosis, a 20-mm lesion was detected in the sixth liver segment in January, 2001. Left: The lesion was embolized with lipiodol (arrow) in March, 200l. Right: A computed tomography scan 2 months later shows shrinking of the embolized lesion and atrophy of the surrounding liver parenchyma (arrow).

lesions < 5 cm at the National Cancer Center Hospital (Tokyo, Japan) and showed local recurrence rates of 33.2% at 1 year and 37.8% at 2 years. At that large center, the postoperative recurrence rate was 54% at 14.5 months.[22] The cumulative recurrence rates after percutaneous ethanol injection therapy (the most widely used treatment modality) have been 33.8% at 1 year and 60.8% at 2 years according to Ebara et al.,[8] who developed this new technique.

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