Radiology

Ethanol Ablation of Hepatocellular Carcinoma Up to 5.0 cm by Using a Multipronged Injection Needle with High-Dose Strategy[1]

Ming Kuang, MD, PhD
Ming-De Lu, MD, DMSc
Xiao-Yan Xie, MD, PhD
Hui-Xiong Xu, MD, PhD
Zuo-Feng Xu, MD
Guang-Jian Liu, MD
Xiao-Yu Yin, MD, PhD
Jie-Fu Huang, MD, PhD
Riccardo Lencioni, MD, PhD

Purpose: To investigate whether ethanol ablation by using a multipronged needle delivery system (multipronged ethanol ablation) could eradicate hepatocellular carcinoma (HCC) up to 5.0 cm in diameter with a single-session high-dose strategy.

Materials and Methods: The hospital ethics committee approved the prospective study, and each patient provided written informed consent. One hundred forty-one patients (125 men, 16 women; mean age, 53 years; range, 27–76 years) with 164 primary or recurrent HCC ranging from 1.3 to 5.0 cm in diameter (mean, 2.9 cm ± 0.9) were treated with high-dose multipronged ethanol ablation. Patients were unsuitable for surgery, declined surgery and radiofrequency ablation, or had tumors located at unfavorable sites. Primary technique effectiveness (PTE) (complete ablation within two sessions), local tumor progression (LTP), and complications after the treatment were observed. Twenty risk factors of local effectiveness and complications were analyzed by means of univariate and multivariate analysis.

Results: Mean number of treatment sessions was 1.1. The mean volume of ethanol per tumor was 31 mL (range, 8–68 mL). PTE was achieved in 134 (95%) of 141 patients and was significantly associated with tumor pattern (capsulated vs noncapsulated, $P = .018$). After a mean follow-up period of 25 months, LTP was observed in 16 (12%) of 134 patients, and in nine (56%) patients, LTP occurred in tumors 3.1–5.0 cm in diameter. Alanine aminotransferase level ($P = .023$) was the independent risk factor for LTP. Three (2%) of 141 patients had major complications.

Conclusion: Multipronged ethanol ablation with a high-dose strategy can be used to treat HCC up to 5.0 cm in diameter effectively and safely, often in a single session.

[1] From the Department of Hepatobiliary Surgery (M.K., M.D.L., X.Y.Y.), Department of Medical Ultrasonics (M.D.L., X.Y.X., H.X.X., Z.F.X., G.J.L.), and Institute of Diagnostic and Interventional Ultrasound (M.K., M.D.L., X.Y.X., H.X.X., Z.F.X., G.J.L., X.Y.Y.), the First Affiliated Hospital, Sun Yat-Sen University, 58 Zhongshan Road 2, Guangzhou 510080, People's Republic of China; Department of Hepatobiliary Surgery, Peking Union Medical University, Beijing, People's Republic of China (J.F.H.); and Division of Diagnostic and Interventional Radiology, Department of Oncology, Transplant and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy (R.L.). Received November 27, 2008; revision requested January 28, 2009; final revision received April 27; accepted May 5; final version accepted May 12. **Address correspondence to** M.D.L. (e-mail: *lumd@21cn.com*).

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and its incidence is increasing (1,2). Patients at an early stage of HCC (one HCC of ≤ 5.0 cm in diameter or three nodules of ≤3.0 cm in diameter each) benefit from curative therapies, such as hepatic resection, liver transplantation, or percutaneous ablation (3–5). Percutaneous local ablative therapies are the best option for such patients who are not candidates for resection or transplantation (6–8). Besides, about half of patients develop tumor recurrence within 2 years after resection, and the incidence rises to 70%–85% within 5 years (9–11). Although repeated hepatectomy is the most effective treatment for recurrent HCC, impaired liver function and/or the presence of multicentric tumors limits its use in more than 80% of recurrent cases (12). Percutaneous ablation is particularly suitable for treating recurrent HCC because postsurgical recurrence can be detected at an early stage while the nodules are still small and, therefore, amenable to percutaneous ablation (13).

During the past 20 years, ethanol ablation (also named percutaneous ethanol injection) has been widely used as a secondary option when surgery is precluded in patients with early HCC (5,14). However, routine ethanol ablation accomplishes limited necrosis in tumors larger than 3 cm, because of the incomplete ethanol infiltration inside the whole tumor tissue that results from the incapability of disrupting the intratumoral septa and/or inadequate placement of the needle (3,5). Moreover, ethanol ablation often requires repeated injections on separate days for completion of a treatment (15). Researchers in randomized clinical trials (16–18) revealed that a higher rate of complete response with fewer treatment sessions, compared with ethanol ablation, can be achieved with thermal ablative techniques, such as radiofrequency (RF) ablation. However, RF ablation of tumors at a subcapsular location or adjacent to a critical structure, such as the hepatic hilum or gallbladder, increases the complication rate (19,20) above the reported baseline of 7%–10% (19,21). In an intention-to-treat analysis, Lencioni et al (22) reported that 9% of tumors could not be treated by using RF ablation because of the high-risk location of the tumor. On the contrary, ethanol ablation is a low-risk procedure with a major complication rate of 1.3%–3.2% and a mortality rate of 0.09%, as indicated in a clinical study in which 270 patients with HCC were enrolled (23). Therefore, percutaneous ethanol injection will continue to play a role in the treatment of HCC (14).

To improve the conventional ethanol ablation technique, a retractable multipronged injection needle was developed (24). The purpose of this study was to investigate whether ethanol ablation by using this needle delivery system (multipronged ethanol ablation) could eradicate HCC up to 5.0 cm in diameter with a single-session high-dose strategy, and we evaluated the treatment responses and complications.

Advances in Knowledge

- Ethanol ablation with a multipronged needle (multipronged ethanol ablation) enabled the intratumoral delivery of high-dose ethanol in multiple directions with one injection.
- High doses of ethanol used in one treatment session for ablation of hepatocellular carcinoma (HCC) up to 5.0 cm in diameter could be safely injected, with local anesthesia and low frequency of severe complications.
- HCC up to 5.0 cm in diameter could be completely eradicated by using multipronged ethanol ablation with one to two treatment sessions.
- Multipronged ethanol ablation could destroy tumors at unfavorable locations effectively and safely.

Implications for Patient Care

- Multipronged ethanol ablation could be a useful alternative to ablation of HCC up to 5.0 cm, especially for HCC located at unfavorable sites.
- Compared with other ablation techniques, the relatively simpler and cheaper multipronged ethanol ablation technique could benefit more patients with small and intermediate HCC.

Materials and Methods

This study was performed according to the guidelines of the Helsinki Declaration, and the study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-Sen University (Guangzhou, People's Republic of China). Written informed consent was obtained from each patient before treatment.

Patients

From August 1, 2004, to October 31, 2008, 141 consecutive patients (125 men, 16 women; mean age, 53 years; range, 27–76 years) with a total of 164 HCC nodules were enrolled in this study. Patients were included in the study if they met the following criteria: *(a)* Barcelona-Clinic-Liver-Cancer stage A (3) or recurrent HCC with a single nodule of 5.0 cm or smaller in diameter or up to three nodules of 3.0 cm or smaller in diameter each; *(b)* an ultrasonographic (US) image

Published online before print
10.1148/radiol.2532082021

Radiology 2009; 253:552–561

Abbreviations:
ALT = alanine aminotransferase
AFP = α-fetoprotein
DR = intrahepatic distant recurrence
HCC = hepatocellular carcinoma
IRI = injection rotation injection
LTP = local tumor progression
PTE = primary technique effectiveness
RF = radiofrequency
SI = Système International

Author contributions:
Guarantors of integrity of entire study, M.D.L., X.Y.X., H.X.X., J.F.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, M.K., X.Y.X., H.X.X., X.Y.Y., J.F.H.; clinical studies, M.K., X.Y.X., H.X.X., Z.F.X., G.J.L., X.Y.Y.; statistical analysis, M.K., X.Y.X., H.X.X.; and manuscript editing, M.K., M.D.L., X.Y.X., H.X.X., X.Y.Y., R.L.

Authors stated no financial relationship to disclose.

that showed clear delineation of the target tumors and the surrounding anatomy; *(c)* liver function test results with or without cirrhosis classified as Child-Pugh class A or B; *(d)* no evidence of vascular invasion or extrahepatic spread; *(e)* a platelet count of 50 × 10^3/μL (50 × 10^9/L) or more or prothrombin activity of more than 50%; *(f)* tumors with a location considered unfavorable for ablation by using other techniques, defined as tumors located close (<5 mm) to the tumor capsule, the gallbladder, the gastrointestinal tract, the inferior vena cava, the hilum, the heart, or the diaphragm; and *(g)* a tumor that was not suitable for resection or the patient declined surgery or RF ablation. Patients with liver function test results with Child-Pugh class C disease, those with uncontrolled coagulopathy, or those with a history of ethanol allergy were excluded from the study. Cirrhosis of the liver was determined by means of a combined assessment of hepatitis history, clinical manifestations, and imaging findings. Portal hypertension was defined as the existence of esophageal varices or splenomegaly, with a platelet count of less than 100 × 10^3/μL (100 × 10^9/L). Diagnosis of HCC was confirmed with US-guided fine-needle biopsy in 102 patients or with noninvasive means (8) in 39 patients. Tumor diameters were determined as the largest dimension measured by using US. The numbers of the tumors were determined with US and contrast material–enhanced computed tomographic (CT) findings. B-mode US was used to detect vascular invasion. Tumor capsule was defined as the presence of a peritumoral hypoechoic halo on a US image. Diagnostic and treatment decisions were made in consensus by a team of hepatobiliary surgeons and interventional radiologists.

Multipronged Ethanol Ablation Equipment

A multipronged injection needle device (Quadra-Fuse; Rex Medical, Raleigh, NC) was used for ethanol ablation. This device includes an 18-gauge 20-cm-long puncture needle consisting of an echogenic tip; three retractable tines, each with two evenly spaced through-holes (four fluid exits); and a connector with extension tubing (Fig 1). The extent of tine deployment could be adjusted up to 5 cm.

Imaging Equipment

A real-time US scanner (Acuson Sequoia 512; Siemens, Berlin, Germany), with a 2–5-MHz vector transducer and a puncture guide device, was used in this study. During contrast-enhanced US, the mechanical index value ranged from 0.15 to 0.21 for contrast pulse sequencing. The contrast agent (SonoVue; Bracco, Milan, Italy) was administered intravenously at a dose of 2.4 mL per injection in a bolus fashion (within 1–2 seconds), followed by a flush of 5 mL of normal saline. The target tumor was observed continuously for 6 minutes, including arterial (8–30 seconds from the beginning of contrast agent injection), portal (31–120 seconds), and late (121–360 seconds) phases. B-mode US was performed for all procedures as stated previously and at follow-up. Contrast-enhanced US was used for identification of intrahepatic tumors. US was performed by two of three authors (including X.Y.X., H.X.X., and G.J.L., who had 20, 13, and 7 years of experience, respectively, with US).

Contrast-enhanced CT was performed by using a single-section helical CT scanner (Xpress/SX; Toshiba, Tokyo, Japan) before October 2005 and a 64-section helical CT scanner (Aquilion; Toshiba) thereafter. The single-section helical CT parameters included 5-mm collimation, a pitch of 1.0, 120 kV, and 250 mAs. The 64-section CT protocol involved a 0.5 mm section thickness and 64 detector rows, 120 kV, and 150–200 mAs. The standard dual-phase scan procedure was used. After an unenhanced helical scan was obtained through the liver, 50–100 mL (1.5 mL/kg) of nonionic iodinated contrast material (Ultravist; Schering, Berlin, Germany) was administered through the antecubital vein by using a power injector (Stellant D; Medrad, Indianola, Pa) at a rate of 3 mL/sec (single-section CT) or 4 mL/sec (64-section CT). The arterial phase sequence was performed 25–32 seconds after injection, and a portal venous phase sequence was performed at 50–60 seconds. Contrast-enhanced CT was used for diagnosis in cases in which patients did not undergo biopsy and for follow-up after ablation in all cases.

Treatment Procedure

Patients were hospitalized before the treatment. Local anesthesia was achieved with 1% lidocaine hydrochloride (Hui Da Pharmaceutical, Shan Xi, People's Republic of China), and conscious analgesia–sedation was induced by means of intravenous administration of 0.1 mg of tramadol hydrochloride (Grunenthal, Aachen, Germany), 2.5 mg of droperidol (Xu Dong Hai Pu Pharmaceutical, Shanghai, China), and 0.1 mg of fentanyl citrate (Yi Chang Pharmaceutical, Hu Bei, China). Ablation procedures were performed by two authors (M.K., X.Y.X., who had 10 and 13 years of experience with ablation, respectively). With US

Figure 1

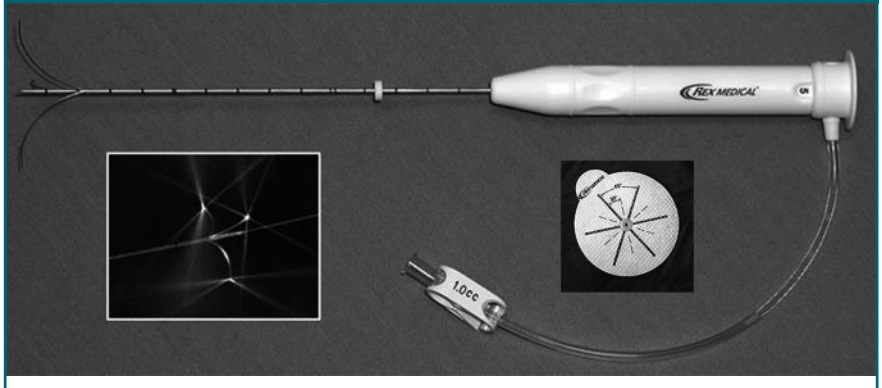


Figure 1: Multipronged injection needle used for ethanol ablation. The 18-gauge puncture needle consists of three retractable tines, each with four fluid exits and connector with extension tubing clamp.

Table 1

Patient Demographic and Tumor Characteristic Data

Data	Value
Patient characteristics	
No. of patients	141
Sex	
No. of men	125
No. of women	16
Age (y)*	53 ± 13 (26–76)
Cause	
No. with hepatitis B	126
No. with hepatitis C	1
No. with other	14
Cirrhosis	
No. without	17
No. with	124
Child-Pugh class	
No. with class A	131
No. with class B	10
Portal hypertension	
No. with	42
No. without	99
Serum ALT level (U/L)†	53 ± 45
Serum total bilirubin (μmol/L)‡	17 ± 10
Serum albumin (g/L)‡	41 ± 6
Prothrombin time (s)‡	13 ± 2
Platelet count ($\times 10^9$/L)‡	139 ± 68
Serum AFP level	
No. with ≤200 μg/L	95
No. with >200 μg/L	46
Tumor distribution	
No. with 1 tumor	118
No. with 2–3 tumors	23
Tumor characteristics	
No. of tumors	164
Tumor type	
No. of primary tumors	103
No. of recurrent tumors	61
Size of main tumor (cm)*	2.9 ± 0.9 (1.3–5.0)
Tumor diameter	
No. of tumors ≤3.0 cm	98
No. of tumors 3.1–5.0 cm	66
Tumor location	
No. in unfavorable site	96
No. in favorable site	68
Tumor pattern	
No. of capsulated tumors	118
No. of noncapsulated tumors	46
Tumor grade§	
No. with available grade	102
No. with grades 1–2	93
No. with grades 3–4	9

* Values are continuous data, expressed as means ± standard deviations. Numbers in parentheses are the ranges.

† Value is a continuous datum, expressed as the mean ± standard deviation. To convert to Système International (SI) units in microkatals per liter, multiply by 0.0167.

‡ Values are continuous data, expressed as means ± standard deviations.

§ Tumor grade is the Edmondson tumor grade.

guidance, the needle was introduced percutaneously into the center of the tumor nodule and the needle tip was positioned at the bottom of the target tumor. The maximal extent of tine deployment followed the intention of accomplishing an ablative margin of 0.5–1.0 cm or was equal to the largest diameter of the target tumor in cases where tumor was close to critical structures. An injection-rotation-injection (IRI) maneuver was used. To treat an HCC of 3.0 cm or smaller in diameter, the three tines were deployed initially at the pretreatment-decided maximum extent, and the first half of the planned volume of ethanol was injected. While injecting the ethanol, the tines were gradually withdrawn with a 1-cm deployment interval until they were completely retracted into the needle cannula. After completion of the first injection, the needle was rotated 60°, and the tines were redeployed to the former maximum extent. Injection of another half of the volume of ethanol with the same tine-withdrawing process was performed. Ablation of a tumor that was 3.1–5.0 cm in diameter required two rounds of IRI maneuvers (four injections overall, 25% of the planned ethanol volume per injection). After the injection of half of the planned ethanol volume at the far end of the tumor with the first round of the IRI maneuver, the tines were completely retracted and the needle was withdrawn 1–2 cm. The second round of the IRI maneuver, including deployment of tines, rotation of needle, and redeployment of the tines, was performed accompanied with the injection of the other half of the ethanol. If excessive leakage of ethanol into the large intrahepatic vessels was observed, injection was stopped immediately and the tines were redeployed in other directions. During any necessary pause of the ethanol injection, 0.5–1 mL of saline solution treated with heparin was immediately injected to prevent possible thrombosis in the tines. After the completion of all injections, the needle was left in the tumor for 1–2 minutes to prevent possible ethanol reflux and then was removed.

The ethanol was injected until the whole tumor appeared completely hyperechoic (7). The volume of injected eth-

anol depended on the tumor size and patient compliance. For tumors of 3.0 cm or smaller in diameter, the volume of injected ethanol was calculated as the volume of an oversized sphere, as follows: $V = 4/3\ \pi\ [(D/2 + 0.5)^3]$, where V is volume in milliliters and D is the largest tumor dimension in centimeters. For tumors that were 3.1–5.0 cm in diameter, the least amount of ethanol was equal to the volume of the tumor ($V = 4/3\ \pi\ [(D/2)^3]$), and the upper limit of ethanol volume per session was 60 mL, to minimize toxic effects of ethanol to the patient (25). The injection was stopped when the calculated volume was reached or if clinical symptoms, such as choking, coughing, or tachycardia (>120 beats per minute), occurred. For patients with two to three HCC nodules, multipronged ethanol ablation of all tumors was performed in one session, following the same strategies mentioned previously. In cases in which the total amount of injected ethanol was more than 60 mL, two sessions of treatment, 1 week apart, were performed.

Assessment of Treatment Response and Follow-up

Local effectiveness of multipronged ethanol ablation was assessed by using contrast-enhanced CT performed 1 month after the treatment, as immediate postablation CT is difficult to perform in our hospital. Primary technique effectiveness (PTE), local tumor progression (LTP), and intrahepatic distant recurrence (DR) in this study were assessed on a patient-by-patient basis. Image interpretation was performed in consensus by two authors (H.X.X., G.J.L., who had 10 and 5 years of experience with abdominal CT interpretation, respectively). Treatment response was defined following the reporting criteria of image-guided tumor ablation (26). Technical success meant that the tumor was treated according to the protocol. Complete ablation was defined as no enhancement in the tumor area assessed by using CT 1 month after treatment. Another session of multipronged ethanol ablation was performed if CT revealed a residual tumor. If the tumor was still viable after two treatment sessions, ethanol ablation was considered to have failed and the patient was referred for other therapies. PTE rate was the percentage of tumors in which complete ablation was achieved after one or two treatment sessions. Patients with tumors in which PTE was achieved entered follow-up. Follow-up was performed by using US and the serum α-fetoprotein (AFP) level every 3 months and contrast-enhanced CT every 6 months.

LTP was defined as the regrowth of tumor inside the initially completely ablated nodule. DR was defined as the appearance of new intrahepatic tumors other than in the treated area. In cases with suspicious US findings and/or an elevated AFP level, contrast-enhanced US plus contrast-enhanced CT or fine-needle biopsy was performed. For patients with LTP or DR, additional treatment with ethanol ablation, RF ablation, microwave ablation, or transarterial chemoembolization was offered. Any ethanol ablation–related major complications, minor complications, and side effects were defined according to Goldberg et al (26) and were documented by two authors (X.Y.Y., Z.F.X.) with chart and image reviews.

Statistical Analysis

Software (SPSS package, version 13.0; SPSS, Chicago, Ill) was used for statistical analysis. Continuous data were expressed

Table 2

Local Effectiveness of Multipronged Ethanol Ablation of HCC

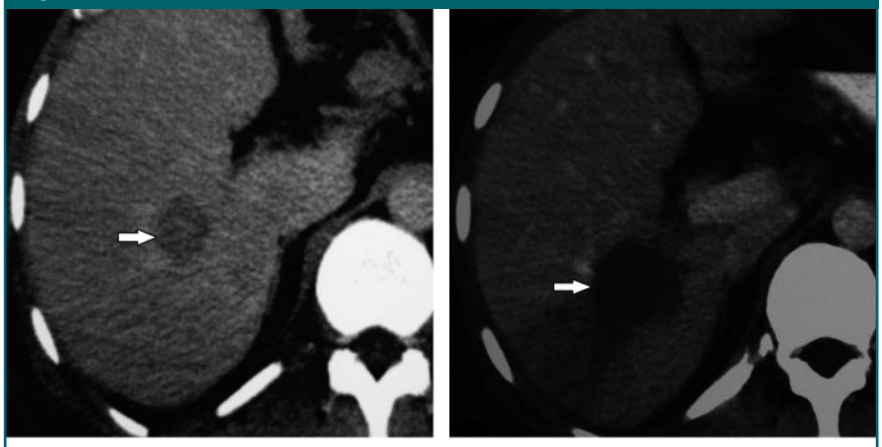
Data	All Patients (n = 141)	Patients with Tumors of ≤3.0 cm (n = 81)	Patients withTumors of 3.1–5.0 cm (n = 60)
Tumor diameter (cm)*	2.9 ± 0.9	2.3 ± 0.5	3.8 ± 0.6
Ethanol volume per tumor (mL)*	31 ± 12	24 ± 7	40 ± 10
Complete ablation rate (%)†	88 (124/141)	91 (74/81)	83 (50/60)
PTE rate (%)‡	95 (134/141)	99 (80/81)	90 (54/60)
LTP rate (%)‡	12 (16/134)	9 (7/80)	17 (9/54)

* Values are continuous data, expressed as means ± standard deviations.

† Complete ablation rate after the first session of multipronged ethanol ablation. Numbers in parentheses were used to calculate the percentages.

‡ Numbers in parentheses were used to calculate the percentages.

Figure 2

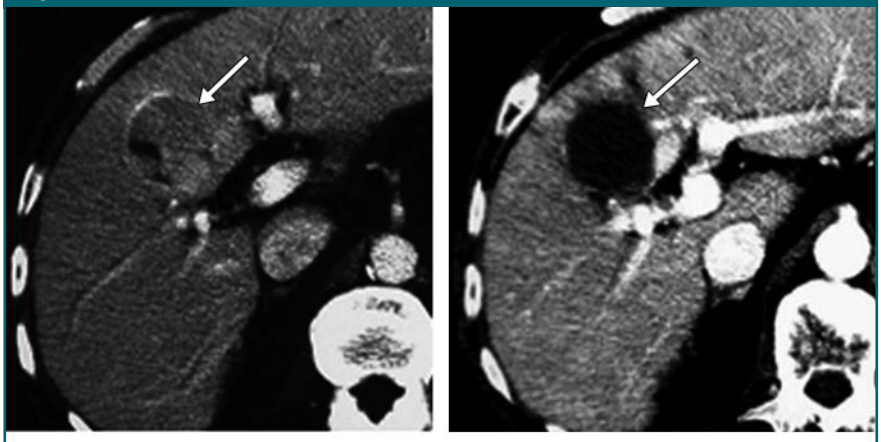


a. b.

Figure 2: Transverse contrast-enhanced CT scans in 37-year-old male patient who underwent multipronged ethanol ablation of HCC. **(a)** Pretreatment scan (portal phase) shows 1.8 × 2.5-cm HCC (arrow). **(b)** Scan obtained 1 month after ethanol ablation (one session, 30 mL of ethanol injected) shows nonenhancing zone of hyperattenuation enveloping tumor (arrow, portal phase).

as the mean ± standard deviation. Twenty risk factors, including sex, age, presence of hepatitis, presence of cirrhosis, Child-Pugh class for cirrhosis, presence of portal hypertension, serum alanine aminotransferase (ALT) level, serum total bilirubin level, serum albumin level, prothrombin time, platelet count, serum AFP level, tumor type (primary vs recurrent), size of main tumor (tumor with the largest dimension), tumor number, tumor pattern (capsulated vs noncapsulated), tumor location (favorable vs unfavorable), tumor grade (Edmondson grade 1–2 vs 3–4) when available, ethanol volume per tumor, and ethanol volume per patient with respect to PTE and complications, were analyzed by means of the Fisher exact probability test for categorical variables and a *t* test for continuous variables. Multiple logistic regression was used for multivariate analysis of factors associated with PTE and complications. The Kaplan-Meier method (log-rank test) was used for univariate analysis of risk factors for LTP and DR, whereas the Cox proportional hazards regression model was used for multivariate analysis. A difference with two-tailed $P < .05$ was considered significant.

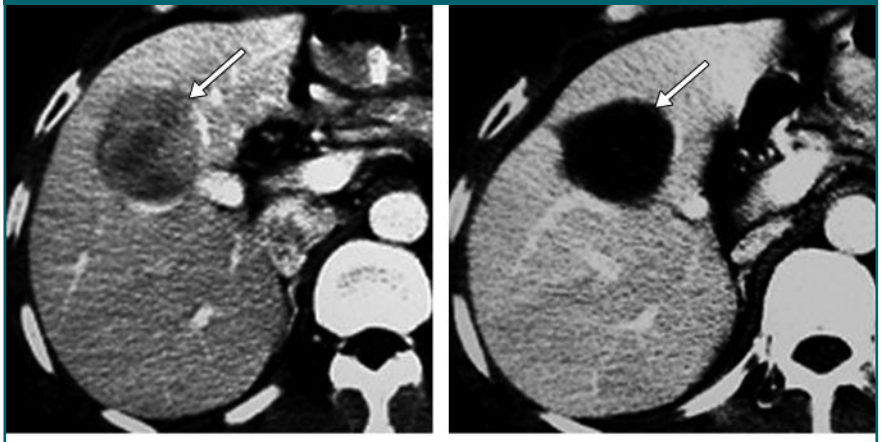
Figure 3



a. b.

Figure 3: Transverse contrast-enhanced CT scans in 53-year-old male patient who underwent multipronged ethanol ablation of HCC at unfavorable location. **(a)** Preablation scan (portal phase) shows 4.0 × 4.2-cm tumor (arrow) located close to porta hepatis. **(b)** Scan obtained 1 month after ethanol ablation (one session, 35 mL of ethanol injected) shows hypoattenuating ablation zone completely enveloping target tumor site (arrow, portal phase).

Figure 4



a. b.

Figure 4: Transverse contrast-enhanced CT scans in 55-year-old female patient who underwent multipronged ethanol ablation of HCC at unfavorable location. **(a)** Preablation scan (portal venous phase) shows 4.1 × 4.5-cm tumor (arrow) located above bifurcation of left and right portal veins. **(b)** Scan obtained 1 month after ethanol ablation (one session, 40 mL of ethanol injected) shows hypoattenuating change of whole target tumor area (arrow).

Results

Patients and Tumor Profile

One hundred twenty-four (88%) patients had underlying cirrhosis. One hundred thirty-one (93%) patients had Child-Pugh class A disease, and the remaining 10 (7%) had Child-Pugh class B disease. Forty-two (30%) patients had portal hypertension. The serum AFP level was 200 μg/L or lower in 95 (67%) patients and elevated (>200 μg/L) in 46 (33%) patients. Eighty-eight (62%) patients received a first-time diagnosis of HCC, and 53 (38%) had recurrence after hepatectomy ($n = 25$), microwave ablation ($n = 12$), RF ablation ($n = 13$), and transarterial chemoembolization ($n = 3$). The tumor nodules ranged in diameter from 1.3 to 5.0 cm (mean, 2.9 cm ± 0.9 [standard deviation]). There were 81 (57%) patients with tumors of 3.0 cm or smaller in diameter and 60 (43%) patients with tumors of 3.1–5.0 cm in diameter. One hundred (71%) patients had capsulated tumors and 41 (29%) had noncapsulated HCC. Eighty-nine (63%) patients had nodules located at unfavorable sites. The detailed characteristics of the patients and tumor profiles are shown in Table 1. The mean hospitalization time was 3 days ± 3 (range, 1–23 days).

Local Effectiveness and Recurrence

Technical success was achieved in all patients; no treatment sessions were prematurely terminated due to immediate procedural complications. A total of 158 multipronged ethanol ablation sessions were performed (mean, 1.1 ses-

sions per patient), which included 141 initial sessions and 17 repeated sessions owing to incomplete ablation. The mean volume of injected ethanol per tumor was 31 mL ± 12 (range, 8–68 mL) for all tumors (Table 2).

The complete ablation rate after the first multipronged ethanol ablation session was 88% (124 of 141) on a patient-by-patient basis and 89% (146 of 164) on a tumor-by-tumor basis (Figs 2–4). In 17 patients with a residual viable tumor, complete ablation was achieved with a second session of multipronged ethanol ablation in 10 patients. Overall, PTE was achieved in 95% (134 of 141) of patients. In patients with tumors of 3.0 cm or smaller in diameter and those with tumors of 3.1–5.0 cm in diameter, the PTE rate was 99% (80 of 81) and 90% (54 of 60), respectively (Table 2). Significantly better PTE rates were achieved in patients with capsulated tumors, those with small tumors (≤3.0 cm in diameter), those without portal hypertension, and those with a normal platelet count than were achieved in patients with noncapsulated tumors, those with intermediate tumors (3.1–5.0 cm in diameter), those with portal hypertension, and those with a low platelet count ($P = .022$, .042, .025, and .031, respectively). However, multivariate analysis revealed that only tumor pattern was an independent risk factor for PTE (Table 3).

All 134 patients with PTE entered follow-up. The mean follow-up period was 25 months ± 12 (range, 3–47 months). In 134 patients, the numbers of those who were followed up for fewer than 12 months, 12–23 months, 24–35 months, and 36–47 months were 18 (13%), 43 (32%), 37 (28%), and 36 (27%), respectively. LTP was observed in 16 (12%) of 134 patients, with occurrence in all at 2–17 months (mean, 8 months ± 5) after the initial treatment. LTP rates were significantly higher in patients with an elevated serum ALT level than in those with normal values in the multivariate analysis ($P = .023$) (Table 3). Seven of 16 patients with LTP were treated with multipronged ethanol ablation again. The other nine patients underwent resection ($n = 1$), RF ablation ($n = 3$), microwave ablation ($n = 3$), or transarterial chemoembolization ($n = 2$). At 2–28 months (mean, 7 months ± 6) after the initial ethanol ablation, the DR rate was 34% (46 of 134), which was significantly associated with tumor type ($P = .001$) and cirrhosis ($P = .01$) (Table 3). Results with the Cox proportional hazards regression model indicated that both tumor type and cirrhosis were independent risk factors for DR. Among 46 patients with DR, 43 received additional treatments, including the following: ethanol ablation, 11 patients; RF ablation, 13; microwave ablation, 10; transarterial chemoembolization, six; and liver transplantation, three. Three patients resorted to using Chinese herbs,

Table 3

Risk Factors of Treatment Responses

A: Risk Factors in Terms of Treatment Success and Failure

Variable	Patient Subgroup		*P* Value	
	No. with PTE ($n = 134$)	No. with Treatment Failure ($n = 7$)	Univariate Analysis*	Multivariate Analysis†
Tumor pattern			.022	.018
No. with capsulated	98	2		
No. with noncapsulated	36	5		
Tumor size			.042	.052
No. with ≤3.0-cm-diameter tumors	80	1		
No. with >3.0-cm-diameter tumors	54	6		
Portal hypertension			.025	.817
No. with	37	5		
No. without	97	2		
Platelet count			.025	.343
No. with count $<100 \times 10^9$/L	37	5		
No. with count $\geq 100 \times 10^9$/L	97	2		

B: Risk Factors in Terms of LTP

Variable	Patient Subgroup		*P* Value	
	No. with LTP ($n = 16$)	No. without LTP ($n = 118$)	Univariate Analysis*	Multivariate Analysis†
Serum ALT level			.036	.023
No. with level ≤40 U/L‡	5	70		
No. with level >40 U/L‡	11	48		
Platelet count			.043	.053
No. with count $<100 \times 10^9$/L	1	36		
No. with count $\geq 100 \times 10^9$/L	15	82		

C: Risk Factors in Terms of DR

Variable	Patient Subgroup		*P* Value	
	No. with DR ($n = 46$)	No. without DR ($n = 88$)	Univariate Analysis*	Multivariate Analysis†
Tumor type			.001	<.001
No. with recurrent tumors	26	26		
No. with primary tumors	20	62		
Liver cirrhosis			.01	.011
No. with	45	72		
No. without	1	16		

* The Fisher exact test was used for tumor pattern, tumor size, presence of portal hypertension, and platelet count as categorical variables. The log-rank test (Kaplan-Meier method) was used for univariate analysis of risk factors to LTP and DR, including serum ALT level, tumor type, and presence of liver cirrhosis.

† The multiple logistic regression model was used to test the significance of tumor pattern, tumor size, presence of portal hypertension, and platelet count. The Cox proportional hazards regression model was used for multivariate analysis of serum ALT level, tumor type, and presence of liver cirrhosis.

‡ To convert the cutoff value for serum ALT level to SI units in microkatals per liter, multiply by 0.0167.

because of extrahepatic metastasis or personal preference.

Side Effects and Complications

Fifty-two (37%) of 141 patients complained of grade 1 (Common Toxicity Criteria, version 2.0; National Cancer Institute, Bethesda, Md) pain during the procedure, and the pain was relieved immediately after completion of the ethanol injection. Fifty-one (36%) of 141 patients had a low-grade fever lasting 12–72 hours after the treatment. In most of the patients, both serum ALT and aspartate aminotransferase levels increased two to six times over the baseline levels during the first 3–5 days following the treatment. Two patients complained of grade 2 pain at the treatment site, and this pain was relieved with the use of analgesics. Asymptomatic self-limiting intraperitoneal bleeding ($n = 1$), transient gross hematuria ($n = 2$), and asymptomatic pleural effusion ($n = 3$) were observed in six patients and required no medical intervention. Major complications occurred in three (2%) of 141 patients and included hepatic encephalopathy requiring emergent treatment ($n = 1$), infarction of the left lateral liver lobe requiring antibiotics and analgesics ($n = 1$), and liver abscess requiring drainage ($n = 1$) (Table 4). All patients with major complications recovered in 1 month. Tumor seeding was not found in any patient. There was no treatment-related death. In the univariate analysis, the diameter of the main tumor (≤3.0 cm vs >3.0 cm, $P = .002$), ethanol volume per tumor (≤30 mL vs >30 mL, $P = .021$), and ethanol volume per patient (≤40 mL vs >40 mL, $P = .032$) were significantly related to the occurrence of complications, but only ethanol volume per patient was an independent risk factor in the multivariate analysis.

Discussion

With conventional ethanol ablation, a complete necrosis rate of 80% is achieved in HCC smaller than 3.0 cm but only a rate of 50% in those 3.0–5.0 cm in size (6,7,14). In a randomized study (17) for treatment of HCC of 4.0 cm or smaller in size, complete tumor necrosis of 70% was achieved with conventional ethanol ablation and the use of a single 22-gauge percutaneous transhepatic cholangiographic needle, 2–5 mL of ethanol per session, and six to 12 sessions. Complete necrosis of 72% was achieved with higher-dose ethanol ablation and two to three percutaneous transhepatic cholangiographic needles, 4–10 mL of ethanol per session, and three to six sessions (17). The 2-year LTP rate was observed to be 33%–43% for conventional ethanol ablation (17,27) and 24% for higher-dose ethanol ablation (17). In the current study, a PTE rate of 99% in HCCs smaller than 3.0 cm and 90% in HCCs of 3.0–5.0 cm was achieved with multipronged ethanol ablation, with 1.1 treatment sessions and an LTP rate of 14%.

Local effectiveness obtained in the present study demonstrates that, with multipronged ethanol ablation, the shortcomings of conventional ethanol ablation may be overcome by allowing a single session and 3-day hospitalization to eradicate tumors of 5.0 cm or smaller. This technique appears to offer multiple advantages. First, ethanol injected simultaneously through three prongs and in 12 directions may accomplish homogeneous alcohol distribution in the whole tumor tissue, because ethanol usually diffuses for a radius of 2–3 cm around a single needle tip toward the periphery of the tumor (28). The IRI maneuver probably helps distribute the ethanol more evenly within the tumor. Second, the multipronged technique allows infusion of ethanol in large aliquots with one injection. A study in animals has shown that the multipronged technique enabled greater fluid infusion (mean, 15–53 mL ± 3) into a solid tumor than did standard needle injection (mean, 8 mL ± 1) before reflux was observed at the puncture site (24). With the multiple-needle ethanol ablation technique, complete necrosis of target tumors could be achieved, but an average of six sessions and 10 days of hospitalization were required to complete a treatment course (18). Third, the retractable tines that can be deployed up to 5.0 cm may

Table 4

Periprocedural Complications and Side Effects of Multipronged Ethanol Ablation

Case No.	No. of Tumors	Tumor Diameter (cm)*	Ethanol Volume (mL)†		Complication
			Per Tumor	Per Patient	
1	1	4.5	40	40	Grade 2 pain during procedure
2	2	3.5	30	46	Hepatic encephalopathy‡
3	2	2.7	25	55	Grade 2 pain during procedure
4	1	4.2	35	35	Transient hematuria
5	1	4.3	68	68	Transient hematuria
6	2	4.0	40	60	Infarction of left lateral lobe of liver§
7	1	2.9	32	32	Intraperitoneal bleeding
8	2	3.5	33	68	Asymptomatic pleural effusion
9	1	2.5	30	30	Asymptomatic pleural effusion
10	1	4.2	39	39	Liver abscess‖
11	1	5.0	52	52	Asymptomatic pleural effusion

* For two tumors, the diameter is that of the larger nodule.

† Volume of ethanol injected in one treatment session. For cases involving two tumors, the ethanol volume used for treatment of the larger tumor was considered.

‡ This 64-year-old male patient with Child-Pugh class B disease had hepatic encephalopathy 2 days after treatment. This complication was a major one, which required hospital admission and intensive medical intervention, but the patient recovered.

§ This 47-year-old male patient had two tumors, both located at segment III, and injection of 60 mL of ethanol resulted in infarction of the whole left lateral lobe (segments II and III). This complication was a major one, which required hospital admission and intensive medical intervention, but the patient recovered.

‖ This 73-year-old male patient had a liver abscess after the treatment of a 4.2-cm-diameter tumor. This complication was a major one, which required hospital admission and intensive medical intervention, but the patient recovered.

make it possible not only to completely eradicate tumors but also to provide an ablation margin to reduce possible LTP, because tumors smaller than 2.0 cm in size already manifest local micrometastases located less than 1 cm from the parent nodule (29).

In conventional ethanol ablation, ethanol is delivered into the tumor in small aliquots (2–10 mL) at multiple sessions. A high-dose single-session strategy was used in our treatment scheme. The mean dose of injected ethanol was 31 mL per tumor. The formula $V = 4/3\ \pi\ [(D/2 + 0.5)^3]$ used for tumors 3.0 cm or smaller was much greater than the volume of the tumor, and a PTE rate of 99% was achieved, with a major complication rate of 0%. The ethanol injected simultaneously in multiple directions seemed to have produced thorough necrosis of the whole tumor. However, the increased risks of ethanol toxicity must be considered when ethanol is used in large aliquots, because an amount of ethanol larger than 40 mL per patient can induce a choking sensation, cough, or tachycardia, and an amount larger than 60 mL may cause respiratory depression (25). Hence, for ablation of tumors of 3.1–5.0 cm, the amount of injected ethanol was equal to or only slightly greater than the volume of the target tumor. The results revealed that this dosage could achieve a PTE of 90%, with a 2% major complication rate in those tumors. We believe that this dosage protocol could achieve an appropriate balance between local effectiveness and the occurrence of complications.

Necrosis in capsulated tumors was more easily achieved than that in noncapsulated tumors in our study, regardless of size. Tumor pattern was the only independent risk factor of PTE. Perhaps the presence of a capsule may have prevented the ethanol from leaking outside of the tumor, thereby contributing to the complete tumor destruction.

Tumor diameter was a substantial factor of PTE in the univariate analysis. In fact, six (86%) of seven of those tumors in which treatment failed were larger than 3.0 cm. The ethanol volume chosen for treatment of larger tumors may not have been enough to infiltrate the whole tumor tissue, when considering a balance to avoid adverse effects of ethanol toxicity. A potential solution to this problem might be repeated injections or combined use of RF ablation and ethanol ablation.

The major complication rate found in this study (2%, three of 141) is similar to that of conventional ethanol ablation or RF ablation, with rates of 1.7%–2.2% (7,19). Of note, however, is the fact that the complication rate for treating tumors in unfavorable locations was not higher than that for treating tumors in a favorable location. These results demonstrate that multipronged ethanol ablation is safe in eradicating HCC up to 5.0 cm, no matter whether the location is favorable or unfavorable. There were three severe complications in the current study, including one case of hepatic encephalopathy that occurred in a patient with Child-Pugh class B disease after injection of 46 mL of ethanol, one infarction of the left lateral lobe that occurred after injection of 60 mL of ethanol, and one liver abscess that formed after injection of 39 mL of ethanol. Therefore, the toxicity of ethanol in high-dose ethanol ablation treatment should not be underestimated.

DR was more commonly observed in patients with primary rather than recurrent HCC, which is similar to information in another report about RF ablation and microwave ablation (30). Cirrhosis is also known to play a significant role in the occurrence of DR after curative treatments of HCC such as hepatectomy (31), and this result, too, was found in our study.

RF ablation is now the most popular ablation modality for HCC. With RF ablation, a PTE rate of 90% and a LTP rate of 10%–14% can be achieved, with 1.1 sessions, in early-stage HCC and complete ablation of 60%–70% in 3.0–5.0-cm tumors (17,22). Our data indicate that multipronged ethanol ablation has similar local effectiveness. An advantage of the multipronged technique is that 63% of tumors in the present study were located in sites that were considered unfavorable for RF ablation, and in patients who underwent treatment for such tumors, no significant differences in PTE and LTP rates were observed when these rates were compared with those for tumors in favorable locations. These results demonstrate that multipronged ethanol ablation could be used as a useful alternative to RF ablation.

The major limitation of our study was that it dealt with a single arm of HCC treatment and, therefore, lacked any direct comparison with conventional ethanol ablation or RF ablation. Randomized clinical trials with multiple treatment arms are needed to provide a complete evaluation of this newer ablation technique for the treatment of HCC.

In conclusion, high-dose single-session multipronged ethanol ablation can be used to treat early-stage or recurrent HCC up to 5.0 cm effectively and safely and may be applied even for lesions at high-risk locations. Multipronged ethanol ablation should be carefully used in patients with inadequate hepatic function or those with large tumors.

Acknowledgments: We thank Li-Jian Liang, MD, Bao-Gang Peng, MD, PhD, Dong-Ming Li, MD, Shao-Qiang Li, MD, Jia-Ming Lai, MD, and Pei Huang, MD (the First Affiliated Hospital, Sun Yat-Sen University), for assistance in the clinical studies and Hai-Bo Wang, MD, PhD (Queen Mary Hospital, University of Hong Kong, Pok Fu Lam, Hong Kong, People's Republic of China), and Yuan-Tao Hao, PhD (Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University), for help in the statistical analysis.

References

1. Peto J. Cancer epidermiology in the last century and the next decades. Nature 2001;411:390–395.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750.
3. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.
4. Llovet JM, Fuster J, Bruix J; Barcelona-Clínic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004;10(2 suppl 1):S115–S120.
5. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–1917.
6. Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004;40:1352–1360.
7. Livraghi T, Giorgio A, Marin G, et al. Hep-

atocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995;197:101–108.

8. Okada S. Local ablation therapy for hepatocellular carcinoma. Semin Liver Dis 1999;19:323–328.
9. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519–524.
10. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. Ann Surg 1999;229:790–800.
11. Lee WC, Jeng LB, Chen MF. Estimation of prognosis after hepatectomy for hepatocellular carcinoma. Br J Surg 2002;89:311–316.
12. Jarnagin WR, Fong Y. Repeat resection for liver tumors. In: Clavien PA, ed. Malignant liver tumors: current and emerging therapies. Boston, Mass: Blackwell Science, 1999; 150–158.
13. Lu MD, Yin XY, Xie XY, et al. Percutaneous thermal ablation for recurrent hepatocellular carcinoma after hepatectomy. Br J Surg 2005;92:1393–1398.
14. Lencioni R, Llovet JM. Percutaneous ethanol injection for hepatocellular carcinoma: alive or dead? J Hepatol 2005;43:377–380.
15. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radiofrequency ablation versus ethanol injection. Radiology 1999;210:655–661.
16. Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228:235–240.
17. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or = 4 cm. Gastroenterology 2004;127:1714–1723.
18. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129:122–130.
19. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radiofrequency ablation: complications encountered in a multicenter study. Radiology 2003;226:441–451.
20. Llovet JM, Vilana R, Brú C, et al. Increased risk of tumor seeding after radiofrequency thermal ablation for single hepatocellular carcinoma. Hepatology 2001;33:1124–1129.
21. Curley SA, Marra P, Beaty K, et al. Early and late complications after radiofrequency ablation of malignant liver tumors in 608 patients. Ann Surg 2004;239:450–458.
22. Lencioni R, Cioni D, Crocetti L, et al. Early-stage hepatocellular carcinoma in cirrhosis: long term results of percutaneous image-guided radiofrequency ablation. Radiology 2005;234:961–967.
23. Ebara M, Okabe S, Kita K, et al. Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. J Hepatol 2005;43:458–464.
24. Hines-Peralta A, Liu ZJ, Horkan C, Solazzo S, Goldberg SN. Chemical tumor ablation with use of a novel multiple-tine infusion system in a canine sarcoma model. J Vasc Interv Radiol 2006;17:351–358.
25. Ho CS, Kachura JR, Gallinger S, et al. Percutaneous ethanol injection of unresectable medium-to-large-sized hepatomas using a multipronged needle: efficacy and safety. Cardiovasc Intervent Radiol 2007;30:241–247.
26. Goldberg SN, Grassi CJ, Cardella JF, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria. Radiology 2005;235:728–739.
27. Lencioni R, Cioni D, Crocetti L, Bartolozzi C. Percutaneous ablation of hepatocellular carcinoma: state-of-the-art. Liver Transpl 2004;10(2 suppl 1):S91–S97.
28. Livraghi T. Role of percutaneous ethanol injection in the treatment of hepatocellular carcinoma. Dig Dis 2001;19:292–300.
29. Kojiro M. Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. Liver Transpl 2004;10(2 suppl 1):S3–S8.
30. Izumi N, Asahina Y, Noguchi O, et al. Risk factors for distant recurrence of hepatocellular carcinoma in the liver after complete coagulation by microwave or radiofrequency ablation. Cancer 2001;91:949–956.
31. Ko S, Kanehiro H, Hisanaga M, Nagao M, Ikeda N, Nakajima Y. Liver fibrosis increases the risk of intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. Br J Surg 2002;89:57–62.

Radiology 2009

This is your reprint order form or pro forma invoice

(Please keep a copy of this document for your records.)

Reprint order forms and purchase orders or prepayments must be received 72 hours after receipt of form either by mail or by fax at 410-820-9765. It is the policy of Cadmus Reprints to issue one invoice per order. **Please print clearly**.

Author Name _____
Title of Article _____
Issue of Journal_____ Reprint # _____ Publication Date _____
Number of Pages_____ KB # _____ Symbol Radiology
Color in Article? Yes / No (Please Circle)

Please include the journal name and reprint number or manuscript number on your purchase order or other correspondence.

Order and Shipping Information

Reprint Costs **(Please see page 2 of 2 for reprint costs/fees.)**

_____ Number of reprints ordered $_____
_____ Number of color reprints ordered $_____
_____ Number of covers ordered $_____
Subtotal $_____
Taxes $_____

(*Add appropriate sales tax for Virginia, Maryland, Pennsylvania, and the District of Columbia or Canadian GST to the reprints if your order is to be shipped to these locations*.)

First address included, add $32 for each additional shipping address $_____

TOTAL $_____

Shipping Address **(cannot ship to a P.O. Box) Please Print Clearly**

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity_____ Fax _____
Phone: Day _____ Evening _____
E-mail Address _____

Additional Shipping Address* **(cannot ship to a P.O. Box)**

Name _____
Institution _____
Street _____
City _____ State _____ Zip _____
Country _____
Quantity _____ Fax _____
Phone: Day _____ Evening _____
E-mail Address _____

** Add $32 for each additional shipping address*

Payment and Credit Card Details

Enclosed: Personal Check _____
Credit Card Payment Details _____

Checks must be paid in U.S. dollars and drawn on a U.S. Bank.

Credit Card: __ VISA __ Am. Exp. __ MasterCard
Card Number _____
Expiration Date_____
Signature: _____

Please send your order form and prepayment made payable to:

Cadmus Reprints
P.O. Box 751903
Charlotte, NC 28275-1903

Note: Do not send express packages to this location, PO Box.

FEIN #:541274108

Invoice or Credit Card Information

Invoice Address **Please Print Clearly**

Please complete Invoice address as it appears on credit card statement

Name _____
Institution _____
Department _____
Street _____
City _____ State _____ Zip _____
Country _____
Phone _____ Fax _____
E-mail Address _____

Cadmus will process credit cards and *Cadmus Journal Services* will appear on the credit card statement.

If you don't mail your order form, you may fax it to 410-820-9765 with your credit card information.

Signature _____ Date _____

Signature is required. By signing this form, the author agrees to accept the responsibility for the payment of reprints and/or all charges described in this document.

RB-1/01/09

Radiology 2009

Black and White Reprint Prices

Domestic (USA only)						
# of Pages	50	100	200	300	400	500
1-4	$239	$260	$285	$303	$323	$340
5-8	$379	$420	$455	$491	$534	$572
9-12	$507	$560	$651	$684	$748	$814
13-16	$627	$698	$784	$868	$954	$1,038
17-20	$755	$845	$947	$1,064	$1,166	$1,272
21-24	$878	$985	$1,115	$1,250	$1,377	$1,518
25-28	$1,003	$1,136	$1,294	$1,446	$1,607	$1,757
29-32	$1,128	$1,281	$1,459	$1,632	$1,819	$2,002
Covers	$149	$164	$219	$275	$335	$393

International (includes Canada and Mexico)						
# of Pages	50	100	200	300	400	500
1-4	$299	$314	$367	$429	$484	$546
5-8	$470	$502	$616	$722	$838	$949
9-12	$637	$687	$852	$1,031	$1,190	$1,369
13-16	$794	$861	$1,088	$1,313	$1,540	$1,765
17-20	$963	$1,051	$1,324	$1,619	$1,892	$2,168
21-24	$1,114	$1,222	$1,560	$1,906	$2,244	$2,588
25-28	$1,287	$1,412	$1,801	$2,198	$2,607	$2,998
29-32	$1,441	$1,586	$2,045	$2,499	$2,959	$3,418
Covers	$211	$224	$324	$444	$558	$672

Color Reprint Prices

Domestic (USA only)						
# of Pages	50	100	200	300	400	500
1-4	$247	$267	$385	$515	$650	$780
5-8	$297	$435	$655	$923	$1194	$1467
9-12	$445	$563	$926	$1,339	$1,748	$2,162
13-16	$587	$710	$1,201	$1,748	$2,297	$2,843
17-20	$738	$858	$1,474	$2,167	$2,846	$3,532
21-24	$888	$1,005	$1,750	$2,575	$3,400	$4,230
25-28	$1,035	$1,164	$2,034	$2,986	$3,957	$4,912
29-32	$1,186	$1,311	$2,302	$3,402	$4,509	$5,612
Covers	$149	$164	$219	$275	$335	$393

International (includes Canada and Mexico))						
# of Pages	50	100	200	300	400	500
1-4	$306	$321	$467	$642	$811	$986
5-8	$387	$517	$816	$1,154	$1,498	$1,844
9-12	$574	$689	$1,157	$1,686	$2,190	$2,717
13-16	$754	$874	$1,506	$2,193	$2,883	$3,570
17-20	$710	$1,063	$1,852	$2,722	$3,572	$4,428
21-24	$1,124	$1,242	$2,195	$3,231	$4,267	$5,300
25-28	$1,320	$1,440	$2,541	$3,738	$4,957	$6,153
29-32	$1,498	$1,616	$2,888	$4,269	$5,649	$7028
Covers	$211	$224	$324	$444	$558	$672

Minimum order is 50 copies. For orders larger than 500 copies, please consult Cadmus Reprints at 800-407-9190.

Reprint Cover

Cover prices are listed above. The cover will include the publication title, article title, and author name in black.

Shipping

Shipping costs are included in the reprint prices. Domestic orders are shipped via FedEx Ground service. Foreign orders are shipped via a proof of delivery air service.

Multiple Shipments

Orders can be shipped to more than one location. Please be aware that it will cost $32 for each additional location.

Delivery

Your order will be shipped within 2 weeks of the journal print date. Allow extra time for delivery.

Tax Due

Residents of Virginia, Maryland, Pennsylvania, and the District of Columbia are required to add the appropriate sales tax to each reprint order. For orders shipped to Canada, please add 7% Canadian GST unless exemption is claimed.

Ordering

Reprint order forms and purchase order or prepayment is required to process your order. Please reference journal name and reprint number or manuscript number on any correspondence. You may use the reverse side of this form as a proforma invoice. Please return your order form and prepayment to:

Cadmus Reprints
P.O. Box 751903
Charlotte, NC 28275-1903

Note: Do not send express packages to this location, PO Box.
FEIN #:541274108

Please direct all inquiries to:

Rose A. Baynard
800-407-9190 (toll free number)
410-819-3966 (direct number)
410-820-9765 (FAX number)
baynardr@cadmus.com (e-mail)

Reprint Order Forms and purchase order or prepayments must be received 72 hours after receipt of form.