Table 1. Clinical Characteristics of the Patients in the 2 Study Groups

	Radio frequency ablation (n = 118) (%)	Ethanol injection (n = 114) (%)
Demography		
Age (*y*) (≤65/>65)	44 (37)/74 (63)	41 (36)/73 (64)
Men/women	79 (67)/39 (33)	87 (76)/27 (24)
Cause of liver dysfunction		
HBV/HCV/non-B non-C[a]	18 (15)/90 (76)/10 (8)	11 (10)/98 (86)/5 (4)
Alcohol intake (*g/day*)		
≤80/>80	101 (86)/17 (14)	87 (76)/27 (24)
Underlying liver disease		
Chronic hepatitis/liver cirrhosis	21 (18)/97 (82)	13 (11)/101 (89)
Child–Pugh Class		
A/B	85 (72)/33 (28)	85 (75)/29 (25)
Ascites		
Absent/present	107 (91)/11 (9)	103 (90)/11 (10)
Encephalopathy		
Absent/present	115 (97)/3 (3)	113 (99)/1 (1)
Laboratory data		
Albumin (*g/dL*) (≤3.5/3.5>)	60 (51)/58 (49)	49 (43)/65 (57)
Total bilirubin (*mg/dL*) (≤1.0/>1.0)	84 (71)/34 (29)	86 (75)/28 (25)
Serum AST (*IU/L*) (≤80/>80)	85 (72)/33 (28)	91 (80)/23 (20)
Serum ALT (*IU/L*) (≤80/>80)	84 (71)/34 (29)	90 (79)/24 (21)
Platelet count (*/L*) ($\leq 10^{11}/>10^{11}$)	55 (47)/63 (53)	61 (54)/53 (46)
Prothrombin time (%) (≤80/>80)	58 (49)/60 (51)	63 (55)/51 (45)
Indocyanine clearance (%) (≤24/>24)	55 (47)/63 (53)	63 (55)/51 (45)
Distribution of tumor markers		
Serum AFP (*ng/mL*) (≤100/101–400/>400)	93 (79)/19 (16)/6 (5)	89 (78)/18 (16)/7 (6)
Serum DCP[b] (*mAU/mL*) (≤40/>40)	87 (74)/30 (26)	87 (78)/25 (22)
Serum AFP-L3 (%) (≤10/>10)	94 (80)/24 (20)	85 (75)/29 (25)
Tumor characteristics		
Tumor number[c] (1/2/3/4)	72 (61)/26 (22)/17 (14)/3 (3)	60 (53)/34 (30)/16 (14)/4 (4)
Tumor size (*cm*) (≤2.0/>2.0)	45 (38)/73 (62)	57 (50)/57 (50)
Edmondson's grade[d] (I/II,III)	24 (22)/87 (78)	27 (26)/78 (74)
Tumor stain in enhanced CT (present/absent)	102 (86)/16 (14)	90 (79)/24 (21)

[a]Non-B non-C: Patients negative for both HBs antigen and HCV antibody.
[b]Serum DCP level could not be measured in 3 patients because they were on warfarin.
[c]Before allocation, all patients were thought to have 3 or fewer lesions. A fourth lesion was, however, later found in 7 patients.
[d]Hepatocellular carcinoma was histopathologically diagnosed in 216 cases. In the remaining 16 cases, diagnosis was based on typical imaging findings of dynamic CT.

elevated although CT scan and ultrasonography did not show recurrence in the liver or if patients had symptoms suggesting extrahepatic recurrence.

The original treatment was used for recurrence if the patient still met the inclusion criteria. If multiple recurrences were not treatable with radiofrequency ablation or ethanol injection, transcatheter arterial embolization was performed.

Statistical Analysis

We calculated that a sample size of at least 114 patients would be needed to detect a difference in survival at 5% type-I error and 80% power for a 2-tailed log-rank test.[31] When we planned this study, we estimated that 4-year survival rate would be 74% with radiofrequency ablation and 54% with ethanol injection, according to our past data in microwave ablation and ethanol injection.[22] We also estimated that 5% of patients would be lost to follow-up.

Data were presented as mean ± SD for quantitative variables and as absolute frequencies for qualitative variables. Differences between the 2 groups were analyzed by the unpaired *t* test for continuous variables and Fisher exact test or Wilcoxon rank sum test for categorical variables.

Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. Recurrence rates were calculated by the Gaynor method[32] and compared by the Gray test.[33] All time estimates were made from the date of randomization. The interval between randomization and the first procedure was 1 to 3 days. All patients were followed up until death or until CT and ultrasonography between March and June 2003.

Prognostic relevance of a treatment assignment and 23 baseline variables (Table 1) to survival, overall recurrence, and local tumor progression was analyzed by univariate and multivariate Cox proportional hazards regression models. All variables with a *P* value less than .05 by univariate comparison were subjected to the multivariate analysis. Results of univariate or multivariate analyses were presented as relative risks with corresponding 95% confidence intervals (CI), with *P*

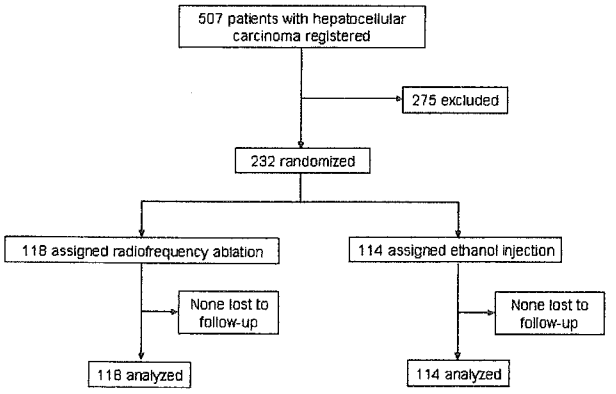


Figure 1. Flow of participants into the study.

values from the Wald test. All significance tests were 2-tailed, and differences with a P value less than .05 were considered statistically significant.

Role of the Funding Source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Patients

Between April 1999 and January 2001, hepatocellular carcinoma was diagnosed in 507 patients. Among them, 232 (45.8%) patients met the eligibility criteria and agreed to take part in the study (Figure 1). Of the 275 patients excluded, 97 had more than 3 lesions, 92 had lesions over 3 cm in diameter, 71 were Child–Pugh class C, 8 had vascular invasion, 5 had extrahepatic metastasis, and 2 refused to take part, requesting ethanol injection. One hundred eighteen patients were assigned to radiofrequency ablation and 114 to ethanol injection. Baseline characteristics were not significantly different between the 2 groups (Table 1).

Protocol Violations

Before allocation, all patients were thought to have 3 or fewer lesions. However, a fourth lesion was later found in 3 patients assigned to radiofrequency ablation and in 4 patients assigned to ethanol injection. In addition, 3 patients underwent assigned ethanol injection to treat the primary lesions but requested and underwent radiofrequency ablation when disease recurred. These 10 patients remained in the study and were included in the intention-to-treat analysis.

Physician's Experience, Session Number, and Hospitalization Length

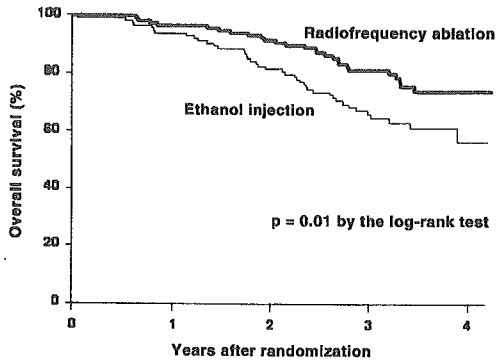
Neither radiofrequency ablation nor ethanol injection was cancelled in any patient because of lesion location or other reasons. Lesions were judged to be entirely necrotic in the final CT in all cases.

Physician's experience was not different between the 2 treatments (P = .68). Radiofrequency ablation was performed by the highly experienced physicians in 52 cases, moderately experienced in 44, and less experienced in 22; and ethanol injection was performed by the highly experienced physicians in 48 cases, moderately experienced in 42, and less experienced in 24.

The number of treatment sessions was smaller (2.1 ± 1.3 times vs 6.4 ± 2.6 times, respectively, $P < .0001$) and the length of hospitalization was shorter (10.8 ± 5.5 days vs 26.1 ± 9.9 days, respectively, $P < .0001$) in radiofrequency ablation than in ethanol injection.

Survival

No patients were lost to follow-up. Median follow-up was 3.1 years (range, 0.6–4.3 years) in radiofrequency ablation and 2.9 years (range, 0.1–4.2 years) in ethanol injection. Twenty-five patients treated with radiofrequency ablation and 40 with ethanol injection died. Causes of death were recurrent cancer (16 patients), liver failure (5), esophageal variceal rupture (1), and miscellaneous (3) in the radiofrequency-ablation group and recurrent cancer (26), liver failure (8), esophageal variceal rupture (2), and miscellaneous (4) in the ethanol-injection group. Survival was significantly higher in the radiofrequency-ablation group than the ethanol-injection group (P = .01 by the log-rank test; Figure 2). The



Number at risk

Radiofrequency ablation	118	114	108	72	13
Ethanol injection	114	107	93	51	8

Figure 2. Survival in the 232 eligible patients, according to the treatment group. The actuarial 4-year survival rate was 74% in the radio frequency-ablation group, whereas it was 57% in the ethanol-injection group.

actuarial 4-year survival rate was 74% (95% CI: 65%–84%) in radiofrequency ablation, whereas it was 57% (95% CI: 45%–71%) in ethanol injection. Besides treatment assignment, 11 of the 23 variables were also relevant to survival in univariate analysis (Table 2). In multivariate analysis, however, treatment allocation was the sole variable related to survival. Radiofrequency ablation lowered the risk of death by 46% (adjusted relative risk, 0.54 [95% CI: 0.33–0.89], $P = .02$; Table 2).

A subgroup analysis found the same tendency in the patients with a solitary tumor that survival rates were higher in radiofrequency ablation than in ethanol injection ($P = .103$): 99%, 93%, 86%, and 77% at 1, 2, 3, and 4 years, respectively, in radiofrequency ablation and 95%, 85%, 73%, and 64% at 1, 2, 3, and 4 years, respectively, in ethanol injection. In the patients with multiple tumors, there was also the same tendency. The survival rates were 94%, 89%, 73%, and 70% at 1, 2, 3, and 4 years, respectively, in radiofrequency ablation and 93%, 78%, 60%, and 48% at 1, 2, 3, and 4 years, respectively, in ethanol injection ($P = .089$). There was no difference in the diameter of the lesion between the patients with a single lesion and those with multiple lesions ($P = .418$). The diameter of the lesion in the patients with a single tumor was 2.14 ± 0.56 cm, whereas that of the largest lesion in the patients with multiple tumors was 2.20 ± 0.51 cm.

Recurrence

Recurrence was found in 78 cases treated with radiofrequency ablation and in 90 with ethanol injection. Patterns of recurrence were appearance of new lesion

Table 2. Univariate and Multivariate Analysis of the Relative Risks for Survival, Overall Recurrence, and Local Tumor Progression

Variable	Univariate analysis (*P* value)	Multivariate analysis: Relative risk (95% CI)	Multivariate analysis: *P* value
Survival			
Treatment (radiofrequency ablation vs ethanol injection)	.01	0.54 (0.33–0.89)	.02
Age (*y*) (>65 vs ≤65)	.04	1.61 (0.90–2.87)	.11
Underlying liver disease (liver cirrhosis vs chronic hepatitis)	.02	2.16 (0.64–7.32)	.21
Child–Pugh class (B vs A)	.008	1.15 (0.55–2.42)	.71
Ascites (present vs absent)	.041	1.19 (0.52–2.71)	.68
Albumin (*g/dL*) (≤3.5 vs >3.5)	.001	1.67 (0.86–3.24)	.13
Total bilirubin (*mg/dL*) (>1.0 vs ≤1.0)	.04	1.03 (0.60–1.77)	.92
Prothrombin time (≤80 vs >80)	.005	1.58 (0.89–2.78)	.12
Serum AFP (*ng/mL*) (>100 vs ≤100)	.007	1.28 (0.69–2.37)	.44
Serum AFP-L3 (%) (>10 vs ≤10)	<.0001	1.75 (0.96–3.19)	.07
Tumor number (multiple vs single)	.02	1.48 (0.90–2.45)	.12
Tumor stain in enhanced CT (absent vs present)	.03	0.49 (0.20–1.17)	.11
Overall recurrence			
Treatment (radiofrequency ablation vs ethanol injection)	.0007	0.57 (0.41–0.80)	.0009
HCV antibody (positive vs negative)	.0006	1.60 (0.97–2.64)	.07
Underlying liver disease (cirrhosis vs chronic hepatitis)	.004	2.19 (1.19–4.05)	.01
Albumin (*g/dL*) (≤3.5 vs >3.5)	.03	1.08 (0.75–1.55)	.67
Platelet count (*/L*) ($\leq 10^{11}$ vs $>10^{11}$)	.01	1.00 (0.70–1.43)	.99
Prothrombin time (≤80 vs >80)	.002	0.64 (0.46–0.91)	.01
Serum AFP (*ng/mL*) (>100 vs ≤100)	.009	1.44 (0.92–2.26)	.11
Serum AFP-L3 (%) (>10 vs ≤10)	.04	1.31 (0.86–2.01)	.21
Tumor number (multiple vs single)	<.0001	1.69 (1.21–2.36)	.002
Edmondson's grade (I vs II, III)	.001	0.55 (0.35–0.88)	.01
Tumor stain in enhanced CT (absent vs present)	.04	0.88 (0.54–1.43)	.60

Local tumor progression[a]	Univariate analysis (*P* value)	Univariate analysis: Relative risk (95% CI)	Univariate analysis: *P* value
Treatment (radiofrequency ablation vs ethanol injection)	0.12 [0.03–0.55]	0.006	—
Platelet count (*/L*) ($\leq 10^{11}$ vs $>10^{11}$)	3.21 [1.02–10.1]	0.05	—
Serum DCP (*mAU/mL*) (>40 vs ≤40)	2.94 [1.07–8.13]	0.04	—

[a]Multivariate analysis was not performed because the number of the event was small.

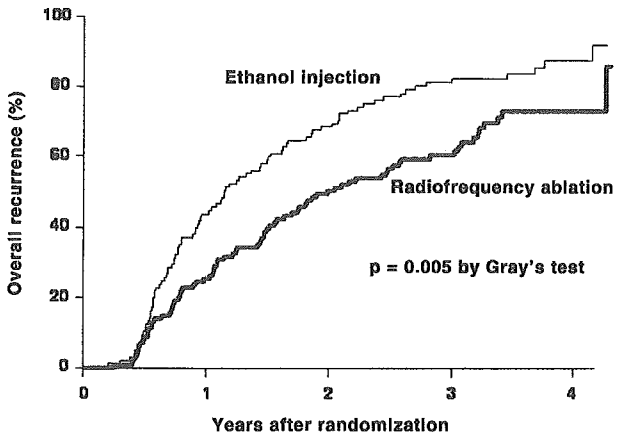


Figure 3. Overall recurrence in the 232 eligible patients, according to the treatment group. The estimated 4-year rate of overall recurrence was 70% in the radiofrequency-ablation group, whereas it was 85% in the ethanol-injection group.

away from the original one (74 cases), local tumor progression (2 cases), and extrahepatic recurrence (2 cases: 1 lung metastasis and 1 pleural seeding) in the radiofrequency-ablation group and, in the ethanol-injection group, recurrence separate from the primary lesion (73 cases), local tumor progression (13 cases), and extrahepatic recurrence (4 cases: 1 bone metastasis, 1 lung metastasis, 1 adrenal metastasis, and 1 peritoneal seeding). Radiofrequency ablation reduced the risk of overall recurrence by 43% (adjusted relative risk, 0.57 [95% CI: 0.41–0.80], $P = .0009$ by the Wald test; Figure 3; Table 2). Radiofrequency ablation had an 88% smaller risk of local tumor progression than ethanol injection (relative risk, 0.12 [95% CI: 0.03–0.55], $P = .006$ by the Wald test; Figure 4; Table 2).

Adverse Events

Pain during the procedures was evaluated. Additional analgesics were necessary in 60 cases in radiofrequency ablation and in 60 in ethanol injection ($P = .79$). Continual fever of 37.5°C or higher for 3 days or longer was encountered in 51 cases in radiofrequency ablation and in 49 in ethanol injection ($P > .99$). None had fever beyond 7 days.

The incidence of serious adverse events (grade 3 or 4) was not different between the 2 therapies ($P = .54$). Transient jaundice (1 case), skin burn (1), hepatic infarction (1), and seeding of malignant cells (3) were encountered after radiofrequency ablation, whereas liver abscess (1) and neoplastic seeding (2) developed after ethanol injection.

In the 5 cases of malignant seeding, the diameter of the largest tumor was 2.18 ± 0.46 cm. Two patients had a single lesion, 1 patient had 2, and the remaining 2 patients had 3. Only 1 patient had a subcapsular lesion. Two patients had Edmondson grade II hepatocellular carcinoma, and the remaining 3 patients had Edmondson's grade III carcinoma.

Discussion

This study demonstrated that radiofrequency ablation improves survival of patients with small hepatocellular carcinoma compared with ethanol injection. This result can probably be explained by the fact that radiofrequency ablation reduces overall recurrence and local tumor progression through its more reliable local antitumor effect. Actually, there was no statistical difference in the recurrence rates away from the original lesion between the 2 therapy groups ($P = .560$), and thus the difference in overall recurrence was mainly due to the difference in the local control of the primary tumor. Radiofrequency ablation has been expected to improve survival over ethanol injection.[6,21–23] A randomized controlled trial by Lencioni et al showed higher local tumor progression-free and disease-free survival of radiofrequency ablation, but it failed to show higher survival, probably because of limited observation period and subject number.[23] The other randomized controlled trial recently reported by Lin et al demonstrated that the local tumor progression rate was lower in radiofrequency ablation than in conventional or high-dose ethanol injection and that overall survival and cancer-free survival were higher in radiofrequency ablation than in conventional or high-dose ethanol injection,[34] which are consistent with the findings in this study.

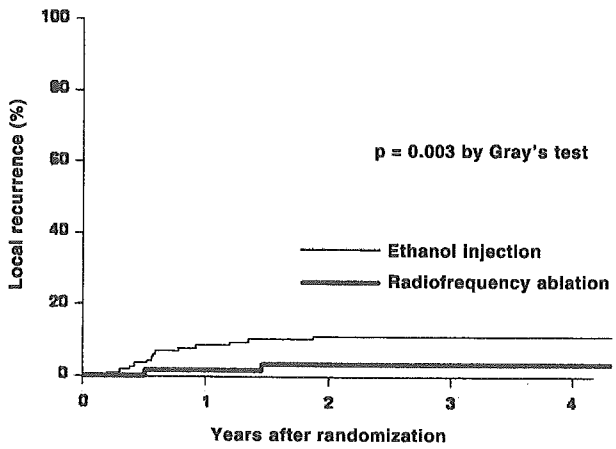


Figure 4. Local tumor progression in the 232 eligible patients, according to the treatment group. The actuarial 4-year rate of local tumor progression was 1.7% in the radiofrequency-ablation group, whereas it was 11% in the ethanol-injection group.

In the subgroup analyses of survival in the patients with a solitary tumor and those with multiple tumors, radiofrequency ablation tended to have higher survival compared with ethanol injection, although the difference did not reach the statistical significance because of the insufficient sample size. In this prospective study, the sample size had been determined to compare the survival between the 2 therapy groups. We had not planned to do the subgroup analyses.

The outcomes of ethanol injection in this study were similar to or better than most previous ones, meaning that the apparent benefit of radiofrequency ablation cannot be attributed to shorter-than-expected survival in patients undergoing ethanol injection. In ethanol injection, 3-year survival rates range from 43% to 84%,[14–17] with 3-year overall recurrence and local tumor progression rates of 41% to 81% and 14% to 33%, respectively.[35] As for radiofrequency ablation, few data have been published on long-term survival and recurrence. Three-year survival rates of radiofrequency ablation are 45% to 62%,[36,37] with 1-year local tumor progression rates of 9% to 15%.[38,39] Long-term overall recurrence rates have not been reported.

Our first option for resectable hepatocellular carcinoma was surgery. However, most patients who came to our department visited us because they did not want surgical resection. Thus, many patients in this study underwent radiofrequency ablation or ethanol injection not because of unresectable lesions but because of refusal of surgery. Those who preferred surgery would have directly gone to the surgical department that has wide experience in hepatic resection.[40]

It is said to be common policy for surgeons to restrict surgical resection to Child–Pugh's class A patients with solitary hepatocellular carcinoma,[41] although there are many other criteria to assess whether the cancer is resectable or not. Among the 232 patients, 100 patients had multiple lesions, 62 had Child–Pugh class B liver dysfunction, 6 had severe cardiopulmonary problems, and 8 were 80 years of age or older (some patients were counted repeatedly). Thus, 89 patients (48 treated by radiofrequency ablation and 41 by ethanol injection) were considered good candidates for surgical resection.

We have put no restrictions on lesion location. We have successfully performed radiofrequency ablation or ethanol injection on more than 99% of patients, some of whom had lesions near the heart, gallbladder, diaphragm, or on the surface of the liver. In this study, we did not have any case in which we had to give up treatment because of tumor location.

We have not restricted the number of treatment sessions. We have repeated radiofrequency ablation or ethanol injection until CT demonstrates entire tumor necrosis. As a result, we have successfully ablated tumors in more than 99% of cases. In this study, we did not have any case in which the final CT demonstrated incomplete tumor ablation.

The incidence of adverse events was not significantly different between the 2 treatments, although previous comparison studies have suggested that radiofrequency ablation would have higher complication rates than ethanol injection.[21,23] Reported mortality rates are 0.3% to 0.5%, and morbidity rates are 2.2% to 8.9% in radiofrequency ablation,[42,43] whereas they are 0.1% and 3.2%, respectively, in ethanol injection.[44] Common complications are bleeding, biliary injury, and seeding of malignant cells in both procedures.

Consistent with other studies,[21,23,39] radiofrequency ablation required fewer treatment sessions and shorter hospitalization than ethanol injection. Patients may not stay in the hospital until the end of therapies in other countries, but the tendency would be the same as it was shown in this study. Although we did not evaluate the quality of life, judging from these results, radiofrequency ablation may reduce patient distress and improve the quality of life.

Because outcomes of these interventions depend on experience, our results might not be reproducible in other institutions with limited experience. We have performed ethanol injection on the total number of 3000 patients and radiofrequency ablation on the total number of 1200 patients. Those not accustomed to using the radiofrequency ablation system and inserting the large-diameter electrode may have difficulty in performing this procedure, resulting in poorer outcomes than expected. Furthermore, our results might not be reproducible with different radiofrequency ablation systems. Several types of systems are commercially available.[24]

This study was restricted to tumors 3 cm or less in diameter, although larger tumors have also been treated with these procedures. We speculate that superiority of radiofrequency ablation to ethanol injection would be more significant in middle-size or large tumors because of its more reliable local effect. This study was also restricted to patients with relatively good liver function, although some patients in Child–Pugh class C have been treated with these procedures. We are not sure that radiofrequency ablation could achieve better outcomes in patients with poor liver function because preserving liver function might be more important than achieving curative treatment.

In conclusion, judging from the higher survival but similar adverse events compared with ethanol injection, radiofrequency ablation may be a treatment of choice in patients with small, unresectable hepatocellular carcinoma.

References

1. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med 1999;340:745–750.
2. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. Lancet 1997;350:1142–1143.
3. Okuda K, Okuda H. Primary liver cell carcinoma. In: McIntyre N, Benhamou JP, Bircher J, Rizzetto M, Rodes J, eds. Oxford textbook of clinical hepatology. Volume 2. Oxford, England: Oxford University Press, 1991:1019–1052.
4. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, Teratani T, Tohgo G, Toda N, Ohashi M, Ogura K, Niwa Y, Matsumura M, Omata M. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. Hepatology 1995;22:1027–1033.
5. Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology 2000;31:330–335.
6. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodes J, EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35:421–430.
7. Ryder SD, British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003;52(suppl 3):iii1–8.
8. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–1917.
9. Balsells J, Charco R, Lazaro JL, Murio E, Vargas V, Allende E, Margarit C. Resection of hepatocellular carcinoma in patients with cirrhosis. Br J Surg 1996;83:758–761.
10. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–699.
11. Livraghi T, Giorgio A, Marin G, Salmi A, de Sio I, Bolondi L, Pompili M, Brunello F, Lazzaroni S, Torzilli G. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995;197:101–108.
12. Shiina S, Imamura M, Omata M. Percutaneous ethanol injection therapy (PEIT) for malignant liver neoplasms. Semin Interv Radiol 1997;14:295–303.
13. Shiina S, Tagawa K, Unuma T, Takanashi R, Yoshiura K, Komatsu Y, Hata Y, Niwa Y, Shiratori Y, Terano A, Sugimoto T. Percutaneous ethanol injection therapy for hepatocellular carcinoma. A histopathologic study. Cancer 1991;68:1524–1530.
14. Castells A, Bruix J, Bru C, Fuster J, Vilana R, Navasa M, Ayuso C, Boix L, Visa J, Rodes J. Treatment of small hepatocellular carcinoma in cirrhotic patients: a cohort study comparing surgical resection and percutaneous ethanol injection. Hepatology 1993; 18:1121–1126.
15. Livraghi T, Bolondi L, Buscarini L, Cottone M, Mazziotti A, Morabito A, Torzilli G. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. Italian Cooperative HCC Study Group. J Hepatol 1995;22:522–526.
16. Lencioni R, Pinto F, Armillotta N, Bassi AM, Moretti M, Di Giulio M, Marchi S, Uliana M, Della Capanna S, Lencioni M, Bartolozzi C. Long-term results of percutaneous ethanol injection therapy for hepatocellular carcinoma in cirrhosis: a European experience. Eur Radiol 1997;7:514–519.
17. Orlando A, D'Antoni A, Camma C, Albanese M, Livraghi T, Torzilli G, Virdone R, Sciarrino E, Simonetti RG, Maringhini A, Pagliaro L, Cottone M. Treatment of small hepatocellular carcinoma with percutaneous ethanol injection: a validated prognostic model. Am J Gastroenterol 2000;95:2921–2927.
18. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–1440.
19. Dodd GD III, Soulen MC, Kane RA, Livraghi T, Lees WR, Yamashita Y, Gillams AR, Karahan OI, Rhim H. Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. Radiographics 2000;20:9–27.
20. Rossi S, Di Stasi M, Buscarini E, Cavanna L, Quaretti P, Squassante E, Garbagnati F, Buscarini L. Percutaneous radio frequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. Cancer J Sci Am 1995;1:73–81.
21. 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.
22. Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radio frequency ablation. Oncology 2002; 62:64–68.
23. Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228:235–240.
24. Goldberg SN. Radio frequency tumor ablation: principles and techniques. Eur J Ultrasound 2001;13:129–147.
25. Galandi D, Antes G. Radiofrequency thermal ablation versus other interventions for hepatocellular carcinoma. Cochrane Database Syst Rev 2002;3:CD003046.
26. Matsui O, Ueda K, Kobayashi S, Sanada J, Terayama N, Gabata T, Minami M, Kawamori Y, Nakanuma Y. Intra- and perinodular hemodynamics of hepatocellular carcinoma: CT observation during intra-arterial contrast injection. Abdom Imaging 2002;27: 147–156.
27. Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 1954;7: 462–503.
28. Araki T, Itai Y, Furui S, Tasaka A. Dynamic CT densitometry of hepatic tumors. AJR Am J Roentgenol 1980;135:1037–1043.
29. Goldberg SN, Charboneau JW, Dodd GD III, Dupuy DE, Gervais DA, Gillams AR, Kane RA, Lee FT Jr, Livraghi T, McGahan JP, Rhim H, Silverman SG, Solbiati L, Vogl TJ, Wood BJ, International Working Group on Image-Guided Tumor Ablation. Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. Radiology 2003;228:335–345.
30. Shiina S, Hata Y, Niwa Y, Komatsu Y, Tanaka T, Yoshiura K, Hamada E, Ohshima M, Mutoh H, Unuma T, Kawabe T, Okano K. Multiple-needle insertion method in percutaneous ethanol injection therapy for liver neoplasms. Gastroenterol Jpn 1991;26:47–50.
31. Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for nonuniform patient entry, losses to follow-up, noncompliance, and stratification. Biometrics 1986;42:507–519.
32. Gaynor JJ, Feuer EJ, Tan CC, Wu DH, Little CR, Straus DJ, Clarkson BD, Brennan MF. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. J Am Stat Assoc 1993;88:400–409.
33. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist 1988;16:1141–1154.
34. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radio frequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma ≤4 cm. Gastroenterology 2004;127: 1714–1723.

35. Koda M, Murawaki Y, Mitsuda A, Ohyama K, Horie Y, Suou T, Kawasaki H, Ikawa S. Predictive factors for intrahepatic recurrence after percutaneous ethanol injection therapy for small hepatocellular carcinoma. Cancer 2000;88:529–537.
36. Buscarini L, Buscarini E, Di Stasi M, Vallisa D, Quaretti P, Rocca A. Percutaneous radio frequency ablation of small hepatocellular carcinoma: long-term results. Eur Radiol 2001;11:914–921.
37. Guglielmi A, Ruzzenente A, Battocchia A, Tonon A, Fracastoro G, Cordiano C. Radio frequency ablation of hepatocellular carcinoma in cirrhotic patients. Hepatogastroenterology 2003; 50:480–484.
38. Ikeda M, Okada S, Ueno H, Okusaka T, Kuriyama H. Radio frequency ablation and percutaneous ethanol injection in patients with small hepatocellular carcinoma: a comparative study. Jpn J Clin Oncol 2001;31:322–326.
39. Horiike N, Iuchi H, Ninomiya T, Kawai K, Kumagi T, Michitaka K, Masumoto T, Onji M. Influencing factors for recurrence of hepatocellular carcinoma treated with radiofrequency ablation. Oncol Rep 2002;9:1059–1062.
40. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, Takayama T, Makuuchi M. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003;138:1198–1206.
41. Johnson P, Bruix J. Hepatocellular carcinoma and the art of prognostication. J Hepatol 2000;33:1006–1008.
42. Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, De Wever I, Michel L. Complications of radiofrequency coagulation of liver tumors. Br J Surg 2002;89:1206–1222.
43. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN, and for the Collaborative Italian Group using cool-tip radio frequency. Treatment of focal liver tumors with percutaneous radiofrequency ablation: complications encountered in a multicenter study. Radiology 2003;226:441–451.
44. Di Stasi M, Buscarini L, Livraghi T, Giorgio A, Salmi A, De Sio I, Brunello F, Solmi L, Caturelli E, Magnolfi F, Caremani M, Filice C. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. A multicenter survey of evaluation practices and complication rates. Scand J Gastroenterol 1997;32:1168–1173.

Received June 29, 2004. Accepted March 30, 2005.

Address requests for reprint to: Shuichiro Shiina, MD, Department of Gastroenterology, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. e-mail: sshiina-tky@umin.ac.jp; fax: (81) 3-3814-0021.

Supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan.

Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma

An Analysis of 1000 Cases

Ryosuke Tateishi, M.D.
Shuichiro Shiina, M.D.
Takuma Teratani, M.D.
Shuntaro Obi, M.D.
Shinpei Sato, M.D.
Yukihiro Koike, M.D., Ph.D.
Tomonori Fujishima, M.D.
Haruhiko Yoshida, M.D., Ph.D.
Takao Kawabe, M.D., Ph.D.
Masao Omata, M.D., Ph.D.

Department of Gastroenterology, University of Tokyo, Tokyo, Japan.

BACKGROUND. Radiofrequency ablation (RFA) was introduced recently as a therapeutic modality for hepatocellular carcinoma (HCC), an alternative to percutaneous ethanol injection therapy (PEIT), which is coming into use worldwide. Previously reported treatment efficacy and complication rates have varied considerably.
METHODS. Between February 1999 and February 2003, the authors performed 1000 treatments of RFA to 2140 HCC nodules in 664 patients with a cooled-tip electrode at the University of Tokyo Hospital (Tokyo, Japan). Short-term and long-term complications were analyzed by treatment and session basis. Cumulative survival was also assessed in 319 patients who received RFA as primary treatment (naive patients) and 345 patients who received RFA for recurrent tumor after previous treatment including resection, PEIT, microwave coagulation therapy, and transarterial embolization (nonnaive patients).
RESULTS. A total of 40 major complications (4.0% per treatment, 1.9% per session) and 17 minor complications (1.7% per treatment, 0.82% per session) were observed during the observation period until March 31, 2004. There were no treatment-related deaths. Surgical intervention was required in one case each of bile peritonitis and duodenal perforation. The cumulative survival rates at 1, 2, 3, 4, and 5 years were 94.7%, 86.1%, 77.7%, 67.4%, and 54.3% for naive patients, whereas the cumulative survival rates were 91.8%, 75.6%, 62.4%, 53.7%, and 38.2% for nonnaive patients, respectively.
CONCLUSIONS. The authors confirmed the safety and efficacy of RFA for HCC in a large-scale series and long-term prognosis was satisfactory. ***Cancer* 2005;103: 1201–9.** *© 2005 American Cancer Society.*

KEYWORDS: hepatocellular carcinoma, interventional radiology, postoperative complications, survival analysis, cirrhosis.

Hepatocellular carcinoma (HCC) is a common malignancy worldwide, with an increasing incidence in the United States.[1,2] Current options for the treatment of this cancer consist of surgical resection, transcatheter arterial embolization (TAE), and percutaneous ablation therapy. Although surgical resection usually is considered to be the first-choice treatment,[3,4] it is not infrequently contraindicated by underlying chronic liver diseases based on hepatitis B or C virus (HCV) infection.[5,6] Orthotopic liver transplantation (OLT) is a strategy that can treat both cancer and liver dysfunction, and indeed has shown excellent survival in patients at an early stage of the cancer (e.g., a single nodule of ≤ 5 cm in dimension or < 3 nodules of ≤ 3 cm in dimension).[7,8] However, with an increasing demand for donor tissue but a limited supply, the waiting time for an OLT is now > 1 year in Europe and the United States.[8,9] TAE is a widely performed

Dr. Tateishi and Dr. Shiina contributed equally to the article.

Address for reprints: Haruhiko Yoshida, M.D., Department of Gastroenterology, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; Fax: (011) 81-3-3814-0021; E-mail: yoshida-2im@h.u-tokyo.ac.jp

Received January 23, 2004; revision received November 6, 2004; accepted November 18, 2004.

DOI 10.1002/cncr.20892
Published online 2 February 2005 in Wiley InterScience (www.interscience.wiley.com).

procedure for patients with multiple hypervascular nodules. However, complete necrosis rarely is achieved.[10] Percutaneous ethanol injection therapy (PEIT) continues to play an important role in the treatment of small HCCs, and is considered to be a bridge treatment for OLT. Long-term outcomes after PEIT, such as 5-year survival, are comparable to those of surgery.[11,12] However, the efficacy of PEIT is dependent on tumor size, and a local tumor progression rate of > 20% was reported for tumors > 3 cm.[13,14]

Radiofrequency ablation (RFA) is a recently introduced alternative technique to PEIT and is rapidly gaining use worldwide.[15–19] An area of ≤ 3 cm in diameter can be ablated with a single application of RFA.[20,21] The predictability of the ablation area is one of the merits of RFA compared with PEIT. The treatment efficacy and complication rate of RFA have been described in various studies.[22,23] We have performed 1000 treatments of RFA to 2140 HCC nodules in 664 patients and we assessed the early and late complication rates of RFA as well as long-term outcomes in this large case series.

MATERIALS AND METHODS

Patients

Since we introduced RFA to our department in February 1999, we had treated 664 patients with HCC by RFA in 4 years by February 28, 2003. All those patients were included in the current study. Ablation therapy was used either because patients were considered not to be suitable for resection (n = 419) by consideration of liver function impairment, number and distribution of the tumors, and cardiopulmonary dysfunction, or because they voluntarily preferred ablation with informed consent (n = 245) despite surgery also being feasible. Inclusion criteria for RFA were as follows: total bilirubin concentration < 3 mg/dL, platelet count ≥ $5 \times 10^5/mm^3$, and prothrombin activity ≥ 50%. Ascites should be controlled beforehand by diuretics. Patients with portal vein tumor thrombosis or extrahepatic metastasis were excluded. We also excluded patients who had a history of bilioenteric anastomosis or sphincterotomy that are considered as high risk for hepatic abscess formation. Written informed consent was obtained from all enrolled patients, and the protocol was approved by the ethics committee of the University of Tokyo Hospital (Tokyo, Japan).

Technical Terms

We defined a session as a single intervention episode that consists of one or more ablations performed on one or more tumors and a treatment as the completed effort to ablate one or more tumors that consists of one or more sessions according to the working party report on image-guided tumor ablation.[24]

Diagnosis of Hepatocellular Carcinoma

HCC was diagnosed based on typical findings by ultrasonography and computed tomography (CT) scans (hyperattenuation in the arterial phase and hypoattenuation in the portal-venous phase). The diagnosis of HCC also was confirmed histopathologically with ultrasound-guided biopsy in 302 of 319 naive patients. Ultrasonography was performed with a 3.5–6.0-MHz convex probe using an Aloka SSD-5500 (Aloka, Tokyo, Japan) or Toshiba SSA-370A machine (Toshiba Medical Systems, Tokyo, Japan). The dimension of the tumor nodule was measured by visualization of the largest dimension of the tumor.

Using dual-phase dynamic CT scans, arterial and portal phase images were obtained 31–33 seconds and 120 seconds, respectively, after the initiation of contrast material injection. Spiral CT scans were performed with 5-mm–thick sections at a table feed speed of 5–7 mm/sec. Using CT scans during arterial portography, scanning began 30 seconds after contrast medium injection. Using CT scans during hepatic arteriography, images were obtained after injection of 30 mL of contrast medium at a rate of 1.2 mL/sec. When > 3 hypervascular nodules were detected or the largest nodule was > 3 cm on these examinations, we subsequently performed TAE. Immediately after injection of 2–10 mL of iodized oil (Lipiodol Ultra-Fluid, Shering Japan, Osaka, Japan), feeding arteries were embolized selectively with gelatin sponge particles (Spongel, Yamanouchi Pharmaceutical Co., Tokyo, Japan). Otherwise, 1–2 mL of iodized oil only was injected to intensify the radiologic visibility of the target nodules. In February 2003, we changed the size criterion for performing TAE from > 3 cm to > 2 cm in diameter.

Specimens for histologic evaluation were obtained by ultrasound-guided needle biopsy using a 20-gauge needle (Bard Monopty, C.R. Bard, Inc., Covington, GA). Histopathologic grading of tumor differentiation was done according to the criteria of Edmondson and Steiner.[25]

Electrode Insertion and Radiofrequency Ablation

A 17-gauge, cooled-tip electrode was inserted under real-time ultrasound guidance. For the intercostal approach, we adjusted the operating table so that patients had a rotated or head-up position to allow for electrode insertion as square to the thoracic wall as possible. For the subcostal approach, patients usually remain in the head-up position to allow the electrode to be inserted without the patient taking a deep

breath. We also utilized an intrapleural infusion technique when the tumor was located adjacent to the diaphragm to visualize the entire image of the tumor.[26] A glucose solution (5%, 500 mL) was infused into the right pleural cavity under ultrasonographic guidance before needle insertion.

An electrode with a 2-cm or 3-cm exposed tip was connected to a 500-kHz RF generator (Radionics, Burlington, MA), which produces 200 W at 50Ω of impedance.[20,27] The equipment also allows the measurements of generator output, tissue impedance, and electrode tip temperature. A tip temperature of 10–20 °C is maintained by a peristaltic pump infusing chilled saline solution. After insertion of the electrode into the lesion, we started ablation at 60 W for the 3-cm exposed tip and 40 W for the 2-cm exposed tip. The power was increased to 140 W at a rate of 20 W/min. When a rapid increase in impedance was observed during thermal ablation, we minimized the output for 15 seconds and restarted the emission at a lower output.[28] The duration of a single ablation was 12 minutes for the 3-cm electrode and 6 minutes for the 2-cm electrode. After RF exposure, the pump was stopped and the temperature of the needle tip was measured. When the temperature was < 65 °C, additional ablation was performed. When the target nodule was > 2 cm in diameter, we performed multiple ablations. When the total ablation time in a treatment was > 60 minutes, we divided a treatment into ≥ 2 sessions in consideration of burden to the patient.

Antibiotics were administered before and after the procedure on the treatment day and on the morning of the next day. We continued to administer antibiotics when the patients had a fever > 37.5 °C.

Assessment of Treatment Efficacy and Follow-Up

After 1–2 sessions of RFA, dynamic CT scans with section thickness of 5 mm were performed to evaluate the ablation. Complete ablation of HCC was defined as hypoattenuation of the lesion including the surrounding liver parenchyma. Patients received additional sessions of RFA until the treatment was judged as complete. Follow-up consisted of monthly blood tests and monitoring of tumor markers at the outpatient clinic, and ultrasonography and dynamic CT scans were performed every 3–4 months. Intrahepatic HCC recurrence was classified as either tumor recurrence at a site distant from the primary tumor or adjacent to the treated site (local tumor progression). If HCC recurrence was suspected, further examinations including dynamic CT scans and CT angiography were performed. When recurring HCC tumors were identified, RFA was performed if the same initial inclusion criteria were again satisfied.

Complications were assessed on the basis of the number of treatments and sessions. Major complications were defined as those that, if left untreated, might threaten the patient's life, lead to substantial morbidity and disability, or result in hospital admission or substantially lengthen hospital stay according to the previously described guidelines.[24] All other complications were considered minor. Complications were classified into 3 categories according to the time after the last ablation: immediate complications ($\leq$ 6–24 hours after the procedure), periprocedual complications (within 30 days), and delayed complications. In assessing delayed complications, follow-up was censored either on March 31, 2004 or in the event of death.

Survival analysis was performed on patient basis. Survival time was defined as the interval between the first RFA and the death or the last visit to outpatient clinic until March 31, 2004. Six-hundred sixty-four patients were divided into 2 groups: 319 patients who received RFA as the initial treatment for HCC (naive patients) and 345 patients who received RFA as a treatment for tumor recurrence after primary treatments including hepatic resection, PEIT, percutaneous microwave coagulation therapy (PMCT), and TAE. A cumulative survival curve was plotted using the Kaplan–Meier method. Survival was also assessed in naive patients among subgroups divided by age, gender, etiology of background liver disease, Child–Pugh class, tumor size and number, pathologic grade of tumor, and tumor markers. Difference between these subgroups was tested by the log-rank test.

Tumor recurrence was analyzed among 306 of the 319 naive patients, excluding 13 in whom several nodules were left untreated with the initial RFA therapy. The observation period for tumor recurrence was defined as the interval between the first RFA and either of the detection of tumor recurrence, death, or the last visit before March 31, 2004, whichever came first. As death and tumor recurrence are competing risks, we used cumulative incidence estimation with competing risks for the analysis of cumulative tumor recurrence as described by Gray.[29] Differences with $P < 0.05$ were statistically significant. All statistical analyses were performed with S-plus 2000 software (MathSoft, Inc., Seattle, WA).

RESULTS

Patient Profile

The mean age of the patients was 67 years (range, 44–90 years). Patients were male dominant (69%) and the majority were HCV positive (Table 1). The mean tumor size was 2.6 cm (range, 0.8–9.7 cm). As 227 of 664 patients received ≥ 2 treatments during the period

TABLE 1
Characteristics of 664 Patients Treated by RFA

Variables	Naive patients (n = 319) (%)	Nonnaive patients (n = 345) (%)
Mean age (yrs)[a]	67.4 ± 7.8	66.6 ± 8.4
Male gender	212 (66.5)	247 (71.6)
Etiology		
HBs-Ag positive only	31 (9.7)	36 (10.4)
HCV-Ab positive only	251 (78.7)	284 (82.3)
Both positive	5 (1.6)	6 (1.9)
Both negative	32 (10.0)	19 (5.5)
Alcohol consumption >80 g/day	52 (16.3)	59 (17.1)
Child-Pugh class		
A	221 (69.3)	225 (65.2)
B	94 (29.5)	111 (32.1)
C	4 (1.3)	9 (2.6)
Tumor size (cm)		
≤2.0	87 (27.2)	113 (32.8)
2.1–5.0	215 (67.4)	209 (60.6)
>5.0	17 (5.3)	23 (6.7)
Tumor no.		
Single	193 (60.5)	138 (40.0)
2–3	105 (32.9)	141 (40.9)
>3	21 (6.6)	66 (19.1)
Tumor markers		
AFP (ng/mL)		
≤20	152 (47.6)	156 (45.2)
21–100	86 (27.0)	97 (28.1)
101–400	47 (14.7)	43 (12.5)
>400	34 (10.7)	49 (14.2)
DCP (mAU/mL)		
≤40	225 (70.5)	226 (65.5)
41–100	36 (12.9)	49 (14.2)
101–400	37 (11.6)	40 (11.6)
>400	21 (6.6)	30 (8.7)

RFA: radiofrequency ablation; HBs-Ag: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; AFP: α-fetoprotein; DCP: des-gamma carboxyprothrombin.
[a] Values are expressed as mean ± standard deviations.

TABLE 2
Major Complications after RFA

Complications	No. of complications	Prevalence (%) Per treatment	Per session
Immediate (within 24 hrs)			
Intraperitoneal hemorrhage requiring blood transfusion	4	0.4	0.19
Pleural effusion requiring drainage	4	0.4	0.19
Hepatic infarction	2	0.2	0.096
Pneumothorax requiring drainage	1	0.1	0.048
Hemothorax requiring drainage	1	0.1	0.048
Bile peritonitis	1	0.1	0.048
Periprocedual (within 30 days)			
Hepatic abscess requiring drainage	7	0.7	0.34
Bronchobiliary fistula	2	0.2	0.096
Duodenal perforation	1	0.1	0.048
Colonic penetration	1	0.1	0.048
Gastric penetration	1	0.1	0.048
Delayed			
Neoplastic seeding	15	1.5	0.72
Total	40	4.0	1.9

RFA: radiofrequency ablation.

TABLE 3
Minor Complications after RFA

Complications	No. of complications	Prevalence (%) Per treatment	Per session
Immediate (within 24 hrs)			
Self-limiting hemobilia	3	0.3	0.14
Skin burn (entrance point)	3	0.3	0.14
Periprocedual (within 30 days)			
Self-limiting portal vein thrombosis	4	0.4	0.19
Delayed			
Biloma	7	0.7	0.34
Total	17	1.7	0.82

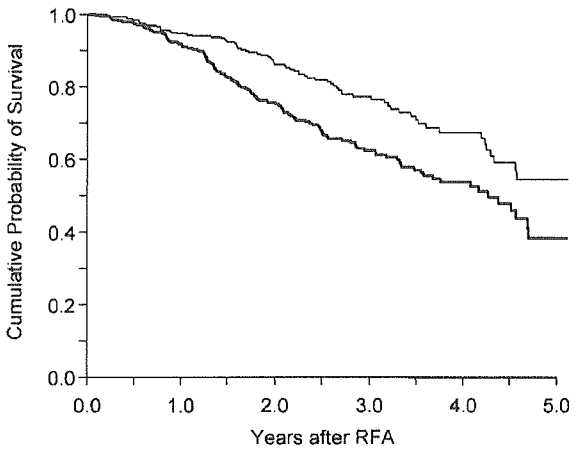
RFA: radiofrequency ablation.

for tumor recurrence, the total number of treatments (cases) received was 1000.

Treatment Efficacy and Complications

One thousand treatments to 664 patients consisted of 2082 sessions of RFA to 2140 nodules. The distribution of nodules was as follows: 367 nodules (17.1%) in the lateral segment, 238 (11.1%) in the medial segment, 891 (41.6%) in the anterior segment, 609 (28.5%) in the posterior segment, and 35 (1.6%) in the caudate lobe. The mean number of electrode insertions according to tumor size are as follows: 1.5 times for nodules < 2 cm, 2.3 times for nodules 2.1–3.0 cm, 4.2 times for nodules 3.1–5.0 cm, and 11.7 times for nodules > 5 cm. One hundred thirty-seven of 319 naive patients and 145 of 345 nonnaive patients received TAE before RFA. All nodules were ablated completely in 934 treatments. RFA was performed for debulking the tumor burden in the remaining 66 treatments. The α-fetoprotein (AFP) declined to < 100 ng/mL in 184 of 247 treatments (74.4%) in which the pretreatment AFP level was > 100 ng/mL. DCP normalized (≤ 40 mAU/mL) in 279 of 326 treatments (85.6%).

A total of 40 major complications (4.0% per treatment, 1.9% per session) and 17 minor complications (1.7% per treatment, 0.82% per session) were observed within the follow-up period (Tables 2, 3). There were no complication-related deaths. Side effects such as moderate pain controlled by analgesics, nausea, or infection-unrelated fever relieved by antifebriles were



No. at risk						
Naive	319	301	206	99	46	7
Others	345	314	196	102	49	5

FIGURE 1. The cumulative survival rates of naive (thin line) and nonnaive (thick line) patients who received radiofrequency ablation (RFA). The cumulative survival rates estimated by the Kaplan–Meier method at 1, 2, 3, 4, and 5 years were 94.7%, 86.1%, 77.7%, 67.4%, and 54.3% for naive patients and 91.8%, 75.6%, 62.4%, 53.7%, and 38.2% for nonnaive patients, respectively.

not included. As for major complications, intraperitoneal hemorrhage was observed in four patients. In one patient, bleeding was detected during RF exposure, and arterial hemorrhage was identified by color Doppler ultrasonography. We reablated the needle track to stop the bleeding. The remaining three patients recovered after transfusion under careful observation. Hepatic infarction, defined as an increase in serum aspartate aminotransferase levels > 1000 IU/mL and/or an appearance of a wedge-shaped hypoattenuated area no smaller than a subsegment by dynamic CT scan, occurred in 2 patients. Both recovered spontaneously, although they suffered from high-grade fever lasting for 1–2 weeks. Hepatic abscess formation was found in seven patients and percutaneous drainage was performed in all. Two of them were complicated with bronchobiliary fistula and recovered after endoscopic biliary drainage. Intestinal perforation/penetration (duodenum, stomach, or colon) was observed after ablation in three patients. One patient with duodenal perforation was complicated with peritonitis and treated by surgical intervention. Colonic penetration occurred in one patient after hepatic abscess. The abscess was treated by percutaneous drainage and the anastomosis to the colon was closed by colonoscopic procedure. The patient with gastric penetration recovered with total parenteral nutrition without surgical intervention. In 1 patient, bile peritonitis occurred approximately 12 hours after RFA, requiring surgical and endoscopic biliary drainage. The patient showed intrahepatic bile duct dilatation before RFA, probably due to bile duct damage by previous PMCT.

When the 1000 treatments were divided into 2 groups as the earlier 500 and the later 500, there was a trend toward a decrease in the rates of immediate and periprocedual major complications (from 3.4% to 1.6% per treatment, $P = 0.105$ by chi-square test).

As a late complication, carcinoma seeding was identified in 15 patients with a median occult period of 17 months after the last ablation (range, 2–28 months). The area of tumor seeding was localized in nine patients and was surgically resected. Microwave coagulation was performed under thoracoscopic guidance in one patient with dissemination to the pleura. One patient with localized spread of tumor received radiotherapy. Two patients with intraperitoneal tumor spread were treated by systemic chemotherapy. The remaining two patients received best supportive care, as their liver function was impaired severely.

Long-Term Outcomes

Of the 664 patients included in the current series, 203 had died by March 31, 2004. Eight patients (1.2%) were lost to follow-up. The median observation period was 2.3 years (range, 0.17–5.1 years). Causes of death were cancer progression in 136 patients, hepatic failure in 36 patients, upper gastrointestinal bleeding in 8 patients, and liver-unrelated causes in 23 patients. The cumulative survival rates estimated by the Kaplan–Meier method at 1, 2, 3, 4, and 5 years were 94.7%, 86.1%, 77.7%, 67.4%, and 54.3% for naive patients whereas the respective rates were 91.8%, 75.6%, 62.4%, 53.7%, and 38.2% for nonnaive patients, respectively (Fig. 1). Significant differences were observed in subgroups divided by Child–Pugh class ($P = 0.000388$), tumor size ($P = 0.000234$), AFP level ($P = 0.0103$), and DCP ($P = 0.00000473$; Fig. 2 and Table 4). There was no significant difference in subgroups divided by age ($P = 0.378$), gender ($P = 0.921$), etiology of background liver disease ($P = 0.909$), number of tumors ($P = 0.464$) or pathologic grade ($P = 0.111$).

Tumor recurrence was identified in 165 of 306 patients. The median observation period for tumor recurrence was 1.59 years (range, 0.12–4.98 years). Of 165 patients with tumor recurrence, 142 (86.1%) had ≤ 3 recurrent nodules. Among these 142 patients, 137 were treated by second RFA, 4 by ethanol injection, and 1 by hepatic resection. Most of the remaining 23 patients with multiple recurrent nodules (> 3) were treated by TAE. Cumulative probabilities of tumor recurrence at 1, 2, 3, and 4 years were 20.4%, 43.4%, 59.8%, and 65.9%, respectively. Cumulative probabilities of death without tumor recurrence at 1, 2, 3, and 4 years were 3.9%, 7.0%, 8.7%, and 10.9%, respectively

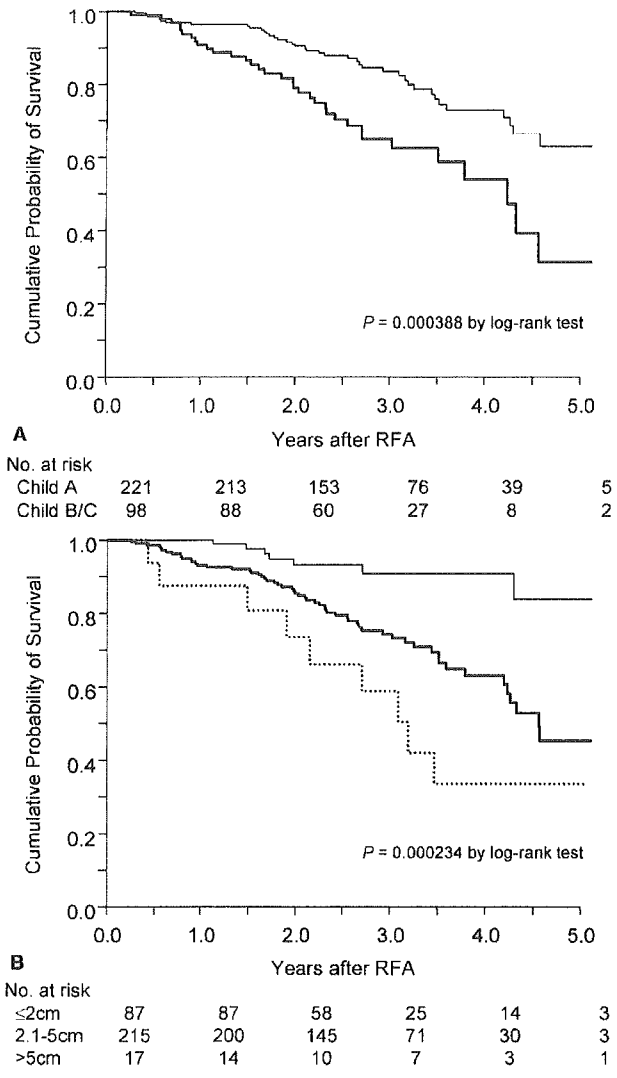


FIGURE 2. Cumulative survival rates of naive patients divided by (A) Child–Pugh Class and (B) tumor size. (A) The cumulative survival rates at 1, 2, 3, 4, and 5 years were 96.4%, 90.4%, 83.4%, 72.9%, and 63.1% for Child–Pugh A patients (thin line) and 90.7%, 79.0%, 65.0%, 53.9%, and 31.4% for Child–Pugh B/C patients (thick line), respectively. (B) The cumulative survival rates at 1, 2, 3, 4, and 5 years were 100%, 93.2%, 90.8%, 90.8%, and 83.8% for patients with tumors ≤ 2 cm (thin line), 93.0%, 85.4%, 74.3%, 63.0%, and 45.2% for patients with tumors 2.1–5.0 cm (thick line), and 87.5%, 73.4%, 58.7%, 33.6%, and 33.6% for patients with tumors > 5.0 cm (dashed line), respectively. RFA: radiofrequency ablation.

(Fig. 3A). When the patients were divided by Child–Pugh class, there was no significant difference in overall recurrence rate between Class A and Class B/C patients ($P = 0.38$ by Gray's test), whereas a significant difference in death without tumor recurrence was observed between the 2 groups ($P = 0.0026$; Fig. 3B). Cumulative probabilities of local tumor progression at 1, 2, 3, and 4 years were 1.3%, 2.4%, 2.4%, and 2.4%, respectively. (Fig. 4). No extrahepatic metastasis was observed in these 306 patients except for 2 patients with neoplastic seeding.

TABLE 4
Three-Year Survival of Patients with HCC Treated by RFA

Parameter	No. of patients	3-Year survival rate (95% CI)	*P* value
Overall	319	77.7 (72.4–83.2)	
Age (yrs)			
>68	159	76.0 (68.5–84.2)	0.378
≤68	160	79.2 (72.1–87.1)	
Gender			0.921
Male	212	77.7 (71.5–84.5)	
Female	127	77.1 (67.8–87.8)	
Etiology			0.909
HBs-Ag positive only	30	80.5 (66.3–97.8)	
HCV-Ab positive only	252	78.3 (72.5–84.6)	
Both negative	33	70.8 (54.1–92.6)	
Child-Pugh class			0.000388
A	221	83.4 (77.7–89.5)	
B/C	98	65.0 (54.9–76.3)	
Tumor size (cm)			0.000234
≤2.0	87	90.8 (83.8–98.4)	
2.1–5.0	215	74.3 (67.7–81.5)	
>5.1	17	58.7 (38.0–90.8)	
Tumor no.			0.464
Single	193	77.3 (70.1–85.2)	
2–3	105	77.5 (69.2–86.9)	
>3	21	67.5 (48.6–93.6)	
Edmondson grade			0.111
1	61	83.7 (72.6–96.7)	
2	214	76.9 (70.5–93.9)	
3	27	66.0 (48.9–89.1)	
AFP (ng/mL)			0.0103
≤100	238	82.3 (76.9–88.1)	
101–400	47	72.2 (58.6–88.8)	
>400	34	47.6 (28.6–79.4)	
DCP (mAU/mL)			0.00000473
≤40	225	86.3 (81.4–91.5)	
41–100	36	62.4 (46.6–83.4)	
>100	58	56.1 (42.4–74.4)	

HCC: hepatocellular carcinoma; RFA: radiofrequency ablation; HBsAg: hepatitis B surface antigen; HCV-Ab: hepatitis C virus antibody; AFP: α-fetoprotein; DCP: des-gamma carboxyprothrombin.

DISCUSSION

In the current study, we have shown that RFA is a safe and effective strategy for the treatment of HCC. The incidence of major complications within 30 days after the procedure was satisfactorily low (2.5% per treatment), and there were no treatment-related deaths.

As an immediate complication, intraperitoneal bleeding is a potentially fatal condition. Thus, a careful estimation of the underlying coagulopathy is important to avoid hemorrhage. We set the minimum of prothrombin time and platelet count for the indica-

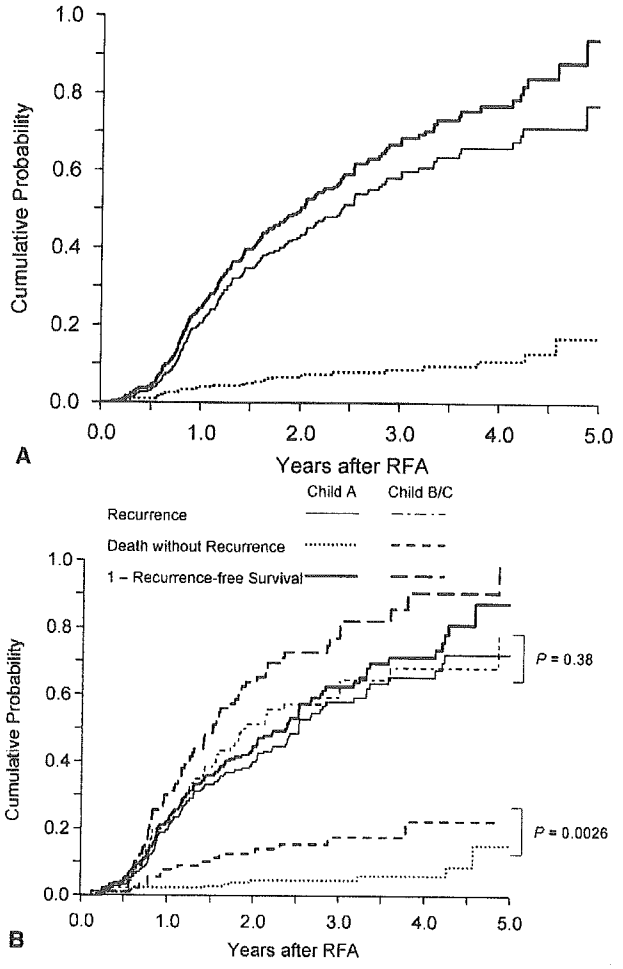


FIGURE 3. (A) Cumulative probabilities of tumor recurrence (thin line) and death without tumor recurrence (dotted line) of patients who received radiofrequency ablation (RFA) as initial treatment for hepatocellular carcinoma (HCC). The sum of the 2 probabilities is equivalent to 1 – tumor recurrence-free survival (thick line). (B) Cumulative probabilities of tumor recurrence and death without tumor recurrence of patients who received RFA as initial treatment for HCC divided by Child–Pugh class. There were significant differences between the cumulative probabilities of death without tumor recurrence of Child–Pugh A and Child–Pugh B/C patients, whereas no significant difference was observed between the cumulative tumor recurrence probabilities.

tion of RFA at higher levels (> 50% and > 5.0×10^4/mm^3) than those for PEIT.[12] The observed frequency of peritoneal bleeding (0.4% per treatment) was similar to that previously reported (0.3–0.5%).[22,23,30] Gastrointestinal perforation, another potentially fatal complication, can occur when the target nodule is located adjacent to the intestine, especially when the patients have a previous history of gastrointestinal surgery.[22,23] The observed frequency of gastrointestinal perforation/penetration (0.3% per treatment) was the same as previously reported, although none of

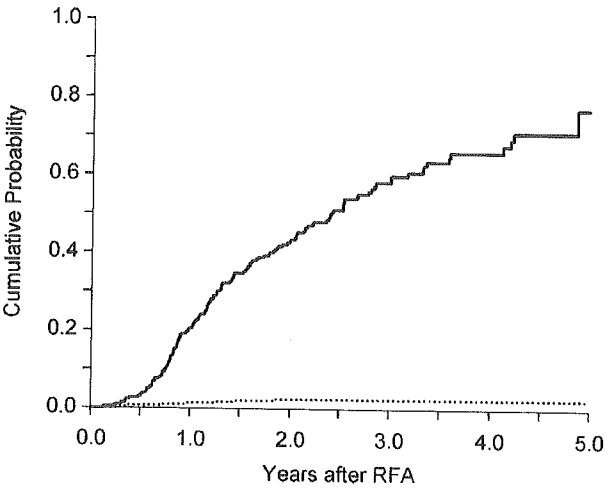


FIGURE 4. Cumulative probabilities of overall tumor recurrence (solid line) and local tumor progression (dotted line). RFA: radiofrequency ablation.

those patients had a history of surgery. We recently introduced an intraperitoneal infusion technique, by which 500–1000 mL of 5% glucose solution is injected before and during the ablation for the purpose of creating space between the lesion and the intestine. The efficacy of this procedure is yet to be assessed fully.

It is well understood that the risk of complications can be reduced by proficiency in technique and refinement in pretreatment assessments. We observed a trend toward a decrease in the rates of immediate and periprocedual complications (from 3.4% to 1.6% per treatment). Conversely, we encountered an increase in the number of patients with neoplastic seeding. The main reason for that is the prolonged follow-up period because the majority of those patients were identified > 17 months after the last ablation. The rate of neoplastic seeding (1.5%) was higher than that previously reported (0.2–0.5%), although it was still very low compared with the value (12.5%) reported by Llovet et al.[31] The high incidence of seeding was likely to be related directly to the finding that tract cauterization was not performed.[23] Another possible reason is the tumor biopsy we performed in most of the patients to obtain the pathologic confirmation.[32]

The overall tumor recurrence rate for RFA in the current study was compatible with that of PEIT and hepatectomy.[33–35] The local tumor progression rate was 2.4% during a median of 19 months of follow-up, a very low rate compared with that reported elsewhere. Local tumor progression after RFA occurs mainly at the surrounding tissue.[36,37] To completely ablate a tumor ≥ 2 cm in diameter with a sufficient safety margin, multiple electrode insertion is neces-

sary by the 3-cm–exposed electrode. Thus, we decided to perform TAE with Lipiodol to tumors > 2 cm to delineate the border of the tumors at the CT scan for treatment evaluation after ablation. We tried to make sure that the entire tumor was surrounded as completely as possible by a nonenhanced area on an evaluation CT scan. It is known that occlusion of arterial flow during RFA significantly enlarges the zone of coagulation.[38,39] Our results for local tumor progression rate may be contributed by the effect although the exact impact of this confounding factor is precisely unknown when RFA is performed > 7 days after embolization (as we did) compared with when it is performed immediately (within 3 days) after embolization.

Louha et al.[40,41] reported on the likelihood of spreading cancer cells into peripheral blood by liver resection, ethanol injection, and transarterial embolization. However, the risk of hematogenous dissemination of HCC cells is negligible, because most patients had three or fewer nodules at HCC recurrence, and extrahepatic metastasis was rare in our patient series.

RFA can be repeated in patients with tumor recurrence as long as liver function is relatively intact. The finding that the majority of patients with tumor recurrence underwent RFA indicates that the initial RFA was not so invasive as to seriously damage liver function. As a locoregional therapy, RFA does not prevent de novo carcinogenesis in the remnant liver with chronic viral infection. Another strategy including viral eradication is needed to prevent overall tumor recurrence.[42]

The prognosis of patients with HCC is dependent mainly on tumor characteristics and liver function also in case of RFA. Patients with severely impaired liver function may not be eligible for RFA. The poorer survival among Child–Pugh Class B and C patients indicates that other strategies including OLT should be considered for longer survival.

RFA is a safe and effective method with satisfactory curability at least locally, and it can be repeated against tumor recurrence. The 5-year survival rate may be better than that previously reported for ethanol injection[11,43] and is obviously better than that of natural course.[44,45] Thus, RFA can be the first choice in the treatment of small HCC, although further follow-up will be necessary for the assessment of longer survival.

REFERENCES

1. Di Bisceglie AM, Rustgi VK, Hoofnagle JH, Dusheiko GM, Lotze MT. NIH conference. Hepatocellular carcinoma. *Ann Intern Med.* 1988;108:390–401.
2. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med.* 1999;340:745–750.
3. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. *Semin Surg Oncol.* 1993;9:298–304.
4. Fan ST, Ng IO, Poon RT, Lo CM, Liu CL, Wong J. Hepatectomy for hepatocellular carcinoma: the surgeon's role in long-term survival. *Arch Surg.* 1999;134:1124–1130.
5. Shiratori Y, Shiina S, Imamura M, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C-viral infection in Japan. *Hepatology.* 1995;22(4 Pt. 1):1027–1033.
6. Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of hepatocarcinogenesis by interferon Therapy. *Ann Intern Med.* 1999;131:174–181.
7. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334:693–699.
8. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology.* 1999;30:1434–1440.
9. Sarasin FP, Giostra E, Mentha G, Hadengue A. Partial hepatectomy or orthotopic liver transplantation for the treatment of resectable hepatocellular carcinoma? A cost-effectiveness perspective. *Hepatology.* 1998;28:436–442.
10. Higuchi T, Kikuchi M, Okazaki M. Hepatocellular carcinoma after transcatheter hepatic arterial embolization. A histopathologic study of 84 resected cases. *Cancer.* 1994;73:2259–2267.
11. Livraghi T, Giorgio A, Marin G, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology.* 1995;197:101–108.
12. Shiina S, Tagawa K, Niwa Y, et al. Percutaneous ethanol injection therapy for hepatocellular carcinoma: results in 146 patients. *AJR Am J Roentgenol.* 1993;160:1023–1028.
13. Ishii H, Okada S, Nose H, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer.* 1996;77:1792–1796.
14. Sato S, Shiratori Y, Imamura M, et al. Power Doppler signals after percutaneous ethanol injection therapy for hepatocellular carcinoma predict local recurrence of tumors: a prospective study using 199 consecutive patients. *J Hepatol.* 2001;35:225–234.
15. Rossi S, Di Stasi M, Buscarini E, et al. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. *AJR Am J Roentgenol.* 1996;167:759–768.
16. Allgaier HP, Deibert P, Zuber I, Olschewski M, Blum HE. Percutaneous radiofrequency interstitial thermal ablation of small hepatocellular carcinoma. *Lancet.* 1999;353:1676–1677.
17. Curley SA, Izzo F, Delrio P, et al. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. *Ann Surg.* 1999;230:1–8.
18. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology.* 1999;210:655–661.

19. Curley SA, Izzo F, Ellis LM, Nicolas Vauthey J, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. *Ann Surg.* 2000;232:381–391.
20. Lorentzen T. A cooled needle electrode for radiofrequency tissue ablation: thermodynamic aspects of improved performance compared with conventional needle design. *Acad Radiol.* 1996;3:556–563.
21. Goldberg SN, Gazelle GS, Halpern EF, Rittman WJ, Mueller PR, Rosenthal DI. Radiofrequency tissue ablation: importance of local temperature along the electrode tip exposure in determining lesion shape and size. *Acad Radiol.* 1996;3: 212–218.
22. Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. *Radiology.* 2003;226:441–451.
23. de Baere T, Risse O, Kuoch V, et al. Adverse events during radiofrequency treatment of 582 hepatic tumors. *AJR Am J Roentgenol.* 2003;181:695–700.
24. Goldberg SN, Charboneau JW, Dodd GD 3rd, et al. Image-guided tumor ablation: proposal for standardization of terms and reporting criteria. *Radiology.* 2003;228:335–345.
25. Edmondson HA, Steiner PE. Primary carcinoma of the liver. A study of 100 cases among 4900 necropsies. *Cancer.* 1954; 7:462–503.
26. Ishikawa T, Shiina S, Teratani T, et al. Efficasy and safety of percutaneous radiofrequency ablation therapy with intrapleural infusion technique for the patients with hepatocellular carcinoma in the hepatic dome [abstract]. *Gastroenterology.* 2002;122(4 Suppl. 1):A661.
27. Goldberg SN, Gazelle GS, Solbiati L, Rittman WJ, Mueller PR. Radiofrequency tissue ablation: increased lesion diameter with a perfusion electrode. *Acad Radiol.* 1996;3:636–644.
28. Goldberg SN, Stein MC, Gazelle GS, Sheiman RG, Kruskal JB, Clouse ME. Percutaneous radiofrequency tissue ablation: optimization of pulsed-radiofrequency technique to increase coagulation necrosis. *J Vasc Interv Radiol.* 1999;10: 907–916.
29. Gray R. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16:1141–1154.
30. Mulier S, Mulier P, Ni Y, et al. Complications of radiofrequency coagulation of liver tumours. *Br J Surg.* 2002;89: 1206–1222.
31. Llovet JM, Vilana R, Bru C, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. *Hepatology.* 2001;33: 1124–1129.
32. Livraghi T, Goldberg SN, Gazelle GS, Lazzaroni S, Meloni MF, Solbiati L. The risk of tumor seeding after percutaneous RF ablation in HCC [abstract]. *Radiology.* 2002;225(Suppl.): 490.
33. Ikeda K, Saitoh S, Tsubota A, et al. Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. *Cancer.* 1993;71:19–25.
34. Okada S, Shimada K, Yamamoto J, et al. Predictive factors for postoperative recurrence of hepatocellular carcinoma. *Gastroenterology.* 1994;106:1618–1624.
35. Koike Y, Shiratori Y, Sato S, et al. Risk factors for recurring hepatocellular carcinoma differ according to infected hepatitis virus—an analysis of 236 consecutive patients with a single lesion. *Hepatology.* 2000;32:1216–1223.
36. Shiina S, Tagawa K, Unuma T, et al. Percutaneous ethanol injection therapy for hepatocellular carcinoma. A histopathologic study. *Cancer.* 1991;68:1524–1530.
37. Chopra S, Dodd GD 3rd, Chintapalli KN, Leyendecker JR, Karahan OI, Rhim H. Tumor recurrence after radiofrequency thermal ablation of hepatic tumors: spectrum of findings on dual-phase contrast-enhanced CT. *AJR Am J Roentgenol.* 2001;177:381–387.
38. Buscarini L, Buscarini E, Di Stasi M, Quaretti P, Zangrandi A. Percutaneous radiofrequency thermal ablation combined with transcatheter arterial embolization in the treatment of large hepatocellular carcinoma. *Ultraschall Med.* 1999;20: 47–53.
39. Rossi S, Garbagnati F, Lencioni R, et al. Percutaneous radiofrequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. *Radiology.* 2000;217:119–126.
40. Louha M, Poussin K, Ganne N, et al. Spontaneous and iatrogenic spreading of liver-derived cells into peripheral blood of patients with primary liver cancer. *Hepatology.* 1997;26:998–1005.
41. Louha M, Nicolet J, Zylberberg H, et al. Liver resection and needle liver biopsy cause hematogenous dissemination of liver cells. *Hepatology.* 1999;29:879–882.
42. Shiratori Y, Shiina S, Teratani T, et al. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med.* 2003;138:299–306.
43. Shiina S, Teratani T, Obi S, Hamamura K, Koike Y, Omata M. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. *Oncology.* 2002;62(Suppl. 1):64–68.
44. Livraghi T, Bolondi L, Buscarini L, et al. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. Italian Cooperative HCC Study Group. *J Hepatol.* 1995;22:522–526.
45. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology.* 1999;29:62–67.

Ablation Therapy in Containing Extension of Hepatocellular Carcinoma: A Simulative Analysis of Dropout From the Waiting List for Liver Transplantation

Noriyo Yamashiki, Ryosuke Tateishi, Haruhiko Yoshida, Shuichiro Shiina, Takuma Teratani, Shinpei Sato, Norio Mine, Yuji Kondo, Takao Kawabe, and Masao Omata

The dropout from the waiting list for liver transplantation among patients with hepatocellular carcinoma (HCC) is reportedly as high as 12% to 40% per year, mostly due to tumor progression. Considering the scarcity of donor organs, it would be beneficial if we could retain them within the Milan criteria with a bridging therapy. We retrospectively analyzed the prognosis of 288 HCC patients with relatively preserved liver function we treated with ablation therapy between 1997 and 2001, concentrating on whether they subsequently remained in the criteria, and analyzed the risk factors of dropout with Cox proportional hazards model. During a median follow-up period of 39 months (range, 1-86 months), 33 (11%) died without tumor progression, while 85 (30%) dropped out due to tumor progression. The overall dropout rate was 9.0% and 32.8% at 1 and 3 years, respectively, and that due to tumor progression was 6.2% and 23.0%. Cox regression analysis indicated that a high serum level of alpha-fetoprotein or des-γ-carboxy prothrombin, and a tumor size exceeding 3 cm in diameter affected the dropout due to tumor progression, while low albumin concentration was a risk factor of death independently of tumor progression. In conclusion, local ablation therapy for HCC was effective in containing the tumor progression within the Milan criteria in selected patients. (*Liver Transpl 2005;11: 508-514.*)

Orthotopic liver transplantation is an ideal therapy, at least theoretically, for patients with hepatocellular carcinoma (HCC) complicated with cirrhosis, and it could treat both cancer and impaired liver function simultaneously. Survival of patients with HCC, meeting certain conditions, after liver transplantation is reportedly similar to that of patients without HCC.[1-6] Recent proposals submitted in Europe and also in the United States indicated that the optimal candidates for liver transplantation are patients with HCC within "Milan criteria"; i.e., a single nodule smaller than 5 cm in diameter or less than 4 nodules with the maximum size smaller than 3 cm.[2,3,7] In a report of Mazzaferro and associates, a high rate of recurrence-free survival after transplantation was observed in selected group of patients with small tumors. Similar results were also demonstrated by other groups, with 3-year survival being >70%. More recent report from the international tumor registry showed that tumor size >5 cm, positive node metastasis, bilobar distribution of tumor lesions, and vascular invasion were associated with tumor recurrence after transplantation.[8]

However, the increasing number of candidates for liver transplantation is surpassing the number of cadaveric donor organs, and the relative shortage has substantially prolonged the waiting time for liver transplantation.[9,10] The organ allocation system in the United States, the Model for End-Stage Liver Disease (MELD), has been revised so that patients with early HCC are now given higher priority.[7,11-14] Nevertheless, tumor progression during the waiting time may contraindicate transplantation, which is still a major cause of dropout from the waiting list.[10,11,15]

Various attempts have been made to reduce the dropout during waiting time by applying adjuvant therapies for HCC. Recent reports showed effectiveness of chemoembolization,[16,17] and partial hepatectomy has been performed on cases with preserved liver function, to be followed by liver transplantation as the salvage.[18,19] Local ablation therapies for HCC—namely, percutaneous ethanol injection (PEI), microwave coagulation therapy, and radiofrequency ablation (RFA)—can be performed in the presence of compensated cirrhosis,[20-22] and previous studies showed safety and effectiveness of tumor ablation in pretransplant HCC patients.[23,24]

Abbreviations: HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; RR, risk ratio; CI, confidence interval.

From the Department of Gastroenterology, University of Tokyo, Graduate School of Medicine, Tokyo, Japan.

Address reprint requests to Noriyo Yamashiki, MD, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. Telephone: 81-3-3815-5411; FAX: 81-3-3814-0021; E-mail: nyamashiki-gi@umin.ac.jp

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lt.20392

Table 1. Baseline Demographics and Tumor Characteristics of 288 Patients

Factors	Value
Age, yrs, mean (range)	66 (41-86)
Gender, male/female	177 (61.5%)/111 (38.5%)
Etiology of liver disease	
Hepatitis C	229 (79.5%)
Hepatitis B	34 (11.8%)
Alcohol (with/without viral hepatitis)	52 (18.1%)
Cryptogenic	11 (3.8%)
Blood type (A/B/O/AB)	91/42/65/30 (60 unknown)
AFP ng/dL, median (range)	18 (1-16,709)
DCP mAU/mL, median (range)	22 (10-15,654)
Serum albumin (g/dL) mean ± SD	3.6 ± 0.4
Serum bilirubin (mg/dL) mean ± SD0	0.9 ± 0.4
Prothrombin time (INR) mean ± SD	1.2 ± 0.1
Serum creatinine (mg/dL) mean ± SD0	0.7 ± 0.3
Ascites	34 (11.8%)
Hepatic encephalopathy	9 (3.1%)
Child-Turcotte-Pugh classification, A/B/C	207 (71.9%)/77 (26.7%)/4 (1.4%)
MELD score (range)	9 (6-15)
Size (cm), mean ± SD	2.3 ± 0.8
Number of tumors, 1/2/3	210/58/20
Primary treatment, PEI/MCT/RFA	118/22/158
Histologic grade, I/II/III/IV	59/140/20/2

Abbreviations: AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PEI, percutaneous ethanol injection; mAU, micro arbitrary unit; MCT, microwave coagulation therapy; RFA, radiofrequency ablation.

In Japan, cadaveric liver transplantation has rarely been performed because of extreme scarcity of deceased organ donors. Living donor liver transplantation is frequently performed on adult recipients with HCC and cirrhosis, but suitable donors are not always available.[25,26] Thus, when hepatic resection is contraindicated by impaired liver function, local tumor ablation is the only possibly curative treatment in most cases. The authors have performed local ablation therapy for HCC on more than 1,000 HCC patients.[22] Although most of these patients were not intended to and did not undergo liver transplantation, the observation among this cohort may be used to validate the local ablation therapy as pretransplantation bridging therapy to reduce dropout. In this study, we simulated the dropout rate from the waiting list for liver transplantation after HCC ablation based on the actual observation of tumor progression. We also analyzed the factors affecting the outcome.

Patients and Methods

Selection of Subjects

Between January 1997 and December 2001, 458 consecutive patients were admitted for the evaluation and treatment of naive HCC at the Department of Gastroenterology, University of Tokyo Hospital. The diagnosis of HCC was confirmed on the findings of contrast-enhanced computed tomography or magnetic resonance imaging, and percutaneous ultrasound-guided tumor biopsy was performed when indicated. Of those 458 patients, 302 had HCC within the Milan criteria, i.e., a solitary nodule smaller than 5 cm in diameter or less than four nodules all smaller than 3 cm. Two cases received surgical resection, 9 received transcatheter arterial embolization because of impaired liver function, and 3 received no treatment. The remaining 288 patients received percutaneous ablation therapy as the initial treatment for HCC and constituted the subjects of this study. The selection criteria for local ablation therapy were as follows: absence of vascular or biliary invasion, absence of uncontrollable ascites, total bilirubin level lower than 3 mg/dL, prothrombin time greater than 50%, and platelet count greater than 50,000 mm^3. In 1997 and 1998, PEI or microwave coagulation therapy was used for ablation; we used RFA after the modality became available in Japan in 1999. As a result, 108 patients underwent PEI, 15 underwent microwave coagulation therapy, 155 underwent RFA, and 10 underwent more than one modality. The baseline characteristics of patients are shown in Table 1.

Initial Ablation and Follow-Up

Each ablation therapy was performed as described elsewhere.[22] HCC was histologically confirmed through ultra-

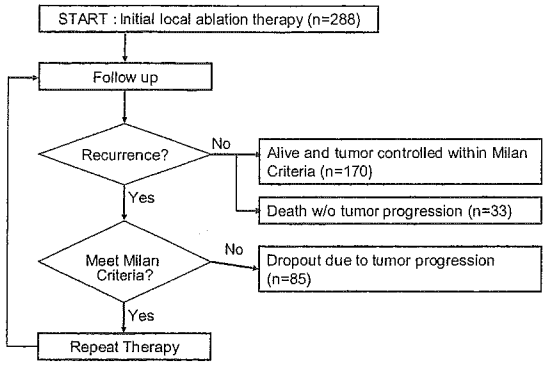


Figure 1. Study design. After initial local ablation therapy, all patients were followed periodically until February 29, 2004. At the detection of recurrence, those patients with recurrence tumor within Milan criteria underwent repeated tumor ablation therapy, while those with recurrence tumor extent beyond Milan criteria were considered as dropout. Death without tumor progression was also considered as an event: dropout due to death.

sound-guided biopsy in 221 patients, while the diagnosis was made on the basis of typical angiographic findings in the others. Histologic grade was assessed using Edmondson and Steiner's classification.[27] We confirmed complete ablation of all detectable HCC nodules by subsequently taking contrast-enhanced computed tomography or magnetic resonance imaging. After the initial treatment, each patient was followed up with blood tests for liver function and HCC biomarkers every 1 to 2 months, with abdominal ultrasound every 3 months, and with contrast-enhanced computed tomography or magnetic resonance imaging whenever indicated. Whether the recurrence was a new focus or local tumor progression (i.e., local reappearance of viable HCC after radiographically complete initial ablation) was assessed radiographically on a lesion-by-lesion basis.[28] When HCC recurrence was detected, local ablation therapy was repeated when both HCC extent and liver function met our criteria for ablation therapy; otherwise, surgical resection, transcatheter arterial embolization, or chemotherapy was considered.

Statistics

In the analysis of virtual dropout from the waiting list for liver transplantation, either tumor progression beyond the Milan criteria or death, whichever came first, was considered the event. The follow-up was terminated when a patient showed HCC recurrence beyond the Milan criteria, although in reality treatment was repeated as long as the conditions remained within the local ablation criteria. If the recurrence was within the transplantation criteria, we continued follow-up until viable HCC progressed beyond the criteria or the patient died. Risk factors for tumor progression beyond the Milan criteria or those for death without tumor progression were analyzed by using Cox proportional hazards regression model independently for tumor progression and death. Only those variables that showed P value < 0.1 in univariate analysis were analyzed in multivariate analysis. As death and tumor progression beyond Milan criteria are "competing risks," we used cumulative incidence estimation with competing risks for the analysis of cumulative recurrence as described by Gray et al.[15,29-31] Because dropout rate may be affected by liver function, univariate and multivariate analyses were repeated by liver function stratification analysis; patients with Child-Turcotte-Pugh class A and Child-Turcotte-Pugh class B or C were compared.[32] The difference in the risk ratio among subgroups was tested by the log-rank test. Correlation among the risk factors was evaluated with Pearson's correlation coefficient, with logarithmic transformation of highly skewed variables. All statistical analyses were performed with S-plus 2000 (MathSoft Inc., Seattle, WA).

Results

Probability of Dropout

The median follow-up period was 39.1 months (range, 46 days to 86.2 months, a minimum of 10 months for a censored patient). During the follow-up, HCC recurrence was diagnosed at least once in 163 cases (56.6%). Local tumor progression was seen in 5 cases during the follow-up period. Four of them were found within the Milan criteria and successfully treated with local ablation. Eighty-five patients (29.5%), including one with local tumor progression, had revealed tumor progression beyond the Milan criteria, 33 (11.5%) had died without tumor progression, and 170 (59.0%) were alive without viable HCC or with recurrent HCC controlled within the Milan criteria. The cumulative incidence of dropout from the fictitious transplantation waiting list is shown in Figure 2, where the overall dropout rate at 1, 3, and 5 years was 9.0%, 32.8%,

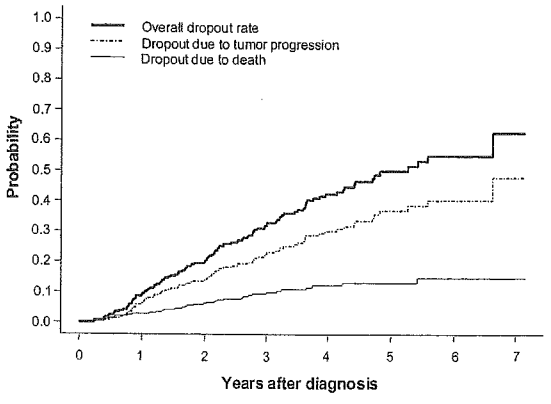


Figure 2. Cumulative probability of dropout. Overall probability of dropout is shown as a heavy solid line. This consists of two separate events: death without tumor progression (thin solid line), and dropout due to tumor progression (dotted line).

Table 2. Results of Stepwise Cox Regression Analysis

Factors	Dropout due to tumor progression		Death without tumor progression	
	Univariate analysis, *P*	Multivariate analysis *P* (RR, 95% CI)	Univariate analysis, *P*	Multivariate analysis *P* (RR, 95% CI)
Age >65 years	0.40		0.064	
Male gender	0.79		0.371	
HCV Ab positive	0.36		0.156	
HBs Ag positive	0.67		0.252	
AFP >100 ng/mL	<0.001	0.007 (1.917, 1.190-3.088)	0.294	
DCP >100 mAU/mL	<0.001	0.004 (2.195, 1.278-3.770)	0.083	
Bilirubin >1 mg/dL	0.441		0.177	
Albumin <3.5 g/dL	0.023		<0.001	0.002 (3.968, 1.668-9.438)
Prothrombin time (INR)	0.329		0.086	
Size >3.0 cm	0.001	0.021 (1.841, 1.095-3.095)	0.635	
≥2 tumor nodules	0.403		0.281	
Child-Turcotte-Pugh B/C (vs. A)	0.398		<0.001	<0.001 (3.761, 1.892-7.475)*
Ascites	0.665		<0.001	0.033 (2.391, 1.074-5.324)
PEI	0.219		0.063	
RFA	0.449		0.280	
MCT	0.124		0.850	
Histologic grade III/IV (vs. I/II)	0.286		0.375	

Abbreviations: RR, risk ratio; CI, confidence interval; HCV Ab, hepatitis C virus antibody; HBs Ag, hepatitis B surface antigen; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin; mAU, micro arbitrary unit; INR, international normalized ratio; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; MCT, microwave coagulation therapy.
*Child-Turcotte-Pugh class B/C was the only significant factor when associated factors (serum albumin, bilirubin, ascites, and prothrombin time) were removed from the multivariate analysis.

and 49.8%, respectively. The cumulative incidence of dropout due to tumor progression was 6.2%, 23.0%, and 36.9% at 1, 3, and 5 years, respectively, and that due to death without tumor progression was 2.7%, 9.8%, and 12.9%, respectively.

Causes of Failure

The causes of Milan criteria violation were as follows: an increase in the number of HCC lesions in 43, an increase in lesion size in 22, portal vein tumor invasion in 8, distant metastasis in 7, tumor seeding in 4, tumor rupture in 1, and bile duct invasion in 1. The violation occurred at the first recurrence in 55, at the second in 18, at the third in 8, and at a later recurrence in 4. Each recurrence within the criteria was treated by means of local ablation therapy. Among 33 deaths without tumor progression beyond the Milan criteria, 17 were liver related (14 from liver failure and 3 from esophageal variceal rupture) and the remaining 16 were liver unrelated, including 5 from cerebrovascular diseases and 2 from extrahepatic neoplasms. In addition, 48 patients died after dropout due to tumor progression (42 from HCC, 3 from liver failure, 1 from esophageal variceal rupture, and 2 from other diseases). Overall survival rate and 95% confidence interval, as calculated by the Kaplan-Meier method, were 96% ± 2%, 79% ± 4%, and 67% ± 8% at 1, 3, and 5 years, respectively.

Patients Without Failure

Among 170 patients who remained at risk at the end of the study, 97 showed no HCC recurrence while 73 had at least one episode of recurrence (once in 45, twice in 16, three times in 8, four times in 3, and five times in 1), all of which had been treated with local ablation therapy.

Risk Factors for Dropout From the List

Risk factors for the dropout from the transplantation waiting list due to tumor progression are shown in Table 2. In univariate analysis, higher serum alpha-fetoprotein (AFP, >100 ng/dL) or des-γ-carboxy prothrombin (DCP, >100 mAU/mL), lower serum albumin (<3.5 g/dL), larger tumor size (>3 cm) had a *P* value < 0.1. Multivariate analysis with stepwise selection of factors indicated that AFP ($P = 0.007$, risk ratio [RR]: 1.917, 95% confidence interval [CI]: 1.190-3.088), DCP ($P = 0.004$, RR: 2.195, CI: 1.278-3.770), and the tumor size ($P = 0.021$, RR: 1.841, CI: 1.095-3.095) were significant. Tumor size was significantly associated with AFP ($r^2 = 0.280$, $P < 0.001$) and