Survival Rates Are Comparable After Radiofrequency Ablation or Surgery in Patients With Small Hepatocellular Carcinomas

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BACKGROUND & AIMS: Differences in efficacy of radiofrequency ablation (RFA) and surgical resection (SR) are not clear for patients with hepatocellular carcinoma (HCC). **METHODS:** From 2002 to 2007, 419 patients with HCCs ≤5 cm were enrolled consecutively in the study. Among these patients, 190 and 229 patients received RFA and SR, respectively, as their first treatment. Factors were analyzed in terms of overall survival and recurrence by multivariate analysis and propensity score matching analysis. **RESULTS:** The SR group had younger age, a higher male-to-female ratio, higher prevalence of hepatitis B virus, lower prevalence of hepatitis C virus, better liver function reserve, and larger tumor size than the RFA group. The cumulative 5-year overall survival rates were 79.3% in the SR group and 67.4% in the RFA group. During the follow-up period, tumors recurred in 244 patients in a median time of 14.5 ± 15.7 months. Before propensity-score matching, the RFA group had shorter overall survival time ($P = .009$) and higher tumor recurrence rate ($P < .001$) than the SR group. After matching, RFA was comparable to SR in overall survival time ($P = .519$), but the RFA group still had a greater incidence of tumor recurrence ($P < .001$). In patients with Barcelona Clinic Liver Cancer (BCLC) stage 0 HCC, RFA was as effective as SR for overall survival time and recurrence. **CONCLUSIONS: Patients with small HCCs have a higher rate of tumor recurrence following RFA than surgery, but overall survival rates are comparable between therapies. RFA is as effective as surgery in patients with BCLC stage 0 HCC.**

Keywords: Liver Surgery; Liver Tumor; Hepatic.

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Hepatocellular carcinoma (HCC) is the third most common cause of cancer mortality in the world.[1,2] It is estimated that more than 600,000 people die of HCC annually worldwide.[3] Surgical resection (SR), liver transplantation, and local ablation therapies are currently regarded as potentially curative treatment modalities.[4–6] Because of scarcity of liver transplantation donors in Taiwan, SR and local ablation therapies are applied in most patients with small HCC and well-preserved liver function.

Among the local ablation therapies, percutaneous radiofrequency ablation (RFA) is superior to others because of fewer sessions, better local tumor control, and higher overall survival rates.[7–13] Compared with SR, RFA is associated with less destruction of non-neoplastic tissue, greater repeatability for recurrence, and lower costs and complications rates.[14–18] Nevertheless, the efficacy between RFA and SR is still debated because there is only 1 prospective randomized control trial that has directly compared the prognosis of patients with small HCC who underwent RFA or surgery.[19]

Because the demographic data of patients undergoing RFA and SR are frequently different, it is very complicated to evaluate the real impact of these 2 different modalities on outcomes. Moreover, it is also very difficult to conduct a prospective double-blind trial to compare their efficacies. To minimize confounding factors in nonrandomized retrospective studies, propensity score matching analysis has been introduced to overcome potential selection biases in recent years.[20–22] However, it has been rarely applied for comparison of therapy efficacies between RFA and SR.

This study aimed to evaluate the results of patients with HCC who underwent RFA or SR by using not only multivariate analysis but also propensity score matching analysis to mimic a randomized trial in a nonrandomized retrospective cohort study.

Materials and Methods

Patients and Follow-Up

This cohort study retrospectively reviewed patients who underwent RFA or SR in Taipei Veterans General Hospital from 2002 to 2007, and 419 consecutive patients who fulfilled the diagnostic criteria of HCC by the American Association for the Study of Liver Disease (AASLD consensus, 2005) were enrolled.[6]

Abbreviations used in this paper: AASLD, American Association for the Study of Liver Disease; AFP, alpha-fetoprotein; Alk-p, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CHB, chronic hepatitis B; CHC, chronic hepatitis C; CT, computed tomography; EASL, European Association for the Study of the Liver; HR, hazard ratio; ICG-15R, indocyanine green dye intravenously injected at 15 minutes; INR, international normalized ratio; MRI, magnetic resonance imaging; PT, prothrombin time; RFA, radiofrequency ablation; RITA, radiofrequency interstitial tissue ablation; SR, surgical resection.

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Among them, 190 and 229 patients received RFA (RFA group) and SR (SR group) as their first treatment modality, respectively. The inclusion criteria were HCC with size ≤5 cm and without extrahepatic metastasis, tumor number 3 or less, Child's classification of liver function A or B, and no other major diseases that might complicate RFA or SR. The study complied with the standards of the Declaration of Helsinki and current ethical guidelines. It was approved by the Institutional Review Board.

The criteria for HCC resection and the operative procedures were as previously described.[23,24] All of the patients who underwent SR received anatomical resection, with the tumor tissue completely excised on the basis of macroscopic evidence.

For patients who received RFA, 2 different RFA devices were used: the Cool-Tip Radiofrequency System (Radionics, Burlington, MA) for 175 patients and the Radiofrequency Interstitial Tissue Ablation (RITA) device (Rita Medical Systems, Mountain View, CA) for the remaining 15 patients. With the Cool-Tip device, treatment was performed with a single (2- or 3-cm active tip) needle electrode. Each tumor had 1–4 ablations per session, depending on the tumor size. With the RITA device, ablation was performed with an expandable needle electrode (StarBurst, 2–3 cm, or StarBurst XL, 3–5 cm; AngioDynamics, Queensbury, NY).

RFA was performed with real-time ultrasonography guidance, and the RF electrode was advanced into the tumor. After RFA, all patients underwent immediate follow-up ultrasonography to evaluate the possibility of bleeding or fluid accumulation. Dynamic computed tomography (CT) scan was done 1 month after all of the tumors were ablated by RFA. Magnetic resonance imaging (MRI) was performed in the cases of patients who were allergic to contrast medium of CT scan, with renal insufficiency, or with inconclusive diagnosis of CT scan. When these confirmed residual tumors by showing contrast enhancement during the arterial phase and washout in venous phase, subsequent RFA was conducted. If no viable tumor was detected, RFA was completed, and the patient was regularly followed up. Consequently, the starting date of follow-up for tumor recurrence was the day when all of the tumors ablated by RFA were confirmed by CT scan or MRI.

All of the patients had been visited regularly every 3 months after surgery or RFA for testing serum liver biochemistries, alpha-fetoprotein (AFP) levels, and arranging ultrasonography examinations until January 31, 2010. All patients were followed up until their last visit in our hospital or death. All of the ultrasonography examinations were performed by using the same protocol at the same facility.

Tumor recurrence was suspected if serum AFP levels were elevated (>20 ng/mL) or new lesions were detected by surveillance ultrasonography. The diagnosis was further confirmed by dynamic CT or MRI. Hence, they had comparable method and frequency of monitoring for tumor recurrence.

Biochemical and Serologic Markers

Serum hepatitis B surface antigen (HBsAg) was tested by using radioimmunoassay (Abbott Laboratories, North Chicago, IL), and anti-hepatitis C virus (HCV) was measured by using a second-generation enzyme immunoassay kit (Abbott Laboratories). Serum biochemistries including albumin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alk-P), creatinine, glucose, and prothrombin time/international normalized ratio (PT/INR) were measured by a systemic multiauto-analyzer (Technicon SMAC; Technicon Instruments, Corp, Tarrytown, NY). Serum AFP level was also measured by using a radioimmunoassay kit (Serono Diagnostic SA, Coinsin/VD, Switzerland).

Statistical Analysis

Baseline characteristics to be evaluated with outcomes were selected according to the European Association for the Study of the Liver (EASL) guidelines published in 2001.[25] Pearson χ^2 analysis was used to compare categorical variables, and the Mann–Whitney U test was used to compare continuous variables. Cumulative recurrence rates or overall survival rates were estimated by the Kaplan–Meier method and compared by using Cox proportional hazards model.

Propensity scores were used to control for selection bias[20–22] and performed by using binary logistic regression to generate a propensity score for each patient who underwent RFA or SR. Variables entered in the propensity model were age, sex, tumor size, tumor number, platelet counts, serum bilirubin, ALT, AST, Alk-P, PT/INR, albumin, AFP, and status of HBsAg and anti-HCV antibody. Subsequently, a one-to-one match between the RFA and SR groups was obtained by using the nearest-neighbor matching method.[22] Survival analysis was repeated to analyze the overall survival and total recurrence amended from these confounding factors.

Variables with statistical significance ($P < .05$) or proximate to it ($P < .1$) by univariate analysis underwent multivariate analysis by using forward stepwise logistic regression model. A two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS 17.0 for Windows; SPSS Inc, Chicago, IL).

Results

Baseline Clinical Characteristics

The baseline demographic data are shown in Table 1. Patients in the RFA group were significantly older than those in the SR group ($P < .001$). In both groups there was male predominance, but the male-to-female ratio was higher in the SR group. Chronic hepatitis B (CHB) patients were more prevalent in the SR group than in the RFA group (59.8% vs 46.3%, $P = .004$), whereas chronic hepatitis C (CHC) carriers were more common in the RFA group (44.7% vs 26.6%, $P < .001$). Liver functional reserve, including albumin, total bilirubin, PT/INR, and indocyanine green dye intravenously injected at 15 minutes (ICG-15R), was relatively poor for patients in the RFA group. Patients who underwent RFA also had lower platelet counts and higher ALT, AST, Alk-P, and glucose levels.

The tumor sizes were larger in the SR group than in the RFA group (2.88 ± 1.06 cm vs 2.37 ± 0.92 cm, $P < .001$), as well as AFP levels ($P = .043$).

Factors Associated With Overall Survival

After a median follow-up of 42.1 ± 23.5 months, 83 patients died, and 336 were still alive on their last visit. Among the 190 patients who underwent RFA, 41 (21.6%) died during the follow-up period, 97 (51.1%) were alive with regular visits until January 31, 2010, and the remaining 52 (27.4%) were lost to follow-up sometime before 2010. For 229 patients who underwent resection surgery, 42 (18.3%) died, 120 (52.4%) were alive with persistent visits until January 31, 2010, and the remaining 67

Table 1. Comparison of Demographic Data Between HCC Patients Who Underwent RFA or SR

Parameter	RFA group (n = 190)	SR group (n = 229)	*P* value
Patient demographics			
Age (*y*) (mean ± SD)	67.42 ± 11.45	60.07 ± 12.56	<.001
Sex (M:F) (*%*)	121/69 (63.7/36.3)	184/45 (80.3/19.7)	<.001
Viral factors			
HBsAg positive/negative	88/97 (46.3%/51.1%)	137/81 (59.8%/35.4%)	.004
Anti-HCV positive/negative	85/101 (44.7%/53.2%)	61/151 (26.6%/65.9%)	<.001
Serum biochemistry tests and liver function tests			
Albumin (*g/dL*) (mean ± SD)	3.85 ± 0.55	4.09 ± 0.40	<.001
Total bilirubin (*mg/dL*) (mean ± SD)	0.99 ± 0.60	0.81 ± 0.48	.001
ALT (*U/L*) (mean ± SD)	71.84 ± 56.08	59.83 ± 49.75	.022
AST (*U/L*) (mean ± SD)	71.43 ± 56.55	50.58 ± 37.67	<.001
Alk-P (*U/L*) (mean ± SD)	114.08 ± 56.02	91.25 ± 42.06	<.001
Creatinine (*mg/dL*) (mean ± SD)	1.20 ± 1.05	1.08 ± 0.51	.159
Glucose (*mg/dL*) (mean ± SD)	117.40 ± 57.83	105.91 ± 40.47	.026
ICG-15R (*%*) (mean ± SD)	23.42 ± 20.55	13.10 ± 8.26	.002
(median; 25th and 75th percentiles)	19.50; 8.00, 29.00	11.50; 7.00, 16.00	
PT/INR (mean ± SD)	1.06 ± 0.12	1.03 ± 0.06	.002
Platelet (/mm^3) (mean ± SD)	128,889 ± 62,029	162,078 ± 61,612	<.001
Tumor factors			
Tumor size (*cm*) (mean ± SD)	2.37 ± 0.92	2.88 ± 1.06	<.001
(median; 25th and 75th percentiles)	2.20; 1.70, 2.90	2.70; 2.00, 3.70	
Single tumor/multi-nodularity (*%*)	152/38 (80.0/20.0)	181/48 (79.0/21.0)	.904
AFP (*ng/mL*) (mean ± SD)	209.40 ± 1362.86	514.22 ± 1697.41	.043
(median; 25th and 75th percentiles)	17.86; 7.30, 49.87	17.88; 6.59, 190.25	

SD, standard deviation.

(29.3%) were lost to follow-up sometime before 2010. For those patients who were lost to follow-up, the median (25th–75th percentiles) follow-up duration after therapy was 27.8 (12.6–44.5) months. In addition, only 28 patients (6.7%) had a follow-up period less than 1 year. The survival status of these patients was censored in the survival analysis.

The RFA, older age (>65 years), lower serum albumin levels (≤4 g/dL), higher bilirubin (>1.6 mg/dL) and AST (>90 U/L) levels, lower platelet counts (≤10^5/mm^3), higher ICG-15R (>10%), higher PT/INR (>1.1), elevated AFP (>20 ng/mL) levels, and multi-nodularity were associated with poor overall survival by univariate analysis (Table 2).

The cumulative overall survival rates at 1, 2, 3, and 5 years were 97.3%, 92.2%, 88.2%, and 79.3% in the SR group and 96.6%, 86.7%, 77.3%, and 67.4% in the RFA group, respectively (Figure 1*A*; P = .009).

Although ICG-15R had statistical significance in univariate analysis, it was not included in the multivariate analysis because it was not a routine test before RFA, and only 266 patients had available data. In multivariate analysis, age >65 years (hazard ratio [HR], 1.988; P = .003), lower albumin levels (≤4 g/dL) (HR, 1.751; P = .025), total bilirubin >1.6 mg/dL (HR, 2.032; P = .040), PT/INR >1.1 (HR, 2.114; P = .004), AFP >20 ng/mL (HR, 1.680; P = .022), and multiple tumors (HR, 1.851; P =

Table 2. Factors Associated With Poor Overall Survival After Curative Therapy for HCC

		Univariate analysis		Multivariate analysis	
Variable	No. of cases	HR (95% confidence interval)	*P* value	HR (95% confidence interval)	*P* value
RFA/SR	190/229	1.783 (1.147–2.770)	.010		
Age >65/≤65 y	202/217	1.909 (1.226–2.972)	.004	1.988 (1.266–3.121)	.003
Sex (female/male)	114/305	1.487 (0.939–2.356)	.091		
HBsAg (positive/negative)	225/178	0.793 (0.507–1.242)	.311		
Anti-HCV (positive/negative)	146/252	1.175 (0.740–1.866)	.495		
Albumin ≤4/>4 g/dL	216/185	2.128 (1.339–3.390)	.001	1.751 (1.073–2.857)	.025
Bilirubin >1.6/≤1.6 mg/dL	29/388	4.102 (2.215–7.597)	<.001	2.032 (1.033–3.998)	.040
ALT >80/≤80 U/L	105/314	1.100 (0.670–1.805)	.706		
AST >90/≤90 U/L	67/352	2.123 (1.269–3.552)	.004		
Platelet ≤10^5/>10^5/mm^3	96/323	2.358 (1.49–3.704)	<.001		
ICG-15R >10%/≤10%	153/113	2.066 (1.092–3.906)	.026		
PT/INR >1.1/≤1.1	79/339	2.480 (1.557–3.951)	<.001	2.114 (1.275–3.506)	.004
AFP >20/≤20 ng/mL	197/219	1.655 (1.066–2.568)	.025	1.680 (1.079–2.617)	.022
Multiple tumor (yes/no)	86/333	1.929 (1.212–3.068)	.006	1.851 (1.139–3.007)	.013
Tumor size >2/≤2 cm	278/141	1.347 (0.833–2.179)	.225		

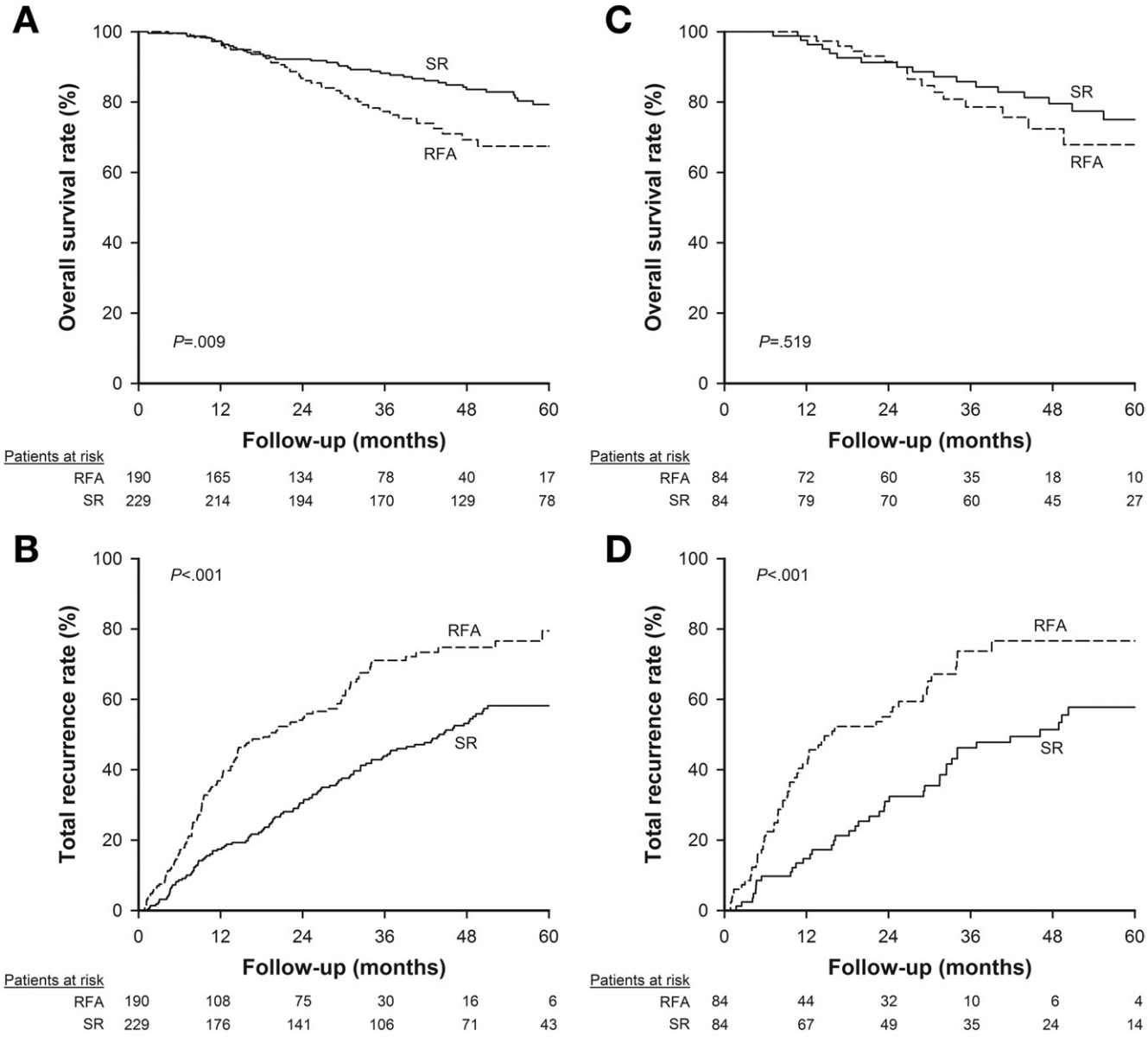

Figure 1. Cumulative curves of overall survival and recurrence plotted by Kaplan–Meier method and compared by log-rank test. Patients in RFA group had (*A*) lower overall survival rate ($P = .009$) and (*B*) higher recurrence rate than those in SR group ($P < .001$). (*C*) After propensity score matching, RFA was not inferior to SR in overall survival ($P = .519$). (*D*) SR had lower incidence of developing recurrence than RFA ($P < .001$).

.013) were independent risk factors predicting poor overall survival. Compared with SR, RFA was not an independent risk factor associated with poor overall survival.

Factors Associated With Recurrence

During the follow-up period, 244 patients developed tumor recurrence, with median time of recurrence of 14.5 ± 15.7 months. Univariate analysis showed that RFA, older age (>65 years), HCV carrier, lower serum albumin levels (≤4 g/dL), higher bilirubin (>1.6 mg/dL), higher ALT (>80 U/L) and AST (>90 U/L) levels, lower platelet counts ($\leq 10^5/mm^3$), and multi-nodularity were associated with higher incidence of tumor recurrence after therapy (Table 3). The cumulative recurrence rates at 1, 2, 3, and 5 years were 17.4%, 30.5%, 43.9%, and 59.1% in the SR group and 37.4%, 54.1%, 71.0%, and 79.5% in the RFA group, respectively (Figure 1*B*; $P < .001$).

By multivariate analysis, RFA remained as an independent factor associated with higher recurrence rate (HR, 1.949; $P < .001$) after therapy, together with lower platelet counts ($\leq 10^5/mm^3$) (HR, 1.420; $P = .031$) and multiple tumors (HR, 1.798; $P < .001$).

Factors Associated With Overall Survival and Tumor Recurrence After Propensity Score Correction With One-to-One Nearest-Neighbor Matching Method

Subsequently, propensity analysis with one-to-one nearest-neighbor matching method was applied to minimize the confounding factors, including age, sex, tumor size, tumor number, platelet counts, bilirubin, ALT, AST, Alk-P, INR, albumin, AFP, HBsAg, and anti-HCV antibody. Eighty-four patients were matched in each group, and the previously mentioned factors appeared to be well-matched between these 2 groups (Table 4).

Table 3. Factors Associated With Tumor Recurrence After Curative Therapy for HCC

	Univariate analysis		Multivariate analysis	
Variable	HR (95% confidence interval)	*P* value	HR (95% confidence interval)	*P* value
RFA/SR	2.049 (1.582–2.653)	<.001	1.949 (1.479–2.571)	<.001
Age (>65/≤65 *y*)	1.361 (1.058–1.751)	.017		
Sex (female/male)	1.241 (0.940–1.639)	.127		
HBsAg (positive/negative)	1.001 (0.772–1.297)	.994		
Anti-HCV (positive/negative)	1.355 (1.040–1.767)	.025		
Albumin (≤4/>4 g/dL)	1.565 (1.203–2.033)	.001		
Bilirubin (>1.6/≤1.6 mg/dL)	1.995 (1.260–3.158)	.003		
ALT (>80/≤80 U/L)	1.338 (1.010–1.774)	.042		
AST (>90/≤90 U/L)	1.726 (1.250–2.383)	.001		
Platelet (≤10^5/>10^5/mm^3)	1.931 (1.453–2.571)	<.001	1.420 (1.033–1.949)	.031
ICG-15R (>10%/≤10%)	1.219 (0.869–1.710)	.251		
PT INR (>1.1/≤1.1)	1.238 (0.902–1.698)	.186		
AFP (>20/≤20 ng/mL)	1.018 (0.791–1.311)	.888		
Multiple tumor (yes/no)	1.737 (1.306–2.312)	<.001	1.798 (1.344–2.405)	<.001
Tumor size (>2/≤2 cm)	1.077 (0.825–1.406)	.587		

After matching, the overall survival rate of the RFA group was not inferior to that of the SR group ($P = .519$, Figure 1*C*), whereas total recurrence remained higher in the RFA group ($P < .001$, Figure 1*D*).

Comparison of Overall Survival Rate and Recurrence Rate Between the RFA and SR Groups in Barcelona Clinic Liver Cancer Stage 0 Hepatocellular Carcinoma

Patients with solitary HCC <2 cm in size defined as very early small HCC (Barcelona Clinic Liver Cancer [BCLC] stage 0) were included for further analysis.[6] Among them, 66 and 50 patients received RFA and SR as the first treatment modality, respectively. Compared with the SR group, patients who underwent RFA had older age, lower incidence of hepatitis B virus (HBV) carriers, higher rate of positive anti-HCV in sera, lower platelet counts, and albumin and AFP levels, but higher Alk-P levels (Supplementary Table 1).

The cumulative overall survival rates at 1, 2, 3, and 5 years were 100%, 95.9%, 91.1%, and 84.6% in the SR group and 98.3%, 94.9%, 86.5%, and 77.8% in the RFA group, respectively (Figure 2*A*, $P = .358$). Moreover, the cumulative recurrence rates at 1, 2, 3, and 5 years were 18.9%, 29.3%, 57.4%, and 74.8% in the SR group and 18.2%, 28.3%, 40.5%, and 54.8% in the RFA group, respectively (Figure 2*B*, $P = .104$). There were no significant differences statistically in terms of overall survival and recurrence between the RFA and SR groups.

After propensity score matching, patients in the RFA group and SR group still had similar prognosis in both overall survival (Figure 2*C*, $P = .981$) and recurrence (Figure 2*D*, $P = .700$).

Discussion

In this cohort study, patients who chose RFA as the first treatment modality were significantly older than those who

Table 4. Comparison of Demographic Data Between Patients Who Underwent RFA and SR in Small HCC by Propensity Analysis With One-to-One Nearest-Neighbor Matching Method

Parameter	RFA group (n = 84)	SR group (n = 84)	*P* value
Age (*y*) (mean ± SD)	64.8 ± 12.1	63.8 ± 11.2	.570
Sex (M/F) (*%*)	63/21 (75.0/25.0)	65/19 (77.4/22.6)	.856
Albumin (*g/dL*) (mean ± SD)	4.0 ± 0.5	4.0 ± 0.4	.861
Total bilirubin (*mg/dL*) (mean ± SD)	0.82 ± 0.42	0.82 ± 0.35	.944
ALT (*U/L*) (mean ± SD)	66.5 ± 54.5	63.2 ± 48.7	.684
AST (*U/L*) (mean ± SD)	57.8 ± 38.4	57.1 ± 40.3	.902
Alk-P (*U/L*) (mean ± SD)	97.0 ± 37.3	98.3 ± 52.8	.845
PT-INR (mean ± SD)	1.04 ± 0.11	1.05 ± 0.08	.788
Platelet (k) (/*mm*^{3}) (mean ± SD)	143.7 ± 64.1	145.2 ± 49.7	.869
Tumor size (*cm*) (mean ± SD)	2.58 ± 0.98	2.47 ± 0.86	.444
Single tumor/multi-nodularity (*%*)	70/14 (83.3/16.7)	64/20 (76.2/23.8)	.337
AFP (*ng/mL*) (median ± SD)	3363.8 ± 1991.8	464.7 ± 1675.2	.652
(median; 25th and 75th percentiles)	12.7; 5.1, 51.2	21.5; 8.5, 193.3	
HBsAg (positive/negative)	50/34 (59.5%/40.5%)	51/33 (60.7%/39.3%)	1.000
Anti-HCV (positive/negative)	24/60 (28.6%/71.4%)	28/56 (33.3%/66.7%)	.617

SD, standard deviation.

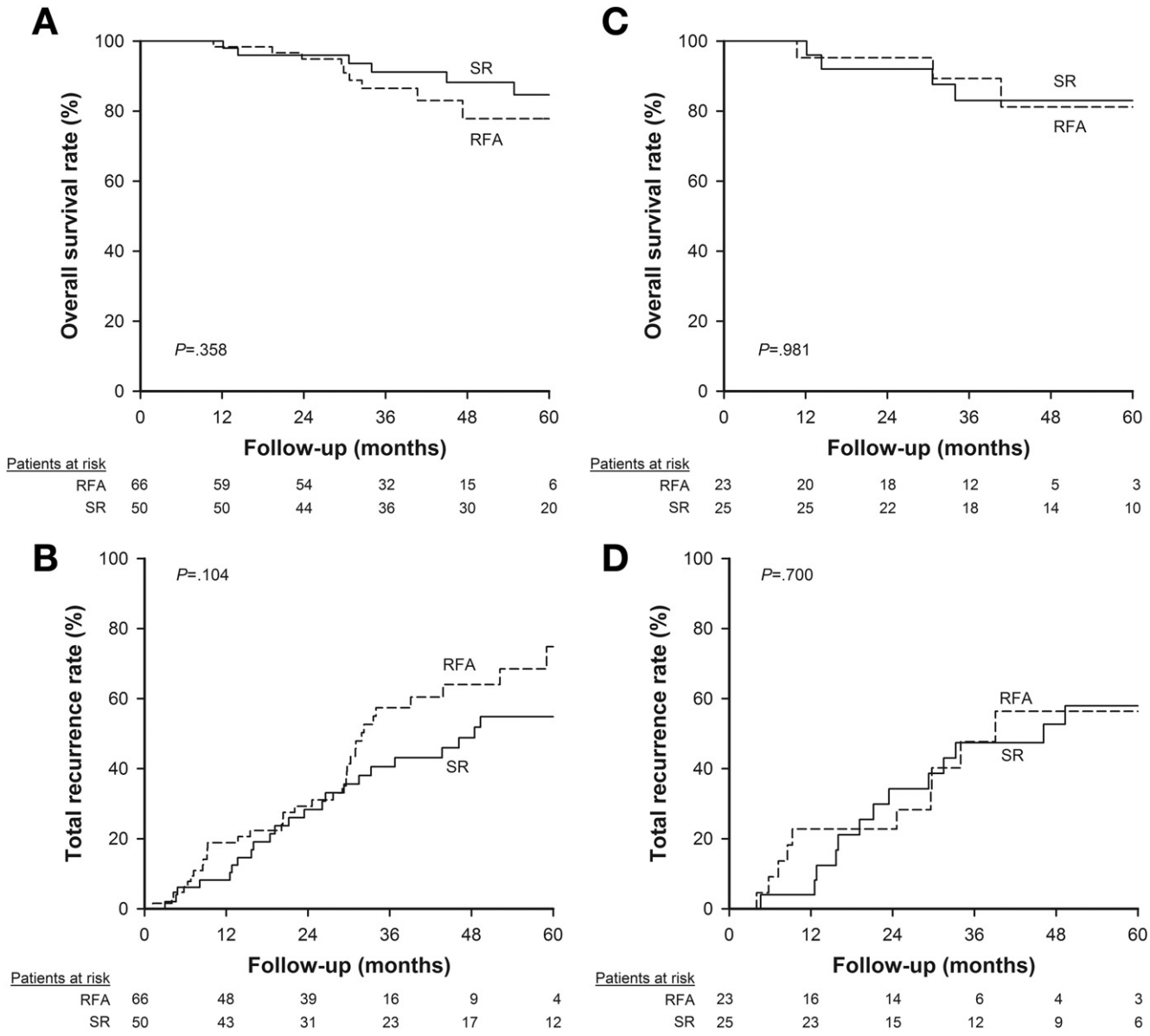

Figure 2. Cumulative curves of overall survival and recurrence plotted by Kaplan–Meier method and compared by log-rank test in BCLC stage 0 HCC patients. There was no statistical significance between RFA and SR in (*A*) overall survival ($P = .358$) and (*B*) recurrence ($P = .104$). After propensity score matching, patients in RFA group and SR group still had similar prognosis in both (*C*) overall survival ($P = .981$) and (*D*) recurrence ($P = .700$).

underwent SR. There are several reasons for this phenomenon. First, according to the AASLD (2005) guidelines, SR is the first choice of curative therapy in patients with single tumor <2 cm, whereas RFA and percutaneous ethanol injection are recommended for patients with associated disease who cannot undergo resection surgery.[6] Older patients might choose RFA because they more commonly have comorbidities that make SR unfeasible. Second, compared with SR, RFA is less invasive and has lower rates of complications and costs and higher repeatability when recurrence occurs.[14,16] Therefore, older patients tend to choose local ablation therapies as their first treatment modality. It is consistent with data from a large, nationwide cohort study from Japan.[26]

This selection tendency also results in different HBV and HCV prevalence rates in the RFA and SR groups in this cohort. In chronic HBV infection, HCCs tend to occur in younger age, larger tumor size, and less severe cirrhosis than those of HCV-related HCCs.[27,28] Men develop HCC 3 times more often than women,[29] and male-to-female ratio tends to be higher in HBV-related HCC than in HCV-related HCC in the Asia-Pacific region, where chronic HBV is endemic.[6,28,30] Accordingly, the less invasive characteristic of RFA causes the selection bias, which results in older age, lower male-to-female ratio, higher HCV prevalence, lower HBV prevalence, and poorer liver functional reserve in the RFA group.[18]

In the present study, older age, lower serum albumin levels, higher bilirubin levels, prolonged PT/INR, higher serum AFP levels, and multi-nodularity are associated with poorer overall survival in HCC treatment. These factors have been confirmed by previous studies.[31–33] However, RFA was not shown to be

inferior to SR with respect to overall survival by multivariate analysis in the present study. The slightly lower significant overall survival in the RFA group might be attributed to older age and poorer liver functional reserve but not the treatment modality. A previous study has shown that in patients with single HCC <5 cm in size, laparoscopic RFA leads to similar survival rates with SR.[16] Our current study further demonstrates that overall survival remains similar in RFA and SR when patients have small HCCs, especially for those in BCLC stage 0.

By multivariate analysis, RFA, lower platelet counts, and multiple tumors are associated with higher incidence of tumor recurrence after curative therapies, which is consistent with previous studies.[31,32] Although the RFA group had higher ALT levels and poorer liver functional reserve associated with higher tumor recurrence, RFA remains an independent factor associated with higher rate of tumor recurrence compared with SR by both multivariate analysis and propensity score matching analysis. It demonstrates that SR has the advantage of complete excision of tumor tissue and hepatic parenchyma around the tumor, which might contain undetectable micrometastases and microvascular invasion.[34] Therefore, SR with safe tumor-free margins has better results than RFA in tumor recurrence.

The novelty of this study is the application of propensity score matching analysis to compensate for the selection bias between the RFA and SR groups. It helps to better clarify the true impact of therapy modality on the prognosis of small HCCs. After the one-to-one nearest-neighbor matching method, the patients were reanalyzed with comparable clinicopathologic characteristics. Although the recurrence rate remained higher in the RFA group, RFA was comparable to SR in overall survival for treatment of small HCCs. Because a majority of the patients with recurrence after RFA were detected by close surveillance, the sizes of recurrent tumors were small, which can be treated completely by another session of local ablation therapy. Accordingly, long-term outcomes remain relatively good. It highlights the importance of close surveillance after local ablation therapy.

SR is recommended as the first-line treatment modality in BCLC stage 0 HCC.[6] In this cohort, RFA is comparable to SR in both overall survival and recurrence by multivariate analysis and propensity score matching analysis. Interestingly, patients in the RFA group appeared to have a trend of higher risk of recurrence than the SR group 2 years after therapy (Figure 2*B*). Our recent study demonstrates that tumor factors dominate the emergence of early recurrence (occurring within 2 years of therapy), whereas field factors like inflammation and liver functional reserve are crucial in developing late recurrence (occurring 2 years after therapy).[35] Because patients in the RFA group have relatively higher ALT levels and poorer liver functional reserve, this might lead to higher incidence of developing late recurrence than in the SR group. After correcting these parameters by propensity score matching, the incidences of recurrence (including late recurrence) seem very similar between these 2 groups. Accordingly, the clinical implication of our study is that RFA might be a good alternative for SR for BCLC stage 0 HCC. However, prospective studies are warranted to further compare prognosis between RFA and SR in treating small HCC, especially in BCLC stage 0.

Conclusions

Although recurrence rate is higher, the overall survival rate of RFA is comparable to SR in patients with small HCC. Moreover, RFA is as effective as SR in BCLC stage 0 HCC.

Supplementary Material

Note: To access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2010.08.018.

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Conflicts of interest

The authors disclose no conflicts.

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