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Comparison of 2 curative treatment options for very early hepatocellular carcinoma

Efficacy, recurrence pattern, and retreatment

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Abstract

Curative treatments for very early-stage hepatocellular carcinoma (HCC), defined as single HCC with a maximum diameter of <2 cm in patients with well-preserved liver function, consist of surgical resection or radiofrequency ablation (RFA). In this retrospective study, we compared the efficacy of both treatments in 154 patients with very early-stage HCCs who underwent resection or RFA as initial therapy and were followed up for a median of 56.8 months. Propensity score matching analysis was also conducted. Overall survival was comparable between treatment groups (median survival time of 143 vs 97 months for resection and RFA, respectively; $P = .132$). Resection group; however, demonstrated a significantly lower recurrence rate after initial therapy than RFA group (42.3% vs 65.7%; $P = .006$) with a longer median recurrence-free survival time (66.7 vs 33.8 months; $P = .002$), which was confirmed even after matching ($P = .04$). In contrast, the recurrence pattern in advanced-stage (9.6% vs 1.0%; $P = .01$) or incurable recurrences (19% vs 13%; $P = .04$) was more frequent following resection than RFA. Recurrent lesions were comparatively more curable in RFA group than in resection group (80% vs 54.5%; $P = .02$). The recurrence of HCC was independently associated with lower serum albumin level ($P = .027$), the presence of comorbid diabetes mellitus ($P = .010$), and RFA ($P = .034$). In conclusion, in patients with very early-stage HCC, surgical resection has achieved significantly better recurrence-free survival than RFA. A closer follow-up is required after resection.

Abbreviations: AFP = alpha-fetoprotein, ALT = alanine aminotransferase, BCLC = Barcelona clinic liver cancer, CI = confidence interval, CR = complete response, CT = computed tomography, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hazard ratio, INR = international normalized ratio, MRI = magnetic resonance imaging, PT = prothrombin time, RFA = radiofrequency ablation, RFS = recurrence-free survival, TACE = transarterial chemoembolization.

Keywords: catheter ablation, hepatocellular carcinoma, recurrence, surgery, survival

1. Introduction

Hepatocellular carcinoma (HCC), which accounts for 80% of primary liver cancer, causes impairment of liver function, high rate of recurrence after treatment, and high cancer-related mortality.[1] HCC mostly originates from chronic viral hepatitis B or C and liver cirrhosis. Many preventive measures have been taken, such as treatment with antiviral agents, but the incidence of HCC remains high and has been reported to be approximately 25.5 and 8.1 per 100,000 in South Korea and worldwide, respectively.[1,2] These rates may be due to the extension of average life expectancy. Hence, it is important to detect HCC early and cure it completely. In South Korea, the proportion of patients detected with an early stage of HCC has gradually increased since surveillance programs using periodic ultrasonography or computed tomography (CT) and the serum alpha-fetoprotein (AFP) test have been established for those at high risk for HCC, such as those with chronic viral hepatitis and/or cirrhosis.[3]

Patients with very early-stage HCC, defined as single HCC of < 2 cm in the maximum diameter in those with well-preserved liver function according to the Barcelona clinic liver cancer (BCLC) staging system, can be treated with curative intent, using either hepatic resection or radiofrequency ablation (RFA).[4] Therefore, the efficacy of both treatments for very early-stage HCC has been compared in many studies, but the results have been inconsistent. In some studies, no significant differences in overall survival or

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THK and JMC contributed equally to this work.

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recurrence rate between the 2 treatment modalities have been demonstrated.[5–11] Conversely, other studies have shown significant differences in overall survival or recurrence.[12–15] These discrepancies may be due to the differences in race, region, the causes of underlying liver disease, hepatic functional reserve at initial therapy, and capability of health care systems, ultimately resulting in a diverse pattern of recurrence after each treatment. However, few studies have addressed the recurrence pattern after initial curative therapy for very early-stage HCC and the tumor response after retreatment against recurrent HCCs.

Thus, in this study, we compared the prognosis of patients with very early-stage HCC after receiving surgical resection or RFA as their initial therapy at a single center in hepatitis B virus (HBV)-endemic area, especially focusing on the pattern of recurrent HCCs and the curability of recurrent lesions following retreatment.

2. Materials and methods

2.1. Study design

We reviewed the medical records of patients with a single HCC smaller than 2 cm, good health performance status, and well-preserved liver function of Child-Pugh class A. A flow diagram of the study is shown in Figure 1. Patients who received surgical resection or RFA as initial therapy for HCC from March 2004 to December 2014 were included. Patients who did not receive the initial therapy at our hospital were excluded. The included patients were split into 2 groups according to the initial therapies. Overall survival and recurrence rates were established as the primary outcomes. This retrospective cohort study was approved by the institutional review boards of the Korea University Anam Hospital (2017AN0199) and conducted in agreement with the ethical principles of the Declaration of Helsinki. A waiver of informed consent was obtained, and patient records were anonymized and de-identified before analysis.

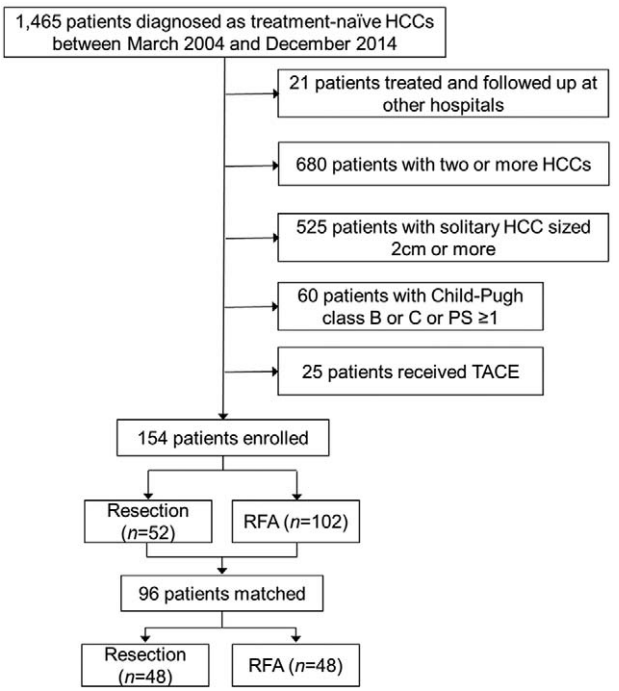

Figure 1. Flow diagram for the study. HCC = hepatocellular carcinoma, PS = performance status, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

2.2. Diagnostic criteria and definitions

HCC diagnoses were confirmed using the guidelines of the European Association for the Study of the Liver and the Korean Liver Cancer Association.[4,16]

Tumor recurrence was defined as the appearance of new lesions with typical radiological features of HCC after a complete response (CR) was attained according to the modified response evaluation criteria in solid tumors.[17] Recurrence-free survival (RFS) was defined as the interval between the date of treatment and first relapse, or death. Local recurrence was defined by the reappearance of viable tumor directly adjacent to the ablated or resected site or within the treated segment. Remote recurrence included intrahepatic distant relapse other than local recurrences and extrahepatic recurrences.

The presence of cirrhosis was based on liver histology, gross findings during surgery, or radiological findings of an irregular liver margin with ascites, varices, or thrombocytopenia ($<10^5$ cells/mm^3).[18]

All outcomes were evaluated at the end of the maximum follow-up period. The date of overall mortality was obtained from medical records and from the Korea National Health Insurance Service.

2.3. Treatment and follow-up

Surgical resection was conducted under general anesthesia using standard hepatectomy techniques by experienced surgeons (KDS and YYD, et al). The type of surgery, anatomical or non-anatomical resection, was decided according to tumor location and underlying liver status.

The patients in the RFA group preferred noninvasive treatment, refused general anesthesia, and were concerned about insufficient postoperative hepatic reserve and co-morbidities after surgical resection. RFA procedures were performed under ultrasonographic guidance with local anesthesia and conscious sedation by experienced radiologists (CSB and KYH). CT-guided RFA was applied to patients with a poor ultrasonographic window. Commercially available electrode systems with generators (Cool-tip RF System [Covidien, Mansfield, Mass], the VIVA RF system [STARmed, Ilsan, Korea], or cooled-wet electrode system [RFMedical, Seoul, Korea]) were used. Radiofrequency current was emitted generally for 12 minutes by a 200-W generator set to deliver maximum power using the automatic impedance control method. Our therapeutic aim for RFA was to create an ablative margin of at least 0.5 cm in the surrounding nontumor liver parenchyma. Patients treated with RFA underwent CT examinations immediately after the procedure to determine the technical success and to assess immediate complications, while patients in the resection group underwent CT imaging if complications were clinically suspected during a postoperative hospital stay.

After discharge, the patients in both groups underwent a multiphasic CT, chest radiography, and laboratory tests including serum AFP 1 month after initial treatment, every 3 months during the first 2 years, and every 4 to 6 months thereafter. Magnetic resonance imaging (MRI) was conducted instead of CT in patients with renal disorders. For cases in which

extrahepatic recurrence was suspected on the basis of clinical symptoms or unexplained elevation of tumor marker levels, we performed chest CT, brain MRI, whole-body bone scintigraphy, and positron emission tomography. In addition, gadoxetate MRI or CT during hepatic arteriography and arterial portography were performed for further characterization when a new indeterminate hepatic lesion was detected on CT examination during follow-up. For cases in which recurrent tumors were identified during follow-up, optimal subsequent therapy such as resection, RFA, transarterial chemoembolization (TACE), liver transplantation, or radiation therapy was performed according to the clinician's judgment based on the characteristics of the recurrent tumor, liver function, and general condition of the patient.

2.4. Statistics

We analyzed the data using the Statistical Package for Social Science (SPSS) version 20 (SPSS, Chicago, IL) and R version 3.3.0 (The R Project, Vienna, Austria), and we compared continuous variables using Student *t* test and the Mann–Whitney *U* test, and categorical variables using the chi-square test.

We calculated and compared the cumulative rates of overall survival and recurrence of HCC using Kaplan–Meier plots and the log-rank test, censoring the patients who were lost to follow-up. To investigate factors associated with overall survival, recurrence rate, and local recurrence rate of HCC, we conducted univariate and multivariate analyses using the Cox proportional hazard regression model. The assumptions of proportionality for the Cox model were confirmed using log minus log hazard plots.

We also performed propensity score matching using a binary logistic regression model to minimize the potential confounding effects for the resection and the RFA groups. The variables used to derive propensity scores were age, cirrhosis presence, platelet count, serum albumin and bilirubin levels, and prothrombin time (PT) international normalized ratio (INR). The matched data in the groups were compared using the paired *t* test for continuous variables and the McNemar test for categorical variables.

Two-tailed *P* values of $<.05$ were considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

Enrolled patients with BCLC stage 0 HCC underwent resection (n = 52) or RFA (n = 102) as initial therapy for HCC. The patients were predominantly male (73.7%) with a mean age of 59.3 years, and HCC was mainly associated with HBV infection (63%). The baseline characteristics for liver function, tumor status, and accompanying disease according to initial treatment are shown in Table 1. At diagnosis, patients in the RFA group were significantly older and there were more cases of cirrhosis (69.2% vs 90.2%; $P = .001$) and gastrointestinal varices on endoscopy (5/39 vs 53/91; $P = .001$) in the RFA group than in the resection group (all, $P < .01$). The RFA group exhibited inferior hepatic functional reserve relative to the resection group as represented by their lower serum albumin and higher bilirubin levels, higher PT INR, and higher Child-Pugh and model for end-stage liver disease (MELD) scores with lower platelet counts (all, $P < .05$). The etiologies of HCC were comparable between treatment groups. In addition, 87.6% of HBV-related patients successively received antiviral treatment after initial therapy for HCC, with no significant differences between groups (84.2% vs 89.9%).

In the resection group, 25 patients (48.1%) received nonanatomic resection such as wedge resection, and 27 patients (51.9%) received anatomic resection such as segmentectomy and sectionectomy. Twelve surgeries (23.1%) were conducted laparoscopically. In the histologic examination of the resected tissues, 4 (7.7%), 26 (50%), 19 (36.5%), and 3 (5.8%) cases were Edmonson grade I, II, III, and IV, respectively. Satellite nodules were identified in 2 samples (3.8%), and microscopic vascular invasion was detected in 13 samples (25%).

3.2. Therapeutic outcomes for the entire cohort

3.2.1. Immediate outcomes. Surgical resection achieved CR in all patients, and only 1 session was required (Table 1). RFA failed to achieve CR in 3 patients (2.9%); it required an average of 1.25 months to achieve CR, and 2 or more sessions were required in 12.1% of patients to achieve CR ($P = .009$ vs resection). The duration of hospitalization per session and total hospital stay for achieving CR was significantly shorter in the RFA than the resection group (both, $P < .001$) (Table 1). Post-procedural complications occurred in 6 patients receiving surgery (11.5%; portal vein thrombosis in 4, biloma in 1, and bleeding in 1) and 3 patients receiving RFA (2.7%; portal vein thrombosis, bleeding, abscess, each in 1). For RFA, nonanatomical resection and anatomical resection, respectively, the costs per session were \$550, \$910, and \$2090, and the mean total cost to achieve CR was \$720, \$910, and \$2090.

3.2.2. Survival. During the median 56.8-month (range, 4.1–166.5 months) follow-up period, a total of 55 patients (35.7%) died. The most common causes of death were HCC progression and liver failure, with no significant differences with respect to the initial treatments (Table 2). Overall survival did not differ significantly between the resection and RFA groups (median survival time of 143 vs 97 months for resection and RFA, respectively; $P = .132$), with the cumulative probabilities of survival at 1-, 3-, 5-, and 7-years being 98.1%, 89.7%, 78.3%, and 69.6%, respectively, for the resection group, and 97.0%, 85.1%, 74.3%, and 55.5%, respectively, for the RFA group (Fig. 2A).

3.2.3. Recurrence and RFS. A total of 87 patients (57.6%) presented with recurrence during the study period. Excluding the 3 patients who did not achieve CR, the overall HCC recurrence rates were significantly lower in the resection group than in the RFA group (median time to recurrence of 78.3 vs 34.7 months; $P = .003$), with cumulative probabilities at 1, 3, 5, and 7 years of 9.7%, 38.5%, 38.5%, and 51.1%, respectively, for the resection group, and 12.8%, 53.0%, 74.6%, and 84.8%, respectively, for the RFA group (Fig. 2C). Reflecting these results, the RFS was better in the resection group than in the RFA group (median RFS time of 66.7 vs 33.8 months for resection and RFA, respectively; $P = .002$), with cumulative RFS rates at 1, 3, 5, and 7 years of 88.5%, 59.0%, 56.1%, and 44.6%, respectively, for the resection group, and 85.5%, 42.4%, 23.5%, and 14.1%, respectively, for the RFA group ($P = .001$).

The cumulative local recurrence rates were also significantly lower in the resection group than in the RFA group ($P < .001$), with cumulative probabilities at 1, 3, 5, and 7 years of 5.9%, 8.5%, 8.5%, and 8.5%, respectively, for the resection group, and

Table 1

Baseline characteristics and treatment responses of patients with very early HCC in the entire and matched cohort.

	Entire cohort			Matched cohort		
Factors	**Resection (n = 52)**	**RFA (n = 102)**	***P***	**Surgery (n = 48)**	**RFA (n = 48)**	***P***
Age, yr	56.4 ± 9.1	61.6 ± 10.3	.003*	56.2 ± 8.9	58.7 ± 9.8	.183§
Follow-up period, mo	50.3 (35.4–80.5)	59.2 (37.8–80.9)	.480†	59.1 ± 37.3	63.3 ± 30.4	.547§
Male, n	42 (80.8)	69 (67.6)	.086†	38 (79.2)	35 (72.9)	.473‖
DM, n	11 (21.2)	32 (31.4)	.181†	9 (18.8)	15 (31.2)	.157‖
BMI, kg/m^2	23.2 (21.5–25.2)	23.7 (22.3–26.1)	.355‡	23.6 ± 2.8	23.9 ± 3.5	.548§
Cirrhosis, n	36 (69.2)	92 (90.2)	.001†	35 (72.9)	39 (81.2)	.466‖
Etiology, n			.187†			.163‖
HBV	38 (73.1)	59 (57.8)		36 (75.0)	34 (70.8)	
HCV	6 (11.5)	12 (11.8)		5 (10.4)	8 (16.7)	
Alcohol	7 (13.5)	23 (22.5)		6 (12.5)	2 (4.2)	
Others	1 (1.9)	8 (7.8)		1 (2.1)	4 (8.3)	
Platelet, $\times 10^3$/mm^3	127 (110–163)	99.5 (63–134)	<.001‡	136.3 ± 42.7	127.1 ± 49.9	.332§
ALT, IU/L	28 (19–43)	29 (18–39)	.637‡	36.5 ± 27.7	30.4 ± 15.5	.186§
Albumin, g/dL	4.2 ± 0.4	3.9 ± 0.5	<.001‡	4.14 ± 0.44	4.09 ± 0.46	.585§
Bilirubin, mg/dL	0.62 (0.40–0.79)	0.76 (0.55–1.20)	.005‡	0.69 ± 0.41	0.76 ± 0.45	.425§
Prothrombin time, INR	1.04 (0.99–1.11)	1.12 (1.05–1.21)	<.001‡	1.07 ± 0.11	1.10 ± 0.13	.241§
Creatinine, mg/dL	0.94 (0.81–1.05)	0.90 (0.79–1.00)	.070‡	0.95 ± 0.19	0.90 ± 0.20	.185§
CTP score 6, n	9 (17.3)	36 (35.3)	.020†	9 (18.8)	12 (25.0)	.459‖
MELD	7 (7–8)	8 (7–10)	<.001‡	7.9 ± 2.0	8.2 ± 1.5	.416§
AFP, ng/mL	19.1 (4.3–135.0)	16.0 (4.8–77.9)	.740‡	137.1 ± 255.3	146.2 ± 280.7	.869§
Tumor size, cm	1.6 (1.3–1.8)	1.6 (1.3–1.9)	.724‡	1.57 ± 0.30	1.53 ± 0.32	.484§
Subcapsular tumor	35 (67.3)	52 (51.0)	.078†	33 (68.8)	28 (58.3)	.080‖
Complete response, n	52 (100)	99 (97.1)	.551†	48 (100)	48 (100)	⊠
Session to complete responses	1	1.25 ± 1.10	.098*	1	1.38 ± 1.50	.089§
Complete response after 1 session, n	52 (100)	87 (87.9)	.009†	48 (100)	41 (85.4)	.006‖
Time to complete response, mo	0	0.28 ± 1.03	.111*	0	0.35 ± 1.03	.021¶
Hospital stay per session, d	9 (8–12)	4 (2–6)	<.001‡	11.4 ± 9.8	5.5 ± 5.1	<.001¶
Hospital stay for CR, d	9 (8–12)	4 (3–6)	<.001‡	11.4 ± 9.8	6.3 ± 5.7	.009¶

The data are presented as mean ± standard deviation, n (%), or median (interquartile range). The matched cohorts were selected by propensity-score matching in the resection and RFA groups.
AFP = α-fetoprotein, ALT = alanine aminotransferase, AVT = antiviral treatment, BMI = body mass index, DM = diabetes mellitus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, PT INR = prothrombin time international normalized ratio, RFA = radiofrequency ablation.

* Student *t* test.

† Chi-squared test.

‡ Mann–Whitney *U* test.

§ Paired *t* test.

‖ McNemar test.

9.7%, 33.5%, 46.7%, and 49.2%, respectively, for the RFA group (Fig. 2E).

The cumulative remote recurrence rates did not significantly differ between the resection and RFA groups ($P = .406$), with cumulative probabilities at 1, 3, 5, and 7 years of 7.8%, 37.2%, 37.2%, and 50.1%, respectively, for the resection group, and 5.4%, 33.6%, 54.2%, and 73.1%, respectively, for the RFA group (Fig. 2F).

Table 2

The causes of death in the present study.

	All	Resection	RFA	*P*
HCC progression	25 (45.5)	7 (53.8)	18 (42.9)	.505
Liver failure	11 (20.0)	1 (7.7)	10 (23.8)	.073
Infection	7 (12.7)	3 (23.1)	4 (9.5)	.603
Variceal bleeding	7 (12.7)	2 (15.4)	5 (11.9)	.766
Others	5 (9.1)	0	5 (11.9)	.105

Data are presented as number (%).
HCC = hepatocellular carcinoma, RFA = radiofrequency ablation.

3.2.4. Pattern of recurrence and curability. The pattern of first tumor recurrence was presented according to the tumor features at the first time of HCC recurrence; local/remote, intrahepatic/extrahepatic, BCLC stage, tumor number, maximum tumor size, vessel invasion (Table 3). Overall recurrence, local recurrence, and recurrence in BCLC stage 0 occurred more frequently in the RFA group than in the resection group (all, $P < .01$). In contrast, the recurrence pattern in BCLC stage C (advanced stage with vascular invasion or extrahepatic metastasis) was significantly more frequent in the resection versus the RFA group. The regular image follow-up appointment for HCC recurrence was not kept in 31.3% of patients with intermediate and advanced stage pattern of HCC recurrence.

Subsequent therapies following the first recurrence were as follows: RFA only or RFA combined with TACE (56.3%), TACE only (27.6%), surgical resection (5.7%), transplantation (2.3%), external radiation (1.1%), cryotherapy (1.1%), and best supportive care (5.7%) (Table 4). Following treatment against recurrent HCCs, CR was more frequently achieved in the RFA group (80.0% vs 54.5%; $P = .02$) despite the RFA group having more overall recurrences than the resection group. Incurable recurrent HCC cases were more common in the resection group than in RFA group (19% vs 13%, $P = .040$) (Table 3).

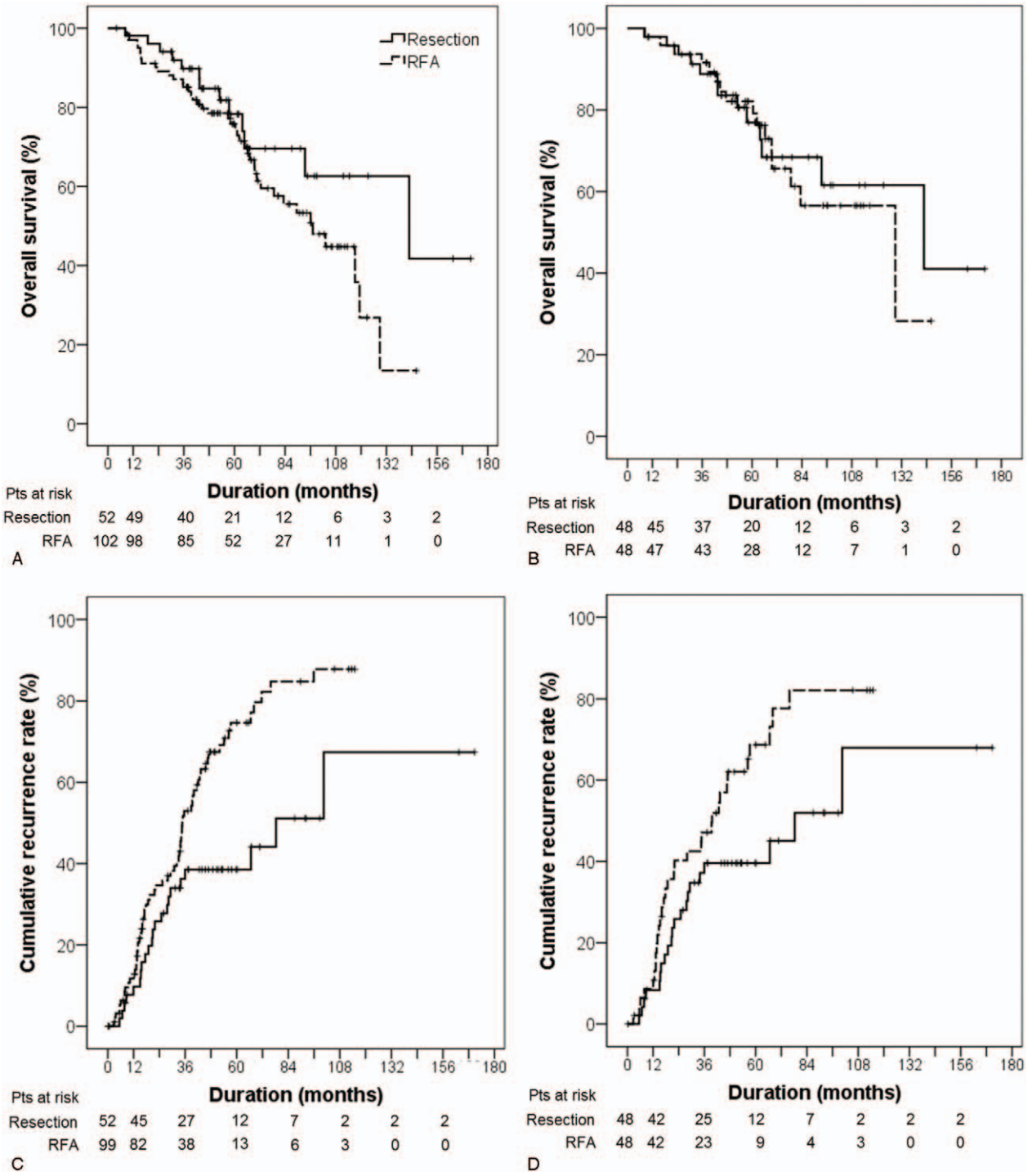

Figure 2. Kaplan–Meier plots for overall survival and cumulative recurrence according to initial treatments in the entire cohorts and matched cohorts. (A) Overall survival rates after surgical resection and RFA in the entire cohort. The 2 treatment groups did not show significant differences (median time, 142.8 vs 97.1 mo for the resection and RFA group, respectively; $P = .132$). (B) Overall survival rates in the matched cohorts. The 2 matched groups did not show significant differences (median time, 142.8 vs 128.9 mo; $P = .776$). (C) The cumulative recurrence rates in the entire cohort. The resection group presented significantly lower recurrence rates than the RFA group (median time, 78.3 vs 34.7 mo; $P = .003$). (D) The cumulative recurrence rates in the matched cohorts. The resection group presented significantly lower recurrence rates than the RFA group (median time, 78.3 vs 39.6 mo; $P = .029$). (E) The cumulative local recurrence rates in the entire cohort. The resection group presented significantly lower recurrence rates than the RFA group (mean time, 157.4 vs 83.8 mo; $P < .001$). (F) The cumulative remote recurrence rates in the entire cohort. The 2 treatment groups did not show significant differences (median time, 78.3 vs 54.1 mo for the resection and RFA group, respectively; $P = .406$). Pts = patients, RFA = radiofrequency ablation.

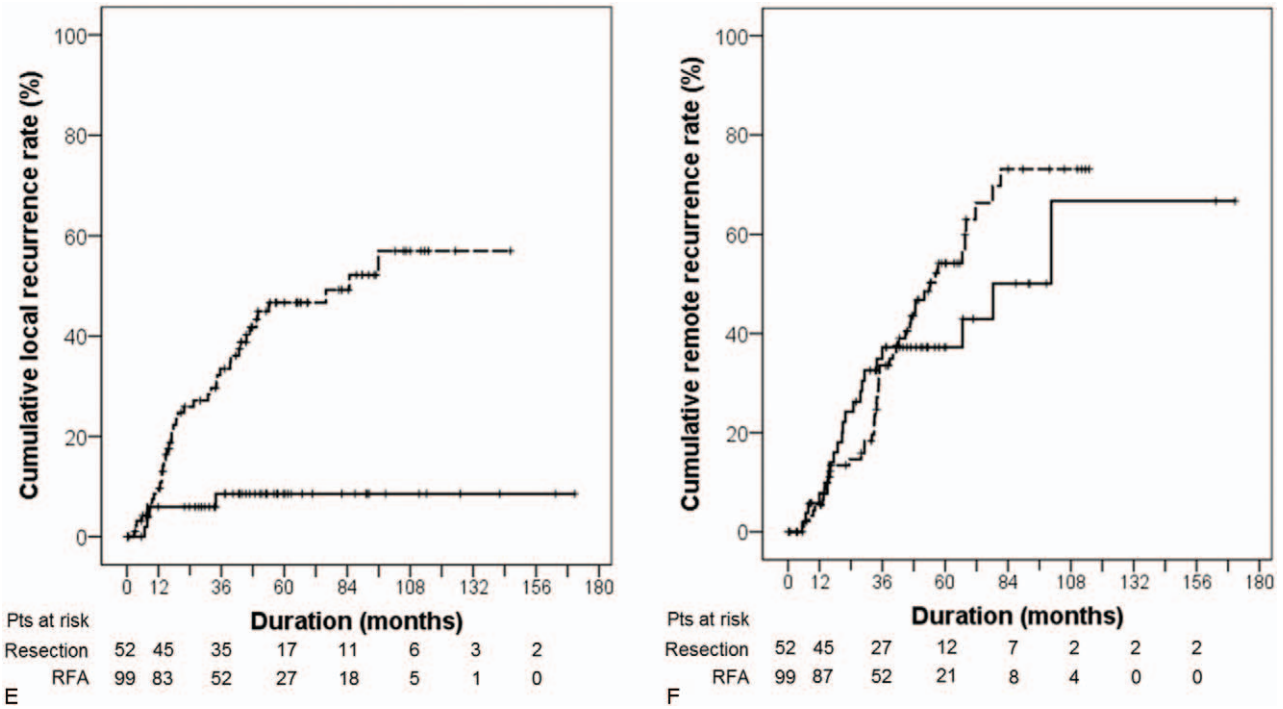

Figure 2. Continued.

3.3. Predictive factors associated with recurrence and overall survival

On multivariate analysis, overall survival was negatively associated with non-HBV-related liver disease (hazard ratio [HR], 4.591; $P<.001$) and prolonged PT INR (HR, 9.779; $P=.030$) (Table 5). Patients with higher serum creatinine levels (HR, 2.418; $P=.072$) had a tendency of shorter survival.

HCC recurrences occurred more frequently in patients with diabetes mellitus (HR, 1.793; $P=.01$), lower serum albumin levels (HR, 1.653; $P=.03$), and those who underwent RFA (HR, 1.712; $P=.03$) instead of surgical resection as initial therapy.

The local recurrence of HCC was more frequent after conducting RFA (HR, 6.398; 95% confidence interval [CI], 2.291–17.868; $P<.001$) rather than surgical resection as initial therapy.

The remote recurrence of HCC was independently associated with the presence of diabetes mellitus (HR, 2.279; 95% CI, 1.377–3.770; $P=.001$) and serum albumin levels (HR, 0.542; 95% CI, 0.324–0.906; $P=.02$).

Table 3

First recurrence of HCC after complete response to initial treatment.

	Resection (n=52)	RFA (n=99)	P
Overall recurrence	22 (42.3)	65 (65.7)	.006*
Intrahepatic recurrence	20 (38.5)	64 (64.6)	.002*
Local	2 (3.8)	32 (32.3)	<.001*
Remote	16 (30.8)	26 (26.3)	.557*
Local and remote	2 (3.8)	6 (6.1)	.564*
Extrahepatic recurrence	5 (9.6)	1 (1.0)	.010*
Extrahepatic alone	2 (3.8)	1 (1.0)	.235*
BCLC stage of recurred HCC			.001*
0	8 (15.4)	36 (36.4)	.007*
1	5 (9.6)	22 (22.2)	.055*
2	4 (7.7)	6 (6.1)	.702*
3	5 (9.6)	1 (1.0)	.010*
Number of recurred HCCs	1 (1.0–3.3)	1 (1.0–1.0)	.083†
Maximum size of recurred HCCs, cm	1.7 (1.2–1.9)	1.5 (1.2–2.1)	.673†
Vascular invasion of recurred HCC	3 (13.6)	0	.003*
Incurable recurrence	10 (19.2)	13 (13.1)	.040*

Data are presented as number (%) and median (interquartile range). Local refers to the first relapse of HCC within the treated segment, and remote refers to the first recurrence elsewhere, except for the treated segment. Local and remote refers to the concurrent detection of the first local and remote recurrence.

BCLC = Barcelona clinic liver cancer, LT = liver transplantation, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

* Chi-squared test.

† Mann–Whitney *U* test.

3.4. Therapeutic outcomes from propensity score matching

The baseline characteristics between the 2 matched groups did not differ significantly (Table 1). The overall survival rates at 1, 3, 5, and 7 years were 97.9%, 88.8%, 77.0%, and 68.4%, respectively, for the resection group, and 97.9%, 91.6%, 79.2%, and 56.5%, respectively, for the RFA group ($P=.776$) (Fig. 2B). The RFS rates at 1, 3, 5, and 7 years were 89.6%, 57.7%, 54.7%, and 43.5%, respectively, for the resection group, and 87.3%, 50.5%, 29.9%, and 17.1%, respectively, for the RFA group ($P=.04$). The cumulative recurrence rates at 1, 3, 5, and 7 years were 8.4%, 39.6%, 39.6%, and 52.0%, respectively, for the resection group, and 10.8%, 47.1%, 68.7%, and 82.1%, respectively, for the RFA group ($P=.03$) (Fig. 2D). The cumulative local recurrence rates at 1, 3, 5, and 7 years were 6.4%, 9.2%, 9.2%, and 9.2%, respectively, for the resection

Table 4

The proportion of patients who had a complete response following treatments for first recurrence according to recurrent patterns and treatment modalities performed.

Initial therapy	Retreatment for 1st recurrence	CR after retreatment	According to the location of 1st recurrence				According to BCLC stage at 1st recurrence			
			Local	Remote	Both	Extrahepatic alone	0	A	B	C
Resection	RFA ± TACE	8/14 (57.1)	0/1	8/11 (72.7)	0/2		5/5 (100)	3/3 (100)	0/4	0/2
	TACE	1/1 (100)		1/1 (100)			1/1 (100)			
	Resection	1/1 (100)		1/1 (100)			1/1 (100)			
	Transplantation	2/2 (100)		2/2 (100)			1/1 (100)	1/1 (100)		
	External radiation	0/1				0/1				0/1
	Supportive care	0/3	0/1	0/1		0/1		0/1		0/2
	Overall	12/22 (54.5)	0/2	12/16 (75)	0/2	0/2	8/8 (100)	4/5 (80)	0/4	0/5
RFA	RFA ± TACE	32/37 (86.5)	15/19 (78.9)	16/16 (100)	1/2 (50)		22/24 (91.7)	10/11 (90.9)	0/2	
	TACE	16/21 (76.2)	10/12 (83.3)	6/8 (75)	0/1		11/12 (91.7)	5/6 (83.3)	0/3	
	Resection	4/4 (100)	1/1 (100)	3/3 (100)				4/4 (100)		
	Cryotherapy	0/1				0/1				0/1
	Supportive care	0/2			0/2			0/1	0/1	
	Overall	52/65 (80.0)	26/32 (81.3)	25/27 (92.6)	1/5 (20)	0/1	33/36 (91.7)	19/22 (86.4)	0/6	0/1

The data shows the number of patients who presented a complete response to treatment for the first recurrence/the number of patients who received the treatment for the first recurrence (%). Local refers to the first relapse of HCC within the treated segment, and remote refers to the first recurrence elsewhere, except for the treated segment. Local and remote refers to the concurrent detection of the first local and remote recurrence.

BCLC = Barcelona clinic liver cancer, CR = complete response, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

group, and 6.6%, 34.3%, 44.6%, and 49.6%, respectively, for the RFA group ($P < .001$). The cumulative remote recurrence rates at 1, 3, 5, and 7 years were 6.3%, 38.2%, 38.2%, and 50.8%, respectively, for the resection group, and 4.3%, 32.2%, 51.0%, and 66.4%, respectively, for the RFA group ($P = .85$).

4. Discussion

As surveillance tests are becoming more common for patients at risk for HCC, the detection rate of small HCC, especially of lesions sized <2 cm, has increased.[3] There are many studies and meta-analyses comparing the outcomes after resection and RFA treatment for solitary HCC <2 cm.[5–14,19,20] However, the superiority of any method has not yet been demonstrated definitively. Some studies support the equivalence of RFA to surgical resection; others have supported resection over RFA.

In the present study, resection was the preferable treatment for achieving CR. Surgical resection allowed the achievement of CR in all patients and also required significantly fewer sessions and shorter time to reach CR than the RFA treatment. In addition,

Table 5

Variables independently associated with overall survival and recurrence rate of HCC on multivariate analyses using the Cox regression model.

Variable	Overall survival						HCC recurrence					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age	1.047	1.018–1.076	.001		–	.194	1.014	0.994–1.035	.178			
Sex, (male vs female)	1.444	0.760–2.743	.262				1.386	0.855–2.248	.186			
Etiology (non-HBV vs HBV)	4.568	2.597–8.037	<.001	4.591	2.610–8.075	<.001	1.698	1.089–2.648	.019		–	.348
DM (yes vs no)	1.632	0.928–2.869	.089		–	.350	2.078	1.340–3.223	.001	1.793	1.152–2.792	.010
BMI, kg/m^2	0.938	0.852–1.033	.196				1.018	0.949–1.092	.616			
Cirrhosis (yes vs no)	2.991	1.161–7.704	.023		–	.361	1.810	0.982–3.336	.057		–	.454
Platelet, $\times 10^3$/mm^3	0.998	0.993–1.003	.528				0.996	0.991–1.000	.055		–	.897
ALT, IU/L	0.998	0.991–1.005	.632				1.002	0.997–1.007	.372			
Albumin, g/dL	0.402	0.224–0.722	.002		–	.276	0.515	0.335–0.792	.003	0.605	0.387–0.946	.027
Bilirubin, mg/dL	1.154	0.661–2.012	.615				1.217	0.789–1.876	.374			
PT INR	8.880	1.153–68.364	.036	9.779	1.244–76.879	.030	6.866	1.288–36.590	.024		–	.818
Creatinine, mg/dL	2.656	1.009–6.991	.048	2.418	0.924–6.327	.072	1.416	0.617–3.245	.412			
AFP, ng/mL	1.000	0.999–1.001	.884				1.000	0.999–1.001	.415			
Tumor size, cm	1.335	0.543–3.282	.529				1.177	0.604–2.296	.632			
Tumor location (subcapsular vs deep)	1.060	0.624–1.805	.827				1.198	0.786–1.827	.400			
Treatment, (RFA vs SR)	1.619	0.861–3.044	.135				2.072	1.276–3.362	.003	1.712	1.041–2.815	.034

AFP = α-fetoprotein, ALT = alanine aminotransferase, BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, PT INR = prothrombin time international normalized ratio, RFA = radiofrequency ablation, SR surgical resection.

Table 6

Summary of outcomes in previous studies comparing surgical resection and RFA for patients with HCC of BCLC stage 0.

Author, yr	Study design, liver function	Treatment	No.	Overall survival (%) 1yr/3yr/5yr	*P*	Recurrence rate (%) 1yr/3yr/5yr	*P*	RF-survival (%) 1yr/3yr/5yr	*P*
Hong, 2005[5]	Retrospective cohort, Child-Pugh grade A	SR	25	nd/87.2/nd	.12	nd		nd/64/nd	.15
		RFA	16	nd/67.1/nd		nd		nd/55.6/nd	
Hung, 2011[7]	Retrospective cohort, Child-Pugh grade A	SR	50	100/91.1/84.6	.358	18.2/40.5/54.8	.104		
		RFA	60	98.3/86.5/77.8		18.9/57.4/74.8			
Peng, 2012[12]	Retrospective cohort, Child-Pugh grade A	SR	74	90.5/70.9/62	.048			75.6/56.1/51	.548
		RFA	71	98.5/87.7/72				76.4/65.2/60	
Wang, 2012[13]	Retrospective cohort, PS-matched, Child-Pugh grade A	SR	52	98/98/91.5	.269			89.8/62.1/40.7	.031
		RFA	52	98.1/82.8 /82.8				67.1/46.4 /38.0	
Hasegawa, 2013[20]	Retrospective cohort, Liver damage A	SR	785	nd/92.9/83.9	.04	HR 0.6	.001		
		RFA	1241	nd/92.0/nd					
Kim, 2016[15]	Retrospective cohort, Child-Pugh grade A	SR	64	nd/nd/91†	.416			nd/nd/41	<.001
		RFA	181	nd/nd/85.9†				nd/nd/71	
Liu, 2016[14]	Retrospective cohort, PS-matched, Child-Pugh grade A	SR	79	97/97/80	.034			92/65/48	<.001
		RFA	79	97/83/66				68/36/18	
Ng, 2017[11]	Subgroup in RCT, Child-Pugh grade A*	SR	29	100/93/76	.95			83/66/52	.896
		RFA	26	100/89/69				77/62/46	
The present study	Retrospective cohort, PS-matched, Child-Pugh grade A	SR	48	97.9/88.8/77.0	.776	8.4/39.6/39.6	.027	89.6/57.7/54.7	.036
		RFA	48	97.9/91.6/79.2		10.8/47.1/68.7		87.3/50.5/29.9	

BCLC = Barcelona clinic liver cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, nd = not documented, No. = number of patients, PS = propensity score, RCT = randomized controlled trial, RFA = radiofrequency ablation, RF-survival = recurrence-free survival, SR = surgical resection, TACE = transarterial chemoembolization.

* Including 2 patients belonging to Child grade B in RFA group.

† HCC-specific survival.

surgical resection reduced the recurrence of HCC more reliably than RFA in very early-stage HCC patients. However, overall survival did not differ significantly based on the initial treatment. Several studies have presented similar results.[13,15] In particular, propensity score-matched studies on early-stage HCC have shown significantly lower recurrence after resection than RFA[13,14]

The reason for the similar survival rates despite the higher recurrence rates observed in the RFA group than in the resection group seems to be the recurrence pattern in the RFA group. A considerable fraction of first recurrences in the RFA group could be attributed to local recurrence (Table 3). In addition, the first recurrence pattern consisting of vascular invasion or BCLC stage C, in which it was difficult to achieve CR, was significantly less frequent in the RFA group than in the resection group. Therefore, most recurrences in the RFA group were manageable by additional treatment (Table 4), resulting in extension of overall survival comparable to that of the resection group. Moreover, despite lower overall recurrence rate compared with the RFA group, the high proportion of recurrence with an advanced pattern in the resection group may have caused the overall survival to be similar to that of the RFA group. In this regard, it should be noted that approximately a third of patients who presented with intermediate or advanced stage HCC recurrence did not undergo strictly regular follow-up examinations after achieving CR. We speculate that if a stricter long-term close follow-up had been performed following resection, it might have improved the survival of resection group by reducing the cases of recurrent HCC that had not been detected sufficiently early to prevent progression.

The results of several other studies were consistent with those of the present study (Table 6). One particular study[13] using propensity-score matching showed similar results to the present study. A nationwide cohort study[20] from Japan showed that surgical resection was significantly superior to RFA in terms of overall survival as well as HCC recurrence, although their follow-up durations were relatively short. Of note, there were obvious differences in primary outcomes between the studies. A retrospective study by Peng et al[12] indicated that RFA yielded lower mortality rates than surgical resection, and recommended RFA over resection for patients with very early HCC. However, overall survival after resection in that study was excessively low compared to other studies. Conversely, the study by Liu et al[14] showed a considerably lower 5-year survival after RFA than those of other studies. These findings imply that the efficiency of the selected procedure and patient management varies according to the institute, which suggests that therapy protocols must be changed by the institute.

Multivariate analyses using the Cox regression model showed that risk factors for mortality were non-HBV-associated liver disease, PT prolongation, and high levels of serum creatinine. The better prognosis of patients with an HBV-associated liver disease may be due to the use of antiviral agents for HBV infection. Antiviral agents improve liver function, fibrosis, and prognosis of patients with chronic HBV infection. In particular, antiviral treatment has been reported to decrease the occurrence and the recurrence of HCC by reducing HBV DNA.[21–23] PT is one of the factors contributing to the Child-Pugh score and the MELD and represents the liver function of patients with chronic liver disease. Moreover, PT has also been associated with prognosis of patients with chronic liver disease who underwent invasive procedures.[24–27] The serum creatinine level is also a factor contributing to the MELD, and its increase indicates injury to other organs, especially the kidney. The use of contrast media on surveillance testing or subsequent therapy such as TACE for HCC recurrence can easily aggravate existing kidney injury and

the prognosis of patients with a high level of serum creatinine. Overall survival appeared to be associated with baseline liver function and comorbidities rather than treatment modality.

Risk factors for recurrence of HCC include the presence of diabetes mellitus, lower serum albumin levels, and the use of RFA as a treatment method instead of surgical resection. Diabetes has been reported as an important carcinogenic factor in cirrhotic patients and an aggravating factor for overall survival and recurrence in HCC patients.[27–30] Low levels of serum albumin, which is indicative of chronic liver disease progression, has also been suggested to accelerate the recurrence of HCC in several studies.[31,32] Surgical resection has been demonstrated to be effective in preventing HCC recurrence, especially local recurrence defined as intrahepatic metastasis rather than de novo HCC.

The present study used a retrospective cohort which has inherent limitations. However, we attempted to overcome these shortages by investigating a comparable number of subjects as in previous studies and by conducting propensity-score matching to avoid bias and potential confounders.

In conclusion, the present study indicates that surgical resection has the benefit of reducing HCC recurrence even though it does not have an impact on overall survival. We suggest that surgical resection should still be considered as the first line of treatment in patients with very early HCC, but the proficiency for each procedure at an institute must also be considered. In addition, regular surveillance testing for early detection of recurrence is important to extend survival of patients with very early-stage HCC.

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CJM and USH: study concept and design.
JH and AH: statistical analysis.
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