

## Role of Radiofrequency Ablation in Patients with Hepatocellular Carcinoma Who Undergo Prior Transarterial Chemoembolization: Long-Term Outcomes and Predictive Factors

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**Background/Aims:** The role of radiofrequency ablation (RFA) remains uncertain in patients with viable hepatocellular carcinoma (HCC) after transarterial chemoembolization (TACE). **Methods:** A total of 101 patients (April 2007 to August 2010) underwent RFA for residual or recurrent HCC after TACE. We analyzed their long-term outcomes and predictive factors. **Results:** The overall survival rates after RFA were 93.1%, 65.4%, and 61.0% at 1, 3, and 5 years, respectively. Predictive factors for favorable overall survival were Child-Pugh class A (hazard ratio [HR], 3.45;  $p=0.001$ ), serum  $\alpha$ -fetoprotein (AFP) level  $<20$  ng/mL (HR, 2.90;  $p=0.02$ ), and recurrent tumors after the last TACE (HR, 3.14;  $p=0.007$ ). The cumulative recurrence-free survival rate after RFA at 6 months was 50.1%. Predictive factors for early recurrence (within 6 months) were serum AFP level  $\geq 20$  ng/mL (HR, 3.02;  $p<0.001$ ), tumor size  $\geq 30$  mm at RFA (HR, 2.90;  $p=0.005$ ), and nonresponse to the last TACE (HR, 2.13;  $p=0.013$ ). **Conclusions:** Patients with recurrent or residual HCC who undergo prior TACE show a favorable overall survival, although their tumors seem to recur early and frequently. While good liver function, a low serum AFP level, and recurrent tumors were independent predictive factors for a favorable overall survival, poor response to TACE, a high serum AFP level, and large tumors are associated with early recurrence. (*Gut Liver* 2014;8:543-551)

**Key Words:** Carcinoma, hepatocellular; Transarterial chemoembolization; Radiofrequency ablation; Outcome; Recurrence

### INTRODUCTION

Radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) have been used worldwide for local ablation therapies in hepatocellular carcinoma (HCC). Currently, RFA is considered the initial curative treatment of choice because of its favorable results in patients with small unresectable HCC.<sup>1,2</sup> Meta-analysis showed that RFA was superior to PEI in terms of survival and local control of the tumor in patients with HCC.<sup>3,4</sup> Five-year overall survival and recurrence-free survival were about 60% and 20% in patients who received RFA as first-line therapy for HCC.<sup>5,6</sup> RFA is no less effective in the overall survival of HCC than surgical resection. RFA is superior to surgical resection in terms of peri-procedural mortality while local recurrence rate is higher in RFA than surgical resection.<sup>7</sup> RFA has also been applied to patients with recurrent HCC after surgical resection, and RFA could be effective in treating intrahepatic recurrence of HCC after surgical resection. The 5-year overall survival rate was over 50% in patients with RFA for recurrent HCC after surgical resection although the recurrence rate after RFA was over 90% at 5 years.<sup>8</sup> Pre-RFA level of serum  $\alpha$ -fetoprotein (AFP) and resected tumor size were associated with long-term survival.<sup>8</sup> Also, a recent cohort study showed that repeated RFA can successfully control the intrahepatic recurrences of HCC after RFA. The estimated 5-year overall and disease-free survival rates after repeated RFAs were 40.1% and 38.0%, respectively.<sup>9</sup>

Transarterial chemoembolization (TACE) has been widely applied for HCC which is not suitable for curative treatment including surgery, liver transplantation, and local ablation. It is recommended as palliative therapy for intermediate stage of HCC since its beneficial effect on overall survival in unresectable HCC has been shown.<sup>1,2</sup> In actual clinical practice, RFA is

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one of the various treatment modalities for residual or recurrent tumors after TACE. However, there are few studies on the outcome of RFA for viable tumors after TACE.

The aim of this study is to determine the role of RFA for recurred (residual or newly developed) HCC after TACE. We investigated the effect of RFA on an overall survival and recurrence-free survival in patients with recurred HCCs after TACE. Also, the predictive factors for overall survival and recurrence were evaluated in patients with RFA therapy for recurred HCCs after TACE.

## MATERIALS AND METHODS

### 1. Study patients

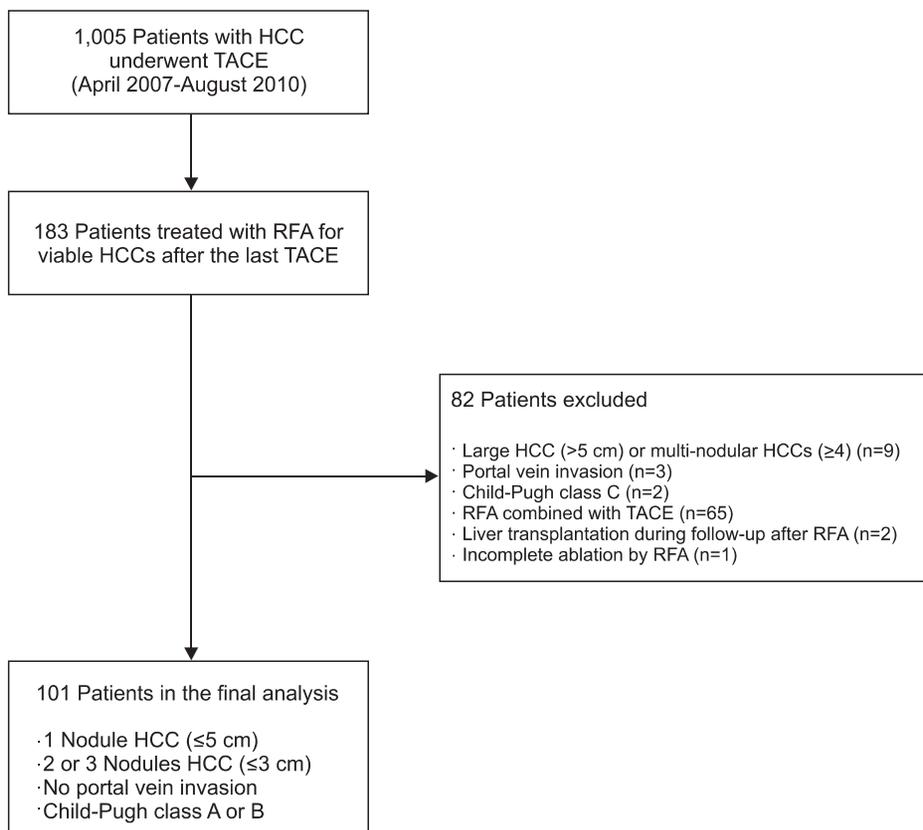
A total of 1,005 patients with HCC underwent TACE between April 2007 and August 2010 at our hospital. HCC was diagnosed histologically or clinically according to the Korean Liver Cancer Study Group guideline.<sup>10,11</sup> The clinical diagnosis of HCC was made based on the combination of characteristic image findings at dynamic computed tomography (CT) or magnetic resonance imaging and elevated serum AFP levels in patients with Chronic hepatitis B, hepatitis C, or liver cirrhosis.

A total of 183 patients were treated with RFA for residual or recurrent HCC after TACE. Among them, 101 patients receiving RFA for residual (n=63) or recurrent (n=38) tumors after TACE and fulfilling the following criteria were included in the final

analysis (Fig. 1): 1) single nodular HCC with  $\leq 5$  cm in diameter or multinodular HCCs ( $\leq 3$  in number) with  $\leq 3$  cm in diameter; 2) no evidence of portal vein invasion; and 3) Child-Pugh class A or B. Eighty-two patients were excluded due to the following reasons: nine cases with large HCC ( $>5$  cm in diameter) or four or more tumors, three cases with portal vein invasion, two cases with Child-Pugh class C, 65 cases receiving RFA combined with TACE (RFA performed within 14 days after TACE), two cases undergoing liver transplantation during follow-up after RFA, and one case with incomplete ablation by RFA.

### 2. TACE and RFA

At our institution, TACE was performed as follows. After a celiac and superior mesenteric arteriogram, the hepatic artery was catheterized using a 5-French catheter (Cook, Bloomington, IN, USA). The 3-French microcatheter (Microferret; Cook) was used to find the tumor-feeding arteries for selective embolization. After the feeding artery to the tumor was selected, the segmental embolization of the tumor supplying artery was done using an emulsion of iodized oil (Lipiodol; Andre Gurbet, Aulnay-sous-Bois, France) and doxorubicin hydrochloride (Adriamycin RDF; Ildong Pharmaceutical, Seoul, Korea). The dose of emulsion agent was determined taking into consideration the tumor size, number of tumors, supplying vessel, and underlying liver function. This emulsion agent was infused until stasis of arterial flow had been achieved and/or the iodized oil was seen in the portal



**Fig. 1.** Flow diagram of the patients in this study. HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation.

branches. Thereafter, embolization with gelatin sponge particles (1 to 2 mm in diameter, Gelfoam; Upjohn, Kalamazoo, MI, USA) was performed. Immediately after embolization, angiogram was done again to evaluate the extent of the vessel occlusion.

In terms of RFA, ultrasound was used to guide safe entry. It was also helpful for targeting the index tumor, and monitoring the ablation process. The procedure was performed using internally cooled electrodes with an exposed tip (Cool-tip RFA system, Valleylab, Boulder, CO, USA; or VIVA RF System, STARmed, Goyang, Korea). Based on the manufacturer's instructions for each device, impedance-based control of the generator was adjusted to transfer the radiofrequency energy. If the sonic window for the target was poor or the tumor was adjacent to the colon or the diaphragm, an infusion to create an artificial ascites was performed.<sup>12</sup> To control procedure-related pain, the patients were treated with a local injection of 2% lidocaine hydrochloride followed by an intravenous drip infusion of 50 mg pethidine hydrochloride mixed with 50 mL of 5% dextrose in water. The drip infusion was started at a rate of 2 mL/min. Thereafter, the infusion rate was modulated according to the intensity of pain. Dynamic abdominal CT was performed for checking the complete ablation of the tumor within 2 hours after RFA procedure. All patients had complete ablation with technical success for the treated lesions by RFA. Complete ablation was defined as complete necrosis of all tumors and surrounding normal hepatic parenchyma of at least 5 mm width. To achieve an adequate ablation margin, multiple overlapping ablations were performed if needed. After the ablation of the target tumor, the electrode was retracted cautiously to prevent tumor seeding or bleeding.

### 3. Baseline characteristics, clinical outcomes and factors associated with survival and early recurrence

The baseline characteristics of the total 101 patients were evaluated as follows: age, gender, etiology of liver disease, Child-Pugh class, Barcelona Clinic Liver Cancer (BCLC) tumor stage at initial diagnosis, modality of initial therapy for HCC, total number of TACE sessions before RFA, response to the last TACE, duration between the last TACE and RFA, the pattern of recurrence after TACE (residual tumor after TACE versus newly developed tumor), tumor location, size, number, and serum AFP level. All variables were described at RFA unless otherwise mentioned. The efficacy of the last TACE was evaluated by four phase dynamic CT 3 or 4 weeks after the procedure. The response to TACE was classified into four categories (complete remission [CR], partial remission [PR], stable disease [SD], and progressive disease [PD]) based on the dynamic CT findings 1 month after the last TACE according to a modified Response Evaluation Criteria in Solid Tumors guideline.<sup>13</sup> We classified our patients into two groups: responders (CR and PR) versus nonresponders (SD and PD).

Overall survival rates, recurrence-free survival rates, and

**Table 1.** Baseline Characteristics (n=101)

Characteristic	Value
Age, yr	63.2±9.4
Gender	
Women	24 (24)
Men	77 (76)
Etiology	
HBV	71 (70)
HCV	17 (17)
HBV and HCV	1 (1)
Alcohol	5 (5)
Others	7 (7)
Child-Pugh class	
A	86 (85)
B	15 (15)
Tumor stage (BCLC) at initial diagnosis	
Very early	9 (9)
Early	68 (67)
Intermediate	22 (22)
Advanced	2 (2)
Initial treatment modality	
TACE	69 (68)
RFA	17 (17)
Surgical resection	15 (15)
Sessions of TACE before RFA	
1	26 (26)
2	24 (24)
3	18 (18)
4 or more	33 (32)
Response to the last TACE	
Complete response	38 (36)
Partial response	39 (38)
Stable disease	13 (13)
Progressive disease	13 (13)
Residual or recurrent HCC after TACE	
Residual tumor after TACE	63 (62)
Newly developed tumor	38 (38)
Duration between the last TACE and RFA, days	95 (26–673)
Tumor location	
Right lobe	75 (73)
Left lobe	21 (22)
Both lobe	5 (5)
Maximum diameter of viable tumor, mm	18.8±8.4
Tumor no.	
1	81 (80)
2	18 (18)
3	2 (2)
Serum AFP level, ng/mL	16.5 (1.3–19,812.0)

Data are presented as mean±SD, median (range), or number (%). HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; AFP,  $\alpha$ -fetoprotein.

predictive factors for overall survival and early recurrence after RFA were evaluated. This study was approved by the Institutional Review Board of Samsung Medical Center.

#### 4. Statistical analysis

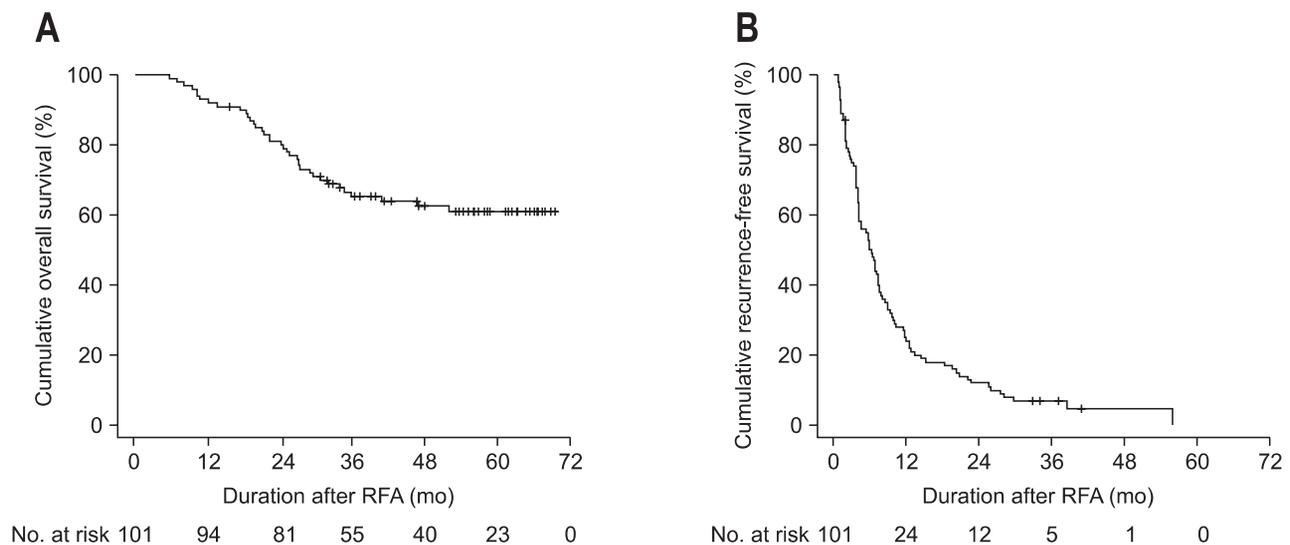
Cumulative overall survival rates and recurrence-free survival rates were calculated by the Kaplan-Meier curve. To compare the overall survival and early recurrence according to significant risk factors, log-rank test was used. Univariate and multivariate Cox proportional hazard models were used to assess the predictive factors for overall survival and early recurrence of HCC after RFA. If p-value was less than 0.05, the result was

considered statistically significant. All statistical analyses were performed using SPSS for Window release 18.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### 1. Baseline characteristics

Baseline characteristics of the enrolled 101 patients were as follows (Table 1). The median age of the enrolled patients was 63 years (range, 41 to 84 years) at RFA therapy. Of these patients, men were 77 patients (76%). The etiology of the underlying liver disease was hepatitis B virus (HBV) infection (n=71),



**Fig. 2.** Clinical outcomes after radiofrequency ablation (RFA) in 101 patients with residual or recurrent hepatocellular carcinoma who underwent previous transarterial chemoembolization. (A) The cumulative 1-, 3-, and 5-year overall survival rates were 93.1%, 65.4%, and 61.0%, respectively. (B) The cumulative 1-, 2-, and 3-year recurrence-free survival rates were 24.0%, 12.0%, and 7.0%, respectively.

**Table 2.** Univariate and Multivariate Analyses of the Predictive Factors for a Favorable Overall Survival in Patients Who Received RFA for Residual or Recurred HCC after TACE

	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age <70 yr at RFA	1.05 (0.51–2.17)	0.899	-	-
Women	0.66 (0.33–1.34)	0.251	-	-
Etiology: hepatitis B	1.76 (0.90–3.42)	0.097	-	-
Child-Pugh class A	3.51 (1.68–7.35)	0.001	3.45 (1.63–7.31)	0.001
BCLC stage (0 or A)	1.17 (0.52–2.65)	0.709	-	-
No. of TACE ≤2 sessions	2.48 (1.24–4.93)	0.010	-	-
TACE responder (CR or PR)	2.57 (1.33–4.97)	0.005	-	-
Newly developed tumor (compared to residual tumor)	3.19 (1.40–7.27)	0.006	3.14 (1.37–7.18)	0.007
Tumor location (unilobar)	1.55 (0.37–6.45)	0.549	-	-
Tumor size (<30 mm)	1.05 (0.37–2.97)	0.924	-	-
Single tumor	1.22 (0.56–2.67)	0.623	-	-
Serum AFP level (<20 ng/mL)	2.62 (1.33–5.15)	0.005	2.90 (1.47–5.74)	0.02

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; CR, complete remission; PR, partial remission; AFP,  $\alpha$ -fetoprotein.

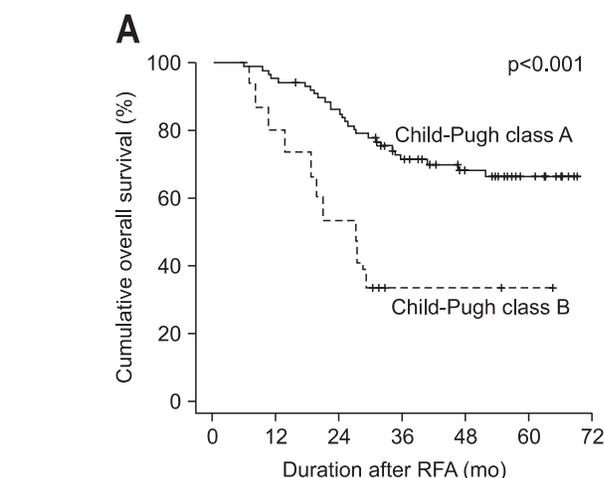
hepatitis C virus (HCV) infection (n=17), co-infection with HBV and HCV (n=1), alcohol (n=5), and others (n=7). Child-Pugh class of the patients was class A in 86 and class B in 15 patients. At the initial diagnosis, tumor stages (BCLC) were very early in nine patients, early in 68, intermediate in 22, and advanced in two patients. Among these patients, 69 patients were treated with TACE, 17 with RFA, and 15 with surgical resection as an initial therapy. The total number of TACE sessions applied before RFA was one in 26 cases, two in 24 cases, three in 18 cases, and four or more in 33 cases (median, three sessions; range, 1 to 14). The responses to the last TACE were CR in 37 patients, PR in 38, SD in 13, and PD in 13. RFA was done for residual tumor (n=63) or newly developed intrahepatic tumor (n=38) after the last TACE. The median duration from last TACE to RFA was 95 days. The number of tumors was one in 81 patients, two in 18 patients, and three in two patients. The tumors treated with RFA were located in right lobe (n=75), left lobe (n=21), and both

lobes (n=5). The maximal size of a viable tumor treated with RFA was 18.8±8.4 mm. The median level of serum AFP was 16.5 ng/mL.

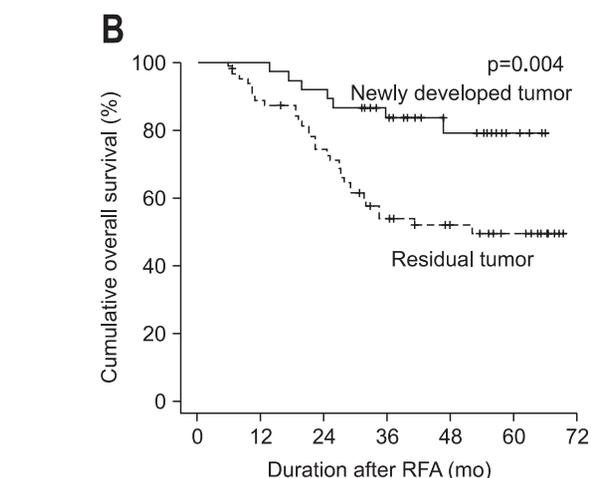
### 2. Overall survival and its predictive factors

During median follow-up duration of 39.0 months (range, 5.9 to 69.4 months), 37 patients died. Cumulative overall survival rates after RFA at 1, 3, and 5 years were 93.1%, 65.4%, and 61.0%, respectively (Fig. 2A).

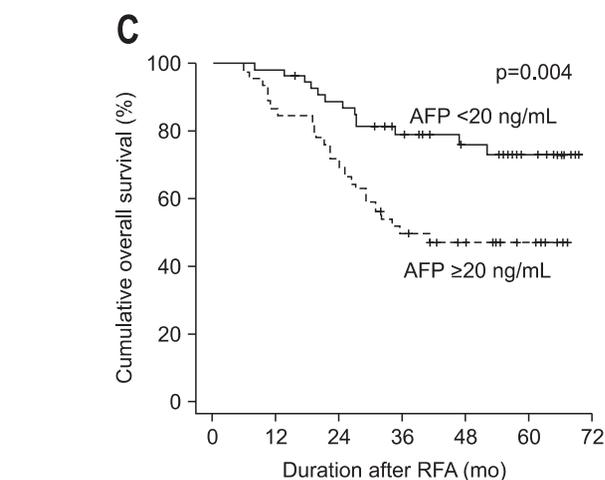
Predictive factors for overall survival were analyzed. A univariate analysis demonstrated that the predictive factors for favorable overall survival were Child-Pugh class A at RFA, sessions of TACE ≤2, responder to the last TACE, newly developed tumor after TACE, and pre-RFA serum AFP <20 ng/mL. The independent predictive factors for favorable overall survival shown by multivariate analysis were Child-Pugh class A at RFA (hazard ratio [HR], 3.45; p=0.001), newly developed tumor after



No. at risk	0	12	24	36	48	60	72
Child-Pugh class A	86	82	73	53	38	22	0
Child-Pugh class B	15	12	8	2	2	1	0



No. at risk	0	12	24	36	48	60	72
Newly developed	38	38	35	26	18	7	0
Residual	63	56	46	29	22	16	0



No. at risk	0	12	24	36	48	60	72
AFP <math><20</math> ng/mL	55	54	48	33	25	12	0
AFP <math>\geq 20</math> ng/mL	46	40	33	22	15	11	0

**Fig. 3.** The cumulative overall survival rates according to the independent predictive factors. (A) The 1-, 3-, and 5-year cumulative survival rates in patients with Child-Pugh class A were 95.3%, 71.2%, and 66.3%, which were significantly higher than the rates of 80.0%, 33.3%, and 33.3% in those with Child-Pugh class B ( $p<0.001$ ). (B) The cumulative 1-, 3-, and 5-year survival rates after radiofrequency ablation (RFA) in patients with newly developed tumors were significantly higher than those with residual tumors after the last transarterial chemoembolization (100%, 83.6%, and 79.2% versus 88.9%, 54.2%, and 49.8%;  $p=0.004$ ). (C) Patients with a serum  $\alpha$ -fetoprotein (AFP) level <math><20</math> ng/mL showed cumulative 1-, 3-, and 5-year survival rates superior to those with a serum AFP level p=0.004). A log-rank test was used to compare the differences in the overall survival according to each risk factor.

**Table 3.** Univariate and Multivariate Analyses of the Predictive Factors for Early (within 6 Months) Recurrence in Patients Who Received RFA for Recurred HCC after TACE

	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age $\geq 70$ yr at RFA	0.83 (0.44–1.59)	0.581	-	-
Men	0.71 (0.38–1.32)	0.278	-	-
Etiology: other than chronic hepatitis B	1.89 (1.07–3.33)	0.028	-	-
Child-Pugh class B	1.44 (0.72–2.89)	0.299	-	-
BCLC stage (B or C)	1.18 (0.61–2.31)	0.624	-	-
No. of TACE $\geq 3$ sessions	1.05 (0.60–1.83)	0.860	-	-
TACE nonresponder (SD or PD)	1.99 (1.11–3.58)	0.022	2.13 (1.17–3.85)	0.013
Residual tumor (compared to newly developed tumor)	1.58 (0.87–2.86)	0.134	-	-
Tumor location (bilobar)	0.83 (0.20–3.42)	0.798	-	-
Tumor size ( $\geq 30$ mm)	3.07 (1.48–6.36)	0.003	2.90 (1.39–6.04)	0.005
Tumor number ( $\geq 2$ )	1.28 (0.65–2.50)	0.475	-	-
Serum AFP level ( $\geq 20$ ng/mL)	3.13 (1.74–5.63)	<0.001	3.02 (1.69–5.38)	<0.001

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; SD, stable disease; PD, progressive disease; AFP,  $\alpha$ -fetoprotein.

TACE (HR, 3.14;  $p=0.007$ ), and pre-RFA serum AFP  $<20$  ng/mL (HR, 2.90;  $p=0.02$ ) (Table 2).

The cumulative 1-, 3-, and 5-year survival rates in patients with Child-Pugh class A were significantly higher than those with Child-Pugh class B (95.3%, 71.2%, and 66.3% versus 80.0%, 33.3%, and 33.3%;  $p<0.001$ ) (Fig. 3A). The cumulative 1-, 3-, and 5-year survival rates after RFA in patients with the newly developed tumor after TACE were 100%, 83.6%, and 79.2%, which were significantly higher than those with the residual tumor after the last TACE (88.9%, 54.2%, and 49.8%;  $p=0.004$ ) (Fig. 3B). The cumulative 1-, 3-, and 5-year survival rates were 98.2%, 79.1%, and 73.3% in patients with serum AFP  $<20$  ng/mL and were 87.0%, 49.7%, and 47.3% in those with AFP  $\geq 20$  ng/mL (Fig. 3C). The patients with low AFP levels had better survival than those with high AFP levels ( $p=0.004$ ).

### 3. Recurrence-free survival and predictive factors for early recurrence

Recurrence of HCC after RFA was noted in 95 patients (94%), local tumor progression in 13 patients (13%), intrahepatic distant recurrence in 79 patients (78%), and extrahepatic metastasis in three patients (3%). Cumulative recurrence-free survival rates after RFA at 1, 2, and 3 years were 24.0%, 12.0%, and 7.0%, respectively (Fig. 2B).

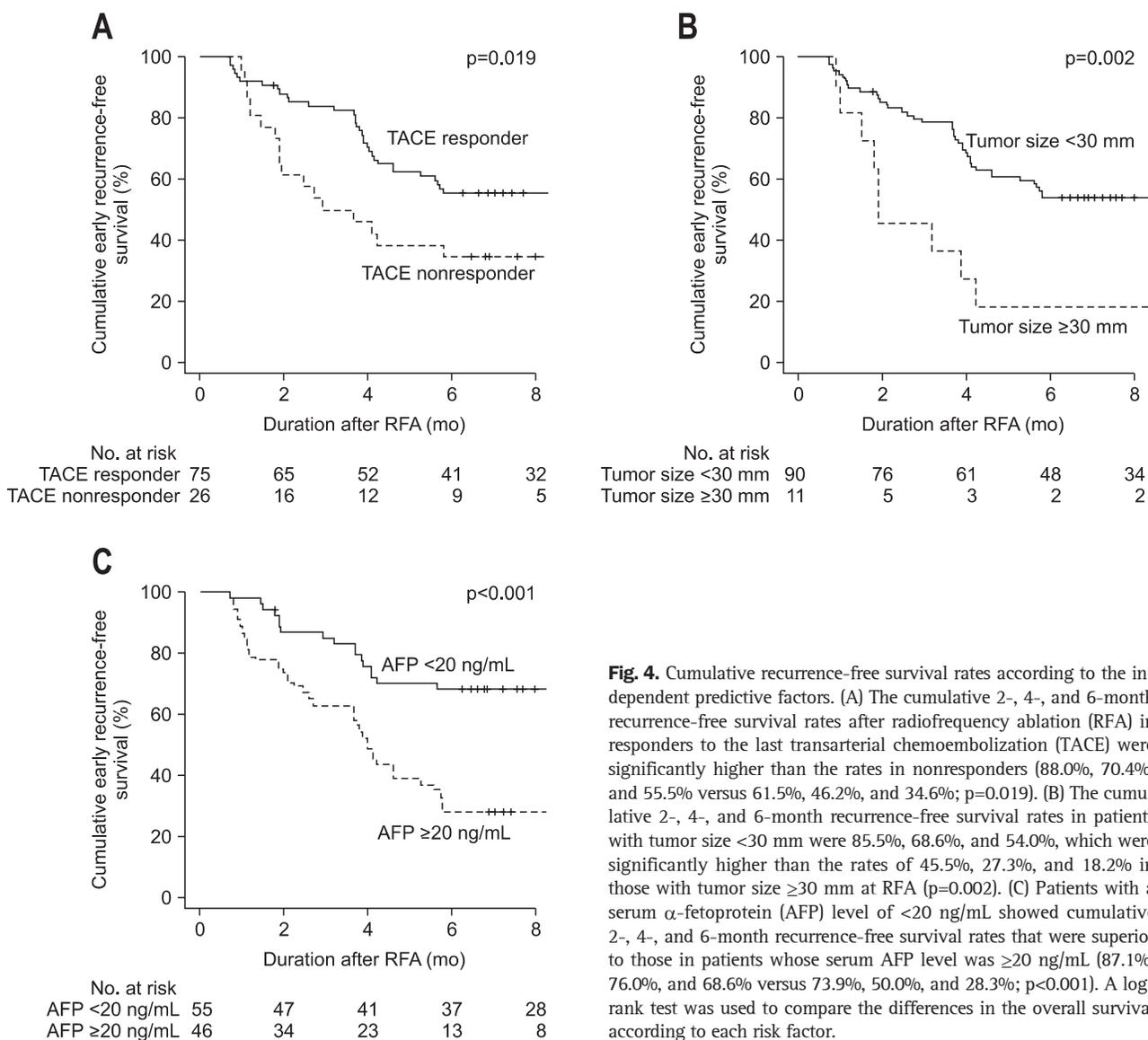
Since median duration to recurrence was 5.8 months, we analyzed the predictive factors for early recurrence (defined as recurrence within 6 months) after RFA. A univariate analysis showed that the predictive factors for early recurrence were etiology other than chronic hepatitis B (HR, 1.89;  $p=0.028$ ), nonresponder to the last TACE (HR, 1.99;  $p=0.022$ ), tumor size  $\geq 30$  mm at RFA (HR, 3.07;  $p=0.003$ ), and pre-RFA serum AFP  $\geq 20$  ng/mL (HR, 3.13;  $p<0.001$ ). Patients with residual tumors

after TACE showed a tendency for early recurrence compared to those with the newly developed tumors; however, it did not reach a statistical significance (HR, 1.58;  $p=0.134$ ). The predictive factors for early recurrence by multivariate analysis were pre-RFA serum AFP  $\geq 20$  ng/mL (HR, 3.02;  $p<0.001$ ), tumor size  $\geq 30$  mm at RFA (HR, 2.90;  $p=0.005$ ), and nonresponder to the last TACE (HR, 2.13;  $p=0.013$ ) (Table 3).

The cumulative 2-, 4-, and 6-month recurrence-free survival rates were 88.0%, 70.4%, and 55.5% in responders to the last TACE and were 61.5%, 46.2%, and 34.6% in nonresponders to the last TACE. Recurrence-free survival rates were significantly lower in nonresponders compared to responders ( $p=0.019$ ) (Fig. 4A). The cumulative 2-, 4-, and 6-month recurrence-free survival rates were 85.5%, 68.6%, and 54.0% in patients with tumor size  $<30$  mm at RFA and were 45.5%, 27.3%, and 18.2% in those with tumor size  $\geq 30$  mm at RFA. Recurrence-free survival rates after RFA were inferior in patients with tumor size  $\geq 30$  mm compared to those with  $<30$  mm at RFA ( $p=0.002$ ) (Fig. 4B). The cumulative 2-, 4-, and 6-month recurrence-free survival rates were 87.1%, 76.0%, and 68.6% in pre-RFA serum AFP  $<20$  ng/mL and were 73.9%, 50.0%, and 28.3% in pre-RFA serum AFP  $\geq 20$  ng/mL (Fig. 4C). Patients with high AFP levels showed a poorer recurrence-free survival rate than those with low AFP levels ( $p<0.001$ ).

## DISCUSSION

Previous studies have already shown the outcomes and predictive factors after RFA in treatment-naïve HCC patients or in those with recurrent HCC after radical therapy (surgical resection or local ablation).<sup>5,6,14–16</sup> However, the role of RFA in residual or recurred HCCs after TACE remains uncertain. There-



**Fig. 4.** Cumulative recurrence-free survival rates according to the independent predictive factors. (A) The cumulative 2-, 4-, and 6-month recurrence-free survival rates after radiofrequency ablation (RFA) in responders to the last transarterial chemoembolization (TACE) were significantly higher than the rates in nonresponders (88.0%, 70.4%, and 55.5% versus 61.5%, 46.2%, and 34.6%;  $p=0.019$ ). (B) The cumulative 2-, 4-, and 6-month recurrence-free survival rates in patients with tumor size <30 mm were 85.5%, 68.6%, and 54.0%, which were significantly higher than the rates of 45.5%, 27.3%, and 18.2% in those with tumor size  $\geq 30$  mm at RFA ( $p=0.002$ ). (C) Patients with a serum  $\alpha$ -fetoprotein (AFP) level of <20 ng/mL showed cumulative 2-, 4-, and 6-month recurrence-free survival rates that were superior to those in patients whose serum AFP level was  $\geq 20$  ng/mL (87.1%, 76.0%, and 68.6% versus 73.9%, 50.0%, and 28.3%;  $p<0.001$ ). A log-rank test was used to compare the differences in the overall survival according to each risk factor.

fore, we enrolled 101 patients with recurrent or residual HCC after previous TACE and investigated their overall survival, recurrence-free survival rates after RFA, and predictive factors for overall survival and early recurrence. One-, 3-, and 5-year overall survival rates after RFA were 93.1%, 65.4%, and 61.0%, respectively, and Child-Pugh class A at RFA, pre-RFA serum AFP <20 ng/mL, and the newly developed tumor after TACE were significant predictive factors for favorable overall survival according to the multivariate analysis. One-, 2- and 3-year recurrence-free survival rates were 24.0%, 12.0%, and 7.0%, respectively, and pre-RFA serum AFP  $\geq 20$  ng/mL, tumor size  $\geq 30$  mm at RFA, and nonresponder to the last TACE were significant predictive factors for early recurrence. Hence, we showed favorable overall survival rates after RFA, despite the high recurrence rate, in patients with viable HCC undergoing previous TACE and we suggested the possible predictive factors in these patients.

In this study, overall survival rates of the patients with RFA

therapy for residual or recurred HCCs after TACE were 93.1%, 65.4%, and 61.0% at 1, 3, and 5 years, respectively. Shiina *et al.*<sup>5</sup> reported that the 1-, 3-, and 5-year survival rates were 96.6%, 80.5%, and 60.2%, respectively in patients who received RFA as first-line treatment for HCC. N'Kontchou *et al.*<sup>6</sup> showed that the 3- and 5-year survival rates of cirrhotic patients after initial RFA therapy for HCC were 60% and 40%, respectively. In patients with RFA for recurred HCC after surgical resection, overall survival rates were reported to be 93.9%, 65.7%, and 51.6% at 1, 3, and 5 years, respectively.<sup>8</sup> Three- and 5-year survival rates were 67.0% and 40.1% in repeated RFAs for small HCCs in patients with cirrhosis.<sup>9</sup> Clinical outcomes of RFA for recurred or residual HCCs after TACE in our study were similar to those for recurred HCCs after surgical resection or repeated RFA, but inferior to those of RFA as a first-line therapy for HCC.

Our findings showed that the independent predictive factors for overall survival were Child-Pugh class, the pattern of recur-

rent HCC after TACE (residual or newly developed), and the level of serum AFP in patients with RFA for recurred HCC after TACE. Several studies regarding RFA as the first-line treatment revealed that age, antibody to hepatitis C virus, Child-Pugh class, prothrombin time, tumor size, tumor number, tumor location, and serum tumor marker are related to overall survival.<sup>5,6,17</sup> Meanwhile serum AFP, ablated and resected tumor size, serum albumin, and the duration between initial hepatectomy and tumor recurrence were associated with overall survival in the patients with RFA for recurred HCC after surgical resection.<sup>8,16</sup> The predictive factors for overall survival in repeated RFA for HCC were HBV and HCV co-infection, Child-Pugh class, time of first recurrence, and type of first recurrence.<sup>9</sup> In the present study, a notable predictive factor was the pattern of recurrent HCC after TACE. Patients with RFA for newly developed HCC after TACE had a significantly favorable survival compared to patients with residual tumor after TACE. It suggests that the overall survival in HCC patients with RFA after TACE may be associated with tumor biology including susceptibility to TACE therapy. When HCC is well-controlled by TACE, another newly developed HCC can be a good candidate for RFA. It is expected that RFA therapy can provide the more survival gain in newly developed tumor after controlling the original HCC by TACE than residual tumor after TACE.

While overall survival was comparatively favorable in this study, the recurrence of HCC after RFA was very frequent and considerably early. Recurrence rates were 76.0%, 88.0%, and 93.0% at 1, 2, and 3 years, respectively. Previous studies showed that 1-, 3-, and 5-year recurrence rates were 27%, 63%–66.5%, and 78%–82%, respectively in patients who received RFA as the first-line treatment for HCC.<sup>5,6</sup> In patients with RFA for recurred HCCs after surgical resection, recurrence rates were 47.8%–46.6%, 78.7%–86%, and 92.8% at 1, 3, and 5 years, respectively.<sup>8,14</sup> Three- and 5-year recurrence rates were 32.0%, and 62.0%, respectively in repeated RFAs for small HCCs (one or two nodules with  $\leq 35$  mm in diameter) in patients with cirrhosis. In this study, the recurrence rates were so high and the median of recurrence-free duration was as short as 5.8 months. These findings might come from the difference in tumor biology between the patients included in the previous studies and ours. Although all patients included in the final analysis of this study had HCC within the indication of RFA therapy regarding tumor size, tumor number, Child-Pugh class, and no portal vein invasion at the time of RFA, the presence of recurrent or residual tumor after palliative treatment might suggest the presence of more aggressive tumor biology in these patients compared to those with treatment-naïve tumor or recurrent tumor after curative treatment.

We investigated the predictive factors for early recurrence, defined as recurrence within 6 months, in the present study because the recurrence of HCC after RFA was noted in 95 patients (94%) and the median duration of recurrence was 5.8

months. The predictive factors for early recurrence were high levels of serum AFP, large tumor size, and a nonresponder to the last TACE. Several studies of RFA as an initial treatments revealed that antibody to hepatitis C virus, Child-Pugh class, platelet counts, tumor size, tumor number, and serum tumor marker were associated with recurrence.<sup>5,6</sup> Serum AFP, resected tumor size, extent of the resection, and microvascular invasion were related to tumor recurrence in the patients with RFA for recurred HCC after surgical resection.<sup>8,14</sup> The predictive factors for recurrence in repeated RFA for HCC were tumor number and tumor size.<sup>9</sup> The present study showed that nonresponders to the last TACE had higher recurrence rates than responders among patients with RFA for recurred HCC after TACE. The more aggressive nature of HCC resistant to TACE might be reflected in the higher recurrence rates after RFA therapy.

This study has some limitations. First, although our study included patients who fell within Milan criteria and had good liver function of Child A or B class, they were quite a heterogeneous group with respect to their demographic profiles, extent of the initial tumor, tumor biology, and previous treatments. Hence, we tried our best to elucidate independent predictive factors by multivariate analysis. Second, decision to perform RFA was made based on corresponding physician's choice, not on a predetermined fixed protocol. This might have given rise to a possible bias in this study as a retrospective one.

Despite the above limitations, the present study has considerable significance as the first study suggest the outcomes and predictive factors of RFA for recurred or residual HCC after TACE at a clinical practice in the real world setting. Further studies including a prospective trial might be warranted to clarify the role of RFA in these patients.

In conclusion, the overall survival after RFA is considerably favorable in patients with recurrent or residual HCC undergoing previous TACE, although HCC seems to recur early and frequently in these patients. While good liver function, low serum AFP level, and newly developed tumor are associated with favorable long-term survival, poor response to TACE, high serum AFP level, and large tumor were independent predictive factors for early recurrence.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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