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Original Article

Long-term outcome of intraoperative radiofrequency ablation for hepatocellular carcinoma and its efficacy as a primary treatment

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Backgrounds/Aims: We conducted this study to identify long-term outcomes following intraoperative radiofrequency ablation (IO-RFA) for hepatocellular carcinoma (HCC) and to reveal independent prognostic factors for survival. **Methods:** From December 1998 to February 2019, 183 patients underwent IO-RFA for HCC. These patients were divided into two groups according to whether RFA was done as a first-line (1-RFA group, n=106) or secondary-line (2-RFA group, n=77) treatment. Furthermore, we compared the survival outcomes between the 1-RFA and 2-RFA groups. **Results:** There were no significant differences in type of surgical approaches between the two groups (p=0.079). The number of tumors and largest tumor size were not significantly different between the two groups. Overall recurrence rate was 53%, and the 2-RFA group showed a higher recurrence rate (46.2% in 1-RFA group versus 62.3% in 2-RFA group; p=0.031). The 5-year overall survival (OS) and disease-free survival (DFS) rates of all the patients were 75.2% and 27.9%, respectively. The OS and DFS rates were significantly higher in the 1-RFA group. The 5-year OS rates were 83.6% and 64.9% in the 1-RFA and 2-RFA groups, respectively (p=0.010), whereas the 5-year DFS rates were 32.2% and 21.6%, respectively (p=0.012). On multivariate analysis, HBV-LC, 2-RFA, recurrence, and postoperative complications were independent predictive factors for survival. **Conclusions:** Therapeutic outcomes of IO-RFA were comparable to those of surgical resection. Additionally, 1-RFA might be an alternative treatment for naïve HCC in patients with uncompensated liver function and severe comorbidities. **(Ann Hepatobiliary Pancreat Surg 2020;24:24-32)**

Key Words: Hepatocellular carcinoma; Radiofrequency ablation; First-line; Second-line; Outcome

INTRODUCTION

Hepatocellular carcinoma (HCC) is currently the 5th most frequent cancer and a leading cause of cancer-related mortality worldwide.[1-3] Although potentially curative treatment options, such as hepatic resection and liver transplantation, are associated with significant survival benefits, only 10-30% of patients with HCC are eligible for surgery at the time of diagnosis.[4] Radiofrequency ablation (RFA) has been proposed as an alternative treatment owing to its safety and effectiveness for patients with early to intermediate stage HCC.[5,6] A meta-analysis of 31 studies comparing 16,103 patients who received either ablation or hepatic resection showed comparable long-term outcomes in lesions ≤2 cm in size, with significantly fewer complications and shorter hospital stay durations associated with ablation.[7] Furthermore, for those patients ineligible for surgery, ablation is a potentially curative modality, which has demonstrated a significant clinical efficacy with an overall 5-year survival rate between 68% and 76% for tumors ≤5 cm in size.[8,9] However, other studies showed that approximately 68.9% of patients had tumor recurrence after RFA, which is higher than the rate for liver transplantation and surgical resection.[10-12]

We conducted this study to identify long-term outcomes following intraoperative RFA (IO-RFA) and reveal independent prognostic factors for survival. Furthermore, we classified and compared survival outcomes according to whether the patients were treated with RFA as the first-line or second-line treatment.

PATIENTS AND METHODS

From December 1998 to February 2019, a total of 541

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patients underwent surgery for HCC at our institution. Among them, 342 patients underwent surgical resection, and 16 patients who underwent surgical resection with IO-RFA were excluded. The remaining 183 patients who

Table 1. Demographics and clinicopathologic data

	IO-RFA (n=183)	1-RFA (n=106)	2-RFA (n=77)	*p* value
Sex (male:female)	136 (74.3):47 (25.7)	72 (67.9):34 (32.1)	64 (83.1):13 (16.9)	**0.020**
Age (years, mean±SD)	63.3±9.11	64.3±8.81	61.9±9.4	0.076
Co-morbidity (n, %)				
HTN	74 (40.4)	38 (35.8)	36 (46.8)	0.138
DM	61 (33.3)	34 (32.1)	27 (35.1)	0.672
Chronic liver disease				
HBV-LC	113 (61.7)	62 (58.5)	51 (66.2)	0.287
HCV-LC	29 (15.8)	20 (18.9)	9 (11.7)	0.189
Alc-LC	44 (24)	26 (24.5)	18 (23.4)	0.857
Idiopathic LC	5 (2.7)	3 (2.8)	2 (2.6)	1.000
Tb	8 (4.4)	2 (1.9)	6 (7.8)	0.071
Other abdominal op	19 (10.4)	12 (11.3)	7 (9.1)	0.625
Previous Tx for HCC (n, %)				
Hepatectomy	20 (10.9)	2 (1.9)	18 (23.4)	**<0.001**
TACE	79 (43.2)	13 (12.3)	66 (85.7)	**<0.001**
Percutaneous RFA	26 (14.2)	15 (14.2)	11 (14.3)	0.979
Intraoperative RFA	30 (16.4)	16 (15.1)	14 (18.2)	0.578
Laboratory findings				
Hb	13.5±1.94	13.4±1.94	13.5±1.95	0.978
Plt	115±48.75	119.1±50	109.5±46.7	0.187
Alb	3.78±0.47	3.8±0.52	3.7±0.39	**0.048**
TB	1.09±0.58	1.04±0.56	1.16±0.61	0.186
INR	1.13±0.12	1.12±0.13	1.13±0.11	0.801
Tumor marker				
AFP	78.3±243.2	84.7±254.7	70.1±229	0.702
PIVKA II	72.9±189.0	51.3±77.25	99.5±268.61	0.207
ICG 15 min	27±15.2	27±14.6	28±16.6	0.935
Operation type (n, %)				0.079
Laparoscopic	163 (89.1)	95 (89.6)	68 (89.5)	
Open	11 (6)	8 (7.5)	3 (3.9)	
Open conversion	6 (3.3)	1 (0.9)	5 (6.6)	
Conversion from resection	2 (1.1)	2 (1.9)	0	
Tumor location (n, %)				
S1	3 (1.6)	1 (0.9)	2 (2.6)	0.574
S2	22 (12)	12 (11.3)	10 (13)	0.732
S3	30 (16.4)	18 (17)	12 (15.6)	0.801
S4	43 (23.5)	21 (19.8)	22 (28.6)	0.168
S5	35 (19.1)	17 (16)	18 (23.4)	0.213
S6	41 (22.4)	18 (17)	23 (29.9)	**0.039**
S7	58 (31.7)	33 (31.1)	25 (32.5)	0.848
S8	75 (41)	53 (50)	22 (28.6)	**0.004**
Number of tumors (mean±SD)	1.54±0.86 (1-6)	1.44±0.81	1.69±0.91	0.052
Largest tumor size (cm, mean±SD)	1.71±0.65 (0.3-4)	1.73±0.64	1.67±0.66	0.517

IO-RFA, intraoperative radiofrequency ablation; 1-RFA, primary radiofrequency ablation; 2-RFA, secondary radiofrequency ablation; HTN, hypertension; DM, diabetes mellitus; HBV-LC, hepatitis B virus-associated liver cirrhosis; HCV-LC, hepatitis C virus-associated liver cirrhosis; Alc-LC, alcoholic liver cirrhosis; LC, liver cirrhosis; Tb, tuberculosis; Tx, treatment; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; Hb, hemoglobin; Plt, platelet; Alb, albumin; TB, total bilirubin; INR, international normalized ratio; AFP, alpha fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; ICG, indocyanine green; SD, standard deviation

underwent IO-RFA only were finally included in the analysis. These patients were divided into two groups according to whether RFA was done as a primary or secondary treatment for HCC, which are as follows: primary RFA (1-RFA) and secondary RFA (2-RFA) groups. Primary RFA was defined as the first-line treatment for HCC after diagnosis. When the RFA was done for recurrent or incompletely treated lesions after a previous treatment, such as hepatic resection or transarterial chemoembolization (TACE), it was referred to as secondary RFA.

All patients were diagnosed and staged preoperatively by contrast computed tomography (CT) with arterial, portal, and delayed phases; magnetic resonance imaging (MRI) was also done routinely. Patients who showed typical HCC on imaging studies did not have additional biopsies. Tumor markers including alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were checked preoperatively and used for the postoperative follow-up. To evaluate the liver function, indocyanine green (ICG) test was done, and the retension rate 15 minutes after the injection was applied.

Most patients who underwent IO-RFA were laparoscopically approached, but the earlier phase of this cohort was conducted using laparotomy. Moreover, in cases wherein the localization of the tumor was not possible with intraoperative ultrasound or cases of severe adhesion due to previous surgery, the technique was converted to laparotomy. Three or four trocars were used for laparoscopic RFA. All patients underwent CT the next day of surgery to assess the adequacy of RFA.

Follow-up was updated from the electronic medical records on an outpatient. These evaluations included regularly scheduled physical examinations, CT or MRI scans, and serum level of AFP and PIVKA-II. Death, local recurrence, and distant metastasis were considered, and when no events were recorded, the patients were censored at the last date of follow-up. Overall survival (OS) and disease-free survival (DFS) were determined from the date of initial surgery to the date of death and recurrence or the last contact. For the patients whose long-term follow-up was discontinued, data from the Statistics Korea were applied.

Differences in numerical data between 1-RFA and 2-RFA groups were examined using the Chi-square test or Fischer's exact test. Student's t-test was applied to compare continuous variables. The OS and DFS rates were calculated using the Kaplan-Meier method. The log-rank test was used to analyze differences between survival curves. Cox proportional hazard regression was applied to determine independent predictive factors for survival and recurrence. A p-value <0.05 was considered statistically significant. All statistical analyses were done using SPSS software (version 24.0, IBM, New York, USA).

RESULTS

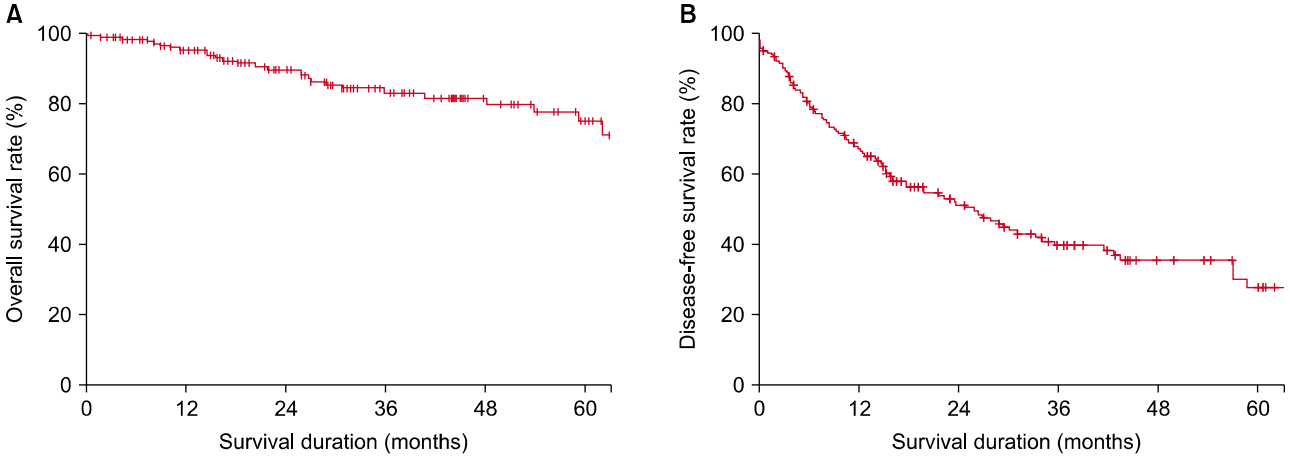
Patient demographics, clinicopathologic characteristics, and surgical outcomes

The demographics and clinicopathologic data of 183 patients who underwent IO-RFA for HCC are presented

Table 2. Surgical outcomes

	Intraop RFA (n=183)	1-RFA (n=106)	2-RFA (n=77)	p value
Operation duration (min, mean±SD)	117.6±52.6	111.4±50.7	126.1±54.3	0.063
Postop stay (day, mean±SD)	5.2±3.69 (2-35)	4.8±2.85	5.7±4.56	0.119
Complications (n, %)	31 (16.9)	17 (16)	14 (18.2)	0.703
Grade II	20 (10.9)	10 (9.4)	10 (13)	0.447
Grade IIIa	3 (1.6)	2 (1.9)	1 (1.3)	1.000
In-hospital mortality (n, %)	1 (0.5)	1 (0.9)	0	1.000
Recurrence (n, %)	97 (53)	49 (46.2)	48 (62.3)	**0.031**
Incomplete ablation	6 (3.3)	2 (1.9)	4 (5.2)	0.241
New lesion	60 (38.3)	37 (34.9)	33 (42.9)	0.275
Marginal recurrence	15 (8.2)	7 (6.6)	8 (10.4)	0.357
Distant metastasis	5 (2.7)	3 (2.8)	2 (2.6)	1.000

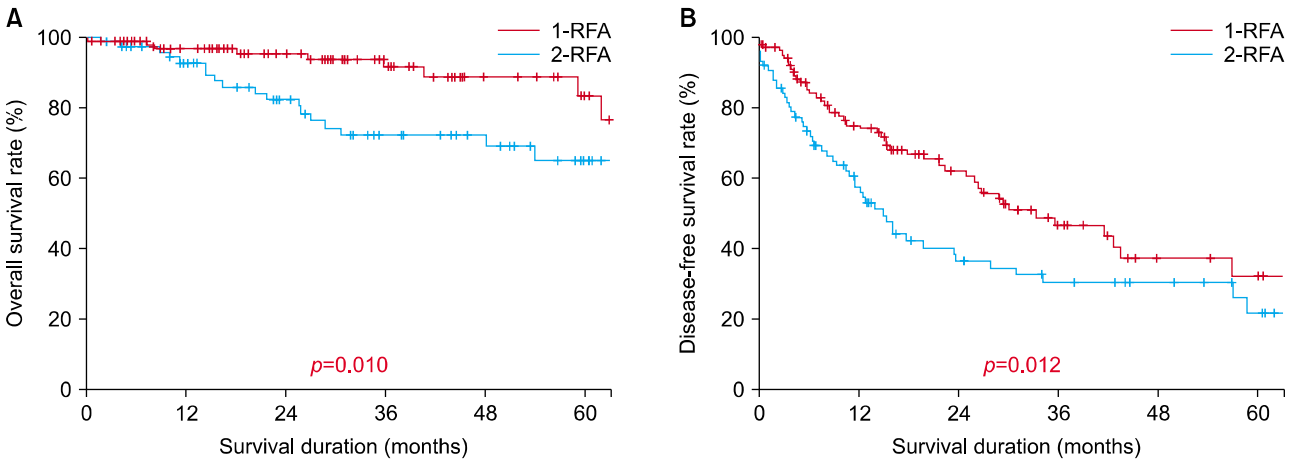
1-RFA, primary radiofrequency ablation; 2-RFA, secondary radiofrequency ablation; SD, standard deviation



n=183	1 yr	3 yr	5 yr
OS (%)	95.2	83.1	75.2
No at risk (n)	144	70	25

n=183	1 yr	3 yr	5 yr
DFS (%)	67.8	39.7	27.9
No at risk (n)	104	35	10

Fig. 1. (A) Overall survival rate of the whole cohort. (B) Disease-free survival of the whole cohort.



		1 yr	3 yr	5 yr
OS (%)	Primary (n=106)	96.9	91.6	83.6
	Secondary (n=77)	92.9	72.2	64.9
No at risk (n)	Primary (n=106)	84	40	14
	Secondary (n=77)	60	30	11

		1 yr	3 yr	5 yr
DFS (%)	Primary (n=106)	74.3	46.7	32.2
	Secondary (n=77)	57.6	30.3	21.6
No at risk (n)	Primary (n=106)	65	21	5
	Secondary (n=77)	38	14	5

Fig. 2. (A) Overall survival rate between the 1-RFA and 2-RFA groups. (B) Disease-free survival rate between the 1-RFA and 2-RFA groups.

in Table 1. According to whether RFA was done as a primary or secondary treatment, 106 (57.9%) and 77 (42.1%) patients were categorized into the 1- and 2-RFA groups, respectively. Most preoperative parameters were not significantly different between the two groups, but the 2-RFA group showed a significantly higher proportion of male (67.9% in 1-RFA group versus 83.1% in 2-RFA group; p=0.020), whereas the preoperative level of serum albumin was slightly higher in the 1-RFA group (3.8±0.52 in 1-RFA group versus 3.7±0.39 in 2-RFA group; p=0.048). There are no significant differences in the type of surgical approaches between the two groups (p=0.079). The number of tumors located at segment 6 was higher in the 2-RFA group (17% in 1-RFA group versus 29.9% in 2-RFA group; p=0.039), whereas that at segment 8 was higher in the 1-RFA group (50% in 1-RFA group versus 28.6% in 2-RFA group; p=0.004). The number of tumors and largest tumor size were not significantly different be-

tween the two groups.

Surgical outcomes are described in Table 2. Operative time was 117.6±52.6 minutes in the whole cohort, and it did not differ between the two groups (111.4±50.7 in 1-RFA group versus 126.1±54.3 in 2-RFA group; p=0.063). Postoperative hospital stay and rate of complications were also not significantly different between the two groups. One case of in-hospital mortality was found in the 1-RFA group due to postoperative liver failure and bleeding. Overall recurrence rate was 53%, and the 2-RFA group showed a higher recurrence rate (46.2% in 1-RFA group versus 62.3% in 2-RFA group; p=0.031). However, there were no significant differences in recurring patterns. The accuracy for RFA was 96.7% and 6 (3.3%) patients showed incomplete ablation on postoperative CT. Of 6 patients with incomplete ablation, we could not identify the tumor by intraoperative sonography in 3 patients. The accuracy was not significantly different between two groups (1.9% in 1-RFA group versus 5.2% in 2-RFA group; p=0.241).

Survival and prognostic factors

The median follow-up duration was 27.1 months (32.4±23.4 months). The 5-year OS and DFS rates of the

Table 3. Factors influencing overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age ＞70 years	1.718	0.747-3.951	0.203			
Female sex	0.470	0.162-1.361	0.164			
HTN	1.152	0.534-2.484	0.718			
DM	1.544	0.715-3.332	0.269			
TB	0.684	0.093-5.055	0.710			
HBV-LC	0.430	0.199-0.927	**0.031**	0.310	0.140-0.687	**0.004**
HCV-LC	1.501	0.604-3.731	0.382			
Alc-LC	1.930	0.881-4.226	0.100			
Idiopathic LC	2.450	0.577-10.408	0.225			
Op Hx	3.987	1.671-9.511	**0.002**	2.359	0.870-6.399	0.092
Secondary RFA	2.759	1.239-6.146	**0.013**	2.768	1.208-6.345	**0.016**
Hb ＜10	1.264	0.299-5.341	0.750			
Plt ＜100,000	1.224	0.575-2.605	0.600			
Alb ＜3	1.508	0.356-6.393	0.577			
TB ＞2	0.319	0.043-2.357	0.263			
INR ＞1.2	1.498	0.602-3.727	0.385			
AFP ＞7	1.536	0.696-3.389	0.288			
PIVKA ＞40	2.341	0.797-6.882	0.122			
ICG ＞20%	1.183	0.422-3.315	0.749			
Multiplicity	1.762	0.827-3.757	0.142			
Largest size ＞2 cm	1.377	0.545-3.483	0.499			
Postop stay ＞5 days	3.103	1.450-6.640	0.004	2.017	0.825-4.931	0.124
Recurrence	7.927	1.873-33.553	0.005	7.468	1.755-31.786	0.007
Marginal recurrence	2.036	0.703-5.898	0.190			
Distant meta	3.055	0.721-12.947	0.130			
New lesion	1.764	0.802-3.879	0.158			
Incomplete ablation	4.124	0.951-17.880	0.058			
Complications	3.904	1.778-8.572	0.001	3.486	1.557-7.807	0.002
Cx G II	2.897	1.163-7.215	0.022	0.433	0.118-1.592	0.208
Cx G IIIa	2.654	0.355-19.864	0.342			

HTN, hypertension; DM, diabetes mellitus; HBV-LC, hepatitis B virus-associated liver cirrhosis; HCV-LC, hepatitis C virus-associated liver cirrhosis; Alc-LC, alcoholic liver cirrhosis; LC, liver cirrhosis; Hx, history; RFA, radiofrequency ablation; Hb, hemoglobin; Plt, platelet; Alb, albumin; TB, total bilirubin; INR, international normalized ratio; AFP, alpha fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; ICG, indocyanine green; SD, standard deviation; CI, confidence interval; HR, hazard ratio

Table 4. Factors influencing recurrence

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age ＞70 years	1.273	0.805-2.014	0.301			
Female sex	0.721	0.447-1.163	0.179			
HTN	1.061	0.704-1.599	0.777			
DM	1.156	0.753-1.777	0.507			
TB	1.0440	0.421-2.567	0.932			
HBV-LC	0.940	0.620-1.424	0.770			
HCV-LC	1.381	0.816-2.337	0.229			
Alc-LC	1.134	0.709-1.815	0.599			
Idiopathic LC	1.082	0.342-3.424	0.893			
Op Hx	1.875	1.021-3.441	**0.043**	2.165	1.172-3.998	**0.014**
Secondary RFA	1.665	1.112-2.493	**0.013**	1.719	1.142-2.585	**2.165**
Hb ＜10	1.109	0.483-2.542	0.808			
Plt ＜100,000	1.238	0.826-1.854	0.301			
Alb ＜3	1.111	0.451-2.737	0.819			
TB ＞2	0.814	0.393-1.687	0.580			
INR ＞1.2	2.015	1.235-3.287	**0.005**	2.102	1.287-3.432	**0.003**
AFP ＞7	1.519	0.990-2.330	0.055			
PIVKA ＞40	1.507	0.836-2.716	0.173			
ICG ＞20%	1.391	0.788-2.456	0.255			
Multiplicity	1.451	0.964-2.185	0.074			
Largest tumor size ＞2 cm	0.956	0.562-1.625	0.867			
Postop stay ＞5 days	1.505	0.988-2.293	0.057			
Complications	1.563	0.933-2.617	0.090			
Cx G II	1.787	0.993-3.217	0.053			
Cx G IIIa	1.794	0.440-7.318	0.415			

HTN, hypertension; DM, diabetes mellitus; HBV-LC, hepatitis B virus-associated liver cirrhosis; HCV-LC, hepatitis C virus-associated liver cirrhosis; Alc-LC, alcoholic liver cirrhosis; LC, liver cirrhosis; Hx, history; RFA, radiofrequency ablation; Hb, hemoglobin; Plt, platelet; Alb, albumin; INR, international normalized ratio; AFP, alpha fetoprotein; PIVKA II, protein induced by vitamin K absence or antagonist-II; ICG, indocyanine green; SD, standard deviation; TB, total bilirubin; CI, confidence interval; HR, hazard ratio

whole cohort were 75.2% and 27.9%, respectively (Fig. 1). The OS and DFS rates were significantly higher in the 1-RFA group (Fig. 2). The 5-year OS rates were 83.6% and 64.9% in the 1-RFA and 2-RFA groups, respectively (p=0.010), whereas the 5-year DFS rates were 32.2% and 21.6% in the 1-RFA and 2-RFA groups, respectively (p=0.012).

Univariate analysis revealed that hepatitis B virus-associated liver cirrhosis (HBV-LC), previous history of abdominal surgery, 2-RFA, postoperative hospital stay of ＞5 days, recurrence, and surgical complications were associated with OS (Table 3). On multivariate analysis, HBV-LC, 2-RFA, recurrence, and postoperative complications were independent predictive factors for survival.

Similarly, a previous history of abdominal surgery, 2-RFA, and preoperative INR of ＞1.2 were associated with recurrence on univariate analysis. On multivariate analysis, all these variables were revealed to be independent prognostic factors for recurrence (Table 4).

DISCUSSION

Given that surveillance tests are becoming more common for patients at risk for HCC, the detection rate of small HCC, especially those ＜2 cm in size has increased.[13] There are many studies and meta-analyses comparing the outcomes after surgical resection and RFA for solitary HCC.[14-23] However, the superiority of any method has not yet been demonstrated definitively, and RFA would be a potentially curative treatment for HCC in the early stages.[1,24] In particular, because RFA can provide higher rates of complete necrosis of the target tumor than other locoregional therapies, it plays a pivotal role as a locoregional neoadjuvant therapy prior to liver transplantation.[25,26] Fontana et al.[27] first reported in 2002 a complete necrosis in 59.5% of 37 nodules treated with RFA. Subsequently, Pompili et al.[28] described a complete necrosis rate of 41.3% in 46 nodules, with an increased rate for nodules ＜3 cm in size of up to 61.9%. In 2004, Mazzaferro et al.[29] reported a complete necrosis in 55% of 60 nodules, which increased to 63% when the nodules were ＜3 cm in diameter. In our study, the complete ablation rate was only 96.7% among all patients (183), and marginal recurrence was found in 8.2% of the patients during the entire follow-up period. This result may not be worse than the previous studies.[15]

The 1-, 3-, and 5-year OS for the entire cohort were 95.2%, 83.1%, and 75.2%, respectively. These results are much better than a previous multicenter study reported by Pompili et al.[17] The main reason is thought to be that the current study included only the patients who received IO-RFA. The 1-, 3-, and 5-year DFS of all patients were 67.8%, 39.7%, and 27.9%, respectively. The DFS rate is much worse than the OS rate, indicating that all patients had underlying liver cirrhosis, which leads to a high relapse rate, but there were still effective treatment modalities that can improve survival after recurrence.

The 1-RFA group showed significantly higher OS and DFS rates than the 2-RFA group, which could be due to the fact that all patients in the 2-RFA group had recurrence after previous treatments, such as surgical resection, TACE, and RFA. Furthermore, the recurrence rate following IO-RFA was also significantly higher in the 2-RFA group. In patients who had recurrence, the next treatment could extend the survival duration, but the tumors were more likely to recur again. It was found that 2-RFA and recurrence were independent prognostic factors for poor survival in the multivariate analysis, which can support the abovementioned findings.

Among the entire cohort, three cases of Clavian-Dindo grade IIIa complications and one case of in-hospital mortality due to hepatic failure. However, surgical resection would be more strongly associated with major complications than RFA, suggesting that RFA might be safer than surgical resection.[31]

Moreover, HBV-LC was found to be associated with survival by multivariate analysis. Non-HBV-LC was a negative risk factor for long-term survival. Previous studies reported a significant association between antiviral treatment and the prognosis of HCC.[32] 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.[33-35] In the whole cohort, 61.7% had HBV-LC in our study.

Contrary to other studies,[36-38] incomplete ablation, tumor number, tumor size, and serum AFP levels were not related to survival. This is probably because of the relatively small number of patients included in our study.

This study has several limitations. First, because it had a retrospective and non-randomized nature, some degree of selection bias was involved. Moreover, only the patients who underwent IO-RFA were included; thus, the data of other patients who received surgical resection, TACE, and percutaneous RFA except IO-RFA were not collected. This would hinder the generalization of the results of the current study. To strengthen the validity of these findings, a large-scale randomized clinical trial is required. Second, there may have been some differences in the types of electrodes and RFA techniques used, and these could be potential confounders.

In conclusion, therapeutic outcomes of IO-RFA were revealed to be comparable to those of surgical resection. Additionally, 1-RFA might be an alternative treatment for naïve HCC in patients with uncompensated liver function and severe comorbidities.

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Conceptualization: Jongduk Kwon. Data curation: Jongduk Kwon, Sunjong Han. Formal analysis: Jongduk Kwon, Kwang-Sik Chun, In-Sang Song, Seok-Hwan Kim, Sunjong Han. Funding acquisition: Kwang-Sik Chun. Methodology: Jongduk Kwon, Kwang-Sik Chun, Sunjong Han. Project administration: Kwang-Sik Chun. Visualization: Jongduk Kwon. Writing - original draft: Jongduk Kwon, Sunjong Han. Writing - review & editing: Jongduk Kwon, Kwang-Sik Chun, Sunjong Han.

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