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Efficacy of radiofrequency ablation for initial recurrent hepatocellular carcinoma after curative treatment: Comparison with primary cases

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ABSTRACT

Objective: To determine the efficacy of radiofrequency ablation (RFA) for initial recurrence of small hepatocellular carcinoma (HCC; ≤3 nodules, each nodule ≤3 cm in diameter) after curative treatment and identify prognostic factors affecting therapeutic outcome, we compared clinical and outcome factors between patients with primary HCC and those with initial recurrent HCC who underwent RFA.
Methods: In this retrospective cohort study, 211 HCC patients who underwent RFA were enrolled and comprised two groups: primary group (n = 139) and initial recurrent group (n = 72). We compared local tumor progression, overall survival (OS), disease-free survival (DFS), and RFA safety between the groups.
Results: Median follow-up was 53 months. Local tumor progression rate was 5.8% in the primary group and 4.2% in the recurrent group. OS rates at 5 years and 10 years were 63.2% and 25.5% in the primary group and 54.5% and 33.4% in the recurrent group, respectively. Corresponding DFS rates were 30.7% and 14.6% and 19.2% and 11.0%. DFS was significantly shorter in the recurrent group (hazard ratio [HR] = 1.81; 95% confidence interval [CI], 1.27–2.57; P = 0.001). In the recurrent group, time from primary HCC development to recurrence was a determinant of OS (≤2 years; HR = 3.42; 95% CI, 1.52–7.72; P = 0.003).
Conclusion: Although local tumor control and OS were similar between the groups, the recurrent group had shorter DFS than the primary group. Time from primary HCC development to recurrence was a prognostic factor for recurrence of HCC.

1. Introduction

Japanese and American clinical practice guidelines recommend hepatectomy and radiofrequency ablation (RFA) as curative treatments for small hepatocellular carcinoma (HCC; ≤3 nodules and each ≤3 cm in diameter) [1,2]. However, intrahepatic recurrence is very common after such curative treatments; it occurs in 50–70% of patients within 5 years of hepatectomy because of undetected intrahepatic spread or multicentric tumor occurrence [3–5]. Treatment selection is therefore important for improved survival, but the algorithms recommended in the above-mentioned guidelines are for primary HCC not recurrent HCC.

Although repeat hepatectomy has been effective in treating recurrent HCC [6–9], additional hepatectomy is contraindicated in most patients. Deterioration of liver function reserve from repeat treatments for recurrent HCCs and/or progression of background liver disease restrict the treatment options available. Less invasive curative treatments than hepatectomy are desirable and RFA is suitable in this respect, but its effectiveness for recurrent HCC has not been established.

RFA is regarded as safe and effective for small HCC as a first-line treatment [10–15], and a small number of studies have found RFA to be promising for recurrent HCC [16–18]. However, prognosis remains to be fully evaluated for patients who received percutaneous RFA for recurrent HCC after curative treatment such as hepatectomy, percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), or percutaneous RFA.

This retrospective study sought to clarify the effectiveness of RFA for initial recurrent HCC after curative treatment and to identify prognostic factors affecting therapeutic outcome. We compared clinical and outcome factors following RFA treatment between patients with primary HCC and those with initial recurrent HCC.

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2. Materials and methods

2.1. Patients

The following inclusion criteria were used: (1) primary HCC or initial recurrent HCC after curative treatment, (2) ≤3 nodules and each ≤3 cm in diameter, (3) no vascular invasion and no extrahepatic metastasis, (4) Child–Pugh class A or B, and (5) prothrombin activity >40% and platelet count >50,000/μl. We reviewed 401 consecutive HCC patients treated with RFA between January 2001 and June 2013 at our hospital. Among them, 211 patients with 263 small HCCs who met the inclusion criteria were evaluated. Patients were divided into two groups: primary HCC group (n = 139) and initial recurrent HCC group (n = 72) (Fig. 1).

2.2. Imaging and confirmation of diagnosis

Before RFA treatment, all patients underwent imaging studies including abdominal ultrasonography (US), contrast-enhanced dynamic CT or magnetic resonance imaging (MRI), and angiography combined with CT during arterial portography and hepatic arteriography. In 155 patients, HCC was diagnosed based on the following classic imaging manifestations: (i) early enhancement at the arterial phase and hypoattenuation at the portal venous phase or equilibrium phase on contrast-enhanced dynamic CT or MRI; and (ii) hyperattenuation on CT during hepatic arteriography and hypoattenuation on CT during arterial portography [19,20]. HCC was diagnosed in the remaining 56 patients by pathology.

2.3. RFA procedure

All RFA procedures were performed percutaneously under ultrasonographic guidance with patients under conscious sedation with pentazocine (5–10 mg, Pentagin; Sankyo, Tokyo, Japan) and midazolam (1–4 mg, Dormicum; Astellas, Tokyo, Japan) administered intravenously. We used a Cool-tip RF Ablation System (Covidien, Boulder, CO) with a 17-gauge cool-tip electrode. A 2-cm exposed tip (for nodules <1.5 cm in diameter) or a 3-cm exposed tip (for nodules measuring 1.5–3.0 cm) was inserted into the center of the nodule. In 172 patients (82%) with hypervascular HCC nodules confirmed on CT during hepatic arteriography, TACE was performed an average 3 days before RFA. TACE was performed through the femoral artery using the technique of Seldinger under local anesthesia. An angiographic catheter was inserted selectively into the hepatic feeding artery of a segment or subsegments containing the target tumor. Cisplatinum (Randa; Nippon Kayaku, Tokyo, Japan) was mixed with iodized oil (Lipiodol; Nihon Schering, Tokyo) at a concentration of 10 mg/ml and injected at a dose of 10–40 mg/body. The selected dose was based on tumor size. Injection was discontinued upon full accumulation of iodized oil in the tumor vessels.

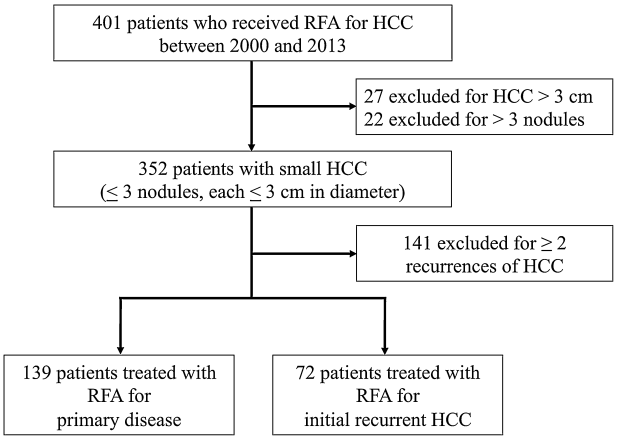

Fig. 1. Flow chart of patients treated by radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC).

RFA data assessment was performed in accordance with the Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-Guided Tumor Ablation [22].

2.4. Assessment of therapeutic efficacy of RFA

Contrast-enhanced dynamic CT was performed 1–3 days after the RFA treatment session. On CT images, the non-enhancing area was measured as the ablated area. A complete effect was defined as disappearance of tumor enhancement with surrounding non-enhancing areas of ≥5 mm [22]. An incomplete effect was defined as a necrotic area diameter closely similar to that of the tumor without the ablation margin or partial enhancement of the tumor; in such case, additional RFA sessions were performed at 3- to 5-day intervals later until a complete effect was achieved. RFA outcome was evaluated on CT images 3–4 weeks after the final RFA session.

2.5. Follow up

All patients received follow-up examinations including US or contrast-enhanced dynamic CT or MRI every 3–4 months. Serum HCC-specific tumor markers including α-fetoprotein (AFP), its lectin fraction 3, and des-γ-carboxy prothrombin (DCP) were measured every 1–2 months.

Local tumor progression was defined as the reappearance of tumor enhancement around the ablated zone. Distant recurrence was defined as the appearance of new HCC in the untreated liver or extrahepatic sites. Early recurrence was defined as that occurring within 2 years and late recurrence as that occurring after more than 2 years.

Survival analysis was performed on a patient-by-patient basis. Disease-free survival (DFS) was defined as survival time from RFA to last follow-up, local tumor progression, occurrence of new HCC in the liver, distant metastasis, or death, whichever occurred first.

2.6. Complications

Complications after percutaneous RFA were evaluated using Society of Interventional Radiology grading criteria [21]. Major complications were defined as those requiring treatment or additional hospitalization or resulting in permanent adverse sequelae. All other complications were considered minor. Complications were assessed for each ablation session.

2.7. Statistical analysis

Rates of local tumor progression and primary and secondary effectiveness were determined by counting tumor number. Rates of local tumor progression, overall survival (OS), and DFS were estimated by the Kaplan–Meier method, and differences between the curves were determined using the log-rank test. Prognostic factors affecting OS and DFS survival rates after RFA for initial recurrent HCC were determined using Cox's proportional hazard model. Chi-square and Mann–Whitney U tests were used to compare differences in clinical features between the groups. P values <0.05 were considered significant. Data processing and analysis was performed with commercially available software (SPSS for Windows, version 9.0; SPSS, Chicago, IL).

Table 1
Characteristics of patients with primary or initial recurrent hepatocellular carcinoma treated by radiofrequency ablation.

Characteristic	Primary group (n = 139)	Recurrent group (n = 72)	P-value
Age (years)	69 (45–84)	70 (35–86)	0.329
Sex (male/female)	88/51	46/26	0.934
Etiology (HBV/HCV/non-B, non-C viral)	12/118/9	10/58/4	0.49
Child–Pugh class (A/B)	118/21	62/10	0.813
Total bilirubin level (mg/dl)	1.0 (0.3–2.0)	0.8 (0.4–1.6)	0.306
Prothrombin activity (%)	86 (51–130)	85 (53–108)	0.775
Serum albumin (g/dl)	3.9 (2.7–5.2)	3.9 (2.7–5.1)	0.375
ICG-R (%)	20.8 (3.1–55.4)	20.0 (4.7–46.6)	0.792
AFP (ng/ml)	17 (1.7–2973.6)	16.5 (1.7–302.4)	0.531
DCP (mAU/ml)	23 (10–405)	28 (10–288)	0.521
Tumor size (mm)	17 (9–30)	16 (8–30)	0.11
Tumor number (solitary/2–3)	111/28	53/19	0.302
Vascularity (hyper/hypo)	113/26	59/13	0.908

Values are median (range) number of patients unless stated otherwise.
AFP, α-fetoprotein; DCP, des-γ-carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG-R, indocyanine green retention rate at 15 min.

3. Results

As shown in Table 1, no significant differences were observed in patient background or tumor characteristics (e.g., tumor size, number, and vascularity) between the primary group (n = 139) and recurrent group (n = 72). Previous curative treatments in the recurrent group were hepatectomy (n = 36), RFA (n = 27), PEI (n = 6), MCT (n = 2), and combined hepatectomy and RFA (n = 1). The interval between initial treatment and recurrence ranged from 2 to 120 months (median, 24 months). All patients underwent RFA within 1–2 months after diagnosis of recurrence.

3.1. Local tumor progression

Local tumor progression occurred in 11 of the total 211 patients (5.2%) during a median follow-up of 53 months (range, 7–148 months), with no significant difference between the primary group (5.8%, 8/139) and recurrent group (4.2%, 3/72).

3.2. Overall survival

Among the 102 patients who died (48.3%, 102/211), the most frequent cause of death was HCC progression (53.9%, 55/102), followed by hepatic failure or cirrhosis complications (27.5%, 28/102), and other causes (18.6%, 19/102). OS rates at 3, 5 and 10 years did not differ significantly between the groups (primary group: 81.6%, 63.2%, and 25.5%; recurrent group: 84.4%, 54.5%, and 33.4%, respectively; Fig. 2a).

As shown in Table 2, multivariate analysis identified several host and tumor factors as independent factors associated with OS: age <70 years (P = 0.001), Child–Pugh class A (P = 0.004), indocyanine green retention rate at 15 min (ICG-R) <15% (P = 0.001), and solitary tumor (P = 0.001).

3.3. Disease-free survival

DFS rates at 3, 5, and 10 years was 43.6%, 30.7%, and 14.6% in the primary group and 27.8%, 19.2%, and 11.0% in the recurrent group, respectively (Fig. 2b). DFS was significantly shorter in the recurrent group (HR = 1.81, 95% CI = 1.27–2.57, P = 0.001).

Table 2 shows the results of multivariate analysis. The host and tumor factors identified as independent factors associated with DFS were as follows: ICG-R < 15% (P = 0.009), tumor size ≤20 mm (P < 0.001), solitary tumor (P = 0.005) and primary group (P = 0.001).

3.4. Sub-analysis of overall survival in the recurrent group

In the recurrent group, 38 patients had early recurrence (≤2 years from primary HCC development to initial recurrence) and 34 had late recurrence (>2 years). Kaplan–Meier curves for OS after RFA according to time from primary HCC to initial recurrence are shown in Fig. 3. OS was significantly worse for patients with early recurrence than for those with late recurrence (P = 0.046).

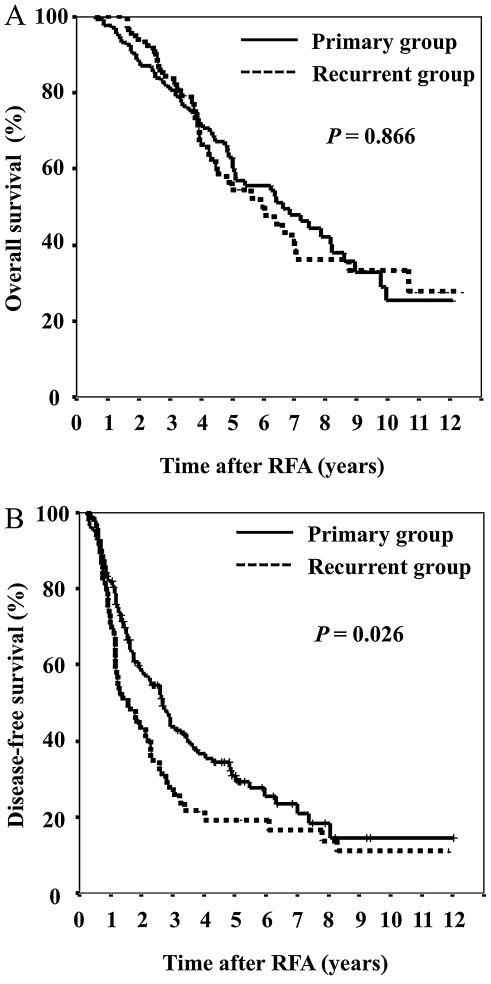

Fig. 2. Survival curves of HCC patients who received RFA. (a) Overall survival and (b) disease-free survival for patients with primary versus initial recurrent disease.

Table 2
Predictive factors for overall survival and disease-free survival in 211 patients with HCC after radiofrequency ablation.

Characteristics	Overall survival				Disease-free survival			
	Univariate		Multivariate		Univariate		Multivariate	
	P-value	Hazard ratio	95% CI	*P*-value	*P*-value	Hazard ratio	95% CI	*P*-value
Age (<70/≥70 years)	0.001	2.08	1.38–3.15	0.001	0.057			
Sex (male/female)	0.248				0.098			
Child–Pugh classification (A/B)	<0.001	1.99	1.24–3.20	0.004	0.43			
Total bilirubin level (≤1.5/>1.5 mg/dl)	0.049				0.798			
Prothrombin activity (≤70/>70%)	0.584				0.943			
Serum albumin (≤3.5/>3.5 g/dl)	0.121				0.159			
ICG-R (<15/≥15%)	<0.001	2.42	1.43–4.09	0.001	0.014	1.69	1.14–2.49	0.009
AFP (<50/≥50 ng/ml)	0.044				0.984			
DCP (<100/≥100 mAU/ml)	0.197				0.138			
Tumor size (≤20/>20 mm)	0.026				<0.001	2.31	1.60–3.35	<0.001
Tumor number (solitary/2–3)	<0.001	2.1	1.36–3.23	0.001	0.001	1.75	1.19–2.57	0.005
Vascularity (hypo/hyper)	0.969				0.654			
Primary group/Recurrent group	0.866				0.026	1.81	1.27–2.57	0.001

AFP, α-fetoprotein; CI, confidence interval; DCP, des-γ-carboxyprothrombin; ICG-R, indocyanine green retention rate at 15 min

Table 3
Predictive factors for overall survival in the recurrent hepatocellular carcinoma group ($n = 72$).

Characteristic	Univariate		Multivariate	
	P-value	Hazard ratio	95% CI	*P*-value
Age (<70/≥70 years)	0.1	3.27	1.53–6.96	0.002
Sex (male/female)	0.96			
Child–Pugh classification (A/B)	0.015	2.75	1.09–6.92	0.032
Total bilirubin level (≤1.5/>1.5 mg/dl)	0.74			
Prothrombin activity (≤70/>70%)	0.32			
Serum albumin (≤3.5/>3.5 g/dl)	0.078			
ICG-R (<15/≥15%)	0.046	3.22	1.32–7.85	0.01
AFP (<50/≥50 ng/ml)	0.48			
DCP (<100/≥100 mAU/ml)	0.2			
Tumor size (≤20/>20 mm)	0.025	3.89	1.66–9.13	0.002
Tumor number (solitary/2–3)	0.05	2.66	1.24–5.70	0.018
Time interval to initial recurrence (>2 years/<2 years)	0.046	3.42	1.517–7.72	0.003

AFP, α-fetoprotein; CI, confidence interval; DCP, des-γ-carboxyprothrombin; ICG-R, indocyanine green retention rate at 15 min

As shown in Table 3, multivariate analysis revealed age <70 years old, Child–Pugh class A, ICG-R <15%, tumor size ≤20 mm, and solitary tumor were independently associated with OS. Shorter time from primary HCC development to recurrence (i.e., ≤2 years) was an additional determinant of prognosis ($P = 0.003$).

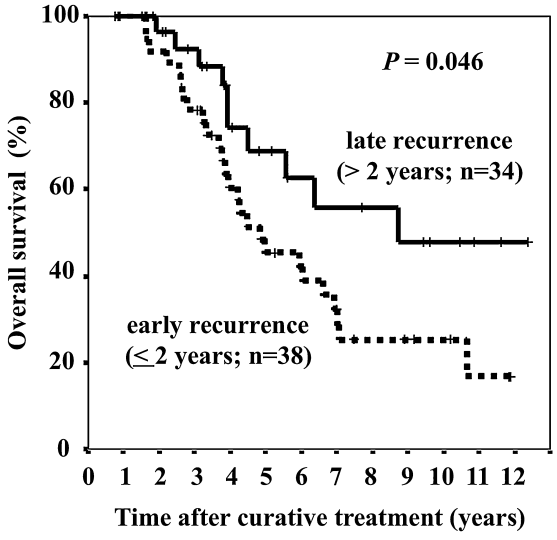

Fig. 3. Cumulative overall survival for patients with recurrent disease according to time from primary HCC development to initial recurrence.

3.5. Complications

From a total of 317 RFA sessions performed to treat 263 HCCs in 211 patients, 12 complications were recorded during follow up (3.8% per session, 12/317). The incidence rates of complications per session were 3.3% (7/212) in the primary group and 4.8% (5/105) in the recurrent group. Major complications were observed in three patients: two experienced portal vein thrombosis requiring systemic thrombolysis, and one experienced hemobilia requiring bile duct tube placement. Minor complications were observed in nine patients: hepatic infarction ($n = 4$), pleural effusion ($n = 2$), self-limiting pneumothorax ($n = 2$), and biloma ($n = 1$). No procedure-related deaths occurred.

4. Discussion

The results of this study showed no significant difference in local tumor progression or OS after RFA treatment between the primary and recurrent groups, but DFS was significantly shorter in the recurrent group. There was no significant difference in the RFA complication rate between these groups. Taken together, these findings suggest that RFA is an effective and safe treatment option for initial recurrent small HCC.

RFA is considered to be an effective and safe first-line treatment for small HCC [10–15] and possibly also for recurrent HCC, although the findings concerning the latter are limited at this time. The 5-year overall survival rate is reported to range from 29% to 51% after RFA for recurrent disease [16–18]. In the present study, RFA was performed in 139 patients with primary HCC and in 72 patients

with initial recurrent HCC after curative treatment. Although no significant difference was observed in OS between the two groups, RFA for recurrent HCC was able to achieve long-term survival outcomes similar to those seen with RFA for primary HCC and OS was longer than in previously reported studies [16–18]. In our study, both host factors (age, Child–Pugh class, and ICG-R15) and tumor-related factor (number of tumor) were significant associated with overall survival. These results are similar to those found in previous study [14,18].

Second hepatectomy is an alternative to RFA, and the rate of second hepatectomy is reported to be 20–25% in patients with HCC recurrence [7,8]. The 5-year OS rate after second hepatectomy for patients with recurrent HCC is reported to be 35–55% [6–9]. Second hepatectomy is often technically more challenging than initial hepatectomy, however, because of the presence of severe adhesion, progressive liver dysfunction, or multiple tumors. Moreover, the more often hepatectomy is repeated, the more difficult the resection becomes [5–7,23]. Even after a successful second hepatectomy, the re-recurrence rate is still high [6–9]. It is therefore important to consider both therapeutic efficacy and the impact of treatment on remnant liver function when deciding among treatment options such as second hepatectomy and RFA for recurrent HCC. Moreover, in the present study, the estimated 3-, 5-, and 10-year DFS rates were 43.6%, 30.7%, and 14.6% in the primary group and 27.8%, 19.2%, and 11.0% in the recurrent group, respectively. In our study, lower ICG-R, tumor size $\leq$20 mm, and a solitary tumor were significant favorable prognostic factors for disease-free survival, and this result is also well correlated with that seen in a previous study [14]. In addition, recurrent group was also a significant predicting factor for poor disease-free survival in our study. Although the OS rate was similar between the groups, DFS was shorter in the recurrent group. In a previous study of patients treated with repeat hepatectomy, the more times hepatectomy was repeated, the shorter the recurrence-free interval became [8]. There is the possibility that HCC patients with recurrence have a higher potential for carcinogenesis than those with primary disease. With repeated recurrence, both DFS and hepatic reserve are adversely affected. The less invasive nature of RFA and its repeatability appear to offer benefits over hepatectomy for patients with repeated recurrences of HCC.

In sub-analysis of the recurrent group, time from primary HCC development to recurrence was a significant prognostic factor for overall survival, in addition to both host factors and tumor-related factors. Previous studies have shown that the time interval from resection of HCC to recurrence is an independent prognostic factor for survival [5,24]. In the present study, OS was worse in patients with early recurrence than in those with late recurrence. Intrahepatic recurrence of HCC after curative treatment has two distinct etiologies, intrahepatic metastasis and multicentric occurrence [25,26]. Early recurrence is thought to arise primarily from the former. In the present study, in addition to several host and tumor factors associated with recurrence, time from primary HCC development to recurrence was an additional determinant of prognosis. It is necessary, therefore, to carefully consider treatment options for patients with suspected intrahepatic metastases.

RFA for recurrent HCC was as safe as RFA for primary HCC in this study. No procedure-related deaths were recorded, and the complication rates were comparable between the groups (3.3% primary group, 4.8% recurrent group), consistent with the low complication rates previously reported [10–14]. The higher complication rates of 11–23% for second hepatectomy reported previously [8–10] suggest that RFA may be a safer treatment option for recurrent HCC than repeated hepatectomy.

The limitations of our study are its retrospective and single-center design. Given the evidence accumulated from the small number of studies conducted to date, including this study, large-scale prospective studies are warranted to assess the benefits of RFA for recurrent small HCC. A prospective randomized trial is needed to verify whether RFA is safer and more effective than repeated hepatectomy.

In conclusion, this study found that RFA for initial recurrent HCC after curative treatment is a safe and effective treatment for patients with small HCC ($\leq$3 nodules and each $\leq$3 cm in diameter). Patients with recurrent disease should be followed closely due to a low DFS rate.

Funding

None.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of interest

All authors declare that they have no conflict of interest.

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