Superior long-term outcomes after surgery in child-pugh class a patients with single small hepatocellular carcinoma compared to radiofrequency ablation

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Abstract

Background and aims There are insufficient data comparing long-term prognoses after radiofrequency ablation (RFA) and surgery.

Methods We compared the baseline characteristics and survival rates of patients (single, ≤ 3 cm, and Child-Pugh class A) treated surgically ($n = 215$) and with RFA ($n = 255$) from January 2000 to December 2007 at our institution.

Results The surgery group was characterized by younger age, higher prevalence of HBsAg, less cirrhosis, and an increased chance of Child-Pugh score of 5 and CLIP score of 1, compared to the RFA group. During the median follow-up period of 42 months (range 1–109), the 3-, 5- and 7-year overall survival rates in the surgery group were 98, 94, and 94%, respectively, which were significantly higher than those in the RFA group (92, 87, and 76%, respectively, $P = 0.002$). The 3- and 5-year recurrence-free survival rates were 72 and 66%, respectively, in the surgery group, which were significantly higher than those in the RFA group (34 and 24%, respectively, $P < 0.001$).

The superiority of the survival rates in the surgery group persisted in most patients throughout the subgroup analysis, based on the Child-Pugh score and CLIP score. Multivariate analysis showed that age and surgery as a procedure type were the significant predictive factors for both overall survival [HR = 1.04 (CI 1.001–1.08), $P = 0.047$ for age; HR = 2.97 (CI 1.19–7.45), $P = 0.02$ for surgery] and recurrence-free survival [HR = 1.02 (CI 1.01–1.04), $P = 0.01$ for age; HR = 2.44 (CI 1.76–3.37), $P < 0.001$ for surgery].

Conclusions The long-term outcome after surgery for Child-Pugh class A and single small HCC is superior to that after RFA.

Keywords Hepatocellular carcinoma · Hepatectomy · Radiofrequency catheter ablation · Survival · Recurrence · Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of death from cancer in men and the sixth most common cause in women worldwide [1]. The incidence of HCC is rising faster than those of most other cancers, owing to the increasing prevalences of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection worldwide [2]. Fortunately, since the introduction of surveillance in patients at high risk of HCC, the diagnosis of small HCC has increased, especially in endemic areas, such as Korea [3–6]. Partial hepatectomy and liver transplantation are the main forms of curative treatment for small HCC [3, 7, 8]. However, surgery is only suitable for 9–27% of patients with HCC because of severe underlying liver disease, advanced tumor stages, or co-morbid conditions [9–12]. In

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addition, liver transplantation has been performed in only limited number of patients due to high costs, shortages of organ donor, and typically advanced disease status. [13].

Hence, various locoregional therapeutic modalities have been developed for the treatment of HCC. Amongst them, radiofrequency ablation (RFA) induces temperature changes using high-frequency alternating current via electrodes placed within the tissue to induce coagulation necrosis and tissue desiccation. Percutaneous RFA has been shown to be effective for local tumor control and does not require general anaesthesia. Also shorter duration of hospitalization is needed for RFA, usually two nights and 3 days, when compared with the surgery hospitalization. Moreover, RFA is shown to be superior to percutaneous ethanol injection (PEI) [14] or microwave coagulation therapy (MCT) [15]. Nowadays, RFA has been commonly applied as an alternative curative therapy to surgical resection for small HCC.

Several previous studies comparing the outcomes of surgery and RFA for HCC have reported variable results probably caused by differences in the patients characteristics included in each study. Our group previously conducted a study only involving patients with well-preserved liver function and single small HCC. Although overall and recurrence-free survival after surgery was similar to those after RFA in this study (83.9 vs. 72.7%, $P = 0.24$ for 3-year overall survival rates; 54.7 vs. 40.2%, $P = 0.54$ for 3-year recurrence-free survival rates), our study has limitation of a small-sized retrospective study with relatively short-term follow-up period [16]. An Italian study reported that outcomes, 3 years after resection, were higher than those after RFA (65 vs. 33%, $P = 0.002$ for overall survival rates; 50 vs. 20%, $P = 0.001$ for recurrence-free survival rates). However, the advantage of surgery was mainly evident for Child-Pugh class A patients and single tumor of more than 3 cm in diameter, while outcomes after resection were similar to those after RFA for Child-Pugh class A patients and single tumor of 3 cm or smaller size [17]. Recently, a large scale Japanese prospective study for HCC (≤ 3 cm, ≤ 3 tumors and child A/B) showed that the lower tumor recurrence for resection (time-to-recurrence rates at 1 and 2 years in the resection and RFA were 17.0, 35.5% and 26.0, 55.4%, respectively, $P = 0.001$) [18]. However, follow-up duration of this study was too short to elucidate any conclusive data about comparing long-term results of the treatment groups (median follow-up period 10.4 months). So far, data regarding the comparison of long-term prognoses between the two therapeutic modalities in large patient samples are scarce [15].

We compared the long-term therapeutic results of surgical resection and percutaneous RFA as an initial treatment for patients with single small HCC and Child-Pugh class A hepatic function. In addition, we examined

prognostic factors for a better outcome after treatment for HCC in these patients.

Patients and methods

Patients

Patients who met all of the following criteria were included in this study: (1) patients who had undergone partial hepatectomy or percutaneous RFA for HCC at our institute from January 2000 to December 2007, (2) single tumor of 3 cm or less in diameter without extrahepatic metastasis and vascular invasion detected during pretreatment imaging, such as 3 phase CT and dynamic magnetic resonance imaging (MRI), (3) patients with liver cirrhosis whose Child-Pugh class is A or those without cirrhosis, and (4) no previous history of surgical or non-surgical treatment for HCC. The diagnosis of HCC was based on pathologic confirmation or on the basis of elevated serum α -fetoprotein (α FP) (≥ 400 ng/ml) with radiological findings, or at least two coincident radiological findings compatible with HCC in high-risk patients [3, 19].

The 470 eligible patients included 368 males and 102 females, with a mean age of 54.6 years (range 24–82). Routine physical examination, laboratory testing, and imaging studies including 3-phase dynamic CT and dynamic MRI were performed in all the patients included in this study. For evaluation of functional hepatic reserve, an ICG test was performed if HCC was considered resectable. A number of 215 patients underwent hepatectomy (surgery group) and 255 patients underwent RFA (RFA group). The surgery group included 57 (26.5%) tumorectomy, 124 (57.7%) segmentectomy, 7 (3.3%) bi- or tri-segmentectomy, and 27 (12.6%) lobectomy patients. The reasons for undergoing RFA rather than hepatectomy included: refusal of surgery or general anaesthesia (94 patients, 36.9%), insufficient postoperative hepatic reserve on ICG test (84 patients, 33%), high operative risk associated with a previous comorbidity, such as cardiovascular disease or other chronic disease (21 patients, 8%), central tumor location (6 patients, 2.4%), and others (50 patients, 19.6%). RFA was performed percutaneously with an internally cooled electrode system (Cool-Tip; Valley-Lab, Boulder, CO, USA). This system was equipped with a 200-W generator [20].

Methods

We reviewed pretreatment patient characteristics including age, sex, risk factors for HCC, presence of liver cirrhosis, and Child-Pugh score. Tumor characteristics including size of tumor nodule, tumor site, serum α FP values, and the

Cancer of the Liver Italian Program (CLIP) score [21] were also evaluated (Table 1).

Recurrence and survival after completion of surgery or percutaneous RF were monitored. All patients were evaluated by dynamic CT and serum α PF level 1 month after RFA or hepatectomy. We evaluated the technical success rate by CT or contrast-enhanced ultrasonography (US) on the next morning after the RFA and the primary effectiveness by CT 4 weeks later [22]. Follow-up monitoring included serum α PF level measurements and dynamic CT scans performed every 3 months during the first 2 years, and every 6 months thereafter. Local tumor progression was defined as the appearance of a contrast-enhanced lesion at the margin of surgical resection or around the RFA ablated area on the CT finding. Remote recurrence was defined as emergence of distant metastasis or intrahepatic metastasis in the hepatic parenchyma other than the area treated by surgical resection or RFA. The median follow-up for the surgery group was 40 months (ranging from 1 to 106 months), which was similar to 37 months (ranging from 1 to 109 months) for the RFA group ($P = 0.41$). Overall and recurrence-free survival rates were compared between the two groups. Any predictive factors for overall and recurrence-free survival were explored using univariate and multivariate analysis. Factors that showed statistical significance in univariate analyses were included in multivariate analyses using Cox proportional

hazards models. This study was approved by the Institutional Review Board of our hospital and is in accordance with the Helsinki Declaration of 1975.

Statistical analysis

Differences in qualitative variables were assessed by the χ^2 test. Differences between the means of the two groups were assessed by Student's t test. Local recurrence rate, remote recurrence rates, overall survival rate, and recurrence-free survival rate were calculated by the Kaplan–Meier method. Differences between the curves were assessed using the log-rank test. Factors that showed statistical significance in univariate analyses were included in multivariate analyses using Cox proportional hazards models. P values < 0.05 were considered statistically significant. PASW statistics 17.0 software (SPSS, Chicago, IL, USA) was used to perform the analysis.

Results

Baseline characteristics of patients and tumors

The surgery group was characterized by younger age, higher prevalence of HBs Ag, less chance of accompanying

Table 1 Baseline characteristics of patients and tumors

	Surgery (<i>n</i> = 215)	RFA (<i>n</i> = 255)	<i>P</i> value
Age (years, mean $\pm$ SD)	51.7 $\pm$ 9.7	57.0 $\pm$ 9.9	<0.001
Sex			0.58
Male	171 (79.5%)	197 (77.3%)	
Female	44 (20.5%)	58 (22.7%)	
Etiology			0.001
HBV	186 (86.5%)	192 (75.3%)	
HCV	11 (5.1%)	45 (17.6%)	
Alcohol	4 (1.9%)	5 (2.0%)	
Others	14 (6.5%)	13 (5.1%)	
LC	139 (64.7%)	201 (78.8%)	0.01
Platelet ($10^3/\mu\text{L}$)	148 $\pm$ 45.7	115 $\pm$ 47.6	<0.001
Total bilirubin (mg/dl)	0.7 $\pm$ 0.3	0.8 $\pm$ 0.4	0.003
PT (s)	14.1 $\pm$ 0.9	14.8 $\pm$ 1.1	<0.001
Albumin (g/dl)	4.0 $\pm$ 0.3	3.7 $\pm$ 0.4	<0.001
Child-Pugh score			<0.001
5	197 (91.6%)	170 (66.7%)	
6	18 (8.4%)	85 (33.3%)	
AFP (ng/ml, mean $\pm$ SD)	476.3 $\pm$ 1208.1	307.4 $\pm$ 1148.8	0.13
Tumor size (cm, mean $\pm$ SD)	2.1 $\pm$ 0.5	2.1 $\pm$ 0.5	0.49
CLIP score			0.02
0	162 (77.5%)	218 (86.2%)	
1	47 (22.5%)	35 (13.8%)	

cirrhosis, and a tendency of having a Child-Pugh score of 5 and CLIP score of 1, compared to the RFA group. Other characteristics were similar between the two groups (Table 1).

Local tumor progression and remote recurrence

During the median follow-up period of 42 months (range 1–109), 51 (10.9%) of 470 patients were lost; 31 patients (12.2%) in the RFA group ($n = 255$) and 20 patients (9.3%) in the surgery group ($n = 215$). While 13 patients (25.5%) were referred back to local hospitals for regular check up after procedure, another 13 patients (25.5%) with aggravated symptoms were transferred to other hospital for supportive care. Reason for follow-up loss remains unknown in the remaining 25 patients (49.0%).

In the RFA group, the technical success rate surveyed by CT on the next morning after the procedure was 100% and the primary effectiveness 4 weeks later was 96.9%. The local tumor progression rate of the surgery group was significantly lower than that of the RFA group. The cumulative 1-, 3-, and 5-year local tumor progression rates were 0.5, 1.7, and 4.2%, respectively, in the surgery group and 8.9, 26.3, and 29.2%, respectively, in the RFA group ($P < 0.001$, Fig. 1a). In addition, there were statistically significant differences in the cumulative 1-, 3-, and 5-year remote recurrence rates, which were 13.2, 25.0, and 31.2% for the surgery group and 20.1, 53.6, and 63.8% for the RFA group, respectively ($P < 0.001$, Fig. 1b).

Overall and recurrence-free survival

During the follow-up period, 31 of 470 patients died; 25 patients in the RFA group ($n = 255$) and 6 patients in the surgery group ($n = 215$). Causes of death in the RFA group were liver failure in seven patients, gastrointestinal bleeding in five patients, sepsis in three patients, renal failure in one patient, and unknown in nine patients; two patients died of liver failure and cause of death remains unknown in four patients in the surgery group. The cumulative 1-, 3-, 5-, and 7-year overall survival rates in the surgery group were 100, 98, 94, and 94%, respectively, whereas those in the RFA group were 98, 92, 87, and 76%, respectively. These differences were statistically significant ($P = 0.002$) (Fig. 2). The cumulative 1-, 3-, and 5-year recurrence-free survival rates were 86, 72, and 66%, respectively, in the surgery group, which were significantly higher than those in the RFA group (73, 34, and 24%, respectively, $P < 0.001$).

Subgroup analysis was done to evaluate the survival of patients in each group in detail based on the Child-Pugh score and CLIP score. While the 3- and 5-year overall survival rates of the surgery group were significantly higher than those of the RFA group in Child-Pugh score of 5 (98.7 and 94.7% vs. 92.1 and 88.5%, $P = 0.007$), there was no significant overall survival rate difference between the two groups in Child-Pugh score of 6 (91.7 and 91.7% vs. 90.9 and 85.3%, $P = 0.39$; Fig. 3a). In contrast, the 3- and 5-year recurrence-free survival rates of the surgery group were significantly higher than the RFA group in

Fig. 1 Comparison of recurrence rates between the surgery and RFA groups. The local recurrence rates (a) and remote recurrence rates (b) in the surgery group were significantly lower than those of the RFA group ($P < 0.001$ for both)

Fig. 2 Comparison of survival rates between the surgery and RFA groups. The overall survival rates of the surgery group were significantly higher than those of the RFA group ($P = 0.002$)

Child-Pugh score of 5 (73.8 and 66.2% vs. 39.9 and 29.7%, $P < 0.001$) and score of 6 (72.2 and 64.2% vs. 22.3 and 16.7%, $P = 0.005$; Fig. 3b). As for CLIP score, the 3- and 5-year overall survival rates of the surgery group were higher than those of the RFA group in CLIP score of 0 (99.1 and 94.6% vs. 91.8 and 87.6%, $P = 0.01$) and score of 1 (95 and 95% vs. 90.3 and 83.9%, $P = 0.04$). Likewise,

the 3- and 5-year recurrence-free survival rates of the surgery group were better than those of the RFA group in CLIP score of 0 (71.7 and 63.9% vs. 35.6 and 31.2%, $P < 0.001$) and score of 1 (80.8 and 71.0% vs. 47.8 and 42.5%, $P = 0.001$) Fig. 4.

Predictive factors for overall and recurrence-free survival

A young age and surgery as a procedure type were associated with superior overall survival in univariate analysis. Multivariate analysis showed that age [HR 1.04 (CI 1.001–1.08), $P = 0.047$] and surgery [HR 2.97 (CI 1.19–7.45), $P = 0.02$] were independent predictive factors for overall survival (Table 2). Age, absence of cirrhosis, Child-Pugh score of 5, and surgery as a procedure type were related to recurrence-free survival rates in univariate analysis. Multivariate analysis indicated that age [HR 1.02 (CI 1.01–1.04), $P = 0.01$] and surgery as a procedure type [HR 2.44 (CI 1.76–3.37), $P < 0.001$] were the independent predictive factors for recurrence-free survival (Table 3).

Discussion

Although RFA has been applied as one of curative treatment modalities for small HCC [13, 23], little data is available about the long-term outcomes after RFA in a large-scale study, compared to those after surgical

Fig. 3 Comparison of survival rates for patients with a Child-Pugh score of 5 and 6 between the surgery group and the RFA groups. **a** While the overall survival rates of the surgery group were significantly higher than those of the RFA group in Child-Pugh score of 5 ($P = 0.007$), there was no significant difference in overall

survival rates between two groups in score of 6 ($P = 0.39$). **b** The recurrence-free survival rates of the surgery group were significantly higher than the RFA group in Child-Pugh score of 5 ($P < 0.001$) and score of 6 ($P = 0.005$)

Fig. 4 Comparison of survival rates for patients with CLIP score of 0 or 1 between the surgery and RFA groups. **a** The overall survival rates of the surgery group were higher than those of the RFA group in CLIP score of 0 ($P = 0.01$) and score of 1 ($P = 0.04$). **b** The recurrence-

free survival rates of the surgery group were better than those of the RFA group in a CLIP score of 0 ($P < 0.001$) and score of 1 ($P = 0.001$)

Table 2 Univariate and multivariate analyses of predictors for overall survival

Factors	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.05 (1.02–1.09)	0.006	1.04 (1.001–1.08)	0.047
Sex (male vs. female)	0.89 (0.36–2.17)	0.79		
Etiology				
NBNC	1			
HBV	0.85 (0.19–3.49)	0.77		
HCV	3.97 (0.88–17.79)	0.07		
LC (no LC vs. LC)	1.11 (0.51–2.42)	0.79		
Child-Pugh score (5 vs. 6)	1.99 (0.93–4.26)	0.08		
Size (≤ 2 cm vs. > 2 cm)	1.25 (0.61–2.53)	0.54		
AFP	1.00 (1.00–1.00)	0.3		
CLIP score (0 vs. 1)	1.01 (0.41–2.48)	0.98		
Procedure type (Surgery vs. RFA)	3.67 (1.50–8.95)	0.004	2.97 (1.19–7.45)	0.02

NBNC non-viral hepatitis B and C, LC liver cirrhosis

resection [15, 18]. Hence, we compared the long-term outcomes (median 42 months, range 1–109 months) of patients (single HCC, ≤ 3 cm, and Child-Pugh class A) treated surgically ($n = 215$) and those treated with RFA ($n = 255$). The overall and recurrence-free survival rates of surgery group were higher than those of RFA group. This superiority of surgery remained valid in most patients throughout the subgroup analysis based on Child-Pugh score and CLIP score. In addition, we demonstrated that age and surgery were the significant predictive factors for overall survival and recurrence-free survival.

Various factors have been suggested to be associated with outcome after RFA, surgery, or both. Age, Child-Pugh

score, and serum AFP levels were suggested as prognostic factors for survival in a previous large-scale study from our institution involving only patients receiving RFA [24]. The Japanese prospective study described above showed that procedure type (surgery), AFP level, Child-Pugh class, and the presence of HCV antibody were significant prognostic factors for overall death and HCV antibody was also a prognostic factor for recurrence [17]. Another study comparing the two treatments reported that improved disease-free survival of the patient was only related to the tumor size (below diameter 3.5 cm) and procedure type (resection) [24]. The results of the present study indicated that age and surgery as a procedure type were the significant

Table 3 Univariate and multivariate analyses of predictors for recurrence-free survival

Factors	Univariate		Multivariate	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age	1.03 (1.02–1.05)	<0.001	1.02 (1.01–1.04)	0.006
Sex (male vs. female)	0.97 (0.69–1.37)	0.87		
Etiology				
NBNC	1			
HBV	0.98 (0.58–1.63)	0.92		
HCV	1.70 (0.91–3.06)	0.10		
LC (no LC vs. LC)	1.67 (1.19–2.33)	0.003	1.35 (0.96–1.91)	0.08
Child-Pugh score (5 vs. 6)	1.75 (1.28–2.39)	<0.001	1.17 (0.84–1.62)	0.35
Size (≤ 2 vs. > 2 cm)	1.19 (0.91–1.58)	0.21		
AFP	1.0 (1.0–1.0)	0.27		
CLIP score (0 vs. 1)	0.69 (0.47–1.02)	0.07		
Procedure type (Surgery vs. RFA)	2.89 (2.13–3.93)	<0.001	2.44 (1.76–3.37)	<0.001

predictive factors for both overall survival [HR = 1.04 (CI 1.001–1.08), $P = 0.047$ for age; HR = 2.97 (CI 1.19–7.45), $P = 0.02$ for surgery] and recurrence-free survival [HR = 1.02 (CI 1.01–1.04), $P = 0.01$ for age; HR = 2.44 (CI 1.76–3.37), $P < 0.001$ for surgery]. These discrepancies might come from differences in study design, such as different inclusion criteria.

To the best of our knowledge, this is the first study to demonstrate the superiority of resection in long-term overall and recurrence-free survival rates (up to 7 years) in a relatively large number of HCC patients with homogeneous liver function and tumor extent. We compared the long-term outcomes of resection and RFA in a large-scale HCC patient group with uniform tumor and liver function to overcome the confounding effects of heterogeneity of tumor stage and liver function, small number of patients, and short follow-up duration. Moreover, our study demonstrated, for the first time, the advantage of partial hepatectomy in patients with small single HCC and well-preserved liver function, which are ideal targets for RFA. Previously, the superiority of surgery was primarily reported in patients with tumors larger than 3 cm, who are not good candidates for RFA [18, 25, 26]. Finally, this study was performed with patients selected by a uniform diagnosis and treatment protocol at a single institution. The patients were consecutively recruited from a single medical centre. Treatment protocol and indication are set up and revised through regular conferences and active inter-department consultations.

As a retrospective study, ours has a limitation that the two treatment groups differed in several baseline characteristics, such as age, HBs Ag positivity, accompanying cirrhosis, Child-Pugh score, and CLIP score. Nonetheless, the benefit of surgical resection on long-term outcomes persists in most patients throughout the subgroup analysis according to Child-Pugh score and CLIP score. Similar

overall survival rates in patients with Child-Pugh score of 6 were minor exceptions arising from a relatively small surgery group with Child-Pugh score of 6 ($n = 18$). Other factors, such as HBV status and LC, were not found to be independent predictive factors for outcome on multivariate analysis. Therefore, we can suggest that both young age and surgery as a procedure type were the significant predictive factors for overall survival and recurrence-free survival via multivariate analysis. Excellent overall survival rates in our surgery group (i.e. 5-year overall survival rate exceeding 90%) can be explained for the following reasons. Firstly, they were highly selected group with well-known strong factors for favourable prognosis; Child-Pugh class A liver function and single small HCC (≤ 3 cm). It is notable that 91.6% of patients had Child-Pugh score 5. Secondly, risk for surgical complication could be avoided as possible by applying alternative curative methods including RFA during our study period (2000–2007). In the past, surgery would have been carried out even for a centrally located small tumor in the right lobe, since no alternatives were available. Surgery was mainly performed for peripherally located tumors in our study. Lastly, segmentectomy, bi- or tri-segmentectomy, or lobectomy were performed in 73.5% of surgical patients while tumorectomy was performed in only 26.5%. This systemic resection could lead more patients to achieve curative goals.

Despite a few limitations as a single-center retrospective study, the results of the present study demonstrate superior long-term outcomes of surgical resection in patients with well-preserved liver function and small single HCC, who would be considered ideal candidates for RFA. A randomized controlled multicenter and prospective study would be an ideal solution to overcome the limitations of our retrospective study. However, RFA has already been accepted as an established standard curative treatment for selective HCC patients and the treatment of choice depends

on size, site, relation with adjacent vessel of tumors, liver function and general condition of patients, experience, and preference of physicians [27] Therefore, it would be very difficult to perform a prospective randomized controlled multicenter study to compare the outcomes of resection and RFA. Comparing RFA and surgery in our study, only patients fulfilling the strict inclusion were included to remove the confounding effect of tumor extent and liver function. In daily clinical practice, more flexible and sophisticated application of the therapeutic modality is warranted.

In conclusion, this study demonstrates that surgery in patients with single, 3 cm, or smaller HCC and a Child-Pugh score of A would result in superior overall and recurrence-free long-term survival, compared to RFA.

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