



Surgical resection versus radiofrequency ablation for Barcelona Clinic Liver Cancer very early stage hepatocellular carcinoma: long-term results of a single-center study

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ARTICLE INFO

Article history:

Received 27 December 2019

Received in revised form

9 March 2020

Accepted 19 March 2020

Keywords:

Hepatocellular carcinoma

Radiofrequency ablation

Surgical resection

ABSTRACT

Background: We aimed to compare long-term outcomes of surgical resection (SR) and percutaneous radiofrequency ablation (RFA) for Barcelona Clinic Liver Cancer (BCLC) very early stage hepatocellular carcinoma (HCC).

Methods: Total of 387 patients (SR group, 156; RFA group, 231) with well-preserved liver function (Child-Pugh A) diagnosed with a solitary HCC less than 2 cm were included. The overall survival (OS) and recurrence-free survival (RFS) rates were compared.

Results: The median follow-up period was 39 months. The overall tumor recurrence rate was 16.7% in the SR group and 27.7% in the RFA group. The 1-, 3-, and 5-year OS rates were 100%, 97.2%, and 93.4%, respectively, in the SR group, compared with 100%, 88.6%, and 73.5%, respectively, in the RFA group ($P < 0.001$). The 1-, 3-, and 5-year RFS rates were 94.6%, 84.1%, and 78.3%, respectively, in the SR group, and 87.7%, 62.1%, and 46.8%, respectively, in the RFA group ($P < 0.001$).

Conclusions: Surgical resection provides better OS and RFS compared with percutaneous RFA for patients with BCLC very early HCC in long-term follow-up.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, and the second most common cause of cancer-related deaths.^{1,2} Barcelona Clinic Liver Cancer (BCLC) stage 0, defined as very early stage disease, comprises patients with well-preserved liver function (Child-Pugh A) diagnosed with a solitary HCC less than 2 cm. Very early stage HCC is associated with a five-year overall survival (OS) rate of 90% after surgical resection³; however, long-term recurrence is still a problem. The 5-year risk of recurrence of HCC after resection is as high as 70%.³

Treatment options for early stage HCC include surgical resection, tumor ablation, and liver transplantation.^{2,4} Although liver transplantation potentially provides the best outcome,^{5,6} it is not

commonly used in very early stage HCC, due to cost, and is not usually an option in many regions because of organ shortage. Radiofrequency ablation (RFA) and surgical resection remain the most common options in Asian countries.^{7,8}

Recommendations of clinical practice guidelines for the treatment of early stage HCC in patients with adequate liver reserve are still controversial. The American Association for the Study of Liver Diseases recommends that adults with Child-Pugh class A cirrhosis and resectable T1 or T2 HCC choose resection over RFA; however, single tumors <2.5 cm that are favorably located “may be equally well treated by either resection or ablation” [2]. The European Association for the Study of the Liver (EASL) clinical practice guidelines had recommended resection as standard treatment for BCLC stage 0 HCC, and local ablation had been reserved for patients not suitable for surgery, but revised guidelines in 2018 recommend resection and RFA equally.⁴ The Asian Pacific Association for the Study of the Liver (APASL) revised guidelines advises both resection and RFA as standard

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treatment options for HCC ≤ 3 cm, and when no more than 3 nodules are present.⁹

It is still not clear whether surgical resection or RFA is the better choice for the treatment for early stage HCC. Previous studies, including 5 randomized controlled trials, have failed to demonstrate a universally accepted conclusion.^{10–14} Comparisons of long-term survival and recurrence rates of surgical resection vs. RFA for BCLC very early stage HCC are lacking.

We designed a study to compare long-term survival and recurrence rates of surgical resection and RFA at a high-volume tertiary care center. To our knowledge, this is the largest single-center study comparing surgical resection and RFA for BCLC very early stage HCC in the world.

Materials and methods

Patients

This study was approved by the Ethics Committee of National Taiwan University Hospital, and the study was carried out in accordance with the approved guidelines. We retrospectively reviewed the records of 387 patients with well-preserved liver function (Child-Pugh A) diagnosed with a solitary HCC less than 2 cm who underwent either surgical resection or percutaneous RFA as first-line treatment between January 2007 and December 2015. Data extracted from the medical records included demographic characteristics, and disease and survival information. Data were collected and provided by the Cancer Registry, Medical Information Management Office, National Taiwan University Hospital.

Treatment

The decision to perform resection or percutaneous RFA was made after discussions between the physician and the patient, and based on the disease status (such as tumor location, previous abdominal surgery, feasibility of treatment modality), and the patient's preference. All treatments adhered to the clinical guidelines for the management of HCC at the time. Surgical resection was either by traditional open laparotomy or by laparoscopy, according to feasibility and preference. Percutaneous RFA was always performed under image-guidance such as sonography or computed tomography (CT).

Follow-up and surveillance

Patients received regular monthly or bimonthly follow-up at the outpatient clinic after treatment. Physical examinations and routine blood tests for liver function were checked at each visit, and an abdominal imaging examination with sonography, CT, or magnetic resonance imaging (MRI) was performed every 3–6 months, or as needed. If patients had specific complaints or abnormal blood test results, additional imaging studies were performed as necessary. Recurrence was established according to imaging findings (typical HCC imaging findings) or histopathologic confirmation (atypical HCC imaging findings). A member of the liver cancer team also regularly contacted the patients or their families to follow-up on their survival at 1-, 3-, and 5 years after the initial treatment.

Statistical analysis

Data were expressed as mean \pm standard deviation, median [interquartile range (IQR) or range], or number (percentage) when appropriate. Categorical variables were compared using Fisher's exact test and Pearson's chi-square test. Continuous variables were compared using the Student's t-test and Mann–Whitney *U* test, as

appropriate. Survival curves were estimated using the Kaplan–Meier method, and compared using the log-rank test. *P* values < 0.05 were considered significant. Statistical analyses were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL).

Results

Patient characteristics

The demographic data of the 387 patients with BCLC very early stage HCC are summarized in Table 1. The median follow-up time was 39 months (IQR, 10.3–52.3 months). The mean age of the SR and RFA groups were 58.8 ± 11.7 (range, 27–82) years and 62.2 ± 12.3 (range: 31–84) years, respectively ($P = 0.006$). There was no difference in sex distribution between the SR and RFA groups. Hepatitis B infection was more prevalent in resection group, and hepatitis C infection was more prevalent in RFA group. No significant difference of α -fetoprotein between groups. All patients in the SR group had pathology-confirmed HCC. Tumor biopsy was done in 159 patients (68.8%) in the RFA group, and 128 of them (80.5%) had pathology-confirmed HCC. The mean tumor size was 14.6 ± 3.1 mm (range: 5–19 mm) in the SR group, and 15.8 ± 2.4 mm (range: 8–19 mm) in the RFA group ($P < 0.001$).

Overall survival

Six of 156 (3.8%) patients in the SR group, and 26 of 231 (11.3%) patients in the RFA group had all-cause mortality during follow-up. The median time of death was 33.6 months (range: 13.2–56.1 months) in the SR group, and 37.3 (range, 15.4–63.3 months) in the RFA group. HCC-related deaths occurred in 2 patients (1.3%) in the SR group, and 16 patients (6.9%) in the RFA group. Kaplan–Meier curves for OS are shown in Fig. 1. The 1-, 3-, and 5-year OS rates were 100%, 97.2%, and 93.4%, respectively, in the SR group, compared with 100%, 88.6%, and 73.5%, respectively, in the RFA group ($P < 0.001$).

Recurrence

Twenty-six of 156 (16.7%) patients in the SR group, and 64 of 231 (27.7%) patients in the RFA group had tumor recurrence during follow-up. The median time of tumor recurrence was 21.2 months (IQR: 7.7–36.2 months) in the SR group, and 17.5 months (IQR: 8.1–26.7 months) in the RFA group. Four patients (1.7%) in the RFA group had tumor recurrence less than 60 days after treatment, while none in the SR group had a recurrence within 60 days, suggesting treatment margin failure. Fifteen patients (9.6%) in the SR group and 38 patients (16.5%) in the RFA group had recurrences between 60 days and 2 years after surgery. Long-term recurrence (2 years after initial treatment) occurred in 11 patients (7.1%) in the SR group, and 22 patients (9.5%) in the RFA group. Kaplan–Meier curves for RFS are shown in Fig. 2. The 1-, 3-, and 5-year RFS rates were 94.6%, 84.1%, and 78.3%, respectively, in the SR group, compared with 87.7%, 62.1%, and 46.8%, respectively, in the RFA group ($P < 0.001$).

Impact of recurrence on survival

Patients without recurrent HCC had better survival compared with patients with recurrent HCC (log-rank test; $P = 0.015$) (Fig. 3). The estimated survival of patients with and without recurrence was 5.7 ± 0.2 years and 6.2 ± 0.1 years, respectively. However, survival from the time of recurrence was similar among patients who underwent SR or RFA (log-Rank test; $P = 0.299$) (Fig. 4).

Table 1
Patient demographic and clinical characteristics.

	All patients (n = 387)	Resection (n = 156)	RFA (n = 231)	P-value
Age (range)	60.8 ± 12.2 (27–84)	58.8 ± 11.7 (27–82)	62.2 ± 12.3 (31–84)	0.006*
Male sex	236 (61)	95 (61)	141 (6)	1.0
HBsAg positive	233 (60.2)	110 (70.5)	123 (53.2)	0.001*
HCV-Ab positive	156 (40.3)	49 (31.4)	107 (46.3)	0.004*
HBsAg plus HCV-Ab	22 (5.7)	11 (7.1)	11 (4.8)	0.375
Alcoholism	8 (2.1)	5 (3.2)	3 (1.3)	0.277
α-fetoprotein, ng/ml	22.1 (5.4–127)	31.8 (5.3–190)	19.1 (5.5–98.5)	0.136
Pathology confirmed	284 (73.4)	156 (100)	128 (55.4)	<0.001*
Tumor size, mm (range)	15.3 ± 2.8 (5–19)	14.6 ± 3.1 (5–19)	15.8 ± 2.4 (8–19)	<0.001*
Recurrence	90 (23.3)	26 (16.7)	64 (27.7)	0.014*
Less than 60 days	4	0	4	
60 days to 2 years	53	15	38	
After 2 years	33	11	22	
Time to recurrence [#]	18.5 (8.1–28.8)	21.2 (7.7–36.2)	17.5 (8.1–26.7)	0.364
All-cause mortality	32 (8.3)	6 (3.8)	26 (11.6)	0.013*
HCC-related death	18 (4.7)	2 (1.3)	16 (6.9)	0.012*
Follow-up time [#]	39.0 (10.3–52.3)	42.9 (13.2–65.1)	18.6 (8.9–46.8)	<0.001*

Data were presented with number (percentage), mean ± standard deviation, or median (interquartile range). Abbreviations: RFA, radiofrequency ablation; mo, month. *P < 0.05. [#]months.

Discussion

Our study results showed that, compared with RFA, SR provided better long-term OS and RFS in patients with BCLC very early stage

HCC. Surgery is the gold standard treatment, and enables physicians to create a safety margin under direct vision, resect adjacent parenchyma around the tumor, and resect satellite nodules that could not be identified on preoperative imaging.¹⁵ The drawbacks

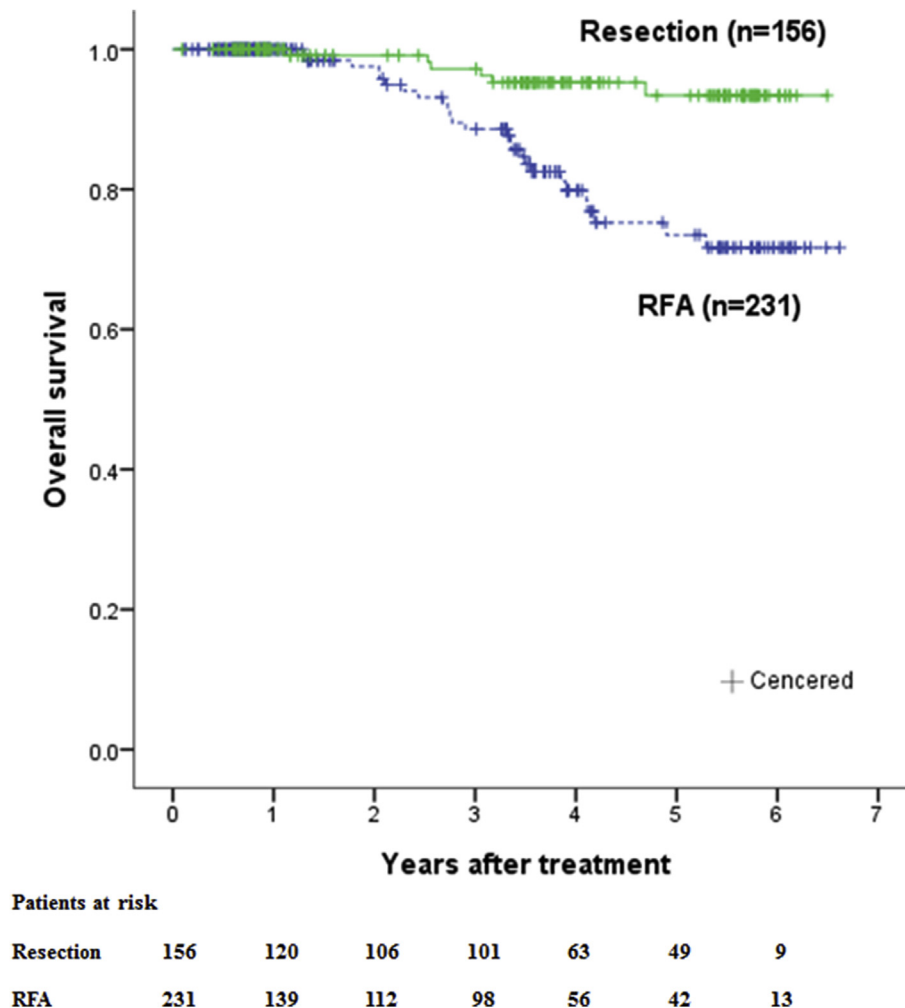
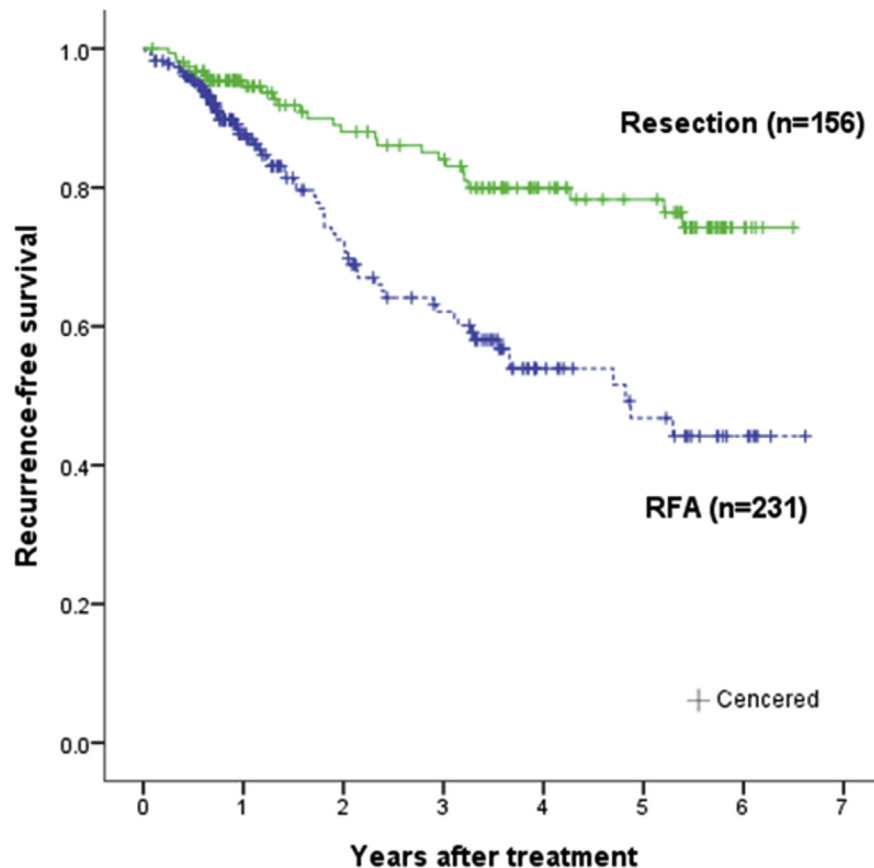


Fig. 1. Overall survival of patients with BCLC very early stage HCC who underwent SR and RFA (P < 0.001).



Patients at risk

Resection	156	113	93	84	54	43	7
RFA	231	122	81	62	28	19	7

Fig. 2. Recurrence-free survival of patients with BCLC very early stage HCC who underwent SR and RFA ($P < 0.001$).

of surgery are: increased cost, longer hospital stay,^{14,16} a complicated procedure and surgical stress to patients, and sacrifice of a greater amount of non-tumor liver parenchyma. RFA is a relatively less invasive procedure with less stress, expense, and shorter hospital stay, better preservation of liver function, and better repeatability.¹⁷ However, the efficacy of RFA is highly operator-dependent, and does not provide any definite evidence regarding the completeness of ablation. In addition, some studies have reported needle tract tumor seeding.^{18–20}

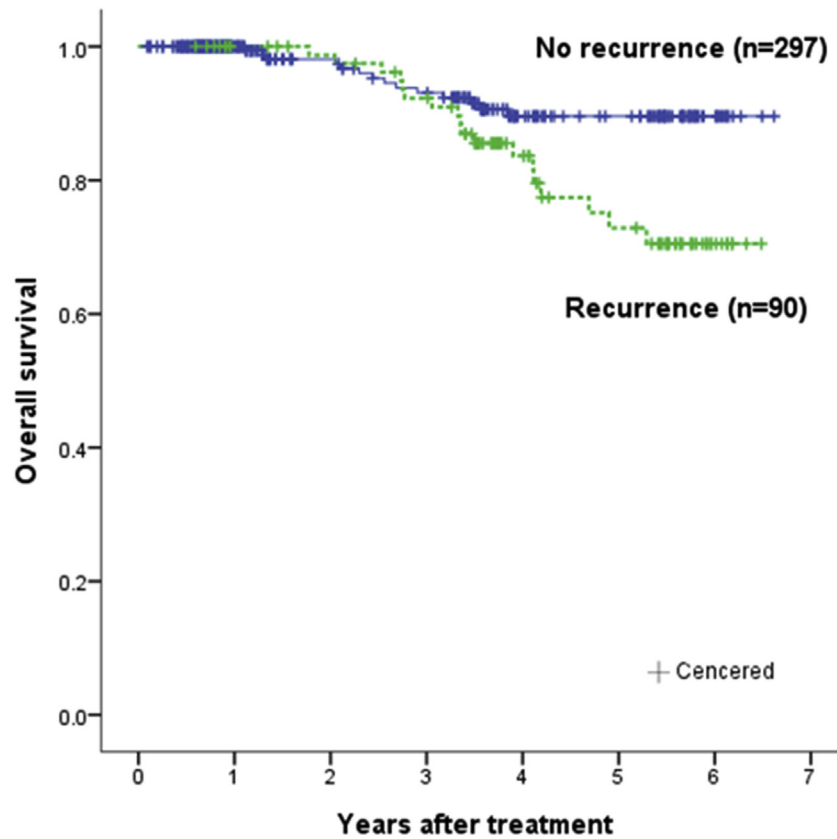
Whether RFA produced as good an outcome in terms of OS and RFS as surgical resection for early stage HCC has been debated for a long time.^{21,22} According to different inclusion criteria of tumor size and number, 3 major controversial results have been reported: resection is superior in respect to OS and RFS^{23–27}; resection is superior with respect to RFS but similar in OS^{28,29}; and RFA has comparable OS and RFS with resection.^{23,30}

Most previous studies were retrospective analyses with small sample sizes and limited follow-up periods. One meta-analysis³¹ of 16,103 patients from 31 studies concluded that the 3- and 5-year OS and RFS rates in patients who received resection were significantly higher for HCC ≤ 3 cm, whereas there were no significant differences between resection and RFA for HCC ≤ 2 cm. Another large nationwide survey of 12,968 patients from Japan³² reported better survival and less recurrence with resection with a single tumor ≤ 2 cm. Although these studies had large sample sizes, the

treatment principle and efficacy were highly different among different local hospitals, which may have affected the results of the 2 studies.

Five RCTs comparing SR and RFA for early HCC have been reported, with contradictory results.^{10–14} SR was shown to be associated with survival rates similar to RFA in 3 studies,^{10,12,14} whereas it was better than RFA in terms of patient survival and tumor recurrence in the other 2 studies.^{11,13} Those RCTs reduced the influence of confounding factors that are present in retrospective studies; however, they had relatively small sample sizes with limited follow-up periods.

In this study we included 387 BCLC very early stage HCC patients treated at a tertiary referral center over a 9-year period, and with long-term follow-up results. There was homogeneity of the patients, and both SR and RFA were mature treatment modalities at our hospital with a stable quality of treatment. This study is currently the largest single-center report comparing the outcomes of SR and RFA in BCLC stage 0 patients. Our results showed that SR had better results with respect to OS and RFS compared to RFA. We noted a better OS among the SR group beginning 3 years after the initial treatment, but there was a stable difference in RFS between the SR and RFA groups since the initial treatment (Figs. 1 and 2). There was almost no difference in OS during the first 36 months after treatment, but there was a dramatic difference between the 2 groups beginning the fourth year of follow-up. Even more



Patients at risk

No recurrence	297	177	140	128	75	59	14
Recurrence	90	82	78	71	44	32	8

Fig. 3. Impact of tumor recurrence on overall survival of patients with BCLC very early-stage HCC. Patients without recurrent HCC had better survival beginning the 4th year after initial treatment compared with patients with recurrent HCC (log-rank test; $P = 0.029$).

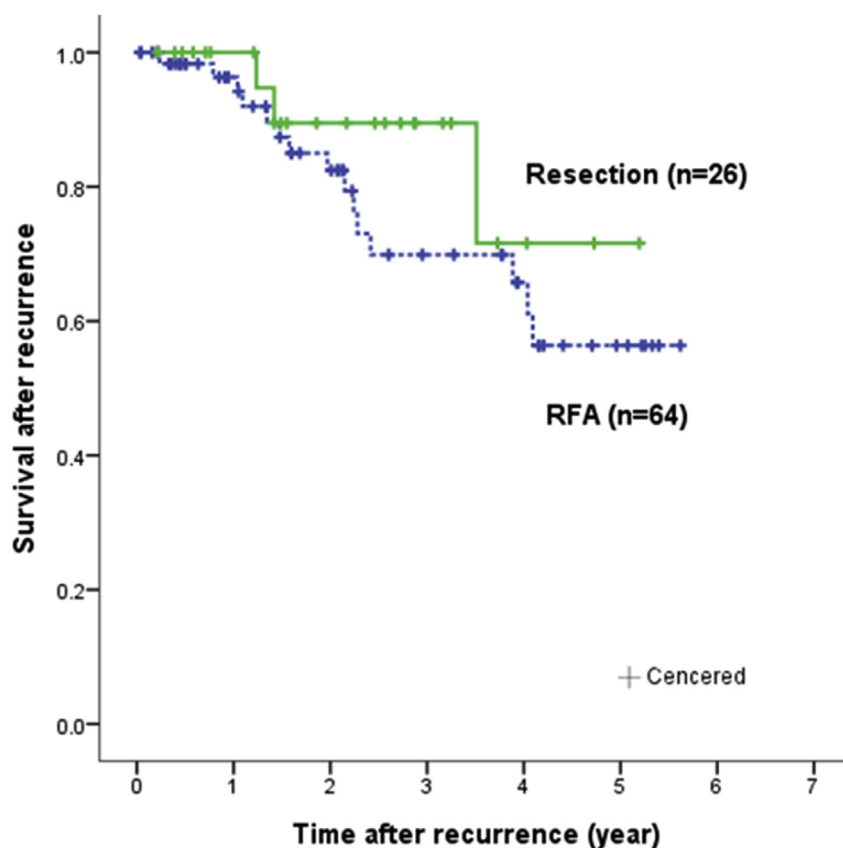
interesting was the fact that there was no difference in OS between patients with and without tumor recurrence in the first 36 months after treatment. Beginning in the fourth year of follow-up, however, a dramatic change occurred, in which there was a significant difference in OS (Fig. 3).

Tumor recurrence may be one of the most important factors affecting long-term survival in patients with very early HCC. Three-year survival rates of BCLC stage 0 cases can reach 85%.³³ Even if there is a recurrence after very early HCC, patients still have many chances of secondary radical treatment by a variety of treatment modalities, and have a relatively good prognosis. When there is small sample size with limited follow-up of patients with very early HCC, the survival differences may not be evident between SR and RFA groups, as well as between patients with recurrence and recurrence-free patients.

The most important goal in the treatment of very early HCC is radical removal of as many malignant cells as possible under a tolerable risk of treatment. With improvements of medical care and advances in surgical techniques and devices, the mortality rate of hepatectomy is now lower than 0.5% in experienced treatment centers, with a reasonable complication rate and predictable outcome.³⁴ While we believe that current RFA needles can theoretically create an ablation zone of 3–5 cm (or even more) to destroy small-size HCC; however, in clinical practice the complete ablation rate depends not only on tumor size, but also tumor location and the ablation technique of the operator.

The completeness and safety margin of tumor resection can be directly evaluated and measured intraoperatively by the surgeon, plus a postoperative histopathological examination by the pathologist. However, during RFA reports, there was no objective evaluation of safety margin and ablation effect. Besides, there are several risk factors of recurrence associated with RFA but not with resection. Tumor biopsy, which is sometimes performed along with RFA, is a risk factor for needle tract seeding and local recurrence.³⁵ Viable tumor cells might adhere to the RFA electrode, due to sudden increases in intratumor pressure and thus cause tumor dissemination along the puncture route.^{18–20} Mechanical or thermal damage during ablation has been proposed to be one of the causes of aggressive tumor recurrence.³⁶ Therefore, it is not surprising that higher recurrence rates with RFA than resection for treatment of early HCC has been frequently reported.

The conclusion of whether RFA can provide equal treatment outcomes to resection may not be made if we consider only “early stage” or “size,” without considering “location,” since there is a higher rate of incomplete ablation in difficult locations, such as with a tumor located at the liver surface, or near the main hepatic vessels or hilum. While treating a difficult surgical candidate with early HCC, resection may be accompanied with more complications such as greater blood loss, but rarely compromises oncological results. However, the complete ablation rate is usually decreased in treating an early HCC with difficult ablation site. Therefore, there are two essential requirements when using RFA for treating BCLC



Patients at risk

Resection	26	19	13	7	3	1
RFA	64	45	32	20	14	6

Fig. 4. Impact of tumor recurrence on overall survival of patients with BCLC very early-stage HCC. Survival rate from the time of tumor recurrence was similar between patients who underwent SR or RFA (log-rank test; $P = 0.331$).

very early stage HCC: an experienced operator and suitable tumor location.

This study had some limitations. It was a single-center retrospective analysis, which spanned a long time period. Improvements in surgical and ablative equipment, and advances in medical care over the time period may have influenced the results. We did not consider the location of HCC and did not analyze the type of recurrence. Future studies may help provide more information leading to a clearer understanding of recurrence.

Conclusions

This study demonstrated that in clinical practice, SR appears to leads to a lower recurrence rate than RFA when treating BCLC very early stage HCC, and the recurrence rate has a significant impact on long-term survival.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

All authors have no conflict of interest to disclose.

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