

Liver resection versus radiofrequency ablation for hepatitis B virus-related small hepatocellular carcinoma

Bin Liang^{1,2}
Siyang Yao²
Jiapeng Zhou³
Zongkui Li^{1,2}
Tianqi Liu²

¹Department of Graduate School,
The Guangxi Medical University,

²Department of Hepatobiliary Surgery,
The People's Hospital of Guangxi
Zhuang Autonomous Region, Nanning,

³Department of Hepatobiliary
Surgery, The First People's Hospital of
Qinzhou, Qinzhou, People's Republic
of China

Background: To compare the outcomes of liver resection (LR) with radiofrequency ablation (RFA) for patients with hepatitis B virus (HBV)-related small hepatocellular carcinoma (HCC).

Methods: A total of 122 HBV-related small HCC patients who underwent LR (n=64) or RFA (n=58) were involved in this retrospective study. Their basic clinical data, postoperative complications, survival outcomes, and prognostic factors were compared and analyzed.

Results: Patients in the LR group had more serious complications (11 versus 0) and longer postoperative hospital stays (11.3 versus 6.0 days) than those in the RFA group (all $P < 0.05$). LR was associated with better recurrence-free survival (RFS) rates at 1, 3, and 5 years compared with RFA (90.4%, 65.9%, and 49.5% versus 79.3%, 50.3%, and 35.6%, $P = 0.037$), but there was no significant difference in overall survival (OS) (95.2%, 78.1%, 58.6% versus 93.1%, 71.3%, 52.9%, $P = 0.309$). Multivariate Cox analysis showed that the hepatic cirrhosis (hazard ratio [HR]: 2.13), tumor number (HR: 3.73), tumor diameter (HR: 1.92), and postoperative anti-HBV therapy (HR: 0.53) had predictive values for RFS, and the latter three (HR: 4.34, 2.30, and 0.44) were independent predictors of OS (all $P < 0.05$).

Conclusion: LR might be considered the preferred method for patients with HBV-related small HCC, while RFA could apply to selective cases. Anti-HBV therapy after treatment was recommended.

Keywords: liver resection, hepatitis B virus, hepatocellular carcinoma, radiofrequency ablation, survival

Background

Hepatocellular carcinoma (HCC) is one of the most prevalent primary malignancies of the liver and is the leading cause of cancer-related deaths.¹ The high incidence is partly due to the elevated chronic hepatitis B virus (HBV) prevalence, which is seen in 55%–60% of persons worldwide and in more than 70% in Asian countries in patients with HCC.² Currently, liver resection (LR) and radiofrequency ablation (RFA) are usually considered as curative treatments of small HCCs, while the donor shortage greatly limits the applicability of liver transplantation.³

Over the past decades, although many studies worldwide have investigated the treatment of LR and RFA in patients with small HCCs, the use of these methodologies remains a controversial issue and has not yet been standardized, especially in the East, with its high prevalence of HBV infection.⁴ In this study, we compared the outcomes and explored the relevant prognostic factors of patients with HBV-related small HCC who underwent LR or RFA as the primary treatment through retrospective

Correspondence: Tianqi Liu
Department of Hepatobiliary Surgery,
The People's Hospital of Guangxi Zhuang
Autonomous Region, 6 Taoyuan Road,
Nanning, Guangxi Zhuang Autonomous
Region 530021, People's Republic of
China
Tel/fax +86 771 218 6550
Email ljrtq@126.com

analysis, aiming to determine the efficacy of different treatment selection.

Methods

Patients

This study was approved by the People's Hospital of Guangxi Zhuang Autonomous Region Institutional Review Board and conformed to the ethical guidelines of the Declaration of Helsinki. A total of 578 patients with HCC underwent LR or RFA as the primary treatment from January 2011 to December 2016 in our hospital. Their medical records were retrospectively reviewed. Of these, 122 patients were selected in this study who met the following criteria: 1) the presence of small HCC (≤ 5 cm or ≤ 3 cm and no more than 3 lesions); 2) comorbid chronic HBV infection; 3) Child–Pugh class A or B and good performance status; 4) absence of vascular invasion, decompensated liver cirrhosis, and metastatic disease; and 5) follow-up for at least 6 months.

Because of the retrospective nature of the study, patient consent to review their medical records was waived by the approving of the People's Hospital of Guangxi Zhuang Autonomous Region Institutional Review Board. The presented data of participants are anonymized, and the risk of identification is low.

Diagnosis

The diagnosis of HCC was confirmed by histopathology after resection for patients in the LR group, while percutaneous needle biopsy was performed for all of the patients in the RFA group. Primary treatment was defined before any previous treatment in both groups at the time of diagnosis of HCC. HBV-related HCC was identified in the patients with HCC who were diagnosed with coexisting presence of serum hepatitis B surface antigen.⁵ Contrast-enhanced ultrasound and/or multiphase contrast-enhanced spiral computed tomography scan with an instrumental criterion was used in the diagnosis of cirrhosis and in the measurement of the tumor number and diameter. Recurrence was defined as the emergence of a new tumor inside or outside the liver, including residual active tumor within or near the previous site found more than 1 month following the first treatment.

Treatments

The therapeutic benefits and potential risks of LR and RFA were provided to each patient in detail, and the final treatment modality was determined by individual patients after the surgeon's suggestion was given. Informed consent forms were signed by all of the included patients before the treatment of LR or RFA.

Both LR and RFA were performed by the same experienced surgical group. Anatomical liver resection (ALR) was given priority to be applied to the patients while it was possible, and nonanatomical liver resection (NALR) was used in tumors adjacent to the main vasculature, and attempts were made to maintain an adequate surgical margin of at least 1.0 cm. Percutaneous RFA was conducted under sonographic (SSD-3500, Aloka, Chiba, Japan) guidance operated by the same experienced sonographer, and the tumors were completely ablated in automatic impedance control mode with the Radiofrequency System (RF 2000, USA). Percutaneous ethanol injection (PEI) was combined with RFA when the HCC lesions were in high-risk locations, such as near major vasculature, the liver surface, the gallbladder, or the gastrointestinal tract.⁶

Follow-up

All of the patients selected in the study were followed up with biochemical liver function and serum alpha-fetoprotein (AFP) tests and ultrasonography or computed tomography/magnetic resonance imaging examinations every 3–6 months until death or the end of the study. Recurrent tumors were managed by individualized therapy plans, which included repeated LR or RFA, transcatheter arterial chemoembolization, and oral sorafenib therapy. The time to tumor recurrence and overall survival (OS) were recorded. Follow-up data were collected until December 31, 2016.

Statistical analysis

The data of the patients were statistically analyzed using IBM SPSS software, version 22.0 (Armonk, NY, USA) for Windows. Continuous variables were evaluated with a single-factor analysis of variance. Categorical variables were compared using the chi-square test. Recurrence-free survival (RFS) and OS data were analyzed using the Kaplan–Meier method, and all survival curves in the two groups were compared using the log-rank test. Moreover, a Cox regression model was used to identify the prognostic factors. Multivariate analysis was executed for those factors with P -values < 0.2 in univariate analysis. A P -value < 0.05 was considered to indicate a statistically significant difference.

Results

Patients' characteristics

In this study, 122 patients who satisfied the inclusion criteria were selected: 64 of these underwent LR and 58 were treated with RFA. In the LR group, 47 patients received ALR, and 17 underwent NALR. In the other group, 37 patients were

treated with RFA alone, and the remaining 21 had combined therapy with PEI. All of them were diagnosed with HCC by histopathology after treatment. The median follow-up times were 34.9 months (range, 7–66 months) in the LR group and 36.1 months (range, 9–66 months) in the RFA group.

The baseline characteristics of all of the patients in both the LR and RFA groups are shown in Table 1. All the data of sex, age, serum carcinoembryonic antigen (CEA), the positive rate of AFP, total bilirubin (TB), albumin (ALB), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), platelet count (PLT), the hepatitis B virus DNA levels (HNB-DNA), Child–Pugh classification, the presence of cirrhosis, the tumor number, and the maximum tumor diameter in both groups showed no significant differences between the two groups (all $P>0.05$). In addition, the number of patients who received anti-HBV therapy after surgery was

34 (53.1%) in the LR group and 37 (63.8%) in the RFA group ($P=0.233$), respectively.

Postoperative characteristics

Postoperative characteristics are presented in Table 2. Patients in the LR group tended to have lower ALB and higher ALT and AST than those in the RFA group (all $P<0.001$), and they were also more vulnerable to having procedure-related complications (11 versus 0, $P=0.001$), including hydrothorax (1 case), ascites (2 cases), elevated serum pancreatic α -amylase (6 cases), bleeding (1 case), and subphrenic infection (1 case). Furthermore, patients who received resection experienced longer postoperative hospital stays than those who underwent ablation; the median postoperative hospital days were 11.3 days (range, 7–25 days) in the LR group and 6.0 days in the RFA group (range, 3–10 days) ($P<0.001$). However, postoperative TB, 7-days AFP >400 ng/mL, and temperature $\geq 38.5^\circ\text{C}$ were not significantly different between the two groups. There were no perioperative deaths in either group.

Recurrence and survival

At the time of censoring, recurrence was observed in 23 of 64 (35.9%) patients in the LR group and 32 of 58 (55.2%) in the

Table 1 Baseline characteristics of 122 patients treated with LR or RFA

Characteristics	LR group (n=64)	RFA group (n=58)	P-value
Sex			0.810
Male	54 (84.3%)	48 (82.8%)	
Female	10 (15.6%)	10 (17.2%)	
Age (years)	48.8 (26–74)	51.4 (30–85)	0.218
Serum biochemistry			
CEA ($\mu\text{g/L}$)	1.3 (0.5–4.6)	1.6 (0.5–4.3)	0.087
AFP (>400 ng/mL)	18 (28.1%)	9 (15.5%)	0.094
TB (mg/dL)	13.2 (3.4–36.4)	14.2 (4.4–31.0)	0.333
ALB (g/dL)	38.6 (30.0–45.2)	37.8 (28.7–44.4)	0.180
ALT (U/L)	49.2 (9–151)	33.5 (13–104)	0.132
AST (U/L)	34.9 (16–134)	35.1 (14–71)	0.971
PLT ($\times 10^3/\text{L}$)	187.8 (68–417)	177.7 (74–274)	0.385
HBV DNA levels (>500 U/mL)	42 (65.6%)	32 (55.2%)	0.238
Child–Pugh classification			0.884
A	58 (90.6%)	53 (91.4%)	
B	6 (9.4%)	5 (8.6%)	
Hepatic cirrhosis			0.729
Absent	24 (37.5%)	20 (34.5%)	
Present	40 (62.5%)	38 (65.5%)	
Number of tumors			0.251
1	47 (73.4%)	37 (63.8%)	
2 or 3	17 (26.6%)	21 (36.2%)	
Maximum tumor diameter (cm)	3.1 (1.5–5.0)	2.9 (1.2–5.0)	0.070
Postoperative anti-HBV therapy	34 (53.1%)	37 (63.8%)	0.233
Follow-up times (months)	34.9 (7–66)	36.1 (9–66)	0.661

Abbreviations: LR, liver resection; RFA, radiofrequency ablation; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; HBV, hepatitis B virus.

Table 2 Postoperative characteristics of 122 patients treated with LR or RFA

Characteristics	LR group (n=64)	RFA group (n=58)	P-value
Postoperative serum biochemistry			
TB (mg/dL)	23.0 (5.0–59.4)	23.5 (8.3–52.7)	0.817
ALB (g/dL)	31.7 (23.0–42.7)	34.8 (23.0–44.8)	<0.001
ALT (U/L)	315.8 (30–926)	135.2 (39–369)	<0.001
AST (U/L)	286.7 (40–880)	178.2 (51–421)	<0.001
7-days AFP (>400 ng/mL)	12 (18.8%)	8 (13.8%)	0.460
Postoperative febrile ($\geq 38.5^\circ\text{C}$)	25 (39.0%)	18 (31.0%)	0.354
Serious complications (total)	11 (17.2%)	0	0.001
Hydrothorax	1	0	
Ascites	2	0	
Serum pancreatic α -amylase elevated	6	0	
Postoperative bleeding	1	0	
Subphrenic infection	1	0	
Hospital mortality			NA
Postoperative hospital days	11.3 (7–25)	6.0 (3–10)	<0.001
Recurrent cases	23 (35.9%)	32 (55.2%)	0.033
Death cases	14 (21.9%)	19 (32.8%)	0.177

Abbreviations: LR, liver resection; RFA, radiofrequency ablation; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AFP, alpha-fetoprotein; NA, not available.

RFA group ($P=0.033$). The cumulative RFS rates at 1, 3, and 5 years were estimated to be 90.4%, 65.9%, and 49.5% in the LR group and 79.3%, 50.3%, and 35.6% in the RFA group, respectively (Figure 1A). The RFS rates were significantly higher in the LR group ($P=0.037$). There were 14 (21.9%) patients who died in the LR group and 19 (32.8%) in the RFA group ($P=0.177$). The 1-, 3-, 5-year cumulative OS rates in the LR group were 95.2%, 78.1%, and 58.6% and those in the RFA group were 93.1%, 71.3%, and 52.9%, respectively (Figure 1B). There were no significant differences between the two groups in OS ($P=0.309$).

Prognostic factors for outcomes

In univariate analysis of RFS, the P -values for CEA, AST, PLT, hepatic cirrhosis, number of tumors, maximum tumor diameter, and postoperative anti-HBV therapy were all <0.20 . The multivariate analysis of these seven variables showed that hepatic cirrhosis (hazard ratio [HR]: 2.13, 95% CI: 1.13–2.76, $P=0.019$), number of tumors (HR: 3.73, 95% CI: 1.93–7.20, $P<0.001$), maximum tumor diameter (HR: 1.92, 95% CI: 1.34–2.76, $P<0.001$), and postoperative anti-HBV therapy (HR: 0.49, 95% CI: 0.30–0.91, $P=0.022$) were independent prognostic factors associated with RFS.

For OS, univariate analysis showed that the P -values of AST, number of tumors, maximum tumor diameter, and postoperative anti-HBV therapy were all <0.20 . However, by

multivariate analysis, the number of tumors (HR: 4.34, 95% CI: 1.98–9.52, $P<0.001$), maximum tumor diameter (HR: 2.30, 95% CI: 1.44–3.69, $P=0.001$), and postoperative anti-HBV therapy (HR: 0.44, 95% CI: 0.22–0.89, $P=0.023$) were significant, independent predictors of OS. Further details are presented in Tables 3 and 4.

Discussion

HBV infection is one of the most prevalent risk factors in the development of HCC worldwide, and a large body of research has confirmed the association between viral infection and the occurrence of HCC.^{7,8} Although routine HCC surveillance of HBV-infected subjects could improve their survival, it has been reported that HBV-related HCC patients have significantly poorer outcomes after treatment than those without HBV infection.^{9,10} In past decades, numerous studies have compared the outcomes of patients with HCC who underwent LR or RFA; however, there has not been a consistent opinion on which treatment method is superior. Some researchers have confirmed that patients who receive LR have a significantly higher survival rate than those who receive RFA,^{11–15} while some investigations have indicated similar long-term outcomes between the two treatments,^{16–19} and have even reported that RFA was associated with better treatment efficacy than LR in patients with small HCC.²⁰ Currently, among HBV-related small HCC cases, there are no

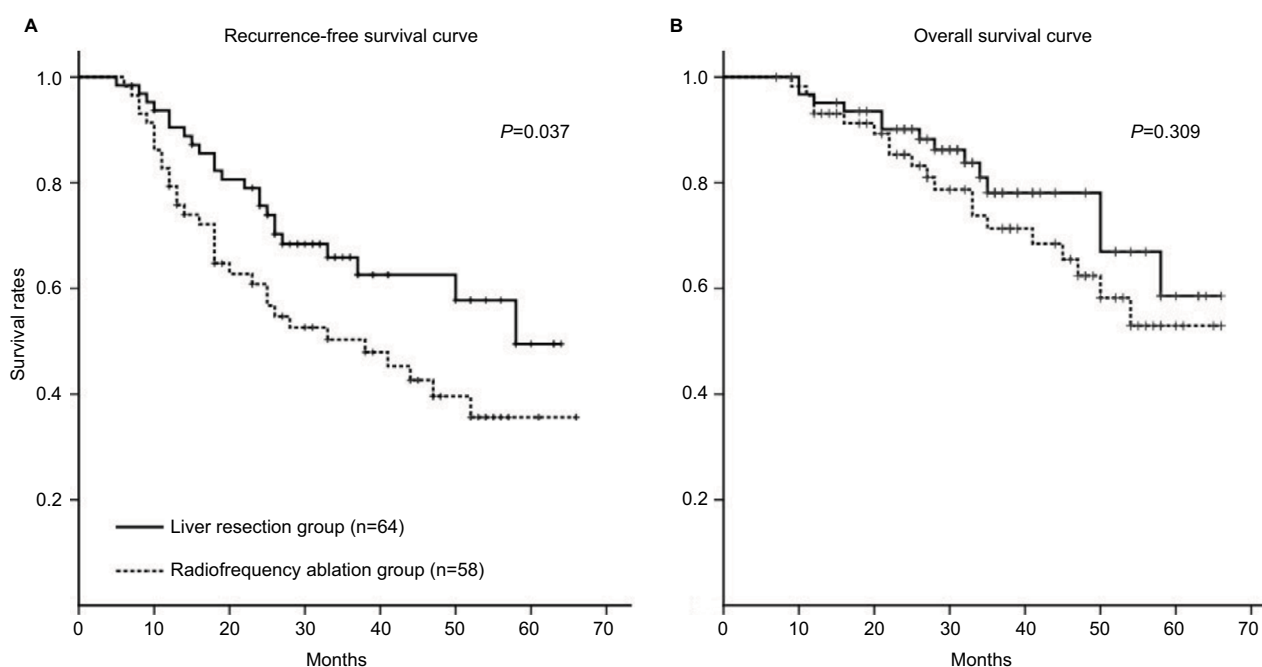


Figure 1 RFS and OS curves for 122 patients treated with LR or RFA.

Notes: (A) Patients who undergo LR have better RFS rates than those who undergo RFA ($P=0.037$); (B) There is no significant difference between two groups in OS rates ($P=0.309$).

Abbreviations: LR, liver resection; OS, overall survival; RFS, recurrence-free survival; RFA, radiofrequency ablation.

Table 3 Univariate and multivariate analysis of RFS in patients with HBV-related small HCC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (per 1 year)	1.01 (0.98–1.03)	0.694		
CEA ($\mu\text{g/L}$)	1.21 (0.91–1.62)	0.193	1.05 (0.80–1.38)	0.734
AFP ($>400\text{ ng/mL}$)	1.01 (0.53–1.91)	0.982		
TB (mg/dL)	0.99 (0.95–1.04)	0.749		
ALB (g/dL)	1.01 (0.93–1.09)	0.876		
ALT (U/L)	1.00 (0.98–1.01)	0.755		
AST (U/L)	1.01 (1.00–1.03)	0.068	1.01 (0.99–1.02)	0.409
PLT ($<100\times 10^3/\text{L}$)	1.00 (0.99–1.00)	0.110	1.00 (0.99–1.00)	0.413
HBV DNA levels ($>500\text{ U/mL}$)	0.97 (0.56–1.66)	0.907		
Child–Pugh classification (A/B)	1.23 (0.53–2.87)	0.636		
Hepatic cirrhosis (Yes/No)	1.97 (1.07–3.61)	0.029	2.13 (1.13–2.76)	0.019
Number of tumors (1/2 or 3)	2.72 (1.58–4.66)	<0.001	3.73 (1.93–7.20)	<0.001
Maximum tumor diameter (cm)	1.49 (1.11–1.99)	0.007	1.92 (1.34–2.76)	<0.001
Postoperative anti-HBV therapy (Yes/No)	0.49 (0.29–0.84)	0.010	0.53 (0.30–0.91)	0.022

Abbreviations: RFS, recurrence-free survival; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; HBV, hepatitis B virus.

Table 4 Univariate and multivariate analysis of OS in patients with HBV-related small HCC

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (per 1 year)	1.01 (0.98–1.04)	0.637		
CEA ($\mu\text{g/L}$)	1.23 (0.83–1.82)	0.308		
AFP ($>400\text{ ng/mL}$)	0.82 (0.34–1.98)	0.651		
TB (mg/dL)	1.01 (0.95–1.07)	0.749		
ALB (g/dL)	0.94 (0.84–1.04)	0.222		
ALT (U/L)	1.00 (0.98–1.02)	0.804		
AST (U/L)	1.02 (1.00–1.03)	0.067	1.01 (0.99–1.03)	0.129
PLT ($<100\times 10^3/\text{L}$)	1.00 (0.99–1.00)	0.289		
HBV DNA levels ($>500\text{ U/mL}$)	1.23 (0.60–2.50)	0.574		
Child–Pugh classification (A/B)	1.54 (0.54–4.38)	0.423		
Hepatic cirrhosis (Yes/No)	1.06 (0.52–2.16)	0.869		
Number of tumors (1/2 or 3)	2.90 (1.45–5.81)	0.003	4.34 (1.98–9.52)	<0.001
Maximum tumor diameter (cm)	1.71 (1.17–2.49)	0.006	2.30 (1.44–3.69)	0.001
Postoperative anti-HBV therapy	0.44 (0.22–0.88)	0.021	0.44 (0.22–0.89)	0.023

Abbreviations: OS, overall survival; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; AFP, alpha-fetoprotein; TB, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; HBV, hepatitis B virus.

data comparing the clinical outcomes of LR with RFA, and our study was performed to explore the difference between these two treatments in such a cohort.

Recently, several studies have reported that LR was associated with a lower recurrence risk but similar OS, compared with RFA in early-stage HCC patients.^{14,21,22} Consistent with this finding, our study also found the same outcomes between LR and RFA in HBV-related small HCC. Patients in the LR group achieved better cumulative RFS rates at 1, 3, and 5 years than those in the RFA group ($P=0.037$) but comparable OS rates between the two groups ($P=0.309$). LR has the advantage of removing the tumor-adjacent territory, likely including minute satellite lesions, especially in patients who underwent anatomical resection, which could

offer better local control of HCC than RFA.²³ In the present study, recurrence was observed in 55.2% (32/50) of cases in the RFA group, which was significantly higher than in the LR group with 35.9% (23/64) relapse during the follow-up period ($P=0.033$). According to previous reports, the recurrence rate in HBV-related HCC patients who underwent RFA treatment was 52.4%–60.8% after a 5-year follow-up, and the risk of recurrence was increased with the lower PLT, higher HBV DNA levels, and the tumor topographical factors (including the number, larger size, and proximity to major vessels or the diaphragm).^{24–28}

Despite a significantly lower RFS in the RFA group, the OS was comparable in both groups. Such outcomes could probably be attributed to regular visits after surgery, which

could detect early recurrence and ensure that patients received timely retreatment with individual methods.²¹ Additionally, our study showed that patients who underwent RFA experienced fewer treatment-related complications and shorter postoperative hospital stays. These results were consistent with previous studies.^{11–14,16} Accompanied by the advantage of liver functional reserve, offering better tolerability, good repeatability, and cost-effectiveness,²⁹ RFA could be considered an alternative therapy for selected patients with small HCC, such as those with worse liver function and older candidates.

In these patients, the results of multivariate analysis in our study showed that the presence of hepatic cirrhosis, multiple tumors, and larger tumor diameter were significant independent risk predictors of RFS, while only multiple tumors and larger tumor diameter were risk factors associated with OS. Similarly, a previous study demonstrated that intervention (resection versus ablation), tumor number, tumor diameter, and a high level of serum AFP were independent risk factors for RFS and OS for early-stage HCC.¹³ This finding suggests that HBV-related HCC patients with hepatic cirrhosis, multiple tumors, and larger tumor diameters should undergo enhance surveillance after treatment, especially those who undergo RFA.

Our study showed that postoperative anti-HBV therapy was an independent protective factor for both RFS and OS. This result was in agreement with several previous studies.^{30–33} A randomized controlled trial demonstrated that anti-HBV therapy after treatment significantly reduced recurrence and improved OS in patients with HBV-related HCC.³⁰ Urata et al³¹ suggested that a high serum level of HBV DNA was a notable risk factor for recurrence after surgery for HBV-related HCC, and antiviral therapy could improve the long-term outcomes. Ke et al³² indicated that postoperative anti-HBV therapy could significantly prolong survival time by increasing the likelihood of the patient receiving curative treatments in the event of a relapse and that it prevented death due to liver failure, especially in patients with early- or median-stage HCC. Hence, anti-HBV therapy after LR or RFA can be highly recommended in patients with HBV-related small HCC to attain the benefit of better outcomes.

There were several limitations in our study. First, because of the retrospective study design, there was potential for selection bias, as well as with the presence of uncontrolled confounding factors between the two groups. Second, there is no comparison of recurrence patterns and treatment modalities for recurrent tumor which may influence the results in this study. However, we plan to further our study by increasing

the sample size and comparing the recurrence to confirm the outcomes of these cohorts after treatment.

Conclusion

For patients with HBV-related small HCC, LR provided better RFS than RFA but had a similar OS in comparison. Patients who underwent RFA had fewer complications and shorter postoperative hospital stays. LR might be considered the preferred method for these patients, while RFA could apply to selective patients who would be unable to tolerate surgical resection. Hepatic cirrhosis, tumor number, and maximum tumor diameter were independent prognostic factors of long-term outcomes in this cohort, and anti-HBV therapy after treatment was recommended.

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Disclosure

The authors report no conflicts of interest in this work.

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