Original Article

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Repeat laparoscopic hepatectomy versus radiofrequency ablation for recurrent hepatocellular carcinoma: A multicenter, propensity score matching analysis

Zihui Ma[1,§], Xiaolu Lin[1,§], Jinglei Zhang[2,§], Xingchao Song[3,§], Maolin Yan[4], Lei Guo[1], Jie Xue[1], Chongde Lu[1], Jie Shi[1], Shuqun Cheng[1,*], Weixing Guo[1,*]

[1] Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, The Third Affiliated Hospital of Naval Military Medical University, Shanghai, China;
[2] Department of Ultrasonic Intervention, Eastern Hepatobiliary Surgery Hospital, The Third Affiliated Hospital of Naval Military Medical University, Shanghai, China;
[3] Department of Hepatobiliary and Pancreatic Surgery, Xuzhou Municipal First People's Hospital, Xuzhou, China;
[4] Department of Hepatobiliary and Pancreatic Surgery, Fujian Provincial Hospital, The Shengli Clinical Medical College of Fujian Medical University, Fuzhou, China.

SUMMARY This study aimed at analyzing and comparing the clinical efficacy and prognosis of repeat laparoscopic hepatectomy (r-LH) and radiofrequency ablation (RFA) in treating recurrent hepatocellular carcinoma (RHCC). Clinicopathological data of RHCC patients who underwent r-LH or RFA as treatment from three medical centers were retrospectively reviewed. Baseline characteristics at the recurrence time after initial hepatectomy and clinical outcomes following treatment of RHCC were compared between the two groups. Using the Kaplan–Meier method, survival curves for the two groups of patients were generated, and the log-rank test was used to compare survival differences. Propensity score matching (PSM) analysis was used to match patients of the r-LH and RFA groups in a 1:1 ratio. A total of 272 patients were enrolled, including 133 patients who underwent r-LH and 139 patients who received RFA. After PSM, 76 patients were matched in each study group. Compared with the r-LH group, the RFA group had shorter hospitalization and fewer postoperative complications. However, the r-LH group had significantly better overall survival (OS) and disease-free survival (DFS) than the RFA group before and after PSM. Subgroup analysis demonstrated that RHCC patients with solitary tumor or those with tumors located near the diaphragm, visceral surface or vessels, had survival benefits from r-LH. When tumor diameter ≤ 5 cm, r-LH appears to be an effective priority to RFA with a significantly higher OS and DFS rate in treating RHCC patients, especially for patients with solitary tumor and those with tumors located near the diaphragm, visceral surface or vessels.

Keywords recurrent hepatocellular carcinoma, survival outcomes, propensity score matching, repeat laparoscopic hepatectomy (r-LH), radiofrequency ablation (RFA)

1. Introduction

Hepatocellular carcinoma (HCC), the third leading cause of cancer-related mortality worldwide (*1,2*), is one of the most common malignant diseases with insidious onset and rapid development. Hepatectomy is one of the first-line treatment modalities for HCC. However, tumor recurrence is common even after initial curative treatment. The 5-year recurrence rate after hepatectomy is 42-52% (*3,4*). Therefore, the management of recurrent hepatocellular carcinoma (RHCC) is pivotal in enhancing patients' long-term prognosis. To date, accounts of salvage treatment options can be considered for patients with RHCC, such as repeat hepatectomy (RH), salvage liver transplantation, transarterial chemoembolization (TACE), stereotactic body radiation therapy(SBRT), chemotherapy, radiotherapy, immunotherapy, and so on (*5*). Hepatectomy, RFA, and liver transplantation are all radical treatments. Due to the shortage of liver donors, hepatectomy and RFA are currently the most commonly considered treatments for RHCC. Medical professionals have always had difficulty deciding which treatment is most reasonable. Nevertheless, limited clinical guidelines and consensus have been proposed for treating RHCC.

RH, including repeat open hepatectomy (r-OH) and repeat laparoscopic hepatectomy (r-LH), has been

proven to be a potentially curative option for patients with RHCC, yielding the best chance at long-term overall survival as well as low morbidity and mortality (*6-8*). With significant developments in laparoscopic instruments and surgical techniques, laparoscopic hepatectomy (LH) has been increasingly performed by experienced surgeons in HCC patients (*9,10*). An increasing number of centers are attempting laparoscopic hepatectomy for RHCC. R-LH may still be beneficial to patients who have intrahepatic recurrences presenting with an adequate functional liver remnant, good liver function, and high performance status (*11*). Though the feasibility of r-LH is restricted by insufficient residual liver volume and technical difficulties owing to expected postoperative adhesion (*12,13*), it is still favored by surgeons for improved perioperative outcomes, postoperative complications, and hospital stays with comparable operation times, overall survival (OS) and recurrence-free survival (RFS) (*14*). For patients, especially those who have undergone laparotomy as their first surgery, LH tends to be a more preferable choice when it comes to the second operation due to the trauma caused by the initial surgery.

In contrast, RFA, as a nonsurgical, less invasive, safe, and repeatable therapeutic approach, has emerged as a new treatment modality and has attracted great interest because of its effectiveness and safety for small HCC (diameter ≤ 5 cm) (*15-17*). It is generally regarded as a safe and effective alternative to partial hepatectomy for early HCC tumors up to 5 cm (*15,18,19*) or intrahepatic recurrences, especially for patients with impaired liver function and when liver transplantation is not indicated (*20-22*). However, RFA has some limitations, including tumor proximity to major vessels, size discrepancies, and limited accessibility of ultrasonography (US) (*23-25*).

In this study, we retrospectively analyzed and compared the efficacy, feasibility, and safety of the two minimally invasive treatments (r-LH and RFA) for patients after the first recurrence of HCC (diameter ≤ 5 cm). The aim of our study was to provide a useful clinical reference and establish a logical treatment algorithm for patients who developed local RHCC following initial hepatectomy for their primary HCC.

2. Patients and Methods

2.1. Patients

From February 2019 to December 2022, a total of 1,027 patients who were admitted to the Eastern Hepatobiliary Surgery Hospital (EHBH), Fujian Provincial Hospital (FPH) and Nanchang University Second Affiliated Hospital with confirmation having recurrent hepatocellular carcinoma by history data and imaging were included in this study. The treatment strategies and surgical methods for individual patients were based on full discussions of multidisciplinary team (MDT) meetings at each medical center. Finally, a total of 272 patients were enrolled, including 133 patients who received r-LH (the r-LH group) and 139 patients who received RFA (the RFA group) (Figure 1). The study protocol was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki and approved by the institutional ethics committee (Approval number: EHBHKY2023-H004-P001).

Clinicopathological variables included sex, age, body mass index (BMI), HBV infection, antiviral therapy, hypertension, diabetes mellitus, routine blood tests, blood biochemical examination, serum alpha-fetoprotein (AFP), Child-Pugh class, cirrhosis, time to recurrence from initial hepatectomy, surgery-related variables, tumor number, size, and location.

2.2. Inclusion and exclusion criteria

The inclusion criteria for the study were as follows: *i*) age ≥ 18 years, *ii*) recurrent hepatocellular carcinoma based on a history of partial hepatectomy for primary hepatocellular carcinoma, and American Association for the Study of Liver Diseases diagnostic criteria for HCC, *iii*) the initial procedure involved performing an R0 resection of primary tumor without visible vascular invasion or extrahepatic distant metastasis, *iv*) no residual disease detected in the first 2 months after initial primary hepatectomy, *v*) computed tomography (CT) or magnetic resonance imaging (MRI) scans at one month after r-LH or RFA confirmed complete tumor clearance at the first reexamination, *vi*) Child-Pugh class A or selected B (score ≤ 7), and *vii*) kidney function and cardiopulmonary function are normal.

We excluded RHCC patients who did not undergo curative hepatectomy as initial treatment or had distant metastasis, incomplete serological, pathological, or follow-up data.

2.3. Diagnosis standard for RHCC

Tumor recurrence was described as the appearance of a new intra- or extrahepatic lesion. Intrahepatic recurrence was defined as a new lesion with arterial contrast enhancement and portal venous washout. The diagnosis of HCC recurrence is mainly determined by the history of previous hepatectomy treatment and the clinical features of the reoccurring tumor by the diagnostic criteria of the National Health Commission (NHSC) or the European Association for the Study of the Liver (EASL) guideline (*1*). Pathological diagnosis of tumor tissue can be obtained by resection or puncture.

2.4. Follow up

All patients received CT or MRI of the liver at one month after r-LH or RFA as the first reexamination

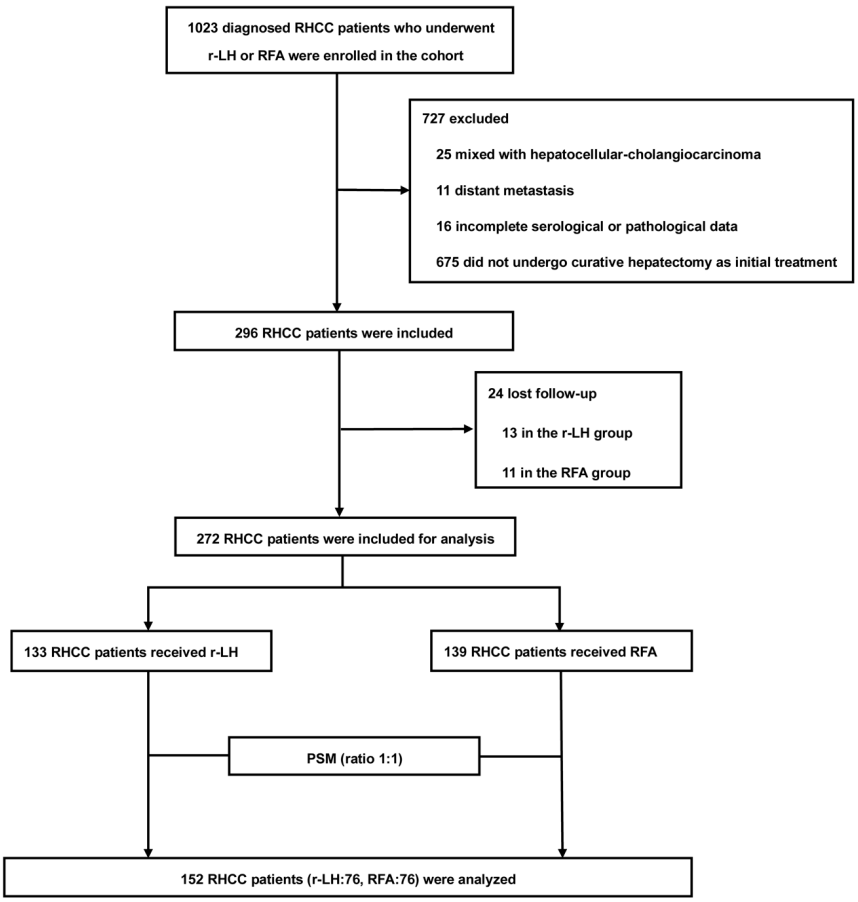

Figure 1. Study flowchart. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; PSM, propensity score matching.

to confirm complete tumor clearance. Thereafter, surveillance for recurrent HCC consisted of measurements of serum alpha-fetoprotein (AFP), liver biochemistry, and ultrasonography, CT scan, or MRI scans of the liver every three months. In case of recurrence of the tumor, follow-up treatment was recommended by the multidisciplinary team. Once tumor recurrence occurred, aggressive management, including RH, TACE, RFA, SBRT, molecular targeted therapy, or immunotherapy, was adopted based on the stage of RHCC and liver function of patients. All patients were followed up regularly until March 2024. The date of tumor recurrence, the date of last follow-up, and the date of death were recorded.

2.5. Study outcomes

The primary outcomes were overall survival (OS), disease-free survival (DFS), and complications. In this study, OS was defined as the time interval between the treatment of RHCC and death from any cause or censoring at the last follow-up, and DFS was defined as the time interval between the treatment of 1st RHCC and 2nd local tumor recurrences in patients. The secondary outcomes included surgery-related parameters, postoperative length of hospital stay and perioperative complications.

2.6. Statistical analyses

For normal distributed continuous variables, means with standard deviation (SD) were shown, and student's *t* test was used to compare differences. For skewed distributed continuous variables, medians with interquartile range (IQR) were expressed, and Mann–Whitney *U* test was applied to compare differences. Categorical data were shown as frequencies and percentages, and compared using Chi-square test or Fisher's exact test as appropriate. The Kaplan–Meier method was used to generate survival curves and the log-rank test was used to compare survival differences. Independent factors associated with DFS and OS were determined using Cox regression models. Hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs) were also estimated using Cox regression models. In Cox regression analysis, multivariate analysis was performed with variables yielding $p < 0.05$ in univariate analysis.

Propensity score matching (PSM) analysis was used to minimize the potential confounders and selection

bias and balance the patient baseline characteristics between groups. A 1:1 match between the RFA and r-LH groups was done using the nearest neighbor method with a caliber of 0.2 to prevent poor matching. Variables including sex, age, HBV infection, antiviral therapy, cirrhosis, Child–Pugh class, WBC, platelet, TBIL, ALT, ALB, PT, AFP, time to recurrence from initial hepatectomy, tumor diameter, tumor number and tumor location were matched.

Statistical significance was set as a p value < 0.05 at two-tailed level for all analyses. IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, N.Y., USA) was utilized for data analyses and visualization in our study.

3. Results

3.1. Baseline characteristics of the patients

The clinicopathological baseline characteristics are shown in Table 1. Among the 272 participants with RHCC, 133 patients underwent r-LH, and 139 patients underwent RFA. 85.7% were males and a total of 80.5% of patients had hepatitis B virus (HBV) infection. Compared with the RFA group, the r-LH group had a lower percentage of cirrhosis (45.1% *vs*. 69.1%, p < 0.001), a higher percentage of WBC > 4×10^9/L (85.0% *vs*. 66.9%, p < 0.001), a higher percentage of TBIL ≤ 17.1μmol/L (79.7% *vs*. 41.7%, p < 0.001), a higher percentage of ALT ≤ 44 (66.9% *vs*. 48.9%, p = 0.003), a lower percentage of PT ≤ 13s (73.7% *vs*. 87.1%, p = 0.005), a lower percentage of AFP ≤ 400ng/mL (76.7% *vs*. 90.6%, p = 0.002), significantly more patients with solitary tumor (85.0% *vs*. 52.5%, p < 0.001). After PSM, all these clinicopathological features were well balanced, and 76 cases in each group were matched and included in the analyses (Table 1).

3.2. Long term outcomes

The Kaplan-Meier method was used to evaluate prognostic value of r-LH and RFA in treatment of patients with RHCC. The median follow-up time of the whole cohort was 51.7 months (95% CI: 47.3-56.0 months), and approximately 40% of the patients (n = 109, 40.1%) died during follow-up. Before PSM, the OS of the r-LH group was significantly longer than that of the RFA group (median OS time, not reached *vs*. 47.7 months; 1-year, 99.2% *vs*. 93.5%; 2-year, 96.2% *vs*. 78.4%; 3 -year, 91.7% *vs*. 62.6%; p < 0.001; Figure 2A). Similarly, the DFS of the r-LH group was markedly longer than that of the RFA group (49.8 months *vs*. 14.2 months; 1-year, 87.2% *vs*. 59.7%; 2-year, 68.4% *vs*. 27.3%; 3-year, 60.9% *vs*. 7.2%; p < 0.001; Figure 2B). The results indicated that the long-term oncological outcomes were significantly better in the r-LH group compared with the RFA group.

After PSM, the long-term prognosis of the r-LH group was also significantly better than the RFA group (for OS: median OS time, not reached *vs*. 58.0 months; 1-year, 100.0% *vs*. 97.4%; 2-year, 97.4% *vs*. 93.4%; 3-year, 93.4% *vs*. 82.9%; p = 0.044; Figure 2C; for DFS: 52.0 months *vs*. 20.8 months; 1-year, 86.8% *vs*. 72.4%; 2-year, 65.8% *vs*. 44.7%; 3-year, 63.2% *vs*. 11.8%; p < 0.001; Figure 2D). The results after PSM still showed better long-term oncological outcomes in the r-LH group compared with the RFA group.

3.3. Independent risk factors associated with OS and DFS

Before PSM, univariate and multivariate analyses demonstrated that WBC < 4×10^9/L, PT > 13s, and RFA treatment were independent risk factors for OS. WBC < 4×10^9/L, multiple tumors, tumors located in other liver segments, and RFA treatment were independent risk factors for DFS (Table 2).

After PSM, as presented in Table 3, univariate and multivariate analyses demonstrated that cirrhosis, WBC < 4×10^9/L, tumors located in other liver segments, and RFA treatment were independent risk factors for OS. Besides, RFA treatment, multiple tumors were independent risk factors for DFS.

3.4. Postoperative complications

As is shown in Table 4, there was no treatment-related mortality in the whole study population. The complication rate in the RFA group was significantly lower than the r-LH group. Before PSM, compared with the r-LH group, there was one patient with bile fistula (0.7% *vs*. 10.5%, p <0.001), one patient with ascites (0.7% *vs*. 21.1%, p < 0.001), two patients with pleural effusion (1.4% *vs*. 15.0%, p <0.001), six patients with fever (4.3% *vs*. 13.5%, p = 0.007), and one patient with needle tract seeding (0.7% *vs*. 0%, p = 0.327) in the RFA group. There were three patients with hepatic failure and nine patients with pulmonary/abdominal infection in the r-LH group. Patients in the RFA group had a shorter median hospital stay and operative time, and a lower transfusion rate compared with the r-LH group (all p < 0.001).

After PSM, minor complications were observed in the RFA group. Compared with the r-LH group, there was one patient with bile fistula (1.6% *vs*. 7.8%, p < 0.001), and three patients with fever (3.9% *vs*. 17.1%, p = 0.008) in the RFA group. There was one patient with hepatic failure, twenty patients with ascites, twelve patients with pleural effusion, and five patients with pulmonary/abdominal infection in the r-LH group. Patients in the RFA group had a shorter median hospital stay (p < 0.001) and operative time (p < 0.001), and a lower transfusion rate (p < 0.001) compared with the r-LH group

Table 1. Baseline clinicopathological characteristics of RHCC patients with treatment of r-LH or RFA before and after PSM analysis

Characteristics	Before PSM			After PSM		
	r-LH (n = 133)	RFA (n = 139)	p value	r-LH (n = 76)	RFA (n = 76)	p value
Age > 60 (%)	60 (45.1%)	47 (33.8%)	0.057	23 (35.9%)	28 (43.8%)	0.367
Sex, male (%)	112 (84.2%)	121 (87.1%)	0.504	65 (85.5%)	62 (81.6%)	0.512
HBV infection (%)	119 (89.5%)	126 (90.6%)	0.746	65 (85.5%)	66 (86.8%)	0.814
Antiviral therapy (%)	105 (78.9%)	114 (82.0%)	0.523	64 (84.2%)	62 (81.6%)	0.667
Cirrhosis (%)	60 (45.1%)	96 (69.1%)	**< 0.001**	42 (55.3%)	47 (61.8%)	0.410
Child–Pugh class						
A	120 (90.2%)	125 (89.9%)	0.935	67 (88.2%)	66 (86.8%)	0.806
B	13 (9.8%)	14 (10.1%)		9 (11.8%)	10 (13.2%)	
WBC($\times 10^9$/L)						
≤ 4	20 (15.0%)	46 (33.1%)	**< 0.001**	14 (18.4%)	11 (14.5%)	0.512
> 4	113 (85.0%)	93 (66.9%)		62 (81.6%)	65 (85.5%)	
Platelet count ($\times 10^9$/L)						
≤ 100	28 (21.1%)	19 (13.7%)	0.107	19 (25.0%)	15 (19.7%)	0.436
> 100	105 (78.9%)	120 (86.3%)		57 (75.0%)	61 (80.3%)	
TBIL (μmol/L)						
≤ 17.1	106 (79.7%)	58 (41.7%)	**< 0.001**	52 (68.4%)	44 (57.9%)	0.179
> 17.1	27 (20.3%)	81 (58.3%)		24 (31.6%)	32 (42.1%)	
ALB (g/L)						
≤ 35	15 (11.3%)	8 (5.8%)	0.102	7 (9.2%)	5 (6.6%)	0.547
> 35	118 (88.7%)	131 (94.2%)		69 (90.8%)	71 (93.4%)	
ALT (U/L)						
≤ 44	89 (66.9%)	68 (48.9%)	**0.003**	52 (68.4%)	44 (57.9%)	0.179
> 44	44 (33.1%)	71 (51.1%)		24 (31.6%)	32 (42.1%)	
PT (s)						
≤ 13	98 (73.7%)	121 (87.1%)	**0.005**	62 (81.6%)	67 (88.2%)	0.258
> 13	35 (26.3%)	18 (12.9)		14 (18.4%)	9 (11.8%)	
AFP (ng/mL)						
≤ 400	102 (76.7%)	126 (90.6%)	**0.002**	60 (78.9%)	66 (86.8%)	0.196
> 400	31 (23.3%)	13 (9.4%)		16 (21.1%)	10 (13.2%)	
Time to recurrence from initial hepatectomy (year)						
≤ 1	101 (75.9%)	103 (74.1%)	0.726	55 (72.4%)	57 (75.0%)	0.713
> 1	32 (24.1%)	36 (25.9%)		21 (27.6%)	19 (25.0%)	
Tumor diameter (cm)						
≤ 3	97 (72.9%)	101 (72.7%)	0.960	58 (76.3%)	57 (75.0%)	0.850
3-5	36 (27.1%)	38 (27.3%)		18 (23.7%)	19 (25.0%)	
Tumor number						
Solitary	113 (85.0%)	73 (52.5%)	**< 0.001**	59 (77.6%)	50 (65.8%)	0.105
Multiple	20 (15.0%)	66 (47.5%)		17 (22.4%)	26 (34.2%)	
Tumor location						
Proximity to diaphragm,visceral surface or vessels	60 (45.1%)	71 (51.1%)	0.325	33 (43.4%)	32 (42.1%)	0.870
Other	73 (54.9%)	68 (48.9%)		43 (56.6%)	44 (57.9%)	

Notes: The symbol bold reflected inside table showed that p-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; PSM, propensity score matching; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; HBV, hepatitis B virus; WBC, white blood cell; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha-fetoprotein.

3.5. Subgroup survival analysis in patients associated with tumor number and tumor location

After PSM, post-hoc subgroup analyses showed that among patients with solitary tumor, tumor location with proximity to diaphragm, visceral surface or vessels, patients had significant OS benefits from r-LH than those with RFA (both $p = 0.001$) (Figure 3A, 4A). Furthermore, patients derived significant DFS benefits from r-LH if they had solitary tumor, tumor location with proximity to diaphragm, visceral surface or vessels (both $p < 0.001$) (Figure 3B, 4B). However, no significant differences for OS in patients with multiple tumors, tumors located in other liver segments (both $p > 0.05$) (Figure 3C, 4C) were observed between the r-LH and the RFA group. Besides, no significant differences for DFS in patients with multiple tumors were observed between the r-LH and the RFA group ($p > 0.05$) (Figure 3D).

4. Discussion

HCC is among the most common cancers and is the

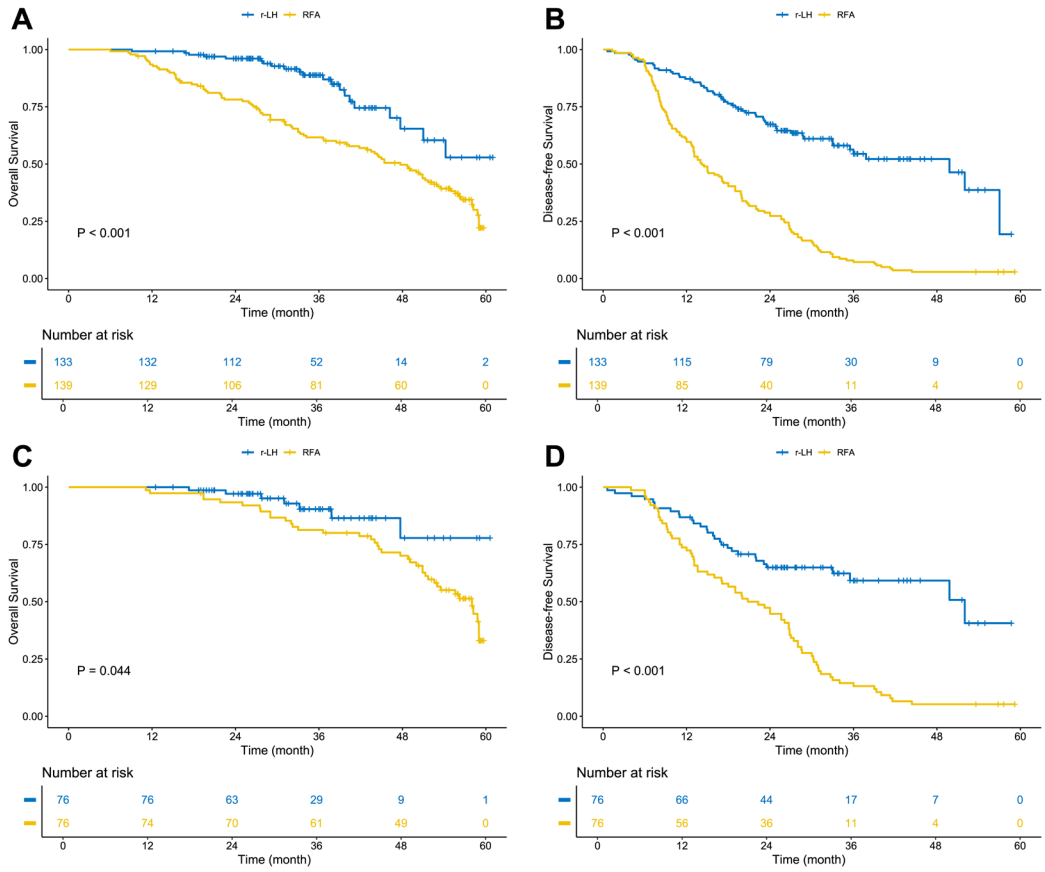

Figure 2. Overall survival (OS) and disease-free survival (DFS) of RHCC patients treated with r-LH or RFA before and after PSM. OS **(A)** and DFS **(B)** of RHCC patients before PSM. OS **(C)** and DFS **(D)** of RHCC patients after PSM. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; PSM, propensity score matching.

leading cause of cancer-related mortality worldwide, with recurrence being a significant clinical challenge after initial surgery. Considering the poor prognosis, RHCC often necessitates complex and multifaceted treatment strategies. Patients who have undergone initial radical hepatectomy face multiple physical and psychological difficulties. In response to RHCC, they often prefer less invasive treatments to avoid exacerbating the distress of their body. R-LH and RFA have emerged as promising therapeutic options, offering minimally invasive approaches with favorable outcomes. In the absence of a structured algorithm for the management of patients with RHCC, r-LH remains the golden choice, while RFA represents a feasible alternative with comparable short- and long-term outcomes. To our knowledge, no high-quality study has examined r-LH vs RFA in the treatment of patients with RHCC. Therefore, in our study, we retrospectively analyzed and compared the long-term oncological outcomes of the patients undergoing either r-LH or RFA, in order to assess the efficacy of these minimally invasive treatments in RHCC patients and determine the optimal treatment approach.

Compared with r-LH, RFA is a highly target-selective thermal treatment technique to conserve non-tumorous liver parenchyma and minimize the degree of surgical insult to the limited liver reserve, preserving the maximum liver remnant (*26*). The characteristics and benefits of less invasiveness and highly-targeted tumor treatment improved the feasibility of patients and repeatability of RFA for RHCC. Compared to surgical intervention, RFA can be safely conducted under conscious sedation, significantly reducing the duration of hospital stay, thereby rendering it a more economically viable option than surgical resection. Given its low complication rates, RFA minimizes perioperative stress, which can even be diminished if performed percutaneously for easily accessible hepatic lesions. These advantages provide the rationale for RFA for RHCC. Nevertheless, studies on primary HCC have revealed that the likelihood of complete ablation diminishes as the tumor diameter increases (*27,28*). In our study, in order to reduce the impact of tumor diameter on prognosis, we selected patients with tumor diameter less than 5cm, and tumor diameter had no effect on OS and DFS benefits between the two subgroups with a diameter of 1-3cm and 3-5cm.

Unlike the surgical approach, the success rate of RFA treatment is influenced by ablative volume, adequate tumor-free margin and necrosis level. High rates of local recurrence with RFA may be attributed to incomplete tumor ablation, satellite tumor nests, and microvascular invasion (*29*). Whether the ablative volume encompasses

Table 2. Univariate and multivariate analysis of overall and disease-free survival for RHCC patients before PSM

Characteristics	HR Comparison	OS						DFS					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	> 60 *vs.* ≤ 60, year	1.19	0.82-1.75	0.362				0.88	0.65-1.18	0.377			
Sex	Female *vs.* Male	0.72	0.44-1.17	0.179				1.01	0.67-1.50	0.980			
HBV infection	Yes *vs.* No	0.89	0.49-1.62	0.697				1.01	0.63-1.60	0.982			
Antiviral therapy	Yes *vs.* No	0.86	0.54-1.36	0.515				0.84	0.59-1.18	0.314			
Cirrhosis	Yes *vs.* No	0.99	0.67-1.46	0.965				1.41	1.05-1.90	**0.021**	1.17	0.86-1.59	0.321
Child–Pugh class	A or B	0.92	0.49-1.71	0.779				0.82	0.51-1.34	0.437			
WBC	> 4 *vs.* ≤ 4, $\times 10^9$/L	2.99	2.00-4.48	**< 0.001**	2.49	1.62-3.83	**< 0.001**	1.92	1.40-2.63	**< 0.001**	1.59	1.13-2.23	**0.008**
Platelet count	> 100 *vs.* ≤ 100, $\times 10^9$/L	1.42	0.82-2.46	0.205				1.14	0.77-1.67	0.515			
TBIL	> 17.1 *vs.* ≤ 17.1, μmol/L	1.26	0.86-1.84	0.235				1.50	1.13-1.99	**0.006**	1.00	0.74-1.35	0.989
ALB	> 35 *vs.* ≤ 35, g/L	1.82	0.84-3.94	0.127				1.45	0.84-2.50	0.182			
ALT	> 44 *vs.* ≤ 44, U/L	0.82	0.56-1.20	0.306				0.64	0.48-0.85	**0.002**	0.75	0.56-1.01	0.058
PT	> 13 *vs.* ≤ 13, s	1.67	1.02-2.71	**0.040**	1.67	1.00-2.78	**0.050**	1.02	0.70-1.47	0.938			
AFP	> 400 *vs.* ≤ 400, ng/mL	0.78	0.44-1.40	0.407	1.20	0.65-2.22	0.561	0.83	0.55-1.25	0.380			
Time to recurrence from initial hepatectomy	> 1 *vs.* ≤ 1, year	0.83	0.55-1.25	0.378				0.94	0.68-1.30	0.701			
Tumor diameter	3-5 *vs.* ≤ 3, cm	0.88	0.58-1.34	0.555				0.93	0.67-1.29	0.662			
Tumor number	Solitary *vs.* multiple	1.88	1.29-2.75	**0.001**	1.45	0.96-2.17	0.077	2.61	1.93-3.52	**< 0.001**	1.93	1.40-2.67	**< 0.001**
Tumor location	Proximity to diaphragm,visceral surface or vessels *vs.* other	0.55	0.38-0.81	**0.002**	0.73	0.49-1.09	0.122	0.63	0.47-0.84	**0.001**	0.69	0.51-0.93	**0.017**
Treatment methods	r-LH *vs.* RFA	0.37	0.23-0.60	**< 0.001**	0.43	0.25-0.73	**0.002**	0.27	0.19-0.36	**< 0.001**	0.34	0.24-0.48	**< 0.001**

Notes: The symbol bold reflected inside table showed that *p*-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; HBV, hepatitis B virus; WBC, white blood cell; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha-fetoprotein.

Table 3. Univariate and multivariate analysis of overall and disease-free survival for RHCC patients after PSM

Characteristics	HR Comparison	OS						DFS					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
		HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	> 60 *vs.* ≤ 60, year	1.93	1.08-3.46	**0.026**	1.77	0.98-3.17	0.056	1.06	0.71-1.58	0.760			
Sex	Female *vs.* male	0.58	0.30-1.16	0.122				0.85	0.52-1.40	0.517			
HBV infection	Yes *vs.* No	1.06	0.49-2.27	0.891				0.97	0.56-1.67	0.898			
Antiviral therapy	Yes *vs.* No	0.61	0.31-1.21	0.156				0.95	0.57-1.56	0.828			
Cirrhosis	Yes *vs.* No	0.54	0.30-0.96	**0.036**	0.44	0.24-0.80	**0.008**	1.07	0.72-1.59	0.753			
Child–Pugh class	A or B	0.75	2.30-1.90	0.541				0.89	0.49-1.63	0.706			
WBC	> 4 *vs.* ≤ 4, $\times 10^9$/L	2.40	1.17-4.96	**0.018**	2.53	1.19-5.40	**0.016**	1.05	0.62-1.76	0.860			
Platelet count	> 100 *vs.* ≤ 100, $\times 10^9$/L	1.44	0.67-3.08	0.353				1.03	0.65-1.65	0.885			
TBIL	> 17.1 *vs.* ≤ 17.1, μmol/L	0.66	0.35-1.22	0.180				0.81	0.54-1.22	0.320			
ALB	> 35 *vs.* ≤ 35, g/L	2.65	0.64-11.00	0.180				1.27	0.59-2.73	0.547			
ALT	> 44 *vs.* ≤ 44, U/L	0.88	0.49-1.58	0.661				0.77	0.52-1.15	0.203			
PT	> 13 *vs.* ≤ 13, s	1.08	0.38-3.04	0.892				1.22	0.71-2.11	0.476			
AFP	> 400 *vs.* ≤ 400, ng/mL	1.50	0.72-3.11	0.279				0.90	0.53-1.54	0.703			
Time to recurrence from initial hepatectomy	> 1 *vs.* ≤ 1, year	0.79	0.43-1.47	0.458				0.93	0.60-1.45	0.932			
Tumor diameter	3-5 *vs.* ≤ 3, cm	0.91	0.47-1.75	0.771				0.89	0.57-1.40	0.610			
Tumor number	Solitary *vs.* multiple	1.54	0.85-2.78	0.152				1.88	1.23-2.85	**0.003**	1.62	1.06-2.47	**0.025**
Tumor location	Proximity to diaphragm,visceral surface or vessels *vs.* other	0.56	0.31-1.00	**0.050**	0.50	0.27-0.91	**0.024**	0.71	0.48-1.06	0.093			
Treatment methods	r-LH *vs.* RFA	0.44	0.19-1.00	**0.050**	0.39	0.17-0.90	**0.027**	0.33	0.22-0.51	**< 0.001**	0.35	0.23-0.54	**< 0.001**

Notes: The symbol bold reflected inside table showed that *p*-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; HBV, hepatitis B virus; WBC, white blood cell; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; PT, prothrombin time; AFP, alpha-fetoprotein.

Table 4. Intraoperative and postoperative short-term results of RHCC patients who underwent r-LH or RFA before and after PSM

Characteristics	Before PSM			After PSM		
	r-LH (n = 133)	RFA (n = 139)	p value	r-LH (n = 76)	RFA (n = 76)	p value
Surgical variables						
Transfusion(yes)	27 (20.3%)	0 (0%)	< 0.001	14 (18.4%)	0 (0%)	< 0.001
Hospitalization	11 (10-139)	3 (3-59)	< 0.001	11 (10-139)	3 (3-59)	< 0.001
Operative time	140 (110-1809)	20 (20-309)	< 0.001	131 (110-1809)	25 (20-309)	< 0.001
Perioperative complications						
Hepatic failure	3 (2.3%)	0 (0%)	0.075	1 (1.3%)	0 (0%)	0.316
Bile fistula	14 (10.5%)	1 (0.7%)	< 0.001	5 (6.6%)	1 (1.3%)	0.096
Ascites	28 (21.1%)	1 (0.7%)	< 0.001	20 (26.3%)	0 (0%)	< 0.001
Pleural effusion	20 (15.0%)	2 (1.4%)	< 0.001	12 (15.8%)	0 (0%)	< 0.001
Pulmonary/abdominal infection	9 (6.8%)	0 (0%)	0.002	5 (6.6%)	0 (0%)	0.023
Needle tract seeding	0 (0%)	1 (0.7%)	0.327	0 (0%)	1 (1.3%)	0.316
Fever	18 (13.5%)	6 (4.3%)	0.007	13 (17.1%)	3 (3.9%)	0.008

Notes: The symbol bold reflected inside table showed that p-value < 0.05, which means there was a significant difference between the two groups. *Abbreviations*: RHCC, recurrent hepatocellular carcinoma; PSM, propensity score matching; r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation.

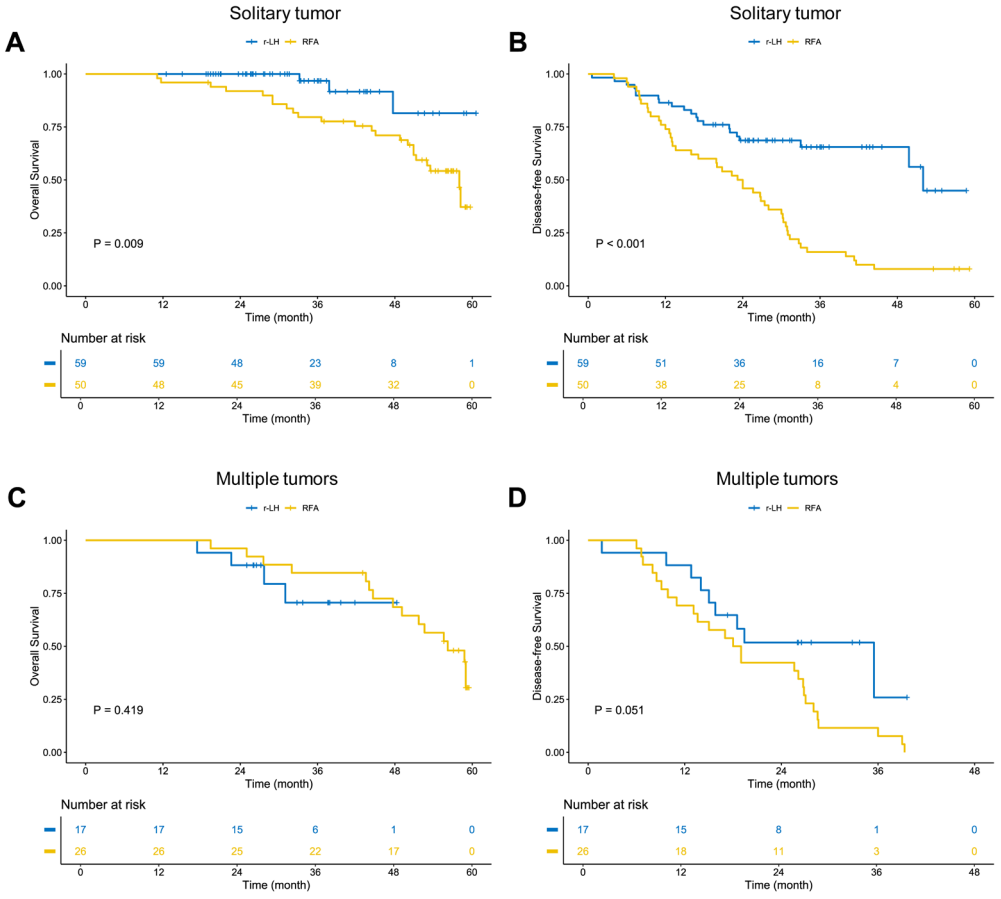

Figure 3. Subgroup analysis OS and DFS based on tumor number. (A, C) Subgroup division according to solitary tumor, and Kaplan-Meier analyses were performed for OS **(A)** and DFS **(C)** associated with r-LH or RFA. **(B, D)** Subgroup division according to other multiple tumors, and Kaplan-Meier analyses were performed for OS **(B)** and DFS **(D)** associated with r-LH or RFA. *Abbreviations*: r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; OS, overall survival; DFS, disease-free survival.

the micrometastasis and microvascular invasion may directly affect the treatment effect of RFA. When performed near a large vessel or liver capsule, it may be associated with potential risk of tumor seeding along the electrode's track and potentially dangerous thermal injury. Generally, it is widely accepted that RFA is

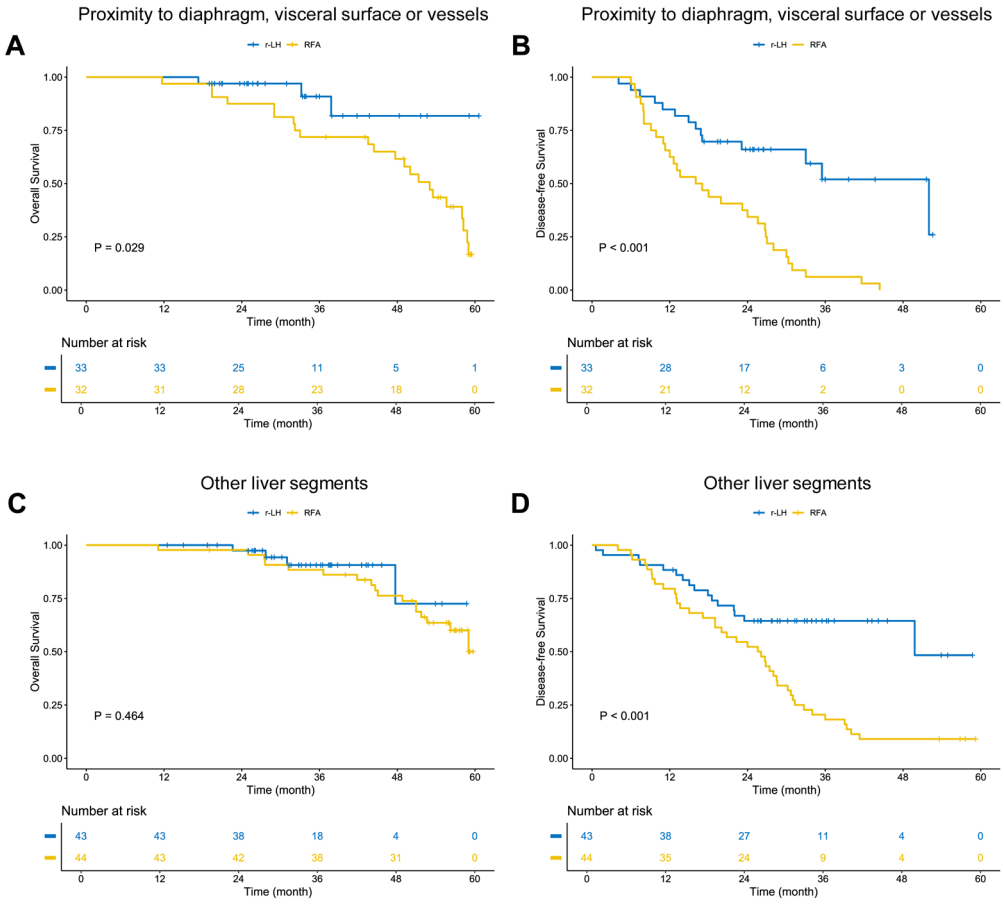

Figure 4. Subgroup analysis OS and DFS based on tumor location. (A, C) Subgroup division according to proximity to diaphragm, visceral surface or vessels, and Kaplan-Meier analyses were performed for OS **(A)** and DFS **(C)** associated with r-LH or RFA. **(B, D)** Subgroup division according to other liver segments, and Kaplan-Meier analyses were performed for OS **(B)** and DFS **(D)** associated with r-LH or RFA. *Abbreviations*: r-LH, repeat laparoscopic hepatectomy; RFA, radiofrequency ablation; OS, overall survival; DFS, disease-free survival.

technically challenging visualizing the tumor. RFA of tumors in subphrenic (*30*) is associated with higher local recurrence (*31-33*) and risk of major complication rates (*34,35*) due to poor invisibility under US guidance (*30,36*). In addition, when tumors are in proximity to a visceral surface and abutting vital organs such as the heart, stomach or other organs (*37*), they might cause reduction of energy application (*38*). Due to the inconspicuousness of the tumor during ablation, it is somewhat difficult to achieve an adequate ablative margin (*39*). Besides, when the tumor is located next to a major blood vessel (*i.e.*, the portal vein or a major branch of the hepatic vein), the lower blood temperature "cools" the tumor adjacent to the vessel, resulting in an incomplete ablation and "heat-sink" effect (*40,41*). Our study showed that patients derived significant OS benefits from r-LH tumor location with proximity to diaphragm, visceral surface or vessels, while two groups had similar OS benefit if tumors were located in other liver segments. In clinical practice, the local temperature and the ablation time are sometimes insufficient to cause irreversible cell damage in the whole tumor due to the heat sink effect, resulting in a partially viable tumor that subsequently develops into a recurrent lesion after the ablation procedure (*42*). Therefore, tumor location is an important factor affecting the clinical efficacy of RFA for patients with RHCC. Moreover, the achievement of a full ablation rate is influenced not solely by the tumor's location but also by the operator's level of expertise. Therefore, it comes as no surprise that RFA has been frequently reported to have higher recurrence rates than resection for the treatment of HCC (*43*). While RFA was associated with acceptable short and long term outcomes, r-LH was associated with lower re-recurrence and longer overall survival time versus RFA. Several factors could contribute to this phenomenon: Firstly, the rapid heating of the tumor during RFA may lead to the dissemination of tumor cells around the ablation zone or even result in the formation of iatrogenic intra-tumoral shunts, which facilitate the spread of tumor cells to the peripheral regions of the liver (*44*), thereby increasing the risk of tumor recurrence. Secondly, post-RFA, residual microscopic tumor foci may escape detection by post-ablation CT imaging (*45,46*), potentially compromising the assessment of treatment efficacy.

With improvements in liver function assessment,

surgical techniques, perioperative care, and decrease in postoperative morbidity, r-LH, a minimally invasive surgical technique, has gained increased adoption in the management of RHCC. Its advantages include reduced postoperative pain, shorter hospital stays, and faster recovery. R-LH offers the possibility of achieving tumor-free margins while minimizing surgical trauma (*18*), resulting in superior local tumor control. The efficacy of r-LH for RHCC, similar to hepatectomy for primary HCC, remains highly dependent on tumor number and location, patient overall fitness and even more importantly liver function (*7*). In our study, subgroup analyses demonstrated that the two groups had similar OS and DFS benefits if they had multiple tumors, while patients derived significant OS and DFS benefits from r-LH with a solitary tumor. Our results also suggest that the number of tumors affects the efficacy of r-LH in the treatment of RHCC.

R-LH faces greater challenges than the initial hepatectomy due to a range of complexities. Impaired liver function, insufficient liver remnants, postoperative tissue adhesions, and anatomical alterations resulting from previous surgeries all contribute to increased difficulty. The limited visual access and working space, coupled with the presence of adhesions and a deformed liver, increase the risks of severe vital organ injury and uncontrollable bleeding (*47*). Anatomical abnormalities and liver deformation can lead to forced conversion from laparoscopic to open surgery (*48,49*). Despite these challenges, abdominal adhesions offer some advantages in the laparoscopic setting. Tension of the adhesion band can be intensified by gas pneumoperitoneum, making it easier to separate adhesions (*50*). In addition, the small abdominal accesses help preserve portosystemic venous and lymphatic collaterals compared to open surgery, and the targeted laparoscopic vision allows precise surgery without extensive abdominal mobilization, especially in cases of posterior lesions that involve large scars and manipulations of the liver in open surgery (*51,52*). Crucially, preserving the remnant liver function is paramount in r-LH. Excessive resection can exacerbate postoperative liver dysfunction (*53*), necessitating careful surgical planning and execution to minimize such risks. Therefore, a meticulous approach is essential to ensure the safety and success of r-LH.

A comprehensive meta-analysis revealed that repeated surgical resection for RHCC was associated with a notably elevated rate of procedure-related morbidity in comparison to RFA (*54*). Our study also showed procedure-related complication rates were higher in the r-LH group than that in the RFA group. This phenomenon may be attributed to that r-LH is still invasive and carries certain surgical risks. R-LH requires the manipulation of instruments into the abdominal cavity, which may cause some degree of damage to surrounding tissues and organs, such as the gallbladder and intestines, due to the adhesion of the abdominal cavity resulting from the initial surgery, which may increase the incidence of complications. Besides, patients in the RFA group had a shorter median hospital stay and operative time, and a lower transfusion rate compared with the r-LH group before and after PSM.

Several limitations should be acknowledged in this study. First of all, this is a nonrandomized retrospective study with its inherent selection bias and potential confounders. Many patients who are not suitable for surgery were referred for RFA, and this could be a confounding factor. Even if a 1:1 propensity score matching was performed to minimize baseline differences between the r-LH and RFA groups, some other unbalanced variables might still exist. Second, r-LH is still a more complex surgical technique than primary laparoscopic hepatectomy and is gradually being used in the treatment of RHCC. Some patients in the r-LH group have incomplete five-year follow-up data, leading to biased survival outcome comparisons. Third, although the patients included in our study came from three high-volume medical centers, the sample size of the whole cohort was relatively small, which increases the risk of a beta error. Therefore, multi-center and large sample randomized controlled trials should be carried out to further verify our conclusion.

In conclusion, in our study, when tumor diameter ≤ 5 cm, r-LH demonstrated superior OS rate and DFS rate in the treatment of RHCC patients, especially for patients with a solitary tumor and those with tumors located near the diaphragm, visceral surface or vessels. RFA, on the other hand, exhibited a lower postoperative complication rate. Minimally invasive treatment cannot be exchanged at the cost of survival. When survival is the primary goal, r-LH should be the priority for RHCC.

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[§]These authors contributed equally to this work.
*Address correspondence to:
Weixing Guo and Shuqun Cheng, Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, 225 Changhai Road, Shanghai 200433, China.
E-mail: weixingg88@126.com (WG), chengshuqun@aliyun.com (SC)

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