



# The effects of ultrasound-guided radiofrequency ablation and laparoscopic hepatectomy in the treatment of small hepatocellular carcinoma: a retrospective analysis

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**Contributions:** (I) Conception and design: H Xu; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: H Xu, L Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Background:** Hepatocellular carcinoma (HCC) is a commonly-seen cancer in the clinical setting. Laparoscopic hepatectomy (LH) and radiofrequency ablation (RFA) are used for the treatment of HCC, yet the effects and safety difference of LH and RFA for HCC treatment need further investigation.

**Methods:** This study was a retrospective study design. HCC patients treated with LH or RFA in our hospital were identified. All the patients underwent 2-year long follow-up. The characteristics and details of LH and RFA groups during hospitalization were collected and compared. The Kaplan-Meier method was used to calculate the cumulative survival, and the survival curve was drawn and compared.

**Results:** A total of 94 HCC patients were included. The duration of surgery, estimated intraoperative blood loss, pain score on the first day after surgery, time to get out of bed after operation, time to oral eating, aspartate transaminase (AST) on the second day after surgery, C-reactive protein (CRP) on the second day after surgery, total medical cost in RFA group were significantly less than that of LH group (all  $P < 0.05$ ). The incidence of abdominal infection and biliary fistula in RFA group were significantly less than that of LH group (all  $P < 0.05$ ), and there was no significant difference in the incidence of bleeding and pleural effusion between two groups (all  $P > 0.05$ ). The 2-year overall survival and recurrence-free survival of the two groups had no significant statistical difference (all  $P > 0.05$ ).

**Conclusions:** RFA and LH have similar effects in the treatment of small HCC. And RFA has the advantages of less trauma, shorter operation duration, and quick postoperative recovery.

**Keywords:** Hepatocellular carcinoma (HCC); laparoscopic hepatectomy (LH); radiofrequency ablation (RFA); surgery; treatment

Submitted Feb 27, 2021. Accepted for publication Aug 09, 2021.

doi: 10.21037/tcr-21-367

**View this article at:** <https://dx.doi.org/10.21037/tcr-21-367>

## Introduction

Hepatocellular carcinoma (HCC) ranks 6th among the most common cancers in the world and the 3rd cause of tumor related death in the world (1). China is the country with most liver cancer patients. It's been reported that there are 854,000 new cases of HCC worldwide each year, and specifically in China there are 466,000 HCC patients, accounting for 55% of the world's total HCC cases (2,3).

Surgical resection is the main strategy for the treatment of HCC. Traditional open hepatectomy has disadvantages such as large intraoperative blood loss, more perioperative complications, and longer hospital stay (4). Laparoscopic hepatectomy (LH) is superior to open surgery in many regards (5). Previous studies (6,7) have shown that LH is safe, feasible and effective in treating HCC. Compared with open liver resection, laparoscopic liver resection can provide

higher body surface aesthetics, less intraoperative blood transfusion, and shorter hospital stay. Previous studies have pointed out that radiofrequency ablation (RFA) therapy can also achieve a radical cure for liver tumors with a diameter of  $\leq 6$  cm, and its short-term and long-term survival rates are comparable to those of surgery. In addition, RFA has advantages independent of surgery with several advantages such as minimally invasive, shorter hospital stay, and higher patient satisfaction (8). Although both LH and RFA can achieve satisfactory results in the treatment of recurrent liver cancer, LH is prone to complications such as abdominal mucus, and RFA may have the problem of incomplete lesion removal (9). Therefore, there are no clear conclusions regarding the choice of recurrent HCC (RHCC) treatment. Previous studies have compared the efficacy of LH and RFA in the treatment of HCC, yet the sample size is small and the population is limited. The choice of treatment for HCC still lacks recommendations based on higher-level evidence-based medicine. Therefore, we aimed to compare the perioperative and long-term results of LH and RFA for the treatment of HCC, to provide evidence to the management of HCC.

We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tcr-21-367>).

## Methods

### *Ethical concerns*

This study was a retrospective design. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Sir Run Run Shaw Hospital (NO.: 161102-9c), and written informed consent was taken from all the patients.

### *Patients*

HCC patients treated in our hospital from Aug 1, 2016 to Aug 31, 2018 were identified for potential candidate. All the patients either underwent LH or RFA treatment. The inclusion criteria were: (I) the single tumor had a diameter of  $\leq 6$  cm; (II) two or more examinations such as contrast-enhanced ultrasound, enhanced computed tomography (CT), enhanced magnetic resonance imaging (MRI) or puncture had been conducted for HCC diagnosis (10); (III) the patients was not in the decompensated stage of cirrhosis,

and had no invasion of portal vein, hepatic arteriovenous or inferior vena cava, no metastasis to other organs outside the liver; (IV) patients either underwent LH or RFA treatment (V) patients were well informed and agreed to participant in this study. Exclusion criteria: (I) patients had ascites that was difficult to relieve; (II) patients with history of upper abdominal surgery; (III) patients did not agree to participant in this study. The patients randomly selected RFA or LH with their own willingness based on the criteria.

### *RFA treatment*

The details of the RFA treatment were as follows: the radio frequency equipment chooses Talon radiofrequency needle (Valleylab Cooltip, USA) and related cold circulation system, the ultrasound contrast agent was sonovue (Bracco, Italy), and ultrasound contrast was routinely given before surgery to reconfirm the size, location and blood supply of the lesion, Peripheral organs and surrounding large blood vessels. We selected the puncture point and needle path, and punctured the radiofrequency needle into the tumor under ultrasound guidance. According to the size of the tumor and the surrounding conditions of the tumor, the power was generally 60–80 W, and the action duration was 10–20 min. For masses close to important organs and large blood vessels, ablation could be performed after injection of absolute alcohol on the adjacent sides of important organs or large blood vessels. In general, the treatment range should be fully covered by the tumor and more than 0.5 cm beyond the edge of the mass to eliminate the lesion. Liver contrast-enhanced ultrasound was performed immediately after ablation to observe the extent of liver tumor ablation and the boundary to the surrounding dangerous parts. If there was residual or suspicious residual, additional ablation could be performed. The needle was ablated while the needle was withdrawn to prevent bleeding or spread of the tumor.

### *LH treatment*

LH was an anatomical hepatectomy in our study, and the details of the LH treatment were as following: after general anesthesia, the observation port under the umbilicus was taken to establish a pneumoperitoneum, a laparoscope was placed, and then other 3 to 4 trocars and related operating instruments were placed in the upper abdomen. We chose whether to place the hilar blocking band according to the specific situation. After the pre-cut line was drawn, the

ultrasound knife gradually cut into the liver parenchyma. We carefully separated the tumor edge, the pulse triple system was separately ligated. And the cross-section adopted electrocoagulation or bipolar hemostasis. The liver cross-section was carefully checked with dry gauze, and absorbable hemostatic fibers (Johnson & Johnson, USA) was used for cover if necessary. After confirming that there was no obvious active bleeding and bile leakage, the abdominal drainage tube was placed.

### **Data collection**

We observed and collected the characteristics of patients, including age, gender, cases of hepatitis B antigen positive and liver cirrhosis, alanine transaminase (ALT), aspartate transaminase (AST), blood platelet (PLT), American Society of Anesthesiologists (ASA) classification, alpha-fetoprotein level (AFP), Child-Pugh classification, fasting blood glucose. And we collected the treatment details including duration of surgery, estimated intraoperative blood loss, pain score on the first day after surgery, time to get out of bed after operation, time to oral eating, AST on the second day after surgery, C-reactive protein (CRP) on the second day after surgery, total medical cost. Furthermore, the related complications including abdominal infection, bleeding, biliary fistula and pleural effusion were detected and analyzed.

### **Postoperative follow-up**

All the patients underwent 2-year long follow-up. All patients were rechecked with conventional B-ultrasound, enhanced CT or contrast-enhanced ultrasound and serum tumor markers in the outpatient clinic one month after surgery to determine whether the tumor was completely ablated or removed. Contrast-enhanced CT showed no enhancement in the ablation lesion, and contrast-enhanced ultrasound showed no contrast agent filling in the lesion, and it was judged that the tumor was completely ablated or removed. If the tumor was incompletely ablated, the patients would be re-admitted to the hospital for RFA. Routine B-ultrasound and serum tumor marker examinations was performed every 3–6 months. If routine B-ultrasound prompted suspicious lesions or serum tumor markers to rise again for a short period of time, further improve the enhanced CT, MRI or contrast-enhanced ultrasound examination to confirm the diagnosis. The deadline for follow-up was Aug 31, 2020 or if the patient

died or was lost during the follow-up.

### **Statistical methods**

We compared and analyzed the perioperative indicators and long-term results of the two groups of patients, and we used SPSS 22.0 statistical software for analysis. The continuous data were expressed as mean  $\pm$  standard deviation, independent sample *t*-test was used for comparison between groups;  $\chi^2$  test was used for categorical variables comparison. The Kaplan-Meier method was used to calculate the cumulative survival, and the survival curve was drawn by GraphPad PRISM 7.0 software. The test level was  $\alpha=0.05$ , and  $P<0.05$  indicated that the difference was statistically significant.

## **Results**

### **The characteristics of patients**

A total of 94 HCC patients were included, of which 46 patients underwent RFA treatment, and 48 patients underwent LH treatment. As presented in *Table 1*, there were not significant differences in the age, gender, cases of hepatitis B antigen positive and liver cirrhosis, number of HCC nodules, location of HCC, ALT, AST, PLT, ASA classification, AFP level, Child-Pugh classification, fasting blood glucose between two groups (all  $P>0.05$ ), indicating that the preoperative characteristics of patients were comparable.

### **The intraoperative and postoperative variables comparison**

As indicated in *Table 2*, the duration of surgery, estimated intraoperative blood loss, pain score on the first day after surgery, time to get out of bed after operation, time to oral eating, AST on the second day after surgery, CRP on the second day after surgery, total medical cost in RFA group were significantly less than that of LH group (all  $P<0.05$ ).

### **The postoperative complications comparisons between the two groups**

As presented in *Table 3*, the incidence of abdominal infection and biliary fistula in RFA group were significantly less than that of LH group (all  $P<0.05$ ), and there was no significant difference in the incidence of bleeding and pleural effusion between two groups (all  $P>0.05$ ).

**Table 1** The preoperative characteristics of patients

Variables	RFA group (n=46)	LH group (n=48)	$\chi^2/t$	P
Age (years), mean $\pm$ SD	56.33 $\pm$ 12.49	57.24 $\pm$ 13.23	12.154	0.238
Male/female	36/10	39/9	1.022	0.142
Hepatitis B antigen positive, n (%)	42 (91.30)	43 (89.58)	1.127	0.205
liver cirrhosis, n (%)	41 (89.13)	40 (83.33)	1.215	0.0189
ALT (U/L), n (%)	42.63 $\pm$ 21.03	44.75 $\pm$ 21.11	10.107	0.093
AST (U/L), n (%)	43.12 $\pm$ 23.59	42.55 $\pm$ 21.94	11.082	0.101
PLT ( $\times 10^3/L$ ), n (%)	105.35 $\pm$ 38.05	106.41 $\pm$ 34.06	19.178	0.131
Number of HCC nodules, mean $\pm$ SD	3.18 $\pm$ 1.96	3.11 $\pm$ 1.93	1.244	0.076
Location of HCC, n (%)				
Upper left	7 (15.22)	9 (18.75)	2.472	0.101
Lower left	9 (19.57)	8 (16.67)		
Upper right	16 (34.78)	16 (33.33)		
Lower right	14 (30.43)	15 (31.25)		
ASA classification, n (%)				
I	30 (65.22)	32 (66.67)	1.282	0.113
II	16 (34.78)	16 (33.33)		
AFP level, n (%)				
>400 ng/mL	14 (30.43)	13 (27.08)	1.150	0.126
$\leq$ 400 ng/mL	32 (69.57)	35 (72.92)		
Child-Pugh classification, n (%)				
A	44 (95.65)	44 (91.67)	1.082	0.094
B	2 (4.35)	4 (8.33)		
Fasting blood glucose (mmol/L), mean $\pm$ SD	5.31 $\pm$ 1.94	5.42 $\pm$ 1.77	1.224	0.125

AFP, alpha-fetoprotein; ALT, alanine transaminase; ASA, American Society of Anesthesiologists; AST, aspartate transaminase; HCC, hepatocellular carcinoma; LH, laparoscopic hepatectomy; RFA, radiofrequency ablation; PLT, platelet; SD, standard deviation.

### *The survival prognosis of patients*

Of the 94 patients in this study, 8 patients were gradually lost to follow-up within 2 years, and the remaining 86 patients were completed for all the followed up. As showed in *Figure 1*, the 2-year overall survival of the two groups had no significant statistical difference ( $P=0.106$ ). As showed in *Figure 2*, there was no significant difference in the recurrence-free survival between two groups ( $P=0.075$ ).

### **Discussion**

HCC currently ranks sixth in the world in incidence and

third in tumor-related deaths (11). Although surgical resection is still the gold standard for radical treatment for HCC, radical resection is used for some small liver cancer patients. The overall survival rate at 3 years after surgery can be close to 90%, but the recurrence rate at 5 years after radical resection is as high as 70% (12,13). The LH technique has been used for nearly 30 years, and its safety, feasibility and effectiveness in the treatment of primary or recurrent liver cancer have been widely recognized (14). The efficacy of RFA in small liver cancer, especially with cancer nodules  $\leq 3$  cm, has been widely accepted by the medical profession and proved to be a treatment equivalent to surgical resection, and its 3-year overall survival rate

**Table 2** Comparison of intraoperative and postoperative variables between the two groups

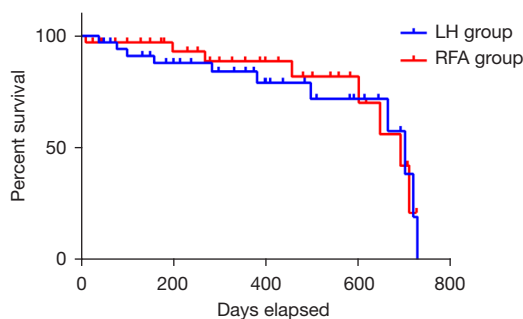
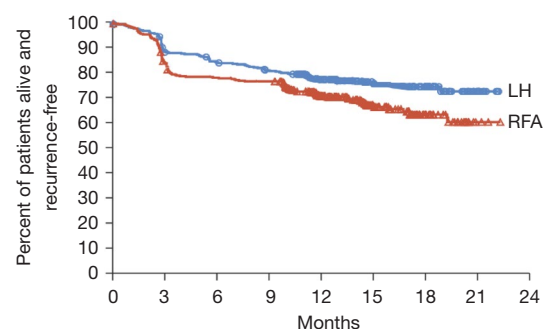
Variables	RFA group (n=46)	LH group (n=48)	<i>t</i>	P
Duration of surgery (min)	29.13±12.36	122.35±24.66	12.185	0.009
Estimated intraoperative blood loss (mL)	9.23±2.11	102.25±22.09	4.238	0.012
Pain score on the first day after surgery	0.92±0.34	3.11±0.77	1.123	0.014
Time to get out of bed after operation (days)	0.71±0.22	2.33±0.95	1.081	0.022
Time to oral eating (days)	1.12±0.14	2.43±0.61	1.124	0.048
AST on the second day after surgery (U/L)	76.33±36.75	154.95±54.21	19.130	0.015
CRP on the second day after surgery (mg/L)	28.17±12.92	33.73±20.06	12.036	0.035
Total medical cost (RMB)	22,740.12±2,093.26	31,042.84±3,452.81	112.729	0.011

AST, aspartate transaminase; CRP, C-reactive protein; LH, laparoscopic hepatectomy; RFA, radiofrequency ablation.

**Table 3** Comparison of postoperative complications between the two groups

Variables	RFA group (n=46)	LH group (n=48)	$\chi^2$	P
Abdominal infection	2 (4.35)	6 (12.50)	1.024	0.014
Bleeding	1 (2.17)	3 (6.25)	1.116	0.069
Biliary fistula	1 (2.17)	5 (10.42)	1.094	0.012
Pleural effusion	1 (2.17)	3 (6.25)	1.116	0.069

LH, laparoscopic hepatectomy; RFA, radiofrequency ablation.

**Figure 1** Comparison of overall survival between the two groups (LH group and RFA group). LH, laparoscopic hepatectomy; RFA, radiofrequency ablation.**Figure 2** Comparison of recurrence-free survival between the two groups (LH group and RFA group). LH, laparoscopic hepatectomy; RFA, radiofrequency ablation.

is equivalent to that of open liver resection (15,16). The results of this present study have found that the RFA has more advantages over LH in reducing duration of surgery, estimated intraoperative blood loss, pain score on the first day after surgery, time to get out of bed after operation, time to oral eating, AST on the second day after surgery, CRP on the second day after surgery, total medical cost. Furthermore, the incidence of abdominal infection and

biliary fistula in RFA groups are significantly less than that of LH group, and the 2-year overall survival of RFA and LH does not have significant difference, indicating that for the HCC with a diameter of  $\leq 3$  cm, RFA may be a better treatment option.

At present, for primary liver cancer with a diameter of  $\leq 3$  cm, the methods recognized at home and abroad



that can achieve radical cure include liver transplantation, surgical resection, and RFA (17). Among them, liver transplantation has the best long-term effect, but due to its high requirements for technics, high cost, and lack of donors, its promotion and application are limited. With the improvement of laparoscopic equipment and technology, LH is being used more and more clinically. There are reports (18,19) showing that the short-term effect of LH for small liver cancer is better than that of open surgery, while the long-term effect is equivalent. The advantage of RFA is to cause coagulation and necrosis of tumor tissue, the treatment range is accurate, and the damage to normal liver tissue is greatly reduced (20). At the same time, it can activate the body's immune function and can be applied to some patients with small tumors and tricky location that are difficult to undergo surgical treatment (21,22). Especially for primary liver cancer with a diameter of  $\leq 3$  cm, the effect is better, and patients with stage 0 liver cancer who cannot undergo liver transplantation in the BCLC staging treatment are recommended to give priority to ablation treatment by the guidelines (23,24).

Although LH is a minimally invasive treatment method compared with traditional open surgery, various factors such as the removal of part of the liver, the absorption of CO<sub>2</sub> from the pneumoperitoneum during the operation, and the need for incisions in the abdominal wall to take specimens are still affecting the prognosis of patient (25-27), but these conditions are basically not present in RFA treatment. During our treatment, both groups of patients recovered smoothly, and no perioperative death occurred, indicating that both RFA and LH are generally safe and reliable. However, RFA has a lower complication rate in the treatment of HCC and has advantages in minimally invasiveness, which is consistent with previous reports (28,29).

According to the follow-up results, three cases of recurrence occurred after AFA. For cancers close to larger blood vessels, the heat loss during ablation caused poor ablation, but complete remission can still be achieved after re-ablation treatment (30). There was no residual tumor in the laparoscopic liver resection group, which may be related to the more thorough removal of tumor and surrounding liver tissue (31). At the same time, there was no significant difference in the 2-year overall survival between the two groups. However, the scope of application of the two methods may be different (32,33). For example, for a single small liver cancer located deep in the liver, surgical treatment is more difficult, and RFA may be applicable.

While for small liver cancers like the caudal lobe of the liver, RFA is more difficult. LH may be more applicable at this time.

Several limitations must be considered in this present study. Firstly, since our study was a retrospective analysis, many details regarding the RFA and LH could not be included for analysis. Secondly, we selected HCC patients treated in our hospital from Aug 1, 2016 to Aug 31, 2018 as study population and made 2-year follow-up, the sample size was small, it might be not power enough to detect the differences between groups, future studies with larger sample size were needed. Thirdly, we only conduct 2-year long follow-up for HCC patients, it's been reported that the recurrence rate of HCC was significantly increased 3 years after surgery, we will conduct longer follow-up to evaluate the effects and safety of RFA and LH in the future.

## Conclusions

In conclusion, both RFA and LH are generally safe and effective for HCC treatment. RFA has many advantages of reduced perioperative complication, less trauma, and higher safety, and there is no significant difference in the 2-year survival prognosis. Clinicians can choose to carry out RFA or LH based on the patient's condition and their own technical level to improve the prognosis of HCC patients.

## Acknowledgments

*Funding:* This work was funded by Zhejiang Provincial Natural Science Foundation of China under Grant (No. LSY19H180012).

## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://dx.doi.org/10.21037/tcr-21-367>

*Data Sharing Statement:* Available at <https://dx.doi.org/10.21037/tcr-21-367>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/tcr-21-367>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Sir Run Run Shaw Hospital (No.: 161102-9c), and written informed consent was taken from all the patients.

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**Cite this article as:** Xu H, Zhou L, Jin Q. The effects of ultrasound-guided radiofrequency ablation and laparoscopic hepatectomy in the treatment of small hepatocellular carcinoma: a retrospective analysis. *Transl Cancer Res* 2021;10(11):4794-4801. doi: 10.21037/tcr-21-367