Original Article

Pure laparoscopic liver resection versus percutaneous radiofrequency ablation for small hepatocellular carcinoma: a propensity score and multivariate analysis

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Background: In treatment of hepatocellular carcinoma (HCC), both laparoscopic liver resection (LLR) and radiofrequency ablation (RFA) provided similar short-term advantages. However, there was no robust clinical trial comparing the efficacy of LLR and RFA especially for small HCC. This study aimed to compare the short-term and long-term outcomes of LLR and RFA for patients with small HCC using a propensity score matching analysis to minimize potential selection bias. Factors affecting survival were then identified with multivariate analysis.

Methods: All patients underwent RFA or LLR for small HCC [defined as Barcelona Clinic Liver Cancer (BCLC) stage 0 or A, size ≤3 cm, ≤3 nodules on contrast CT scan or MRI with no evidence of macrovascular invasion] from April 2005 to August 2020 were included. Propensity score matching was conducted to match patients in the LLR group and RFA group. Prognostic indicators, i.e., age, gender, tumor size, tumor number, Child's grading, albumin, bilirubin, platelet count, international normalized ratio, alpha-fetoprotein level and presence of cirrhosis on imaging were chosen for propensity score calculation. The demographic data, tumor characteristics, operative data, post-operative outcomes and survival data of the two groups were compared. A multivariate analysis based on Cox regression was used to identify factors associated with survival.

Results: Median follow-up was 34 months. LLR and RFA had similar overall survival (91.8% *vs.* 79.2% at 5-year, P=0.060); while the LLR had a significantly better disease-free survival (49.0% *vs.* 30.3% at 5-year, P=0.002) and local recurrence-free survival (96.0% *vs.* 63.7% at 5-year, P<0.001) when compared with the RFA. Multivariate analysis showed that treatment received by patient (LLR *vs.* RFA), prothrombin time and platelet counts were significantly associated with disease-free survival. On the other hand, the only factor associated with local recurrence-free survival was the treatment received by patient.

Conclusions: Both RFA and LLR are safe and feasible treatment options for patients with small HCC. LLR should be considered for patients with preserved liver function with a better disease-free survival; while RFA offered a comparable overall survival with less surgical trauma and shorter hospital stay.

Keywords: Hepatocellular carcinoma (HCC); laparoscopic hepatectomy; radiofrequency ablation (RFA); long-term survival outcome; multivariate analysis

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Introduction

Hepatocellular carcinoma (HCC) was ranked as the fifth most common malignancy and the second leading cause of cancer death worldwide (1). Liver transplantation and liver resection remain as the main curative treatments for early HCC. Liver resection can be performed as open or laparoscopic hepatectomy. With gaining evidence on its short-term benefits, which included shorter operative time (2,3), decreased blood loss (2,4), shorter hospital stay (2-6), and decreased overall morbidity (3-7), laparoscopic liver resection (LLR) had emerged as a valuable treatment option for selected patients (8). Recent publications had shown comparable oncological outcomes in terms of disease-free survival and overall survival for LLR and open liver resection (2-7,9). Nevertheless, only 30% of patients with HCC were able to undergo liver resection. Radiofrequency ablation (RFA) could achieve a radical cure effect and long-term survival similar to surgery for small HCCs (10-12). It also provided the advantages of minimal invasive treatment, more rapid recovery, and low morbidity and mortality (13,14). However, these advantages were largely identified in studies comparing RFA with open hepatectomy. To date, there was no robust clinical trial comparing the efficacy of LLR and RFA especially for small HCC. This study aimed to compare the short-term and long-term outcomes of LLR and RFA for patients with small HCC using a propensity score matching analysis to minimize potential selection bias. Factors affecting survival were then identified with multivariate analysis. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1045/rc).

Methods

This was a single-center retrospective analysis of a prospectively collected database. Diagnosis of HCC was made based on contrast enhancement on cross-sectional imaging such as triphasic computed tomography (CT scan) or magnetic resonance imaging (MRI). All patients underwent RFA or LLR for small HCC (defined as BCLC stage 0 or A, sized ≤3 cm, ≤3 nodules on contrast CT scan or MRI with no evidence of macrovascular invasion) from April 2005 to August 2020 were included. All patients followed the same protocol of preoperative workup and investigations including blood tests to determine liver function and alpha fetoprotein (AFP) level, as well as radiological assessment using contrasts CT scan and/or MRI. Tumors located in segment 7 or 8 were defined as posterosuperior lesions.

The selection criteria and operative technique for LLR in our center were described previously (15). In general, liver resection was first considered in all cases. RFA were generally performed for patients with small deep-seated intraparenchymal tumors contraindicated to major liver resections. Patients' preference was considered if the lesion was amenable to both treatments.

For LLR, a 12-mm camera trocar was inserted at the subumbilical region, and 4–5 trocars of diameter 5–12 mm were used by the surgeon and assistant. Ultrasonic shear device or Cavitron Ultrasonic Surgical Aspirator (CUSA) was used to conduct liver parenchymal transection. Pringle maneuvers were employed selectively. Anatomical liver resection was defined as removal of the whole hepatic segment or subsegments supplied by the tumor bearing tributaries.

RFA were performed percutaneously using the Cool-tip™ RF Ablation System (Medtronic, USA) under local anesthesia. The RFA electrode was inserted under non-contrast ultrasound or CT scan guidance, with an intended ablative margin of at least 1 cm. Drain was placed only when clinically indicated. All LLR and RFA were performed by the same team of hepatobiliary surgeons and interventional radiologists respectively.

Conversion from laparoscopic to open surgery, blood transfusion, morbidity, mortality, and duration of hospital stay were all recorded as procedure-related factors. R0 resection was defined as resection margin more than or equal to 1 mm. Data on post-operative complications were classified according to the Clavien-Dindo Grading (16). Both groups of patients followed the same post-treatment surveillance protocol (15). In general, 6-monthly triphasic contrast CT scans and chest X-rays were performed. Additional contrast CT scans were performed at first and third month after RFA to detect any early local recurrence. Liver function tests and serum alpha-fetoprotein levels were assessed 3-monthly for the first two years, then 6-monthly. The date of recurrence was defined as the date of radiological recurrence. The development of new HCC foci in contact with a tumor that had been excised or ablated was characterized as local recurrence. A new lesion developing at a distance from the initial location was characterized as a new recurrence. Re-resection, microwave or RFA, trans-arterial chemoembolization (TACE), or systemic therapy were administered when needed.

1:3 propensity score matching was conducted to match

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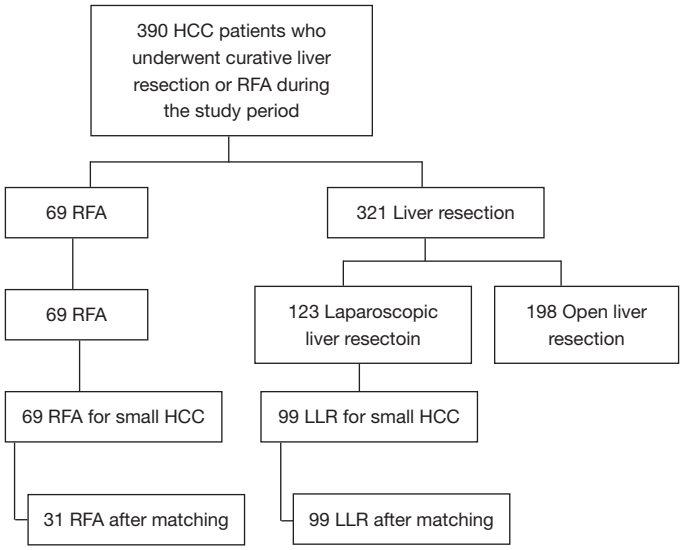

Figure 1 Flow diagram of participants at each stage of study.

patients in the LLR group and RFA group. Prognostic indicators, i.e., age, gender, tumor size, tumor number, Child's grading, albumin, bilirubin, platelet count, international normalized ratio, alpha-fetoprotein level and presence of cirrhosis on imaging were chosen for propensity score calculation. In our investigation, we used the genetic matching approach, which automatically adjusted the covariate balance between the two groups (17,18). The two groups' demographics, tumor features, surgical data, post-operative results, and survival data were compared. The analysis was carried out on an intention-to-treat basis.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central/Kowloon East) (The Hospital Authority manages 43 public hospitals and institutions in Hong Kong including Kwong Wah Hospital, No.: KC/KE-21-0241/ER-2) and informed consent was not required for retrospective study of a database.

Statistical analysis

Statistical analysis was performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) if the data is skewed. Student *t*-test or Mann-Whitney U test were used to analyze continuous variables as appropriate, and Chi-square test was used for categorical variables. Survival was analyzed by Kaplan-Meier method and compared using the log rank test. Statistical significance was set at P value ≤0.05. To identify variables related with survival, a multivariate analysis based on Cox regression was employed. The multivariate regression model includes all variables having a P value of 0.1 in the univariate analysis.

Results

During the study period, 99 and 69 patients underwent LLR and RFA for small HCC, respectively. After propensity score matching, there were 99 patients in the LLR group and 31 patients in the RFA group (*Figure 1*). All LLR were performed without hand-port or robotic assistance and all RFA were performed percutaneously; 45.5% of LLR were anatomical liver resection and Pringle maneuver was used in 3.0%. The demographic and clinicopathological data were depicted in *Table 1*. There was no difference in the baseline characteristics including age, gender, hepatitis carrier status, cirrhosis, liver function, AFP level, tumor size and tumor number between the two groups. There were more tumors in the posterosuperior segments in RFA group (58.1% *vs.* 41.9%, P=0.002).

Regarding short-term post-operative outcomes, no significant difference was seen in blood transfusion, overall and major complication rates and 30-day mortality (*Table 2*). One patient in LLR group had laparoscopic segment 5 segmentectomy performed and complicated with gallbladder perforation required emergency laparoscopic

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Table 1 Demographic and clinicopathological data

Data	LLR (n=99)	RFA (n=31)	P value
Age, years, mean ± SD	63.60±9.86	65.48±11.73	0.376
Gender, male, n (%)	82 (82.8)	22 (71.0)	0.150
Hepatitis B, n (%)	82 (82.8)	22 (71.0)	0.150
Hepatitis C, n (%)	12 (12.1)	8 (25.8)	0.183
Cirrhosis, n (%)	21 (21.2)	4 (12.9)	0.306
Child-Pugh grade, n (%)			
Grade A	83 (96.5)	27 (93.1)	0.435
Grade B	2 (2.3)	2 (6.9)	
Grade C	1 (1.2)	0 (0.0)	
AFP, U/L, median (IQR)	47 (6.0–423.0)	34 (3.5–242.5)	0.380
Albumin, g/L, mean ± SD	36.72±5.12	37.03±5.53	0.770
Bilirubin, μmol/L, mean ± SD	17.27±6.97	17.61±8.77	0.824
Platelet count, $\times 10^9$/L, mean ± SD	153.68±69.19	143.26±54.57	0.445
INR, median (IQR)	1.07 (1.03–1.15)	1.10 (1.04–1.29)	0.205
Tumour size, cm, mean ± SD	2.31±1.93	1.14±0.70	0.080
Number of tumours, n (%)			
One	96 (97.0)	28 (90.3)	0.124
Two	3 (3.0)	3 (9.7)	
Tumour location			
Anteroinferior	71 (71.7)	13 (41.9)	0.002*
Posterosuperior	28 (28.3)	18 (58.1)	

*, statistical significant. LLR, laparoscopic liver resection; RFA, radiofrequency ablation; SD, standard deviation; IQR, inter-quartile range; AFP, alpha-fetoprotein.

cholecystectomy. Another patient in LLR group died of hospital-acquired pneumonia 12 days after operation. Hospital stay was significantly shorter for the RFA group (3.06 *vs.* 6.05 days, P=0.001).

Median follow-up was 34 months (range, 1–175 months). There were no lost to follow-up or missing data. The overall survival, disease-free survival and local recurrence-free survival were illustrated in *Figures 2-4*. The LLR group and RFA group had similar overall survival rate (91.8% *vs.* 79.2% at 5-year, P=0.060); while the LLR group had a significantly better disease-free survival rate (49.0% *vs.* 30.3% at 5-year, P=0.002) and local recurrence-free rate (96.0% *vs.* 63.7% at 5-year, P<0.001) when compared with the RFA group (*Table 3*).

Multivariate analysis showed that treatment received by patient (LLR *vs.* RFA), prothrombin time and platelet counts were significantly associated with disease-free survival. On the other hand, the only factor associated with local recurrence-free survival was the treatment received by patient (*Tables 4,5*).

Discussion

The selection of LLR versus RFA as the first line treatment for small HCC remains controversial. This study showed that both procedures were safe and feasible. RFA had a shorter hospital stay, while LLR had a lower local recurrence rate and better disease-free survival rate. Nevertheless, the overall survival was comparable between the two groups.

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Table 2 Short-term outcomes

Outcomes	LLR (n=99)	RFA (n=31)	P value
Pringle maneuver used, n (%)	3 (3.0)		
Anatomical resection, n (%)	45 (45.5)		
Conversion, n (%)	6 (6.1)		
Resection margin, mm, median (IQR)	8 [3–10]		
R0 resection	91 (91.9)		
Transfusion, n (%)	12 (12.1)	1 (3.2)	0.150
All complications, n (%)	12 (12.1)	2 (6.5)	0.374
Major (grade 3 or above) complications, n (%)	1 (1.0)	0 (0.0)	0.574
30-days mortality, n (%)	1 (1.0)	0 (0.0)	0.574
Hospital stay, days, mean ± SD	6.05±4.57	3.06±2.25	0.001*

*, statistical significant. LLR, laparoscopic liver resection; RFA, radiofrequency ablation; SD, standard deviation; IQR, inter-quartile range.

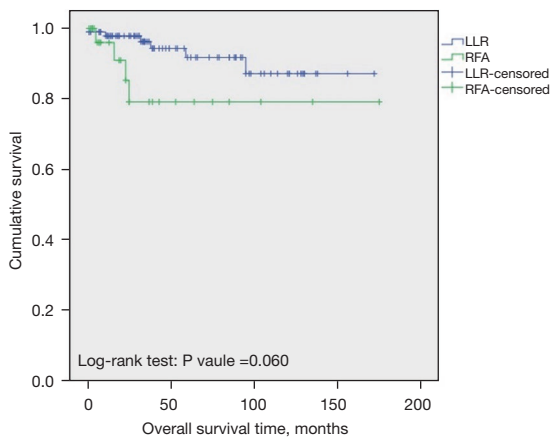

Figure 2 Kaplan-Meier curves for overall survival.

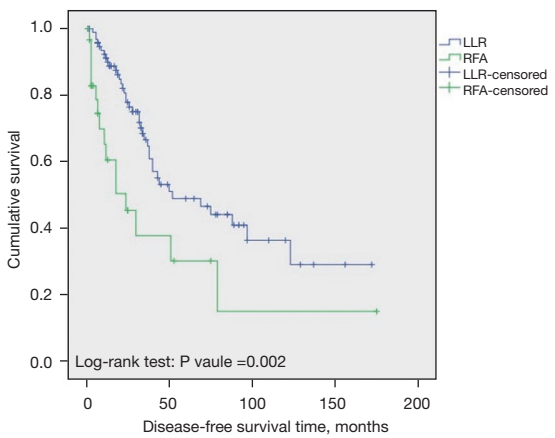

Figure 3 Kaplan-Meier curves for disease-free survival.

Two comparative studies on small HCC were published in 2020. Chong *et al.* performed a propensity score matching comparing 59 pairs of patients with BCLC stage 0/A HCC, who received minimally invasive treatment (19). 50.8% of LLR were performed with robotic assistance and only 84.5% of RFA were performed percutaneously. They found that the overall complication rate of the two groups was not significantly different (5.1% *vs.* 1.7%, P=0.625). LLR provided a significantly better 1-, 3-, and 5-year overall and disease-free survival (94.9% *vs.* 96.6%, 88.2% *vs.* 78.7%, 82.5% *vs.* 53.3%, P=0.005 and 86.3% *vs.* 59.3%, 68.0% *vs.* 25.3%, 68.0% *vs.* 15.9%, P<0.001 respectively), though there was no analysis on the recurrence pattern.

Another comparative study from Ogiso *et al.* compared 85 LLR with 136 RFA patients (20). They have the same definition of 'small HCC' as our center and we demonstrated similar results. Their result showed that LLR had a worse short-term outcome when compared with RFA in terms of more blood transfusion (8.2% *vs.* 0%, P<0.001), more overall complications (11.8% *vs.* 2.9%, P=0.020) and longer hospital stay (11 days *vs.* 6 days, P<0.001). However, there were no significant difference in grade 3 or above complications between the two groups (1.2% *vs.* 0%, P=0.385). In spite of the minimally invasive nature of LLR, it still resulted in larger wounds than percutaneous RFA and it had to be performed under general anesthesia, thus resulting in longer hospital stay for post-operative recovery and pain control.

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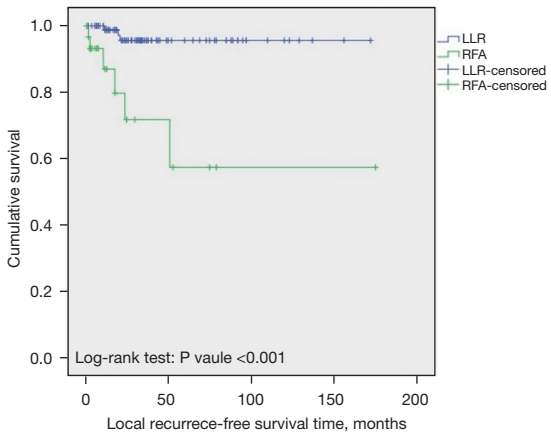

Figure 4 Kaplan-Meier curve for local recurrence-free survival.

Table 3 Long-term outcomes

Outcomes	LLR (n=99)	RFA (n=31)	P value
Overall survival, %			
1-year	97.9	96.0	0.060
3-year	96.2	79.2	
5-year	91.8	79.2	
Disease free survival, %			
1-year	91.2	60.6	0.002*
3-year	66.7	37.9	
5-year	49.0	30.3	
Local recurrence, n (%)	3 (3.0%)	6 (19.4%)	0.002*
Local recurrence-free survival, %			
1-year	98.8	88.3	<0.001*
3-year	96.0	76.4	
5-year	96.0	63.7	

*, statistical significant. LLR, laparoscopic liver resection; RFA, radiofrequency ablation.

Table 4 Univariate analysis of survival

Factors	P value for	
	Disease-free survival	Local recurrence-free survival
LLR *vs.* RFA	0.004	0.002
Age	0.861	0.362
Gender	0.528	0.374
Child's grade	0.448	0.977
Albumin	0.132	0.621
Bilirubin	0.476	0.912
PT	0.004	0.109
Platelet count	0.006	0.199
AFP	0.765	0.589
Number of lesions	0.053	0.752
Tumor size	0.219	0.183

LLR, laparoscopic liver resection; RFA, radiofrequency ablation; PT, prothrombin time; AFP, alpha-fetoprotein.

Table 5 Multivariate analysis of survival

Survival and factors	Hazard ratio	95% CI	P value
Disease-free survival			
LLR *vs.* RFA	1.929	1.045 to 3.562	0.036
PT	1.028	1.009 to 1.047	0.003
Platelet count	0.993	0.988 to 0.998	0.004
Local recurrence-free survival			
LLR *vs.* RFA	9.247	2.299 to 37.200	0.002

LLR, laparoscopic liver resection; RFA, radiofrequency ablation; PT, prothrombin time.

For long-term outcome, our study results concurred with previous studies and we showed that the benefit of disease-free survival and local recurrence-free survival for LLR extended to 5-year post-treatment. The only factor associated with local recurrence is RFA on multivariate analysis. To date, there was no randomized controlled trial comparing the outcomes of LLR and RFA for small HCC. The meta-analysis by Li *et al.* showed that RFA group had lower complication rate, while LLR had a significantly better 1- and 3-year disease-free survival and 5-year overall survival rate than the RFA group (21). However, the 8 retrospective studies included in the meta-analysis had different definition of the 'small HCC'. The most commonly used definitions were either the BCLC stage 0/A or the Milan criteria, yet the tumor size ranged from <3 to <6.5 cm. This meta-analysis showed that LLR had a significantly better 5-year overall survival and better 1- and 3-year disease-free survival than RFA. Tumor size is one of the important factors in considering ablative treatment

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as the efficacy in complete ablation diminished with larger tumour size and local tumour progression was more frequent in larger tumours (22).

In order to achieve comparable long-term outcomes between RFA and LLR, careful patient selection is of utmost importance. HCC has the propensity to invade into the portal and hepatic veins, leading to intrahepatic metastasis, which are two factors proven to be associated with poor prognosis (23-30). With the systematic removal of liver parenchyma supplied by the tumor bearing tributaries (31,32), anatomical liver resection was shown to have significantly better recurrence-free survival (24,33). On the other hand, non-anatomical resection and RFA may leave behind non-perfused ischemic liver tissues which is known to be associated with early recurrence and poor survival after resection of HCC (34). In our series, 45.5% of our LLR were anatomical liver resection.

Furthermore, our multivariate analysis showed that disease-free survival was associated with prothrombin time and platelet counts. These two factors were indicative of the degree of underlying cirrhosis and advanced cirrhosis was an important factor contributing to recurrence after treatment for HCC (35-37). Though LLR provided a better local control, less than 30% of the patients with HCC could undergo resection (38). These patients have underlying cirrhosis and limited liver function reserve. For patients with marginal liver function or small deeply located tumors, RFA could serve as an alternative treatment modality with similar overall survival rate. The higher locoregional recurrence rate did not adversely affect the overall survival as the recurrence could be further treated with re-ablation or resection (39,40).

Our study was limited by its retrospective design and a relatively small sample size. Only patients with small HCC who had been treated with pure LLR or percutaneous RFA were included. Despite the use of propensity score matching to ensure both groups were comparable and represented a homogenous and specific group of patients, there could be some unknown confounding factors that remain unrecognized in this retrospective study (41). Early post ablation (within 24 hours) contrast CT scan was not performed in our center to evaluate completeness of RFA ablation due to limited resources. In fact, only 1 patient (3.2%) in our series suffered from recurrence within first month after RFA. Our incomplete ablation rate was similar to other published series (19,42,43).

Conclusions

In conclusion, both RFA and LLR are safe and feasible treatment options for patients with small HCC. LLR should be considered for patients with preserved liver function with a better disease-free survival; while RFA offered a comparable overall survival with less surgical trauma and shorter hospital stay.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1045/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1045/dss

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-1045/coif). 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 the Hong Kong Hospital Authority Research Ethics Committee (Kowloon Central/Kowloon East) (The Hospital Authority manages 43 public hospitals and institutions in Hong Kong including Kwong Wah Hospital, No.: KC/KE-21-0241/ER-2) and informed consent was not required for retrospective study of a database.

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