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Original Article

Laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma: A propensity case-matched analysis of the long-term survival

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Backgrounds/Aims: Despite the widespread popularity of laparoscopic surgery, laparoscopic liver resection (LLR) remains in evolution. This study aimed to compare the long-term outcomes for patients undergoing laparoscopic versus open hepatectomy for hepatocellular carcinoma (HCC) ≤7 cm. **Methods:** Patients diagnosed with HCC treated by hepatectomy from October 2000 to May 2019 were included. Excluding tumors larger than 7 cm, 1:2 propensity score matching was performed between laparoscopic and open hepatectomies. The perioperative outcomes, 5-year overall survival (OS) and disease-free survival (DFS) of the two groups were compared. **Results:** Forty-five patients who underwent LLR were matched to 90 open hepatectomy (OH) during the same period. LLR group had shorter median hospital stay (5 days vs. 9 days, p=0.00) but required longer operative time (326.0 minutes vs. 272.5 minutes, p=0.018) than the OH group. The 5-year overall survival was better in the LLR group (84.9% vs. 61.1%; p=0.036), though there was no significant difference in the 5-year disease free survival (20.0% vs. 22.2%, p=0.613). The rate of R0 resection was comparable between the 2 groups with a slightly better margin distance in the LLR (5 mm vs. 3 mm, p=0.043). **Conclusions:** Laparoscopic liver resection is safe and feasible for cirrhotic patients with HCC size up to 7 cm. It has better short-term outcomes and comparable perioperative blood loss and complication rates. The resection margin is not jeopardized and the 5-year overall and disease-free survivals are comparable with the open group. **(Ann Hepatobiliary Pancreat Surg 2021;25:1-7)**

Key Words: Hepatocellular carcinoma; Laparoscopic hepatectomy; Survival; Long-term outcome

INTRODUCTION

The adoption of laparoscopic liver resection as standard practice has been slow. Most centers confined their practice to laparoscopic left lateral sectionectomy and wedge resection. Laparoscopic major resections remained exploratory and were recommended to be carried out in high volume centers only.[1-3] Concerns hindering its uptake included difficulty in bleeding control, gas embolism, parenchymal transection techniques and oncological safety.[1] While we are expecting the results from the ORANGE II PLUS trial[4] on the treatment outcomes, data on the long term outcomes of laparoscopic liver resection (LLR) for malignant liver tumors is still scarce.[5-8] Technical considerations aside, the adequacy of oncological clearance and long-term survival remains the most important question to be answered. This study aimed to review the long-term outcomes of LLR and open hepatectomy (OH) for a matched cohort of patients with hepatocellular carcinoma and underlying cirrhosis.

MATERIALS AND METHODS

The clinical data of all patients undergoing hepatectomy for hepatocellular carcinoma (HCC) at our institute from October 2000 to May 2019 were retrospectively analyzed from a prospectively collected database. Patients with typical radiological features of HCC sized ≤7 cm on contrast-computed tomography (CT) or magnetic resonance imaging (MRI) were included. All patients followed the same protocol of perioperative care and investigations. The selection criteria and operating

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technique for LLR and open hepatectomy were described previously.[9] Drain was placed only when clinically indicated. All operations were performed by the same team of hepatobiliary surgeons.

Liver resection was defined according to the Brisbane 2000 classification.[10] A gross resection margin of 1 cm was aimed for all hepatectomies. R0 resection was defined as margin ≥1 mm from the resection surface. Data on post-operative complications was collected from a prospectively managed database and classified according to the Clavien-Dindo Grading.[11] Post hepatectomy liver failure and bile leakage were defined according to the International Study Group of Liver Surgery (ISGLS)[12,13]. Post-operative mortality was defined as death occurring within 90 days after the operation.

Surveillance liver function tests, alpha fetal protein (AFP) level, triphasic contrast CT scan of the liver were performed at regular intervals.[9] The date of recurrence was defined as the date of radiological recurrence. Further treatments, such as re-resection, microwave or radio-frequency ablation, trans-arterial chemo-embolization or systemic treatment were given as appropriate.

Propensity score matching was conducted to match patients in the LLR group and OH group in the ratio ratio of 1:2. Prognostic indicators i.e. age, gender, tumor size, lympho-vascular invasion, alpha-fetoprotein level, R0 resection and presence of cirrhosis were chosen for propensity score calculation.[14-21] The method of genetic matching was adopted in our study, which automatically optimized the covariate balance between the two groups.[22,23] The demographic data tumor characteristics, operative data, post-operative outcomes and survival data of the two groups were compared. The analysis was performed according to the intention-to-treat basis.

Statistical analysis was performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA). Mann-Whitney U test was used for continuous variables, and Chi-square test was used for categorical variables. Survival analysis was analyzed by Kaplan-Meier method and compared using the log rank test. Statistical significance was set at *p*-value ≤0.05.

This study was approved by The Hong Kong Hospital Authority, Kowloon West Cluster Research Ethics Committee (reference number KW/EX-17-005 (107-05)).

Table 1. Patients demographics

	Laparoscopic (n=45)	Open (n=90)	*p*
Age	62 (57.5-68.0)	62 (54.75-71.00)	0.737
Gender (male/female)	37/8	72/18	0.758
Hepatitis B carrier	42 (93.3%)	72 (80%)	0.125
Hepatitis C carrier	2 (4.4%)	11 (12.2%)	0.000
Child's score			0.055
A	45 (100.0%)	83 (92.2%)	
B	0 (0.0%)	7 (7.8%)	
Platelet count ($\times 10^9$/L)	146 (123.5-201.0)	147.5 (106.75-203.0)	0.810
Alpha-fetoprotein (ng/ml)	14 (4.0-358.5)	21.5 (4.75-404.50)	0.419

Data are shown as median (interquartile range) or number (percentage)

Table 2. Perioperative outcomes and complication rates

	Laparoscopic (n=45)	Open (n=90)	*p*
Blood loss (ml)	500 (200-1200)	725 (500-1285)	0.055
Transfusion required	11 (24.4%)	30 (33.3%)	0.420
Blood replacement (ml)	0 (0-125)	0 (0-600)	0.548
Operative time (min)	326 (256.0-452.5)	272.5 (195.00-346.25)	0.018
Pringle maneuvers used	3 (6.7%)	26 (28.9%)	0.003
Hospital stay (days)	5 (4-9)	9 (7-16)	0.000

Data are shown as median (interquartile range) or number (percentage)

RESULTS

From October 2000 to May 2019, 377 hepatectomies were performed in our institute for hepatocellular carcinoma. Two hundred and forty-nine patients underwent hepatectomies for HCC≤7 cm and they were included in the analysis. After matching, there were 45 patients in the LLR group and 90 patients in the OH group. All patients were Eastern Cooperative Oncology Group (ECOG) performance status 0. The demographics were depicted in Table 1.

Most of our patients had cirrhosis (84/135, 62.2%). Less Pringle maneuver was applied in the LLR group (3 vs. 26, p=0.003). The intraoperative blood loss was 500 ml in LLR and 725 ml in OH, though it did not reach statistical significance (p=0.055). The operating time was significantly longer in the LLR group (326.0 minutes vs. 272.5 minutes, p=0.018). The LLR group had a shorter hospital stay (5 days vs. 9 days, p=0.000) (Table 2). There were less Grade I/II post-operative complications in LLR group and there was no significant difference in the Grade III or above complications (Table 3). There were 5 conversions in the LLR group (11.1%). The reasons for conversion included dense intra-abdominal adhesions, threatened resection margin, tumor progression with presence of portal vein thrombus and uncertain anatomy.

The tumor characteristics and pathology were depicted in Tables 4, 5 respectively. There was no difference in the multiplicity and size of the tumor between the two groups. The types of resections and the numbers of anatomical resections were also comparable. With a similar R0 resection rate, the resection margin was significantly wider in the LLR group (5.0 mm vs. 3.0 mm, p=0.043).

The median follow-up period was 36 months in LLR and 43 months in OH (p=0.243). The median disease-free survival was 29 months and 25 months for LLR and OH; while the median overall survival was 135 months in LLR and 128 months in OH group respectively. The 1, 3 and 5-year disease-free survival rates were 80.0%, 40.0%, and 20.0% for LLR; and 73.3%, 41.1%, and 22.2% for OH (p=0.613) (Fig. 1). The 1, 3 and 5-year overall survival

Table 3. Postoperative outcomes

	Laparoscopic (n=45)	Open (n=90)	p-value
Overall complications	8 (17.8%)	32 (35.6%)	0.033
Clavien-Dindo grade			
I/II	7 (15.6%)	30 (33.3%)	0.029
IIIa/IIIb	1 (2.2%)	2 (2.2%)	1.000
General complications			
Respiratory	3	12	
Urinary tract infection	0	1	
Cardiac	2	1	
Surgical related			
Wound complications infection/dehiscence)	2	6	
Fluid collection	1	1	
Internal hemorrhage	0	1	
Liver related			
Bile leak	2	0	
Post hepatectomy liver failure	1	7	
Ascites	1	13	

Data are shown as number (percentage)

Table 4. Type of operations and tumor location

	Laparoscopic (n=45)	Open (n=90)	p
Tumor location			0.121
Antero-lateral	34 (75.6%)	56 (62.2%)	
Postero-superior	11 (24.4%)	34 (37.8%)	
Anatomical resection	27 (60.0%)	61 (67.8%)	0.371
Non-anatomical resection	18 (40.0%)	29 (32.2%)	
Type of resection			0.178
Left hepatectomy	6 (13.3%)	20 (22.2%)	
Right hepatectomy	4 (8.9%)	18 (20.0%)	
Left lateral sectionectomy	2 (4.4%)	6 (6.7%)	
Right posterior sectionectomy	5 (11.1%)	8 (8.9%)	
Right anterior sectionectomy	0 (0.0%)	1 (1.1%)	
Anatomical monosegmentectomy	10 (22.2%)	8 (8.9%)	
Wedge resection	18 (40.0%)	29 (32.2%)	

Data are shown as number (percentage)

Table 5. Tumor characteristics on histology

	Laparoscopic (n=45)	Open (n=90)	*p*
Tumor size (cm)	3.5 (2-5)	4 (3-5)	0.127
Number of tumors			0.117
1	37 (82.2%)	70 (77.8%)	
2	5 (11.1%)	13 (14.4%)	
3	1 (2.2%)	7 (7.8%)	
4	2 (4.4%)	0 (0.0%)	
Cirrhosis in histology	26 (57.8%)	58 (64.4%)	0.451
Lympho-vascular invasion present	13 (28.9%)	27 (30%)	0.894
Satellite lesions present	4 (8.9%)	8 (8.9%)	1.000
Tumor differentiation			0.075
Well	12 (26.7%)	19 (21.1%)	
Moderate	18 (40.0%)	14 (15.6%)	
Poor	3 (6.7%)	11 (12.2%)	
Edmondson-Steiner grade			0.297
I	2 (4.4%)	1 (1.1%)	
II	20 (44.4%)	32 (35.6%)	
III	9 (20.0%)	18 (20.0%)	
IV	0 (0.0%)	4 (4.4%)	
Resection margin involved	4 (8.9%)	8 (8.9%)	1.000
Resection margin width (mm)	5 (2.25-10.00)	3 (0.95-8.00)	0.043

Data are shown as median (interquartile range) or number (percentage)

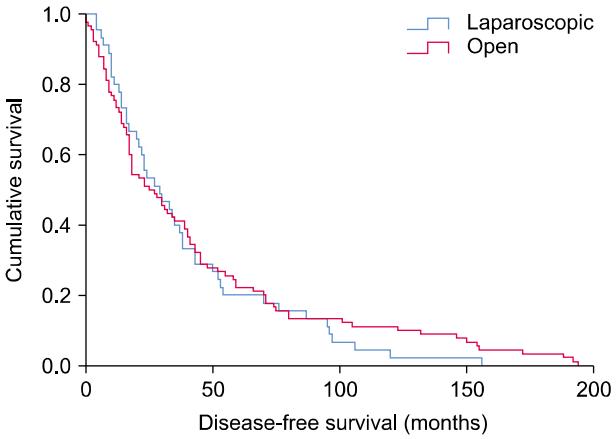

Fig. 1. Kaplan-Meier curve showing disease-free survival of hepatocellular carcinoma patients underwent laparoscopic versus open liver resection.

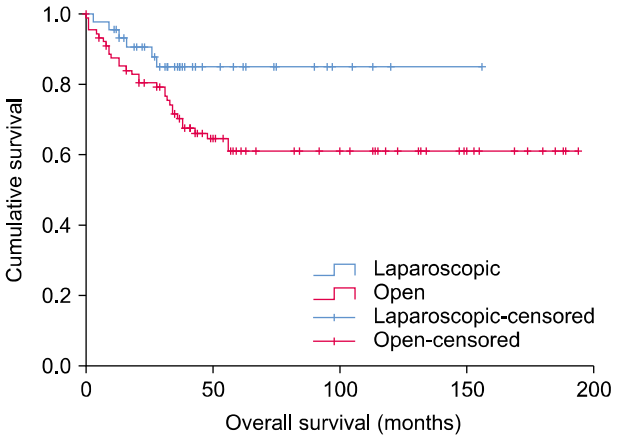

Fig. 2. Kaplan-Meier curve showing overall survival of hepatocellular carcinoma patients underwent laparoscopic versus open liver resection.

were 95.6%, 84.9%, and 84.9% in the LLR group, which compared favorably with the OH group (p=0.036) (Fig. 2).

The postoperative outcomes were shown in Table 3. There were two Clavien Dindo Grade III complications in the laparoscopic group. One patient suffered from duodenal perforation after laparoscopic right posterior sectionectomy, requiring two laparotomies. Another patient developed intra-abdominal collection after left hepatectomy and common bile duct exploration, which was managed by image-guided drainage. There were five post-operative mortalities in the OH group, all occurred in early stage of our hepatectomy learning curve. Two patients suffered from severe hospital-acquired pneumonia after open right hepatectomy and progressed into multi-organ failure. Three other patients developed progressive liver failure[12] after right hepatectomy, despite careful patient selection and maximal support.

DISCUSSION

Hepatectomy for patients with hepatocellular carcinoma remains a challenge in both the laparoscopic and open era. Most of the patients are hepatitis carrier with underlying liver cirrhosis. The associated portal hypertension, hypersplenism and thrombocytopenia imposes significant bleeding risks during parenchymal transection.[10] In our series, 62.2% of the patients had cirrhosis on histology, yet no significant difference was demonstrated in the intraoperative blood loss and transfusion rate between the LLR and open group. With the advances in technology and the improvement in the hemostasis method, laparoscopic liver resection can also be performed safely in cirrhotic patients. Literatures on the short-term outcomes of LLR over the past decades revealed less blood loss, shorter hospital stay and less complications.[14-21,24,25] Our study showed similar results, though the operating time was longer in the LLR group. The intraoperative blood loss was 500 ml compared with the 725 ml in open group, though the difference did not reach statistical significance. Pringle maneuver was prepared in every patient, but it was not routinely applied during parenchymal transection. Intermittent Pringle maneuver induces ischemic reperfusion injury to the normal liver tissue and their microvasculatures. It was shown to be a significant risk factor for perioperative morbidity and mortality independent of blood loss and transfusion.[26] The duration of Pringle maneuver was also an independent predictor of poor survival and tumor recurrence.[27-29] Therefore, Pringle maneuver was applied judiciously in our center, yet the intraoperatively blood loss was not adversely affected in the LLR. The longer operative time in the LLR group could be attributed to the high proportion of patients with cirrhosis in our series, parenchymal transection without Pringle maneuver and hence more difficult hemostasis.

In the Louisville Consensus Statement in 2008,[1] laparoscopic hepatectomy was recommended for tumors smaller than 5 cm. The potential invasion to major vessels, and the anticipated difficulties in achieving inflow or outflow control of the remnant liver might result in increased bleeding risk. Moreover, the large tumor size imposed challenge on retraction and exposure for meticulous dissection. Excessive tumor manipulation was associated with hematogenous dissemination of the tumor cells[30,31], resulting in potential negative influence on the oncological outcome of LLR. Since then, effort has been made to extend the indications to larger sized tumors. Numerous case reports and case series were published on the technical aspect of LLR.[32-38] With the magnified view and ability to reach the posterosuperior by flexible high definition video laparoscope, modification of the techniques, development of better dissecting tools and energy source that allows meticulous dissection of vascular and biliary structures[37-40], the hurdles in exposure and retraction can be overcome. Two single centered studies[41,42] had shown that LLR was still safe and feasible for tumors sized between 5-10 cm with comparable perioperative outcomes but with shorter hospital stay and less complications. The 1- and 3-year overall and disease-free survival rates of LLR were comparable to open hepatectomy. Therefore, in our center, we extended our selection criteria for LLR to tumor sized up to 7 cm. The short-term outcomes and long-term outcomes were shown to be not adversely affected. Nevertheless, the large tumor size posed additional difficulty in the LLR[43] and it should still be cautiously practiced in tertiary centers.

Technical aspects aside, the long-term oncological outcomes and disease-free survival are of utmost importance in determining the role of LLR in management of HCC. Several case matched analyses[44-46] were published, showing no significant difference in the 5-year overall survival and disease-free survival between LLR and OH, even in patients with cirrhosis. The 5-year overall survival and disease-free survival after LLR for HCC ranged from 50-75% and 24.0-45.6% respectively.[47-50] Our data also showed that the 5-year disease-free survival were comparable between LLR and OH. The patients in the LLR group and OH group had comparable tumor size, multiplicity and Edmundson-Steniner grading on pathological examination. The resection margin was significantly wider in the LLR group (5 mm vs. 3 mm, p=0.043). Similar results were reported in the literature, affirming that laparoscopic liver resection could be performed without compromising the resection margin with careful planning and frequent intraoperative sonographic assessment.

On the other hand, the 5-year overall survival for LLR was better than OH (84.9% vs. 61.1%, p=0.036) in our series. This could be attributed to the five perioperative mortalities in the OH group, which occurred all in the first

half of our hepatectomy experience.[9] Some of the post-operative complications, such as chest infection and pleural effusions, could be related to the increased trauma and stress induced by open surgical assess.

There were inherent shortcomings in this single-centered retrospective analysis. The relatively small sample size in our series might have underpowered the study results. Moreover, we included patients undergoing hepatectomies from 2000 to 2019. Though all the operations were performed by the same group of dedicated HPB surgeons, the surgical instruments and techniques matured over time. With gaining experience and overcoming the learning curve, the complexity of the operations increased over time. Therefore, propensity score matching was used to minimize the selection bias and effect of potential confounding covariates. Nonetheless, a properly conducted randomized controlled trial is still warranted in addressing the short term and long-term outcomes of laparoscopic hepatectomy in selected patients. The results of the ongoing ORANGE II PLUS trial[4] are much anticipated to provide unbiased evidence in this regard.

CONCLUSION

Laparoscopic liver resection is a safe treatment option for management of hepatocellular carcinoma, even in the presence of cirrhosis and large tumor size up to 7 cm. The intraoperative blood loss and complication rates are not adversely affected, while conferring a benefit of shorter hospital stay. The resection margin is not jeopardized. The oncological outcomes in terms of overall and disease-free survival are comparable with open hepatectomy.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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AUTHOR CONTRIBUTIONS

Conceptualization: KCC, YPY. Data Curation: FKMC. Formal analysis, Methodology: KMH, KCC. Writing - original draft: KMH. Writing - review and editing: KCC.

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