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Original Research

Laparoscopic Hepatectomy is a Feasible and Safe Choice for Primary Hepatocellular Carcinoma: A Retrospective Case-Control Study

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ABSTRACT

Introduction: Laparoscopic hepatectomy (LH) for hepatocellular carcinoma (HCC) is well known for its advantages, but its specific long-term outcomes are unknown. This study aimed to analyze the perioperative, short-term, and long-term outcomes between LH and open hepatectomy (OH) for patients with primary HCC who underwent LH during the developing period of LH in a single center.

Methods: This retrospective study included patients diagnosed with primary HCC who underwent hepatectomy between January 2013 and December 2019. The patients were divided into the LH (n = 63) and OH (n = 96) groups. Demographic and perioperative data were collected.

Results: A higher percentage of patients in the OH group underwent major resection (38.5% vs. 11.1%, $p < 0.001$). The operative time was 47 minutes shorter, and the intraoperative blood loss was 105 mL less in the LH group. The major postoperative complication rate (33.3% vs. 50.0%, $p = 0.05$) and the 90-day readmission rate (3.2% vs. 12.5%, $p = 0.048$) were lower in the LH group. The overall survival and disease-free survival were similar between the two groups.

Conclusions: LH is a feasible and safe alternative for primary HCC, with less blood loss, fewer major complications, and shorter postoperative hospital stay. LH does not worsen short- or long-term outcomes.

Keywords: Hepatocellular carcinoma, Laparoscopy, Short-term outcome, Long-term outcome, Feasible

Introduction

Hepatocellular carcinoma (HCC) was ranked the sixth most common neoplasm and the third leading cause of cancer death worldwide in 2020, with 905,677 diagnosed cases and 830,180 deaths [1]. Hepatectomy is one of the treatment options for HCC based on the Barcelona Clinic Liver Cancer strategy [2]. In the past, open hepatectomy (OH) was the only option for surgical intervention, but after the first laparoscopic hepatectomy (LH) was described in 1991 [3], LH has been applied gradually as a surgical alternative. Despite several favorable results for LH [4,5], this procedure has still not achieved widespread use [6]. Laparoscopic surgery, though complex, can be performed safely and efficaciously. However, difficulties in liver mobilization, hemorrhage control, loss of manual palpation, deeper surgical field, and intraoperative hazards are barriers to the generalized use of LH [7,8].

Although LH requires expert surgical ability, it has many advantages, including a smaller incision size, shorter operation time, lower transfusion rate, shorter hospital stay [9], and similar overall survival and disease-free survival compared to OH [4]. Therefore, LH is increasingly recommended for the treatment of HCC.

This study aimed to evaluate the perioperative and postoperative short- and long-term outcomes in patients diagnosed with primary HCC and who underwent LH during the developing period of LH in a single center.

Materials and Methods

Patient characteristics

This is a retrospective case-control study. The data were retrospectively collected from the medical records of 159 patients newly diagnosed with HCC and who received hepatectomy in Hualien Tzu Chi General Hospital, a tertiary referral center in eastern Taiwan, from January 2013 to December 2019. The preoperative diagnosis of HCC was based on the results of two sets of noninvasive dynamic imaging in high-risk groups with chronic hepatitis B, chronic hepatitis C, or cirrhosis with or without elevated alpha-fetoprotein (AFP). Postoperative HCC was confirmed by pathological examination of resected specimens in all patients. Patients with a diagnosis of recurrent HCC or synchronous malignancy were excluded. The patients were divided into the LH and OH groups. The criteria for inclusion of patients into the open or laparoscopic group depended on the surgeon's preference, including the age of patients, liver function, tumor size and location, distance to major vessels, and degree of portal hypertension. However, the preference would be adjusted when the skill of laparoscopic intervention became mature. Volumetric evaluation for the tumor was not routinely performed because it was not covered by the National Health Insurance of Taiwan, and most patients could not afford examination. We followed the Makuuchi criteria to decide the resection volume [10]. The medical records were retrospectively reviewed for demographic characteristics, perioperative variables, and follow-up outcomes. The overall median follow-up duration was 29 months.

Definitions

Definitions were adopted from the Brisbane 2000 Guidelines for liver anatomy [11]. Resection of $\geq$3 segments was defined as major resection, and that involving < 3 segments was defined as minor resection. The Clavien–Dindo classification was applied to grade postoperative complications [12]. Major complication was defined as $\geq$ class 3 complications. The definition of bile leakage and posthepatectomy liver failure was adopted from the International Study Group of Liver Surgery [13, 14]. The unfavorable location of the tumor was defined as superior-posterior segments (S4a, S7, and S8).

Surgical techniques

Open hepatectomy

1. Skin incision was made with either reverse L or reverse T incision.
2. Liver mobilization and intraoperative sonography to localize the tumor location were performed.
3. The Pringle's maneuver with hepatoduodenal ligament wrapping was prepared.

4. Active and cycling Pringle maneuver was routinely performed to reduce blood loss and possible hepatocyte protection before bleeding during the parenchymal transection.
5. Parenchymal transection was performed by electrocautery, ultrasonic device, or vessel sealing device under performing the Pringle maneuver.
6. After completing the liver resection, meticulous hemostasis for the resection plane and the placement of a closed drainage tube was performed.
7. Close the fascia and repair the skin.

Laparoscopic hepatectomy

1. Skin incision with either reverse L or reverse T incision was made.
2. Liver mobilization and intraoperative sonography to localize the tumor location were performed.
3. The Pringle's maneuver with hepatoduodenal ligament wrapping was prepared.
4. Active and cycling Pringle maneuver was routinely performed to reduce blood loss and possible hepatocyte protection before bleeding during the parenchymal transection.
5. Parenchymal transection was performed by electrocautery, ultrasonic device, or vessel sealing device under performing the Pringle maneuver.
6. After completing the liver resection, meticulous hemostasis for the resection plane and the placement of a closed drainage tube was performed.
7. Close the fascia and repair the skin.

Statistical analysis

The chi-square test was used to analyze categorical variables, which are presented as numbers and percentages. The Kolmogorov–Smirnov test was used to check the normality of continuous variables. Normally distributed continuous variables are presented as means with standard deviations. Nonnormally distributed continuous variables are presented as medians with interquartile ranges and were analyzed with the Mann–Whitney's *U* test. The Kaplan–Meier curve with the log-rank test was used for the survival analysis. SPSS for MAC ver. 26 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the patients are presented in Table 1. The study included 96 patients (60.3%) in the OH group and 63 (39.6%) in the LH group. The mean patient age was slightly higher in the LH group (67 years) than that in the OH group (64 years) ($p = 0.156$). Most of the patients were male, and the comorbidity rates, including diabetes mellitus, hypertension, and coronary artery disease, were not significantly different between the two groups. Especially, more patients in the LH group were Child–Pugh class A (98.4% vs. 88.9% in the OH group, p = 0.026). The Model for End-stage Liver Disease-Na score was similar in both groups (LH vs. OH: 8 vs. 7, $p = 0.229$). Most patients in both groups were diagnosed with viral hepatitis (LH: 84.1%, OH: 89.6%). The preoperative 15 min retention rate for indocyanine green was 13.3% in the LH group and 9.1% in the OH group ($p = 0.748$).

Perioperative outcomes and pathological findings

More patients in the OH group presented with unfavorable tumor location (56.3% vs. 30.2%, $p = 0.002$). More patients in the OH group received major hepatectomy (38.5% vs. 11.1%, $p < 0.001$). The median operation time was significantly shorter in the LH group than in the OH group (208 minutes vs. 255 minutes, $p = 0.025$). The intraoperative blood loss was significantly less in the LH group than in the OH group (250.0 mL vs. 355.0 mL, $p = 0.005$). The duration of the Pringle maneuver was significantly shorter in the LH group (59.0 minutes vs. 72.9 minutes, $p = 0.021$).
In particular, more patients in the LH group underwent resection for solitary tumor (90.5% vs. 76.0%, $p = 0.022$). The tumor size was significantly smaller in the LH group than in the OH group (3.0 cm vs. 4.0 cm, $p = 0.001$). The margin distance and the differentiation grade showed no significant differences between the two groups.

Postoperative outcomes

The major complication rate was lower in the LH group than that in the OH group (4.8% vs. 9.3%, $p = 0.050$). In the OH group, three patients experienced grade IIIa complications (one had grade B bile leakage and two had pleural effusion); two patients experienced grade IIIb complications (one had grade C bile leakage and the other had deep surgical site infection); two patients experienced grade IVa complication (one had posthepatectomy liver failure and the other had cardiogenic shock); one patient experienced grade IVb complication as acute kidney injury and posthepatectomy liver failure; one patient experienced grade V complication as posthepatectomy liver failure and passed away on postoperative day 39. In the LH group, one patient each experienced grade IIIa complication as superficial surgical site infection; grade IVa complication as acute kidney injury; grade IVb complication as septic shock and acute kidney injury. No grade V complications developed in the LH group.

The postoperative hospital stay was significantly shorter in the LH group (7 days vs. 11 days, $p < 0.001$). The 90-day readmission rate was significantly less in the LH group (3.2% vs. 12.5%, $p = 0.048$) (Table 3). However, the 90-day mortality showed no significant difference between the two groups (1.6% for LH vs. 5.2% for OH, $p = 0.241$). No significant difference was noted in the 24-month overall survival (85.0% vs. 77.6%, $p = 0.317$) and disease-free survival (89.3% vs. 85.2%, $p = 0.293$) rates between the LH and OH groups (Figures 1A, B). The ratio of LH increased gradually and exceeded 50% after 2017 (Table 4).

Discussion

Before the LH procedure was first described in 1991, OH was the only surgical treatment for HCC [3]. The first feasibility study for LH concluded that LH was feasible and safe in patients with left- and right-sided peripheral lesions who required limited resection [5]. The first consensus regarding the indications for LH was the Louisville statement (in 2008), which comprised (1) solitary lesion, (2) tumor size ≤ 5 cm, (3) tumor location in peripheral liver segments 2–6; LH was indicated for only left lateral sectionectomy, anterior segmentectomies, or wedge resection [15]. Thereafter, the indications for LH increased until the Morioka consensus in 2014, which stated that there were no definite indications for LH [16]. According to the previously stated indications for LH from the Louisville statement, we started LH for minor resections with smaller tumors before performing major resections during the developed period in our institution. The ratio of LH to total cases gradually increased and exceeded 50% after 2017. The short- and long-term outcomes did not worsen during the developing period of LH in our institute, and we attributed this outcome to the restricted indications for LH. After 2019, we have continuously extended the criteria for LH for more difficult HCC, and we expect similar outcomes as noted in this study.

The benefits of LH possibly come from the following concepts: (1) the caudal approach may lead to better exposure of the right adrenal gland, inferior vena cava, and Glissonean pedicle at the hilar plate and is different from the OH approach [15,16]; (2) pneumoperitoneum with an intra-abdominal pressure of 10–14 mmHg and low central venous pressure anesthesia may decrease blood loss from the backflow of the hepatic vein; (3) the patient position during LH may shift to the left lateral decubitus position for right posterior sectionectomy and might make the transection plane above the level of the inferior vena cava, which can decrease backflow from the hepatic vein [16]. Due to the above concepts, LH seems to have benefits, comprising reduced intraoperative blood loss, lower incidence of complications, and shorter hospital stay [15,18]. In our study, the above outcomes were noted, with less blood loss, lower major complications rate, and shorter postoperative hospital stay. Moreover, due to the better exposure and less backflow from the hepatic vein, which allowed an undisturbed resection field, a shorter duration of the Pringle maneuver and shorter operative time with LH were noted in this study.

Some studies consider high-volume centers to be institutions where more than 20–50 liver resections are performed yearly [19-21]. However, a study indicated that high-volume centers do not appear to influence in-hospital mortality [21]. Although our study enrolled only 159 patients in 7 years and can be regarded as a borderline high-volume center, compared to OH, LH will not compromise postoperative complications, in-hospital mortality, and 90-day mortality, with lower 90-day morbidity. In this study, as long-term outcomes in the LH group, the 1- and 2-year overall survival rates were 88.7% and 85.0%, and the 1- and 2-year disease-free survival rates were 94.9% and 89.3%, respectively. Compared with previous studies of LH for HCC, the 1- and 3-year overall survival rates were 88%–100% and 73.4%–94.5%, respectively. The 1-year disease-free survival rate was 71.9%–99%, and the 3-year disease-free survival rate was 40.0%–91.2% [22, 23]. As opposed to other high-volume centers, the long-term outcomes of LH for HCC were not compared even during the developed period in our study.

This study still has some limitations. First, it was a retrospective and nonrandomized study, which may have led to observation bias. Second, only oncological data were collected, and no short- or long-term data on the quality of life, such as the wound pain scale and incisional abdominal wall hernia, were available. Third, the study had a relatively small sample size and was conducted in a single center, which may limit the generalizability of our findings to other centers.

Conclusions

LH will be an alternative to OH for primary HCC, with less blood loss, fewer major complications, and shorter postoperative hospital stay. LH will not compromise short-term morbidity/mortality or long-term overall and disease-free survival. LH appears to be a feasible and safe choice for primary HCC.

Figures

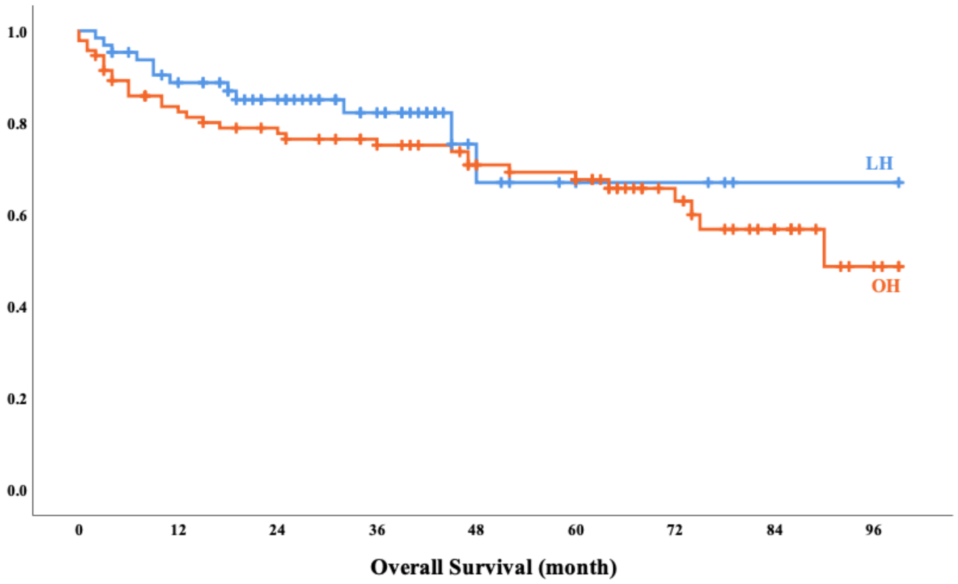

Figure 1A: Kaplan–Meier curve of the overall survival in the LH and OH groups. The 12- and 24-month overall survival rates were 88.7% and 85.0%, respectively, in the LH group and 82.3% and 87.6%, respectively, in the OH group. Log-rank test, *p* = 0.317. LH, laparoscopic hepatectomy; OH, open hepatectomy.

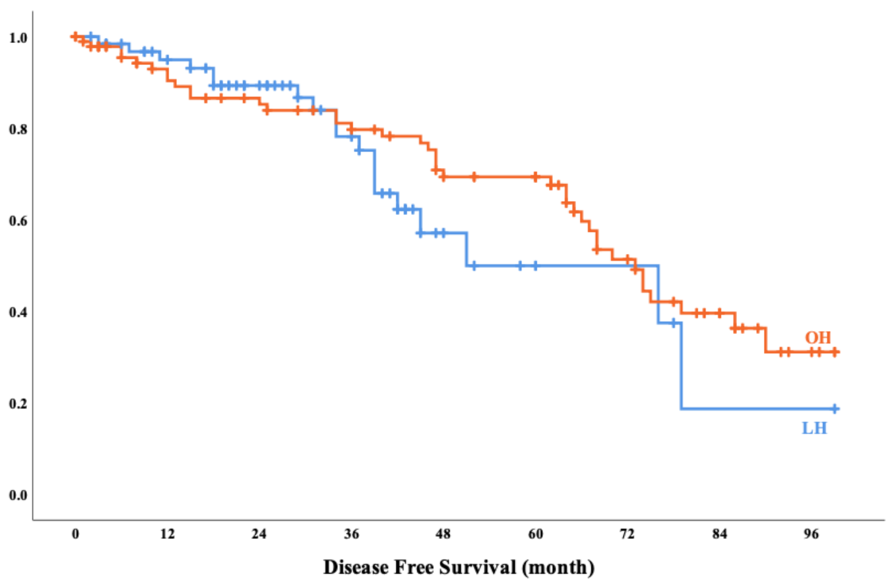

Figure 1B: Kaplan–Meier curve of disease-free survival in the LH and OH groups. The 12- and 24-month disease-free survival rates were 94.9% and 89.3%, respectively, in the LH group and 92.9% and 85.2%, respectively, in the OH group. Log-rank test, *p* = 0.293. LH, laparoscopic hepatectomy; OH, open hepatectomy.

Tables

Table 1. Patient characteristics.

Characteristics	Whole cohort (n = 159)	OH (n = 96)	LH (n = 63)	*p*-value
Age (years) (mean ± SD)	65 ± 10	64 ± 11	67 ± 9	0.156
Sex, male (%)	75.5 (120/159)	72.9 (70/96)	79.4 (50/63)	0.452
BMI (kg/m^2) (mean ± SD)	25.2 ± 3.6	25.0 ± 3.7	25.7 ± 3.6	0.687
Comorbidity (%)				
DM	35.8 (57/159)	29.2 (28/96)	46.3 (29/63)	0.042
HTN	45.3 (72/159)	41.7 (40/96)	51.0 (32/63)	0.329
CAD	6.3 (10/159)	6.2 (6/96)	6.3 (4/63)	0.98
FEV1 (%) (median, IQR)	90.6 (78.8,102.2)	87.3 (74.7,102.0)	90.6 (79.9,95.9)	0.043
FEV1/FVC (%) (median, IQR)	79.3 (72.4,83.5)	78.8 (70.3,82.7)	77.9 (73.2,83.0)	0.244
LVEF (%) (median, IQR)	75.3 (69.3,79.8)	73.9 (66.1,77.8)	75.4 (69.8,79.7)	0.047
Child–Pugh classification stage A (%)	92.8 (141/152)	88.9 (80/90)	98.4 (61/62)	0.026
MELD-Na score (median, IQR)	8 (7,9)	7 (7,8)	8 (10,11)	0.229
ICG-15 (%) (median, IQR)	10.6 (5.2,20.1)	9.1 (4.4,16.3)	13.3 (8.1,16.0)	0.748
Viral hepatitis (%)	87.4 (139/159)	89.6 (86/96)	84.1 (53/63)	0.273

OH, open hepatectomy; LH, laparoscopic hepatectomy; SD, standard deviation; DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; MELD-Na, Model for End-stage Liver Disease-Na; IQR, interquartile range; ICG, indocyanine green.

Table 2. Perioperative results and pathology findings.

Characteristics	**Whole cohort (n = 159)**	**OH (n = 96)**	**LH (n = 63)**	***p*-value**
Tumor location (%)				<0.001
S1	1.3 (2/159)	2.1 (2/96)	0.0 (0/63)	
S2	6.3 (10/159)	4.2 (4/96)	9.5 (6/63)	
S3	13.8 (22/159)	8.3 (8/96)	22.2 (14/63)	
S4a	3.8 (6/159)	6.3 (6/96)	0.0 (0/63)	
S4b	6.3 (10/159)	10.4 (10/96)	0.0 (0/63)	
S5	14.5 (23/159)	14.6 (14/96)	14.3 (9/63)	
S6	11.9 (19/159)	4.2 (4/96)	23.8 (15/63)	
S7	15.7 (25/159)	15.6 (15/96)	15.9 (10/63)	
S8	26.4 (42/159)	34.4 (33/96)	14.3 (9/63)	
Unfavorable location of the tumor (%)	45.9 (73/159)	56.3 (54/96)	30.2 (19/63)	0.002
Major resection (%)	27.7 (44/159)	38.5 (37/96)	11.1 (7/63)	<0.001
Operative time (min) (median, IQR)	248 (181, 340)	255 (195,348)	208 (167,372)	0.025
Pringle maneuver (%)	76.7 (122/159)	81.3 (78/96)	69.8 (44/63)	0.125
Pringle duration (min) (median, IQR)	72.0 (44.8, 101.0)	72.9 (55.0, 100)	59.0 (31, 93.5)	0.021
Blood loss (mL) (median, IQR)	300 (100, 900)	355 (150,730)	250 (125,815)	0.005
Intraoperative transfusion (%)	9.4 (15/159)	10.4 (10/96)	7.9 (5/63)	0.783
Single tumor (%)	81.8 (130/159)	76.0 (73/96)	90.5 (57/63)	0.022
Size (cm) (median, IQR)	3.5 (2.5, 5.5)	4.0 (3.0, 7.5)	3.0 (2.5, 4.2)	0.001
Margin (cm) (median, IQR)	0.7 (0.2, 1.2)	1.0 (0.2, 1.5)	0.5 (0.2, 0.9)	0.049
Ishak score (median, IQR)	4 (1, 6)	3 (0, 6)	5 (3, 5)	0.436

OH, open hepatectomy; LH, laparoscopic hepatectomy; IRQ, interquartile range.

Table 3. Postoperative results.

Characteristics	Whole cohort (n = 159)	OH (n = 96)	LH (n = 63)	*p*-value
Complications (%)	43.4 (69/159)	50.0 (48/96)	33.3 (21/63)	0.050
1+2	35.8 (57/159)	40.7 (39/96)	28.5 (18/63)	
3a	2.5 (4/159)	3.1 (3/96)	1.6 (1/63)	
3b	1.3 (2/159)	2.1 (2/96)	0.0 (0/63)	
4a	1.9 (3/159)	2.1 (2/96)	1.6 (1/63)	
4b	1.3 (2/159)	1.0 (1/96)	1.6 (1/63)	
5	0.6 (1/159)	1.0 (1/96)	0.0 (0/63)	
Postoperative hospital stay (days) (median, IQR)	8 (7, 12)	11 (9, 14)	7 (6, 10)	<0.001
90-day readmission (%)	8.8 (14/159)	12.5 (12/96)	3.2 (2/63)	0.048
90-day mortality (%)	3.8 (6/159)	5.2(5/96)	1.6 (1/63)	0.241

OH, open hepatectomy; LH, laparoscopic hepatectomy; IRQ, interquartile range.

Table 4. Distribution of hepatectomy by year.

Year	Whole cohort (n)	OH (%, n)	LH (%, n)
2013	25	88.0 (22/25)	12.0 (3/25)
2014	32	78.1 (28/32)	21.9 (4/32)
2015	18	83.3 (15/18)	16.7 (3/18)
2016	15	86.7 (13/15)	13.3 (2/15)
2017	25	40.0 (10/25)	60.0 (15/25)
2018	25	16.0 (4/25)	84.0 (21/25)
2019	19	21.1 (4/19)	78.9 (15/19)

OH, open hepatectomy; LH, laparoscopic hepatectomy.

Abbreviations and Symbols

AS, abdominal surgery; CAD, coronary artery disease; DM, diabetes mellitus; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCC, hepatocellular carcinoma; HTN, hypertension; ICG, indocyanine green; LH, laparoscopic hepatectomy; LVEF, left ventricular ejection fraction; OH: open hepatectomy.

Disclosure Policy

The authors declare that there are no conflicts of interest regarding the publication of this article.

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