

Short-term Outcomes of Laparoscopic vs. Open Hepatectomy for Primary Hepatocellular Carcinoma: A Prospective Comparative Study*

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Summary: Laparoscopic hepatectomy (LH) is a newly developed technique associated with advantages as open surgery, but the study on outcome of liver function recovery was scarce. This preliminary report was aimed to comparatively assess the short-term outcomes between LH and open hepatectomy (OH) for primary hepatocellular carcinoma (PHC). This study retrospectively analyzed the demographic data and short-term outcomes of 81 patients who underwent LH or OH for the primary treatment of PHC between Oct. 2017 and May 2018 at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (China). A total of 81 PHC patients who received major liver resection were enrolled. There were 38 (47%) patients in the LH group and 43 (53%) patients in the OH group. The operative time was significantly longer (373.53 ± 173.38 vs. 225.43 ± 55.08 , $P < 0.01$), and hospital stay (17.34 ± 5.93 vs. 21.70 ± 6.89 , $P = 0.003$), exhaust time (2.32 ± 0.62 vs. 3.07 ± 0.59 , $P < 0.01$) and defecation time (2.92 ± 0.78 vs. 3.63 ± 0.58 , $P < 0.01$) were significantly shorter in LH group than in OH group. The recovery of liver function was significantly faster in LH group, including higher serum albumin ($P = 0.002$), higher ratio of albumin/globulin ($P = 0.029$) and lower direct bilirubin ($P = 0.001$) than in OH group. It is suggested that LH can serve as a fast recovery and cheap surgical procedure in the treatment of PHC, which is safe and feasible.

Key words: laparoscope; open hepatectomy; primary hepatocellular carcinoma; short-term outcomes; prospective comparative study

Primary liver cancer is one of the most common malignant tumors in clinical practice and is the leading cause of death worldwide^[1, 2]. Liver cancer treatments are developing rapidly, including local therapy, targeted system therapy, new technologies of internal and external radiotherapy and liver transplantation^[3]. However, the main treatment for primary liver cancer is partial hepatectomy, which can be divided into two surgical methods, laparoscopic hepatectomy (LH) and

open hepatectomy (OH).

After the introduction of laparoscopic surgery in the early 1990s, the use of LH for the treatment of liver tumors increased exponentially over the past two decades^[4, 5]. Numerous studies have confirmed the safety and feasibility of LH. Compared with OH, LH has the advantages of high body surface aesthetics, less intraoperative blood transfusion, less tissue damage, less pain for patients, and shorter hospital stay^[6-8]. However, LH is still a challenging method for surgeons. Due to the difficulty of surgical techniques in bleeding control, LH for primary liver cancer is limited to a few institutions.

Although LH is becoming more and more popular, retrospective studies have been the main focus of relevant studies on LH and OH. Several studies have linked LH to reduce blood loss and shorter hospital stays. However, the present study mainly focused on surgical outcomes, complications, and rehabilitation

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of liver function with little attention before. It's a prospective observational study conducted to compare the postoperative bleeding, hospital stay, liver function and complications of LH and OH, and to further discuss the safety and efficacy of LH and OH in the treatment of liver cancer.

1 MATERIALS AND METHODS

1.1 Patient Selection

The PHC patients admitted to the Department of Hepatobiliary Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, between October 2017 and May 2018 who met the following criteria were enrolled in this study: regardless of age or gender; normal vital organ function; the ability to tolerate general anesthesia; a tumor diameter of <10 cm on imaging; no tumor thrombus in the portal vein, hepatic vein, inferior vena cava or bile duct; no extrahepatic metastasis; Child-Pugh grade A or B; no active hepatitis. Patients were excluded with a severe organic disease or hepatic cirrhosis, or a conversion from a laparoscopic to an open surgery.

Eighty-one patients were divided into two groups [LH group ($n=38$) and OH group ($n=43$)] according to their hospital administration sequence. The study was approved by the institutional review board of the hospital (No. WHUH2018S002) and registered in the International Clinical Trial Registry (No. NCT03585166).

1.2 Surgical Procedures

1.2.1 LH Procedures This procedure was performed according to the Chinese expert consensus on laparoscopic hepatectomy^[9]. Briefly^[10], patients were placed in left semi-decubitus position, and a total intravenous general anesthesia was performed. Intra-abdominal pressure was maintained at 13–15 mmHg (1 mmHg=0.133 kPa). One 10-mm trocar was inserted above the umbilicus for camera use and other four trocars were usually used for hepatic anatomy. The vessel and parenchyma tissue were dissected by harmonic scalpel (Ethicon Endo-Surgery, USA) and laparoscopic cavitron ultrasonic surgical aspirator (Valleylab, USA). Hem-o-lock clips (Weck Surgical Instruments, USA) were used for vessels (≥ 5 mm in diameter). Intraoperative ultrasonography (Toshiba, Japan) was used to identify the location of major intrahepatic ducts and the size of the tumor, including their relationships, and to search for any metastatic site or tumor thrombus^[11].

1.2.2 OH Procedures The same anesthesia with LH was performed. The patients were placed in supine position and the laparotomy was performed through right subcostal incision. Cavitron ultrasonic surgical aspirator was used for vessel and parenchyma tissue

dissection. Bipolar electrocoagulation was applied for intraoperative hemostasis.

1.3 Postoperative Care

Postoperatively, all patients were taken off by the same care and monitoring. Liver function tests and routine blood tests were conducted at 1st, 3rd and 7th day postoperation. When the drainage fluid was serous and in the absence of bile leakage, the abdominal drainage tube was removed. Also, an ultrasound imaging was usually performed before discharge.

1.4 Statistical Analysis

Dichotomous data are presented as number and percentages, whereas continuous data are presented as mean and standard deviation (SD)^[12]. Dichotomous data were compared by the χ^2 test and Fisher's exact test, and continuous data were compared by Student's t test. Intergroup comparison was done by repeated measurement variance analysis. SPSS software (SPSS v9.0) was used for data analysis and a statistically significant difference was considered for a value of $P < 0.05$ ^[13].

2 RESULTS

2.1 Characteristics of Patients Included

The characteristics of 81 patients (38 undergoing LH vs. 43 undergoing OH) included are summarized in table 1. Data for age, sex, body mass index (BMI), hepatitis B positive rate, alpha fetoprotein positive rate and Child-Pugh grade were collected. No significant differences were found between the two groups among these factors.

2.2 Intraoperative and Postoperative Outcomes

Intraoperative data of the two groups are shown

Table 1 Characteristics of patients included

Parameters	LH group	OH group	t/χ^2	$P^{\#}$
Age (years)	53.95±10.61	54.00±9.98	-0.023	0.982
Gender (%)				
Female	5 (13.16)	7 (16.28)	0.156	0.693 [‡]
Male	33 (86.84)	36 (83.72)		
BMI	23.32±3.09	23.81±2.86	-0.732	0.466
Tumor size (cm)	4.99±2.70	5.73±2.54	-1.278	0.205
Tumor type				
Single	28 (73.68)	24 (55.81)	2.803	0.094 [‡]
Multiple	10 (26.32)	19 (44.19)		
HBsAg				
Positive	27 (71.05)	38 (88.37)	3.817	0.051 [‡]
Negative	11 (28.95)	5 (11.63)		
AFP				
Positive	15 (39.47)	25 (58.14)	2.812	0.094 [‡]
Negative	23 (60.53)	18 (41.86)		
Child-Pugh grade				
A	35 (92.11)	37 (86.05)		0.490 [§]
B	3 (7.89)	6 (13.95)		

[†]Student's t test, [‡] χ^2 test, [§]Fisher's exact test. AFP: positive >8.78 $\mu\text{g/L}$, and negative ≤ 8.78 $\mu\text{g/L}$

Table 2 Perioperative outcomes of the laparoscopic vs. open hepatectomy groups

Parameters	LH group	OH group	t/χ^2	P^a
Incision length (cm)	4.83±1.86	21.47±3.85	-25.179	<0.001
Operating time (min)	373.53±173.38	225.43±55.08	5.041	<0.001
Number of patients with intra-operative bleeding* (%)				
Yes	17 (44.74)	19 (44.19)	0.002	0.960 [‡]
No	21 (55.26)	24 (55.81)		
Intra-operative bleeding (mL)	679.41±748.97	691.67±468.49	-0.058	0.954
Number of patients with intraoperative blood transfusion (%)				
Yes	8 (39.47)	16 (41.86)	2.526	0.112 [‡]
No	30 (60.53)	27 (58.14)		
Intra-operative blood transfusion (mL)	831.25±351.46	787.50±256.58	0.348	0.731
Exhaust time (days)	2.32±0.62	3.07±0.59	-5.589	<0.001
Defecation time (days)	2.92±0.78	3.63±0.58	-4.651	<0.001
Use of analgesia (days)	3.68±1.56	6.56±3.03	-5.265	<0.001
Ambulation time (days)	3.92±0.88	5.21±1.52	-4.584	<0.001
Abdominal drainage (days)	7.61±2.86	12.16±4.40	-5.588	<0.001
Hospital stay (days)	17.34±5.93	21.70±6.89	-3.029	0.003
Hospitalization cost (RMB, yuan)	77848.67±22836.10	92239.63±23074.97	-2.815	0.006
Number of patients with post-operative blood transfusion (%)				
Yes	1 (2.63)	8 (18.60)		0.032 [§]
No	37 (97.37)	35 (81.40)		
Post-operative blood transfusion time (days)	5	3.13 ± 2.90	0.61	0.561
Post-operative blood transfusion (mL)	2200	2150.00±1376.33	0.034	0.974
Number of patients with post-operative albumin transfusion (%)				
Yes	10	26	9.528	0.002 [‡]
No	28	17		
Post-operative albumin transfusion time (days)	3.90±4.31	4.65±3.33	-0.56	0.579
Post-operative albumin transfusion (g)	69.00±55.67	76.15±53.00	-0.358	0.723

[‡] χ^2 test, [§]Student's *t* test, [§]Fisher's exact test. *Number of patients with intra-operative bleeding

in table 2. The incision length was significantly shorter and operative time were significantly longer in LH group than in OH group (both $P<0.01$). No significant difference was found in the blood loss and blood transfusion between two groups.

Postoperative outcomes showed that the hospital stay was significantly shorter in LH group than in OH group (17.34±5.93 days vs. 21.70±6.89 days; $P=0.003$). The exhaust and defecation time was significantly shorter in LH group than in OH group (both $P<0.01$). The proportion of patients with transfusion of blood ($P=0.032$) and albumin ($P=0.003$) was significantly lower in LH group than in OH group. The overall cost of hospitalization was significantly cheaper in LH group (77848.67±22836.10 yuan RMB) than in OH group (92239.63±23074.97 yuan RMB; $P=0.006$). The incidence of wound infection ($P<0.01$), pleural effusion ($P=0.013$) and ascites ($P=0.007$) in LH group were significantly lower than those in OH group. The incidence of total complications was also lower in LH group than in OH group ($P<0.01$) (table 3).

2.3 Liver Function

The liver function of patients is summarized in table 4. Preoperatively, no significant difference was present in liver function between the two groups. Postoperatively, serum levels of aspartate

aminotransferase (AST) ($P=0.021$), total bilirubin ($P=0.009$) and direct bilirubin ($P=0.001$) were significantly lower at 7th day in LH group than in OH group. The serum levels of albumin were significantly higher at 3rd and 7th day postoperatively in LH group than in OH group. The intergroup analysis revealed that there was significant difference in the liver function between the two groups, including aspartate aminotransferase (AST), albumin and bilirubin ($P<0.01$).

3 DISCUSSION

Hepatectomy remains the first choice for treatment of PHC^[14, 15]. LH is becoming more and more accepted in the treatment of malignant liver tumors. However, despite the progress made in LH, currently, less than 15% of liver resection operations in many countries have adopted minimally invasive techniques^[16]. In 2008, the first world consensus conference on laparoscopic hepatectomy was organized, which indicated that LH is a safe and effective method^[17]. With the rapid development of laparoscopic technology, laparoscopic surgery has been gradually applied in the treatment of primary liver cancer, and has become the standard surgery instead of OH. However, due to the liver function, anatomical location, and its particularity of

Table 3 The postoperative complications of LH group vs. OH group

Parameters	LH group	OH group	χ^2	$P^{\#}$
Ascites	2	12	7.235	0.007
Pleural effusion	2	11	6.181	0.013
Venous thrombosis of the lower extremities	1	1		1
Incision infection	1	12	9.565	0.002
Bile leakage	0	1		1
Bleeding	1	8	5.211	0.032
Total	5	25	17.503	<0.001*

* χ^2 test, $\#$ Fisher's exact test

Table 4 The liver function of LH group vs. OH group

Parameters	LH group	OH group	F	P^{\dagger}	t	$P^{\#}$
ALT (U/L)						
Pre-operation	32.32±24.61	45.93±61.97	–	–	–1.268	0.209
Post-operation						
1st day	301.16±268.86	345.81±241.18			0.788	0.433
3rd day	285.00±361.06	343.09±239.92	1.210	0.275	–0.862	0.391
7th day	83.00±71.13	103.88±75.5			–1.276	0.206
AST (U/L)						
Pre-operation	31.03±16.05	38.09±18.34	–	–	–1.834	0.070
Post-operation						
1st day	324.47±236.79	435.56±320.43			–1.755	0.083
3rd day	137.26±163.55	184.00±140.23	4.218	0.043	–1.385	0.170
7th days	34.82±12.59	47.79±33.23			–2.375	0.021
Albumin (g/L)						
Pre-operation	40.41±4.84	39.19±5.34	–	–	1.073	0.286
Post-operation						
1st day	31.76±5.18	30.13±5.59			1.360	0.178
3rd day	33.95±4.04	29.79±4.20	10.089	0.002	4.532	0.000
7th day	35.67±3.97	32.21±4.62			3.591	0.001
Globulin (g/L)						
Pre-operation	25.09±4.65	26.01±5.46	–	–	–0.812	0.419
Post-operation						
1st day	20.98±3.62	22.13±5.53			–1.089	0.279
3rd day	21.43±3.97	22.37±5.67	0.856	0.358	0.851	0.397
7th day	24.37±4.45	24.75±5.64			–0.338	0.736
Albumin and globulin ratio						
Pre-operation	1.66±0.35	1.57±0.36	–	–	1.190	0.238
Post-operation						
1st day	1.56±0.37	1.43±0.38			1.516	0.133
3rd day	1.62±0.36	1.40±0.39	4.922	0.029	2.641	0.010
7th day	1.50±0.29	1.37±0.37			1.719	0.090
Total bilirubin (μmol/L)						
Pre-operation	14.26±5.83	15.77±7.13	–	–	–1.035	0.304
Post-operation						
1st day	22.16±12.02	26.78±15.55			1.481	0.143
3rd day	20.39±10.4	26.44±18.92	4.352	0.040	–1.752	0.084
7th day	14.74±5.84	20.15±11.56			–2.707	0.009
Direct bilirubin (μmol/L)						
Pre-operation	5.16±2.74	6.45±4.04	–	–	–1.651	0.103
Post-operation						
1st day	8.24±4.22	12.45±7.28			3.226	0.002
3rd day	8.48±4.74	13.23±9.41	11.905	0.001	–2.919	0.005
7th day	6.08±2.89	10.45±7.38			–3.581	0.001

\dagger repeated measurement variance analysis, $\#$ Student's t test

physiological structure, it's difficult to expose lesions under LH and it's of a high risk of bleeding, all of which would increase the difficulty of laparoscopic surgery and must be performed by experienced surgeons^[18-20]. Consequently LH is not as widely performed as laparoscopic gastrointestinal surgery. At present, the main focus of the debate in this field is the clinical efficacy and safety of surgery. This study is a preliminary report on the safety and feasibility of LH as a rapid recovery surgery method for PHC.

In this study, the incision length was significantly shorter and hospitalization cost was significantly less in LH than in OH. The exhaust and defecation time, analgesia time, ambulation time, hospitalization time and abdominal drainage tube indwelling time after LH were all shorter than those after OH. Previous studies have shown that patients could rehabilitate faster after LH surgery and have shorter postoperative analgesia time, earlier activities and shorter hospital stay^[21]. As compared with OH, LH can cause less tissue damage. Meanwhile, no large abdominal incision is needed in the operation, which can avoid abdominal wall damage, interruption of blood supply to large blood vessels and exposure of abdominal organs, reducing exogenous stimulation to tissues and organs, all these could decrease the stress response^[19, 20]. Less abdominal ascites, small wound surface and reduced stress response are conducive to relieve the direct improvement of postoperative pain, improve the bowel movement and shorten the abdominal drainage time. The rapid recovery of the digestive system was beneficial to improve the nutritional status of patients. It was reported^[22, 23] that laparoscopic surgery has a much more expensive hospitalization cost than traditional open surgery, which may be due to the relatively new developed devices applied in the LH such as LigaSure, high-definition laparoscope, and endoscopic stapler. On the contrary, in this study, we found that the cost of LH (14 390 yuan RMB) was significantly less than that of OH group on average, which may be due to the reform of the Chinese medical system^[24] that drastically cuts the medical costs of the drugs and medical instruments. In addition, the longer hospital stay for OH, the higher the incidence of complications, the higher requirement for blood and albumin transfusion, and the larger hospitalization cost. Some studies suggested that LH may spend more operation time^[25]. Whereas, some other studies hold a different view that the operation time of LH and OH was not significantly different^[26], but in this study, unclear tumor margin was the main factor affecting the longer operation time of LH. On the other hand, because of the anatomical and physiological characteristics of the liver, the deep position of the liver and the double blood supply of the portal vein and hepatic artery are present, making it difficult to expose liver lesions under laparoscopy. Therefore, more time

is needed to perform LH.

In this study, there were no statistically significant differences in preoperative ALT, AST, albumin, globulin, the ratio of albumin to globulin and total bilirubin between the two groups. After LH, AST, total bilirubin and direct bilirubin levels were significantly lower in LH group than those in OH group ($P < 0.05$). The albumin level and the ratio of albumin to globulin after LH surgery were significantly higher than those in OH group ($P < 0.05$). Studies have reported that liver injury in LH is milder and ascites in patients is less, which is conducive to the recovery of liver function in patients. In this study, the recovery of liver function after LH was faster than that after OH due to less damage to the liver by LH. When subjected to trauma or stress, the liver would enhance albumin synthesis and release albumin into the blood, but damage that is severe or exceeds liver compensatory capacity may result in insufficient albumin synthesis^[27]. Obviously more mild injury, earlier feeding time, and lower incidence of postoperative complications all contribute to the recovery of liver function. Early feeding can not only supplement exogenous albumin, but also promote blood circulation in hepatic portal vessels, and facilitate the intestinal absorption of nutrients which can directly enter into the liver and participate in its repair^[28]. The incidence of complications after LH such as ascites, pleural effusion, infection of incision, bleeding was significantly lower than that after OH ($P < 0.05$). Studies have reported that long-term low albumin is one of the reasons for the high incidence of pleural effusion, ascites and wound infection^[29, 30]. LH has shorter hepatic vascular occlusion time than the OH group, which minimizes ischemia-reperfusion injury of residual liver tissue and reduces the incidence of gastrointestinal congestion. At the same time, laparoscopic surgery has less damage to the ligaments and abdominal wall muscles around the liver, so as to that the traffic branch of the portal vein and the abdominal wall vein is partially retained. Therefore, the laparoscopic group would suffer less liver function damage. Accordingly, the incidence of complications such as electrolyte imbalance, ascites, pleural effusion, and hypoproteinemia after the operation is rather lower^[31, 32].

There are several limitations in our present study. First, It's a non-randomized study with a small sample size that may slightly limit the strength of the results. Second, lack of long-term follow-up data can not reveal the long-term survival of the patients. Further studies with larger sample size and longer follow-up data should be conducted to confirm its validity.

In conclusion, this preliminary study demonstrated a better short-term outcomes in LH than in open procedure. LH is an effective surgical treatment with the advantages of quick recovery and low cost, which should be recommended in the treatment of PHC.

Conflict of Interest Statement

The authors of this study declare no conflict of interest.

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