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ORIGINAL ARTICLE

The Extrahepatic Glissonian Versus Hilar Dissection Approach for Laparoscopic Formal Right and Left Hepatectomies in Patients with Hepatocellular Carcinoma

Fei Liu[1] · YongGang Wei[1] · Kefei Chen[1] · HongYu Li[2] · Wentao Wang[1] · Hong Wu[1] · Tianfu Wen[1] · Bo Li[1]

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Abstract

Background Few studies have been performed to evaluate the value of the Glissonian approach (GA) for laparoscopic formal hemihepatectomy. The purpose of this study was to compare the outcomes of extrahepatic GA with those of the conventional hilar dissection approach for laparoscopic formal right and left hepatectomies in patients with hepatocellular carcinoma (HCC).
Methods Between January 2015 and October 2017, a total of 95 HCC patients who underwent pure laparoscopic formal hemihepatectomies, of whom 49 underwent the GA, were included in this study. After a 1:1 propensity score matching, 42 laparoscopic GA hepatectomies were compared to 42 conventional approach (CA) hepatectomies. We have analyzed perioperative and oncologic outcomes of the two different operative approaches for HCC treatments.
Results The GA did not increase the postoperative overall complication rates ($P = 0.415$) or the mean comprehensive complication index ($P = 0.414$) when compared with the CA. However, the operative time was significantly shorter ($P = 0.006$), and intraoperative blood loss was significantly lower ($P < 0.001$) in the GA group than in the CA group. There were no significant differences between the GA and CA groups regarding 3-year overall survival rate ($P = 0.765$) or 3-year disease-free survival rate ($P = 0.622$).
Conclusions Pure laparoscopic extrahepatic GA hemihepatectomy is safe and feasible, and it was associated with similar complication rates and equivalent 3-year survival outcomes compared to the conventional approach in selected patients with HCC.

Keywords Laparoscopic hepatectomy · Extrahepatic Glissonian approach · Hilar dissection approach · Hepatocellular carcinoma

Introduction

Nowadays, the safeness and reproducibility of the laparoscopic technique for minor liver resections have been confirmed in the literature, and laparoscopic left lateral resection is commonly performed for this type of operation.[1,2] Moreover, with the advancements in the design of laparoscopic surgical instruments and improvements in surgical techniques, laparoscopic formal right and left hepatectomies, which are the most commonly performed laparoscopic major liver resections, are increasingly adopted for different liver diseases.[3–6] The approach choice for the treatment of the hepatic hilum, that is, the Glissonian or the conventional hilar dissection approach, is an inevitable question for every hepatopancreatobiliary (HPB) surgeon when performing laparoscopic formal right and left hepatectomies.

The Glissonian approach was firstly introduced as an alternative method with full inflow control of the liver by Lortat-Jacob et al.[7]. The Glissonian pedicle approach hepatectomy, including extrahepatic control of Glisson's pedicle and *en bloc* stapling transection of the portal triad, was pioneered by Launois,[8] Takasaki,[9] and Galperin et al.[10]. Subsequently, the Glissonian approach, due to its simplicity of procedure, was a technical procedure widely used in open hepatectomy.[11,12]

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✉ YongGang Wei
wyonggang688@163.com

✉ Bo Li
cdlibo688@163.com

[1] Department of Liver Surgery&Liver Transplantation Center, West China Hospital, Sichuan University, 37 Guo Xue Road, Chengdu 610041, Sichuan Province, China

[2] Department of Pancreatic Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China

With the development of laparoscopic liver resection (LLR), the Glissonian pedicle approach has been increasingly proposed as a safe and efficient method for laparoscopic liver surgery. For instance, Machado et al.[13] have demonstrated the feasibility and safety of the intrahepatic Glissonian approach for LLR. Meanwhile, Cho et al.[14] reported that the extrahepatic Glissonian approach was also feasible and safe for laparoscopic anatomical resection of the liver. However, the previous studies were mainly focused on the technical feasibility of the Glissonian approach. To our knowledge, few studies have directly analyzed the outcomes of the Glissonian approach versus the conventional hilar dissection approach for LLR.

Machado et al.[15] recently published the first study which compared the intrahepatic Glissonian approach with the conventional hilar dissection approach for LLR, and it was found that the Glissonian approach had several advantages over the hilar dissection approach for LLR, including shorter operative time, lower transfusion rates, and fewer overall complications. Nevertheless, different types of LLRs for both benign and malignant diseases of the liver were included in the study by Machado et al., and the long-term outcomes were not addressed. Moreover, previous studies[16,17] on open liver resections had revealed that the Glissonian approach showed better long-term outcomes for patients with hepatocellular carcinoma (HCC) when compared with the conventional approach. A possible explanation suggested by the authors was that transection of the pedicles above the level of the bifurcation may prevent the intraoperative spread of neoplastic cells. Until now, no study has directly analyzed the long-term outcomes of the extrahepatic Glissonian approach versus the conventional approach for laparoscopic hepatectomy in patients with HCC. Thus, the long-term oncologic outcomes of the Glissonian approach for LLRs in HCC patients are still unclear. To examine these outcomes, we performed this study to compare the outcomes (including survival data) of the extrahepatic Glissonian approach with the conventional approach for laparoscopic formal right and left hepatectomies in HCC patients using the propensity score matching (PSM) method.

Materials and Methods

Patients and Data

The data of HCC patients who underwent LLRs in West China Hospital of Sichuan University between January 2015 and October 2017 were retrospectively collected from a prospectively established database. The selection criteria for patients in this study included (1) patients aged 18–75 years, (2) liver function classified as Child–Pugh class A, (3) pathological confirmation of HCC and maximum tumor size ≤ 10 cm, and (4) patients who underwent laparoscopic formal right or left hepatectomies. The exclusion criteria were the following: (1) HCC involved the hilum, (2) laparoscopic hemihepatectomy combined with other major associated surgical procedures except for cholecystectomy (such as splenectomy/ radiofrequency ablation), and (3) the presence of a known portal vein and/or bile duct anatomic variations. According to our inclusion and exclusion criteria, both the laparoscopic Glissonian approach and the conventional approach were theoretically feasible for these patients. The basic approach used for LLRs in our center was the conventional hilar dissection approach. Meanwhile, the laparoscopic Glissonian approach was gradually introduced in our center since 2009 and this approach was used to perform laparoscopic right hemihepatectomy in 2015. Our criteria for laparoscopic Glissonian approach have been gradually extended from those for smaller tumor at the beginning and are now identical to the general criteria for the conventional approach in tumor size. The therapeutic regimen for all patients and all operations were performed by the same surgical team (consisting of three experienced HPB surgeons and three fellows).

The patients were divided into the Glissonian and conventional approach groups according to the different surgical procedures. The preoperative evaluations were similar for the two groups, including blood examinations, chest X-ray, electrocardiography, abdominal ultrasound, and contrast computed tomography (CT) scan/enhanced magnetic resonance imaging (MRI). Preoperative three-dimensional reconstruction CT and MRI were also performed. In patients with an age of more than 65 years, we performed spirometry and echocardiography. Liver function was assessed by both the Child–Pugh grading and the preoperative indocyanine green (ICG) clearance test. Laboratory blood tests included routine blood tests, conventional coagulation examinations, alanine aminotransferase (ALT), aspartate transaminase (AST), serum total bilirubin (TBIL), albumin (Alb), and serum alpha-fetoprotein (AFP). The primary endpoints were postoperative morbidity, overall survival (OS), and disease-free survival (DFS) rates. The secondary endpoints included the total operative time, the amount of operative blood loss, blood transfusion requirements, and postoperative hospital stay. Informed consents were obtained according to the Declaration of Helsinki, and a written informed consent was obtained from each subject involved in the study. The study was approved by the Ethics Committee of West China Hospital of Sichuan University.

Surgical Procedure

Our LLR techniques were previously described in detail.[18,19] Briefly, in the Glissonian approach group, the Glissonian pedicle was encircled using the extrahepatic Glissonian approach before parenchymal transection, similar to the method of Cho et al.[14]. After removing the gallbladder, the peritoneum of the hepatoduodenal ligament was meticulously dissected at the hepatic hilum (Fig. 1a) and the dorsal side of the hepatoduodenal ligament (Fig. 1b). The dissection was performed using a specialized curved forceps between the hepatic parenchyma and the bifurcation of the right and left Glissonian pedicles. After sufficient dissection, the curved forceps could be smoothly inserted into the latent anatomic space between the hepatic parenchyma and the bifurcation of the right and left Glissonian pedicles (Fig. 1c) and the tip of the curved forceps was visualized (Fig. 1d). Then, the cotton tape was used to isolate the right pedicle (Fig. 1e). When transferring the tail of the cotton tape (the side on the surface of the caudate lobe) to the left side of the hepatoduodenal ligament, the left pedicle could be easily isolated. Figure 1f shows that the right and left Glissonian pedicles were both encircled laparoscopically. When the corresponding Glissonian pedicle was occluded, we marked the ischemic line by electrocautery on the liver capsule. In order to avoid dissemination of the malignant tumor cells and to decrease the blood loss, the Glissonian pedicle was continuously clamped during parenchymal dissection. The superficial parenchyma was dissected by a harmonic scalpel (Ethicon Endo-Surgery, USA) along the demarcation line, while the deeper tissue was dissected by laparoscopic cavitron ultrasonic surgical aspirator (CUSA, Valleylab, Inc., USA) or LigaSure (Valleylab, Inc., USA) along the middle hepatic vein (MHV). Intraparenchymal vascular and biliary structures larger than 5 mm were dissected and clamped by Hem-o-lok clips or titanium clips. After sufficient parenchymal dissection, so that the whole bifurcating Glissonian pedicle was exposed, the hepatic pedicle tissue was transected by a laparoscopic linear stapler with 60-mm blue cartridge (Endopath endocutter; Ethicon Endo-Surgery). It is noteworthy that stapling was done while the tape was retracted toward the contralateral side (Fig. S1), which prevented injury or stricture of the contralateral Glissonian pedicle branch. The corresponding hepatic vein was transected by a linear stapler with a 45-mm white cartridge. If hemostasis on the cutting surface of the liver was inadequate, the BiClamp (VIO 300 D system, ERBE, Germany) was used for further hemostasis.

In the conventional approach group, the portal vein, hepatic artery, and biliary duct were dissected in the hilum by opening the peritoneal fascia (Fig. 2). The corresponding portal vein and hepatic artery were ligated and cut in the right and left hepatectomies before transection of the parenchyma. Next, we marked the cutting line by electrocautery on the liver capsule following the ischemic line on the liver surface. The superficial parenchyma was dissected by a harmonic scalpel along the demarcation line, while the deeper tissue was dissected by laparoscopic CUSA or Ligasure along the MHV. Intraparenchymal vascular and biliary structures larger than 5 mm were dissected and clamped by Hem-o-lok clips or titanium clips. When parenchymal transection reached the bile duct level, the corresponding bile duct was transected by a laparoscopic linear stapler with a 45-mm white cartridge. After parenchymal dissection was finished, the corresponding hepatic vein was transected by a laparoscopic linear stapler with a 45-mm white cartridge. If hemostasis on the cutting surface of the liver was inadequate, the BiClamp was used for further hemostasis.

For both groups, the specimen was put in a retrieval bag and removed through a suprapubic incision without the muscle section. The central venous pressure (CVP) was kept below 5 mmHg during liver parenchymal transection as

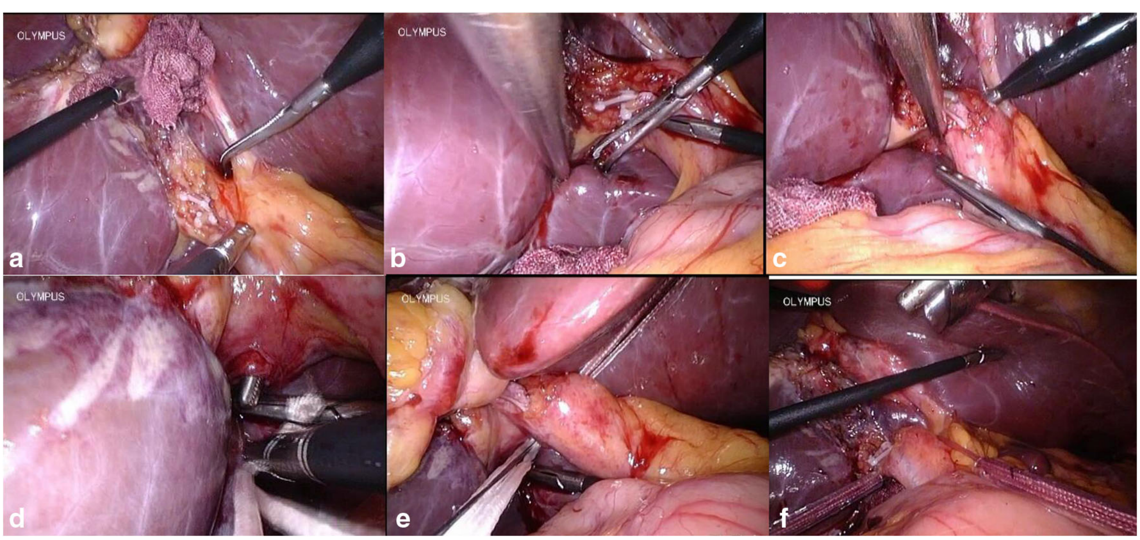

Fig. 1 Some surgical techniques of the laparoscopic extrahepatic Glissonian approach. **a** The peritoneum of the hepatoduodenal ligament was meticulously dissected at the hepatic hilum. **b** The peritoneum of the hepatoduodenal ligament was meticulously dissected at the dorsal side of the hepatoduodenal ligament. **c** The curved forceps was inserted into the latent anatomic space between the hepatic parenchyma and the bifurcation of the right and left Glissonian pedicles. **d** The tip of the curved forceps was visualized. **e** The right Glissonian pedicle was isolated by cotton tape. **f** Both the right and left Glissonian pedicles were encircled laparoscopically

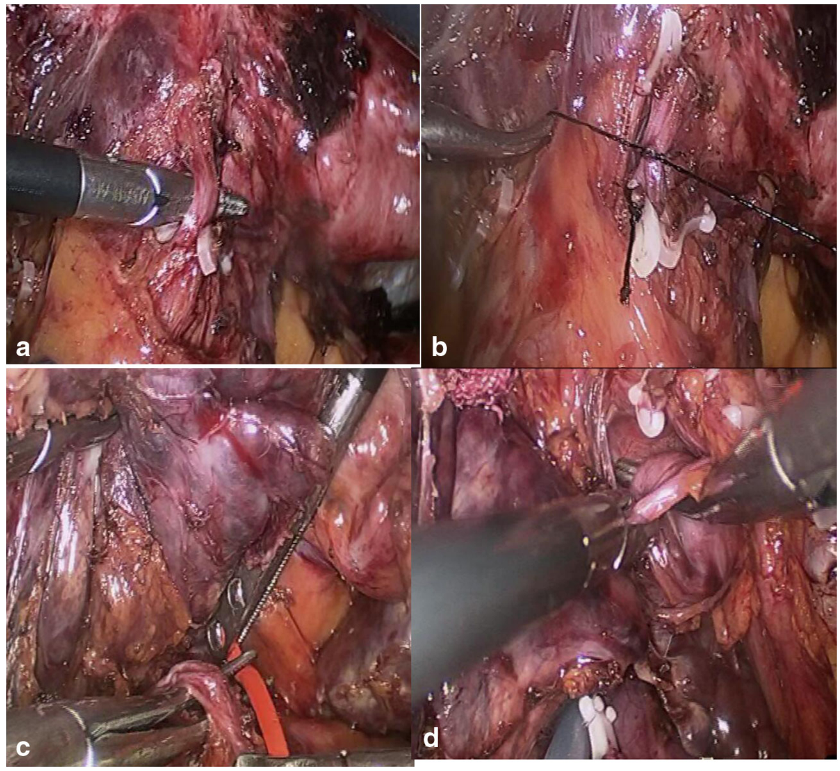

Fig. 2 Some surgical techniques of the laparoscopic conventional hilar dissection approach. **a** The left hepatic artery was isolated by a laparoscopic dissecting forceps. **b** The left portal vein was ligated by silk sutures. **c** The right hepatic artery was isolated and encircled by a traction belt. **d** The right portal vein was isolated by a laparoscopic dissecting forceps

recommended in the literature.[20] In order to achieve this goal, a single anesthesia team experienced in liver resection, especially in low CVP anesthesia, was involved in all cases, maintaining the CVP in each case under 5 mmHg.

Postoperative Management and Follow-Up

Patients in the two groups received the same postoperative care by the same team of surgeons. Postoperative routine blood tests and hepatic function tests, including serum TBIL, ALT, AST, and Alb, were performed on postoperative days 1, 3, 5, and 7 (if the patient was not discharged at postoperative day 7). The abdominal ultrasound examination was repeated on postoperative day 5. Abdominal drainage was removed when ultrasound showed no abnormal findings and the drainage fluid showed no bile leakage. All patients were followed up with a standardized follow-up protocol. Routine blood tests and hepatic function tests, assessment of serum AFP levels, and tests for hepatitis B virus (HBV)-DNA load were required bimonthly in the first postoperative year, and then quarterly if no recurrence was detected. Abdominal enhanced CT was performed 1 month after the operation and quarterly in the first year, and half-yearly afterwards. Recurrence was defined as the appearance of new lesions with HCC-characteristic findings on follow-up CT or MRI.

Definitions

Postoperative morbidities were classified according to the Clavien–Dindo classification,[21] and the comprehensive complication index (CCI)[22] was also used to describe overall morbidity. Postoperative mortality was defined as death occurring during the first 90 days after the operation. Hemorrhage was identified as a drop in hemoglobin level > 3 g/dL postoperatively compared with the postoperative baseline level and/or any postoperative transfusion of packed red blood cells for falling hemoglobin levels.[23] Biliary leakage was defined as a bilirubin concentration in the drained fluid at least three times the serum bilirubin level on or after postoperative day 3.[24] Postoperative ascites was defined as an abdominal drainage output of more than 500 mL/day or which required treatment to be controlled.[25] Posthepatectomy liver failure was defined according to the International Study Group of Liver Surgery.[26]

Statistical Analysis

The Pearson chi-square test or the Fisher exact test was appropriate for categorical data according to the numbers obtained. Continuous variables with a normal distribution are expressed as mean ± standard deviation (SD) and compared using the two-sided Student *t* tests. Continuous variables that were not normally distributed are reported as median (range) values and comparison of this kind of data was achieved by the Mann–Whitney *U* test. OS and DFS were analyzed according to the

Kaplan–Meier estimate. To eliminate possible selection bias, the propensity score analysis model was used. A PSM ratio of 1:1 was achieved based on the "nearest neighbor" method with no replacement.[27] The PSM was estimated using logistic regression which included the following variables, whose *P* values were less than 0.1 between the two groups: age, MBI, preoperative ICG-R15, and tumor size. The matching algorithm was tested by a histogram of the propensity score and a dot plot of standardized mean differences. Matching occurred if the difference in the logit of the propensity score between nearest neighbors was within a caliper width equal to 0.2 times the SD of the logit of the propensity score. Survival curves were compared between the propensity score-matched groups using the log-rank test. All calculations were performed using the SPSS 22.0 statistical software. A *P* value of < 0.05 was considered as statistically significant.

Results

Patient Characteristics

Between January 2015 and October 2017, a total of 95 HCC patients who underwent laparoscopic formal hemihepatectomies were included in this study, of whom 49 patients underwent the extrahepatic Glissonian approach and 46 the conventional approach. The patients' baseline characteristics in the two groups are shown in Table 1. The two groups were similar in terms of sex, HBV carrier status, background cirrhosis, ASA grade, comorbid disease, preoperative AFP, type of resection, previous upper abdominal surgery, and number of tumors. However, age and tumor size were different between the groups. After PSM, 42 patients were included in each group (Table 2). Both groups were well matched, including the age and tumor size. Moreover, there was no significant difference in the type of liver resection between the two groups.

Operation and Postoperative Outcomes

Table 3 summarizes the perioperative outcomes of both groups after PSM. The operative time in the Glissonian group was significantly shorter than in the conventional group (235 vs 270 min, $P = 0.006$), but the need of a Pringle maneuver and clamping time in the two groups were similar. Moreover, the amount of intraoperative blood loss in the Glissonian group was significantly lower than in the conventional group (250 vs 400 mL, $P < 0.001$). Nevertheless, blood transfusion requirement did not differ between the two groups. Two patients in the Glissonian group eventually needed conversion to open surgery; the reasons included a right hepatic vein injury in one patient and an uncontrolled hemorrhage during parenchymal transection in the other patient. Only one patient in the conventional group had to convert to open procedure, with the reason being a right hepatic vein injury.

No mortality was recorded in the two groups. The most common complications for the two groups were similar, i.e., ascites, pleural effusion, and pneumonia. In the Glissonian group, 7 of 42 patients (16.7%) had a complication, compared with 10 of 42 (23.8%) in the conventional group. Both the postoperative overall complication rates (16.7% vs 23.8%, $P = 0.415$) and the mean CCI (3.54 vs 5.23, $P = 0.414$) were not significantly different between the two groups. Furthermore, the overall morbidity rates of Clavien–Dindo grade II and above were also similar (9.5% versus 14.3%, respectively; $P = 0.500$). In addition, the length of postoperative hospital stay was also comparable between the Glissonian and conventional groups (7 vs 8 days, respectively; $P = 0.170$).

Oncological Outcomes

Pathological findings of the two groups are shown in Table S1. Tumor number, tumor size, surgical margin, R0 resection rate, and histological liver cirrhosis were comparable in the two groups. The proportion of patients with satellite nodules and microvascular invasion was not significantly different. Moreover, the distribution of Edmondson–Steiner grades was also similar.

HCC patients were followed until March 2018, and the survival time was calculated from the date of tumor resection to the date of death/recurrence or to the last follow-up. The median follow-up time was 21 months in the Glissonian group and 20.5 months in the conventional group. The 1- and 3-year OS rates were 97.2% and 72.5% in the Glissonian group and 94.5% and 66.3% in the conventional group (Fig. 3a). The 1- and 3-year DFS rates were 87.1% and 63.0% in the Glissonian group and 85.0% and 52.9% in the conventional group (Fig. 3b). There were no significant differences between the groups regarding the 1- and 3-year OS rates ($P = 0.765$) or the 1- and 3-year DFS rates ($P = 0.622$).

Discussion

In recent years, laparoscopic major hepatectomies are increasingly used in different centers worldwide,[28–30] while laparoscopic formal right and left hepatectomies are the most commonly performed laparoscopic major liver resections. Nevertheless, the approach choice for the treatment of the hepatic hilum is likely to depend on the surgeon's preference rather than on objective data because of a lack of relevant evidence. We could not directly use the relevant evidence about open hepatectomy[31] because LLR is somewhat different from open hepatectomy (e.g., movement limitations of the instruments during laparoscopic

Table 1 Patients' baseline and tumor characteristics before propensity score matching

	Glissonian group ($n = 49$)	Conventional group ($n = 46$)	P value
Age, mean (SD)	50.53 ± 10.17	54.85 ± 10.06	0.040[#]
Sex, M/F	43:6	40:6	0.907[+]
BMI, mean (SD)	23.79 ± 1.82	22.99 ± 2.36	0.067[#]
HBV carrier, *n* (%)	41 (83.7)	39 (84.8)	0.882[+]
Liver cirrhosis, *n* (%)	32 (65.3)	32 (69.6)	0.658[+]
ASA grade, *n* (%)			0.363*
I/II	45 (91.8)	45 (97.8)	
III/IV	4 (8.2)	1 (2.2)	
Comorbid disease, *n* (%)	9 (18.4)	13 (28.3)	0.253[+]
HTN	5 (10.2)	7 (15.2)	
DM	3 (6.1)	5 (10.9)	
COPD	1 (2.0)	2 (4.3)	
Preoperative AFP, *n* (%)			0.175[+]
Increased (≥ 400 ng/mL)	18 (36.7)	11 (23.9)	
Not increased (< 400 ng/mL)	31 (63.3)	35 (76.1)	
TB (μmol/L), mean (SD)	14.60 ± 5.81	14.38 ± 7.04	0.867[#]
ALB (g/L), mean (SD)	41.97 ± 3.06	41.90 ± 2.89	0.910[#]
AST (IU/L), mean (SD)	40.61 ± 18.94	41.85 ± 20.60	0.761[#]
ALT (IU/L), mean (SD)	50.88 ± 21.35	52.04 ± 29.09	0.823[#]
Preoperative ICG-R15(%), mean (SD)	7.20 ± 2.50	6.23 ± 2.69	0.072[#]
Type of resection, *n* (%)			0.900[+]
Right hepatectomy	26 (53.1)	25 (54.3)	
Left hepatectomy	23 (46.9)	21 (45.7)	
Previous upper abdominal surgery, *n* (%)	3 (6.1)	4 (8.7)	0.709*
Tumor size (cm), mean (SD)	5.34 ± 1.83	6.17 ± 1.96	0.036[#]
Number of tumors, *n* (%)			0.882[+]
Solitary	41 (83.7)	39 (84.8)	
Multiple	8 (16.3)	7 (15.2)	

AFP alpha-feto-protein, *ALB* albumin, *ALT* alanine transaminase, *ASA* American Society of Anesthesiologists, *AST* aspartate transaminase, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *F* female, *HBV* hepatitis B virus, *HTN* hypertension, *ICG* indocyanine green, *M* male, *SD* standard deviation, *TB* total bilirubin

[#] Student's *t* test

*Fisher exact test

[+] Pearson chi-square test

procedures). Moreover, the previous studies[16,17] on open hepatectomy suggested a possible survival benefit with the Glissonian approach. Therefore, we performed this study to compare the outcomes of the extrahepatic Glissonian approach with the conventional approach for laparoscopic formal right and left hepatectomies in patients with HCC. To the best of our knowledge, this is the first study which compares the outcomes of the extrahepatic Glissonian with the conventional approach for laparoscopic hemihepatectomies in patients with HCC. Our study demonstrates that both techniques are equally effective procedures for treating the hilar structures in laparoscopic formal hemihepatectomy. The Glissonian approach did not increase the postoperative overall complication rates (including biliary complications) or the mean CCI when compared with the conventional approach. However, the operative time was significantly shorter and intraoperative blood loss was significantly lower in the Glissonian approach group. Furthermore, the 3-year OS and 3-year DFS rates were not significantly different between the groups.

One of the main concerns for some surgeons when using the Glissonian approach was the possibility that the Glissonian approach might lead to an increase in the rate of biliary complications, such as bile leaks and bile duct injury. Indeed, a previous study on open hepatectomy[32] reported that accidental

Table 2 Patients' baseline and tumor characteristics after propensity score matching

	Glissonian group ($n = 42$)	Conventional group ($n = 42$)	P value
Age, mean (SD)	50.98 ± 10.74	53.69 ± 9.71	$0.228^{\#}$
Sex, M/F	36:6	38:4	0.500^{+}
BMI, mean (SD)	23.72 ± 1.75	23.20 ± 2.31	$0.252^{\#}$
HBV carrier, n (%)	35 (83.3)	36 (85.7)	0.763^{+}
Liver cirrhosis, n (%)	26 (61.9)	30 (71.4)	0.355^{+}
ASA grade, n (%)			0.616*
I/II	39 (92.9)	41 (97.6)	
III/IV	3 (7.1)	1 (2.4)	
Comorbid disease, n (%)	7 (16.7)	11 (26.2)	0.287^{+}
HTN	3 (7.1)	6 (14.3)	
DM	3 (7.1)	4 (9.5)	
COPD	1 (2.4)	2 (4.8)	
Preoperative AFP, n (%)			0.629^{+}
Increased (≥ 400 ng/mL)	13 (31.0)	11 (26.2)	
Not increased (< 400 ng/mL)	29 (69.0)	31 (73.8)	
TB (μmol/L), mean (SD)	14.40 ± 5.88	14.41 ± 7.23	$0.991^{\#}$
ALB (g/L), mean (SD)	41.91 ± 3.04	41.59 ± 2.79	$0.620^{\#}$
AST (IU/L), mean (SD)	40.02 ± 20.09	42.95 ± 21.14	$0.517^{\#}$
ALT (IU/L), mean (SD)	50.74 ± 22.62	53.57 ± 29.64	$0.624^{\#}$
Preoperative ICG-R15(%), mean (SD)	6.96 ± 2.45	6.40 ± 2.74	$0.320^{\#}$
Type of resection, n (%)			0.275^{+}
Right hepatectomy	19 (45.2)	24 (57.1)	
Left hepatectomy	23 (54.8)	18 (42.9)	
Previous upper abdominal surgery, n (%)	2 (4.8)	4 (9.5)	0.676*
Tumor size (cm), mean (SD)	5.33 ± 1.86	6.05 ± 2.00	$0.090^{\#}$
Number of tumors, n (%)			1.000^{+}
Solitary	35 (83.3)	35 (83.3)	
Multiple	7 (16.7)	7 (16.7)	

AFP alpha-feto-protein, *ALB* albumin, *ALT* alanine transaminase, *ASA* American Society of Anesthesiologists, *AST* aspartate transaminase, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *F* female, *HBV* hepatitis B virus, *HTN* hypertension, *ICG* indocyanine green, *M* male, *SD* standard deviation, *TB* total bilirubin

$^{\#}$ Student's t test

*Fisher exact test

$^{+}$ Pearson chi-square test

ligation of the biliary confluence occurred when stapling the right pedicle, which caused postoperative obstructive jaundice. However, no bile duct injury was recorded in our study and the rate of bile leakage did not differ between the two groups. Moreover, we had no case with bile duct injury when using the laparoscopic Glissonian pedicle approach for different types of hepatectomies.[33] Some detailed strategies which were used to address this issue in our institution can be found in our previous publication.[33]

Consistent with some previous studies[15,34] which investigated the outcomes of the Glissonian versus the conventional approach for open and laparoscopic hepatectomies, we found that the mean operative time in the Glissonian group was significantly shorter than in the conventional group. Although the exact reasons for this difference are not clear, the longer operative time for patients in conventional group could be related to the longer time needed to dissect each element in the hepatic hilum. Although this study did not compare the duration of the hilar dissection in the two groups, a previous randomized controlled trial[31] found that the *en bloc* stapling transection of the hilar structures was faster than the isolated ligature of each element in the pedicle. Moreover, our study suggests that the need of a Pringle maneuver and clamping time in the two groups were similar, indicating that

Table 3 Surgical characteristics and surgical outcomes after propensity score matching

	Glissonian group ($n = 42$)	Conventional group ($n = 42$)	P value
Blood loss (mL)[§]	250 (50–1000)	400 (100–2500)	0.000[#]
Blood transfusion, n (%)	1 (2.4)	3 (7.1)	0.616*
Operation time (minutes)[§]	235 (125–435)	270 (145–470)	0.006[#]
Pringle maneuver, n (%)	36 (85.7)	36 (85.7)	1.000[+]
Clamping times (minutes)[§]	40 (0–100)	40 (0–110)	0.713[#]
Conversion to open laparotomy, n (%)	2 (4.8)	1 (2.4)	1.000*
Postoperative hospital stay (days)[§]	7 (3–39)	8 (5–22)	0.170[#]
Mortality, n (%)	0 (0.0)	0 (0.0)	–
Overall complications, n (%)	7 (16.7)	10 (23.8)	0.415[+]
Clavien–Dindo grade, n (%)			
I	3 (7.1)	4 (9.5)	1.000*
II	2 (4.8)	3 (7.1)	1.000*
III	1 (2.4)	1 (2.4)	1.000*
IV	1 (2.4)	2 (4.8)	1.000*
V	0 (0.0)	0 (0.0)	–
Type of complication	($n = 9$)	($n = 12$)	
Pneumonia	1	0	
Pleural effusion	2	4	
Ileus	0	1	
Wound infection	1	0	
Biliary leakage	1	1	
Ascites	2	4	
Intra-abdomen bleeding	1	0	
Liver failure	1	2	
Clavien–Dindo grade II and above, n (%)	4 (9.5)	6 (14.3)	0.500[+]
Comprehensive complication index†	3.54 (0–47.3)	5.23 (0–47.3)	0.414[#]

[#] Mann-Whitney U test

[+] Pearson chi-square test

*Fisher exact test

[§] Values are median (range)

†Mean (range)

the parenchymal transection time in the two groups was similar, because the Pringle maneuver was routinely used in most cases in this study when transecting parenchyma. Hence, we deduce that the longer operative time in the conventional group was related to the longer time needed to dissect each element in the hepatic hilum.

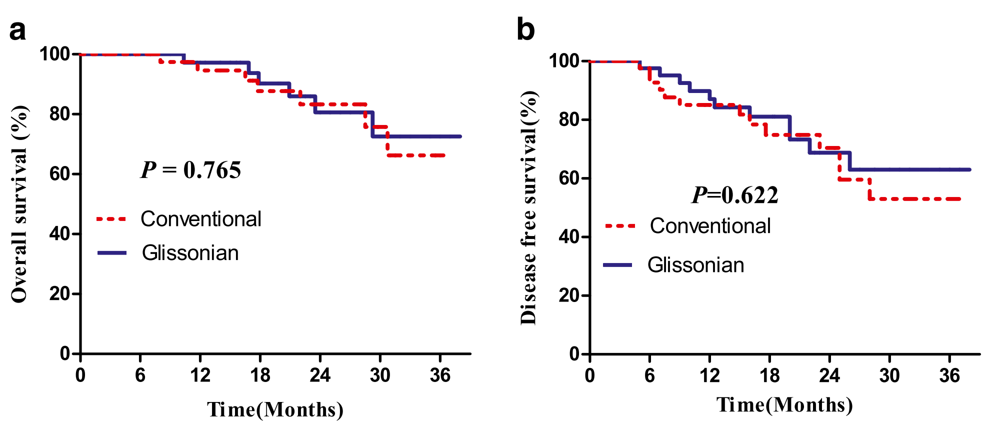

Fig. 3 The survival curve between the extrahepatic Glissonian approach and the conventional approach groups: **a** overall survival rates and **b** disease-free survival rates

In addition, this study also found that the intraoperative blood loss was significantly different between the two groups. The Glissonian group showed significantly better results than the conventional hilar dissection group. Similar results were also observed in previous studies for both open and laparoscopic hepatectomies. For example, Karamarkovic et al.[34] found that the amount of blood loss was significantly lower using the open Glissonian hepatectomy than with the conventional hilar dissection approach. Moreover, Machado et al.[15] published the first study comparing the intrahepatic Glissonian approach with the conventional hilar dissection approach for LLR. They found that the Glissonian approach was associated with lower intraoperative blood loss. Dissection of the hepatic hilum in the conventional group brings a risk of bleeding in patients with cirrhosis, as laparoscopic cholecystectomy in patients with cirrhosis is associated with a high risk of bleeding.[35] In this study, more than 65% of HCC patients suffered from liver cirrhosis, which might contribute to the difference in intraoperative blood loss.

With respect to the oncological outcomes, a previous study[17] on open hepatectomy demonstrated that the Glissonian approach was an independent prognostic indicator for survival over the standard approach in patients with HCC. However, we found that the 3-year OS and DFS rates were not significantly different between the two groups. The authors[17] explained that the Glissonian approach could prevent intraoperative spread of cancer cells dislodged by surgical manipulation by isolating the blood supply of the tumor-bearing area from that of the other parts of the liver. In the present study, the blood supply of the tumor-bearing area was isolated from that of the other parts of the liver before parenchymal transection in both groups. Moreover, the impertinent manipulation during hepatectomy (such as positive surgical margin) and the biological behavior of the HCC would influence the prognosis of patients with HCC. In this study, the tumor-free surgical margin was similar in both groups. Furthermore, the pathological findings suggest that the biological behavior of the HCC was also comparable in the two groups. Therefore, the standardization of operation and the similar characteristics of tumor biology were expected to contribute to the equivalence of oncologic outcomes between the two groups.

In this study, several limitations need to be addressed. Firstly, the potential effect of a learning curve in the laparoscopic Glissonian pedicle approach may exist. In our previous publication,[33] the reasons were explained in detail. Secondly, the current study was conducted by retrospective analysis of a single-center prospective database. To overcome selection bias as much as possible, a PSM was employed, because this model is considered the most effective method to balance the covariates and thus reduce bias in retrospective studies. Moreover, we have already conducted a randomized controlled trial (RCT) to compare outcomes between the Glissonian and the conventional approach for laparoscopic major hepatectomies in patients with HCC (an ongoing RCT, Registration number: ChiCTR-IOR-17013077). Last but not least, our results should be interpreted with caution because our cohort was composed of selected HCC patients without anatomic variations of the portal triad. According to the literature,[36] the presence of anatomic variation is a common reason for technical failure and unfeasibility of the Glissonian approach. Therefore, when considering the Glissonian approach, the presence of anatomic variations of the portal triad should always be considered. Moreover, we also did not include patients with HCC adjacent to the hepatic hilum because tumor margin violation could occur near the portal pedicle during hepatectomy.[31] Therefore, we recommend that the conventional hilar dissection approach should be performed when the tumor lies near the portal bifurcation.

In conclusion, this study assessed the feasibility and outcomes of the extrahepatic Glissonian approach for pure laparoscopic formal hemihepatectomies in patients with HCC compared with the conventional approach. We found that pure laparoscopic Glissonian approach hemihepatectomies could be safely and feasibly performed in selected HCC patients, leading to shorter operative time, lower blood loss, and comparable oncological outcomes compared to the conventional approach. These results suggest that the pure laparoscopic extrahepatic Glissonian approach might be a better alternative to the conventional hilar dissection approach for formal right and left hepatectomies in selected HCC patients.

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Compliance with Ethical Standards

The study was approved by the Ethics Committee of West China Hospital of Sichuan University.

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Dokmak S, Raut V, Aussilhou B, et al. Laparoscopic left lateral resection is the gold standard for benign liver lesions: a case-control study. HPB (Oxford) 2014; 16:183–187.
2. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection a report from the second international consensus conference held in Morioka. Ann Surg 2015; 261:619–629.
3. Chen P, Bie P, Liu J, Dong J. Laparoscopic left hemihepatectomy for hepatolithiasis. Surg Endosc. 2004;18(4):717–8.
4. Zhang Y, Huang J, Chen XM, Sun DL. A Comparison of Laparoscopic Versus Open Left Hemihepatectomy for Hepatocellular Carcinoma. Surg Laparosc Endosc Percutan Tech. 2016;26:146–9.
5. Han HS, Yoon YS, Cho JY, et al. Laparoscopic right hemihepatectomy for hepatocellular carcinoma. Ann Surg Oncol 2010;17:2090–2091.
6. Machado MA, Makdissi FF, Surjan RC, et al. Laparoscopic right hemihepatectomy for hepatolithiasis. Surg Endosc 2008;22:245.
7. Lortat-Jacob JL, Robert HG, Henry C. [Case of right segmental hepatectomy]. Memoires Academie de chirurgie. 1952;78(8–9):244–51.
8. Launois B, Jamieson GG. The posterior intrahepatic approach for hepatectomy or removal of segments of the liver. Surg Gynecol Obstet 1992;174:155–8.
9. Takasaki K, Kobayashi S, Tanaka S, et al. Highly anatomically systematized hepatic resection with Glissonean sheath code transection at the hepatic hilus. Int Surg 1990;75:73–7.
10. Galperin EI, Karagiulian SR. A new simplified method of selective exposure of hepatic pedicles for controlled hepatectomies. HPB Surg 1989;1:119–30.
11. Couinaud CM. A simplified method for controlled left hepatectomy. Surgery 1985; 97: 358–61.
12. Takasaki K, Kobayashi S, Tanaka S. Newly developed systematized hepatectomy by Glissonean pedicle transection method. Shujutsu 1986;40:7–14.
13. Machado MA, Makdissi FF, Galvao FH, Machado MC. Intrahepatic Glissonian approach for laparoscopic right segmental liver resections. American Journal of Surgery. 2008;196:e38–42.
14. Cho A, Yamamoto H, Kainuma O, et al. Safe and feasible extrahepatic Glissonean access in laparoscopic anatomical liver resection. Surg Endosc. 2011;25:1333–6.
15. Machado MA, Surjan RC, Basseres T, et al. The laparoscopic Glissonian approach is safe and efficient when compared with standard laparoscopic liver resection: Results of an observational study over 7 years. Surgery. 2016;160:643–51.
16. Yamamoto M, Takasaki K, Ohtsubo T, Katsuragawa H, Fukuda C, Katagiri S.Effectiveness of systematized hepatectomy with Glisson's pedicle transection at the hepatic hilus for small nodular hepatocellular carcinoma: retrospective analysis. Surgery. 2001;130:443–8.
17. Tsuruta K, Okamoto A, Toi M, et al. Impact of selective Glisson transection on survival of hepatocellular carcinoma. Hepatogastroenterology 2002;49:1607–10.
18. Liu F, Zhang J, Lei C, Wei Y, Li B. Feasibility of laparoscopic major hepatectomy for hepatic paragonimiasis: two case reports. Medicine (Baltimore). 2016;95(38):e4939.
19. Liu F, Wei Y, Li H, et al. LigaSure versus CUSA for parenchymal transection during laparoscopic hepatectomy in hepatocellular carcinoma patients with cirrhosis: a propensity score-matched analysis. Surg Endosc. 2018;32:2454–2465.
20. Tranchart H, O'Rourke N, Van Dam R, et al. Bleeding control during laparoscopic liver resection: a review of literature. J Hepatobiliary Pancreat Sci. 2015; 22:371–378.
21. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009;250:187–196.
22. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013; 258:1–7.
23. Rahbari NN, Garden OJ, Padbury R, et al. Post-hepatectomy haemorrhage: a definition and grading by the International Study Group of Liver Surgery (ISGLS). HPB 2011;13(8): 528–535.
24. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011; 149: 680–688.
25. Figueras J, Llado L, Ruiz D, et al. Complete versus selective portal triad clamping for minor liver resections: a prospective randomized trial. Ann Surg.2005; 241:582–590.
26. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011; 149: 713–24.
27. Guo S, Fraser MW. Propensity Score Analysis: Statistical Methods and Applications. Advanced Quantitative Techniques in the Social Sciences Series. Los Angeles: SAGE Publications, Inc; 2010.
28. Lin NC, Nitta H, Wakabayashi G. Laparoscopic major hepatectomy: a systematic literature review and comparison of 3 techniques. Ann Surg. 2013;257:205–13.
29. Tzanis D, Shivathirthan N, Laurent A, et al. European experience of laparoscopic major hepatectomy. J Hepatobiliary Pancreat Sci. 2013;20:120–4.
30. Dagher I, Gayet B, Tzanis D, et al. International experience for laparoscopic major liver resection. J Hepatobiliary Pancreat Sci. 2014;21:732–6.
31. Figueras J, Lopez-Ben S, Lladó L, et al. Hilar dissection versus the "glissonean" approach and stapling of the pedicle for major hepatectomies: a prospective, randomized trial. Ann Surg. 2003 ;238:111–9.
32. Fong Y, Blumgart L. Useful stapling techniques in liver surgery. J Am Coll Surg. 1997; 185:93–100.
33. Liu F, Xu H, Li Q, et al. Outcomes of pure laparoscopic Glissonian pedicle approach hepatectomy for hepatocellular carcinoma: a propensity score matching analysis. Surg Endosc. 2018 Aug 17. doi: https://doi.org/10.1007/s00464-018-6380-0
34. Karamarkovic A, Doklestic K, Milic N, et al. Glissonean pedicle approach in major liver resections. Hepatogastroenterology. 2012;59:1896–901.
35. Machado NO. Laparoscopic cholecystectomy in cirrhotics. JSLS. 2012;16:392–400.
36. Mouly C, Fuks D, Browet F, et al. Feasibility of the Glissonian approach during right hepatectomy. HPB (Oxford). 2013;15:638–45.