



# Laparoscopic versus open limited liver resection for hepatocellular carcinoma with liver cirrhosis: a propensity score matching study with the Hiroshima Surgical study group of Clinical Oncology (HiSCO)

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## Abstract

**Background** Laparoscopic liver resection (LLR) has evolved as a safe and effective alternative to conventional open liver resection (OLR) for malignant lesions. However, LLR in cirrhotic patients remains challenging. This study analyzed the perioperative and oncological outcomes of LLR for hepatocellular carcinoma (HCC) with cirrhosis compared with OLR using propensity score matching.

**Methods** A multicenter retrospective analysis of records of patients who underwent limited liver resection for HCC and were histologically diagnosed with liver cirrhosis between January 2009 and December 2017 in the eight institutions belonging to the Hiroshima Surgical study group of Clinical Oncology was performed. The patients were divided into two groups: the LLR and OLR groups. After propensity score matching, we compared clinicopathological features and outcomes.

**Results** In total 256 patients with histological liver cirrhosis who underwent limited liver resection for HCC were included in this study; 58 patients had undergone LLR, and the remaining 198 patients OLR. The number of tumors was higher, tumor size was larger, and difficulty score was significantly higher in the OLR group before propensity matching. After the matching, the data of the well-matched 58 patients in each group were evaluated; the intraoperative blood loss was lower in the LLR group ( $p=0.004$ ), and incidence of the postoperative complications was significantly higher in the OLR group ( $p=0.019$ ). The duration of the postoperative hospital stay was significantly shorter in the LLR group ( $p<0.001$ ). There were no differences between two groups in overall survival and recurrent-free survival.

**Conclusions** LLR decreased the incidences of postoperative complications, shortened the duration of postoperative hospital stay. Thus, LLR is a safe and feasible procedure even in patients with cirrhosis.

**Keywords** Laparoscopic liver resection · Limited liver resection · Liver cirrhosis · Hepatocellular carcinoma · Multicenter study · Propensity score matching

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Liver resection plays an important role in the curative treatment of hepatocellular carcinoma (HCC) [1], because liver transplantation is not feasible in most cases due to large-scale donor shortage [2]. Liver cirrhosis often limits the choice of treatment because it is a major risk factor for liver surgery. The patients with liver cirrhosis are associated with high morbidity [3]. In the open liver surgery, since the liver is covered with the costal cavity, an extremely long incision is required for mobilization and resection of the liver. In particular, for patients with cirrhosis, these surgical procedures significantly increase intraoperative blood loss, leading to postoperative complications and prolonged postoperative hospital stay [4–6].

Laparoscopic liver resection (LLR) is currently considered a safe and feasible alternative to open surgery for HCC [7]. It has been gradually accepted as an option for HCC treatment due to improvements in surgical instruments, postoperative management, and surgical techniques [8, 9]. LLR for HCC is associated with similar long-term outcomes but fewer postoperative complications compared to open liver resection (OLR) [10–12]. As described above, since operation for patients with cirrhosis leads to various complications and the prognosis is poor, minimally invasive surgery is required. Moreover, even with minimally invasive surgery, certain oncological curability is required. There have been few reports on the indication of LLR for HCC in cirrhotic patients, and consensus has yet to be achieved [13–15].

The purpose of this retrospective study was to compare the feasibility and safety of LLR for HCC in patients with histologically proven cirrhosis having undergone OLR.

## Materials and methods

From January 2009 to December 2017, 256 patients who had undergone limited liver resection for HCC and were histologically diagnosed with liver cirrhosis in the 8 institutions belonged to Hiroshima Surgical study group of Clinical Oncology (HiSCO) were included in this study. The Institutional Review Board of each institution provided approval for this study (E-1639). OLR had been performed in 198 patients, and LLR in 58 patients. Since there was no difference in the liver function between the LLR and OLR groups, patients were matched one-to-one on the basis of tumor number, tumor size, and difficulty score, which were significantly different. The operations were performed by a board certified expert surgeon in the hepato-biliary Pancreatic field in Japan [16]. All patients were confirmed with liver cirrhosis and stage F4 liver fibrosis that were histologically classified using the pathological findings of resected specimen according to the New Inuyama classification system [17]. The median follow-up period was 2.61 years (range 0.09–8.52 years). Overall survival (OS) was defined

as the interval between initial surgical treatment and death or the last follow-up date. Recurrent-free survival (RFS) was defined as the interval between initial surgical treatment and first recurrence. Patients who had undergone noncurative resection, anatomical liver resection, repeated liver resection, and synchronous resection of a different organ were excluded. The patients' medical records were reviewed retrospectively, and the data were collected.

## Indications for liver resection

Preoperative investigations included computed tomography, magnetic resonance imaging, abdominal ultrasonography and blood tests. The adaptation of liver resection was based on the published flow chart considering the presence of ascites, serum total bilirubin levels, and indocyanine green retention rate at 15 min (ICGR15) [18]. The choice of LLR or OLR completely depended on the comprehensive assessment at each institution. Limited liver resection was defined as any non-anatomical resection that was not an anatomical resection as defined by the Brisbane 2000 Nomenclature of Hepatic Anatomy and Resections [19]. The difficulty score was based on the previous report [20]. Postoperative complications were graded according to the Clavien–Dindo Classification [21]. Posthepatectomy liver failure (PHLF) was defined and graded according to the criteria proposed by the International Study Group of Liver Surgery [22].

## Surgical procedure

The hepatectomy procedure used was as previously reported [23, 24]. OLR was performed through an upward midline incision, and when necessary a subcostal incision was added. Intraoperative ultrasonography was performed routinely. Hepatic parenchymal transection was performed using an ultrasonic surgical aspirator and bipolar forceps with soft coagulation with the Pringle maneuver. For LLR, an umbilical 12 mm port was placed using the open method. After the establishment of pneumoperitoneum, four ports were placed based on the tumor position. Intraoperative ultrasonography was systematically performed. Transection was performed using a combination of the ultrasonic surgical aspirator and bipolar forceps with the Pringle maneuver. Any vessel larger than 3 mm was secured with clips. The specimen was removed in an endoscopic retrieval bag via the umbilical port incision.

## Statistical analysis

The continuous clinicopathological data were expressed as median (range). The continuous variables were analyzed using the Mann–Whitney U test for statistical differences between the two groups. The categorical variables were

**Table 1** Patients' characteristics before propensity score matching

Variables	LLR (N=58)	OLR (N=197)	P value
Age (years)	71 (34–89)	68 (45–88)	0.201
Sex (male/female)	39/19	123/74	0.538
BMI (kg/m <sup>2</sup> )	23.4 (15.6–37.1)	23.5 (15.2–41.5)	0.987
DM (N/Y)	30/25	125/66	0.155
DM, n (%)	25 (45.4)	66 (34.6)	1
HBV, n (%)	10 (17.2)	33 (16.8)	0.359
HCV, n (%)	32 (55.2)	123 (62.4)	0.678
PT (%)	81 (51–116)	80 (13–116)	0.928
T-Bil (mg/dL)	0.8 (0.2–2.9)	0.9 (0.3–2.4)	0.243
AST (IU/L)	49 (11–165)	39 (13–180)	0.219
ALT (IU/L)	31 (10–198)	28 (8–172)	0.601
Alb (g/dL)	3.7 (2.5–4.9)	3.7 (2.4–4.9)	0.531
ICGR (%)	22.4 (2.2–63.1)	22.3 (2.9–59.7)	0.865
AFP (ng/mL)	10.2 (1.7–4188)	10.8 (1–12,772)	0.511
DCP (mAU/mL)	34 (12–6980)	45 (8–17,431)	0.316
Child–Pugh (A/B)	45/13	166/32	0.326
Liver damage (A/B, C)	28/30	93/98	0.191
Tumor number (1/> 1)	48/10	134/64	0.032
Tumor size (mm)	17 (1.2–42)	20 (7–99)	0.006
Difficulty score	3 (1–6)	3 (1–8)	0.045

Values are median (range) unless otherwise indicated

AFP alpha-fetoprotein levels, Alb albumin, AST aspartate aminotransferase, ALT alanine aminotransferase, BMI body mass index, DCP des-gamma-carboxyprothrombin, DM diabetes mellitus, HBV hepatitis B virus, HCV hepatitis C virus, ICGR15 indocyanine green retention rate at 15 min, N No, Plt platelet count, PT prothrombin time, T. Bil total bilirubin, Y Yes

analyzed using the Fisher's exact test. OS and RFS values were calculated using the Kaplan–Meier method and the difference between the curves were compared using the log-rank test. To overcome possible selection bias, one-to-one propensity score matching between the LLR and OLR groups was calculated using multiple logistic regression according to patients' characteristics including number of tumors, tumor size, and difficulty score. One-to-one matching was performed using a caliper width 0.20. Statistical analyses were performed using JMP Pro (version 14; SAS Institute, Cary, NC, USA). All *p*-values < 0.05 were considered statistically significant.

## Results

Patient characteristics of the two groups before propensity score matching are summarized in Table 1. There were no significant differences in age, sex, hepatitis B and C infection, Child–Pugh grade, liver damage grade, and pre-operative blood tests. The number of tumors was higher, tumor size was larger, and difficulty score was higher significantly in the OLR group. Operative results and postoperative complications of the two groups before propensity score matching are shown in Table 2. Although there were no significant differences in the operation time, red cell concentration (RCC) transfusion, duration of the Pringle maneuver and tumor-free margin between the two groups, the intraoperative blood loss was smaller in the LLR group than in the OLR group (*p* < 0.001). Postoperative complications, including ascites, pleural effusion, bile leak,

**Table 2** Operative findings and postoperative complications before propensity score matching

Variables	LLR (N=58)	OLR (N=198)	P value
Operation time (min)	242 (66–682)	216 (52–503)	0.103
Blood loss (mL)	87 (1–7798)	223 (1–4160)	< 0.001
Transfusion (mL)	0 (0–4480)	0 (0–3200)	0.264
Duration of the Pringle maneuver (min)	49 (11–162)	42 (4–121)	0.393
Specimen volume (mL)	21 (1–225)	30 (1–632)	0.026
Tumor-free margin (mm)	3 (0–28)	3 (0–23)	0.877
Complication (N/Y)	49/9	129/69	0.005
Bile leak (N/Y)	57/1	195/3	1
Ascites (N/Y)	54/4	163/35	0.049
Pleural effusion (N/Y)	57/1	184/14	0.202
Wound infection (N/Y)	56/2	180/18	0.263
Portal vein thrombosis (N/Y)	58/0	193/5	0.591
CD (< III/≥ III)	55/3	185/13	1
PHLF (0/A, B, C)	45/13	132/62	0.191
Hospital stay (days)	9 (5–45)	14 (7–380)	< 0.001

CD Clavien–Dindo classification, N No, Y Yes

**Table 3** Patients' characteristics after propensity score matching

Variables	LLR (N=58)	OLR (N=58)	P value
Age (years)	71 (34–89)	72 (45–88)	0.893
Sex (male/female)	39/19 (67.2/32.78)	30/28 (52.5/47.5)	0.132
BMI (kg/m <sup>2</sup> )	23.4 (15.6–37.1)	23.5 (16.1–32.8)	0.531
DM (N/Y)	30/25	36/19	0.331
HBV (N/Y)	48/10	45/13	0.493
HCV (N/Y)	26/32	19/39	0.186
Plt (× 10 <sup>4</sup> /mm <sup>3</sup> )	10.4 (3.4–26.3)	11.1 (3.1–30.6)	0.725
PT (%)	80.8 (50.7–116)	78.6 (13.1–116)	0.358
T-Bil (mg/dL)	0.8 (0.2–2.9)	0.8 (0.4–1.9)	0.799
AST (IU/L)	49 (11–165)	39 (13–89)	0.229
ALT (IU/L)	32 (10–198)	29 (10–94)	0.468
Alb (g/dL)	3.7 (2.5–4.9)	3.6(2.5–4.9)	0.859
ICGR15 (%)	22 (2.2–63.1)	21 (7.8–50.2)	0.792
AFP (ng/mL)	10.2 (1.7–4188)	13.4 (1.5–3870)	0.142
DCP (mAU/mL)	34 (12–6980)	31 (8–2903)	0.465
Child–Pugh (A/B, C)	45/13 (77.6/22.4)	45/13 (77.6/22.4)	1
Liver damage (A/B, C)	28/30 (48.3/51.7)	26/28 (48.2/51.8)	1
Tumor number (1/> 1)	1 (1–4)	1 (1–2)	0.338
Tumor size (mm)	17 (2–42)	16 (8–50)	0.647
Difficulty score	3 (1–6)	3 (1–6)	0.888

AFP alpha-fetoprotein levels, Alb albumin, AST aspartate aminotransferase, ALT alanine aminotransferase, BMI body mass index, DCP des-gamma-carboxyprothrombin, DM diabetes mellitus, HBV hepatitis B virus, HCV hepatitis C virus, ICGR15 indocyanine green retention rate at 15 min, N No, Plt platelet count, PT prothrombin time, T. Bil total bilirubin, Y Yes

portal embolism and wound infection had developed in 69 patients in the OLR group and in 9 patients in the LLR group and the incidence of postoperative complications was significantly higher in the OLR group than in the LLR group ( $p = 0.005$ ). The incidences of pleural effusion, bile leak and wound infection were not different between the groups. There was a significant difference in the incidence of ascites ( $p = 0.049$ ). There was no difference between the proportion of patients who were classified as having Clavien's grade II or smaller and IIIa or higher and posthepatectomy liver failure (PHLF). The duration of the postoperative hospital stay was significantly shorter in the LLR group than in the OLR group ( $p < 0.001$ ).

After propensity matching, a total of 116 patients were matched. All baseline clinical characteristics between the LLR and OLR groups were well balanced (Table 3). There were no significant differences in age, sex, hepatitis B and C infections, Child–Pugh grade, liver damage grade, or preoperative blood tests. There were no differences between tumor number, tumor size, and difficulty score after propensity score matching.

Operative results and postoperative complications of the two groups are shown in Table 4. Although there were no significant differences in the operation time, RCC transfusion, duration of the Pringle maneuver, volume of specimen between the two groups and tumor-free margin, intraoperative blood loss was smaller in the LLR group than in the OLR group ( $p = 0.004$ ). Postoperative complications, including ascites, pleural effusion, bile leak, portal embolism, and wound infection was observed in 21 patients in the OLR group and in 9 patients in the LLR group, and the incidence of postoperative complications

**Table 4** Operative findings and postoperative complications after propensity score matching

Variables	LLR (N=58)	OLR (N=58)	P value
Operation time	242 (66–682)	213 (70–441)	0.081
Blood loss	85 (10–2300)	200 (10–1657)	0.004
Transfusion	0 (0–4480)	0 (0–3200)	0.948
Duration of the Pringle maneuver (min)	49 (11–162)	43 (12–97)	0.674
Specimen volume (mL)	21 (5–225)	27 (2–127)	0.162
Tumor-free margin (mm)	3 (0–28)	3 (0–15)	0.944
Complication (N/Y)	49/9	38/21	0.019
Bile leak (N/Y)	57/1	58/0	0.495
Ascites (N/Y)	54/4	48/10	0.152
Pleural effusion (N/Y)	57/1	54/4	0.364
Wound infection (N/Y)	56/2	56/2	1
Portal vein thrombosis (N/Y)	58/0	55/3	0.243
CD (< III/≥ III)	55/3	55/3	1
PHLF (0/A, B, C)	45/13	41/17	0.526
Hospital stay (days)	9 (5–45)	13 (7–75)	<0.001

CD Clavien–Dindo classification, N No, Y Yes

was significantly higher in the OLR group than in the LLR group ( $p=0.019$ ). The incidence of ascites, pleural effusion, bile leak, and wound infection were not different between the groups. There was no difference between the proportion of patients who were classified as having Clavien's grade II or smaller and IIIa or higher and PHLF. The duration of the postoperative hospital stay was significantly shorter in the LLR group than in the OLR group ( $p<0.001$ ).

The 3-year survival rates of patients with LLR and OLR were 82.0% and 78.4%, respectively. The 5-year survival rates of patients with LLR and OLR were 58.9% and 62.3%, respectively. The difference in survival rates between the groups was not statistically significant ( $p=0.872$ ) (Fig. 1A). The 3-year recurrent-free survival rates of patients with LLR and OLR were 52.6% and 40.3%, respectively. The 5-year recurrent-free survival rates of patients with LLR and OLR were 24.0% and 24.1%, respectively. There was no difference between the two groups with respect to recurrent-free survival ( $p=0.583$ ) (Fig. 1B).

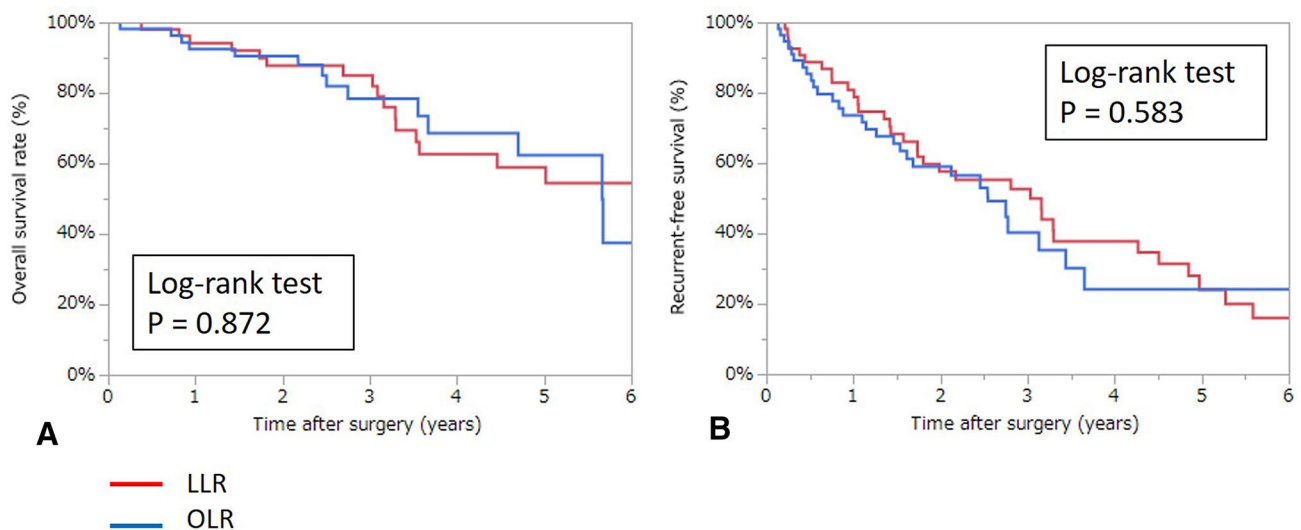
## Discussion

Progress with respect to surgical devices and advances in surgical techniques have greatly improved laparoscopic surgery in recent decades. Although laparoscopy is currently considered as a safe and an oncological alternative method to open surgery, LLR for HCC in cirrhotic patients remains still challenging and requires discussion [25, 26]. Our study consisted only of patients with a histopathological diagnosis of cirrhosis and analyzed in multicenter data. In addition, propensity score matching analysis was carried out to reduce

selection bias, and difficulty score, which was significantly different, was added as a covariate. This aims at the reducing selection bias with respect to the position of the tumor on the liver surface and the tumor in the vicinity of the center. This may clarify the impact of liver cirrhosis on the clinical outcomes of LLR and OLR performed for HCC in a homogeneous sample of patients. It could often be proposed as an oncologically satisfactory result with a small complication rate, short-duration hospital stays, and postoperative outcome, as the first choice for HCC treatment or as a bridging therapy until liver transplantation.

The median blood loss was 85 mL in the LLR group, which was significantly lower than that of the OLR group (200 mL) ( $p=0.004$ ). The patients with impaired liver function had decreased prothrombin activity and lower platelet counts due to decreased protein synthesis in liver, and increased splenic function caused by portal hypertension had been observed in the patients with impaired liver function. A risk factor for increased blood loss during hepatectomy is low prothrombin activity and low platelet counts [27]. Many studies have reported that LLR is associated with lower blood loss compared to OLR [8–11]. It is thought that the laparoscopic magnification effect and pneumoperitoneum pressure effect reduce the amount of bleeding during laparoscopic surgery [28], which might be effective for intraoperative hemostasis in patients with impaired liver function.

Although there was no significant difference between the two groups in each complication, the incidence of postoperative complications was significantly higher in the OLR than in the LLR in the whole complication. With laparoscopic minimally invasive surgery, complications were significantly reduced, resulting in a shorter hospitalization period. There were also little ascites, pleural effusion,



**Fig. 1** Relationship between the two groups of overall survival and recurrent-free survival



and postoperative liver failure in the LLR group, the major complication of liver resection for cirrhotic patients [29]. It did not increase the incidence of bile leakage or portal vein thrombosis. There was no difference in the resected specimen volume and tumor-free margin. That is, similar surgical results could be obtained under similar surgical conditions in case of absence of difference in tumor size and location between the two groups. It is important to secure enough tumor-free margin which affects RFS [30]. It compensates with the intraoperative ultrasonography with the disadvantage of the lack of palpation. The result obtained is superior to OLR. Long-term prognosis OS and RFS did not show any difference under similar surgical conditions between the two groups. It is satisfactory as an oncological treatment. Therefore, LLR is a safe and effective technique for cirrhotic patients as well.

The present study had some drawbacks. The retrospective fashion and absence of randomization may limit the power and precision of the results. Furthermore, a variation in patient management strategy and difference in the number of laparoscopic surgeries conducted between facilities must have existed due to the retrospective multicenter study design. In order to counteract the selection bias due to lack of randomization, we performed the propensity score matching analysis as an effective method to balance the covariates. However, randomized further research should be performed in future.

In conclusion, LLR decreased the incidences of postoperative complications and shortened the duration of postoperative hospital stays. Thus, the LLR is a safe and feasible procedure even in patients with cirrhosis.

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### Compliance with ethical standards

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