# Laparoscopic liver resection for hepatocellular carcinoma with cirrhosis in a single institution

# Takeshi Takahara<sup>1</sup>, Go Wakabayashi<sup>2</sup>, Hiroyuki Nitta<sup>1</sup>, Yasushi Hasegawa<sup>1</sup>, Hirokatsu Katagiri<sup>1</sup>, Daiki Takeda<sup>1</sup>, Kenji Makabe<sup>1</sup>, Akira Sasaki<sup>1</sup>

<sup>1</sup>Department of Surgery, School of Medicine, Iwate Medical University, Iwate, Japan; <sup>2</sup>Department of Surgery, Ageo Central General Hospital, Saitama, Japan

*Contributions:* (I) Conception and design: T Takahara; (II) Administrative support: None; (III) Provision of study materials or patients: T Takahara, G Wakabayashi, H Nitta, Y Hasegawa; (IV) Collection and assembly of data: T Takahara, H Katagiri; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Takeshi Takahara, MD, PhD. Department of Surgery, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan. Email: takahara@iwate-med.ac.jp.

**Background:** In a statement by the second International Consensus Conference for Laparoscopic Liver Resection (LLR), minor LLR was confirmed to be a standard surgical practice, as it has become adopted by an increasing proportion of surgeons. However, it is unclear whether this applies to the more complex group of patients suffering from cirrhosis. Therefore, the aim of this retrospective study was to compare the feasibility and safety of LLR for hepatocellular carcinoma (HCC) between non-liver cirrhosis (NLC) patients and liver cirrhosis (LC) patients at a single high-volume laparoscopy center.

**Methods:** From the beginning of 2000 to the end of 2013, open liver resection (OLR) was performed in 99 HCC patients, and LLR was in 118. The HCC patients who underwent LLR were divided into NLC-LLR (n=60) and LC-LLR (n=58) groups, and we compare the short-term outcomes between them.

**Results:** There was no significant difference in the incidence of blood loss and transfusion requirements between the NLC-LLR group and the LC-LLR group, although wedge resection was mainly performed in the LC-LLR group. There was no significant difference in the complication rate between the two groups, and the remarkable finding was that there was a significantly lower incidence of postoperative ascites in the LC-LLR group than in the NLC-LLR group.

**Conclusions:** According to our experience, it appears that LLR for selected HCC patients with cirrhosis is a feasible and promising procedure that is associated with less blood loss and fewer postoperative complications, especially the incidence of postoperative ascites. Further investigations are clearly warranted.

Keywords: Laparoscopic liver resection (LLR); open liver resection (OLR); cirrhosis; comparative study

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#### Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and the fifth most prevalent cancer worldwide (1,2). The incidence of HCC is associated with an increase in hepatitis B- or C-related cirrhosis. The various treatment options for HCC include hepatic resection, liver transplantation, chemotherapy, transarterial chemoembolization, and local ablative therapy. Liver transplantation is a potentially curative option, but, due to various limitations, such as donor availability, recipient age, and continued alcohol abuse, often it is limited in application (3). Therefore, liver resection is an alternative option that is widely accepted as a potentially curative treatment for HCC in patients with adequate liver function, due to technical advances and improvements in perioperative patient management. However, most patients

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with HCC have underlying chronic liver disease, and a hepatic resection in the setting of cirrhosis adds an extra degree of difficulty. Intra-abdominal varicies, impaired coagulation, a firm liver parenchyma and the specter of postoperative hepatic failure are all potential obstacles to hepatic resection in the cirrhotic population. In open liver surgery, an extremely long incision is necessary for mobilization and resection of the liver, because the liver is anatomically surrounded by the rib cage. In cirrhotic patients, these surgical procedures can result in significant blood loss or the development of intractable postoperative ascites, because of the destruction of collateral circulation in the abdominal wall and the ligaments surrounding the liver.

Laparoscopic procedures for hepatic surgery have been slow to develop, due to the inherent risk of massive bleeding associated with liver resection. The First International Consensus Conference on Laparoscopic Liver Surgery convened in Louisville, Kentucky, in 2008 (4), and since then, the number of laparoscopic liver resections (LLRs) has increased steadily worldwide. Moreover, the number of HCC cases in which LLR is applied has increased steeply over the past five years, especially in Asia and Europe (5). LLR is associated with reduced blood loss, decreased overall and liver-specific complications, and shorter postoperative hospital stays. In a statement by the second International Consensus Conference for Laparoscopic Liver Resection (6), minor LLR was confirmed to be a standard surgical practice, but it is still in the assessment phase (IDEAL 3) (7) as it becomes adopted by an increasing proportion of surgeons. However, it is unclear whether this applies to the more complex group of patients suffering from cirrhosis (8). Therefore, the aim of this retrospective study was to compare the feasibility and safety of LLR for HCC between non-liver cirrhosis (NLC) patients and liver cirrhosis (LC) patients at a single high-volume laparoscopy center. In addition, we reviewed several comparative studies of the perioperative outcomes between LLR and open liver resection (OLR) for HCC patients, recently reported from Asia.

#### **Patients and methods**

This is a retrospective study, based on the prospective collection of patient data from a computerized database of all preoperative, perioperative, and postoperative information. From the beginning of 2000 to the end of 2013, 245 patients underwent various treatments for HCC in the Department of Surgery at School of Medicine, Iwate Medical University in Iwate, Japan. Patients were evaluated before treatment according to a specific protocol that included chest radiography, ultrasonography of the abdomen, 4-phase contrast computed tomography of the abdomen, and blood examinations. During this period, OLR was performed in 99 HCC patients, and LLR in 118. The diagnosis of HCC was confirmed by histologic examination of the resected specimens from all patients. LC was diagnosed using the New Inuyama classification system, which is well known in Japan: F0, no fibrosis; F1, portal fibrosis widening; F3, bridging fibrosis plus lobular distortion; and F4, LC, which corresponds to the New European classifications as follows: F0, no fibrosis; F1, mild fibrosis; F2, moderate fibrosis; F3, severe fibrosis; F4, cirrhosis (9,10). In this study, LC was defined histologically as F4 according to the New Inuyama classification system.

#### Indication for liver resection

Our inclusion criteria for LLR were a tumor size of less than 10 cm and the absence of severe adhesions, invasion to major vessels, or a need for vessel reconstruction. Liver resection was defined according to the Brisbane 2000 classifications, using the following definition: hemihepatectomy, sectionectomy (anterior, posterior, and medial), bisegmentectomy (for resection of two segments), segmentectomy (for resection of one segment), left lateral sectionectomy, and wedge resection (11).

The indications and types of liver resections at our institute were not modified by the use of laparoscopy, similar to the principle in open OLR, and were determined by tumor size, location, and hepatic function. Our criteria for patient eligibility for hepatectomy were based on three parameters: (I) the presence or absence of ascites; (II) total serum bilirubin level; and (III) an indocyanine green retention rate at 15 minutes (ICG R15). The HCC patients who underwent LLR were divided into NLC-LLR (n=60) and LC-LLR (n=58) groups, and we compare the short-term outcomes between them. We defined short-term outcomes as surgical results and the events ocurred for postoperative 90-days.

#### Laparoscopic liver resection (LLR)

For LLR, the patient was placed in the supine position with the primary surgeon on the right side of the patient and the first assistant and scopist positioned on the left. When tumor lesions were located in the right lateral sector, the patient was placed in the semi-left lateral position for right lobe mobilization. Trocars were inserted using Takahara et al. Laparoscopic liver resection for HCC with cirrhosis



**Figure 1** Laparoscopic partial hepatectomy for HCC located in segment 2 with cirrhosis (12). HCC, hepatocellular carcinoma. Available online: http://www.asvide.com/articles/732

the open technique, and a continuous carbon dioxide pneumoperitoneum was induced at a pressure of 10 mmHg. If unexpected bleeding from tiny holes in the hepatic vein were encountered during the parenchymal dissection, we often maintained the pneumoperitoneum pressure at 10–12 mmHg. Intraoperative ultrasonography was often performed to evaluate and determine the tumor location and to assist in liver parenchymal resection.

For pure-laparoscopic minor resection, including left lateral sectionectomy, we extended the indication of the laparoscopic approach according to tumor location. For laparoscopic major resection, we developed a surgical procedure for performing major hepatectomy through a small incision using a hanging maneuver. We have named this procedure laparoscopy-assisted major liver resection, as it is not a hand-assisted LLR. After performing a large number of these advanced surgical techniques in laparoscopy-assisted major hepatectomies, in 2009 we developed a pure laparoscopic major hepatectomy technique for benign diseases and malignant tumors.

The key technical points of LLR are currently as follows:

- An intermittent Pringle maneuver is necessary to minimize hemorrhage during hepatic parenchymal dissection;
- If not performing the Pringle maneuver securely, precoagulation along the transection line with radiofrequency ablation (RFA) or microwave coagulation therapy (MCT) is necessary to minimize hemorrhage during hepatic parenchymal dissection;
- If a deep tumor is not visible during laparoscopy, it may be difficult to measure the distance between the tumor and the resection margin. To secure the

surgical margin, the parenchymal dissection should be performed along the tributaries of the main hepatic vein or the tumor-feeding Glissonean pedicle, which form the landmarks for the deep transection line;

- During parenchymal dissection, effective suction is mandatory to confirm the bleeding point immediately and to keep the resection plane dry (*Figure 1*);
- The resected specimen is placed in a plastic bag and externalized through either a slightly enlarged port site, the small incision site in laparoscopy-assisted liver resection, or the newly created suprapubic incision.

# Comparison between NLC-LLR and LC-LLR

The study criteria for comparing the NLC-LLR group to the LC-LLR group were as follows.

# Preoperative data

The following variables were recorded for each group: sex, age, underlying liver disease status [hepatitis B surface antigen (HBs-Ag) and anti-hepatitis C virus antibody positivity], serum alpha-fetoprotein (AFP) and des-gammacarboxyl prothrombin (DCP) levels, ICGR 15, extent of liver damage (determined according to the criteria of the Liver Cancer Study Group of Japan), Child-Pugh score, and the Japan Integrated Staging (JIS) score (13).

# Intraoperative and surgical results

Pathological tumor size, tumor number, and surgical margins were analyzed. Difficult tumor locations were defined as the postero-superior segments of the liver (segments 1, 7, and 8, and the superior part of segment 4) (14). Postoperative ascites or pleural effusions were defined as conditions requiring the use of diuretics, or thoracentesis, or abdominal paracentesis after the removal of the intraoperative placed drain. Bile leakage was defined as continuous drainage with a bilirubin concentration of 20 mg/dL or 1,500 mg/day, lasting 2 days. Liver failure was defined as hyperbilirubinemia (total serum bilirubin concentration >5 mg/dL for more than 5 days.

# Statistical analysis

The statistical analyses in this study were performed with Stata 13 (Stata Corporation, College Station, TX, USA). In analyses and comparisons of preoperative covariates and clinical parameters, student's *t*-test or the Wilcoxon rank sum test for continuous variables, and the  $\chi^2$  test or Fisher's exact test for categorical variables, were used. All

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Characteristics	LC-LLR (n=58)	NLC-LLR (n=60)	Р
Sex (M)	39 (67.24%)	48 (80%)	0.115
Age	65.67±9.21	65.67±8.37	0.9972
Height (cm)	160.9±10.8	162.0±8.2	0.5153
Weight (kg)	58.6±11.1	63.9±12.7	0.0184
BMI (kg/m²)	22.64±3.77	23.77±4.67	0.1553
HBV positive	17	18	0.125
HCV positive	34	16	0.029
Child-Pugh (A/B)	55/3	60/0	0.074
Liver damage (A/B/C)	41/16/1	56/4/0	0.005
JIS score (0/1/2/3)	13/31/12/2	4/29/21/4	0.047
AFP (ng/mL)	14.7 (5.7, 65.75)	5.1 (2.9, 28.3)	0.008
DCP (AU/mL)	44 (22, 139)	95 (24, 845)	0.0476
ICG R15	20.44±11.07	12.58±5.05	< 0.0001

LC, liver cirrhosis; LLR, laparoscopic liver resection; NLC, non-liver cirrhosis; JIS, Japan Integrated Staging; AFP, alpha-fetoprotein; DCP, des-gammacarboxyl prothrombin; ICG R15, indocyanine green retention rate at 15 minutes.

categorical data were expressed as number or frequency (%), and all continuous data were the mean  $\pm$  standard deviation, or the median (25%, and 75% quartile range). P<0.05 was considered statistically significant.

#### **Results**

The patients' characteristics are shown in Table 1. Preoperative tumor location difficulty and surgical margins were similar (P=0.5764, and P=0.7754, respectively) between the NLC-LLR group and the LC-LLR group, although the tumor size in the LC-LLR group was significantly smaller than in the NLC-LLR group (P<0.001). There was no significant difference in the incidence of blood loss and transfusion requirements between the NLC-LLR group and the LC-LLR group, although wedge resections were mainly performed in the LC-LLR group. There was no significant difference in the complication rate between the two groups. The remarkable finding was that there was a significantly lower incidence of postoperative ascites in the LC-LLR group than in the NLC-LLR group. One patient in the NC group died of heart failure and the other patient died of sepsis subsequently to hemorrhagic shock (Table 2).

#### Discussion

Laparoscopic liver surgery has undergone extreme

improvements in recent decades because of important technological developments, advances in preoperative imaging assessments (15), and increasing surgical experience. Due to the development of sophisticated laparoscopic instruments, such as laparoscopic ultrasonic dissectors, sealing energy devices (16), and vascular staplers, laparoscopic liver parenchymal dissection is now considered a feasible and safe alternative to open surgery (17). The number of HCC cases in which LLR is applied has increased steeply over the past five years, especially in Asia, and the rate of conversion to OLR is gradually decreasing. Tables 3,4 show several recent comparative studies between OLR and LLR for HCC patients in Asia (18-27). There were five comparative studies using propensity score matching, although no randomized controlled trials had been published. Propensity score matched analyses have become increasingly used in retrospective cohorts to reduce the impact of selection bias in the comparison of treatments to a non-randomized control group using observational data (28). These comparative studies including a propensity score matched analysis revealed that the most common short-term advantages of LLR were less intraoperative blood loss, shorter hospital stays, and fewer postoperative complications. In comparing the perioperative outcomes of LLR to those of OLR for HCC, using propensity score matching of relatively large data collected from 31 institutions in Japan, Takahara et al. reported that minor

Variables	LC-LLR (n=58)	NLC-LLR (n=60)	Р
Size (cm)	2.99±1.59	5.24±2.85	<0.0001
Difficulty (yes)	24 (41.38%)	29 (48.33%)	0.5764
Surgical margin (mm)	8.38±7.92	7.97±7.29	0.7754
Procedure			
Hemihepatectomy	10 (17.24%)	13 (21.67%)	
Sectionectomy	4 (6.90%)	21 (35%)	
Bisegmentectomy	0	5 (8.33%)	
Segmentectomy	9 (15.52%)	4 (6.67%)	
Left lateral sectionectomy	4 (6.90%)	8 (13.33%)	
Wedge	31 (53.45%)	9 (15%)	<0.0001
Pure/assist/HALS	40/18/0	35/22/3	0.157
Conversion	0 (0%)	0 (0%)	_
Blood loss (g)	208 (37, 460)	255 (55, 650)	0.2765
Transfusion (rate)	5	5	0.8721
Operation time (min)	244.8±113.4	314.5±126.9	0.0025
Hospital stay (days)	19.6±29.48	16.27±15.46	0.4444
Complication rate	10 (17.24%)	8 (13.79%)	0.608
Ascites	1	3	0.043
Pleural effusion	2	4	0.108
Bile leak	3	3	0.801
Liver failure	1	2	0.223
Others	4	3	0.878
Mortality	0 (0%)	2 (3.33%)	0.161

 Table 2 Intraoperative and surgical results of the two groups

LC, liver cirrhosis; LLR, laparoscopic liver resection; NLC, non-liver cirrhosis.

# Table 3 Comparative studies of LLR and OLR for HCC (part 1)

First author	Country	Year	Journal	Period	No. of p	oatients	Motobing	Liver	LC pat	ents (%)
FIRST AUTION	Country	rear	Journal	Penou	LLR	OLR	- Matching	resection	LLR	OLR
Cheung (18)	China	2015	World J Surg	2004–2014	24	29	Case match	LLS	18 (75.0)	18 (62.1)
Beppu (19)	Japan	2015	Anticancer Res	1999–2011	52	52	Propensity	Various	NA	NA
Takahara (20)	Japan	2015	J Hepatobiliary Pancreat Sci	2000–2010	387	387	Propensity	Various	NA	NA
Cho (21)	Korea	2015	Surgery	2003–2012	24	19	-	RPS	10 (41.7)	NA
Yoon (22)	Korea	2015	Surg Endosc	2007–2011	58	174	Propensity	Various	NA	NA
Xiao (23)	China	2015	Surg Endosc	2010-2012	41	86	-	Various	33 (80.4)	72 (83.7)
Kim (24)	Korea	2014	Surg Endosc	2000-2012	43	162	Propensity	Various	18 (62.1)	19 (65.5)
Kanazawa (25)	Japan	2013	Surg Endosc	2006–2010	28	28	-	Partial	28 (100)	28 (100)
Cheung (26)	China	2013	Ann Surg	2002–2009	32	64	-	Various	28 (87.5)	46 (71.9)
Ai (27)	China	2013	PLoS One	2007–2011	97	178	Propensity	Various	78 (80.4)	143 (80.3)

LLR, laparoscopic liver resection; OLR, open liver resection; HCC, hepatocellular carcinoma.

Time of the co	B	Blood loss (mL)	s (mL)	Transfu	Transfusion (patients, %)	s, %)	Operá	Operation time (min)	ne (min)	Hospit	Hospital stay (days)	lays)	Compl.	Complication rate (%)	(%	Ascit	Ascites (%)	Pleural effusion (%)	(%) uoisr
FIRST AUTION	LLR	LLR OLR	٩	LLR	OLR	4	LLR	OLR		LLR	OLR	٩	LLR	OLR	۵.	LLR	OLR	LLR	OLR
Cheung (18)	100	300	100 300 <0.001	0 (0%)	2 (6.9%)	0.557	190.5	195	0.734	5	9	0.057	4 (16.7%) 2 (6.9%)	2 (6.9%)	0.495	I	I	1 (4.2%)	1 (3.6%)
Beppu (19)	180	473	180 473 <0.001		2 (3.8%) 2 (3.8%)	>0.999	320	345	0.049	11	14	0.002	4 (7.7%)	4 (7.7%) 11 (21.2%)	0.092	0 (0%)	NA	0 (0%)	NA
Takahara (20) 158 400 <0.001	158	400	<0.001	28 (7.2%) 38 (9.8%	38 (9.8%)	0.198	294.4	271	0.025	13	16	<0.001	26 (6.7%)	50 (13.0%)	0.003	7	12	7	5
Cho (21)	NA	NA	I	NA	NA	I	567.4	316.1	<0.001	10.6±1.0 11.1±3.2	11.1±3.2	0.380	2 (8.3%)	4 (21.1%)	0.380	NA	NA	NA	NA
Yoon (22)	NA	NA	I	2 (3.4%)	2 (3.4%) 13 (7.5%)	0.04	207	255	0.00	9.2	15	00.0	2 (3.4%)	8 (4.6%)	I	0 (0%)	1 (0.01%)	0 (0%)	0 (0%)
Xiao (23)	272.2	2 450.1	272.2 450.1 0.001	3 (7.3%)	3 (7.3%) 12 (14.0%) 0.430	0.430	242.4	235.4	0.589	9.44	14.53	0.000	7 (17.1%)	7 (17.1%) 32 (37.2%)	0.021	1 (2.4%)	4 (4.7%)	1 (2.4%)	6 (7.0%)
Kim (24)	483.(	9 261.2	483.9 261.2 0.065	1 (3.4%)	1 (3.4%) 0 (0%)	0.317	210.5	203.5	0.681	7.7	13.4	<0.001	4 (13.8%)	4 (13.8%) 11 (37.9%)	0.118	0 (0%)	5 (17.2%)	NA	NA
Kanazawa (25) 88 505	88	505	0.0003	(%0) 0	4 (14.3%)	0.0379	228	236	0.922	10	19	<0.001	3 (10.7%)	3 (10.7%) 20 (71.4%)	<0.001	3 (10.7%)	3 (10.7%)18 (64.3%)	NA	NA
Cheung (26) 150	150	300	0.001	(%0) 0	3 (4.7%)	0.534	232.5	204.5	0.938	4	7	<0.001	2 (6.3%)	2 (6.3%) 12 (18.8%)	0.184	0 (0%)	1 (1.6%)	0 (0%)	1 (1.6%)
Ai (27)	460	454	460 454 0.913	4.55%	2.81%	0.480	245	225	0.469	8.2	13.5	0.028	0.028 10 (10.3%) 50 (28.1%)	50 (28.1%)	I	0 (0%)	4 (2.2%)	1 (1.0%)	8 (4.5%)

LLR in selected patients was a good option as a standard practice for the treatment of HCC.

In HCC patients with cirrhosis, pleural effusion and ascites often develop after conventional OLR. Nevertheless, liver resection remains the main curative procedure. To perform a liver parenchymal transection, a large incision is usually necessary for the mobilization, cutting the surrounding ligaments, and dissection from the diaphragm. Such a large incision and mobilization causes blockage of the collateral circulation around the liver, and consequently results in secondary portal hypertension. With respect to the complications, the frequency of postoperative ascites and pleural effusion after LLR was lower than after OLR. This result might be explained by less destruction of the collateral blood/lymphatic flow by LLR during mobilization of the liver. The reduction of surgery-induced injury with LLR may lower the risk of postoperative liver failure in HCC patients with severe cirrhosis. In the current study, there were no statistically significant differences in the incidence of postoperative morbidity and mortality between the NLC-LLR group and the LC-LLR group. This important finding supported the safety and feasibility of LLR for HCC in patients with cirrhosis.

Initially, cirrhosis was considered a contraindication for LLR. With the growing surgical experiences and the introduction of new equipment, several studies have reported good short-term outcomes after LLR for HCC in patients with cirrhosis. One of the major obstacles of LLR in cirrhotic patients is the risk of massive bleeding, because these patients have a bleeding tendency related to primary hemostasis dysfunction. In the current study, there was no significant difference in the incidence of blood loss and transfusion requirements between the LC-LLR group and the NLC-LLR group, although there was significant difference in the surgical procedure between the two groups. Shehta et al. reported almost the same results as ours (29). This can be explained by the hemostatic effect of pneumoperitoneal pressure, the use of new devices for parenchymal transection, and the use of the Pringle maneuver. Therefore, we performed LLR safety for the superficially localized small tumor, even if the hepatic reserve of the patient was liver damage B or Child-Pugh score B.

In conclusion, according to the Asian experience, it appears that LLR for selected HCC patients with cirrhosis is a feasible and promising procedure that is associated with less blood loss and fewer postoperative complications, especially the incidence of postoperative ascites. Further

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investigations are clearly warranted.

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# Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

*Ethical Statement*: The study was approved by institutional ethics board.

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