Int Surg 2023;**107:**23–30
DOI: 10.9738/INTSURG-D-21-00023.1

Perioperative and Long-Term Oncologic Outcomes of Laparoscopic Right Hepatectomy Versus Open Right Hepatectomy for Hepatocellular Carcinoma: A Propensity Score–Matching Analysis

Eun-Kyu Park, Rukhsora D. Sultonova, SangHwa Song, Hee Joon Kim, Young Hoe Hur, Chol Kyoon Cho, YangSeok Koh

Department of General Surgery, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun-eup, South Korea

Objective: To evaluate the efficacy and safety of laparoscopic major hepatectomy for hepatocellular carcinoma patients.

Summary of background data: Despite the popularity of laparoscopic hepatectomy, it is still in need of further evidence to assess its safety and efficacy for the treatment of hepatocellular carcinoma.

Methods: From 2008 to 2017, 149 patients (laparoscopic right hepatectomy [LRH], 28 patients; open right hepatectomy [ORH], 121 patients) were included. Baseline characteristics, including tumor characteristics, perioperative outcomes, and survival outcomes, were compared between the 2 groups. For group comparisons, one-to-one propensity score matching was used to minimize selection biases.

Results: After one-to-one propensity score matching, 25 LRHs were compared to 25 ORHs. Operative time was significantly shorter for the ORH group than for the LRH group (mean, 322.5 versus 379.5 minutes; $P = 0.015$), whereas the LRH group showed less intraoperative blood loss ($P = 0.02$) and lower intraoperative transfusion ($P = 0.02$). Postoperative hospital stays were significantly shorter for the LRH group (mean, 14.5 days versus 20.2 days; $P = 0.004$). Overall morbidities were significantly lower in the LRH group (1:13, $P = 0.00$). The

Corresponding author: YangSeok Koh, Department of General Surgery, Chonnam National University Hwasun Hospital, 322 Seoyang-ro, Hwasun-eup, Hwasun-gun, Jeollanam-do 58128, South Korea.
Tel.: 82 10 9000 4329; Fax: 82 61 379 7661; E-mail: yskoh@jnu.ac.kr
Rukhsora D. Sultanova and Eun-Kyu Park have contributed equally to this work.

cumulative 1-, 3-, and 5-year overall survival rates were 100%, 92.0%, and 92.0%, respectively, for the LRH group, and 84.0%, 80.0%, and 64.0%, respectively, for the ORH group. Furthermore, the cumulative 1-, 3-, and 5-year disease-free survival rates were 96.0%, 80.0%, and 75.3%, respectively, for the LRH group, and 72.0%, 48.0%, and 40.0%, respectively, for the ORH group. The LRH group showed significantly longer disease-free survival ($P = 0.009$) and overall survival ($P = 0.028$) than the ORH group.

Conclusion: LRH can be safely performed for hepatocellular carcinoma. LRH was associated with more favorable oncologic outcomes.

Key words: Laparoscopy – Hepatectomy – Hepatocellular carcinoma – Perioperative outcomes – Survival

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the fourth leading cause of cancer-related deaths worldwide.[1] Most HCCs develop in the background of chronic liver disease, including liver cirrhosis, which makes a surgical approach more demanding. For this reason, resectable cases account for only 25% to 30% of patients.[2] Liver transplantation can provide better oncologic outcomes; liver resection, however, is still the treatment of choice because of the donor shortage. Cirrhosis complicates HCC in 80% to 90% of cases worldwide.[3,4] Hence, reducing surgical stress while not affecting oncologic outcomes is important in treating HCC. The advantage of laparoscopic liver resection (LLR) is that it is associated with less postoperative pain, early ambulation, early return to oral feeding, and fewer postoperative complications.[5] Because of its less invasive nature, LLR can reduce postoperative liver failure and ascites.[6]

From 3 consensus meetings,[7–9] minor liver resection has been the standard alternative to open resection. However, major hepatectomy, especially right hepatectomy, for HCC is recommended to be performed in specialized centers. Laparoscopic right hepatectomy (LRH) is technically demanding and has a risk of major vessel injury. Until now, there have been only a few reports on the surgical and oncologic outcomes of major hepatectomy for HCC.[10–13]

The aim of this study was to evaluate the perioperative and long-term oncologic outcomes of LRH by comparing them with those of open right hepatectomy (ORH) for HCC in well-matched patient groups through a propensity score–matched analysis to minimize selection bias.

Methods

After an Institutional Review Board approved the study, the medical records of all patients who underwent right hepatectomy for HCC were retrospectively reviewed. From January 2008 to December 2017, a total of 149 patients underwent right hepatectomy, either through the open or the laparoscopic method. The diagnosis of HCC was entirely based on pathologic examination of resected specimens. Similar inclusion criteria were adopted for both LRH and ORH. Cases with main portal vein invasion and extrahepatic metastasis were excluded from this study. Our institution has a size limitation of 7 cm for LRH.

For LRH, the patient was placed in the reverse Trendelenbeurg position. Five trocars were used (12-mm camera port, two 12-mm working ports, and two 5-mm assistance ports) in all cases. The Glissonian approach was the main method of inflow control. The Cavitron Ultrasonic Surgical Aspirator (Valleylab, Boulder, Colorado) was used in parenchymal dissection. The intermittent Pringle maneuver (15 minutes of clamping and 5 minutes off) was routinely adopted for a clean surgical field. Intra-abdominal pressure was maintained under 12 mmHg and was increased up to 16 mmHg to minimize the blood loss when oozing or minor bleeding was observed. For ORH, an L-shaped incision was used. The Glissonian approach was used for inflow control and the Cavitron Ultrasonic Surgical Aspirator was the main dissection instrument.

After discharge, all patients were followed up according to the Korean HCC guideline.[14] Computed tomography (CT) scan was performed every 3 to 4 months during the first 2 years, and every 4 to 6 months thereafter. At each hospital visit, clinical examination, hepatic function tests, and α-fetoprotein level were measured. Recurrence was defined when confirmed on follow-up CT/magnetic resonance imaging.

To minimize the confounding effect, 1:1 propensity score matching (PSM) was performed using a

Table 1 Baseline characteristics before and after PSM

	All patients			Propensity score–matched patients		
	LRH (n = 28)	ORH (n = 121)	*P*	LRH (n = 25)	ORH (n = 25)	*P*
Age, mean ± SD, y	61.2 ± 10.1	58.7 ± 11.3	0.241	60.6 ± 10.2	57.4 ± 12.6	0.31
Sex, M:F, n	23:5	105:16	0.55	20:5	20:5	1
ASA grade, I:II:III, n	11:17:0	21:91:8	0.029	10:15:0	3:19:3	0.027
BMI, mean ± SD	24.5 ± 3.3	23.4 ± 3.1	0.125	24.5 ± 3.5	23.8 ± 3.2	0.455
Comorbidity, n (%)						
CV	13 (46.4)	43 (35.5)	0.289	11 (44.0)	10 (40.0)	1
DM	5 (17.9)	34 (28.1)	0.344	5 (20.0)	4 (16.0)	1
Pulmonary	1 (2.6)	6 (5.0)	1	1 (4.0)	1 (4.0)	1
Renal	2 (7.1)	3 (2.5)	0.236	2 (8.0)	1 (4.0)	1
Preoperative Abd Op, n (%)	1 (3.6)	17 (14)	0.197	1 (4.0)	3 (12.0)	0.609
Preoperative HCC Tx, n (%)	6 (21.4)	20 (16.5)	0.723	5 (20.0)	2 (8.0)	0.221
Liver disease, n (%)						
HBV	18 (64.3)	73 (60.3)	0.83	16 (64.0)	14 (56.0)	0.773
HCV	2 (7.1)	12 (9.9)	1	2 (8.0)	2 (8.0)	1
Preoperative blood tests, mean ± SD						
ALT, IU/L	46.8 ± 61.2	46.3 ± 46.7	0.971	46.8 ± 61.2	39.4 ± 28.9	0.572
AST, IU/L	47.9 ± 72.1	51.3 ± 41.0	0.826	47.9 ± 72.1	37.9 ± 19.2	0.324
TB, μmol/L	0.71 ± 0.34	0.78 ± 0.39	0.394	0.71 ± 0.34	0.87 ± 0.47	0.133
PT, INR	0.71 ± 0.34	0.78 ± 0.39	0.394	0.71 ± 0.00	0.88 ± 0.47	0.133
Creatinine, mg/dL	0.89 ± 0.17	0.97 ± 0.22	0.078	0.89 ± 0.17	0.98 ± 0.19	0.114
Platelet count, $\times 10^9$/L	197.8 ± 50.3	180.9 ± 70.4	0.15	197.8 ± 50.3	186.4 ± 82.79	0.051
AFP, ng/mL	673.8 ± 1750.7	2030 ± 7385.6	0.132	673.8 ± 1750.7	1813.9 ± 6608.31	0.502
ICGR15, %	12.37 ± 4.98	10.8 ± 6.66	0.184	12.37 ± 4.98	8.27 ± 7.47	0.117
Pathologic characteristics						
Liver cirrhosis, n (%)	11 (39.3)	68 (56.2)	0.141	10 (40.0)	13 (52.0)	0.571
Tumor size, mean ± SD (cm)	4.6 ± 2.7	5.9 ± 3.7	0.051	4.9 ± 2.8	4.6 ± 2.8	0.72
Tumor number, solitary:multiple	23:5	108:13	0.228	21:4	23:2	0.107
Margin involvement, n	0	2	1	0	0	
Lymphovascular invasion, n (%)	4 (14.3)	33 (27.3)	0.114	4 (16.0)	60 (24.0)	0.725
Satellite nodule, n (%)	2 (7.1)	22 (18.2)	0.252	2 (8.0)	11 (44.0)	0.08
Bile duct invasion, n (%)	0 (0)	2 (1.7)	1	0 (0)	1 (4.0)	1
Portal vein invasion, n (%)	6 (21.4)	30 (24.8)	0.849	5 (20.0)	3 (12.0)	0.304
Capsular invasion, n (%)	16 (57.1)	85 (70.2)	0.187	15 (60.0)	17 (68.0)	0.769

Abd Op, abdomen operation; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; HBV, hepatitis B virus; HCC Tx, HCC treatment; HCV, hepatitis C virus; ICGR15, indocyanine green retention rate at 15 minutes; PT, prothrombin time; TB, total bilirubin.

logistic regression model. We matched the following characteristics: age, sex, comorbidity, underlying liver disease, American Society of Anesthesiologists (ASA) grade, blood test, ICGR 15 minutes, α-fetoprotein, previous abdominal operation history, preoperative HCC treatment history, and pathologic findings (tumor size, tumor number). Postoperative morbidity and oncologic outcomes were the primary and secondary end points, respectively. Continuous variables were compared between groups using the Student *t*-test or Mann-Whitney test, as appropriate. Chi-square test or Fisher exact test was used to compare categoric variables; $P < 0.05$ was considered statistically significant. The Kaplan-Meier method was used to calculate survival. Survival curves were compared between 2 groups using the log-rank test. All statistical analyses were performed using SPSS version 26.0 (IBM Corp, Armonk, New York).

Results

Clinicopathologic characteristics of the 2 groups before and after PSM are shown in Table 1. Before and after PSM, the ASA score between the 2 groups showed significant difference ($P = 0.029$ and $P = 0.027$). The ORH group tended to have larger tumor sizes. After PSM, all of the characteristics except ASA score were comparable.

Operative outcomes are summarized in Table 2. Operative time was significantly shorter for the ORH group than for the LRH group (mean, 322.5 versus 379.5 minutes; $P = 0.015$), where the LRH

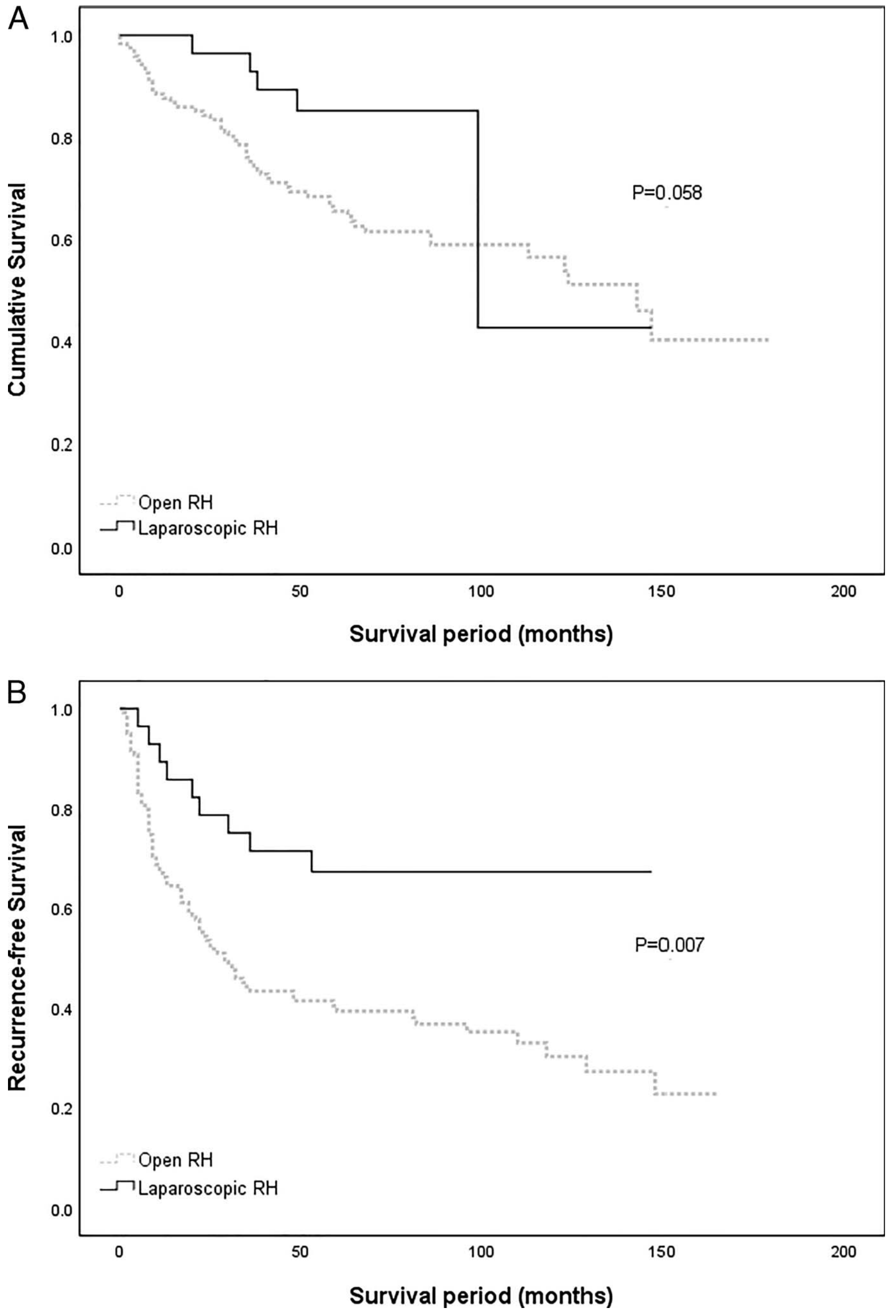

Fig. 1 Survival rates. (A) Cumulative DFS before matching. (B) Cumulative OS before matching. (C) Cumulative DFS after matching. (D) Cumulative OS after matching.

group showed less intraoperative blood loss ($P = 0.02$) and lower rate of intraoperative transfusion ($P = 0.02$). Postoperative hospital stays were significantly shorter for the LRH group (mean, 14.5 days versus 20.2 days; $P = 0.004$). Postoperative mortality was not noted in both groups. Overall morbidity rates were significantly lower in the LRH group (1:13, $P = 0.00$). Grade IIIa complications according to the Clavien-Dindo classification were noted in 1 case in each group.

The median follow-up was 71 months (range, 40–175 months) for the LRH group and 108 months (range, 41–189 months) for the ORH group. Overall survival (OS) and disease-free survival (DFS) curves

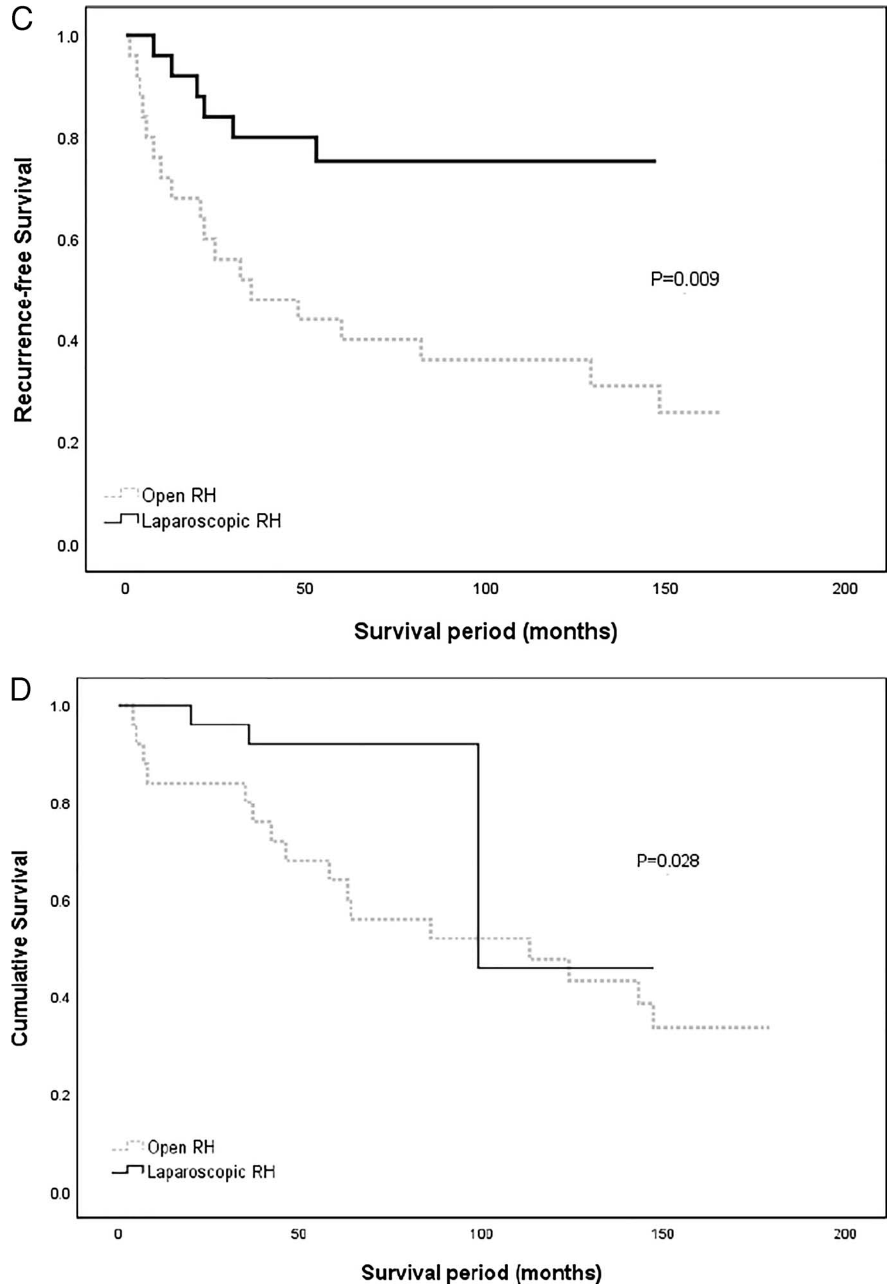

Fig. 1 Continued.

are presented in Fig. 1. DFS ($P = 0.007$) was significantly better in the LRH group before matching (Fig. 1A). Both DFS and OS were significantly better in the LRH group after PSM (DFS, $P = 0.009$; OS, $P = 0.028$). The cumulative 1-, 3-, and 5-year OS rates were 100%, 92.0%, and 92.0%, respectively, for the LRH group, and 84.0%, 80.0%, and 64.0%, respectively, for the ORH group. Furthermore, the cumulative 1-, 3-, and 5-year DFS rates were 96.0%, 80.0%, and 75.3%, respectively, for the LRH group, and 72.0%, 48.0%, and 40.0%, respectively, for the ORH group (Fig. 1).

Discussion

Laparoscopic procedures have become an integral part of all surgical fields. LLR also has been rapidly progressing despite its initial slow pace. Most centers

Table 2 Operative findings and postoperative outcomes

	All patients			Propensity score–matched patients		
	LRH (n = 28)	ORH (n = 121)	*P*	LRH (n = 25)	ORH (n = 25)	*P*
Operative time, mean ± SD, min	379.574.3	301.8 ± 82.5	0.001	379.5 ± 74.3	322.5 ± 62.7	0.015
Estimated blood loss, mean ± SD, mL	506.9 ± 305.4	828.9 ± 656.7	0.004	506.9 ± 305.4	1146.4 ± 827.53	0.02
Intraoperative transfusion, n (%)	2 (7.1)	23 (19.0)	0.166	2 (7.1)	10 (35.7)	0.02
Postoperative hospital stays, mean ± SD, d	14.5 ± 6.2	17.3 ± 7.1	0.045	14.5 ± 6.2	20.25 ± 7.54	0.004
Overall morbidity, n (%)	2 (7.1)	53 (43.8)	0	1 (4.0)	13 (52.0)	0
Pleural effusion	0 (0.0)	42 (34.7)	0	0 (0.0)	11 (44.0)	0
Postoperative bleeding	1 (3.6)	8 (6.6)	1	0 (0.0)	3 (12.0)	0.235
Intra-abdominal abscess	0 (0.0)	1 (0.8)	1	1 (4.0)	0	1
Biloma	0 (0.0)	2 (1.7)	1	0 (0.0)	2 (8.0)	0.49
Ileus	0 (0.0)	8 (6.6)	0.353	0 (0.0)	2 (8.0)	0.49
Reoperation, n (%)	1 (3.6)	3 (2.5)	0.569	0 (0.0)	0 (0.0)	
Clavien-Dindo classification, n (%)			0.005			0.001
I	0 (0.0)	41 (33.9)		0 (0.0)	9 (36.0)	
II	0 (0.0)	4 (3.3)		0 (0.0)	3 (12.0)	
IIIA	1 (0.8)	4 (3.3)		1 (4.0)	1 (4.0)	
V	0 (0.0)	2 (1.7)		0 (0.0)	0 (0.0)	

have adopted laparoscopic minor hepatectomy for the favorably located malignant lesions.[15,16] Major hepatectomy for HCC is gradually being performed, but only by experienced centers because it carries both technical and oncologic concerns. Several centers have reported on the safety and efficacy of LLR and oncologic comparability, mostly for minor LLR. The resection of more than 3 Couinaud segments is considered major hepatectomy for LLR. Only a few centers have published perioperative outcomes and oncologic outcomes with regard to major LLR for the treatment of HCC.[12,17,18]

This study demonstrated the feasibility and safety of LRH for HCC in addition to more favorable oncologic outcomes. On PSM results, the LRH group showed less blood loss and shorter hospital stays than the ORH group. Furthermore, overall morbidity rates were significantly lower in the LRH group than in the ORH group. Operative time was longer in the LRH group.

In this study, OS and DFS analysis was performed to confirm whether the perioperative benefits were associated with better survival outcomes. Both before and after PSM, DFS was significantly better in LRH. Although OS before PSM was comparable between LRH and ORH, OS after PSM showed better results in LRH, similarly to DFS. Most reports contain oncologic outcomes of major LLR for HCC, survival was comparable between laparoscopic and open groups, and the trend was favorable to the laparoscopic group without statistical significance.

Our center initiated an LLR program in 2005. The accumulation of experience and the advancement in terms of instruments have elicited a standardization of both major LLR and minor LLR. Left lateral sectionectomy has been performed entirely under laparoscopy since 2013.[19] The indication for LLR has been widened and the proportion of LLR has continually increased over time. The indication of the laparoscopic approach for HCC is similar to that of the open approach. With regard to a technical point, the Glissonian approach is adopted as the first considered method for inflow control in most of the cases. The intermittent Pringle maneuver has been routinely used to reduce the blood loss and to maintain a dry surgical field.

Anesthetic management also has been improved. Keeping the central venous pressure as low as possible and peak end-expiratory pressure and the restriction of fluid infusion may help to decrease the intraoperative blood loss.

The present study showed that LRH was associated with less blood loss, shorter hospital stays, and lower complication rates than ORH. The anticipated risk of bleeding under a laparoscopic approach has been one of the major concerns of LLR. Contrary to the initial anticipation, most reports regarding the perioperative outcomes of LLR have demonstrated less blood loss and a low rate of intraoperative transfusion. In addition to the meticulous parenchyma division under the magnified view, maintaining low CVP and the use of the intermittent Pringle maneuver have been the main ways employed to control bleeding in those reports.[20,21]

Short-term and long-term oncologic outcomes with regard to LLR were comparable between LMH and OMH groups in most studies.[10–12,18] Our study, however, demonstrated significantly improved survival benefits in both DFS and OS. The reason for the survival benefit of LRH is assumed to be associated with its low rate of intraoperative transfusion. Several studies on the effects of blood loss and blood transfusion in HCC demonstrated lower survival in the transfusion group,[22–25] explaining that blood transfusion is related to immunosuppression.[26–28]

This study has a few limitations despite using PSM to diminish confounding baseline variables between the LRH and ORH groups. It was a retrospective and nonrandomized study in a single center, and the sample size was relatively small to consolidate our findings. A well-designed randomized prospective study involving many centers will be needed to validate the benefits of LRH for HCC.

In conclusion, LRH for HCC showed better oncologic outcomes than ORH. Also, LRH for HCC could be a safe alternative to ORH once it is performed by experienced hepatic surgeons. LRH demonstrated better perioperative outcomes with regard to less blood loss, lower rate of intraoperative blood transfusion, and reduced postoperative morbidity.

Acknowledgments

We acknowledge the Institutional Review Board at Chonnam National University Hwasun Hospital for approving this study. This study was financially supported by Chonnam National University (grant number 2021-2454).

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2018;**68**(6):394–424
2. Are C, Fong Y, Geller DA. Laparoscopic liver resections. *Adv Surg* 2005;**39**:57–75
3. Cho EJ, Kim SE, Suk KT, An J, Jeong SW, Chung WJ, et al. Current status and strategies for hepatitis B control in Korea. *Clin Mol Hepatol* 2017;**23**(3):205–211
4. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004;**127**(5 suppl 1):S35–S50
5. Belli G, Limongelli P, Fantini C, D'Agostino A, Cioffi L, Belli A *et al*. Laparoscopic and open treatment of hepatocellular carcinoma in patients with cirrhosis. *Br J Surg* 2009;**96**(9):1041–1048
6. Shehta A, Han HS, Yoon YS, Cho JY, Choi Y. Laparoscopic liver resection for hepatocellular carcinoma in cirrhotic patients: 10-year single-center experience. *Surg Endosc* 2016;**30**(2):638–648
7. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I *et al*. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 2009;**250**(5):825–830
8. Cho JY, Han HS, Wakabayashi G, Soubrane O, Geller D, O'Rourke N *et al*. Practical guidelines for performing laparoscopic liver resection based on the second international laparoscopic liver consensus conference. *Surg Oncol* 2018; **27**(1):A5–A9
9. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS *et al*. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg* 2015;**261**(4):619–629
10. Kim HJ, Cho JY, Han HS, Yoon YS, Lee HW, Lee JS *et al*. Improved outcomes of major laparoscopic liver resection for hepatocellular carcinoma. *Surg Oncol* 2020;**35**:470–474
11. Kasai M, Cipriani F, Gayet B, Aldrighetti L, Ratti F, Sarmiento JM *et al*. Laparoscopic versus open major hepatectomy: a systematic review and meta-analysis of individual patient data. *Surgery* 2018;**163**(5):985–995
12. Chen K, Pan Y, Hu GY, Maher H, Zheng XY, Yan JF. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2018;**28**(5):267–274
13. Yoon YI, Kim KH, Cho HD, Kwon JH, Jung DH, Park GC *et al*. Long-term perioperative outcomes of pure laparoscopic liver resection versus open liver resection for hepatocellular carcinoma: a retrospective study. *Surg Endosc* 2020;**34**(2):796–805
14. Korean Liver Cancer Association, National Cancer Center. 2018 Korean Liver Cancer Association-National Cancer Center Korea practice guidelines for the management of hepatocellular carcinoma. *Gut Liver* 2019;**13**(3):227–299
15. Chen HY, Juan CC, Ker CG. Laparoscopic liver surgery for patients with hepatocellular carcinoma. *Ann Surg Oncol* 2008; **15**(3):800–806
16. Cherqui D, Laurent A, Tayar C, Chang S, Van Nhieu JT, Loriau J *et al*. Laparoscopic liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: midterm results and perspectives. *Ann Surg* 2006;**243**(4):499–506
17. Cheung TT, Ma KW, She WH, Dai WC, Tsang SHY, Chan ACY *et al*. Pure laparoscopic versus open major hepatectomy for hepatocellular carcinoma with liver F4 cirrhosis without routine Pringle maneuver–a propensity analysis in a single center. *Surg Oncol* 2020;**35**:315–320
18. Komatsu S, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. *Surg Endosc* 2016;**30**(5):1965–1974

19. Kim KH, Koh YS, Cho CK, Hur YH, Kim HJ, Park EK. Outcomes of laparoscopic left lateral sectionectomy vs. open left lateral sectionectomy: single center experience. *J Minim Invasive Surg* 2017;**20**(1):29–33
20. Xu HW, Liu F, Li HY, Wei YG, Li B. Outcomes following laparoscopic versus open major hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a propensity score-matched analysis. *Surg Endosc* 2018;**32**(2):712–719
21. Wang ZY, Chen QL, Sun LL, He SP, Luo XF, Huang LS *et al*. Laparoscopic versus open major liver resection for hepatocellular carcinoma: systematic review and meta-analysis of comparative cohort studies. *BMC Cancer* 2019;**19**(1):1047
22. Asahara T, Katayama K, Itamoto T, Yano M, Hino H, Okamoto Y *et al*. Perioperative blood transfusion as a prognostic indicator in patients with hepatocellular carcinoma. *World J Surg* 1999;**23**(7):676–680
23. Yamamoto J, Kosuge T, Takayama T, Shimada K, Yamasaki S, Ozaki H *et al*. Perioperative blood transfusion promotes recurrence of hepatocellular carcinoma after hepatectomy. *Surgery* 1994;**115**(3):303–309
24. Nagasue N, Ono T, Yamanoi A, Kohno H, El-Assal ON, Taniura H *et al*. Prognostic factors and survival after hepatic resection for hepatocellular carcinoma without cirrhosis. *Br*
25. *J Surg* 2001;**88**(4):515–522
26. Makino Y, Yamanoi A, Kimoto T, El-Assal ON, Kohno H, Nagasue N. The influence of perioperative blood transfusion on intrahepatic recurrence after curative resection of hepatocellular carcinoma. *Am J Gastroenterol* 2000;**95**(5): 1294–1300
27. Gascón P, Zoumbos NC, Young NS. Immunologic abnormalities in patients receiving multiple blood transfusions. *Ann Intern Med* 1984;**100**(2):173–177
28. Kaplan J, Sarnaik S, Gitlin J, Lusher J. Diminished helper/ suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. *Blood* 1984;**64**(1): 308–310
29. Blumberg N, Heal JM. Effects of transfusion on immune function: cancer recurrence and infection. *Arch Pathol Lab Med* 1994;**118**(4):371–379