ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2024.106.6.354
Annals of Surgical Treatment and Research

Long-term outcomes of single-port laparoscopic hepatectomy for hepatocellular carcinoma: a retrospective comparative analysis

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Purpose: Numerous efforts have been made to achieve minimally invasive surgery, such as single-port laparoscopic surgery. However, few studies have provided long-term follow-up information, and the number of patients with hepatocellular carcinoma (HCC) in previous studies has been small. The purpose in this study is to compare the long-term oncological outcomes of HCC patients who underwent single-port laparoscopic hepatectomy (SPLH) with those of patients who underwent multiport laparoscopic hepatectomy (MPLH).
Methods: We retrospectively reviewed the medical records of 135 patients with HCC who underwent laparoscopic liver between January 2008 and December 2018. Of the 135 patients, 53 underwent MPLH, and 82 underwent SPLH.
Results: From January 2008 to December 2018, 135 patients underwent laparoscopic hepatectomy for HCC. Among them, 82 patients underwent SPLH, and 53 patients underwent MPLH. Neither long-term overall survival (P = 0.849) nor recurrence-free survival (P = 0.057) differed significantly between the 2 groups, even though the recurrence rate was higher in the SPLH group. In the univariable analysis of risk factors for recurrence, multiple tumors, SPLH method, and portal vein invasion were statistically significant (P < 0.05). Multivariable analysis showed that the SPLH method and portal vein invasion were independent adverse prognostic factors for recurrence-free survival.
Conclusion: In terms of both short-term and long-term outcomes, the SPLH method seems to be a feasible approach for HCC in select patients. Because the potential risk of margin recurrence might produce poor oncological outcomes, strict patient selection is essential to ensure that an adequate safety margin can be secured.
[Ann Surg Treat Res 2024;106(6):354-360]

Key Words: Hepatocellular carcinoma, Minimally invasive surgery, Recurrence

INTRODUCTION

The laparoscopic approach has been extended to the entire range of abdominal operations since the first application of laparoscopic cholecystectomy in 1987 [1]. Gagner et al. [2] first reported laparoscopic liver resection (LLR) in 1992, but unlike many other laparoscopic procedures, LLR has been difficult to popularize due to its potential bleeding risk, prolonged operation time, and significant learning curve [3]. Despite those drawbacks, LLR has progressed significantly with a better understanding of the anatomic segments of the liver, enhanced imaging by CT and MRI scans, improved postoperative care, and

Received February 20, 2024, **Reviewed** March 9, 2024,
Accepted April 12, 2024

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technical advances [4]. Specifically, LLR has become increasingly prevalent since the first international consensus conference on LLR was held in Louisville, KY, USA, in 2008 [5]. In 2014, the second international consensus conference on LLR was held in Morioka, Japan, to assess the current state and future of the technology [6].

During the past decade, numerous efforts have been made to reduce the number of incisions, paving the way for single-port laparoscopic surgery [7]. Some researchers have suggested that, when performed by a skilled surgeon with careful patient selection, single-port laparoscopic hepatectomy (SPLH) is a feasible and effective procedure [8,9]. There also have been previous studies on the clinical advantages of SPLH for both benign and malignant diseases [10,11]. However, few studies have provided long-term follow-up information, and the number of patients with hepatocellular carcinoma (HCC) in previous studies has been small. Therefore, the purpose of this study is to compare the long-term oncological outcomes of HCC patients who underwent SPLH with those of patients who underwent multiport laparoscopic hepatectomy (MPLH).

METHODS

Data collection

We retrospectively reviewed the medical records of 135 patients with HCC who underwent LLR with curative intent at Seoul St. Mary's Hospital between January 2008 and December 2018. Patients who had emergency operations or concomitant surgery at the same time were excluded. The demographics and clinical data of all patients were obtained from their medical records. Of the 135 patients, 53 underwent MPLH, and 82 underwent SPLH.

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (No. KC21RASI0842). It was performed in accordance with the Declaration of Helsinki and written informed consent was waived due to its retrospective nature.

Surgical procedure

The SPLH technique is based on pure laparoscopy. In general, the patient was positioned supine, and the patient's torso was elevated 10°–20° in the reverse-Trendelenburg position. If the lesion was in the right posterior section, the patient was positioned in a left lateral decubitus position at around 90°. For resection of a left liver lesion, the operator stood on the right side of the patient near the radiology tech; for resection of a right liver lesion, the operator stood between the patient's legs or on the left side of the patient.

A 30–40-mm skin incision was made in the right upper quadrant or periumbilical area depending on the location and size of the liver mass. A glove port (Nelis) that consisted of 4 trocar channels with gas insufflation and exsufflation lines was inserted. We set the pressure for CO_2 pneumoperitoneum at 12 mmHg.

The laparoscopic hepatectomy procedure used was similar to that reported in previous studies. Intraoperative ultrasonography was used in most cases to determine the exact location of the hepatic mass and hepatic vein during the operation. The liver was mobilized using a hook-type electrocautery dissector and an ultrasonic scalpel (Harmonic ACE, Ethicon Endo-Surgery), and we used a laparoscopic ultrasonic dissector (CUSA, Integra LifeSiences) for liver parenchymal dissection. To retrieve the specimen, we extended the trocar site incision to prevent specimen injury. At the end of the operation, a drain was inserted in consideration of the extent of hepatectomy and bleeding tendency. A more detailed surgical method is provided in our previous papers [10,11].

Outcomes

Short-term surgical outcomes and long-term oncological outcomes were obtained and compared between the 2 groups. The extent of hepatic resection was classified as partial hepatectomy, left lateral sectionectomy, or major hepatectomy; all hepatectomies that resected a larger range than sectionectomies were collected and defined as a major hepatectomy group. Patient-controlled analgesia (PCA) was administered routinely for postoperative pain control. In cases of complaints of pain not controlled by PCA, opioid analgesics were administered. For postoperative pain assessment, we analyzed the day of PCA removal, whether it was refilled, and how many times additional analgesics were administered between the 2 groups. The Clavien-Dindo classification of surgical complications was used to grade postoperative complications [12]. To analyze the oncological outcomes, we compared pathological results such as tumor size, tumor number, surgical margin, vascular invasion, and Edmondson-Steiner grade between the 2 groups. To compare the long-term outcomes, the Kaplan-Meier method was used to analyze overall survival and recurrence-free survival.

Statistical analysis

To present numerical variables, mean, standard deviation, and range are used. To compare continuous variables, a Student t-test was applied. The chi-square test was used to examine differences in categorical variables. For multivariable analysis, a logistic regression was used, and a Cox proportional hazards regression model analysis was used to find risk factors that were associated independently with recurrence or survival. The disease-free and overall survival rates were analyzed using the Kaplan-Meier method. The log-rank test was performed to compare the survival times. P-values less than 0.05 were considered statistically significant.

RESULTS

From January 2008 to December 2018, 135 patients underwent laparoscopic hepatectomy for HCC. Among them, 82 patients underwent SPLH, and 53 patients underwent MPLH. The conversion rate of the SPLH group was 8.5% (7 of 82), and that of the MPLH group was 17.0% (9 of 53). The most common cause of conversion was poor visualization due to adhesion (50.0%), and the next most common cause was bleeding (37.5%) which could not be controlled adequately laparoscopically. All patients in both groups who underwent conversion were converted to open laparotomy during the operation. The baseline characteristics of the patients are summarized in Table 1. Patient demographics did not differ significantly between the 2 groups. Preoperative tumor markers (α-FP, protein induced by vitamin K antagonist-II) and characteristics (size, number, and location) did not differ significantly between the 2 groups.

Short-term surgical outcomes

Table 2 compares the short-term surgical outcomes of the 2 groups. Regarding the resection extent, the ratio of greater than sectionectomy was higher in the MPLH group than in the SPLH group (13.2% *vs.* 4.9%), but there was no statistically significant difference between the 2 groups. The patients in the SPLH group had significantly shorter whole operation times (110.9 minutes *vs.* 200.7 minutes, P < 0.001), and the estimated blood loss and packed red cell (PRC) transfusions were higher in the MPLH group. The ratio of drain insertion was less in the SPLH group than in the MPLH group (43.9% *vs.* 79.2%, P < 0.001). There was no statistically significant difference in length of hospital stay, conversion rate, day of PCA removal, PCA refill, or rate of complications, but the need for additional opioids was less in the SPLH group than the MPLH group (0.9 *vs.* 1.8, P = 0.039). Pathologic outcomes such as surgical margin, tumor exposure, and vascular invasion did not differ statistically between the 2 groups.

Long-term oncological outcomes

During a median follow-up duration of 48 months (range, 1–155 months), tumor recurrence occurred in 65 patients and showed a higher rate following SPLH than MPLH (57.3% *vs.* 34.0%, P < 0.001). The comparison of recurrence-free survival and overall survival is shown in Figs. 1 and 2, respectively. Neither long-term overall survival (log-rank = 0.849) nor recurrence-free survival (log-rank = 0.057) differed significantly between the 2 groups, even though the recurrence rate was higher in the SPLH group.

In the univariable analysis of risk factors for recurrence,

Table 1. The baseline characteristics and comparison between the MPLH and SPLH groups

Characteristic	MPLH group	SPLH group	P-value
No. of patients	53	82	
Age (yr)	61.3 ± 10.8	58.9 ± 10.3	0.206
Male sex	39 (73.6)	69 (84.1)	0.134
Body mass index (kg/m^2)	24.1 ± 3.1	24.4 ± 4.8	0.677
ASA PS grade, ≥III	6 (11.3)	9 (11.0)	0.950
Original disease			0.912
Hepatitis B	39 (73.6)	63 (76.8)	
Hepatitis C	3 (5.7)	3 (3.7)	
Alcohol	6 (11.3)	10 (12.2)	
Others	5 (9.4)	6 (7.3)	
CTP score, ≥B	3 (5.7)	2 (2.4)	0.381
ICG R15 (%)	15.6 ± 13.3	12.5 ± 7.0	0.212
α-FP (ng/mL)	168.4 ± 457.4	168.5 ± 777.6	>0.999
PIVKA-II (mAU/mL)	365.9 ± 1,328.7	2,025.4 ± 13,901.2	0.398
No. of tumors	1.1 ± 0.4	1.1 ± 0.4	0.861
Tumor size (cm)	3.0 ± 1.6	3.2 ± 1.6	0.611
Tumor location			0.117
Left lateral section (S2, S3)	11 (20.8)	22 (26.8)	
Left medial section (S4)	4 (7.5)	13 (15.9)	
Right inferior section (S5, S6)	27 (50.9)	40 (48.8)	
Right superior section (S7, S8)	11 (20.8)	7 (8.5)	
Favorable location	38 (71.7)	62 (75.6)	0.613

MPLH, multiport laparoscopic hepatectomy; SPLH, single-port laparoscopic hepatectomy; ASA PS, American Society of Anesthesiologists physical status; CTP, Child-Turcotte-Pugh; ICG, indocyanine green; PIVKA- II, protein induced by vitamin K antagonist-II.

Table 2. Comparison of the short-term surgical outcomes between the MPLH and SPLH groups

Variable	MPLH group (n = 53)	SPLH group (n = 82)	P-value
Resection extent			0.153
Partial hepatectomy	40 (75.5)	63 (76.8)	
Left lateral sectionectomy	6 (11.3)	15 (18.3)	
Major hepatectomy	7 (13.2)	4 (4.9)	
Estimated blood loss (mL)	891.3 ± 1,522.6	437.4 ± 610.7	0.045
PRC transfusion	22 (42.3)	17 (20.7)	0.007
Whole operation time (min)	200.7 ± 139.3	110.9 ± 53.8	<0.001
Length of hospital stay (day)	9.9 ± 7.2	9.2 ± 3.6	0.411
Jackson-Pratt drain insertion	42 (79.2)	36 (43.9)	<0.001
Conversion	9 (17.0)	7 (8.5)	0.138
Postoperative PCA			
Day of removal	2.9 ± 1.3	3.1 ± 1.6	0.369
Refill	3 (7.3)	3 (3.9)	0.417
Additional opioids	1.8 ± 2.2	0.9 ± 1.7	0.039
Complication, CD ≥3	5 (9.4)	5 (6.1)	0.470
ES grade, ≥III	21 (43.8)	26 (33.3)	0.240
Surgical margin (cm)	1.1 ± 1.1	0.9 ± 0.7	0.132
Tumor exposure	1 (2.0)	2 (2.5)	>0.999
Portal vein invasion	2 (3.8)	0 (0)	0.152
Hepatic vein invasion	5 (9.4)	7 (8.5)	0.858
Microvascular invasion	11 (23.4)	24 (30.0)	0.422

MPLH, multiport laparoscopic hepatectomy; SPLH, single-port laparoscopic hepatectomy; PRC, packed red cell; PCA, patient-controlled analgesia; CD, Clavien-Dindo classification; ES grade, Edmondson-Steiner grade.

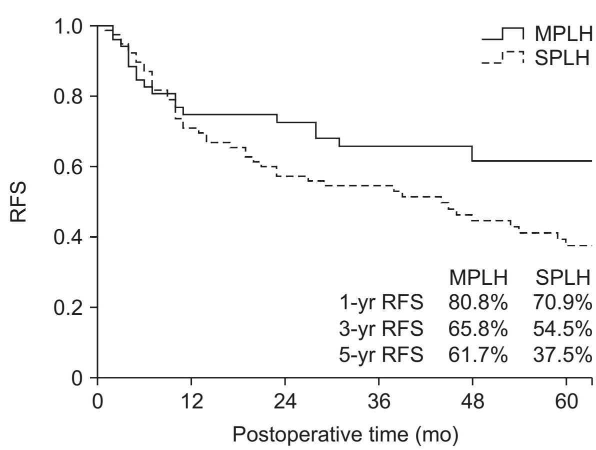

Fig. 1. Recurrence-free-survival (RFS). MPLH, multiport laparoscopic hepatectomy; SPLH, single-port laparoscopic hepatectomy.

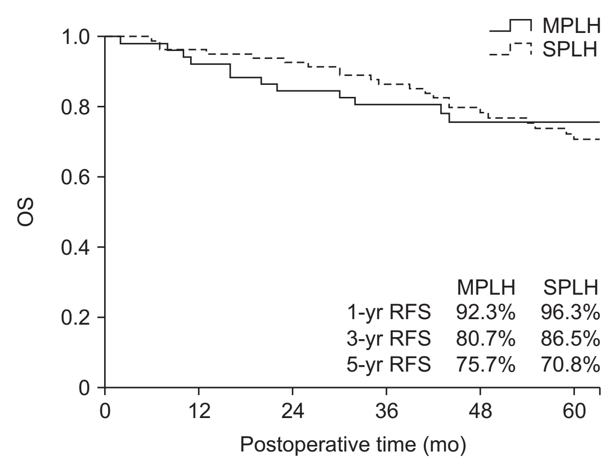

Fig. 2. Overall survival (OS). MPLH, multiport laparoscopic hepatectomy; SPLH, single-port laparoscopic hepatectomy.

multiple tumors, SPLH method, and portal vein invasion were statistically significant ($P < 0.05$). Multivariable analysis showed that the SPLH method and portal vein invasion were independent adverse prognostic factors for recurrence-free survival. In univariable analysis of risk factors for overall survival, α-FP >168 ng/mL, microvascular invasion, portal vein invasion, hepatic vein invasion, and recurrence were statistically significant ($P < 0.05$). Multivariable analysis showed that portal vein invasion, hepatic vein invasion, and recurrence were independent adverse prognostic factors for overall survival. Multivariable analyses of risk factors for recurrence and overall survival are shown in Table 3.

DISCUSSION

As interest in minimally invasive surgery has increased, single-port laparoscopic surgery has been attempted widely in various fields, including hepatobiliary surgery, mainly

Table 3. Multivariable analyses of risk factors associated with recurrence and survival

Variable	Recurrence		Survival	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Male sex		0.501		0.780
Age, >60 yr		0.312		0.849
α-FP, >168 ng/mL		0.127	1.740 (0.79–3.81)	0.168
Multiple tumors	1.745 (0.87–3.48)	0.114		0.216
Tumor size, >5 cm		0.341		0.709
SPLH method	1.820 (1.02–3.22)	0.041		0.850
PRC transfusion		0.790		0.193
Surgical margin, <1 cm		0.919		0.888
Tumor exposure		0.629		0.809
ES grade, III or IV		0.356		0.588
Microvascular invasion		0.314	1.310 (0.57–2.97)	0.518
Portal vein invasion	19.512 (3.70–102.70)	<0.001	6.325 (1.29–30.91)	0.023
Hepatic vein invasion		0.214	4.000 (1.37–11.64)	0.011
Recurrence			4.913 (2.22–10.86)	<0.001

CI, confidence interval; SPLH, single-port laparoscopic hepatectomy; PRC, packed red cell; ES grade, Edmondson-Steiner grade.

Table 4. Comparison of characteristics of the studies

Characteristic	Current study	Aldrighetti et al. [14]	Tsai et al. [8]	Hyun et al. [15]
No. of total single-port cases	82	13	54	15
No. of HCC cases	82	5	14	15
Procedure				
Partial hepatectomy	63	0	21	15
Left lateral sectionectomy	15	13	33	0
Major hepatectomy	4	0	0	0
Operation time (min)	110.9 ± 53.8	195 (125–330)	105.7 ± 40.8	119.0 ± 61.9
Blood loss (mL)	437.4 ± 610.7	175 (100–220)	101.5 ± 93.4	200.0 ± 230.7
Conversion	7 (8.5)	0 (0)	1 (1.9)	0 (0)
Complication	5 (6.1)	3 (23.1)	1 (1.9)	0 (0)
Length of hospital stay (day)	9.2 ± 3.6	6.3 (3–21)	4.2 ± 1.3	2.7 ± 2.0
Long-term outcomes	Yes	No	Yes	No

Values are presented as number only, mean ± standard deviation, or number (%).
HCC, hepatocellular carcinoma.

cholecystectomies [9,13]. However, due to anatomical complexity and a challenging surgical procedure, the adoption of SPLH has been cautious. The adoption of SPLH for HCC has been even more cautious due to concerns about oncological outcomes. Those concerns might explain why few studies have compared the long-term oncological outcomes of SPLH and MPLH for HCC. The previous comparative studies enrolled 13 cases of SPLH including 5 cases of HCC [14], 54 total cases with 14 HCC cases [8], and 15 cases of HCC with propensity score matching [15]. The major differences between this study and the previous studies are that we included only HCC patients to examine their long-term oncological outcomes, and we had the largest number of HCC cases (Table 4). To the best of our knowledge, this is the largest comparative study to analyze the long-term oncological outcomes of HCC patients who underwent SPLH.

In this paper, we compared the long-term oncological outcomes of patients treated with SPLH for HCC with those of patients treated with MPLH. According to our study, operative time, blood loss, and PRC transfusion were less in the SPLH group than in the MPLH group (Table 2). There was no significant difference in long-term overall survival or recurrence-free survival between the 2 groups (Fig. 1).

Long-term outcomes after hepatectomy for HCC might be related to tumor biology itself rather than to the surgical procedure [16-18]. In previous studies, surgical factors such as surgical safety margin, blood loss, or transfusion have been considered as risk factors for long-term prognosis after hepatectomy [19-21]. Therefore, if an appropriate surgical margin can be secured, laparoscopic hepatectomy might be considered reasonable. The surgical margin in this study was smaller in the SPLH group than in the MPLH group. It is well known that a poor surgical margin in HCC patients is a strong predictor of recurrence [22-24]. That fact is a major drawback of the SPLH technique in this study. Therefore, establishing an adequate safety margin during hepatectomy is important in minimally invasive surgery, particularly in SPLH for HCC. Despite that concern, the 5-year survival did not differ between the 2 groups. Although an unsatisfactory surgical margin did not produce negative effects in this study, we do not suggest SPLH for all HCC cases. We have to remember that the potential risk of margin recurrence might cause poor oncological outcomes. Strict patient selection to allow an adequate safety margin, which depends on each surgeon's environment, is recommended.

The major obstacle for SPLH is the easy clashing of laparoscopic instruments fitted into narrow single-port trocars, which results in a relatively unstable surgical environment. Various approaches have been tried to overcome that disadvantage. Choi et al. [15] reported the feasibility of SPLH using a scope holder that provided more working space without interference between the surgeon and scopist. Efforts are being made to alleviate the difficulties that can arise during single-port surgery by using an articulating device [25]. As those surgical techniques advance, a sufficient surgical margin will become possible, making SPLH for HCC more competitive.

Although SPLH is considered a tricky practice that elongates the operation time, our results show that the operation time in the SPLH group was shorter than in the MPLH group. That can be explained by the imbalance between the 2 groups. As shown in Table 2, the proportion of patients receiving major hepatectomy was higher in the MPLH group. On the other hand, the surgical safety margin in the SPLH group was smaller than in the MPLH group, although that difference was not statistically significant. We attempted 4 cases of major hepatectomy with SPLH, but 3 of them required open conversion due to bleeding and difficulty of operation vision. We no longer recommend SPLH for major hepatectomy due to the relatively longer operation time and risk for complications. In SPLH surgery, the location of the tumor is an important factor in terms of securing an adequate surgical margin. As stated in previous studies, laparoscopic access is limited for tumors located in S7 and S8 [6,16], and the SPLH method is not advised in those cases. In our study, there were 22 cases (26.8%) in the left lateral section (S2, S3), 13 cases (15.9%) in the left medial section (S4), 40 cases (48.8%) in the right inferior section(S5, S6), and 7 cases (8.5%) in the right superior section of the liver (S7, S8).

In this study, the rates of transfusion, the length of hospital stay, and the rates of drain placement in both groups seem high. Unexpected bleeding is common in major hepatectomy, and blood transfusion was performed at the discretion of an anesthesiologist regardless of the surgeon's opinion during surgery. A blood transfusion was performed according to the patient's general condition and the findings at the time of surgery. After a major hepatectomy, the hospitalization period is longer than other surgeries due to checking for complications. In particular, in Korea, compared to other developed countries, the hospitalization period is long due to the low cost of hospitalization. The insertion of a drain was determined by the surgeon's judgment in the operating room, and it is preferred to insert a drain to check whether bleeding or bile leakage has occurred after a major hepatectomy.

This study has limitations. Because this is a retrospective study, there is selection bias in choosing patients for SPLH. This bias may mislead the interpretation of research results. In particular, hepatectomy for HCC has its own heterogeneity, so various factors must be considered in choosing the types of surgery, from minor to major hepatectomy. To clarify this, a follow-up study with propensity score matching is needed.

Regarding both short-term and long-term outcomes, the SPLH method seems to be a feasible approach for HCC in selected patients. Because the potential risk of margin recurrence might produce poor oncological outcomes, strict patient selection is essential to ensure that an adequate safety margin can be secured.

ACKNOWLEDGEMENTS

Fund/Grant Support

None.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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