ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2018.95.5.258
Annals of Surgical Treatment and Research

Laparoscopy of hepatocellular carcinoma is helpful in minimizing intra-abdominal adhesion during salvage transplantation

Jinsoo Rhu[1], Jong Man Kim[1], Gyu Seong Choi[1], Choon Hyuck David Kwon[1], Jae-Won Joh[1], Olivier Soubrane[2]

[1]*Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[2]*Hepatobiliary-Pancreatic Surgery, Hospital Beaujon, APHP, Clichy, France*

Purpose: This study analyzes the impact of laparoscopic liver resection on intra-abdominal adhesion.
Methods: Patients who underwent salvage liver transplantation after liver resection for hepatocellular carcinoma from January 2012 to October 2017 at our institution were included. Information about the severity of intra-abdominal adhesions was collected from a prospectively maintained database. Intra-abdominal adhesions were graded after the agreement of 2 surgeons who participated in the salvage liver transplantation based on predetermined criteria. Adhesion severity and demographic, operative, and postoperative data were compared between the laparoscopic group and the open group. Multivariate logistic regression was performed to consider potential factors related to severe adhesion during salvage transplantation.
Results: Sixty-two patients who underwent salvage liver transplantation after liver resection were included in this study. Among them, 52 patients underwent open surgery, and 10 patients underwent laparoscopy. Adhesion was significantly more severe in the open group than in the laparoscopy group (P = 0.029). A multivariate logistic regression model including potential factors related to severe adhesion showed that laparoscopy (odds ratio, 0.168; 95% confidence interval, 0.029–0.970; P = 0.048) was the only significant factor.
Conclusion: Laparoscopic liver resection for hepatocellular carcinoma can minimize intra-abdominal adhesion during salvage liver transplantation.
[Ann Surg Treat Res 2018;95(5):258-266]

Key Words: Hepatocellular carcinoma, Laparoscopy, Liver transplantation, Surgical adhesion

INTRODUCTION

Although liver transplantation (LT) is the most definite treatment for hepatocellular carcinoma (HCC), liver resection (LR) is more frequently performed due to organ shortage, concerns regarding immunosuppression, and decreased morbidity and increased survival following LR. LT is considered when liver function has deteriorated and the tumor meets the Milan criteria [1], whereas LR is usually performed for patients with preserved liver function [2,3]. However, HCC has a high recurrence rate, and some recurring patients undergo salvage liver transplantation (SLT). Consequently, during SLT, surgeons can encounter intra-abdominal adhesions (IAAs) from the previous LR.

As laparoscopic surgery has become popular in many fields of surgery, its benefits have been published by many

Received March 21, 2018, **Revised** April 15, 2018, **Accepted** June 1, 2018

Corresponding Author: Jong Man Kim
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-0277, **Fax:** +82-2-3410-0040
E-mail: yjongman21@gmail.com
ORCID code: https://orcid.org/0000-0002-1903-8354

authors [4-8]. Regarding laparoscopic liver resection (LLR), a study published by Laurent et al. [9] showed that patients who underwent an initial laparoscopic approach had shorter operating times, reduced blood loss, and fewer transfusions during SLT compared to those whose initial surgery used the open approach. Although that study considered only simple comparisons of operating time and blood loss between the 2 groups, it showed that LLR can be beneficial when performing a later SLT. Felli et al. [10] also published a multicenter study showing comparative operative outcome of SLT after LLR compared to open surgery. However, no study has yet analyzed differences in the severity of adhesions following initial LR to determine the impact of laparoscopy on IAA, also taking into account the other factors related to adhesions.

Since the introduction of laparoscopy, most of the LRs performed in our center have been LLRs [11-13]. Because we have a protocol to prospectively describe the severity of IAAs during SLT, we designed this study to compare the severity of IAAs during SLT according to the modality of initial LR.

METHODS

Patients and data

We included LR patients at our institution who underwent SLT after LR for HCC from between January 2012 and October 2017. Patient data were reviewed based on our prospectively updated database for LT, and demographic, clinical, operative, and postoperative data were collected. Whether the patient underwent laparoscopy or open surgery at the time of initial LR and the type of LR were reviewed. Segmentectomy or LR of a lesser extent was considered minor resection, whereas bisegmentectomy or LR of a greater extent was considered major resection. The modality and number of locoregional therapies (LRTs) before SLT were also reviewed.

Operative findings were reviewed based on the description of operative records. In our center, operative findings are determined by a discussion and agreement between the 2 surgeons participating in the operation, according to protocol. Our center categorizes adhesion severity into 3 degrees: negligible, no adhesion or minimal adhesion outside the operative field; moderate, significant IAA requiring adhesiolysis that presents no significant difficulty; and severe, adhesion of almost the entire operation field requiring significant time and effort in adhesiolysis. This system is based on the grading system for adhesions previously reported by Beck et al. [14]: grade 1 (thin filmy adhesion that can be divided by blunt dissection) and grade 2 (thin vascular adhesion that can be easily divided) adhesions correspond to the moderate adhesions in our system, and grade 3 (extensive thick vascular adhesion requiring division by sharp dissection) and grade 4 (dense adhesion that can damage adjacent organs) are severe adhesions in our system. The presence and number of ascites should also be described. The severity of collateral vessels is categorized into 3 degrees: negligible, no different from normal patients; small, increased collateral vascularity unrelated to increased bleeding or surgical difficulty; and many, which critically affects routine procedures by requiring thorough dissection and ligation.

Statistical analysis

Our primary endpoint was to compare IAA severity between the laparoscopy group and the open group. Therefore, we compared demographic, clinical, operative, and postoperative data between patients who underwent LLR and patients who underwent open LR before SLT. The variables were also compared between the patient group with negligible or moderate adhesions and the patient group with severe adhesions. Numerical variables were compared using Student t-test or Mann-Whitney test. Categorical variables were compared with chi-square test, Fisher exact test, or linear-by-linear association.

Our secondary endpoint was to analyze the impact of LLR on IAA during SLT, taking into account the other factors that can influence adhesion severity. For this purpose, we performed multivariate logistic regression analysis using the backward likelihood ratio. Statistical significance was indicated by a 2-tailed P-value <0.05.

All statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2017-10-148). The need for informed consent was waived by the Institutional Review Board of Samsung Medical Center due to the retrospective nature of the study.

RESULTS

During the study period, 709 patients underwent LT in our center. After excluding pediatric patients, LT not related to HCC, and patients who did not undergo LR prior to LT, 10 patients with SLT after LLR and 52 patients with SLT after open LR were included in the study (Fig. 1). IAA severity was categorized into 3 degrees as described above. Only 3 patients (4.8%) had negligible adhesions, whereas 26 patients (41.9%) and 32 patients (51.6%) had moderate and severe adhesions, respectively. The operative field of patients with severe adhesions was characterized by severe adhesion of the entire liver surface, both superiorly with the peritoneal surface of the diaphragm and abdominal wall (Figs. 2A, C) and anteriorly with the omentum and small bowel or colon (Fig. 2B). On the other hand, moderate adhesion is characterized by significant adhesion of a certain portion of the area but not the entire operative field (Fig. 2D).

Comparison between laparoscopy group and open group

Table 1 summarizes the demographic, clinical, operative, and postoperative data according to initial LR. Between the 2 groups, only adhesion severity differed significantly (P = 0.029). Whereas 1 (10.0%), 7 (70.0%), and 2 patients (20.0%) in the laparoscopy group had negligible, moderate, and severe adhesions, respectively, 2 (3.9%), 19 (37.3%), and 30 patients (58.8%) in the open group had negligible, moderate, and severe adhesions. No other variables differed significantly between the groups. In the laparoscopy group, 2 patients (20.0%) underwent laparoscopic right hemihepatectomy, and 8 patients (80.0%) underwent minor resection: 2 laparoscopic left lateral sectionectomies, 2 laparoscopic segmentectomies, 3 laparoscopic wedge resections, and 1 laparoscopic tumorectomy. Thirty patients (57.7%) in the open group underwent minor resection, which was not a statistical difference (P = 0.291). There were no differences in the proportion of patients who underwent LRT before SLT (P = 0.237) or the number of LRTs (P = 0.227). Operation time (537.4 ± 118.3 minutes in laparoscopy *vs.* 574.0 ± 165.2 minutes in open, P = 0.508), estimated blood loss (median 2,750 mL in laparoscopy *vs.* median 1,500 mL in open, P = 0.667) transfusions (30.0% in laparoscopy *vs.* 44.2% in open, 0.499), and infused red cells (median 513 mL in laparoscopy *vs.* median 500 mL in open, P = 0.953) also showed no differences. No patients in the laparoscopy group needed any additional procedures or experienced complications due to adhesions, but 4 patients (7.7%) in the open group required additional procedures due to complications related to adhesion. Nonetheless, that difference was not statistically significant (P > 0.999).

Comparison between negligible or moderate adhesions and severe adhesions

Table 2 summarizes the comparisons of demographic, clinical, operative, and postoperative characteristics according to IAA severity. Because negligible adhesions were present in only 3 patients, we divided the patient groups into negligible or moderate adhesions and severe adhesions. Except for laparoscopy (P = 0.037), there were no significant differences according to adhesion severity. Although LRT was performed in 84.4% of patients with severe adhesion compared to 65.5% of the patients with negligible to moderate adhesion, that difference was not statistically significant (P = 0.136). Similarly, operation time was shorter in the negligible to moderate adhesion group (541.1 ± 176.7 minutes) than in the severe adhesion group (600.6 ± 131.2 minutes), but the difference was without statistical significance (P = 0.138). Although no patient in the negligible to moderate adhesion group needed any additional procedures or experienced complications due to adhesion, 4 patients (12.5%) in the open group required such procedures. Nonetheless, that difference was not statistically significant (P = 0.114).

Factors associated with severe adhesion

Because IAAs can be influenced not only by laparoscopy, but also by the extent of LR, additional LRTs, and other clinical

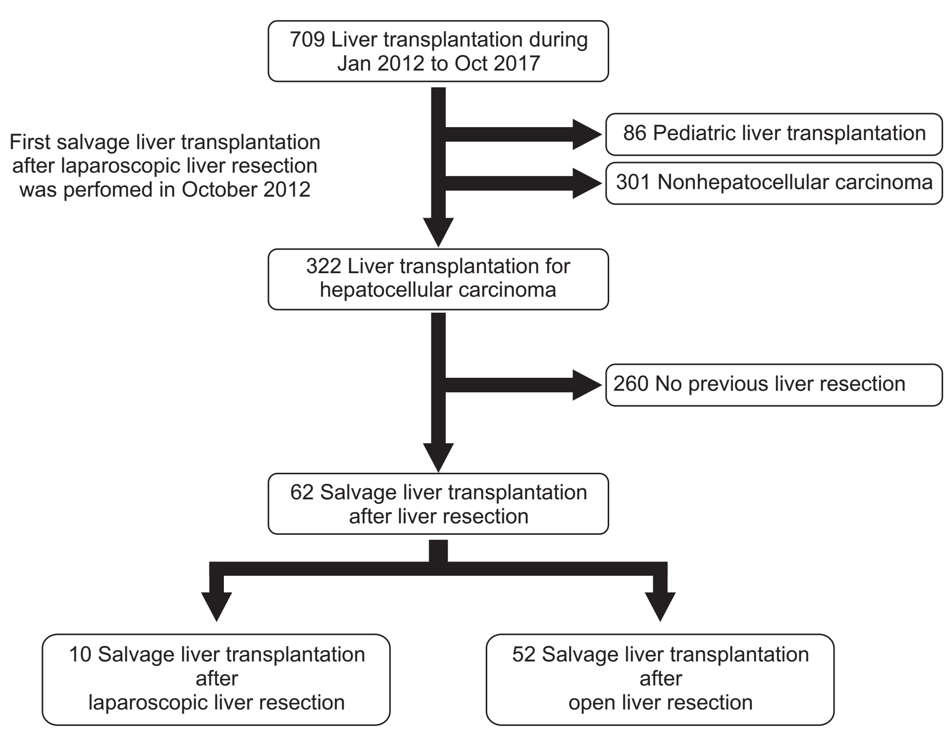

Fig. 1. Among 709 liver transplantations, 62 patients were included in the study population. Eighty-six pediatric patients and 301 nonhepatocellular carcinoma were excluded. Among 322 liver transplantation patients with hepatocellular carcinoma, 260 did not have a history of liver resection before transplantation. In the end, 62 patients, 10 with laparoscopic liver resection and 52 with open liver resection, were included.

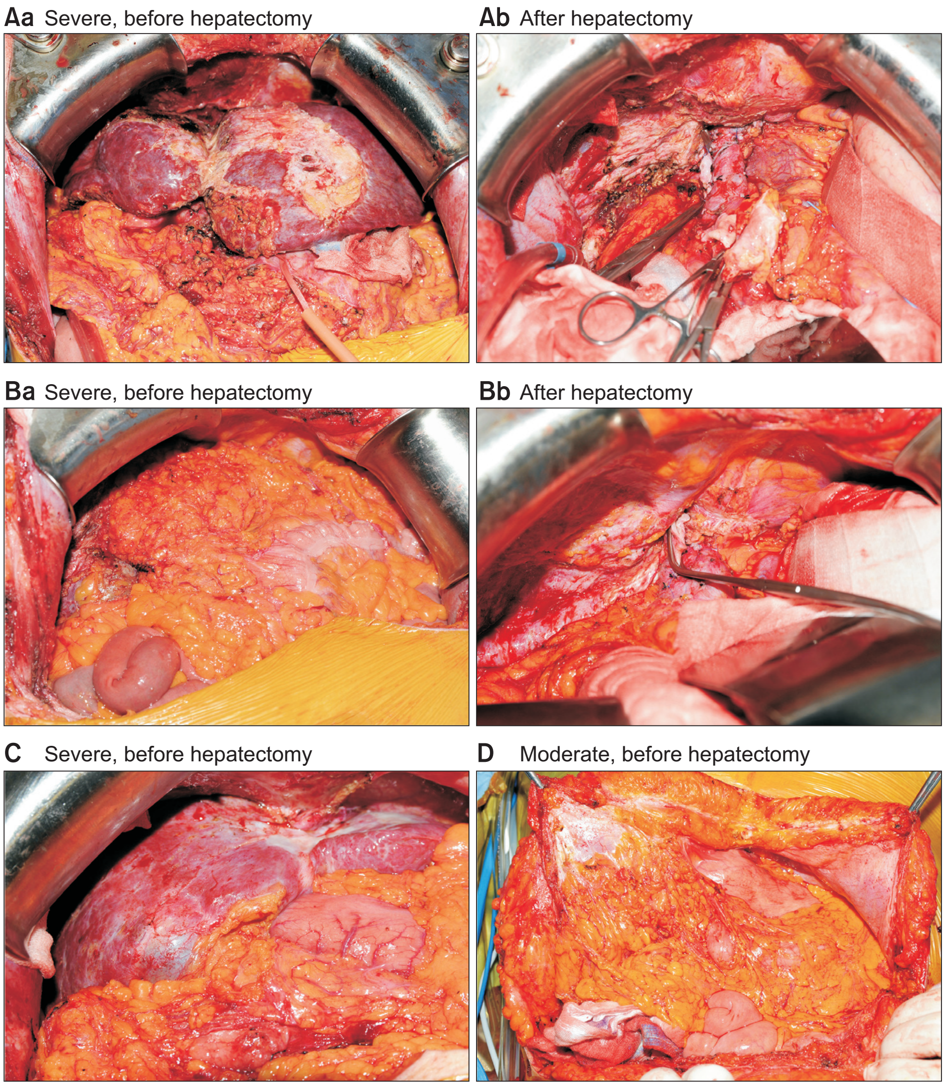

Fig. 2. (Aa) A 51-year-old male patient had severe adhesion of the omentum on the anterior liver surface. (Ab) After hepatectomy, injuries on the surface of the diaphragm wall occurred during adhesiolysis. (Ba) A 52-year-old male patient had severe omental adhesion covering the entire liver surface. (Bb) The patient also had severe adhesion between the liver dome area and the diaphragm. Surface injuries to the diaphragm were exposed after the liver was extracted. (C) A 51-year-old male had severe adhesion between the dome area of the liver surface and the diaphragm, which was injured during adhesiolysis. The patient underwent chest tube insertion. (D) A 61-year-old female patient had only moderate adhesion of the omentum to the peritoneum around the previous incision site, which was easily detached.

conditions, we performed multivariate logistic regression (Table 3). In the final model, only laparoscopy against open surgery showed a significant effect on severe adhesion (odds ratio [OR], 0.168; 95% confidence interval [CI], 0.029–0.970; P = 0.046). Additional LRTs (OR, 4.343; 95% CI, 0.963–19.590; P = 0.056) and liver failure (OR, 4.558; 95% CI, 0.958–21.693; P = 0.057) showed a trend toward severe adhesion but without statistical significance. Major LR (P = 0.610), ascites (P = 0.571), and degree of liver cirrhosis according to the Child-Pugh classification (P = 0.180) showed no relationship with severe adhesion.

Patients who underwent additional procedures or complications related to adhesion

Four patients required additional procedures or experienced complications related to severe IAA (Table 4). A 51-year-old male patient who underwent open segmentectomy of segment 7 and 9 transarterial chemoembolizations, 1 radiofrequency ablation, and 1 radiotherapy had severe adhesion between the liver and diaphragm that led to the opening of the diaphragm (Fig. 2C). The patient was inserted with a chest tube. A 48-year-old male patient who underwent open right hemihepatectomy required a small bowel resection and anastomosis and a wedge resection of the diaphragm due to severe IAA. A 40-year-old male who had previously undergone an open anterior sectionectomy experienced duodenal bulb perforation during SLT due to severe adhesion. The perforation was repaired, and an omental patch was applied. A 56-year-old female patient underwent an open right hemihepatectomy with 6 transarterial chemoembolizations and 4 radiofrequency ablations prior to SLT. After SLT, the patient had persistent bleeding that required reoperation. The source of the bleeding was found to be an adhesiolysis site on the diaphragm. All of these patients underwent open LR as an initial operation and were categorized as having severe IAA during SLT.

Table 1. Comparison of demographic, clinical, and operative characteristics between patients who underwent laparoscopic liver resection and open liver resection before salvage liver transplantation

Variable	Laparoscopy (n = 10)	Open (n = 52)	P-value
Sex, male:female	9:1	43:9	>0.999
Age (yr)	53.8 ± 5.7	48.8 ± 9.5	0.109
Hepatitis B	9 (90.0)	47 (90.4)	>0.999
Hepatitis C	1 (10.0)	3 (5.8)	0.515
Diabetes mellitus	1 (10.0)	4 (7.7)	>0.999
Initial LR			0.291
Major resection	2 (20.0)	22 (42.3)	
Minor resection	8 (80.0)	30 (57.7)	
LRT other than LR	6 (60.0)	41 (78.8)	0.237
No. of LRTs, median (IQR)	1.5 (5)	3.5 (5)	0.227
Reason for liver transplantation			0.693
Recurrent HCC	7 (70.0)	40 (76.9)	
Liver failure	3 (30.0)	12 (23.1)	
Within Milan criteria	3/8 (37.5)	15/41 (36.6)	>0.999
MELD score at SLT	13.3 ± 10.3	10.2 ± 5.9	0.186
Child-Pugh			0.676
A	6 (60.0)	36 (69.2)	
B	3 (30.0)	11 (21.2)	
C	1 (10.0)	5 (9.6)	
Donor hepatectomy			0.500
Living donor, open	7 (70.0)	31 (59.6)	
Living donor, laparoscopy	1 (10.0)	14 (26.9)	
Deceased donor	2 (20.0)	7 (13.5)	
Operative finding on SLT			
Ascites	3 (30.0)	16 (23.2)	0.424
Collateral vessels			0.788
Negligible	4 (40.0)	23 (44.2)	
Small	4 (40.0)	20 (38.5)	
Many	2 (20.0)	9 (17.3)	
Adhesion			0.029
Negligible	1 (10.0)	2 (3.9)	
Moderate	7 (70.0)	19 (37.3)	
Severe	2 (20.0)	30 (58.8)	
Operative data			
Operation time (min)	537.4 ± 118.3	574.0 ± 165.2	0.508
Estimated blood loss (mL), median (IQR)	2,750 (2,100)	1,500 (1,800)	0.667
Transfusion	3 (30.0)	23 (44.2)	0.499
Red blood cell infusion (mL), median (IQR)	513 (2054)	500 (1072)	0.953
Postoperative data			
Hospital stay (day)	30.6 ± 19.5	32.5 ± 16.6	0.753
Complications	4 (40.0)	28 (54.9)	0.496
CCI, median (IQR)	0 (33.7)	20.9 (33.7)	0.487
Clavien-Dindo classification			>0.999
I:II	0:1 (25.0)	1:4 (17.9)	
III:IV:V	2:1:0 (75.0)	19:3:1 (82.1)	
Any additional procedures or complications due to adhesion	0 (0)	4 (7.7)	>0.999
Recurrence	1 (10.0)	12 (23.1)	0.673
Death	0 (0)	5 (9.6)	0.582

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
LR, liver resection; LRT, locoregioneal therapy; IQR, interquartile range; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; SLT, salvage liver transplantation; CCI, comprehensive complication index.

Table 2. Comparison of demographic, clinical, and operative characteristics between patients with negligible or moderate adhesion and patients with severe adhesion during salvage liver transplantation

Variable	Adhesion		P-value
	Negligible or moderate (n = 29)	Severe (n = 32)	
Sex, male:female	25:4	26:6	0.735
Age (yr)	49.4 ± 9.7	49.4 ± 8.6	0.999
Initial LR			0.459
Major resection	19 (65.5)	18 (56.2)	
Minor resection	10 (34.5)	14 (43.8)	
Laparoscopy	8 (27.6)	2 (6.2)	0.037
LRT other than LR	19 (65.5)	27 (84.4)	0.136
No. of LRTs, median (IQR)	2 (6)	3 (6)	0.502
Reason for liver transplantation			
Recurrent HCC	22 (84.6)	22 (68.8)	
Liver failure	4 (15.4)	10 (31.2)	
Within Milan criteria	8/24 (33.3)	10/24 (41.7)	0.551
MELD score at SLT	11.2 ± 8.6	10.3 ± 4.7	0.601
Child-Pugh			0.890
A	21 (72.4)	20 (62.5)	
B	4 (13.8)	10 (31.2)	
C	4 (13.8)	2 (6.2)	
Operative data			
Operation time (min)	541.1 ± 176.7	600.6 ± 131.2	0.138
Estimated blood loss (mL), median (IQR)	1,500 (2,000)	1,550 (2,000)	0.744
Transfusion	10 (34.5)	15 (46.9)	0.326
Red blood cell infusion (mL), median (IQR)	499 (1,002)	511.5 (1,278)	0.480
Postoperative data			
Hospital stay (day)	32.1 ± 14.8	32.6 ± 19.1	0.901
Complications	14 (50.0)	18 (56.2)	0.628
CCI, median (IQR)	20.9 (33.7)	23.6 (33.7)	0.771
Clavien-Dindo classification			0.365
I:II	0:4 (28.6)	1:1 (11.1)	
III:IV:V	7:2:1 (71.4)	14:2:0 (88.9)	
Any additional procedures or complications due to adhesion	0 (0)	4 (12.5)	0.114
Recurrence	6 (20.7)	7 (21.9)	0.910
Death	3 (10.3)	2 (6.2)	0.662

Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.
LR, liver resection; LRT, locoregioneal therapy; IQR, interquartile range; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; SLT, salvage liver transplantation; CCI, comprehensive complication index.

DISCUSSION

This is the first systematic study reporting the relationship between LLR and IAA. Although Laurent et al. [9] reported a favorable outcome for LLR in terms of operation time, blood loss, and transfusion by comparing 12 laparoscopy patients and 12 open patients, they did not compare the degree of adhesion. Our study collected data from prospectively maintained operative records by adjusting a protocol to minimize subjective assessments. As explained above, the degree of adhesion originally introduced by Beck et al. [14] was adjusted to our surgical practice.

In our study, IAA severity was significantly higher in patients who underwent SLT after open LR than in those who first had LLR. Whereas 58.8% of patients in the open group had severe IAA, only 20.0% in the laparoscopy group had severe adhesion. Interestingly, operation time and the number of infused red cells did not differ between the 2 groups, which is not in accordance with the study of Laurent et al. [9]. When comparing the severe adhesion group to the negligible or moderate adhesion group, previous LLR was the only significantly different variable; operation time and number of infused red cells did not differ. We do not consider this finding exceptional because operation time can be influenced by several factors. Adhesiolysis is only a small part of performing a hepatectomy, which is why the operation times for the laparoscopy group and

Table 3. Final model of multivariate logistic regression analysis on potential factors related to severe adhesion during salvage liver transplantation

Variable	No.	OR	95% CI	P-value
Final model				
Laparoscopy (against open surgery)	10	0.168	0.029–0.970	0.046
Additional locoregional therapies	47	4.343	0.963–19.590	0.056
SLT for liver failure (against recurrent HCC)	15	4.558	0.958–21.693	0.057
Variables excluded from the final model				
Major resection (against minor resection)	24	1.428	0.363–5.618	0.610
Ascites	13	1.739	0.256–11.800	0.571
Child-Pugh				
A	41			0.180
B	14	2.143	0.380–12.087	0.388
C	6	0.219	0.020–2.427	0.216

OR, odds ratio; CI, confidence interval; HCC, hepatocellular carcinoma; SLT, salvage liver transplantation.

Table 4. Patients who underwent additional procedures or experienced complications due to intraoperative adhesion during salvage liver transplantation

Sex/age (yr)	LR before SLT	LRT before SLT	Adhesion	Consequence
M/51	Open segmentectomy, S7	9 TACEs, 1 RFA and 1 RT	Severe	Opening of diaphragm, chest tube insertion (Fig. 2C)
M/48	Open right hemihepatectomy, S5 and S8	None	Severe	Small bowel segmental resection and anastomosis Wedge resection of diaphragm
M/40	Open anterior sectionectomy, S5	None	Severe	Duodenal bulb perforation, primary repair and omental patch
F/56	Open right hemihepatectomy, S6 and S7	6 TACEs and 4 RFAs	Severe	Reoperation due to persistent bleeding from diaphragm

LR, liver resection; LRT, locoregional therapy; SLT, salvage liver transplantation; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; RT, radiotherapy.

negligible or moderate adhesion group were shorter than their counterparts but without statistical significance. Regarding transfusions, bleeding during LT is mainly determined by the liver function itself. When liver function has deteriorated, massive transfusions are required. Bleeding during adhesiolysis is also influenced by the coagulation status of the patient. Our data show that patients who underwent LT due to liver failure had significantly larger transfusions than those who underwent LT under other circumstances. When the number of infused red cells was compared according to the reason for LT, patients who underwent LT due to liver failure received more transfused red cells (median, 1241 mL; interquartile range [IQR], 1,865) than patients who underwent LT due to recurrent HCC (median, 499 mL; IQR, 750; P = 0.005).

SLT after a previous upper abdominal operation is much more challenging and correlates with longer operation times and increased blood loss compared with LT as a first operation [15-17]. In fact, the clinical significance of IAA is not just the increased risk of bleeding, but also increased risk of damage to adjacent organs. In our study, all 4 patients who required additional procedures or experienced complications due to severe adhesions had open LR prior to SLT.

Our study is also the first to analyze the effects of LLR on IAA while considering other factors that influence IAA. Our multivariate logistic regression model showed that laparoscopy was the only factor related to IAA severity. With a P-value of 0.046, laparoscopy showed a protective effect against formation of severe IAA. LRTs and LT due to liver failure showed a trend toward statistical significance.

As in many other abdominal surgeries, minimally invasive surgery has become popular in liver surgery [18,19]. Many studies are being published about the benefits of LLR over open LR, such as shorter hospital stay, less bleeding, and smaller incisions with comparable oncological outcomes and safety [6,18-20]. To this point, studies on IAA have been scarce, and the first study announcing the benefits of LLR for subsequent LT had no data on IAA [9]. Our data on IAA are not quantitative because quantifying the amount of adhesion is impossible. Our method of staging the degree of adhesion, which was originally suggested by Beck et al., has also been adjusted by other centers and is gaining reliability [14,21].

The major limitation of this study is that it is retrospective and without matching. However, our data show no significant differences in background characteristics between the laparoscopy and open groups. Therefore, we consider matching of these patient groups to be unnecessary. Also, the clinical effects of IAA seem relatively small compared to those reported by a previous study. However, operation time and bleeding are influenced by several factors, not just IAA severity. Small number of patients included to the study is another limitation, which decrease the statistical power.

HCC is a highly recurrent tumor that can require numerous operations or even SLT. Surgeons should always consider what is best for their patients and their futures by minimizing potential risks. LLR can be beneficial not only for immediate patient recovery after LR, but also for the SLT that might be needed in the future. Because this retrospective study has some shortcomings, we recommend a prospective study on the severity of IAA to clarify the benefits of LLR on IAA.

CONFLICTS OF INTEREST

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

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