Liver Cancer

Research Article

Liver Cancer 2023;12:32–43
DOI: 10.1159/000527294

Received: March 31, 2022
Accepted: September 13, 2022
Published online: October 5, 2022

Surgical Outcomes of Laparoscopic versus Open Hepatectomy for Left Hepatocellular Carcinoma: Propensity Score Analyses Using Retrospective Japanese and Korean Individual Patient Data

Masaki Kaibori[a] Kengo Yoshii[b] Yuzo Umeda[c] Takahito Yagi[c] Takehiro Okabayashi[d] Kenta Sui[d] Akira Mori[e] Yuhei Hamaguchi[e] Kiyoshi Kajiyama[f] Daisuke Hokuto[g] Kazuteru Monden[h] Tomoharu Yoshizumi[i] Yoriko Nomura[j] Kan Toriguchi[k] Jong Man Kim[l] Gi Hong Choi[m] Je Ho Ryu[n] Yangseok Koh[o] Koo Jeong Kang[p] Young Kyoung You[q] Kwang-Sik Chun[r] Young Seok Han[s] Chan Woo Cho[t] Young Il Choi[u] Dong-Sik Kim[v] Jae Do Yang[w] Keita Mori[x] Atsushi Hiraoka[y] Hiroki Yamaue[z] Masafumi Nakamura[A] Masakazu Yamamoto[B] Itaru Endo[C]

[a]Department of Surgery, Kansai Medical University, Osaka, Japan; [b]Department of Mathematics and Statistics in Medical Sciences, Kyoto Prefectural University of Medicine, Kyoto, Japan; [c]Gastroenterological Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan; [d]Department of Gastroenterological Surgery, Kochi Health Sciences Center, Kochi, Japan; [e]Department of Surgery, Japanese Red Cross Osaka Hospital, Osaka, Japan; [f]Department of Surgery, Iizuka Hospital, Fukuoka, Japan; [g]Department of Surgery, Nara Medical University, Nara, Japan; [h]Department of Surgery, Fukuyama City Hospital, Hiroshima, Japan; [i]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [j]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Kurume University School of Medicine, Fukuoka, Japan; [k]Department of Gastroenterological Surgery, Hyogo College of Medicine, Nishinomiya, Japan; [l]Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [m]Division of Hepatobiliary and Pancreas Surgery, Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [n]Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Busan, Republic of Korea; [o]Department of Surgery, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea; [p]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [q]Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [r]Department of Surgery, Chungnam National University Hospital, Daejeon, Republic of Korea; [s]Liver Transplantation and Hepatobiliary Pancreas Surgery, Department of Surgery, Kyungpook National University, School of Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea; [t]Department of Surgery, Yeungnam University College of Medicine, Daegu, Republic of Korea; [u]Department of Surgery, Kosin University Gospel Hospital, Kosin University College of Medicine, Busan, Republic of Korea; [v]Division of HBP Surgery and Liver Transplantation, Department of Surgery, Korea University College of Medicine, Seoul, Republic of Korea; [w]Department of Surgery, Jeonbuk National University Hospital, Jeonbuk National University Medical School, Jeonju, Republic of Korea; [x]Department of Biostatistics, Clinical Research Center, Shizuoka Cancer Center, Shizuoka, Japan; [y]Gastroenterology Center, Ehime Prefectural Central Hospital, Matsuyama, Japan; [z]Second Department of Surgery, Wakayama Medical University, Wakayama, Japan; [A]Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [B]Department of Surgery, Utsunomiya Memorial Hospital, Tochigi, Japan; [C]Gastroenterological Surgery, Yokohama City University Graduate School of Medicine, Kanagawa, Japan

Karger@karger.com
www.karger.com/lic

Karger
OPEN ACCESS

Correspondence to:
Masaki Kaibori, kaibori@hirakata.kmu.ac.jp
Jong Man Kim, jongman94@hanmail.net

Keywords
Hepatocellular carcinoma · Laparoscopic left hepatectomy · Open left hepatectomy · Postoperative complications · Recurrence-free survival · Overall survival

Abstract
Introduction: This study aimed to compare the prognostic impact of laparoscopic left hepatectomy (LLH) with that of open left hepatectomy (OLH) on patient survival after resection of left hepatocellular carcinoma (HCC). ***Methods:*** Among the 953 patients who received initial treatment for primary HCC that was resectable by either LLH or OLH from 2013 to 2017 in Japan and Korea, 146 patients underwent LLH and 807 underwent OLH. The inverse probability of treatment weighting approach based on propensity scoring was used to address the potential selection bias inherent in the recurrence and survival outcomes between the LLH and OLH groups. ***Results:*** The occurrence rate of postoperative complications and hepatic decompensation was significantly lower in the LLH group than in the OLH group. Recurrence-free survival (RFS) was better in the LLH group than in the OLH group (hazard ratio, 1.33; 95% confidence interval, 1.03–1.71; $p = 0.029$), whereas overall survival (OS) was not significantly different. Subgroup analyses of RFS and OS revealed an almost consistent trend in favor of LLH over OLH. In patients with tumor sizes of ≥4.0 cm or those with single tumors, both RFS and OS were significantly better in the LLH group than in the OLH group. ***Conclusions:*** LLH decreases the risk of tumor recurrence and improves OS in patients with primary HCC located in the left liver.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and the fifth most common malignancy worldwide [1]. According to the 20th Nationwide Follow-up Survey of Primary Liver Cancer, hepatectomy, which is known as the most effective procedure and accounts for 37.7% of all treatments, results in a survival rate of 62%, 47%, and 36% at 3, 5, and 7 years postoperatively, respectively [2]. Laparoscopic techniques and instruments have advanced during the past two decades, and laparoscopic liver resection is being increasingly adopted worldwide. Lesser blood loss, fewer postoperative complications, and shorter postoperative hospital stay are the advantages of laparoscopic liver resection, as compared to conventional open surgery, and laparoscopy is now considered a safe, feasible modality for removing malignant and benign liver tumors [3, 4]. A previous study has compared the postoperative outcomes of laparoscopic right hepatectomy with those of open right hepatectomy for HCC [5]. Kim et al. [6] have conducted a retrospective study on the postoperative outcomes of left hepatectomy. They reported that pure laparoscopic left hepatectomy (LLH) was feasible and safe for left HCC. Although the median postoperative hospital stay was significantly shorter in the LLH group than in the open left hepatectomy (OLH) group before and after propensity score matching (PSM), the short-term (complications) and long-term (recurrence and cumulative survival) outcomes were not statistically different between the two groups after matching. The number of cases included after PSM was only 37; thus, examining more cases is essential. In contrast, conducting a randomized controlled study with a multicenter collaborative research design is unrealistic.

The incidence of HCC and number of hepatectomy cases in Japan and South Korea are the highest worldwide [7, 8]. In 2013, a multicenter-based collaboration study on liver disease was proposed by the Korean Association of Hepato-Biliary-Pancreatic Surgery (KAHBPS) and Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS). This study is the second joint project between Japan and South Korea, which was conducted among multiple institutions in both countries; we believe that the findings of this multicenter-based collaboration study of both Japan and Korea are of great clinical significance for HCC treatment.

Methods

This retrospective cohort study is conducted as a project of the multicenter-based collaboration study by the JSHBPS and KAHBPS. Perioperative data of 877 and 286 patients who underwent hepatic resection from 2013 to 2017 at the 97 and 12 institutions that participated in the JSHBPS and KAHBPS, respectively, were collected. The end of the follow-up period was set at the end of December 2018. The patients whose initial treatment for primary HCC was either LLH or OLH were included in this study. "Laparoscopic hepatectomy" included hand-assisted laparoscopic hepatectomy. The exclusion criteria were as follows: patients who underwent surgery for another malignancy during the same operative setting, those who underwent a combination of laparoscopic and OLH, and those who underwent Spiegel lobe resection. Tumor stage was classified according to the American Joint Committee on Cancer (AJCC) International Union Against Cancer (UICC) TNM staging system [9]. Patients with stages IIIB and IIIC were also excluded from the analyses. Briefly, we excluded some cases in which HCC invaded a large branch of the portal or hepatic vein (stage

IIIB), HCC invaded other organs, or HCC ruptured (stage IIIC) because these are relative contraindications for LLH.

Surgical procedures were classified according to the Brisbane 2000 Terminology of Hepatic Anatomy and Liver Resections [10]. The indication for surgery was based on an algorithm that included the presence/absence of ascites, serum total bilirubin concentration, and indocyanine green (ICG) test result as previously described [11, 12]. Liver surgeons in Japan and Korea performed either LLH or OLH depending on the hepatic functional reserve, tumor location, and tumor size. Ultimately, the operative technique was selected depending on the preference of each institution in Japan and Korea. HCC diagnosis was confirmed by histological examination of resected specimens from all patients. This study was approved by the Ethics Committee of the JSHBPS and Institutional Review Board (IRB) of Kansai Medical University (No. 2018206). Given the retrospective nature of this study—without an active intervention planned for the patients—the need for obtaining IRB approval was subject to each institution's policy according to each researcher's discretion. The study protocol was also approved by each participating institution from Japan and Korea. Each representative from Japan and Korea was responsible for communicating with and collecting data from each participating center of each country. A representative from Japan merged and processed the collected data. All data were collected and analyzed at the Department of Mathematics and Statistics in Medical Sciences, Kyoto Prefectural University of Medicine.

For the Japanese participating centers, the training facilities were categorized as follows according to the number of surgical cases: training facility A, >50 highly difficult hepatobiliary and pancreatic surgical cases are performed annually; training facility (B), ≥30 cases are performed annually. However, in addition to the number of surgical cases, the content and bias of the surgery are also subject to examination. Apart from being defined as handling >50 cases of highly difficult hepatobiliary and pancreatic surgical cases per year, training facility A is also described as a facility with ≥10 cases of highly difficult hepatobiliary surgical and highly difficult pancreatic surgical cases per year. Even if a facility performs ≥50 cases of highly difficult hepatobiliary and pancreatic surgical cases, and if <10 cases of highly difficult hepatobiliary surgical and highly difficult pancreatic surgical cases are performed annually, the facility will be categorized as a training facility B. In addition, if a facility performs <5 cases of highly difficult hepatobiliary and pancreatic surgical cases each year, it will not be categorized as a training facility. In this study, training facilities A and B comprised 67 and 30 institutions, respectively. On the other hand, the Korean institutions were not classified based on the number of surgical cases, as only 12 facilities participated in this study.

Follow-Up

Perioperative/postoperative complications or death (i.e., those occurring within 1 month after surgery or during the same hospital admission) was recorded to assess the morbidity and mortality risks of the procedures. After discharge, all patients were followed up by ultrasonography, computed tomography, or magnetic resonance imaging at least every 3–6 months. Moreover, various laboratory parameters were monitored, including serum concentrations of α-fetoprotein (AFP) and protein induced by vitamin K antagonist-II (PIVKA-II).

When HCC recurrence was suspected based on the tumor marker levels or imaging findings, tumor recurrence limited to the remnant liver was treated with transcatheter arterial chemoembolization, lipiodolization, repeat hepatectomy, or ablation therapies, such as percutaneous radiofrequency therapy. Recurrence-free survival (RFS) was defined as the time interval between the date of the operation and the date of diagnosis of the first recurrence or death, which is the last follow-up.

Statistical Analysis

Continuous variables were divided into two groups according to their median value. The clinical characteristics of the two groups were compared using either the χ^2 or Fisher's exact test, as appropriate. The RFS and overall survival (OS) rates after hepatectomy were calculated using the Kaplan-Meier method. The hazard ratio (HR) for OS and RFS and 95% confidence interval (CI) were estimated using the univariate Cox hazard model.

The inverse probability of treatment weighting (IPTW) approach was used to address the potential selection bias inherent in the recurrence and survival outcomes of patients with HCC in the LLH and OLH groups. In the IPTW, the propensity scores were calculated using logistic regression analysis involving a set of covariates deemed to have effects on RFS or OS, including age, preoperative serum albumin level, PIVKA-II level, and maximum tumor size. Weight truncation was performed on all patients outside the 99th percentile to avoid imbalances with patients of extreme weight [13]. The prognostic factors for RFS or OS were evaluated using the IPTW-adjusted Kaplan-Meier method and Cox hazard model. The aforementioned statistical analyses were performed using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). The survival analysis was performed using the R package "survival" and "MatchIt." Forest plot images were generated using the R package "ggplot2." Significance tests were two-tailed, and p values of <0.05 were used to denote statistical significance.

Results

Using our criteria, we identified 1,163 patients from Japan and Korea. The number of patients from Japan was 877 (119 and 758 in the LLH and OLH groups, respectively), whereas that from Korea was 286 (78 and 208 in the LLH and OLH groups, respectively). Patients with insufficient or inappropriate data were excluded (null record, n = 48; intrahepatic cholangiocellular carcinoma (ICC), n = 1; HCC + ICC combined, n = 2; combined resection of segment 1, n = 8; stage IIIB in the UICC/AJCC 7th staging system, n = 65; stage IIIC in the UICC/AJCC 7th staging system, n = 1; and missing data, n = 23), resulting in a total sample of 1,015 patients. The total number of Japanese facilities was 97 (67 and 30 for training facilities A and B, respectively). Twenty-eight and 19 facilities in training facilities A and B, respectively, performed OLH only. Only two facilities in training facility B performed LLH. On the other hand, in Korea, 4 out of 12 facilities performed only OLH, and no facility per-

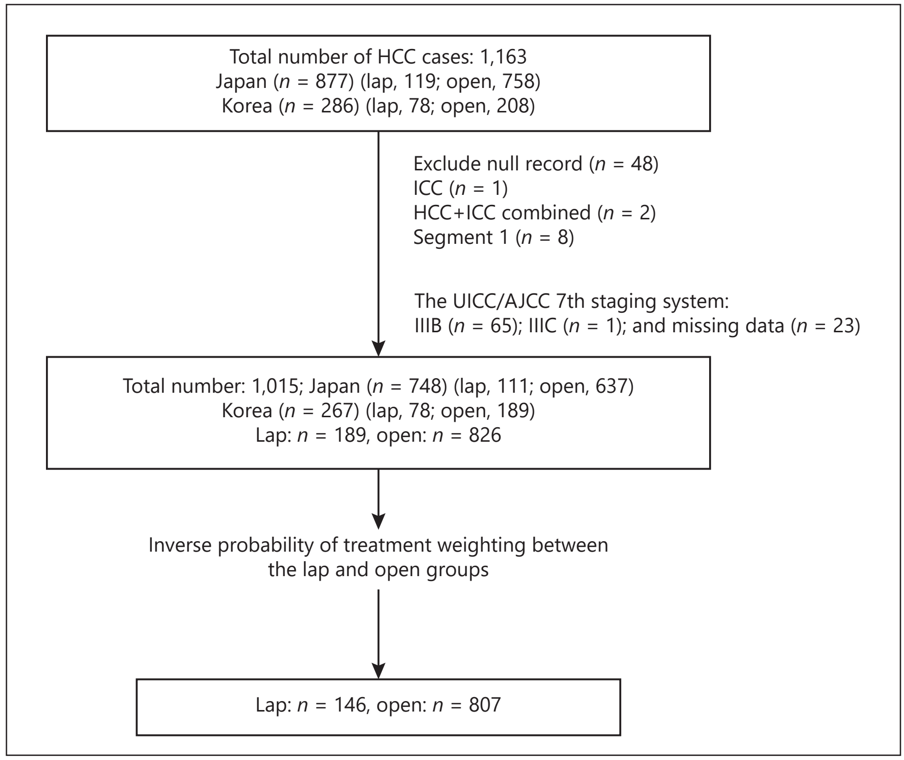


Fig. 1. Patient flowchart. The chart includes all patients with hepatocellular carcinoma (HCC) who underwent laparoscopic or open left hepatectomy in this study. ICC, intrahepatic cholangiocellular carcinoma.

formed LLH. Finally, 953 patients were enrolled using the IPTW approach and divided into the LLH (n = 146) and OLH (n = 807) groups (Fig. 1).

Table 1 shows the perioperative characteristics of both groups before and after IPTW. Significant differences in background variables were observed between the two groups before IPTW. No differences in sex, hepatitis B surface antigen, hepatitis C virus antibody, alcohol intake, serum total bilirubin level, prothrombin activity, platelet count, alanine aminotransferase, American Society of Anesthesiologists physical status, ICG retention rate at 15 min, AFP, and tumor location were found between the two groups. Before matching, significant differences in age and serum albumin and PIVKA-II levels were observed. The operative blood loss and blood transfusion rate were significantly lower in the LLH group than in the OLH group. The pathological features of each group before IPTW are shown in Table 1. The OLH group had a significantly larger maximum tumor size than the LLH group.

IPTW was performed to classify patients into the LLH and OLH groups, resulting in 146 and 807 patients, respectively (Table 1). Preoperative serum levels of albumin and PIVKA-II, operative blood loss, and blood transfusion rate differed significantly between the two groups after matching. However, comparison between the two groups revealed no significant differences in pathological factors (Table 1).

Table 2 presents the postoperative short-term outcomes of both groups before and after IPTW. The postoperative hospital stay and occurrence rates of postoperative complications and hepatic decompensation greater than grade B according to the International Study Group of Liver Surgery (ISGLS) definition were significantly lower in the LLH group than in the OLH group both before and after IPTW. Although there were five cases of in-hospital mortality in the OLH group, no statistical differences in the rate of complications graded according to the Clavien-Dindo classification and in-hospital mortality rate were detected between the two groups.

Long-Term Outcomes

The median follow-up period was 31.3 and 36.0 months in the LLH and OLH groups, respectively. Figure 2 shows a comparison of the long-term outcomes between the LLH and OLH groups in the IPTW-adjusted population. The RFS and OS in the LLH group were significantly better than those in the OLH group. The 5-year RFS rate was 45.2% and 36.1% for the LLH and OLH groups, respectively (HR, 1.33; 95% CI, 1.06–1.68; p = 0.016) (Fig. 2a). The 5-year OS rate was 75.7% and 64.4%

Table 1. Perioperative characteristics of patients in the laparoscopic and open groups before and after IPTW

Variables	Original sample					IPTW sample				
	lap group (n = 189)		open group (n = 826)		p value	lap group (n = 146)		open group (n = 807)		p value
	n	(%)	n	(%)		n	(%)	n	(%)	
Sex										
Male	151	(80)	665	(81)	0.904[a]	115	(78)	650	(81)	0.553[a]
Female	38	(20)	160	(19)		32	(22)	155	(19)	
Age										
<70 years	111	(59)	416	(50)	0.046[a]	75	(51)	414	(51)	1.000[a]
≥70 years	78	(41)	410	(50)		71	(49)	393	(49)	
HBsAg										
None	114	(63)	566	(70)	0.105[a]	99	(71)	546	(69)	0.765[a]
Positive	66	(37)	244	(30)		41	(29)	245	(31)	
HCVAb										
None	142	(75)	593	(72)	0.416[a]	114	(78)	577	(72)	0.129[a]
Positive	47	(25)	232	(28)		32	(22)	229	(28)	
Alcohol intake										
None	148	(79)	598	(74)	0.180[a]	113	(78)	592	(75)	0.409[a]
Positive[b]	39	(21)	209	(26)		31	(22)	199	(25)	
Serum total bilirubin										
<0.7 mg/dL	90	(48)	354	(43)	0.211[a]	68	(47)	343	(43)	0.355[a]
≥0.7 mg/dL	96	(52)	469	(57)		76	(53)	461	(57)	
Prothrombin activity										
<95%	101	(55)	423	(53)	0.692[a]	79	(56)	411	(52)	0.511[a]
≥95%	83	(45)	376	(47)		63	(44)	376	(48)	
Platelet										
$<19.0 \times 10^4$/mm^3	90	(48)	411	(50)	0.642[a]	66	(45)	407	(51)	0.241[a]
$\geq 19.0 \times 10^4$/mm^3	99	(52)	414	(50)		81	(55)	398	(49)	
ALT										
<29 U/L	106	(56)	396	(48)	0.054[a]	83	(57)	392	(49)	0.082[a]
≥29 U/L	83	(44)	429	(52)		63	(43)	414	(51)	
Serum albumin										
<4.0 g/dL	40	(21)	303	(37)	<0.001[a]	31	(21)	276	(34)	0.003[a]
≥4.0 g/dL	148	(79)	523	(63)		115	(79)	530	(66)	
ASA-PS classification										
Class 1	41	(22)	224	(27)	0.080[a]	34	(23)	217	(27)	0.148[a]
Class 2	131	(69)	494	(61)		101	(69)	487	(61)	
Class 3	17	(9)	98	(12)		11	(8)	92	(12)	
ICGR15										
<15.0%	127	(77)	581	(75)	0.755[a]	102	(78)	571	(76)	0.573[a]
≥15.0%	38	(23)	189	(25)		28	(22)	183	(24)	
AFP[‡]										
<15.0 ng/mL	99	(53)	409	(50)	0.564[a]	78	(53)	406	(51)	0.640[a]
≥15.0 ng/mL	89	(47)	409	(50)		69	(47)	397	(49)	
PIVKA-II										
<250 mAU/mL	116	(64)	401	(50)	<0.001[a]	93	(63)	421	(52)	0.017[a]
≥250 mAU/mL	66	(36)	406	(50)		54	(37)	386	(48)	
Location of tumor										
Segment 2 or 3 or 4	125	(66)	486	(59)	0.093[a]	96	(66)	487	(61)	0.299[a]
Segment 2 and 3 or 2, 3, and 4	64	(34)	335	(41)		50	(34)	314	(39)	
Operative blood loss										
<350 mL	142	(75)	354	(44)	<0.001[a]	114	(78)	353	(44)	<0.001[a]
≥350 mL	47	(25)	458	(56)		33	(22)	441	(56)	
Blood transfusion during and/or after the operation										
No	181	(96)	692	(84)	<0.001[a]	142	(97)	681	(85)	<0.001[a]
Yes	8	(4)	129	(16)		5	(3)	121	(15)	
Operating time										
<295 min	101	(53)	409	(50)	0.414[a]	75	(51)	402	(50)	0.852[a]
≥295 min	88	(47)	412	(50)		71	(49)	400	(50)	
Maximum tumor size										
<4.0 cm	113	(60)	332	(40)	<0.001[a]	76	(52)	348	(43)	0.058[a]
≥4.0 cm	74	(40)	493	(60)		70	(48)	458	(57)	

Table 1 (continued)

Variables	Original sample					IPTW sample				
	lap group (*n* = 189)		open group (*n* = 826)		*p* value	lap group (*n* = 146)		open group (*n* = 807)		*p* value
	n	(%)	*n*	(%)		*n*	(%)	*n*	(%)	
Histology										
Well	25	(13)	90	(11)	0.105[a]	16	(11)	92	(11)	0.469[b]
Mod	135	(71)	548	(66)		103	(71)	534	(66)	
Poor	23	(12)	131	(16)		22	(15)	126	(16)	
Necrosis or unknown	6	(3)	57	(7)		5	(3)	55	(7)	
Microscopic vascular invasion in portal vein and/or hepatic vein										
No	105	(56)	417	(51)	0.245[a]	76	(52)	413	(51)	0.927[a]
Yes	84	(44)	408	(49)		70	(48)	393	(49)	
Microscopic bile duct invasion										
No	179	(95)	752	(91)	0.144[a]	136	(93)	734	(91)	0.506[a]
Yes	10	(5)	73	(9)		10	(7)	72	(9)	
Number of tumors										
Single	169	(89)	734	(89)	0.961[a]	133	(91)	718	(89)	0.561[a]
Multiple	20	(11)	91	(11)		13	(9)	88	(11)	
Microscopic surgical margin										
No	185	(98)	791	(96)	0.247[a]	142	(97)	773	(96)	0.585[a]
Yes	4	(2)	35	(4)		4	(3)	33	(4)	
The UICC/AJCC 7th staging system										
I	70	(37)	249	(30)	0.079[a]	51	(35)	250	(31)	0.396[a]
II or IIIA	119	(63)	577	(70)		95	(65)	557	(69)	
Associated liver disease										
Normal liver	29	(15)	154	(19)	0.074[a]	30	(20)	146	(18)	0.672[a]
Chronic hepatitis or liver fibrosis	106	(56)	497	(60)		83	(56%)	486	(60)	
Cirrhosis	54	(29)	174	(21)		34	(23%)	174	(22)	
Intrahepatic recurrence of HCC										
No	107	(58)	433	(54)	0.365[a]	83	(58)	423	(54)	0.423[a]
Yes	79	(42)	376	(46)		61	(42)	366	(46)	
Intrahepatic recurrence of HCC										
Solitary	41	(51)	166	(43)	0.292[a]	31	(50)	165	(44)	0.502[a]
Multiple	40	(49)	216	(57)		31	(50)	206	(56)	
Treatment for recurrent HCC										
TACE	27	(14)	171	(21)	0.128[a]	21	(14)	165	(20)	0.341[a]
Re-resection	13	(7)	56	(7)		12	(8)	56	(7)	
RFA or PEIT or MCT	28	(15)	88	(11)		19	(13)	87	(11)	
Others	121	(64)	511	(62)		95	(65)	499	(62)	
Distant metastasis										
No	124	(88)	625	(84)	0.351[a]	98	(88)	612	(85)	0.479[a]
Yes	17	(12)	115	(16)		13	(12)	106	(15)	
Cause of death										
Liver cancer (related) death	25	(76)	152	(66)	0.582[b]	19	(70)	140	(65)	0.811[b]
Liver failure	3	(9)	22	(10)		3	(11)	21	(10)	
Another reason, etc.	5	(15)	55	(24)		5	(19)	53	(25)	

Data are shown as median (5th percentile to 95th percentile) or *n* (%). IPTW, inverse probability of treatment weighting; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ALT, alanine aminotransferase; ASA-PS, American Society of Anesthesiologists physical status; ICGR15, indocyanine green retention rate at 15 min; PIVKA-II, protein induced by vitamin K absence or antagonist-II; TACE, trans-arterial chemoembolization; RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy; MCT, microwave coagulation therapy. [a]χ^2 test. [b]Fisher's exact test.

for the LLH and OLH groups, respectively (HR, 1.64; 95% CI, 1.14–2.38; $p = 0.009$) (Fig. 2b). The LLH subgroup in the IPTW model had significantly better RFS than their OLH counterparts (Fig. 2c), whereas no significant difference in OS was found between the two subgroups (Fig. 2d). The 5-year RFS rate was 58.3% and 36.2% for the LLH and OLH groups, respectively (HR, 1.33; 95% CI, 1.03–1.71; $p = 0.029$) (Fig. 2c). The 5-year OS rate was 72.7% and 65.6% for the LLG and OLH groups, respectively (HR, 1.47; 95% CI, 0.98–2.21; $p = 0.066$) (Fig. 2d).

We performed several subgroup analyses of RFS and OS between the two groups (Fig. 3). Among male pa-

Table 2. Postoperative short-term outcomes of patients in the laparoscopic and open groups before and after IPTW

Variables	Original sample					IPTW sample				
	lap group (n = 189)		open group (n = 826)		p value	lap group (n = 146)		open group (n = 807)		p value
	n	(%)	n	(%)		n	(%)	n	(%)	
Postoperative hospital stay										
<12 days	140	(74)	352	(43)	<0.001[a]	105	(71)	348	(43)	<0.001[a]
≥12 days	48	(26)	470	(57)		42	(29)	454	(57)	
In-hospital mortality										
No	189	(100)	820	(99)	0.591[b]	146	(100)	801	(99)	1.000[b]
Yes	0	(0)	5	(1)		0	(0)	5	(1)	
Postoperative complications										
No	158	(84)	576	(70)	<0.001[a]	120	(82)	566	(70)	0.004[a]
Yes	31	(16)	250	(30)		26	(18)	241	(30)	
Clavien-Dindo grade										
I	11	(35)	82	(33)	0.970[b]	10	(38)	81	(34)	0.973[b]
II	13	(42)	95	(38)		10	(38)	92	(38)	
III	7	(23)	64	(26)		6	(23)	59	(24)	
IV	0	(0)	4	(2)		0	(0)	4	(2)	
V	0	(0)	5	(2)		0	(0)	5	(2)	
Occurrence hepatic decompensation greater than grade B of the ISGLS definition										
No	188	(100)	774	(97)	0.008[b]	146	(100)	757	(97)	0.037[b]
Yes	0	(0)	24	(3)		0	(0)	23	(3)	

Data are shown as median (5th percentile to 95th percentile) or n (%). IPTW, inverse probability of treatment weighting; ISGLS, International Study Group of Liver Surgery. [a]χ^2 test. [b]Fisher's exact test.

tients, the forest plots show that those who underwent LLH had better RFS and OS than those who underwent OLH. Among patients with preoperative prothrombin activity of ≥95%, the RFS and OS rates were significantly better in the LLH group than in the OLH group. In the analysis of tumor size, among patients with a tumor size of ≥4.0 cm, RFS and OS were significantly better in the LLH group than in the OLH group. In the subgroup with single tumors or negative microscopic surgical margin, both RFS and OS were statistically significantly better in the LLH group than in the OLH group.

Although the analysis of microscopic vascular invasion in the portal and/or hepatic veins and associated liver disease revealed no statistically significant difference in OS between the two groups among patients with positive microscopic vascular invasion in the portal and/or hepatic veins or chronic hepatitis or liver fibrosis, RFS was significantly better in the LLH group than in the OLH group. The subgroup analyses of RFS and OS revealed an almost consistent trend in favor of LLH.

A comparison between the two groups revealed no significant differences in intrahepatic recurrence of HCC, treatment for recurrent HCC, distant metastasis, and cause of death both before and after IPTW (Table 1). The survival curves of training facilities A and B in Japan and Korea before IPTW are shown in online supplementary Figure 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000527294). In training facility B, the number of LLH and OLH cases performed was low, showing no statistical difference; however, in training facility A in Japan and in all 12 facilities in Korea, LLH tended to show better PFS and OS. We also examined the survival rates of the top 10 facilities with the most cases of OLH and LLH using Japanese data before IPTW (online suppl. Fig. 2). The number of cases with LLH was extremely small in facilities with the most cases of OLH, but the number of cases with OLH was almost the same that of facilities with the most cases of LLH. LLH tended to show better PFS and OS in the top 10 facilities with the most cases of LLH in Japan (online suppl. Fig. 2 CD).

Subgroup Analysis

Although propensity scores were calculated for several variables, including age, preoperative serum albumin level, PIVKA-II level, and maximum tumor size in the IPTW, preoperative serum albumin and PIVKA-II levels differed significantly between the two groups after matching. We compared the two groups, stratified by median serum albumin and PIVKA-II levels and maximum tumor size, before and after IPTW (data not shown). In these stratified analyses, significant differences in PIVKA-II levels and tumor diameter remained, even after IPTW only in the two-group comparison of patients with serum albumin level ≥4.0 g/dL. In the stratified analysis of the other five groups, no significant differences were found in the remaining two factors.

The RFS and OS rates were better in the LLH group than in the OLH group before and after IPTW (data not

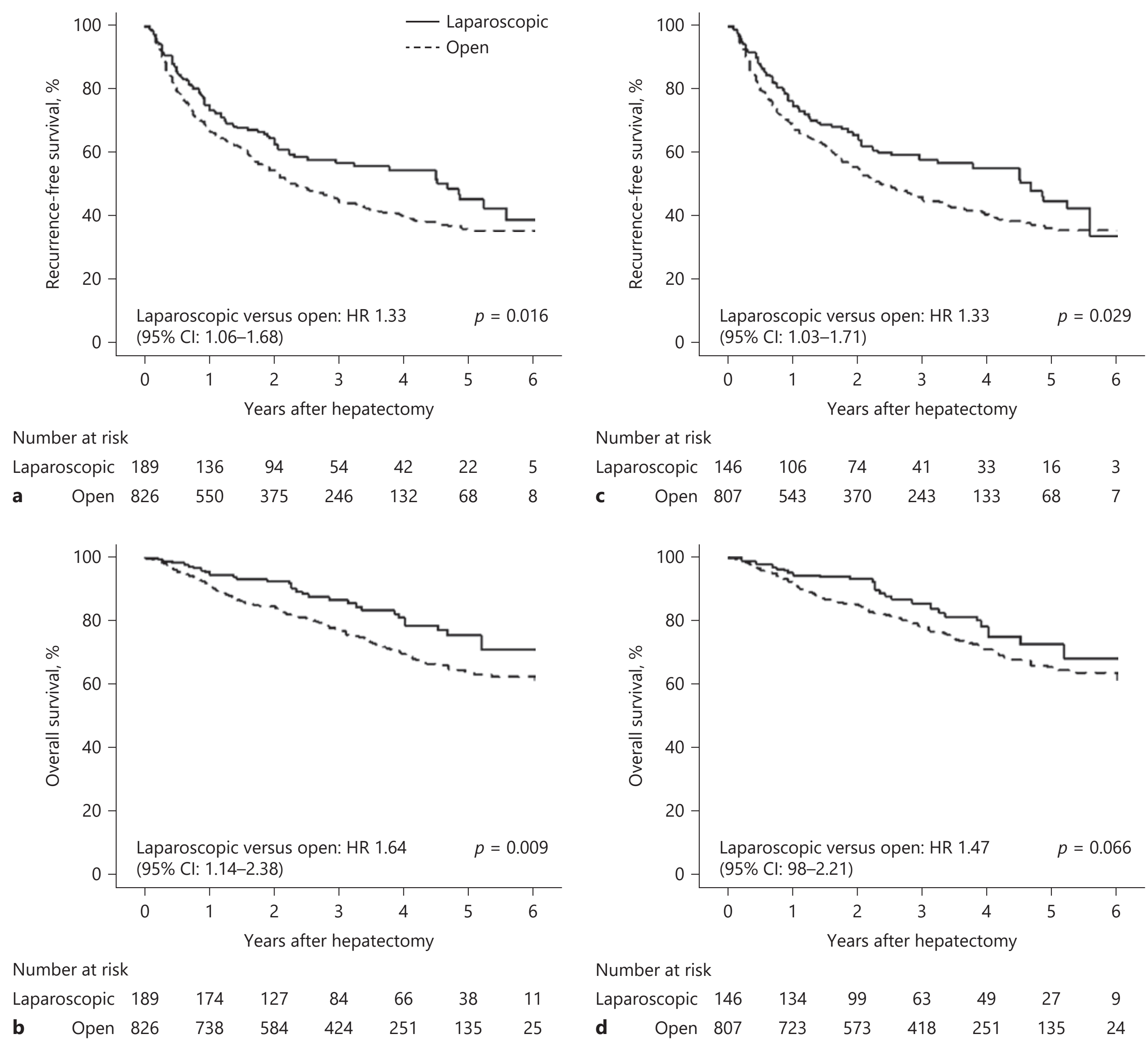
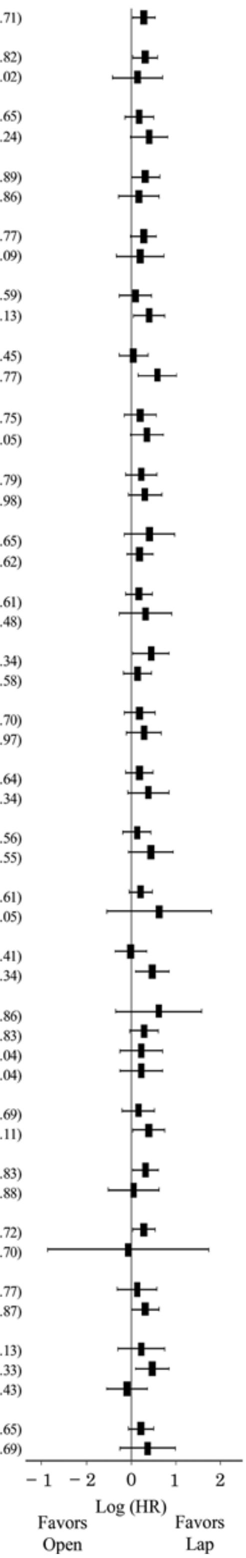
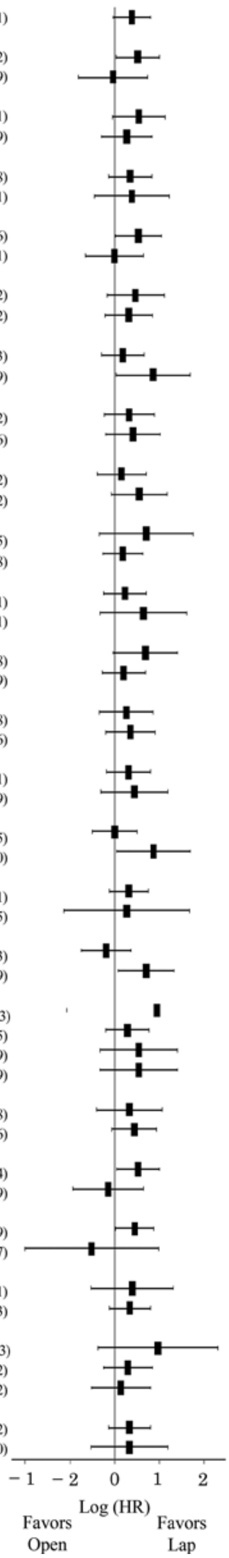


Fig. 2. Survival outcomes between the laparoscopic and open left hepatectomy groups. **a** Recurrence-free survival (RFS) before inverse probability of treatment weighting (IPTW). **b** Overall survival (OS) before IPTW. **c** RFS after IPTW. **d** OS after IPTW. HR, hazard ratio; CI, confidence interval.

Fig. 3. Recurrence-free and overall survival in the selected subgroups. HR, hazard ratio; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; ALT, alanine aminotransferase. *(For figure see next page.)*

Subgroup	N	Recurrence-free Survival HR	(95%CI)	Overall Survival HR	(95%CI)
Overall	953	1.33	(1.03–1.71)	1.47	(0.98–2.21)
Sex					
Male	765	1.37	(1.03–1.82)	1.68	(1.04–2.72)
Female	187	1.16	(0.66–2.02)	0.97	(0.45–2.09)
Age, y					
< 70 y	489	1.20	(0.87–1.65)	1.72	(0.96–3.11)
≥ 70 y	464	1.49	(1.00–2.24)	1.30	(0.74–2.29)
HBsAg					
None	645	1.37	(1.00–1.89)	1.41	(0.88–2.28)
Positive	286	1.19	(0.76–1.86)	1.47	(0.64–3.41)
HCVAb					
None	691	1.32	(0.99–1.77)	1.71	(1.02–2.86)
Positive	261	1.23	(0.72–2.09)	0.99	(0.52–1.91)
Serum total bilirubin					
< 0.7 mg/dL	411	1.11	(0.77–1.59)	1.59	(0.84–3.02)
≥ 0.7 mg/dL	537	1.49	(1.05–2.13)	1.37	(0.80–2.32)
Prothrombin activity					
< 95%	490	1.05	(0.77–1.45)	1.20	(0.75–1.93)
≥ 95%	439	1.81	(1.18–2.77)	2.37	(1.04–5.39)
Platelet					
$< 19.0 \times 10^4/mm^3$	473	1.23	(0.86–1.75)	1.38	(0.79–2.42)
$\geq 19.0 \times 10^4/mm^3$	479	1.42	(0.99–2.05)	1.51	(0.82–2.76)
ALT					
< 29 U/L	475	1.26	(0.89–1.79)	1.17	(0.68–2.02)
≥ 29 U/L	477	1.36	(0.94–1.98)	1.73	(0.93–3.22)
Serum albumin					
< 4.0 g/dL	307	1.50	(0.85–2.65)	2.02	(0.71–5.75)
≥ 4.0 g/dL	645	1.21	(0.91–1.62)	1.20	(0.77–1.88)
ICGR15					
< 15.0 %	673	1.19	(0.89–1.61)	1.26	(0.78–2.01)
≥ 15.0 %	211	1.38	(0.77–2.48)	1.90	(0.72–5.01)
Alpha-fetoprotein‡					
< 15.0 ng/mL	484	1.56	(1.04–2.34)	1.99	(0.97–4.08)
≥ 15.0 ng/mL	466	1.16	(0.85–1.58)	1.22	(0.75–1.99)
PIVKA-II					
< 250 mAU/mL	514	1.21	(0.86–1.70)	1.30	(0.71–2.38)
≥ 250 mAU/mL	440	1.34	(0.90–1.97)	1.42	(0.82–2.46)
Location of tumor					
Segment 2 or 3 or 4	583	1.21	(0.89–1.64)	1.36	(0.84–2.21)
Segment 2, 3 or 2, 3, 4	364	1.47	(0.92–2.34)	1.55	(0.73–3.29)
Operative blood loss					
< 350 ml	467	1.14	(0.83–1.56)	1.00	(0.61–1.65)
≥ 350 ml	474	1.55	(0.95–2.55)	2.39	(1.06–5.40)
Blood transfusion during and/or after the operation					
No	823	1.24	(0.95–1.61)	1.37	(0.89–2.11)
Yes	126	1.88	(0.58–6.05)	1.31	(0.32–5.35)
Maximum tumor size					
< 4.0 cm	424	0.99	(0.70–1.41)	0.82	(0.48–1.43)
≥ 4.0 cm	528	1.61	(1.11–2.34)	2.02	(1.08–3.79)
Histology					
Well	108	1.86	(0.71–4.86)	2.57	(0.34–19.23)
Mod	637	1.34	(0.98–1.83)	1.32	(0.82–2.15)
Poor	148	1.26	(0.78–2.04)	1.72	(0.72–4.09)
Necrosis or unknown	60	1.26	(0.78–2.04)	1.72	(0.72–4.09)
Microscopic vascular invasion in portal vein and /or hepatic vein					
No	489	1.18	(0.82–1.69)	1.39	(0.67–2.88)
Yes	463	1.48	(1.03–2.11)	1.56	(0.95–2.56)
Number of tumors					
Single	851	1.38	(1.04–1.83)	1.69	(1.04–2.74)
Multiple	101	1.06	(0.60–1.88)	0.86	(0.39–1.89)
Microscopic surgical margin					
No	915	1.33	(1.03–1.72)	1.56	(1.02–2.39)
Yes	37	0.94	(0.15–5.70)	0.60	(0.13–2.67)
The UICC/AJCC 7th Staging System					
I	301	1.14	(0.73–1.77)	1.48	(0.59–3.71)
II or IIIA	652	1.37	(1.00–1.87)	1.41	(0.89–2.23)
Associated liver disease					
Normal liver	176	1.26	(0.75–2.13)	2.64	(0.69–10.03)
Chronic hepatitis or liver fibrosis	569	1.60	(1.10–2.33)	1.34	(0.78–2.32)
Cirrhosis	208	0.91	(0.58–1.43)	1.15	(0.60–2.22)
Postoperative complications					
No	686	1.24	(0.94–1.65)	1.40	(0.88–2.22)
Yes	267	1.44	(0.78–2.69)	1.39	(0.59–3.30)





3

Liver Cancer 2023;12:32–43
DOI: 10.1159/000527294

shown). Especially in the group of patients with a maximum tumor size of ≥4 cm, the LLH group had significantly better RFS and OS rates.

Discussion

In this study, we examined the postoperative outcomes of different approaches for performing left hepatectomy for HCC. Currently, the present study has the largest sample size (2,902 cases before matching) for comparing the short- and long-term outcomes between LLH and OLH. LLH was associated with lesser amount of bleeding volume, less frequent intraoperative transfusion, and lower complication rates (Tables 1, 2), which is consistent with the findings reported in previous studies [3, 4, 14, 15]. Although the LLH and OLH groups did not show a significant difference in the frequency of complications graded using the Clavien-Dindo classification, the occurrence rate of hepatic decompensation greater than grade B of the ISGLS definition was significantly lower in the LLH group (Table 2). The RFS and OS, including those in the subgroup analyses, tended to be longer in the LLH group than in the OLH group in the IPTW model (Fig. 2, 3). Especially, in the subgroups with single tumors or primary tumors of ≥4.0 cm in diameter, both RFS and OS were statistically significantly better after LLH than after OLH (Fig. 3). We suggested that a meticulous maneuver in LLH should be performed to reduce several serious complications, including bile leaks, massive bleeding, and intestinal damage, because of the excellent surgical field of view using laparoscopy [3, 14, 16–19]. Furthermore, as previously reported, LLH is thought to have the ability to reduce the occurrence of ascites. This might be because the disruption of the abdominal wall prevents the interruption of large collateral veins; moreover, the lack of exposure of the abdominal viscera restricts fluid resuscitation and decreases electrolytic and protein losses, thus resulting in less postoperative ascites [17, 19]. Additionally, with reduced postoperative pain and early postoperative weaning, the laparoscopic approach may reduce the risk of pulmonary complications, such as respiratory infections, pleural effusion, and respiratory failure [20]. This study showed that the LLH group had a shorter postoperative hospital stay than the OLH group, which is consistent with the findings reported in other studies [15, 16, 18].

Cheung et al. [21] have reported that pure laparoscopic hepatectomy for HCC can be performed safely with favorable short- and long-term outcomes even in patients with liver cirrhosis at high-volume liver cancer centers. They suggested that the better RFS in the laparoscopic group can be explained by two reasons. First, the laparoscopic group had significantly lesser blood loss; a greater amount of blood loss is a risk factor for HCC recurrence [22]. Second, the conventional approach was used in most open hepatectomies, whereas the anterior approach, with less tissue manipulation, was used in all laparoscopic hepatectomies. Moreover, they demonstrated that the "no-touch" technique, an anterior approach used in hepatectomy, was associated with better oncological outcomes [23]. This technique was reported to reduce dissemination of tumor cells into the portal vein during hepatectomy [24]. Additionally, tumor compression during mobilization in open hepatectomy may enhance the spread of tumor cells into the systemic circulation or intrahepatic portal venous system. In contrast, the OS rate tended to be better in the LLH group than in the OLH group (Fig. 2, 3). No differences in the mode of recurrence of HCC and treatment at the time of recurrence were observed between the two groups (Table 1). The exact reason why this OS after IPTW did not significantly differ between the two groups is unknown; however, it is speculated that a difference may occur in OS, as the number of patients undergoing LLH has been increasing.

To overcome selection bias as much as possible, IPTW was employed. The IPTW model reduced the different distributions of covariates among individuals allocated to specific interventions [25]. The IPTW in this study was performed using four variables, which differed between the two groups. These factors were determined before the treatment and could therefore potentially influence the selection of the treatment method. PSM is compromised by the loss of information due to the inability to find a matched pair for every patient in the observed research population. In contrast, IPTW has the potential advantage of reducing selection bias by retaining all weighted samples. Not all background factors were sufficiently balanced even when weighted by the propensity scores we created. Thus, we conducted a subgroup analysis.

In this study, the data were collected from 97 Japanese facilities, including 67 and facilities handling a large and a small number of difficult surgical cases, respectively, and from 12 Korean 12 facilities, which are high-volume centers for liver surgery. Especially in the Japanese facilities, although it is presumed that there was a clear difference in the selection of surgical procedure among institutions, no significant difference in survival rate between the two surgical procedures was observed in the Japanese training facilities classified into two groups and LLH showed a relatively better survival rate (online suppl. Fig. 1, 2).

Additional subgroup analyses were performed, but we were unable to fully adjust the distribution of each group, especially for factors related to the surgical technique, such as blood loss. Further stratified analysis of survival rates for the three factors used for IPTW showed generally better survival rates for LLH. Given that the number of cases in our study was relatively small, future studies comparing the two surgical methods with a large number of are warranted.

Attempting to conduct a study with a larger sample size and identifying populations for which OLH is favorable are important. Although conducting a randomized controlled trial to compare these surgical procedures is desirable, issues regarding the differences in the resection policies among facilities and whether accurate technically laparoscopic resection has been achieved remain; thus, such studies cannot be realized. It should be noted though that this study includes these problems.

In conclusion, we compared the post-hepatectomy prognosis between patients with HCC who underwent LLH and those who underwent OLH using combined data from Japan and Korea. LLH decreases the risk for complications and tumor recurrence and may improve the OS in patients with a primary HCC located in the left liver.

Acknowledgments

We are indebted to the following surgeons for their excellent contributions in the collection and management of data: Shoji Kubo, Takao Ide, Terumasa Yamada, Masaki Ueno, Masashi Utsumi, Shinji Osada, Hiroyuki Ishizu, Sakae Maeda, Motofumi Tanaka, Atsushi Miyoshi, Akinobu Taketomi, Hideaki Kodama, Kazuto Shibuya, Katsutoshi Murase, Hiroaki Nagano, Yoshinao Ohbatake, Atsushi Takebe, Hiroya Iida, Minoru Nagayama, Koji Kitada, Satoshi Katagiri, Makoto Yoshida, Kosuke Matsui, Kazuya Maeda, Hiroshi Yoshida, Tomoya Mizuno, Chie Takishita, Yukio Oshiro, Yuki Hirose, Keishi Sugimachi, Zenichi Morise, Kenji Oshima, Amaya Koji, Masanao Kurata, Kazuaki Nakanishi, Masaaki Hidaka, Yasuyuki Fukami, Atsuyuki Maeda, Keinosuke Ishido, Mizuki Ninomiya, Ryuta Nishitai, Shunichi Ariizumi, Ryo Okada, Daisuke Suzuki, Katsunori Sakamoto, Takashi Aono, Akira Shimizu, Yukiyasu Okamura, Tsukasa Aihara, Junji Ueda, Junji Iwasaki, Masao Ogawa, Shuichi Watanabe, Norifumi Harimoto, Yutaka Takeda, Shigehito Miyagi, Yoshihisa Kubota, Shigeo Hayatsu, Yuko Takami, Hiroyuki Nitta, Akira Tomokuni, Hiroshi Wada, Joe Matsumoto, Yasunari Kawabata, Takafumi Kumamoto, Tsuyoshi Kobayashi, Toshiro Masuda, Tomokazu Kusano, Hideki Yokoo, Keiji Sano, Keiichi Kubota, Masahiko Kawamoto, Masahiro Tominaga, Fumiaki Watabe, Keiichi Okano, Takeshi Sudou, Youichi Matsuo, Junichi Shindoh, Satoshi Iino, Satoru Imura, Yasuji Hashimoto, Tetsuro Hisrose, Naoto Gotoda, Saiho Ko, Kazue Morishima, Takefumi Niguma, Toru Kojima, Fumitoshi Hirokawa, Akishige Kanazawa, Takafumi Machimoto, Takehiro Noda, Hidetake Amemiya, Kojiro Taura, Masato Narita, Kensaku Sanefuji, and Shigehiro Shiozaki. Furthermore, we want to express our sincere appreciation to the Japanese Society and Korean Association of Hepato-Biliary-Pancreatic Surgery.

Statement of Ethics

The study protocol was approved by the Institutional Ethics Committee of Kansai Medical University (reference number: KMU 2018206). Written informed consent from participants was not required in accordance with local/national guidelines. After receiving official approval, this study was conducted as a retrospective analysis of database records based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures were done in accordance with the Declaration of Helsinki. The data were made anonymous before analysis to protect patient privacy. This study received ethical approval for use of an opt-out methodology based on low risk to the participants.

Conflict of Interest Statement

None of the other authors have potential conflicts of interest to declare.

Funding Sources

This research received no external funding.

Author Contributions

Conceptualization, methodology, and project administration, Masaki Kaibori and Jong Man Kim; investigation, resources, and writing – original draft preparation, review, and editing, Masaki Kaibori; data curation, Yuzo Umeda, Takahito Yagi, Takehiro Okabayashi, Kenta Sui, Akira Mori, Yuhei Hamaguchi, Kiyoshi Kajiyama, Daisuke Hokuto, Kazuteru Monden, Tomoharu Yoshizumi, Yoriko Nomura, Kan Toriguchi, Jong Man Kim, Gi Hong Choi, Je Ho Ryu, Yangseok Koh, Koo Jeong Kang, Young Kyoung You, Kwang-Sik Chun, Young Seok Han, Chan Woo Cho, Young Il Choi, Dong-Sik Kim, and Jae Do Yang; visualization, Masaki Kaibori and Kengo Yoshii; formal analysis, Kengo Yoshii, Keita Mori, and Atsushi Hiraoka; supervision, Hiroki Yamaue, Masafumi Nakamura, Masakazu Yamamoto, and Itaru Endo. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Due to the nature of this research, participants in this study could not be contacted regarding whether the findings could be shared publicly; thus, supporting data are not available. The datasets generated and/or analyzed for the current study are not publicly available due to the nature of the research, as noted above. Further inquiries can be directed to the corresponding author.

References

1 Bosch FX, Ribes J, Diaz M, Clèries R. Primary liver cancer: worldwide incidence and trends. Gastroenterology. 2004;127(5 Suppl 1):S5–16.

2 Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shiina S, et al. Report of the 20th Nationwide follow-up survey of primary liver cancer in Japan. Hepatol Res. 2020;50(1):15–46.

3 Han HS, Shehta A, Ahn S, Yoon YS, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: case-matched study with propensity score matching. J Hepatol. 2015;63(3):643–50.

4 Ban D, Tanabe M, Kumamaru H, Nitta H, Otsuka Y, Miyata H, et al. Safe dissemination of laparoscopic liver resection in 27, 146 cases between 2011 and 2017 from the national clinical database of Japan. Ann Surg. 2021;274(6):1043–50.

5 Yoon YI, Kim KH, Kang SH, Kim WJ, Shin MH, Lee SK, et al. Pure laparoscopic versus open right hepatectomy for hepatocellular carcinoma in patients with cirrhosis. A propensity score matched analysis. Ann Surg. 2017;265(5):856–63.

6 Kim JM, Kwon CHD, Yoo H, Kim KS, Lee J, Kim K, et al. Which approach is preferred in left hepatocellular carcinoma? Laparoscopic versus open hepatectomy using propensity score matching. BMC Cancer. 2018;18(1):668.

7 Kaibori M, Kon M, Kitawaki T, Kawaura T, Hasegawa K, Kokudo N, et al. Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2017;24(11):616–26.

8 Kim DS, Kim BW, Hatano E, Hwang S, Hasegawa K, Kudo A, et al. Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a Korea–Japan multicenter study. Ann Surg. 2020;271(5):913–21.

9 Gospodarowicz M, Wittekind C, Sobin L, editors. AJCC 7th ed cancer staging manual. 7th ed. New York: Springer; 2016.

10 Strasberg SM, Belghiti J, Clavien PA, Gadzijev E, Garden J, Lau WY, et al. The Brisbane 2000 terminology of liver anatomy and resections. HPB. 2000;2(3):333–9.

11 Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. Semin Surg Oncol. 1993;9(4):298–304.

12 Takasaki T, Kobayashi S, Suzuki S, Muto H, Marada M, Yamana Y, et al. Predetermining postoperative hepatic function for hepatectomies. Int Surg. 1980;65(4):309–13.

13 Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol. 2008;168(6):656–64.

14 van der Poel MJ, Barkhatov L, Fuks D, Berardi G, Cipriani F, Aljaiuossi A, et al. Multicentre propensity score-matched study of laparoscopic versus open repeat liver resection for colorectal liver metastases. Br J Surg. 2019;106(6):783–9.

15 Morise Z, Aldrighetti L, Belli G, Ratti F, Belli A, Cherqui D, et al. Laparoscopic repeat liver resection for hepatocellular carcinoma: a multicentre propensity score-based study. Br J Surg. 2020;107(7):889–95.

16 Witowski J, Rubinkiewicz M, Mizera M, Wysocki M, Gajewska N, Sitkowski M, et al. Meta-analysis of short- and long-term outcomes after pure laparoscopic versus open liver surgery in hepatocellular carcinoma patients. Surg Endosc. 2019;33(5):1491–507.

17 Peng L, Zhou Z, Xiao W, Hu X, Cao J, Mao S. Systematic review and meta-analysis of laparoscopic versus open repeat hepatectomy for recurrent liver cancer. Surg Oncol. 2019;28:19–30.

18 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):712–9.

19 Kanazawa A, Tsukamoto T, Shimizu S, Kodai S, Yamamoto S, Yamazoe S, et al. Laparoscopic liver resection for treating recurrent hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2013;20(5):512–7.

20 Fuks D, Cauchy F, Ftériche S, Nomi T, Schwarz L, Dokmak S, et al. Laparoscopy decreases pulmonary complications in patients undergoing major liver resection: a propensity score analysis. Ann Surg. 2016;263(2):353–61.

21 Cheung TT, Dai WC, Tsang SHY, Chan ACY, Chok KSH, Chan SC, et al. Pure laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma in 110 patients with liver cirrhosis: a propensity analysis at a single center. Ann Surg. 2016;264(4):612–20.

22 Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg. 2009;249(4):617–23.

23 Liu CL, Fan ST, Lo CM, Tung-Ping Poon R, Wong J. Anterior approach for major right hepatic resection for large hepatocellular carcinoma. Ann Surg. 2000;232(1):25–31.

24 Hayashi N, Egami H, Kai M, Kurusu Y, Takano S, Ogawa M. No-touch isolation technique reduces intraoperative shedding of tumor cells into the portal vein during resection of colorectal cancer. Surgery. 1999;125(4):369–74.

25 Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods. 2010;15(3):234–49.