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Long-term outcomes of laparoscopic liver resection for hepatocellular carcinoma: A propensity score matched analysis of a high-volume North American center

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ABSTRACT

Background: Laparoscopic liver resections for malignancy are increasing worldwide, and yet data from North America are lacking. We aimed to assess the long-term outcomes of patients undergoing laparoscopic liver resection and open liver resection as a treatment for hepatocellular carcinoma.

Methods: Patients undergoing liver resection for hepatocellular carcinoma between January 2008 and December 2019 were retrospectively studied. A propensity score matching was performed using patient demographics, laboratory parameters, etiology of liver disease, liver function, and tumor characteristics. Primary outcomes included overall survival and cumulative incidence of recurrence. Kaplan-Meier and competing risk cumulative incidence were used for survival analyses. Multivariable Cox regression and Fine-Gray proportional hazard regression were performed to determine hazard for death and recurrence, respectively.

Results: Three hundred and ninety-one patients were identified (laparoscopic liver resection: 110; open liver resection: 281). After propensity score matching, 149 patients remained (laparoscopic liver resection: 57; open liver resection: 92). There were no significant differences between groups with regard to extent of hepatectomy performed and tumor characteristics. The laparoscopic liver resection group experienced a lower proportion of ≥Clavien-Dindo grade III complications (14% vs 29%; $P = .01$). In the matched cohort, the 1-, 3-, and 5-year overall survival rate in the laparoscopic liver resection versus open liver resection group was 90.9%, 79.3%, 70.5% vs 91.3%, 88.5%, 83.1% ($P = .26$), and the cumulative incidence of recurrence 31.1%, 59.7%, 62.9% vs 18.9%, 40.6%, 49.2% ($P = .06$), respectively.

Conclusion: This study represents the largest single institutional study from North America comparing long-term oncologic outcomes of laparoscopic liver resection and open liver resection as a treatment for primary hepatocellular carcinoma. The combination of reduced short-term complications and equivalent long-term oncologic outcomes favor the laparoscopic approach when feasible.

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Introduction

Hepatocellular carcinoma (HCC) represents the fourth leading cause of cancer-related death in the world, and its incidence continues to increase in the United States.[1,2] In the 5% to 10% of patients with a single lesion HCC and well-compensated liver disease, liver resection remains the treatment of choice according to European and American guidelines.[3,4] The use of laparoscopic surgery for liver resections (LLR) in HCC has increased worldwide and represents an attractive alternative to conventional open liver surgery (OLR) because it has potential to mitigate perioperative risks and accelerate postoperative functional recovery.[5–7]

Although high-quality randomized trials comparing LLR and OLR for various stages of HCC are lacking, previous retrospective reports have demonstrated favorable short-term outcomes with the laparoscopic approach.[5,8–12] As a result of its relatively recent adoption for HCC resection, lack of long-term clinical follow-up after LLR has limited conclusions of early studies. Additionally, many prior reports included a lower number of major laparoscopic hepatectomies, which may have conferred a potentially unfair oncological advantage to laparoscopic resection. Furthermore, as the majority of series are from Europe and Asia, differences in the patient populations make generalizability challenging.[13–15] Lastly, due to inherent selection bias with retrospective study design, rigorous risk adjustments between groups is imperative, but has been inconsistent and shallow.

Given increased interest in expanding LLR for HCC, we aimed to evaluate the long-term outcomes of patients undergoing laparoscopic versus open resection as a treatment for HCC. We sought to address the aforementioned limitations of prior reports through study of patients from a high-volume North American center and by performing a granular propensity score matched analysis.

Methods

This study was approved by our institutional REB (REB #16–5626), and a waiver of informed consent was obtained.

Study population

We retrospectively studied consecutive adults (≥18 years) who underwent LR for HCC between January 2008 and December 2019 at a single academic institution. Patients with LR before 2008 were excluded because the laparoscopic approach was not used at the institution before that time. Patients resected after 2019 were excluded to allow for enough follow-up time to evaluate tumor recurrence after LR. At the time of analysis, patient data were up to date as of March 13, 2021. The diagnosis of HCC was established according to the American Association for the Study of Liver Diseases guidelines.[3] To perform a sensitivity analysis for the assessment of outcomes over time, the study period was further categorized into an early era (2008–2013) and a late era (2014–2019) to allow an equal number of years in both groups. Patients with mixed hepatocellular carcinoma-cholangiocarcinoma and those with fibrolamellar subtype on pathology were excluded. Moreover, patients were excluded if they had a previous liver transplant, locoregional treatment (including, but not limited to, radiofrequency ablation, transarterial chemoembolization, and microwave ablation), tumor rupture, prior liver resection, or missing pathology reports (Figure 1). This study complies with the STROBE statement for observational studies.[16]

Patient selection and surgical technique

In general, all patients with HCC are presented in a multidisciplinary meeting. After the decision is made to proceed with liver resection, the feasibility of a laparoscopic approach is evaluated. As a rule of thumb, patients who are not considered for laparoscopic resection include patients where vascular reconstructions or an ex vivo procedure is anticipated. Additionally, patients with advanced cirrhosis with portal hypertension that are surgical candidates are typically deferred to a laparoscopic approach. Patients requiring a minor hepatectomy, even in the presence of mild portal hypertension, are considered for resection if the approach is LLR. In some instances, HVPG will be measured, and in those with a gradient <15 mm Hg we will consider proceeding with resection. In considering and performing LLR in such patients, factors that are taken into account include trocar placements (eg, avoiding the midline), the extent of the surgery (major hepatectomy versus minor), and the medical risk and severity of the portal hypertension. Furthermore, in some patients, we will proceed with a laparoscopic approach with a low threshold for conversion. These may include patients with certain medical comorbidities such as heart disease, which is challenging to manage given the required low central venous pressure. In addition, a patient with an extensive upper abdominal surgical history may still be considered for a laparoscopic approach with a low threshold of conversion if timely intraoperative progression cannot be achieved. Overall, the institution has evolved to pursue a minimally invasive surgical approach as often as possible in patients with HCC. Anatomic resection was the preferred surgical technique. However, a non-anatomical or segmental approach was employed if an adequate margin could be obtained and allowed for parenchymal sparing in patients with cirrhosis. A standard technique for LLR has been previously described.[17] Venous and portobiliary pedicles were ligated with vascular stapling devices when necessary. Parenchymal transection was performed with electrocautery in combination with water-jet dissection (Helix Hydrojet, ERBE and AMT Electrosurgery) in OLR. For LLR, the Cavitron ultrasonic surgical aspirator (CUSA: Integra LifeSciences Corporation, NJ), water-jet, and ultrasonic shears were used for fine parenchymal dissection.

Covariates

We recorded patient age, sex, body mass index, etiology of liver disease, previous non-liver upper abdominal surgery, preoperative portal vein embolization, Barcelona Clinic Liver Cancer stage, degree of liver dysfunction (model for end-stage liver disease and Child-Pugh score), laboratory variables (albumin, total bilirubin, international normalized ratio, albumin-bilirubin grade, and platelet count), American Society of Anesthesiologists score, preoperative tumor characteristic (including size, number, and satellite lesions), pathology findings, and postoperative outcomes including length of stay. Major hepatectomy was defined as complete resection of 3 or more liver segments according to the Brisbane 2000 terminology.[18] The difficulty of hepatectomy was dichotomized according to whether a full anatomic segmentectomy was performed of segment 1, 4A, 7, and/or 8.[19,20] AFP was categorized to reflect clinically relevant categories (ng/mL, <20, 20–99, 100–999, and >1000).[21] Pathology characteristics included the size of the largest tumor, tumor number, presence of satellite lesions, tumor differentiation, microvascular invasion, macrovascular invasion, surgical margin positivity, surgical margin distance, and Laennec stage of adjacent liver fibrosis. Tumor differentiation was defined according to the modified Edmondson criteria.[22] Postoperative complications occurring within 90 days of the resection were

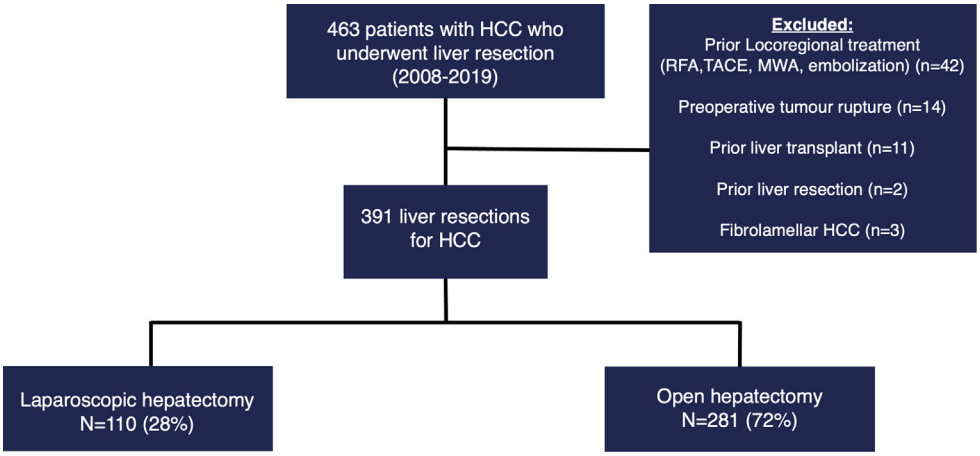

Figure 1. Flow chart of selection criteria.

graded using the Clavien-Dindo classification system.[23] Liver failure and grade of liver failure according to grade A, B, and C was recorded for the first 30 days after resection according to the International Study Group of Liver Surgery definition.[24] Intraoperative variables included operative time (in minutes), packed red blood cell transfusion (in mL), fresh frozen plasma transfusion (in mL), platelet transfusion (in mL), estimated blood loss (in mL), and Pringle maneuver used (binary).

Outcome measures

The study's primary endpoints were post-LR survival and HCC tumor recurrence. In this study, the primary exposure, intended surgical approach (LLR versus OLR), was not a time-varying covariate.

Propensity score matching

A propensity score was constructed based on the predicted probability of receiving laparoscopic surgery using logistic/probit regression (intention to treat). This was performed to control for the effect of confounding and the method chosen to address selection bias. Covariates selected included the following: age; sex; body mass index; extent of resection (major hepatectomy); unfavorable tumor segment; largest preoperative tumor size and number; preoperative satellite lesion; Child-Pugh score; platelet count; albumin-bilirubin grade; etiology of liver disease; year of resection; and preoperative AFP. A sensitivity analysis was performed using only nonconversion cases. Matching was performed for the dependent variable of exposure (LLR versus OLR) using these covariates. The matching method used was a nearest neighbor matching method without replacement with a caliper of 0.1. Matching quality was evaluated with standardized mean differences between the treated and control groups. A difference of <0.2 standardized mean difference between covariates included in the match was used as the threshold of a negligible imbalance between groups.[25]

Follow-up, survival, and recurrence

Postoperatively, patients were followed with AFP and contrast-enhanced computed tomography of the chest and abdomen or ultrasound in 3-month intervals for the first 2 years, then every 6 months for 2 years, and yearly thereafter. In the case of a suspected recurrence, additional imaging studies were obtained, including contrast-enhanced computed tomography, contrast-enhanced ultrasound, or magnetic resonance imaging.[3] Overall survival was calculated from the day of resection to the day of death or last known contact. The time to recurrence was calculated from the day of resection to the first imaging study that confirmed tumor recurrence.

Statistical analysis

Descriptive data were expressed as medians and interquartile ranges (IQR). These were compared using the Mann-Whitney *U* tests. Categorical variables were expressed using numbers and percentages (%). These were compared using χ^2 and Fisher exact tests. Overall survival was estimated using the Kaplan-Meier method, and groups were compared with log-rank tests. A univariable Cox proportional hazard regression model was constructed after matching to assess the association between the exposure of interest (LLR versus OLR) and mortality. The proportional hazard assumption was assessed using Schoenfeld residuals against the transformed time. Instead of the Kaplan-Meier method, which censors for the competing event of death, a cumulative incidence approach was used to account for the presence of a competing risk of death with recurrence.[26] The cumulative incidence was estimated using subdistribution estimates for each cause. A Gray's modified log-rank test was used to compare subdistribution estimates for each cause and to evaluate the quality of the cumulative incidence curve. To assess for the relative change in the hazard of recurrence, a Cox proportional hazard model using Fine-Gray competing risk was used to account for death as a competing event.[27] All 2-sided *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed using R (version 4.0.3 2020, R Foundation for Statistical Computing, Vienna, Austria). Matching was performed using the package MatchIt.

Results

Study population and pathology

Three hundred and ninety-one patients underwent liver resection for HCC over the study period with the number of LLRs performed having increased over time (Supplementary Figure S1). One hundred and ten patients were intended for a laparoscopic approach, and 14 required conversion to open. The reasons for conversion were hemorrhage ($n = 4$), poor visualization ($n = 3$), anatomic issues ($n = 3$), inability to progress ($n = 2$), technical

problems with a device ($n = 1$), and other ($n = 1$). In total, 96 (25%) resections were completed laparoscopically and 295 (75%) open. There was a higher proportion of major hepatectomies in the OLR group (28% vs 57%; $P < .001$). The baseline characteristics of patients in the LLR and OLR groups are summarized in Table I and Supplementary Table S1. Most preresection patient characteristics were similar between groups. Patients in the LLR group had smaller tumors preoperatively (cm [IQR], 4.20 [3.30–5.90] vs 5.10 [3.60–8.70]; $P < .001$) and on pathology (cm [IQR], 4.50 [3.30–6.07] vs 5.50 [3.80–8.50]; $P < .001$). The LLR group also had more solitary tumors (92% vs 80%; $P = .01$) and lower rates of microvascular invasion (45% vs 60%; $P = .02$). The median length of follow-up was 2.84 years (IQR 1.39–5.41). The use of the Pringle maneuver increased over the study period, with a proportionally higher increase in the LLR group over time (Supplementary Figure S2). Length of stay was shorter in the LLR group (median [IQR] 5 [3–6] vs 7 [5–10]; $P < .001$). The LLR group experienced a lower proportion of Clavien-Dindo grade III or greater complications (15% vs 26%; $P < .001$) (Table II).

Survival analysis in the unmatched cohort

The OS was similar between the LLR and OLR groups (Figure 2). Short-term survival was equivalent between the groups (30 days LLR 96.3% [95% CI 92.9–99.9] versus OLR 96.8% [95% CI 94.7–98.9]; $P = .82$; 90 days LLR 96.3% [95% CI 92.9–99.9] versus OLR 93.6% [95% CI 90.7–96.5]; $P = .31$). The 1-, 3-, and 5-year survival rates were: LLR 90.9% (95% CI 83.6–98.8), 73.9% (95% CI 68.5–91.9), 70.5% (95% CI 56.6–87.8) versus OLR 91.3% (95% CI 85.7–97.2), 88.5% (95% CI 82.0–95.5), 83.1% (95% CI 74.8–92.3) ($P = .26$). Similarly, there was no statistically significant difference in the 1-, 3-, and 5-year cumulative incidence of HCC recurrence: LLR 31.1% (95% CI 19.3–43.6), 59.7% (95% CI 43.7–72.5), and 62.9% (95% CI 46.3–75.6) versus OLR 18.9% (95% CI 11.5–27.6), 40.6% (95% CI 30.0–50.9), and 49.2% (95% CI 37.3–60.1) ($P = .06$) (Figure 3).

Survival analysis in the unmatched cohort stratified by eras

Short-term survival in the early were equivalent (30 days LLR 94.9% [95% CI 88.2–100] versus OLR 97.7% [95% CI 95.2–100]; $P = .35$; 90 days LLR 94.9% [95% CI 88.2–100] versus OLR 94.7% [95% CI 91.0–98.6]; $P = 1.00$). The OS in the early era (2008–2013) was better in the OLR ($P = .04$) (Supplementary Figure S3, *A*). The 1-, 3-, and 5-year survival rates were 89.4% (95% CI 80.0–99.8), 72.1% (95% CI 58.8–88.5), and 61.6% (95% CI 46.9–80.8) for LLR and 93.9% (95% CI 90.0–98.1), 86.1% (95% CI 80.2–92.5), and 85.2% (95% CI 79.1–91.8) for OLR ($P = .04$). Short-term survival in the late era was equivalent between the groups (30 days LLR 97.2% [95% CI 93.4–100] versus OLR

Table I
Demographics and clinicopathological characteristics

	Total $n = 391$	Before matching				After matching			
		Lap $n = 110$ (22%)	Open $n = 281$ (78%)	P	SMD	Lap $n = 57$ (38%)	Open $n = 92$ (62%)	P	SMD
Major hepatectomy, ≥3 segments, number (%)	191 (49)	31 (28)	160 (57)	<.001	0.61	21 (37)	38 (41)	.71	0.09
Unfavorable segments,* number (%)	256 (66)	42 (38)	214 (76)	<.001	0.83	28 (49)	51 (55)	.14	0.05
Sex, male, number (%)	315 (81)	86 (78)	229 (82)	.55	0.08	48 (84)	78 (85)	1.00	0.02
Age, year median (IQR)	64 (56–71)	65 (58–72)	63 (56–71)	.20	0.18	64 (56–72))	66 (58–73)	.61	0.03
BMI, median (IQR)	25.1 (22.3–28.4)	26.2 (22.9–29.9)	24.4 (22.0–27.8)	.01	0.31	26.0 (23.5–28.2)	25.1 (22.0–28.0)	.21	0.20
Missing	32	10	22			0	0		
Etiology, number (%)				.85	0.18			-	0.04
HBV	181 (46)	47 (43)	134 (48)			30 (53)	59 (56)		
HCV	86 (22)	27 (25)	59 (21)			11 (19)	23 (22)		
ETOH	23 (6)	8 (7)	15 (5)			2 (4)	5 (5)		
NASH	20 (5)	7 (6)	13 (5)			3 (5)	5 (5)		
HBV+HCV coinfection	2 (1)	1 (1)	1 (0)			0 (0)	0 (0)		
Other	32 (8)	8 (7)	24 (9)			4 (7)	5 (5)		
No underlying liver disease	47 (12)	12 (11)	35 (13)			7 (12)	9 (9)		
Missing	0	0	0			0	0		
Albumin, median (IQR)	42 (39–44)	41 (39–44)	42 (39–43)	.89	0.08	42 (39–44)	42 (40–44)	.95	0.006
Missing	33	9	24			0	0		
Total bilirubin, μmol/L, median (IQR)	10 (8–14)	9 (7–12)	11 (8–15)	.004	0.37	9 (8–13)	11 (8–13)	.16	0.29
Missing	17	7	10			0	0		
INR, median (IQR)	1.01 (0.97–1.06)	1.1 (0.96–1.08)	1.1 (0.97–1.06)	.93	0.08	1.02 (0.95–1.08)	1.1 (0.98–1.05)	.69	0.07
Missing	6	3	3			0	0		
Platelet, median (IQR)	193 (154–245)	186 (148–226)	194 (155–255)	.07	0.28	191 (145–226)	172 (148–216)	.54	0.05
Missing	5	2	3			0	0		
ALBI grade, number (%)				.52	0.10			.79	0.08
1	274 (77)	79 (80)	195 (76)			52 (79)	83 (78)		
2	82 (23)	20 (20)	62 (24)			14 (21)	23 (22)		
Missing	35	11	24			0	0		
Child Pugh score, number (%)				.49	0.15			-	0.04
A5	329 (92)	93 (95)	236 (91)			54 (95)	88 (96)		
A6	23 (6)	4 (4)	19 (7)			3 (5)	4 (4)		
B7	5 (1)	1 (1)	4 (2)			0 (0)	0 (0)		
Missing	34	12	22			0	0		
Preoperative AFP, number (%)				.02	0.39			.82	0.16
<20	185 (53)	65 (63)	120 (49)			36 (63)	51 (55)		
20-99	55 (16)	17 (16)	38 (16)			8 (14)	15 (16)		
100–999	54 (16)	15 (14)	39 (16)			8 (14)	15 (16)		
>1000	53 (15)	7 (7)	46 (19)			5 (9)	11 (12)		
Missing	44	6	38			0	0		

AFP, alfa fetoprotein; *ALBI*, albumin-bilirubin; *BMI*, body mass index; *ETOH*, alcoholic liver disease; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *INR*, international normalized ratio; *IQR*, interquartile range; *NASH*, nonalcoholic steatohepatitis; *SMD*, standardized mean difference.

* Segment 1, 4A, 7, and/or 8.

Table II
Pathology and postoperative variables

	Total $n = 391$	Before matching				After matching			
		Lap $n = 110$ (22%)	Open $n = 281$ (78%)	P	SMD	Lap $n = 57$ (38%)	Open $n = 92$ (62%)	P	SMD
Tumor size at pathology, cm, median (IQR)	5.20 (3.50–8.00)	4.50 (3.30–6.07)	5.50 (3.80–8.50)	<.001	0.56	5.00 (3.60–6.50)	4.85 (3.50–6.39)	.64	0.04
Satellite lesion/s path, number (%)	45 (12)	6 (6)	39 (14)	.03	0.29	4 (7)	8 (9)	.96	0.06
Tumour solitary at path, number (%)	327 (84)	101 (92)	226 (80)	.01	0.33	54 (95)	83 (90)	.50	0.17
Tumor differentiation, number (%)				.03	0.27			.26	0.27
Well diff.	18 (5)	10 (9)	8 (3)			4 (7)	2 (2)		
Mod diff	302 (78)	83 (76)	219 (79)			44 (77)	78 (86)		
Poor	69 (18)	17 (16)	52 (19)			9 (16)	11 (12)		
Missing	2	0	2			0	1		
Severe fibrosis or cirrhosis, number (%)	260 (67)	81 (74)	165 (64)	.08	0.22	41 (72)	59 (64)	.42	0.17
Missing	0	0	0			0	0		
Microvascular invasion, number (%)	214 (56)	49 (45)	165 (60)	.02	0.29	25 (45)	43 (47)	.56	0.09
Missing	7	2	5			1	1		
Macrovascular invasion, number (%)	44 (11)	6 (6)	38 (14)	.03	0.28	5 (9)	7 (8)	.71	0.04
Missing	3	0	3			0	1		
Positive margins, number (%)	13 (3)	1 (1)	12 (4)	.17	0.21	1 (2)	6 (7)	.50	0.14
Missing	2	0	2			0	1		
Margin distance, cm median (IQR)	0.80 (0.30–1.50)	1.10 (0.52–1.98)	0.70 (0.20–1.50)	<.001	0.40	1.00 (0.50–1.90)	0.60 (0.20–1.40)	.01	0.49
Missing	4	0	4			0	2		
Follow-up, years, median (IQR)	2.84 (1.39–5.41)	2.28 (1.24–4.04)	3.240 (1.45–5.89)	.008	0.32	2.77 (1.53–4.15)	4.18 (2.07–6.04)	.02	0.37
Era of resection, number (%)				.04	0.24			.37	0.003
2008–2013	172 (44)	39 (34)	134 (45)			29 (44)	54 (51)		
2014–2019	219 (56)	77 (66)	161 (55)			37 (56)	52 (49)		
LOS days, median (IQR)	6 (5–9)	5 (3–6)	7 (5–10)	<.001	0.40	5 (3–6)	6 (5–10)	<.001	0.41
Missing	0	0	0			0	2		
Complications within 90 days, number (%)				<.001	0.51			.01	0.52
No	176 (45)	69 (63)	107 (38)			36 (63)	36 (39)		
Clavien-Dindo 1–2	125 (32)	25 (23)	100 (36)			13 (23)	29 (32)		
Clavien-Dindo ≥3	90 (23)	16 (15)	74 (26)			8 (14)	27 (29)		
Liver failure within 30 days, number (%)	31 (8)	5 (5)	26 (9)	.18	0.19	2 (4)	8 (9)	.37	0.22
Grade of liver failure, number (%)				.36	0.84			.15	2.45
Grade A	11 (36)	3 (60)	8 (31)			2 (100)	2 (25)		
Grade B	5 (16)	0 (0)	5 (19)			0 (0)	1 (13)		
Grade C	15 (48)	2 (40)	13 (50)			0 (0)	5 (63)		
OR time, minutes, median (IQR)	225 (174–280)	175 (135–268)	235 (190–284)	<.001	0.39	175 (135–276)	218 (176–256)	.14	0.09
pRBC transfusion (mL), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	.03	0.18	0 (0–0)	0 (0–0)	.70	0.03
FFP transfusion (mL), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	.49	0.03	0 (0–0)	0 (0–0)	.54	0.15
Platelet transfusion (mL), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	.32	0.13	0 (0–0)	0 (0–0)	.30	0.19
Estimated blood loss (mL), median (IQR)	700 (300–1200)	300 (100–800)	800 (450–1400)	<.001	0.40	400 (200–800)	700 (400–1300)	.001	0.22
Pringle, number (%)	80 (21)	36 (33)	44 (16)	<.001	0.41	16 (28)	14 (15)	.09	0.32

diff, differentiation; *FFP*, fresh frozen plasma; *IQR*, interquartile range; *LOS*, length of stay; *LR*, liver resection; *OR*, operating room; *path*, pathology; *pRBC*, packed red blood cells; *SMD*, standardized mean difference.

95.9% [95% CI 92.8–99.2]; $P = .66$; 90 days LLR 97.2% [95% CI 93.4–100] versus OLR 92.5% [95% CI 88.4–96.9]; $P = .19$). In contrast, the OS was similar between LLR and OLR in the late era (2014–2019) ($P = .65$) (Supplementary Figure S3, *B*). The 1-, 3-, and 5-year survival rates were 94.1% (95% CI 88.6–99.9), 78.3% (95% CI 66.6–92.1), and 73.7% (95% CI 60.3–90.1) for LLR and 87.4% (95% CI 82.1–93.0), 80.6% (95% CI 73.3–88.7), and 65.0% (95% CI 53.8–78.6) for OLR. The cumulative incidence of recurrence was similar in the early and late eras ($P = .37$ and $P = .61$, respectively) (Supplementary Figure S4, *A–B*, respectively)

Causes of death

In the LLR group, the most common cause of death was progressive HCC ($n = 11$ [46%]) followed by cardiorespiratory failure ($n = 3$ [13%]). In the OLR group, progressive HCC represented the

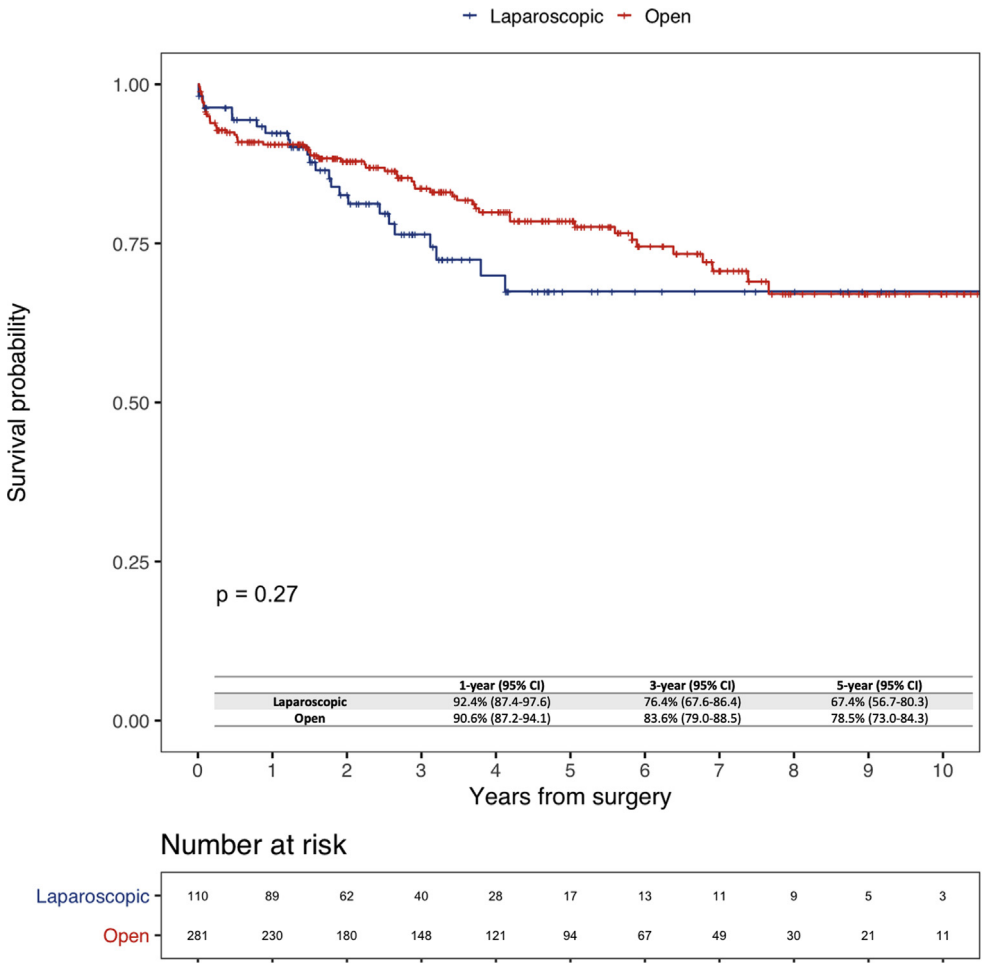

Figure 2. Overall survival after liver resection (overall cohort).

main cause of death ($n = 23$ [40%]), followed by postoperative complications ($n = 7$ [12%]) and liver failure ($n = 6$ [10%]).

Matched cohort

After PSM, 57 patients in the LLR group were matched with 92 patients in the OLR group. There were no significant differences between the groups with regard to the extent of hepatectomy performed and tumor characteristics. The LLR group had shorter LOS (5 [3–6] vs 6 [5–10]; $P < .001$) and lower estimated blood loss (median [IQR] 400 [200–800] vs 700 [400–1300]; $P = .001$). The groups were similar in intraoperative transfusion requirements. The LLR group had a similar rate of margin positivity but a larger margin distance compared with the OLR group (cm median [IQR] 1.00 [0.50–1.90] vs 0.60 [0.20–1.40]; $P = .01$). There was no statistically significant difference between posthepatectomy liver failure or grade of liver failure between the groups. The proportion of Clavien-Dindo grade III or greater complications were lower in the LLR group (14% vs 29%; $P = .01$) (Table II).

Matched survival analysis

Short-term survival was similar between the groups (30 days LLR 96.5% [95% CI 91.8–100] versus OLR 96.7% [95% CI 93.2–100]; $P = .94$; 90 days LLR 96.5% [95% CI 91.8–100] versus OLR 92.4% [95% CI 87.1–98.0]; $P = .33$). There were no statistically significant differences in OS (1-, 3-, and 5-year LLR 90.9% [95% CI 83.6–98.8], 79.3% [95% CI 68.5–91.9], 70.5% [95% CI 56.6–87.8] versus OLR 91.3% [95% CI 85.7–97.2], 88.5% [95% CI 82.0–95.5], 83.1% [95% CI 74.8–92.3]; $P = .26$) (Figure 4) and risk of HCC recurrence (1-, 3-, and 5-year LLR 31.1% [95% CI 19.3–43.6], 59.7% [95% CI 43.7–72.5], 62.9% [95% CI 46.3–75.6] versus OLR 18.9% [95% CI 11.5–27.6], 40.6% [95% CI 30.0–50.9], 49.2% [95% CI 37.3–60.1]; $P = .06$) (Figure 5). The hazard of death (LLR HR 1.55, 95% CI 0.65–3.30; $P = .26$) and recurrence (LLR subdistribution HR 1.39, 95% CI 0.88–2.21; $P = .16$) was equivalent between the groups. For patients who recurred, the pattern of recurrence did not differ between the groups (margin recurrence LLR $n = 8$ [25%] versus OLR 8 [19%]; $P = .50$). Patients requiring conversion from LLR to OLR had a similar survival as those who were completed laparoscopically ($P = .20$).

Discussion

As the prevalence of HCC continues to increase, along with the adoption of laparoscopic liver surgery as a modality for its treatment, it remains paramount to conduct contemporary analyses of this approach on outcomes. The current study represents the largest single institutional study from North America, evaluating short- and long-term outcomes of LLR and OLR for the treatment of HCC. After granular propensity score matching was performed using patient demographics, tumor characteristics, and extent of resection, there was a significantly shorter operative time, shorter

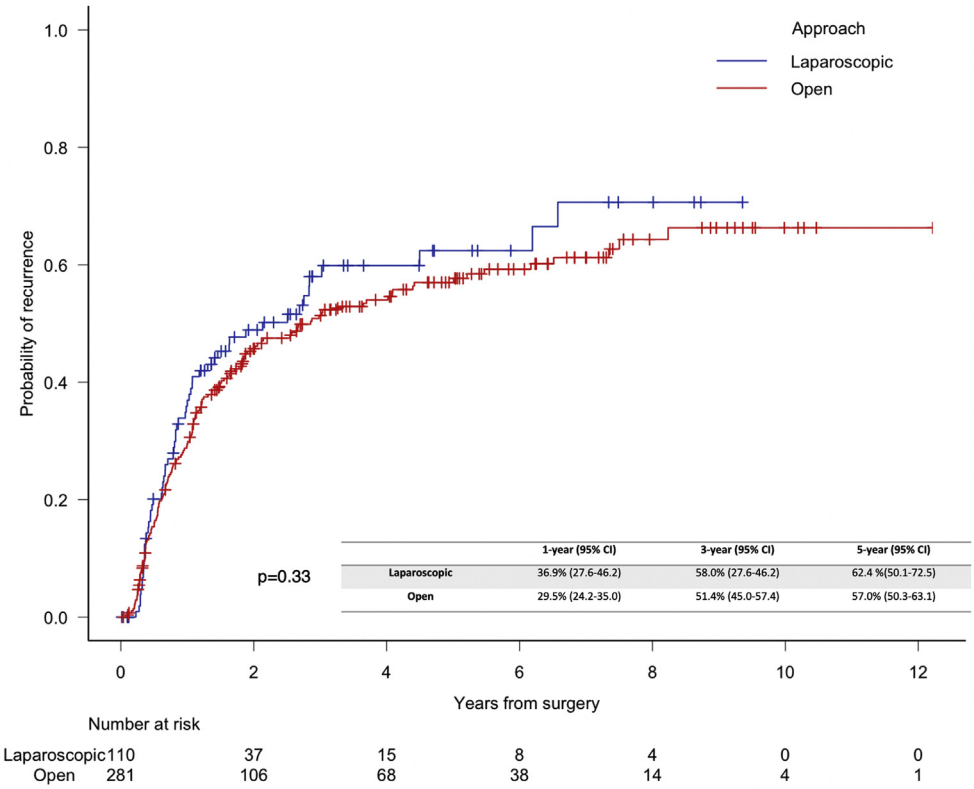

Figure 3. Cumulative incidence of recurrence after liver resection (overall cohort).

LOS, lower estimated blood loss, and larger margin distance for patients undergoing LLR. The major complication rate was lower in the LLR group. Long-term outcomes including OS and HCC recurrence were equivalent.

There has been a considerable increase in the use of LLR over the last 2 decades.[8] Increasing experience has enabled expansion of the LLR technique to safely include major hepatectomies and resection of HCC located in unfavorable locations.[28–30] Prior reports have assessed short-term outcomes of LLR and demonstrated less perioperative blood loss and transfusion requirement, shorter length of stay, and lower morbidity and mortality.[28,31] We similarly found that LLR resulted in a shorter LOS, lower blood loss, and a lower postoperative complication rate. There were no differences between groups in terms of short-term mortality (30- and 90-day). The LLR group had a larger surgical margin distance, which may possibly provide bias toward a more liberal resection margin with the new technique. Nonetheless, it remains unclear what, if any, this small difference between the groups may have where the pattern of recurrence (margin and non-margin) was not statistically significantly different between the groups. With regard to long-term oncologic outcomes, several studies, primarily from Asia, have demonstrated equivalent overall and disease-free survival, which has been corroborated by meta-analyses.[6,9,11–15,31–33] As the etiology of HCC in East Asia is predominantly related to hepatitis B, this differs substantially from patients in North America who tend to have a higher proportion of hepatitis C virus-related HCC and makes these reports difficult to generalize.[34] Specifically, hepatitis C virus-related HCC has been associated with a shorter disease-free survival than hepatitis B–related HCC.[34] Despite this, however, we similarly noted equivalent oncologic outcomes of the LLR group, suggesting that surgical approach does not impact outcomes even when disease etiology is accounted for.

Accounting for potential confounders is imperative to most appropriately assess the impact of technique on outcome. Recently, Ruzzenente et al evaluated a sizeable multi-institutional cohort of HCC patients with portal hypertension using PSM.[35] A total of 1,974 patients were included, with a subsequent 1:1 match of 407 LLR and OLR patients. Although the patient population was different, their study demonstrated similar findings to our report with short-term results favoring the LLR approach and long-term outcomes being equivalent. Another study used the United States National Cancer Database and compared survival outcomes for 190 matched LLR and OLR patients and found equivalent overall survival.[36] Nonetheless, recurrence was unavailable in the data set and was therefore not examined.[36] Indeed, these multi-institutional cohorts and registry studies can amass a large heterogeneous group of patients, with high statistical power. Nonetheless, it is remains difficult to elucidate the exact contribution of individual institutions, which likely differ in their experience level and thus challenge the interpretation of results. Additionally, in pooling the data together, favorable outcomes of larger institutional experiences can mask the outcomes of smaller ones. In the current report, we performed adjustments using a granular PSM on variables most likely to impact long-term outcomes, such as degree of liver disease, preoperative biomarker (AFP) level, and tumor variables. Moreover, as prior studies inconsistently accounted for varying oncologic outcomes over time as institutional/provider experience with LLR increased, we also matched based on the year of resection. Within this context, we observed decreased long-term survival in patients undergoing LLR in the early era compared with OLR. In contrast, in the later era survival was equivalent between the 2 approaches. The reason for decreased survival in the early era is unclear but may be a result of sample size bias.

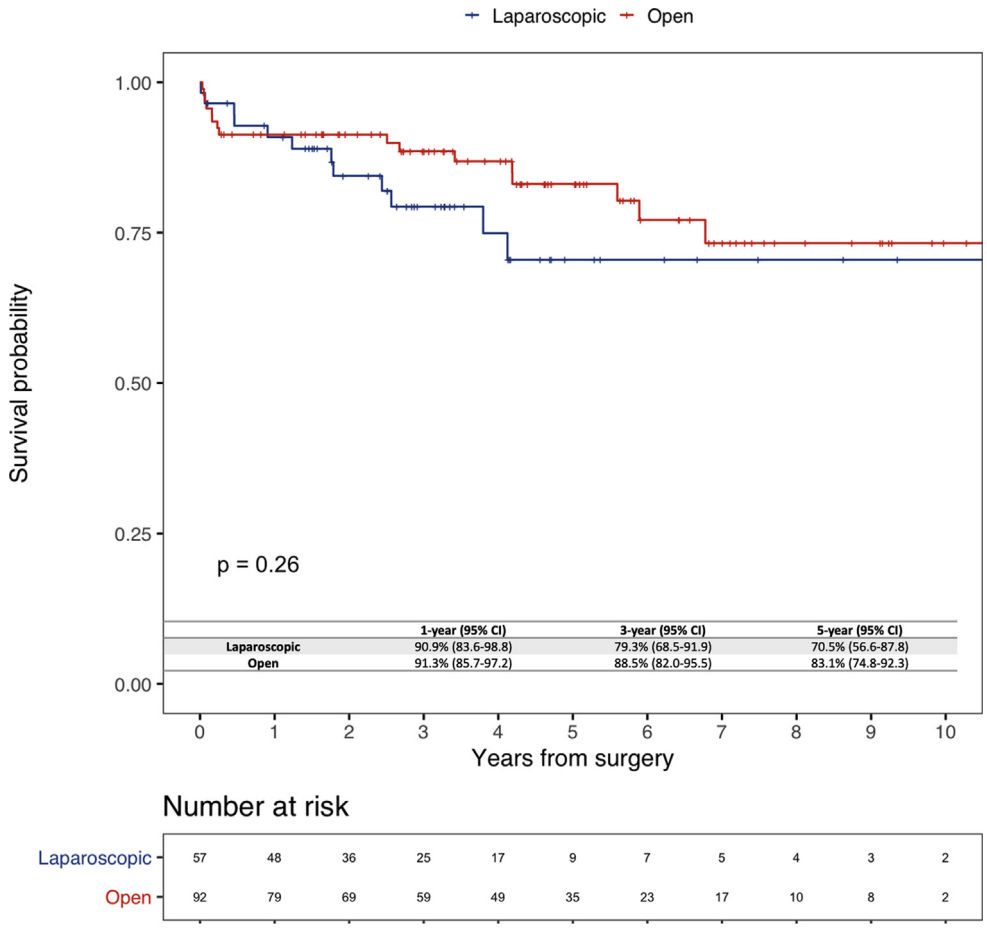

Figure 4. Overall survival after liver resection in the matched cohort univariable Cox proportional hazard Lap (ref: open) HR 1.55, 95% CI 0.65−3.30; $P = .26$.

The learning curve to achieve proficiency with LLR remains to be fully elucidated. Indeed, the number of cases required to achieve procedural proficiency depends on the extent of hepatectomy, with fewer required for less extensive approaches.[37] Previous studies have reported the requirement to be 45 to 75 cases for major hepatectomies, with study endpoints including improvements in conversion rates, operative time, blood loss, and morbidity.[38–41] Although these studies have not specifically evaluated outcomes of HCC patients, these abovementioned numbers represent a valuable benchmark in implementing LLR from a programmatic standpoint. Our study was not designed to directly evaluate the learning curve of LLR. It does, however, highlight that an appropriate resection margin can be achieved using this technique, resulting in equivalent oncologic outcomes to the OLR approach.

As randomized controlled trials between LLR and OLR are desperately needed, they are contingent on the surgical performance of a new technique, which in turn depends on provider and institutional learning curves. Until such high-quality data are available, iterative appraisal of retrospective outcomes is critical, given the rapid adoption of this approach. To this end, our group reported our early institutional experience with the laparoscopic approach.[42] This current study was performed to address the limitations of the prior work, including sample size, a relatively short follow-up, and ability to perform granular matching on a number of important clinicopathologic variables. In the previous report, there was a nonstatistical trend toward a worse DFS in LLR.[42] In addition to the Kaplan-Meier based method for DFS analysis, which censors for the competing event of death, we used a cumulative incidence approach to account for this competing risk in the evaluation of recurrence. In this updated analysis with a longer follow-up and larger sample size, both DFS and cumulative incidence of recurrence were equivalent between LLR and OLR.

This study is limited by its single-center retrospective nonrandomized study design, with the potential for misclassification and selection bias. Though the sample size of the laparoscopic cohort is relatively small, it does represent the largest, single-center experience from North America. The homogeneity afforded by the single institution center design offers an opportunity to evaluate temporal trends in outcomes that may be masked by larger heterogeneous multi-center studies, where the experience of some centers may outweigh those of lower volume institutions and the granularity of available data is lacking. Though granular PSM was performed in an attempt to control for the effect of confounding and address selection bias, there is always the potential for residual confounding.

In conclusion, the combination of reduced short-term complications and LOS and equivalent long-term oncologic outcomes favor the laparoscopic approach for resectable patients with HCC and should be the surgical technique of choice when feasible.

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Conflict of interest/Disclosure

None of the authors have any conflicts of interest.

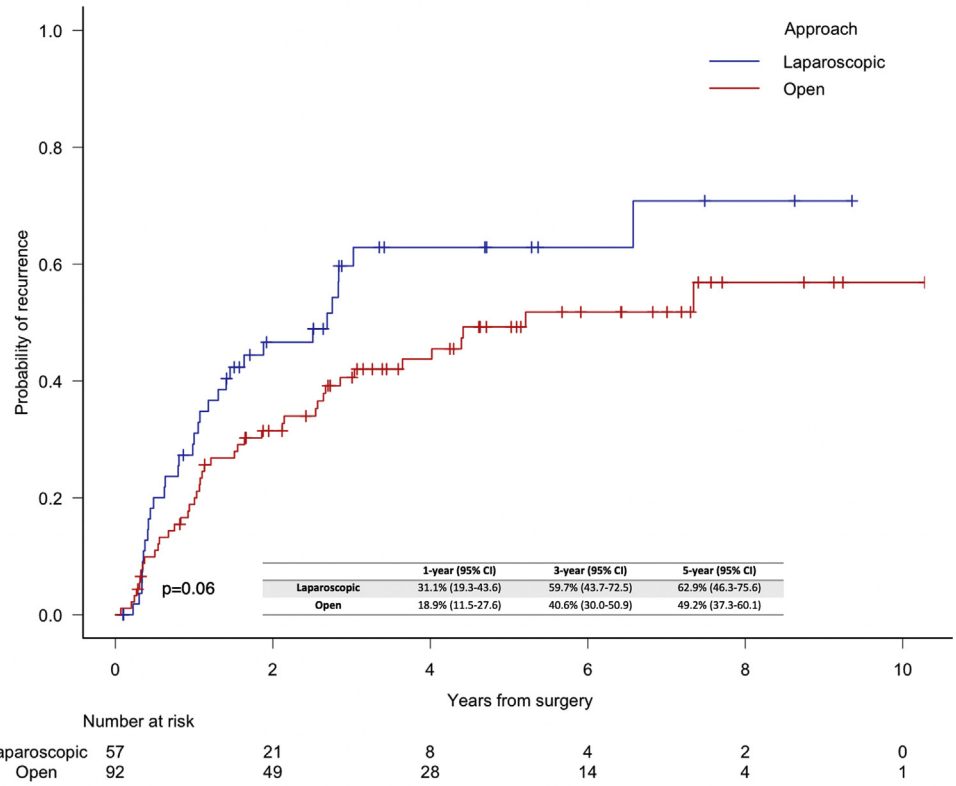

Figure 5. Cumulative incidence of recurrence after liver resection in the matched cohort (univariable Fine-Gray proportional hazard regression for competing event of recurrence subdistribution HR 1.39, 95% CI 0.88–2.21; $P = .16$).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [https://doi.org/10.1016/j.surg.2021.10.017].

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