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Preoperative Prognosticators of Safe Laparoscopic Hepatocellular Carcinoma Resection in Advanced Cirrhosis: a Propensity Score Matching Population-Based Analysis of 1799 Western Patients

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Abstract

Background The safety and oncologic outcomes of patients with advanced cirrhosis undergoing laparoscopic liver resection (LLR) compared to open resection (OLR) for hepatocellular carcinoma (HCC) remain unclear.
Methods Patients with HCC resection during 2010–2014 were identified from the National Cancer Database. Patients with severe fibrosis; single lesions; M0; and known grade, margin status, tumor size, length of hospital stay, 30- and 90-day mortality, 30-day readmission, surgical approach, and complete follow-up were included. A 1:1 propensity score matching analysis of LLR:OLR was performed. Prognostic effect of LLR was assessed by multivariable Cox proportional hazards model.
Results A total of 1799 hepatectomy patients (minor ($n = 491$, 27.3%); major ($n = 1308$, 72.7%)) were included. Of 193 (10.7%) LLR patients, 190 were eligible for matching. The LLR vs OLR did not differ for patient characteristics, resection margin status, and 30-day ($p = 0.141$), 90-day mortality ($p = 0.121$), or 30-day readmission ($p = 0.784$). Median hospital stay was shorter for LLR (6 vs 8 days, $p = 0.001$). Median overall survival (OS) was similar for LLR vs OLR (44.2 and 39.5 months, respectively, $p = 0.064$). Predictors of worse OS were older age (hazard ratio (HR) 1.04, $p = 0.034$), > 2 comorbidities (HR 1.29, $p = 0.012$), grade 3–4 disease (HR 1.81, $p = 0.025$), N1 disease (HR 1.04, $p = 0.048$), and R1 margins (HR 1.34, $p = 0.002$). After adjustment for confounders, LLR vs OLR was not a significant risk factor for OS (HR 1.14, 95% CI 0.76–1.71, $p = 0.522$).
Conclusion While LLR in advanced cirrhosis for patients with HCC proved safe, optimal patient selection based on the preoperatively available factors comorbidities, age, degree of underlying liver disease, and high-quality oncologic surgery will determine long-term survival.

Keywords Hepatocellular carcinoma · Laparoscopic · Cirrhosis · Propensity score

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Abbreviations

HCC	Hepatocellular carcinoma
HR	Hazard ratio
LLR	Laparoscopic liver resection
NCDB	National Cancer Database
OLR	Open liver resection
OS	Overall survival

Introduction

Hepatocellular carcinoma (HCC) is the most common indication for laparoscopic liver resection (LLR) worldwide.[1,2] While reports from consensus conferences[3–5] and expert centers[6–15] suggest a benefit from LLR vs open liver resection (OLR) in patients with HCC specifically, these studies are

from high-volume centers with significant expertise in managing liver cirrhosis and treating HCC.[13,16,17] Whether the data from these expert centers is generalizable to non-specialized practices remains unclear to date. In addition, most series on LLR for HCC are from Asian centers, where HCC is the most common indication for liver resection and where the etiology for the liver cirrhosis leading to HCC is different from the West. These general differences in the surgical treatment of HCC between Eastern and Western countries have been reported.[18] However, it remains unclear whether the surgical approach specifically (LLR vs OLR) impacts outcomes in Western patients.

While HCC is intimately associated with liver cirrhosis (4 out of 5 cases), it is poor liver function rather than HCC that has the greatest negative impact on short- and long-term survival in patients with potentially curable HCC and cirrhosis. In these cirrhotic patients at risk for decompensation, LLR vs OLR has been shown to be associated with less surgical trauma and a lower incidence of peritoneal dissection without compromising oncologic safety.[19] Moreover, in this patient population of curable HCC with cirrhosis, LLR specifically is associated with lower rates of postoperative liver failure and ascites than OLR. Reports on this association of surgical approach and outcome are from specialized centers with significant experience in managing cirrhosis and treating HCC and from carefully selected patient populations.[7,9,12,15,20–22]

To help resolve the controversy regarding any specific benefit of LLR in Western patients with HCC and advanced cirrhosis and whether these benefits can be predicted preoperatively, we compared short- and long-term outcomes of LLR and OLR for HCC in a US population-based cohort. To ensure results are reflective of national trends and generalizable to non-expert centers, we used data from the National Cancer Database (NCDB), a nationwide, facility-based (specialized and non-specialized centers) comprehensive cancer surveillance database that captures information of at least 70% of all newly diagnosed cancers in the USA. Additionally, to minimize the impact of selection bias on the study findings (less advanced cases may be operated via LLR), propensity score matching was employed.

Materials and Methods

Patient Selection Criteria and Data Source

The NCDB was queried to identify patients aged 18 years or older with a histologically confirmed diagnosis of HCC during 2010–2014. Cases of HCC were identified using the *International Classification of Diseases for Oncology*, third edition, primary tumor site code for liver (C22) and morphology codes for HCC (8170/3, 8171/3, 8172/3, 8173/3, 8174/3, and 8175/3). Patients were excluded if they did not have

severe cirrhosis (International Association for Study of the Liver score > 4[23]), if they had M1 disease or multiple liver lesions, if they did not undergo surgery for HCC, if the procedure was converted to open, or if data were unavailable regarding comorbidities (Charlson-Deyo score), type of operation (LLR vs OLR), tumor size, tumor grade, margin status, number of tumors, nodal status, intrahepatic vascular invasion status, length of hospital stay, 30-day and 90-day mortality, or 30-day unplanned readmission (Fig. 1).

Outcomes

The outcomes measured were death within 30 days after liver resection, death within 90 days after liver resection,[24] readmission within 30 days after liver resection,[25] length of hospital stay after liver resection, and overall survival (OS), defined in the NCDB and in our study as the time from liver resection until death of any cause.

Statistical Analysis

Propensity score matching to minimize differences in baseline characteristics between the patients who underwent LLR and the patients who underwent OLR was used (Fig. 2). Factors considered the most important confounders also contributing to survival risk were chosen for the propensity score algorithm (age, sex, hospital volume, comorbidities, tumor size, tumor grade, type of resection, and vascular invasion). These factors were chosen on the basis of previously reported preoperatively available factors predictive of outcome[26–28] and consensus of the investigators achieved via structured communication technique. A 1:1 match on the propensity score, without replacement, was performed with a conservative caliper width of 10% of the standard deviation of the log of propensity score. Given the paired nature of the data, the Mann-Whiney U test was used to compare binary outcomes, and the Wilcoxon signed-rank test was used to compare continuous outcomes. Matched pairs with missing data for either patient were excluded during analysis of the missing outcome.

OS was evaluated using the Kaplan–Meier method and compared using the log-rank test. To adjust for possible confounders (age, sex, comorbidities, tumor size, tumor grade, nodal status, margin status, type of hepatectomy (minor or major), and surgical approach), Cox multivariable regression was performed to identify factors affecting OS and the effect of surgical approach on OS. Major hepatectomy was defined as resection of more than two segments.

All statistical computations were performed using SPSS, version 24 (IBM Inc., Armonk, NY).
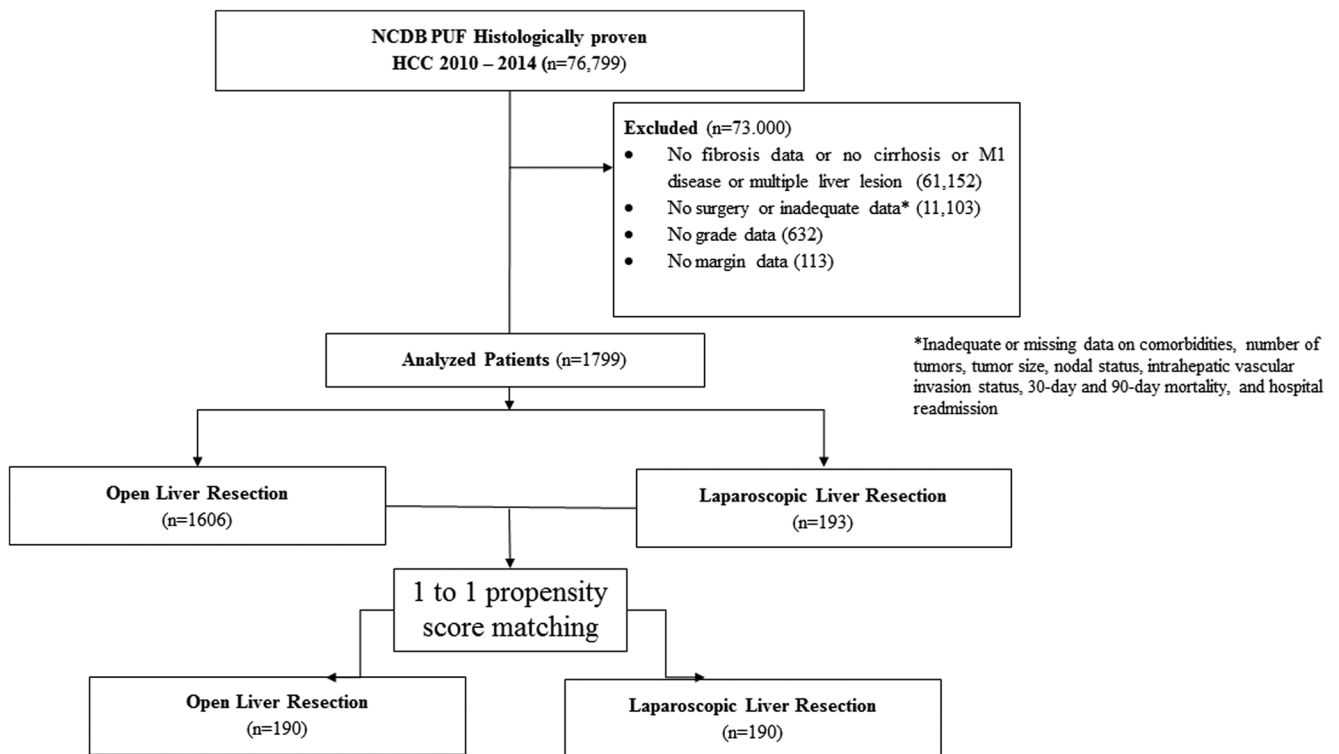
Fig. 1 CONSORT diagram. M1, metastatic disease; NCDB, National Cancer Database; PUF, participant user files; R2, macroscopically positive resection margin

Results

A total of 76,799 patients aged 18 years or older who were diagnosed with HCC were identified in NCDB during 2010– 2014 (Fig. 1). Patients with incomplete data, who did not have severe fibrosis or recorded fibrosis data, did not undergo surgery, or with missing data about tumor grade or margin status, were excluded. This left 1799 patients to be included in the analysis.
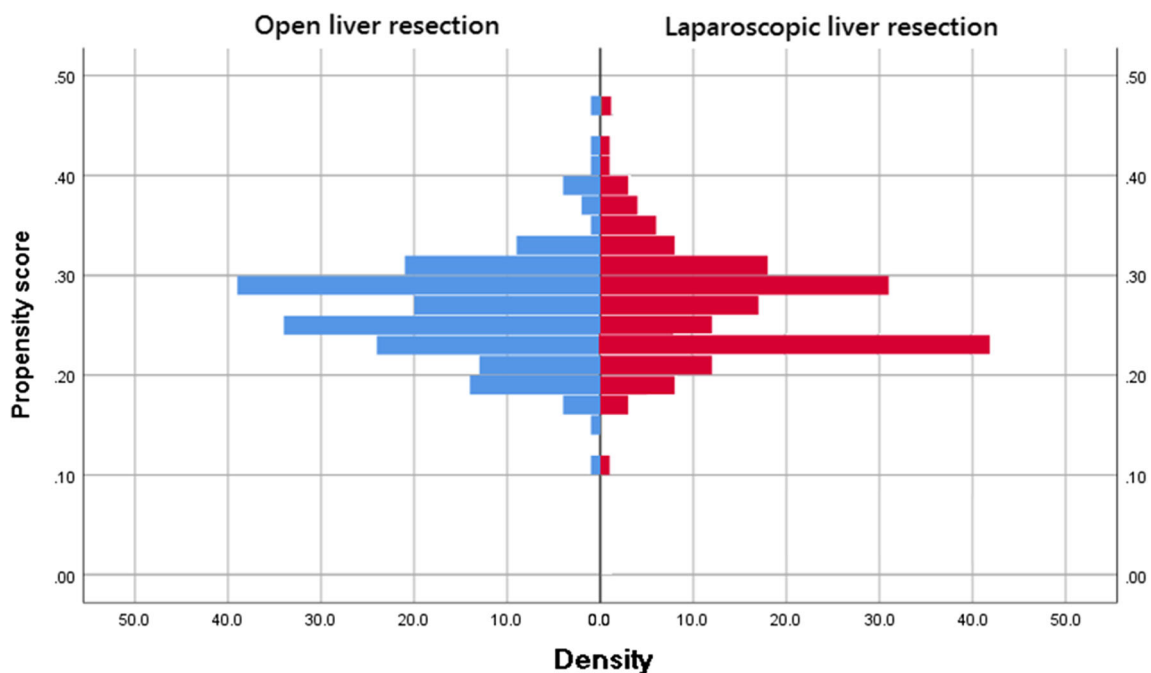

Fig. 2 Histogram of the propensity score distribution after matching by open liver resection and laparoscopic liver resection

Characteristics of the Entire Cohort

Of the 1799 patients, 1606 (89.3%) underwent OLR, and 193 (10.7%) underwent LLR; 491 (27.3%) underwent minor and 1308 (72.7%) major hepatectomies.

The demographic and clinicopathologic characteristics of the entire cohort are summarized in Table 1. No significant differences were observed between patients who underwent OLR and those who underwent LLR with respect to sex, histologic grade, tumor size, N category, or proportion of patients with R1 resection margins. The OLR group was older and had higher rates of 2 or more comorbidities, lymphovascular invasion, and major hepatectomy; the LLR group had a higher rate of minor hepatectomy.

Characteristics of the Matched Cohort

Of the 193 patients who underwent LLR, 190 patients were eligible for 1:1 matching (Table 1). In the matched cohort, no significant differences were observed between the patients who underwent OLR and those who underwent LLR with respect to any measured demographic or clinicopathologic characteristic and facility type where the surgery was performed (Supplementary Table 1), including the proportion of patients with R1 resection margins.

Mortality, Readmission Rate, and Hospital Stay in Patients with OLR vs LLR

In the matched cohort, the OLR and LLR groups did not differ with respect to 30-day mortality, 90-day mortality, or 30-day readmission rate. Median hospital stay was significantly shorter for the LLR group (6 vs 8 days, $p = 0.001$) (Table 2).

Predictors of Readmission and Mortality

On multivariable analysis, predictors of 30-day and 90-day mortality were older age, 2 or more comorbidities, and major hepatectomy (Table 3). LLR vs OLR was not a significant risk factor for mortality. Predictors of 30-day readmission were older age, 2 or more comorbidities, and major hepatectomy (Table 3). LLR vs OLR was not a significant risk factor for 30-day readmission.

Overall Survival in Patients with OLR vs LLR

In the matched cohort, median OS was 42.3 months. Median OS was similar (not inferior) for the OLR group (39.5 months) and LLR group (44.2 months) (log-rank $p = 0.064$) (Fig. 3).

Predictors of OS

On multivariable analysis (Table 3), predictors of poor OS were older age, 2 or more comorbidities, histologic grade 3 or 4, larger tumor size, vascular invasion, positive lymph nodes, and R1 resection margins. Major hepatectomy was a predictor of better OS. LLR vs OLR was not a significant predictor of survival.

Discussion

In this study, we found that, in a Western population–based cohort, LLR in patients with advanced cirrhosis was similar to OLR in terms of OS, 30-day and 90-day mortality, and 30-day readmission rate. Moreover, in the multivariable analysis, the only factors related to mortality and 30-day readmission were advanced age, 2 or more comorbidities, and major hepatectomy. Surgical approach was not related to short-term or long-term outcome.

Prior studies of LLR for HCC in patients with cirrhosis[6,7,10,14,15,20] have suggested that LLR leads to the same oncologic outcome and mortality as OLR in selected patients. However, most of these earlier studies were conducted at specialized centers in a carefully selected Asian population, whereas the current study is based on a representative sample of Western patients treated in both academic and non-academic centers. Therefore, the findings presented are more representative of typical Western practice patterns compared to prior reports.

Further, our results indicate that LLR is comparable to OLR regarding 90-day mortality and OS, even after adjusting for major liver resection which was a significant component of the study population (31.6%). It has been suggested that LLR vs OLR results in less disruption of collateral circulation through the abdominal wall due to the smaller incisions required for ports, less liver mobilization preserving perihepatic collaterals, and lower demand for intravenous fluid replacement due to less sensible losses decreasing the risk of third spacing. These factors result in a decreased risk of prolonged postoperative ascites and liver decompensation after surgery.[7,29] For these reasons, the beneficial effect of laparoscopy may be more prominent in major hepatectomies and in patients with advanced cirrhosis, which was demonstrated here.[15,30] In the LLR group, the incidence of ascites was significantly less than that in the OLR group (9.4 vs 31.3%, $p = 0.030$), while the blood loss, the transfusion requirement, the rate of overall postoperative complications, and the OS and disease-free survival were similar.[30,31] Therefore, in appropriately selected HCC patients with advanced cirrhosis, LLR should be encouraged, when it can be performed safely by surgeons that have surpassed the minimal learning/teaching

Table 1 Demographic and clinicopathologic characteristics

Characteristic	Entire cohort				Matched cohort			
	All patients (N = 1799)	OLR (N = 1606)	LLR (N = 193)	p value	All patients (N = 380)	OLR (N = 190)	LLR (N = 190)	p value
Age, mean (range), year	63.8 (22–85)	64.7 (22–85)	61.87 (34–85)	*0.004*	62.83 (22–85)	63.79 (22–85)	62.87 (34–85)	0.15
Females‡	624 (35)	560 (35)	64 (33)	0.69	126 (62)	62 (33)	64 (34)	0.90
Comorbidities‡								
None	490 (27)	428 (27)	62 (32)	*0.023*	116 (30)	55 (29)	61 (32)	0.88
1	566 (32)	497 (31)	69 (36)		131 (35)	63 (33)	68 (36)	
2 or more	743 (41)	681 (42)	62 (32)		133 (35)	72 (38)	61 (32)	
Grade†								
1	504 (28)	459 (28)	45 (23)	0.11	90 (24)	45 (24)	45 (24)	0.72
2	1045 (58)	934 (58)	111 (57)		221 (58)	111 (58)	110 (58)	
3	243 (13)	207 (13)	36 (19)		67 (18)	33 (17)	34 (18)	
4	7 (0.4)	6 (0.4)	1 (0.5)		2 (0.5)	1 (0.5)	1 (0.5)	
Lymphovascular invasion†	433 (24)	375 (23)	58 (30)	*0.047*	112 (30)	57 (30)	55 (29)	0.91
Tumor size, mean (range), mm‡	33.1 (5–118)	33.7 (5–118)	31.8 (5–85)	0.08	32.3 (5–118)	32.7 (5–118)	31.8 (58)	0.16
N category†								
0	943 (52)	865 (54)	78 (40)	0.27	151 (40)	76 (40)	75 (39)	0.58
1	34 (2)	30 (2)	4 (2)		9 (2)	5 (3)	4 (2)	
X	822 (46)	711 (44)	111 (58)		220 (57.9)	109 (57)	111 (58)	
Hepatectomy†								
Minor	491 (27)	361 (23)	130 (67)	*< 0.001*	262 (69)	132 (69)	130 (68)	0.58
Major	1308 (73)	1245 (77)	63 (33)		118 (31)	58 (31)	60 (32)	
R1 margins†								
0	1646 (91)	1474 (92)	172 (89)	0.13	340 (89)	169 (89)	171 (90)	0.74
1	153 (9)	132 (8)	21 (11)		40 (11)	21 (11)	19 (10)	

Values in table are number of patients (percentage) unless indicated otherwise

Italic format for *p* value < 0.05

LLR, laparoscopic liver resection; *OLR*, open liver resection

†χ^2 test unless indicated otherwise

‡Wilcoxon rank-sum test

curve for complex laparoscopic liver surgery of 45 to 75 cases at the minimum.[32]

Until recently, it has been thought that for the subgroup of patients with HCC and cirrhosis[10] the literature is insufficient to support LLR. This concept that LLR in general should not be recommended for patients with cirrhosis is being confronted by the findings of this study that show that outcomes of appropriately selected LLR patients are at least similar regarding 30- and 90-day mortality and 30-day readmission to OLR in a population-based setting. These results are in agreement with some reports that show no significant difference between LLR and OLR in terms of blood loss, blood

Table 2 Mortality, unplanned readmission rates, and length of hospital stay

Outcome	All patients	OLR	LLR	p value
30-day mortality, N (%)	13 (3.4)	7 (3.6)	6 (3.1)	0.14
90-day mortality, N (%)	24 (6.3)	14 (7.3)	10 (5.3)	0.12
30-day readmission, N (%)	25 (6.6)	13 (6.8)	12 (6.3)	0.78
Length of hospital stay, median (range), days	7 (4–103)	8 (4–55)	6 (4–103)	*0.001*

Italic format for *p* value < 0.05

LLR, laparoscopic liver resection; *OLR*, open liver resection

Table 3 Results of multivariable analysis

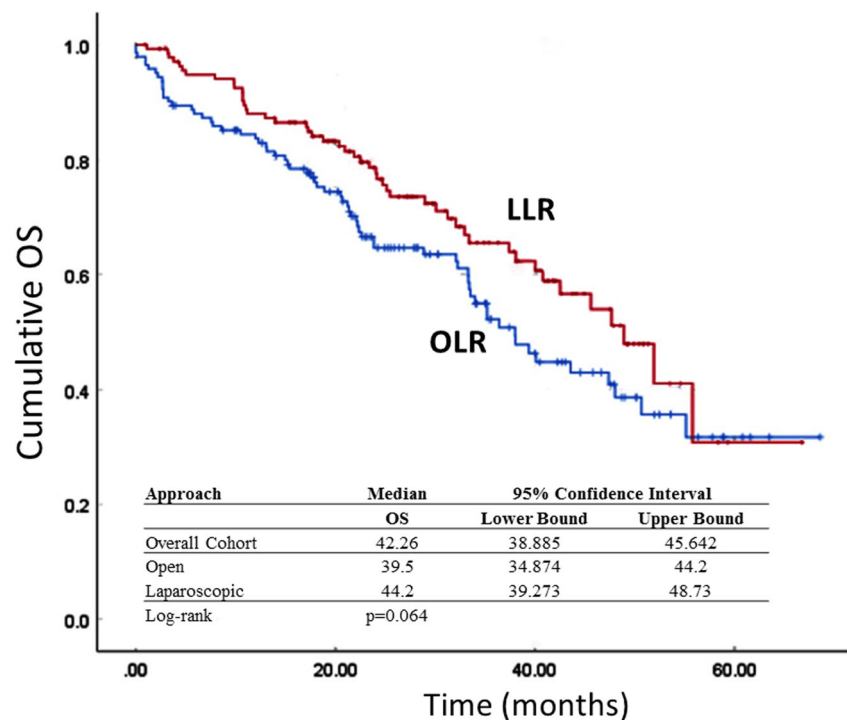| Characteristic	30-day mortality			90-day mortality			30-day readmission			OS		
	OR	(95% CI)	p value	OR	(95% CI)	p value	OR	(95% CI)	p value	HR	95% CI	p value
Age	1.03	(1–1.06)	*0.047*	1.05	(1.03–1.1)	*0.041*	1.02	(1.01–1.03)	*0.047*	1.04	(1.01–1.09)	*0.034*
Sex	0.98	(0.25–3.86)	0.97	0.95	(0.35–2.61)	0.92	0.58	(0.29–1.17)	0.13	1.12	(0.71–1.77)	0.62
Comorbidities												
None	1			1			1			1		
1	0.15	(0.02–1.34)	0.18	0.6	(0.18–2.05)	0.42	1.07	(0.48–2.41)	0.87	0.87	(0.54–1.4)	0.56
2 or more	1.59	(1.33–2.08)	*0.029*	2.27	(1.74–3.02)	*0.016*	1.51	(1.13–2.09)	*0.021*	1.29	(1.04–1.54)	*0.012*
Grade†												
1	1			1			1			1		
2	0.63	(0.13–3.17)	0.58	0.4	(0.13–1.22)	0.11	0.11	(0.01–1.95)	0.13	1.81	(1.21–2.41)	*0.025*
3	0.8	(0.15–4.35)	0.80	0.97	(0.92–1.02)	0.22	0.11	(0.01–1.86)	0.13			
4	0.46	(0.1–2.18)	0.33	1.1	(0.42–2.86)	0.84	0.08	(0.01–1.57)	0.09			
Tumor size	1.00	(0.97–1.03)	0.80	1.00	(0.98–1.02)	0.76	1.00	(0.99–1.02)	0.99	1.01	(1–1.01)	*0.031*
Vascular invasion										1.47	(1.06–2.17)	*0.018*
N category												
N0	1			1			1			1		
NX	0.85	(0.09–7.65)	0.88	0.69	(0.14–3.35)	0.65	0.55	(0.16–1.94)	0.35	0.8	(0.55–1.17)	0.25
N1	1.96	(0.56–6.89)	0.30	1.34	(0.52–3.46)	0.55	0.8	(0.38–1.67)	0.55	1.04	(1–1.54)	***0.048***
Minor vs major resection	2.94	(1.18–4.77)	*0.016*	2.2	(1.16–3.34)	*0.019*	1.72	(1.12–2.57)	*0.007*	0.63	(0.44–0.92)	*0.017*
R1 margins										1.34	(1.11–1.52)	*0.002*
Surgical approach, LLR vs OLR	0.28	(0.06–1.36)	0.11	0.5	(0.18–1.38)	0.18	1.65	(0.79–3.45)	0.19	1.14	(0.76–1.71)	0.52

Multivariable Cox regression was applied with stepwise backward selection. Initially, all factors were included in the model

Italic format for *p* value < 0.05

CI, confidence interval; *HR*, hazard ratio; *LLR*, laparoscopic liver resection; *OLR*, open liver resection; *OR*, odds ratio; *OS*, overall survival

†For multivariable analysis of OS, grade was combined in two groups (1–2 vs 3–4)

Fig. 3 Overall survival (OS) in matched patients by surgical approach. LLR, laparoscopic liver resection; OLR, open liver resection

Approach	Median	95% Confidence Interval	
	OS	Lower Bound	Upper Bound
Overall Cohort	42.26	38.885	45.642
Open	39.5	34.874	44.2
Laparoscopic	44.2	39.273	48.73
Log-rank	p=0.064		

transfusions, operative time, Pringle maneuver duration, overall morbidity, and postoperative mortality.[33] Even liver-specific complications, such as ascites decompensation and postoperative liver failure, have been shown to be similar between LLR and OLR in patients with HCC and early cirrhosis.[7,14,29] However, these reports are from European and Asian expert centers with significant experience in managing cirrhosis and HCC. In a recent study from the USA[6] of LLR in patients with HCC and moderate to advanced cirrhosis, morbidity and mortality did not differ significantly between the 26 patients with Child–Pugh class B ($n = 20$) or class C ($n = 6$) disease and the 80 patients with Child–Pugh class A disease. The decision to perform LLR on 6 patients with Child–Pugh class C can be viewed as controversial evidenced by the resulting severe morbidity and a 90-day mortality rate of 16.6%. These results underscore the results of this study showing that the main determinants of outcome are patient selection and quality of surgery rather than the surgical approach.

While this study showing comparative outcomes between LLR and OLR is representative of a wide range of practice patterns, a recent study[13] reported a volume–outcome relationship between hospital volume and outcome for patients undergoing LLR for primary liver cancer. The mortality in low-volume centers was similar for OLR and LLR and therefore the adoption of LLR does not explain the inferior performance of low-volume centers reported in this study and suggests that outcomes for patients at low-volume centers are more likely related to variations in perioperative care. In the present study, after matching, no difference related to the facility type was found (Supplementary Table 1).

To our knowledge, this is the largest study to date comparing LRR and OLR for HCC in patients with advanced cirrhosis, which accounts for selection bias and minimizes confounding (propensity score matching), there are several limitations. While it is well known that non-quantifiable or unknown measures may impact the treatment, selection cannot be controlled for with this approach or any other method apart from a randomized controlled trial. The statistical approach chosen here may control the most for selection bias while helping to answer the question whether LLR for HCC in advanced cirrhosis is appropriate. Another limitation of this study is that the NCDB, the source of our data, is subject to coding error. To minimize this risk, incongruent data were excluded resulting in a reduction of the source data from 76,799 to reliable 1799 items. Further, in the NCDB, cirrhosis is reported as severe liver fibrosis and traditionally used factors to determine degree of cirrhosis such as Child–Pugh score, portal hypertension, esophageal varices, platelet count, or splenomegaly were not available. Nevertheless, the use of this dataset permitted comparison of LLR vs OLR for HCC in a large

sample of patients with cirrhosis treated at both expert and non-expert centers across the USA, a topic that has previously not been investigated aside from small studies from single-institution expert centers. Our finding that only 11% of the patients with advanced cirrhosis who underwent liver resection for HCC in 2010–2014 underwent LLR shows that LLR remains in an early phase practiced by a few innovators and early adopters.[34] This suggests that the patients in this study were treated by surgeons who may have reached a plateau on their learning curve. While few cirrhotic patients with HCC may benefit from LLR today, the presented data suggest that dissemination of safe implementation of LRR across various practice patterns will allow well-selected patients to have easy access of care while reducing morbidity and postoperative decompensation from LLR.

Conclusion

The presented data show that LLR in patients with cirrhosis and HCC leads to comparable oncologic outcome and mortality as OLR. Further, not the surgical approach but age, tumor characteristics, and comorbidities are the main determinants of outcome. Since it was demonstrated in this population-based cohort of Western patients that the main determinants of outcome are factors that are available preoperatively, careful selection of cirrhotic patients with HCC for LLR will reduce morbidity and hepatic decompensation, while allowing improved access to care encouraging mortality and oncologic outcome.

Compliance with Ethical Standards

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