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ORIGINAL SCIENTIFIC REPORT (INCLUDING PAPERS PRESENTED AT SURGICAL CONFERENCES)

Perioperative Outcomes of Laparoscopic Repeat Liver Resection for Recurrent HCC: Comparison with Open Repeat Liver Resection for Recurrent HCC and Laparoscopic Resection for Primary HCC

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Abstract

Background This study aims to determine the safety and efficacy of laparoscopic repeat liver resection (LRLR) for recurrent hepatocellular carcinoma (rHCC).

Methods Twenty patients underwent LRLR for rHCC between 2015 and 2017. The control groups consisted of 79 open RLR (ORLR) for rHCC and 185 LLR for primary HCC. We undertook propensity score-adjusted analyses (PSA) and 1:1 propensity score matching (PSM) for the comparison of LRLR versus ORLR. Comparison of LRLR versus LLR was done using multivariable regression models with adjustment for clinically relevant covariates.

Results Twenty patients underwent LRLR with three open conversions (15%). Both PSA and 1:1-PSM demonstrated that LRLR was significantly associated with a shorter stay, superior disease-free survival (DFS) but longer operation time compared to ORLR. Comparison between LRLR versus LLR demonstrated that patients undergoing LRLR were significantly older, had smaller tumors, longer operation time and decreased frequency of Pringle's maneuver applied. There was no difference in other key perioperative outcomes.

Conclusion The results of this study demonstrate that in highly selected patients; LRLR for rHCC is feasible and safe. LRLR was associated with a shorter hospitalization but longer operation time compared to ORLR. Moreover, other than a longer operation time, LRLR was associated with similar perioperative outcomes compared to LLR for primary HCC.

Introduction

Presently, liver resection (LR) is commonly used as an effective curative treatment for hepatocellular carcinoma [1]. However, tumor recurrence is common and occurs in up to 80% of patients after curative LR [1, 2]. Tumor recurrence after LR is commonly intrahepatic, and curative treatment in the form of repeat liver resection (RLR), local ablation, or salvage liver transplant may frequently be performed to treat recurrent HCC (rHCC) [3, 4]. Although salvage liver transplant has been proven to provide the best long-term oncologic outcomes for rHCC, [5] its use is limited by organ scarcity and RLR is now a widely accepted and efficacious treatment modality for rHCC [6]. The rate of RLR for rHCC has been reported to range from

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7% to 30% [4, 6], and this is associated with reported 5-year survival rates of approximately 25–87% [6].

The adoption of laparoscopic liver resection (LLR) has rapidly increased worldwide over the past decade especially in high-volume specialist centers [7, 8]. LLR for HCC has been shown in numerous studies to produce superior short-term perioperatives and equivalent long-term oncologic compared to the traditional open approach [9–11]. However, there is presently limited evidence on the role of laparoscopic repeat liver resection (LRLR) for recurrent hepatocellular carcinoma (rHCC) [12–15]. This study aims to determine the safety and efficacy of LRLR for rHCC by reporting our experience with LRLR for rHCC and comparing its outcomes with open RLR (ORLR) and primary LLR for HCC.

Methods

Twenty consecutive patients who underwent attempted LRLR for suspected rHCC after previous LR from January 2015 to April 2017 were identified from our institution prospective LLR database. This study was approved by our center's Institutional Review Board. All patient data were collected from the patients' clinical, radiological, and pathological records. Clinical data were collected from a prospective computerized clinical database (Sunrise Clinical Manager version 5.8, Eclipsys Corporation, Atlanta, Georgia) and patient's clinical charts. Surgical data were obtained from another prospective computerized database (OTM 10, IBM, Armonk, New York). Relevant perioperative outcomes including operation time, estimated blood loss, blood transfusion, postoperative morbidity, and length of stay were recorded.

In this study, various approaches to LLR were adopted including the conventional totally laparoscopic multi-port approach, hand-assisted laparoscopy, robotic-assisted laparoscopy, and laparoscopic-assisted (hybrid approach). Our operative technique has been described in detail in previous studies [7, 16–19]. Postoperative complications were classified according to the Clavien–Dindo grading system [20]. All postoperative morbidity and mortality were recorded up to 30 days from surgery or within the same hospital stay regardless of the length of stay. The choice of treatment modality for patients with rHCC was discussed at our institution multidisciplinary meeting, and final choice of treatment was decided after careful discussion between the managing clinician and the patient. The decision for LRLR or ORLR was mainly based on an individual surgeon's comfort level with the laparoscopic approach. Thirty-day/in-hospital mortality was defined as death within 30 days from surgery on within the same hospital stay.

Statistical analysis

Comparison between LRLR versus ORLR

Propensity score analyses were used to minimize potential treatment selection bias by accounting for baseline patient characteristics which could influence a patient's likelihood of receiving either LRLR or ORLR for recurrent HCC. Propensity scores were calculated through logistic regression modeling based on the following clinically selected covariates: age, gender, tumor size, number of segments involved, hepatitis B status, the presence of cirrhosis, initial major or minor resection, ipsilateral or contralateral lobe recurrence, and difficult posterosuperior tumor location. To address missing baseline covariates, individual scores were derived by averaging the propensity scores generated across 50 multiply-imputed datasets. Discriminatory power, calibration, and goodness-of-fit of the propensity score model were assessed using the methods described by Lemeshow and Hosmer, c-index, and bootstrap validation. The final propensity score model exhibited an area under the receiver operating curve of 0.85 (bias-corrected 95% CI 0.72–0.92; Supplementary Figure S1).

We undertook two propensity score methodologies for comparing baseline and perioperative endpoints of patients who underwent LRLR versus ORLR, with covariate adjustment using the propensity score as the primary analysis and propensity score matching as an additional sensitivity analysis. For the primary analysis, pre- and perioperative variables shown in Table 1 were analyzed using tests for independent samples; accordingly, the Mann–Whitney U test and Fisher's exact test were, respectively, employed to compare medians and proportions. To minimize covariate imbalance, comparisons of perioperative and oncologic outcomes between the LRLR and ORLR groups were adjusted using the linear predictor (log odds) of the propensity scores as a covariate in multivariable regression models. Accordingly, propensity score-adjusted quantile, logistic, and Cox regression models, respectively, were performed to compare conditional medians, proportions, and time-to-event outcomes in Table 2.

Additionally, sensitivity analyses by way of propensity score matching were conducted to verify the robustness of the propensity score adjustment methodology. The LRLR and ORLR patients were paired 1:1 using a greedy algorithm without replacement, and adequacy of matching was assessed using kernel density and histogram plots (Supplementary Figures S2, S3). After propensity score matching, both groups were well-balanced for all variables. The Wilcoxon signed-rank test, McNemar's Chi-square test, and stratified log-rank tests were, respectively, utilized

Table 1 Comparison between the baseline demographic and perioperative data of patients who underwent laparoscopic versus open repeat liver reresection for recurrent HCC in the overall cohort and in a propensity score-matched subset of patients

	All patients			Propensity score-matched subset		
	Laparoscopic (n = 20)	Open (n = 79)	P value	Laparoscopic (n = 20)	Open (n = 20)	P-value
Gender, male (%)	18 (90%)	70 (88.6%)	0.860	18 (90%)	18 (90%)	1.000
Median age (IQR), years	68.5 (67.0–71.75)	63 (57–69)	**< 0.001**	68.5 (67.0–71.75)	69 (63.0–72.25)	0.340
Hepatitis B, n (%)	10 (50%)	58 (73.4%)	**0.044**	10 (50%)	10 (50%)	1.000
ASA score, n (%)			0.373			0.309
1	0/20 (0%)	4/67 (6.0%)		0/20 (0%)	2/19 (10.5%)	
2	13/20 (65%)	47/67 (70.2%)		13/20 (65%)	12/19 (63.2%)	
3	7/20 (35%)	16/67 (23.9%)		7/20 (35%)	5/19 (26.3%)	
Ipsilateral recurrence, n (%)	10 (50%)	41 (51.9%)	0.879	10 (50%)	7 (35%)	0.372
First reresection, n (%)	17/20 (85%)	67/79 (84.8%)	0.875	17 (85%)	17 (85%)	1.000
Second reresection, n (%)	3/20 (15%)	11/79 (13.9%)		3 (15%)	3 (15%)	
Third reresection, n (%)	0/20 (0%)	1/79 (1.3%)				
Initial resection			0.447			0.147
Minor hepatectomy	18 (90%)	61 (77.2%)		18 (90%)	20 (100%)	
Major hepatectomy	2 (10%)	18 (22.8%)		2 (10%)	0 (0%)	
Median interval from first resection, m (IQR)	29 (17.5–63.75)	26.5 (14–57)	0.402	29 (17.5–63.75)	30 (15.0–58.0)	0.804
Median tumor size, mm (IQR)	20 (11.5–27.75)	26 (20–30)	0.082	20 (11.5–27.75)	26 (15.0–30.0)	0.359
Multiple tumors, n (%)	1 (5%)	9 (11.4%)	0.291	1 (5%)	2 (10%)	0.560
Major hepatectomy, n (%)	2 (10%)	10 (12.7%)	0.745	2 (10%)	0 (0%)	0.147
Difficult posterosuperior segments, n (%)	7 (35%)	43 (54.4%)	0.121	7 (35%)	6 (30%)	0.739
No. of segments resected			0.808			0.296
1/Wedge	11 (55%)	47 (59.5%)		11 (55%)	14 (70%)	
2	7 (35%)	22 (27.9%)		7 (35%)	6 (30%)	
≥3 Segments	2 (10%)	10 (12.7%)		2 (10%)	0 (0%)	
Histology of background liver			0.970			1.000
Cirrhosis, n (%)	7 (35%)	51 (64.6%)		7 (35%)	7 (35%)	

to compare medians, proportions, and time-to-event data, taking into account stratification by matched pairs.

Comparison between LRLR versus LLR

Multivariable models were used to minimize confounding by the following covariates: age, gender, tumor size, number of segments involved, hepatitis B status, the presence of cirrhosis, and difficult posterosuperior location. Pre- and perioperative variables shown in Table 3 were analyzed using tests for independent samples; accordingly, the Mann–Whitney U test and Fisher's exact test were, respectively, employed to compare medians and proportions. Quantile, logistic, and Cox regression models, respectively, were performed to compare conditional medians, proportions, and time-to-event outcomes in Table 4.

Time-to-event outcomes were analyzed using Kaplan–Meier methods, while median follow-up was calculated using the reverse Kaplan–Meier for overall survival. All comparisons with a two-sided nominal $P < .05$ were considered statistically significant. Stata (version 13, StataCorp) was used for analyses.

Results

During the study period, 20 consecutive patients underwent LRLR for rHCC of which 18 cases (90%) were performed by a single surgeon (Goh BK). The patients' baseline demographics, perioperative outcomes, and oncologic outcomes are summarized in Tables 1, 2, 3, and 4. LRLR included two major hepatectomies (one central and one left), two right posterior sectionectomies (segment 6/7), one left lateral sectionectomy, and four non-anatomic resections of two segments. The remaining resections were single segment anatomical or wedge resections. Thirteen of 20 LRLR had previous open liver resections. There were

Table 2 Propensity score-adjusted and 1:1 propensity score-matched comparisons between the perioperative and oncologic outcomes of patients who underwent open versus laparoscopic liver reresections for recurrent HCC

	Propensity score-adjusted comparison			Propensity score-matched comparison		
	Laparoscopic (n = 20)	Open (n = 79)	Adjusted P value	Laparoscopic (n = 20)	Open (n = 20)	P value
Median operating time, min (IQR)	315 (181.25–395.0)	160 (115–217.5)	**<0.001**	315 (181.25–395.0)	125 (98.75–183.75)	**<0.001**
Median blood loss, mL (IQR)	200 (100–425)	300 (150–500)	0.641	200 (100–425)	250 (125–475)	0.345
Perioperative blood transfusion, n (%)	2 (10%)	9 (11.4%)	0.906	2 (10%)	1 (5%)	0.560
Median blood transfusion, mL (range)*	3600, 250	660 (300–3600)	NC	3600, 250	300	NC
Pringle maneuver applied, n (%)	4 (20%)	16 (20.3%)	0.948	4 (20%)	5 (25%)	1.000
Median duration of Pringle maneuver, min (IQR)	40 (27.5–52.5)	20 (15–30)	0.397	40 (27.5–52.5)	25 (20–30)	0.2050
Median postoperative stay, d	4 (3–5)	7 (6–9)	**0.002**	4 (3–5)	7.5 (6–9.75)	**0.001**
Postoperative morbidity, n (%)	2 (10%)	22 (27.9%)	0.681	2 (10%)	5 (25%)	0.724
Postoperative major (> grade 2) morbidity, n (%)	0 (0%)	7 (8.9%)	0.915	0 (0%)	1 (5%)	0.480
Reoperations, n (%)	0 (0%)	0 (0%)	1.000	0 (0%)	0 (0%)	1.000
Postoperative 30-day/in-hospital mortality	0 (0%)	8 (10.1%)	0.489	0 (0%)	2 (10.0%)	0.560
Microvascular invasion, n (%)	0 (0%)	15/71 (21.1%)	**0.028**	0 (0%)	3 (15%)	0.248
High tumor grade, n (%)	6 (30%)	33 (48.5%)	0.413	6/18 (33.3%)	7/17 (41.2%)	1.000
Resection margin < 1 mm, n (%)	1 (5%)	6 (8.6%)	0.330	1 (5%)	3 (15%)	0.617

Bold values are statistically significant ($P < 0.05$)

*Volume of blood transfusion for individual patients is presented in the laparoscopic reresection group
NC not calculated, *NR* not reached

three open conversions (15%) including one for intraoperative bleeding and one for inability to localize tumor. The third conversion was in a patient with severely cirrhotic liver which was converted to open resection. However, due to severe cirrhosis, open resection was abandoned and intraoperative microwave ablation was performed. There were no major postoperative morbidities or mortalities.

Comparison between LRLR versus ORLR for rHCC

Comparison between the baseline demographic and preoperative data of patients who underwent LRLR versus ORLR demonstrated that patients who underwent LRLR were significantly older and less likely to have hepatitis B compared to ORLR (Table 1). Propensity score-adjusted analyses demonstrated that LRLR was significantly associated with a longer operation time but shorter length of stay (Table 2).

After 1:1 propensity score matching, there was no difference between the baseline characteristics between patients who underwent LRLR versus ORLR (Table 1). Comparison between perioperative outcomes similarly demonstrated similarly that LRLR was significantly associated with a longer operation time but shorter postoperative stay (Table 2). Both propensity score-adjusted and propensity score-matching analyses demonstrated that LRLR was associated with a significantly longer disease-free survival compared to ORLR (Figs. 1 and 2).

Comparison between LRLR versus LLR

Comparison between the baseline characteristics of patients who underwent LRLR for rHCC versus LLR for primary HCC demonstrated that patients who underwent LRLR were significantly more likely to be older, had a higher ASA score and smaller tumor size (Table 3). Comparison between outcomes demonstrated that LRLR was associated with a significantly longer operation time and decreased frequency of application of the Pringle maneuver.

Discussion

Today, LR is the standard curative treatment for HCC in patients with an adequate liver remnant and preserved liver function [2, 21, 22]. However, intrahepatic tumor

Table 3 Comparison between the baseline demographic and perioperative data of patients who underwent laparoscopic liver reresections for recurrent HCC versus primary resection for primary HCC

	Laparoscopic reresection (*n* = 20)	Initial laparoscopic resection (*n* = 185)	*P* value
Gender, male (%)	18 (90%)	138 (74.6%)	0.125
Median age (IQR), years	68.5 (67–72.5)	63 (57–70)	**<0.001**
Hepatitis B, *n* (%)	10 (50%)	91 (49.2%)	0.945
ASA score, *n* (%)			**0.047**
1	0 (0%)	23 (12.4%)	
2	13 (65%)	132 (71.4%)	
3	7 (35%)	30 (16.2%)	
Median tumor size, mm (IQR)	20 (11–28.5)	28 (20–42)	**0.006**
Multiple tumors, *n* (%)	1 (5%)	26 (14.1%)	0.235
Type of lap resection, *n* (%)			0.606
Totally lap	17 (85%)	167 (90.3%)	
Hand-assisted lap	0 (0%)	6 (3.2%)	
Lap-assist	1 (5%)	4 (2.2%)	
Robotic	2 (10%)	8 (4.3%)	
Major hepatectomy, *n* (%)	2 (10%)	20 (10.8%)	0.911
Difficult posterosuperior segments, *n* (%)	7 (35%)	68 (36.8%)	0.877
No. of segments resected			0.950
1/Wedge	11 (55%)	98 (53.0%)	
2	7 (35%)	64 (34.6%)	
≥ 3 segments	2 (10%)	23 (12.4%)	
Histology of background liver			0.210
Cirrhosis, *n* (%)	13 (65%)	93 (50.3%)	

Bold values are statistically significant ($P < 0.05$)

Table 4 Comparison between the perioperative and oncologic outcomes of patients who underwent laparoscopic liver reresection for recurrent HCC versus laparoscopic liver resection for primary HCC

	Laparoscopic reresection (*n* = 20)	Initial laparoscopic resection (*n* = 185)	Adjusted *P* value
Open conversion, *n* (%)	3 (15%)	27 (14.6%)	0.912
Median operating time, min (IQR)	315 (172.5–400)	225 (150–310)	**0.035**
Median blood loss, mL (IQR)	200 (100–450)	300 (100–700)	0.191
Perioperative blood transfusion, *n* (%)	2 (10%)	42 (22.7%)	0.125
Median blood transfusion, mL (IQR)	3600, 250	530 (330–1200)	NC
Pringle maneuver applied, *n* (%)	4 (20%)	79 (42.7%)	**0.025**
Median duration of Pringle maneuver, min (IQR)	40 (25–55)	40 (25–60)	0.943
Median postoperative stay, d (IQR)	4 (3–5)	4 (3–6)	0.347
Postoperative morbidity, *n* (%)	2 (10%)	35 (18.9%)	0.613
Postoperative major (> grade 2) morbidity, *n* (%)	0 (0%)	6 (3.2%)	0.414
Reoperation, *n* (%)	0 (0%)	3 (1.6%)	0.566
Postoperative 30-day/in-hospital mortality, *n* (%)	0 (0%)	3 (1.6%)	0.507
Microvascular invasion, *n* (%)	0 (0%)	2 (1.1%)	0.599
High tumor grade, *n* (%)	6 (30%)	63 (34%)	0.232
Resection margin < 1 mm, *n* (%)	1 (5%)	7 (3.8%)	0.838

Bold values are statistically significant ($P < 0.05$)

*Volume of blood transfusion for individual patients is presented
NC not calculated

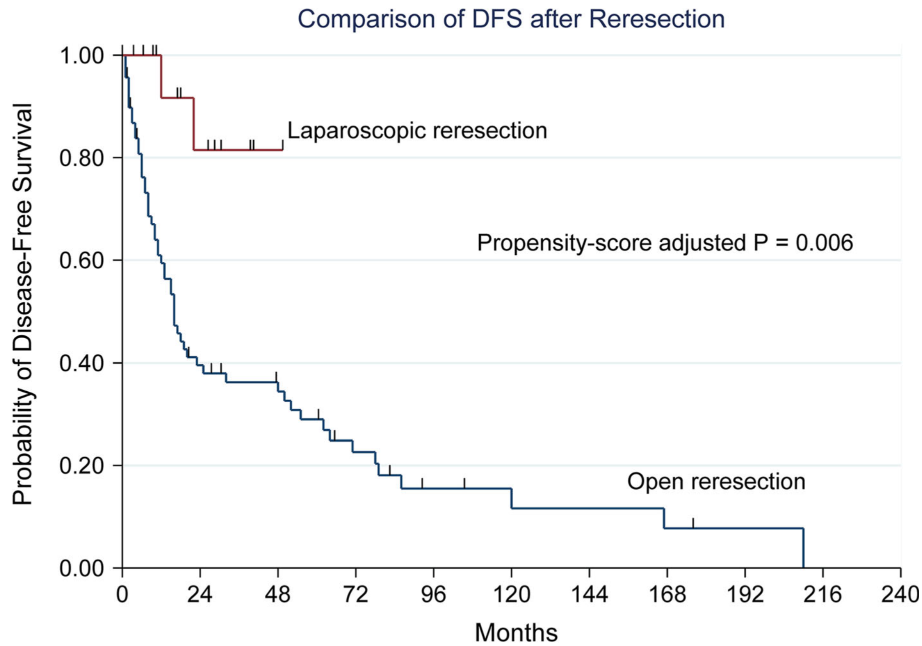

Fig. 1 Propensity score-adjusted comparison of DFS between LRLR versus ORLR

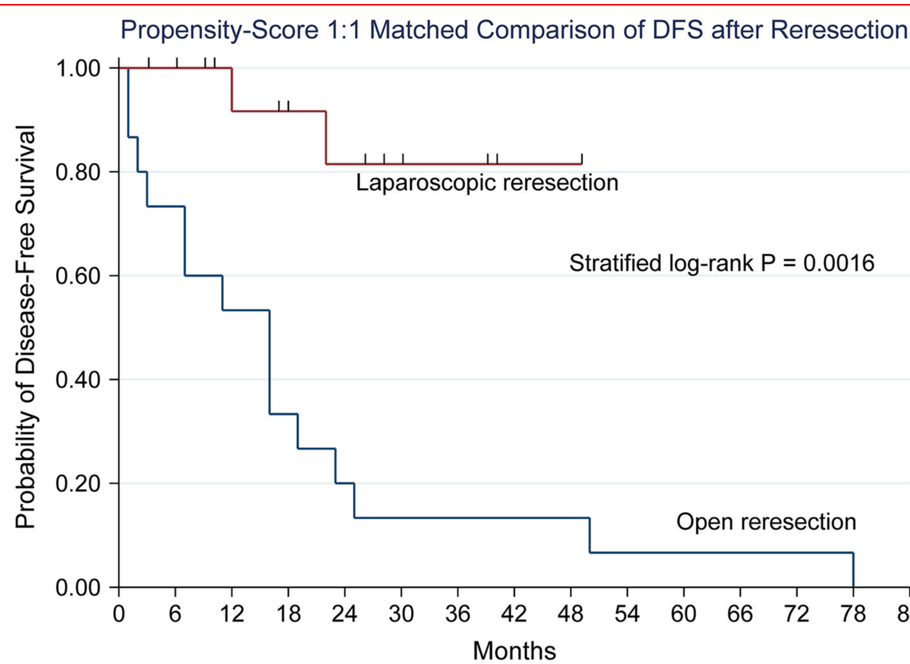

Fig. 2 Propensity-matched comparison of DFS between LRLR versus ORLR

recurrence after LR is common [1, 22]. RLR is now also widely accepted as an effective treatment modality for rHCC in patients with adequate liver function [3, 5, 6]. It has been proven to be safe with excellent postoperative morbidity and mortality outcomes when performed in well-selected patients [3, 5, 6]. LLR for HCC has been increasingly adopted over the past decade, and it has been shown to be superior to open LR in terms of short-term perioperative outcomes such as decreased postoperative stay, blood loss, and pain while producing comparable long-term oncologic outcomes [9–11]. However, although numerous studies [9–11] have reported on the outcomes of LLR for primary HCC, the vast majority of studies on RLR for rHCC have been reported in patients undergoing open liver resection [4, 6]. Presently, the role of LRLR for rHCC remains controversial, and there have only been a limited number of small retrospective studies to date [4, 23].

A recent systematic review of ten studies [4] reporting on 103 LRLR demonstrated that it could be safely performed for a variety of patients including patients who had previously underwent initial open LR, previous major hepatectomy, two previous LR, multiple tumors, liver cirrhosis, ipsilateral HCC recurrence, and recurrent cancers located in the difficult posterosuperior segments. To date, only four comparative studies between ORLR versus LRLR have been performed [14, 23–25] demonstrating that LRLR is superior to ORLR in terms of decreased blood loss, and three studies [14, 23, 24] demonstrated a shorter length of stay. LRLR has also been shown to be associated with decreased morbidity, postoperative pain, and time to ambulation. However, only two of these previous studies [14, 23] comparing LRLR versus ORLR were matched-controlled studies of which only one was via propensity score matching [23]. In the present study, we found LRLR to be associated with a shorter postoperative stay at the expense of a longer operation time compared to ORLR for rHCC.

Unexpectedly, we also observed that patients who underwent LRLR had a significantly superior DFS compared to ORLR. This could be due to a Type 1 error due to the relatively small sample size in this study. Furthermore, the factors we used for PSM and PSA analyses were primarily preoperative factors which could potentially influence perioperative outcomes such as patient age, tumor size, and resection type or extend as this was the primary focus of this study. Hence, several important pathological factors which would influence oncological outcomes were not corrected for such as the presence of microvascular invasion, multiple tumors, and higher tumor grade. These three factors occurred more frequently in the ORLR cohort which could explain the poorer DFS observed in this group compared to LRLR.

LRLR for rHCC is frequently associated with a high technical complexity due to the combination of dense adhesions and the presence of cirrhosis [14, 23]. The risk of bleeding and bowel injury is especially significant in cirrhotic patients as the adhesions are frequently dense with increased vascularity [4, 5, 24]. Furthermore, the distortion of liver anatomy due to liver atrophy/hypertrophy after previous resection further complicates the liver resection [23]. Hence, not unexpectedly, there are limited reports on the role of LRLR for rHCC today [4, 23]. Previous authors have also demonstrated not unexpectedly that the adhesions were denser if the primary resection was performed open compared to laparoscopy [4, 5]. Moreover, contrary to popular perception, some authors have proposed several theoretical advantages associated with LRLR such as minimization of the disruption of collateral blood/lymphatic flow in cirrhotic livers with portal hypertension compared to open surgery and the decreased need for extensive adhesiolysis as certain adhesions may be circumvented by laparoscopic equipment without compromising the operative view [12, 23, 24]. Some authors have also suggested that the performance of more precise lysis of adhesions may be facilitated by the high resolution and magnified view of modern laparoscope cameras together with the introduction of pneumoperitoneum which results in stretching and tension of adhesion bands [4].

We acknowledge several potential limitations associated with this retrospective non-randomized study. Firstly, as in all non-randomized retrospective studies, selection bias is a potential confounding factor. Nonetheless, by performing a propensity-matched and propensity-adjusted comparison between both LRLR and ORLR groups we minimized this selection bias. Secondly, the small sample size in the LRLR may also have given rise to Type 1 or 2 errors. Finally, surgeon bias may also contribute to these results as 18 of the 20 cases (90%) in the LRLR were performed by a single surgeon, whereas the LLR and ORLR cases were by a large group of surgeons.

In conclusion, the results of this propensity matched and adjusted analyses demonstrate that in highly selected patients; LRLR for rHCC is feasible and safe. LRLR is associated with a shorter hospitalization but longer operation time compared to ORLR for rHCC. Moreover, other than a longer operation time, LRLR was associated with similar perioperative outcomes compared to LLR for primary HCC.

Author contributions BKG contributed to conception and design, analysis and interpretation of data, drafting of article, and final approval. NS worked for data acquisition, analysis and interpretation of data, and critical revision. JYT, SYL, CYC, and PCC were involved in data acquisition, conception and design, analysis and interpretation of data, critical revision of article, and final approval. YXG worked for data acquisition, analysis and interpretation of data, critical revision, and final approval. PKC performed analysis and interpretation of data, critical revision of article, and final approval. LLO contributed to conception and design, analysis and interpretation of data, critical revision of article, and final approval. AYC involved in data acquisition, conception and design, acquisition, analysis and interpretation of data, drafting of article, and final approval.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest or declarations in relation to this study.

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