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REVIEW ARTICLE

Short-term outcomes of laparoscopic repeat liver resection after open liver resection: a systematic review

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Abstract

Background Laparoscopic repeat liver resection (LRLR) still represents a challenge for surgeons especially in case with previous open liver surgery. The aim of the study is to perform a systematic review of the current literature to investigate the feasibility of LRLR after open liver resection (OLR) for liver diseases.

Methods A computerized search was performed for all English language studies evaluating LRLR. A meta-analysis was performed to evaluate the short-term outcomes in comparative studies between LRLR with previous laparoscopic liver resection (LLR) and OLR.

Results From the initial 55 manuscripts, 8 studies including 3 comparative studies between LRLR after OLR and LLR were investigated. There was a total of 108 patients. Considering initial surgery, the extent of initial liver resection was major liver resection in 20% of patients in whom it was reported. In all the patients, the most frequent primary histology was hepatocellular carcinoma, followed by colorectal liver metastasis. A half of reported patients had severe adhesions at the time of LRLR. The median operative time for LRLR was ranged from 120 to 413 min and the median blood loss ranged from 100 to 400 mL. There were 11% of the patients conversions to open surgery, hand-assisted laparoscopic surgery, or tumor ablation. The overall postoperative morbidity was 15% of all the patients, and there was no postoperative mortality. The median postoperative hospital stay was ranged from 3.5 to 10 days. The meta-analysis shows that LRLR after OLR is associated with a longer operative time and a more important blood loss compared to LRLR after LLR. However, no difference between LRLR after OLR and LLR was shown as far as hospital stay and morbidity rate are concerned.

Conclusions LRLR after OLR has been described in eight articles with favorable short-term outcomes in highly selected patients.

Keywords Laparoscopy · Repeat liver resection · Repeat hepatectomy · Redo liver surgery · Previous open liver resection · Short-term outcomes

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The number of laparoscopic liver resections (LLRs) has increased steadily since The First International Consensus Conference on Laparoscopic Liver Surgery (Louisville 2008) [1]. Additionally, The Second International Consensus Conference on Laparoscopic Liver Resection (Morioka 2014) defined the current role of LLR and developed relevant recommendations [2]. The improvement in surgical outcomes and more efficient systemic treatments have increased the number of patients eligible for repeat liver resection in case of recurrent diseases. Two single center studies reported that open repeat liver resection is effective for recurrent hepatocellular carcinoma (HCC) [3] and colorectal liver metastases (CRLM) [4]. In contrast, although there has been increasing attention given to LRLR, there is still an insufficient number

of reports describing the feasibility of this technique for resectable liver diseases recurrences. Repeat liver resection has inherent surgical challenges (e.g., adhesions and altered anatomy as a result of the previous resection), which could delay its diffusion and implementation in clinical practice. Laparoscopic repeat liver resection (LRLR) was discussed at the first European Guidelines Meeting on Laparoscopic Liver Surgery (Southampton 2017) [5]. In the consensus guideline of the meeting, it was described that redo liver surgery could be an appropriate option and experts suggested that an initial laparoscopic resection may facilitate repeated resections by limiting the amount of adhesions, thereby providing an important advantage. Additionally, a recent review has provided some evidence regarding the feasibility of LRLR [6], but it is not obviously clarified the specific difficulties and results in patients with previous open liver resection (OLR) who seems to have more severe adhesion than those with previous LLR.

The aim of this study is to review the current literature on perioperative and short-term outcomes of LRLR after previous OLR and to analyze comparative studies between LRLR after previous OLR and LLR.

Materials and methods

Aims of the study

i. Primary aim: to combine, weigh, and summarize the current evidence regarding the short-term outcomes of LRLR after OLR by means of a systematic review.
ii. Secondary aim: to perform a meta-analysis evaluating the short-term outcomes in comparative studies between LRLR with previous LLR and OLR.

Search strategy and general considerations

This systematic review was conducted for all studies published from January 1, 2000, to August 31, 2018, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. Pubmed, Embase, the Cochrane Library were searched, using the following search strategy (laparoscopic [Title] OR laparoscopy [Title] OR minimally [Title]) AND (repeat liver [Title] OR repeat hepatectomy [Title] OR liver recurrence [Title] OR redo liver surgery [Title]) and their associated combinations of controlled vocabulary (medical subject heading-MeSH) terms. The final search was performed on September 15, 2018. There was no need to obtain approval from the local Institutional Review Board or written consent from patients because no data of patients from our hospital was needed for the current review.

Study selection

A flowchart of selected studies is shown in Fig. 1. Inclusion criteria were as follows: human studies, English language, and case series and comparative study in which the patient underwent at least one previous OLR. Exclusion criteria were as follows: animal or experimental study, review, case report, letter, editorial, articles focused on local–regional therapy (radiofrequency or transarterial chemoembolization), and article with insufficient data of the following objects. Review articles were examined for potential additional references. Duplications were identified by matching both author's names and publication centers. In cases where the last manuscript from a center was a global series, the previous manuscripts were considered as duplications and were not included in final count. After the initial screening, full text versions of the selected manuscripts were obtained. Two reviewers (TW and EF), and an independent third one (PP) in case of match, individually assessed each manuscript and rejected those that failed to meet the inclusion criteria.

Definitions

Considering the aims of our study, the following definitions and patterns were considered:

i. Every manuscript was fully screened to evaluate if results on LRLR after OLR from more than one series could be obtained. Therefore, series from some manuscripts that included independent results were differentiated and individually analyzed.
ii. The resection type was based on the Brisbane 2000 terminology [8] with minor resections involving two or less Couinaud segments and major resections involving three or more continuous Couinaud segments.
iii. All case series selected were performed using a laparoscopic approach, including pure laparoscopic and hybrid/laparoscopy-assisted procedures.

Variables and endpoints (endpoints in italics)

i. Variables: number of patients, sex, presence of previous major resection, primary histology, number of patients who underwent neoadjuvant chemotherapy, number of cirrhotic patients, number of patients who have ipsilateral recurrence, surgery interval (months)
ii. Short-term outcomes (perioperative parameters): *laparoscopic approach, extent of LRLR, adhesion grade,*

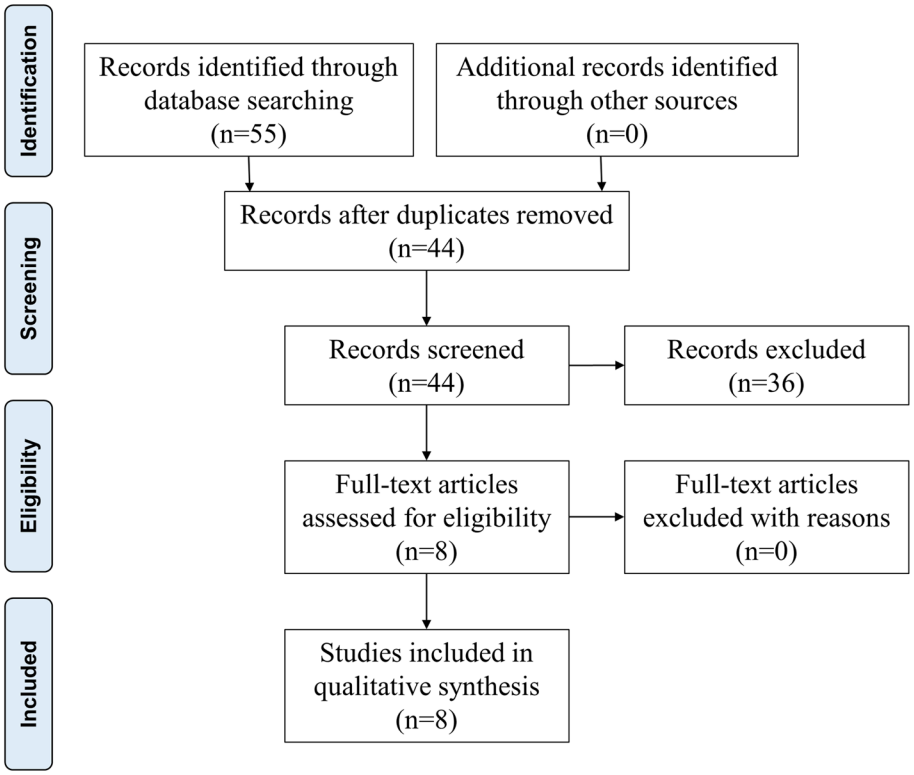

Fig. 1 Study selection

operative time (minutes), blood loss (mL), number of patients requiring conversion

iii. Short-term outcomes (postoperative parameters): *total number of early complications, postoperative hospital stay (days), R0 resection rate (%).*

Quality assessment of the studies included in the meta-analysis

i. *First quality assessment* The first quality assessment was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) [9], methodology that was developed to produce evidence-based clinical guidelines for the National Health Service (NHS).

ii. *Second quality assessment* The second quality assessment was performed in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies (Ottawa Hospital Research Institute) available at http://www.ohri.ca/programs/clinicalepidemiology/oxford.htm. The criteria for "representativeness of cases" were considered as consecutive or obviously representative series of cases without a potential selection bias. Specifically, no star was given if it was > 10 years (due to potential technical bias). Similarly, equal distribution of liver function or presence of liver cirrhosis was an inclusion criteria to be given a star. For the rating of "Control for important factor", two stars were given if patients with previous LLR and OLR were comparable by: age, sex, and extent of LRLR. If any of these factors was not specifically mentioned or not correctly matched, only one star was given.

Statistical analysis

Considering that none of the studies included were randomized trials, Meta-analysis of Observational Studies in Epidemiology guidelines were used for the analysis and data depiction of meta-analyses and systematic reviews of all the studies included in the present manuscript [10]. A meta-analysis was performed including three comparative series with 67 patients and 59 patients in the previous OLR and the previous LLR groups. Analyses were performed using odds ratios (ORs) with a 95% confidence interval (95% CI) for dichotomous variables and weighted mean differences with a 95% CI for continuous variables. The standard heterogeneity test, the I-square statistic, was used to assess the consistency of the effect sizes, which indicates the percentage of the variability in effect estimates because of true between-study variance rather than within-study variance. All data were calculated using a fixed effects model. The Mantel–Haenszel method was the chosen method for dichotomous variables to avoid the fact that estimates of the standard errors of the effect estimates that are used in the inverse variance methods

may be poor [11]. The value of $P = 0.05$ was considered to indicate statistical significance. The meta-analyses were performed using the software package Review Manager (RevMan, The Cochrane Collaboration), version 5.3. To estimate the mean and standard deviation of a sample on the basis of the sample's reported median and range, we used the method devised in elsewhere [12].

Results

Eligible studies and final count

From the initial 55 manuscripts identified in the searches, 8 studies [13–20] including 3 comparative studies [14, 17, 18] between LRLR after OLR and LRLR after LLR remained after the inclusion and exclusion criteria were applied. A total of 108 unique patients treated with LRLR were identified, of which 67 patients were reported in the three comparative studies, and 41 patients with previous OLR were not compared to patients with previous LLR. Quality assessment was then performed for the three comparative studies (Table 1). The three manuscripts reached a minimum requirement of acceptable quality (by SIGN scoring) and 6 points (by NOS) and considered for the meta-analysis.

Our systematic review on patient baseline characteristics and short-term surgical outcomes

Clinicopathologic outcomes of the eight studies are summarized in Table 2. The 8 studies were performed by various institutions worldwide including 6 in Asia (3 China, 2 Japan, 1 Singapore) and 2 in Europe (Italy and France) (Tables 2, 3). There was a total of 108 reported patients, and the median patient age ranged from 50 to 70 years. There were 47/66 (71%) men reported in five studies [13, 15, 18–20]. Five studies reported 12/59 (20%) patients who underwent a previous major liver resection [15, 16, 18–20], and this ranged from 8 to 33%. Primary histology was reported in the eight studies. Hepatocellular carcinoma (HCC) in 72/99 (73%) patients and colorectal liver metastasis (CRLM) in 27/99 (27%) patients were reported, and the remaining 9 patients had a metastatic disease (renal, ampullary, neuroendocrine, or lymphoma), hepatocellular carcinoma or benign diseases. Three studies reported the patients whose disease was CRLM [16, 18, 20]. Fourteen of those 25 patients (56%) received neoadjuvant chemotherapy (FOLFOX, FOLFIRI, 5-FU plus leucovorin, other combination protocols, or unknown agents). Three studies reported patients with HCC in a cirrhotic liver [16, 17, 20] and 12/29 (41%) patients had a cirrhotic liver in those patients. LRLR was performed for an ipsilateral tumor recurrence in 21/35 (60%) patients (4 studies) [13, 15, 19, 20]. The median surgery interval

Table 1 Quality analysis of three comparative studies including Newcastle-Ottawa and SIGN

Author, Country	Quality assessment by Newcastle-Ottawa Scale								Quality judgment (maximum 9 stars)	Sign
	Selection				Comparability	Exposure				
	Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor	Ascertainment of exposure	Same method to ascertain for cases and controls	Non-response rate		
Liu [14], China	–	*	–	*	**	*	*	*	*******	++ High
Kanazawa [17], Japan	–	*	–	*	*	*	*	*	******	+ Acceptable
Shafaee [18], France	–	–	–	*	**	*	*	*	******	+ Acceptable

Table 2 Summary of the clinicopathologic outcomes from eight studies

Author (year)	N	Sex, M [*n* (%)]	Age, median (range) [years]	Previous major LR [*n* (%)]	Primary histology	NAC [*n* (%)]	Cirrhosis [*n* (%)]	Ipsilateral recurrence [*n* (%)]	Surgery Interval, median (range) [months]	Hospital stay, median (range)/ mean ± SD (day)	Morbidity [*n* (%)]	R0 resection [*n* (%)]
Yu et al. (2018) [13]	13	8 (62)	56 (28–72)	NR	13 HCC	-	NR	8 (62)	NR	9 (6–13)	0 (0.0)[a]	NR
Liu K et al. (2017) [14]	21	NR	NR	NR	21 HCC	–	NR	NR	NR	10 (5–29)	2 (10)	NR
Goh et al. (2017) [15]	6	5 (83)	70 (66–78)	1 (17)	6 HCC	–	NR	4 (67)	47 (6-109)	3.5 (3–8)	1 (17)	6 (100)
Cioffi et al. (2015) [16]	6	NR	NR	1 (17)	4 HCC, 2 CRLM	NR	4 (100)	NR	NR	6.4 ± 2.5[b]	0 (0)	6 (100)
Kanazawa et al. (2013) [17]	15	NR	NR	NR	15 HCC	–	5 (33)	NR	NR	9 (5–15)	1 (7)	NR
Shafaee et al. (2011) [18]	31	20 (65)	62 (35–82)	8 (26)	22 CRLM, 9 unknown[c]	13 (59)	NR	NR	NR	6 (2–21)	9 (29)	NR
Hu et al. (2011) [19]	3	3 (100)	50 (48–55)	1 (33)	3 HCC	–	NR	0 (0.0)	20 (16–36)	6 (4–7)	1 (33)	NR
Wakabayashi et al. (2018) [20]	13	11 (85)	70 (54–88)	1 (8)	10 HCC, 3 CRLM	1 (33)	3 (30)	9 (69)	39 (13–129)	10 (6–46)	2 (15)	11 (85)
Overall	108	47/66 (71)	50–70	12/59 (20)	HCC: 72/99 (73), CRLM: 27/99 (27)	14/25 (56)	12/29 (41)	21/35 (60)	20–47	3.5–10	16/108 (15)	23/25 (92)

CRLM colorectal liver metastasis, *NAC* neoadjuvant chemotherapy, *HCC* hepatocellular carcinoma, *LR* liver resection, *M* Male, *NR* not reported, *SD* standard deviation

[a]Severe perioperative complications reported only

[b]Mean for seven cases including six laparoscopic liver resections and one laparoscopic radiofrequency ablation

[c]Metastatic disease (renal, ampullary, neuroendocrine, or lymphoma), hepatocellular carcinoma or benign diseases

Table 3 Perioperative outcomes from eight studies

Author (year)	*N*	Laparoscopic approach	Extent of LRLR	Severe adhesion	Operative time, median (range)/ mean ± SD, (min)	Blood loss, median (range)/ mean ± SD (mL)	Conversion [*n* (%)]
Yu et al. (2018) [13]	13	13 PLR	10 small hepatectomies (< 3 cm), 3 mass resections (≥ 3 cm)	8 (62)	120 (110–200)	280 (120–360)	1 open (8)
Liu K et al. (2017) [14]	21	NR	NR	6 (29)	205 (68–525)	100 (10–600)	3 open (14)
Goh et al. (2017) [15]	6	5 PLR 1 LAR	2 wedge, 2 segmentectomy, 2 RPS	NR	413 (120–530)	200 (30–5000)	1 open (17)
Cioffi et al. (2015) [16]	6	6 PLR	3 wedge, 1 bisegmentectomy, 2 LLS	5 (83)[a]	220 ± 80[a]	297 ± 134[a]	1 open (17)
Kanazawa et al. (2013) [17]	15	15 PLR	NR	NR	287 (120–658)	199 (69–241)	1 HALS
Shafaee et al. (2011) [18]	31	NR	23 minor resections, 8 major resections	NR	186 (100–570)	400 (0–5000)	4 open (13), 1 tumor ablation (3)
Hu et al. (2011) [19]	3	3 PLR	2 wedge, 1 LLS	3 (100)	120 (115–180)	200 (150–250)	0 (0.0)
Wakabayashi et al. (2018) [20]	13	11 PLR 2 LAR	12 wedge, 1 LLS	NR	346 (212–556)	100 (0–870)	0 (0)
Overall	108	PLR: 53/56 (95), LAR: 3/56 (5)	Minor resection[b]: 61/69 (88)	Severe adhesion[d]: 22/43 (51)	120–413	100–400	Open surgery: 10/108 (9)
			Major resection: 8/69 (12)				HALS: 1/108 (1)
			Unclassified[c]: 3				Tumor ablation: 1/108 (1)

HALS hand-assisted laparoscopic surgery, *LAR* laparoscopic-assisted resection, *LLS* left lateral sectionectomy, *LRLR* laparoscopic repeat liver resection, *PLR* purely laparoscopic resection, *RPS* right posterior sectionectomy, *SD* standard deviation

[a]Number or mean for seven patients including six laparoscopic liver resections and one laparoscopic radiofrequency ablation

[b]Minor resection including wedge, segmentectomy, LLS, RPS and small hepatectomies (< 3 cm)

[c]Three mass resections (≥ 3 cm) are described as unclassified

[d]In four articles which described adhesion grade, stage or grade III/IV are regarded as severe adhesion

between previous OLR and LRLR was reported in three studies [15, 19, 20] and ranged from 20 to 47 months.

The perioperative outcomes of the eight studies are summarized in Table 3. The laparoscopic approach was described in six studies [13, 15–17, 19, 20], and the most common laparoscopic approach attempted among 56 LRLR was the pure laparoscopic approach in 53 (95%) patients. Only 3 (5%) patients underwent laparoscopic-assisted liver resection. Six studies described the extent of LRLR [13, 15, 16, 18–20] and major resection was performed in 8/69 (12%) and minor resection was performed 61/69 (88%). Four studies described adhesion grade using each criteria [13, 14, 16, 19] (their original criteria [13] and the Becker's scale [21]). The scales are divided into four levels, and grades 3 and 4 are commonly considered as severe adhesions in the four studies. Consequently, 22/43 (51%) patients had sever adhesions at the time of LRLR. The median operative time for LRLR was reported in the eight studies, and this ranged from 120 to 413 min. The median blood loss was reported in the eight studies ranging from 100 to 400 mL. There were 12 (11%) conversions including 10 (9%) open, 1 (1%) hand-assisted laparoscopic surgery, and 1 (1%) tumor ablation. The reasons of conversion were severe adhesion (5 patients), hemorrhage (3 patients), failure to progress due to tumors located in the posterior segments or others (3 patients), and unknown (1 patient).

The overall postoperative morbidity was reported in the eight studies, and this was 16/108 (15%). The reported morbidity ranged from 0 to 33%, and there was no postoperative mortality among the 108 patients. The most frequent morbidity was bile leakage (6 patients) followed by ascites (4 patients), postoperative ileus (2 patients), and others (4

patients), and all of them are classified as Clavien–Dindo [22] Grade IIIa or less. The median postoperative length of stay was reported in the nine studies, and this ranged from 3.5 to 10 days. Surgical resection margins were reported in three studies [15, 16, 20], and an R0 margin was achieved in 23/25 (92%).

Our meta-analysis of short-term outcomes for LRLR after OLR

We found that LRLR after OLR is associated with a longer operative time [Q (df = 2) = 4.15, Het. $P = 0.13$; I-squared = 52%; mean difference = 77.90 (39.62 to 116.18); $P < 0.0001$] and a larger amount of blood loss [Q (df = 2) = 15.30, Het. $P = 0.005$; I-squared = 87%; mean difference = 153.49 (61.32 to 245.66); $P = 0.001$] as compared to LRLR after LLR. However, no difference between LRLR after OLR and LLR was shown in terms of hospital stay [Q (df = 2) = 11.37, Het. $P = 0.003$; I-squared = 82%; mean difference = 0.43 (− 1.22 to 2.07); $P = 0.61$] and morbidity rate [Q (df = 2) = 0.92, Het. $P = 0.92$; I-squared = 0%; OR = 1.35 (0.53 to 3.42); $P = 0.53$] (Fig. 2).

Discussion

LLR has achieved noticeable improvements during recent decades. One randomized controlled trial has confirmed that laparoscopic surgery was associated with significantly fewer postoperative complications with cost-effectiveness and an equivalent free resection margin rate as compared to open surgery in patients undergoing parenchyma-sparing liver resection for colorectal metastases [23]. In addition, large propensity score-matching studies have revealed that LLR and OLR had equivalent oncological outcomes. However, LLR provided less blood loss, fewer postoperative

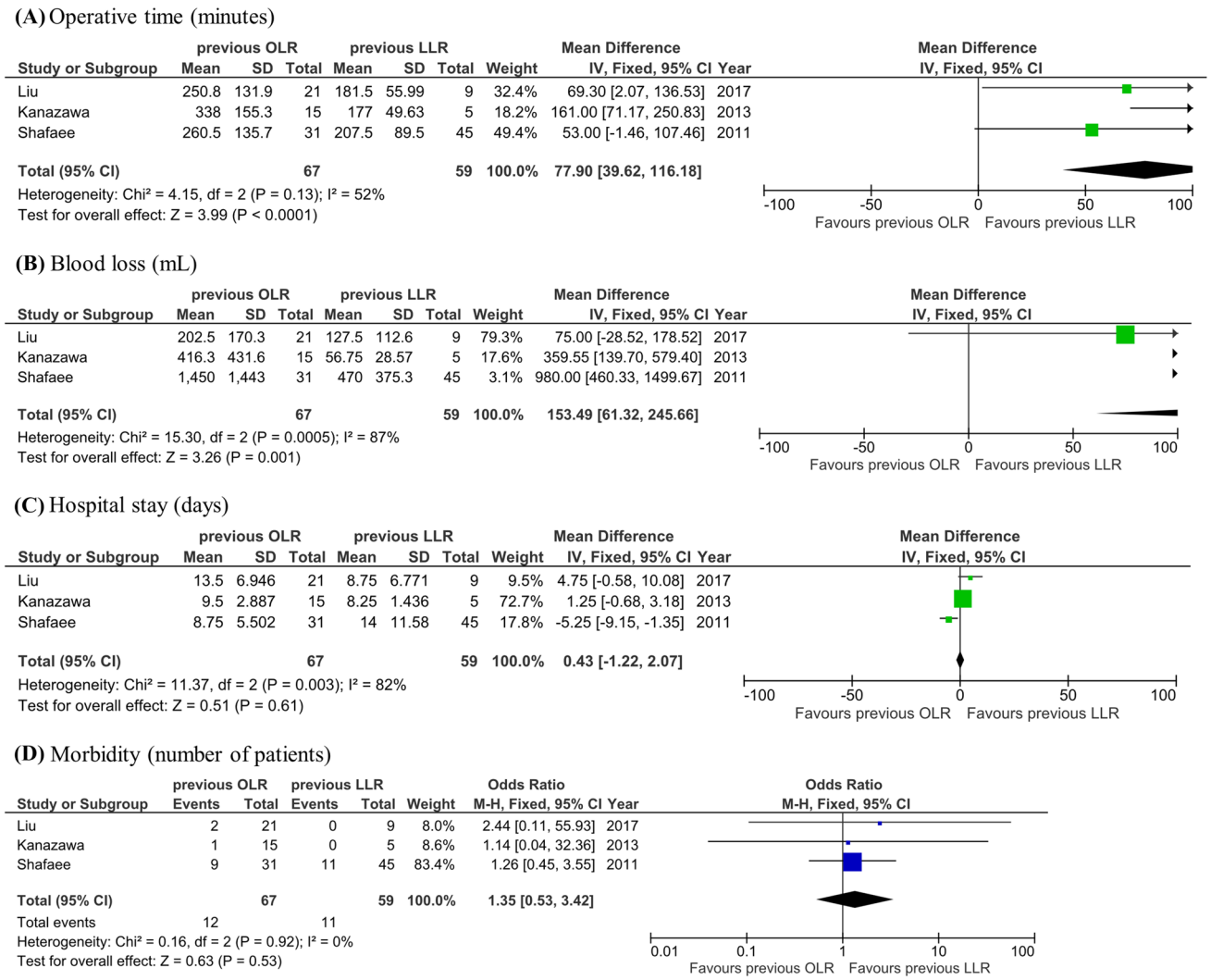

Fig. 2 Results obtained from meta-analysis in three comparative series on perioperative outcomes

complications, and shorter hospital stays in those studies [24, 25]. Moreover, the largest systematic review of LLR including over 9000 cases published, evidenced the growing safety when performed in selected patients and by trained surgeons and suggested that LLR may offer improved short-term patient outcomes when compared to OLR [26].

The improvement in outcomes of surgical, local–regional and systemic treatments has led to increased number of patients eligible for curative repeat liver resection in case of recurrent liver diseases. However, repeat liver resection involves technical challenges and a risk of complications, based on the presence of adhesions and anatomical modifications as a consequence of the previous surgery. Morise reviewed 16 reports of LRLR compared to open repeat liver resection and concluded that LRLR has better short-term outcomes (similar or longer operation time, reduced bleedings, less blood transfusion, less or similar morbidity and shortened hospital stay) with the comparable long-term outcomes [27]. In addition, although two other reviews reported that LRLR for recurrent hepatocellular carcinoma is feasible and safe in highly selected patients, there is still no strong evidence of that as no randomized controlled trial or well-matched case-control studies exist. On the other hand, Shafaee et al. [18] previously mentioned that the optimal candidates for laparoscopic repeat resections are those with previous laparoscopic resections, rather than open resections, and no solid conclusion has not been established on this fact. In order to clarify the current boundary of indication for LLR, we aimed to review the published case with short-term outcomes for patients who underwent LRLR after previous open resections and performed the meta-analysis to compare those between LRLR after previous OLR and LLR. To our knowledge, this is the first review which focuses on the results of LRLR for patients who were previously operated on by means of open liver surgery.

The present systematic review of 108 patients from the eight studies demonstrates that LRLR can be safely performed for selected patients. However, the articles included in the systematic review are supposed to have potential selection biases. Possible selection biases for LRLR after OLR in the current review are tumor location, tumor size, tumor number, vascular involvement, liver function, extent of previous liver resection, tumor numbers, and concomitant resection of other organs. Of these articles, three studies described tumor location as an inclusion criteria [13, 16, 19]; as it is generally considered as "easier" when located in the anterior hepatic segments (Segments II, III, IVb, V, VI), while caudate lobe and posterosuperior segments which are difficult to visualize were excluded in those articles. In addition, exophytic or subcapsular lesions are also considered as favorable indications for LRLR, although deep lesion was considered as suitable for laparoscopic radiofrequency ablation since major LRLR is not recommended [16]. Two studies described patients with tumors with a maximum diameter of 4 to 5 cm or less than 5 cm as an inclusion criterion for LRLR [16, 19]. Two studies mentioned the importance of the number of tumors, and only patients with one or two tumors are included in those studies [14, 20]. Vascular risk was considered in three studies as an inclusion criterion [13, 14, 19], with no involvement of major blood vessels or the bile duct by the tumor. In three studies, only liver function of Child-Pugh grade A was considered an inclusion criteria [13, 14, 16] while only one article described Child-Pugh B as an inclusion criteria [19] and no report described Child-Pugh C as an inclusion criteria. Additionally, one study reported that no previous hemihepatectomy and no concomitant resection of other organs would be an inclusion criteria for LRLR after OLR [20]. Our meta-analysis partially implies that LRLR after OLR might be comparable to LRLR after LLR, although operative time was significantly longer and blood loss was significantly larger, which are compatible with previous articles [5, 16, 28]. However, additional studies including a larger number of patients are strongly required to substantiate our results.

Regarding the technical aspect of LRLR, several authors suggestively summarize the theoretical advantages of laparoscopy compared to open procedures [15, 27, 29–31], as it facilitates more meticulous dissection of adhesions strained by the pneumoperitoneum using a magnified laparoscopic view [27]. A second consideration is that there is a decreased need for extensive adhesiolysis as certain adhesions may be circumvented by laparoscopic equipment without any separation and without compromising the operative view [29, 30]. Laparoscopy requires a smaller working space between adhesions and this allows minimal adhesiolysis, reducing operative time and bleeding [27], and minimization of the disruption of collateral blood/lymphatic flow seen in cirrhotic livers with portal hypertension [15, 31].

The main limitation of this review was that all the studies included were retrospective cohort studies with a small sample size, and only three studies were included in the meta-analysis. In addition, the I-squared values, as an indicator of heterogeneity, were significantly high (over 75%) in two parameters (blood loss and hospital stay). Hence, it is imperative to highlight that the findings of this article should be interpreted with caution. It is also likely that the presented results in the current article were affected by selection and publication bias. LRLR after OLR was most likely to be performed in highly selected patients and performed in experienced centers. Additionally, centers with good results are more likely to report their outcomes compared to centers with less favorable outcomes. Hence, LRLR after OLR cannot be a routine procedure in the usual clinical setting for the moment since there is still no strong evidence for this procedure.

In conclusion, LRLR after OLR has been described in eight articles with case series which demonstrate favorable short-term outcomes. In highly selected patients, LRLR after OLR might be feasible although a longer operative time and a larger blood loss are described, probably as a consequence of severe adhesions and altered anatomy. Further studies preferably in the form of randomized controlled trials or well-matched case-control studies with a larger number size are required to corroborate these findings.

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Compliance with ethical standards

Disclosures Dr. Taiga Wakabayashi, Dr. Emanuele Felli, Dr. Riccardo Memeo, Dr. Pietro Mascagni, Dr. Yuta Abe, Dr. Yuko Kitagawa, and Dr. Patrick Pessaux have no conflicts of interest or financial ties to disclose.

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