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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

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Long-term survival outcome of laparoscopic liver resection for hepatocellular carcinoma

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Abstract

Long-term survival is the most important outcome measurement of a curative oncological treatment. For hepatocellular carcinoma (HCC), the long-term disease-free and overall survival of laparoscopic liver resection (LLR) is shown to be non-inferior to the current standard of open liver resection (OLR). Some studies have reported a superior long-term oncological outcome in LLR when compared to OLR. It has been argued that improvement of visualization and instrumentation and reduced operative blood loss and perioperative blood transfusion may contribute to reduced risk of postoperative tumor recurrence. On the other hand, since most of the comparative studies of the oncological outcomes of LLR and OLR for HCC are non-randomized, it remained inconclusive as to whether LLR confers additional survival benefit compared to OLR. Despite the paucity of level 1 evidence, the practice of LLR for HCC has gained wide-spread acceptance due to the reproducible improvements in the perioperative outcomes and non-inferior oncological outcomes demonstrated by large-scaled, matched comparative studies. Meta-analyses of the outcomes of these studies by multiple systematic reviews have also returned noncontradictory conclusions. On the basis of a theoretical advantage of LLR over OLR in preventing tumor recurrence, the current review aims to dissect from the current meta-analyses and comparative studies any evidence of such superiority.

Key Words: Hepatocellular carcinoma; Laparoscopic hepatectomy; Liver resection; Long-term outcome; Overall survival; Disease-free survival

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Core Tip: Laparoscopic liver resection (LLR) resulted in better perioperative outcomes when compared with open liver resection. However, for long-term outcomes, the

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reported ranges of disease-free survival rate and overall survival rate at 5 years after LLR of hepatocellular carcinoma (HCC) can be as wide as 20%-64% and 47%-95%, respectively. This reflects the heterogeneity of clinical practice and outcome reporting. The purpose of this review is to elucidate the true picture of the oncological efficacy of LLR in the treatment of HCC by critical appraisal of current evidence including meta-analyses and comparative studies.

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INTRODUCTION

Laparoscopic liver resection (LLR) is widely practiced nowadays for the treatment of hepatocellular carcinoma (HCC). The practice of LLR has propagated on the basis of recommendations by the three international consensus statements published in 2008, 2015 and 2018[1-3]. As of the latest recommendation from the 2018 Southampton consensus[3], LLR is preferred over open liver resection (OLR) in selected cases of HCC because of its better early postoperative outcomes and non-inferior oncological outcomes. This recommendation is supported by findings of meta-analyses and large propensity score-matched retrospective studies comparing LLR and OLR for HCC.

As a curative oncological treatment, disease-free and overall survival are the most important outcome measures of LLR. The reported ranges of disease-free survival rate and overall survival rate at 5 years after LLR of HCC can be as wide as 20%-64% and 47%-95%, respectively. This reflects the heterogeneity of clinical practice and outcome reporting. The purpose of this review is to elucidate the true picture of the oncological efficacy of LLR in the treatment of HCC by critical appraisal of current evidence including comparative studies and meta-analyses. Robotic surgeries and single-port surgeries were excluded because they involved different sets of skills and complexity of operations.

COMPARATIVE STUDIES

It appears to be true that LLR has a non-inferior oncological outcome compared to OLR for HCC – a finding supported by multiple comparative studies, despite the presence of heterogeneity of treatment effect among the studies.

In general terms, the survival outcome of a cancer treatment program is a function of the disease spectrum of patients included and the adequacy of treatment delivery. For HCC, predictors of long-term survival after resection of HCC include factors relating to tumor extent (size, number, macrovascular invasion), tumor biology (microvascular invasion, differentiation grading, serum alpha-fetoprotein level, *etc.*), ongoing liver damage and technical success of surgery (resection margin, perioperative transfusion, anatomical resection)[4]. With accumulation of worldwide experience in LLR, reports to address such factors in the practice of LLR have also been published.

Prior to 2018, all studies comparing outcomes of LLR and OLR were non-randomized[5-14]. Selection bias has been a significant concern, especially in the earlier cohorts, in which patients included for LLR tended to have more favorable disease for oncologically adequate resections (tumor size, location, width of tumor-free margin)[5]. Later studies have attempted to ameliorate the impact of selection bias by matching of baseline patient characteristics such as demographic features, tumor status, degree of cirrhosis, American Society of Anesthesiologists (ASA) class, procedure types *etc.* in the LLR and OLR group. Nevertheless, a wider resection margin is often observed in the resected specimens from the LLR group. As acknowledged by Belli *et al*[5], this could be due to the selection of tumors with greater distance of tumor from the vital vasculature for LLR – an important preoperative consideration that is difficult to quantify for the performance of matching. Interestingly, such difference is less frequently observed in the more recent reports,

probably due to the more liberal inclusion of patients for LLR with accumulation of technical experience (Tables 1 and 2).

After 2018, 21 comparative studies of LLR *vs* OLR for HCC can be identified [15-35] (Tables 1-4). Only one was a randomized controlled trial [18], while the rest were non-randomized. Studies with special focus of patient population included major hepatectomy in six, minor hepatectomy in one, cirrhosis in four, small tumors in two, multiple tumors in one and elderly patients in one. All but three of the non-randomized studies adopt propensity score-matching (Table 3). Sporadic differences between the LLR and OLR group were still identifiable in some reports, including: Tumor size in the studies by Li *et al* [25] and Tsai *et al* [23]; prevalence of cirrhosis in the study by Guro *et al* [17]; ASA class in the study by Yoon *et al* [29] and procedure magnitude in the study by Tsai *et al* [23].

The only randomized controlled trial was performed in Egypt [18]. They included patients with Child's A solitary HCC equal to or less than 5 cm, located in the peripheral segments of the liver II-VI, at a distance from the line of transection, hepatic hilum, and the vena cava and treatable by limited resection (< 3 segments). Exclusion criteria were tumors close to the portal pedicle or hepatic veins, located in segments I, VII and VIII, an ASA score exceeding 3, a decompensated cirrhosis (Child B or C), esophageal varices grade > 2, and a platelet count < 80 × 10⁹/L, and patients with previous upper abdominal surgeries. On sample size calculation, a total of 42 patients was required in the study to detect a change of mean hospital stay duration from 8.5 d among patients subjected to OLR to 4.0 d among patients subjected to LRR. The estimated sample size was made assuming 95% confidence interval (CI) and 80% power of study. Eventually, they recruited a total of 50 patients with 25 patients in each group. The LLR group achieved similar disease-free survival to the OLR group (*P* = 0.849). The 1- and 3-year disease-free survival was 88% and 59%, and 84% and 54% for the LLR and OLR groups, respectively. However, survival outcomes were secondary endpoints, with such a small sample size, these survival outcomes were subject to type II error.

Apart from two studies by Tsai *et al* [23] and Ho *et al* [35], all of the oncological outcomes at various time spans were not statistically different. For LLR, the reported ranges of 1-, 3- and 5-year overall survival and disease-free survival were 89.9%-100%, 68%-100% and 45.3%-94.5%, and 67%-93.8%, 36%-79.6% and 24%-67.4%, respectively. In the study by Tsai *et al* [23], the group categorization did have some bias because of the earlier stage of HCC (stage I + II: 85.0% *vs* 57.4%; *P* < 0.001) and lower rate of major resection (22.2% *vs* 45.6%; *P* < 0.001) in the LLR group compared with the OLR group. When long-term oncological outcomes of the LLR and OLR group were assessed in terms of stage-specific overall survival and disease-free survival, the result did not differ significantly. On the other hand, in the study by Ho *et al* [35], the 5-year overall survival for LLR was better than OLR (84.9% *vs* 61.1%; *P* = 0.036), but disease-free survival was similar (20.0% *vs* 22.2%; *P* = 0.613). The survival advantage of LLR could be contributed by the five perioperative mortalities in the OLR group, which occurred all in the first half of the hepatectomy experience. In other words, better perioperative outcome of LLR may contribute to better long-term survival outcome.

No qualitative association between the baseline or operative factors and oncological outcomes is immediately appreciable. Of note, transfusion requirement and margin involvement are rare events for both LLR and OLR nowadays in most of the reported series.

META-ANALYSES

Due to the paucity of randomized controlled trial, meta-analyses of non-randomized comparative studies with low risk of bias represented the highest level of evidence until recently. The majority of meta-analyses were published after the Morioka consensus, although evidence of four meta-analyses have been adopted by the consensus [2]. A summary of the findings of these four meta-analyses is provided in the systematic review of Morise *et al* [36] - there is no difference in disease-free and overall survival with LLR or OLR for HCC, a result with low impact of statistical heterogeneity. This is probably because the studies included four meta-analysis of oncological outcome published between the release of Louisville and Morioka consensus statements, when LLRs were mainly performed for resection of lesions in the antero-lateral segments [37-41].

Following the Morioka consensus meeting in 2014, there was a bloom of publications reporting experience worldwide on the practice of LLR for the treatment of

Table 1 Summary of comparative studies: Operative outcomes

Ref.	Blood loss in mL /transfused %			Resection margin in mm			R0 resection rate %		
	LLR	OLR	P	LLR	OLR	P	LLR	OLR	P
Belli <i>et al</i> [5]	297	580	< 0.001				100	93.6	0.057
Tranchart <i>et al</i> [6]	364.3	723.7	< 0.0001	10.4	10.6	NS			
Lee <i>et al</i> [7]	150	240	NS	1.8	1.05	0.016	97	98	NS
Ahn <i>et al</i> [8]	350	355	NS	17	13	NS			
Memeo <i>et al</i> [9]	200	200	NS	10	6	0.02			
Lee <i>et al</i> [10]	300	700	0.004	13	10	0.25			
Yoon <i>et al</i> [11]	3.4%	7.5%	0.04	2.03	1.12	0.01			
Xiao <i>et al</i> [12]	272	450	0.001				100	98	NS
Sposito <i>et al</i> [13]			NS	6	5	NS	98	98	NS
Cheung <i>et al</i> [14]	100	300	< 0.001				100	93.1	NS
Ryu <i>et al</i> [15]							95	83	NS
Rhu <i>et al</i> [16]	13%	2%	NS	13	12	NS			
Guro <i>et al</i> [17]	1543	1248					97.6	94.6	NS
El-Gendi <i>et al</i> [18]	230	250	NS				100	100	NS
Inoue <i>et al</i> [19]	100	380	< 0.0001	7	5	NS			
Kim <i>et al</i> [20]	300	250	NS	13	15	NS			
Deng <i>et al</i> [21]	150	380	< 0.001				98	90	NS
Wu <i>et al</i> [22]	150	250	NS						
Tsai <i>et al</i> [23]	363	839	< 0.001	5	5.2	NS			
Di Sandro <i>et al</i> [24]	150	200	0.007	5	5	NS			
Li <i>et al</i> [25]	328	396	NS						
Kim <i>et al</i> [26]	152	245		8.5	8.4	NS			
Chen <i>et al</i> [27]	300	500	< 0.1				97	100	NS
Untereiner <i>et al</i> [28]	150	250	NS				91	85	NS
Yoon <i>et al</i> [29]	226	251					98	98	
Peng <i>et al</i> [30]	200	300	NS				100	100	NS
Yamamoto <i>et al</i> [31]	87	223		3	3	NS			
Lee <i>et al</i> [32]	19%	28%	NS	9	16.5	NS			
Navarro <i>et al</i> [33]	234	454	0.021				100	100	NS
Delvecchio <i>et al</i> [34]	13%	25%	NS				95	87	NS
Ho <i>et al</i> [35]	500	725	NS	5	3	0.043	91	91	NS

LLR: Laparoscopic liver resection; NS: Statistically not significant; OLR: Open liver resection.

HCC. While level 1 evidence was lacking at that time, strong recommendations were made regarding the non-inferiority of both minor and major LLR in short-term postoperative and long-term outcomes, as the relative benefits of LLR over OLR had appeared to be reproducible in the larger-scaled, propensity score-matched non-randomized comparative studies conducted worldwide[2]. Yet in 2018, the very “concern of selection bias” that is inherent to non-randomized studies was then resolved with the publication of the OSLO-COMET trial, which convincingly showed that LLR has superior perioperative outcomes, non-inferior oncological safety, similar cost and better gain of life quality to OLR for the treatment of colorectal cancer liver metastases[42].

Table 2 Summary of comparative studies: Baseline clinical-pathological features of both treatment groups

Ref.	Difference between study groups	ICG, %		Child A/B/C, %		Tumor size in cm				Microvascular invasion, %	
		LLR	OLR	LLR	OLR	LLR	+/- SD/95%CI	OLR	+/- SD/95%CI	LLR	OLR
Belli <i>et al</i> [5]	Tumor size, AFP level, margin width			91/9/0	93.6/6.4/0	3.8	+/-1.3	6	+/-2.3	37	39.2
Tranchart <i>et al</i> [6]						3.6	+/-1.75	3.7	+/-2.1	33.3	35.7
Lee <i>et al</i> [7]	Cirrhosis, previous abdominal surgery, margin width					2.5	1.5-9	2.9	1.2-9		
Ahn <i>et al</i> [8]		14.5	13.1			2.6	+/-1.5	2.8	+/-1.2	15.7	19.6
Memeo <i>et al</i> [9]	Margin width			98/2/0	96/4/0	3.2	0.9-11	3.7	0.1-15		
Lee <i>et al</i> [10]	Margin width			97.6/2.4/0	97.6/2.4/0	5.4	2-16	4.4	2-14	52.5	43.5
Yoon <i>et al</i> [11]	Margin width	12.1	12.4			2.87	0.7-4.9	3.04	0.2-4.9		
Xiao <i>et al</i> [12]				95/5/0	96.5/3.5/0	4.22	+/-2.05	4.3	+/-1.49		
Sposito <i>et al</i> [13]		15	15	98/2/0	95/5/0	2.6	1-6.5	2.2	1-8.5	56	37
Cheung <i>et al</i> [14]	Age			100/0/0	96.6/3.4/0	3	1.2-5	3.5	1.5-8.5		
Ryu <i>et al</i> [15]		11.9	14			3.9	1.1-17	4.9	1-14.5	30	40
Rhu <i>et al</i> [16]				37.7/0/0	37.1/0/0	3.1	+/-5.7	3.1	+/-1.7	56.6	58.8
Guro <i>et al</i> [17]	Cirrhosis, tumor size			95/2.4/2.4	88/9.9/7.2	4.1	+/-2.4	6.3	+/-3.8		
El-Gendi <i>et al</i> [18]				100/0/0	100/0/0	3.3	+/-0.57	3.4	0.59	60	68
Inoue <i>et al</i> [19]				89/11/0	100/0/0	2.5		2.6		12	13
Kim <i>et al</i> [20]		9.3	8			2.8		2.8		25	23
Deng <i>et al</i> [21]	Procedure type			100/0/0	100/0/0	2.5		2.8		10.2	16.6
Wu <i>et al</i> [22]						3.5	0.9-12.5	3.5	0.8-11.3	38.4	41.9
Tsai <i>et al</i> [23]	Procedure magnitude, tumor size			93/7/0	98/2/0	3.9	+/-2.6	7.2	+/-5.3		
Di Sandro <i>et al</i> [24]				87/13/0	84/16/0	2.5	2-3.0	2.5	1.8-3.3	29.3	29.3
Li <i>et al</i> [25]	Tumor size					4	+/-2	5.7	+/-3	17	30
Kim <i>et al</i> [26]		10.4	12.8			3	+/-2.1	3.2	+/-3.14	22.2	27.8
Chen <i>et al</i> [27]		6.9	6.9			7.3	+/-3.4	7.6	+/-4.2	37	32
Untereiner <i>et al</i> [28]				64/0/0	73/0/0	3	2.1-4.9	3	2.3-5		
Yoon <i>et al</i> [29]	ASA class, medical disease	13.6	14	66.8/0/0	65.4/0/0	2.83	1.28	2.9	1.31	14.3	15.7
Peng <i>et al</i> [30]				94/6/0	91/9/0	4.8	2-8.5	5.5	2-8.5	30	30
Yamamoto <i>et al</i> [31]				88/22/0	84/16/0	1.7	1.2-4.2	2	0.7-9.9		
Lee <i>et al</i> [32]				90/10/0	91/9/0	2.5	7-14.5	2.6	1.1-14.5	8.6	8.6
Navarro <i>et al</i> [33]						3.5	8.5	3.3	8.1	51.2	51.2
Delvecchio <i>et al</i> [34]				97/3/0	98/2/0	4	3.0-16	7	1.5-14		
Ho <i>et al</i> [35]	Hepatitis C carrier status			100/0/0	92/8/0	3.5	2-5	4	3-5	28.9	30

AFP: Alpha-fetoprotein; ASA: American Society of Anesthesiologists; CI: Confidence interval; ICG: Indocyanine green retention at 15 min; LLR: Laparoscopic liver resection; OLR: Open liver resection; SD: Standard deviation.

The question is now left with HCC though, as obvious difference exists between patients with HCC and colorectal liver metastases. As a majority of HCC patients have underlying cirrhosis, liver decompensation and oncological outcomes are HCC-specific outcomes to consider for LLR. Since the first published meta-analysis on the long-term outcomes of LLR for HCC in 2011[43], there have been about 20 meta-analyses on the topic published, 15 of which were published after 2017. Ciria *et al*[44] published a meta-analysis in 2018 that included 28 non-randomized comparative studies with low risk of bias. In contrast to those included by meta-analyses in the “pre-Morioka era”, the studies reviewed by Ciria *et al*[44] encompassed a much wider spectrum of disease in clinical practice: Three were on major liver resection, twenty-two on minor liver resection, five on Child-Pugh class A cirrhosis, sixteen on solitary tumors and three on unstratified operable patients. For the disease-free and overall survival, meta-analyses could only be performed for studies featuring cirrhotic patients, minor hepatectomy and solitary tumors but not for major hepatectomy. The pooled relative effect of LLR to OLR showed an odds ratio (OR) in favor of LLR for 1-year disease-free survival in patients with minor hepatectomy ($I^2 = 66\%$; OR = 0.133; 95%CI: 0.001–0.265; $P < 0.048$). For patients with Child’s A cirrhosis and solitary tumor, no significant relative benefit or harm were found for the 1-, 3- and 5-year disease-free and overall survivals. For patients with major hepatectomy, meta-analysis was not performed due to lack of data. Moderate to high heterogeneity ($I^2 = 17\%$ – 66%) was noted among the studies of laparoscopic minor hepatectomy. The highest heterogeneity is among the five studies for compilation of 1-year disease-free survival ($I^2 = 66\%$), and the biggest discrepancy of mean relative effect lies between the study by Cheung *et al*[14] and Kobayashi *et al*[45]. This is probably related to the inclusion of recurrent HCC and hybrid or hand-assisted laparoscopic procedures in the study population in the study by Kobayashi *et al*[45]. Moreover, two studies with the greatest tendency to favor LLR came from the same center[14,46] with overlapping study period and study population (left lateral sectionectomy in 25% and 100% of studied population), giving rise to the concern of overestimation of the relative benefit of LLR.

The lack of long-term survival data specifically for laparoscopic major hepatectomies in the above meta-analysis was addressed by a recent meta-analysis by Wang *et al*[47] that included nine studies of the patient population. Interestingly, a favorable result for LLR was again noted in 1-year disease-free survival ($I^2 = 0\%$; OR = 1.55; 95%CI: 1.04–2.31; $P = 0.03$), but not in disease-free or overall survival in another analyzed timespan. Again, one of the constituent studies for the pooled analysis of 1-year disease-free survival is notably out-standing with regard to the tumor recurrence rate in the OLR group, and an apparent reason that is also acknowledged by the author was the significantly bigger tumor size (6.3 ± 3.8 vs 4.1 ± 2.4 cm; $P = 0.000$) included in the OLR arm[17].

In contrast to most of the meta-analyses showing non-significant difference in overall survival, Jiang *et al*[48] meta-analyzed studies of cirrhotic patients and found significant relative benefit of LLR in 1-, 3- and 5-year overall survival and 1-year disease-free survival, with only moderate issue of heterogeneity ($I^2 = 36\%$ – 39%). The apparent reason for the discrepancy between that study and Ciria *et al*[44]’s sub-group analyses for cirrhotic patients is that the two reviews included different sets of studies for analyses. The rationale behind study selection is difficult to judge, but Jiang *et al* [48] excluded the study because the data were not retrievable, which could potentially lead to bias. On the other hand, Ciria *et al*[44] only included three studies for the analyses of long-term outcome of cirrhotic patients, which may not be powerful enough to detect small effects.

DISCUSSION

Theoretically, LLR has a few advantages over OLR that may potentially give rise to a superior oncological outcome; these include reduced perioperative transfusion and reduced tumor manipulation. Practically, such an effect has not been convincingly demonstrated in the currently available evidence. An overall improvement in the pre-

Table 3 Summary of comparative studies: Study design

Ref.	Year	Number of patients		Matching	Study population			
		LLR	OLR		Demographic	Tumor	Cirrhosis	Procedure
Belli <i>et al</i> [5]	2009	54	125	No		< 5 cm, anterolaterally located		
Tranchart <i>et al</i> [6]	2010	42	42	Yes				
Lee <i>et al</i> [7]	2011	33	50	Yes				Minor resection
Ahn <i>et al</i> [8]	2014	51	51	Yes		Solitary		
Memeo <i>et al</i> [9]	2014	45	45	Yes			Cirrhosis	
Lee <i>et al</i> [10]	2015	43	86	Yes				
Yoon <i>et al</i> [11]	2015	58	174	Yes		< 5 cm		
Xiao <i>et al</i> [12]	2015	41	86	No		Posterosuperior		
Sposito <i>et al</i> [13]	2016	43	43	Yes			Cirrhosis	Minor resection
Cheung <i>et al</i> [14]	2016	24	29	Yes				Left lateral sectionectomy
Ryu <i>et al</i> [15]	2018	40	30	No				Anatomical resection
Rhu <i>et al</i> [16]	2018	58	133	Yes				Right posterior sectionectomy
Guro <i>et al</i> [17]	2018	67	110	No				Major hepatectomy
El-Gendi <i>et al</i> [18]	2018	25	25	Randomized		< 5 cm	Child A	
Inoue <i>et al</i> [19]	2018	61	175	Yes		< 5 cm		Parenchymal sparing hepatectomy
Kim <i>et al</i> [20]	2018	37	37	Yes				Left hepatectomy
Deng <i>et al</i> [21]	2018	157	157	Yes				
Wu <i>et al</i> [22]	2019	86	86	Yes			Cirrhosis	
Tsai <i>et al</i> [23]	2019	153	160	Yes				
Di Sandro <i>et al</i> [24]	2018	75	75	Yes			Cirrhosis	Minor hepatectomy
Li <i>et al</i> [25]	2019	41	307	Yes				Mesohepatectomy
Kim <i>et al</i> [26]	2018	18	36	Yes		Central		
Chen <i>et al</i> [27]	2019	38	38	Yes				Right hepatectomy
Untereiner <i>et al</i> [28]	2019	33	33	Yes				
Yoon <i>et al</i> [29]	2020	217	434	Yes				
Peng <i>et al</i> [30]	2019	33	33	Yes		Multiple		
Yamamoto <i>et al</i> [31]	2020	58	197	Yes			Cirrhosis	
Lee <i>et al</i> [32]	2021	58	110	Yes				
Navarro <i>et al</i> [33]	2021	106	299	Yes				Major hepatectomy
Delvecchio <i>et al</i> [34]	2021	38	84	Yes	Elderly			Major hepatectomy
Ho <i>et al</i> [35]	2021	45	90	Yes				

LLR: Laparoscopic liver resection; OLR: Open liver resection.

operative stratification, diverting away of selected patient population to liver transplantation, improved surgical techniques to minimize blood transfusion requirement even in the OLR group, a better medical control of background liver disease activity, *etc.*, might all be possible to ameliorate any marginal survival advantage of LLR over OLR.

Table 4 Summary of comparative studies: Long-term oncological outcomes

Ref.	1-year OS, %			3-year OS, %			5-year OS, %			1-year DFS, %			3-year DFS, %			5-year DFS, %		
	LLR	OLR	P	LLR	OLR	P	LLR	OLR	P	LLR	OLR	P	LLR	OLR	P	LLR	OLR	P
Belli <i>et al</i> [5]	94	85	NS	67	53	NS				78	79	NS	52	52	NS			
Tranchart <i>et al</i> [6]	93.1	81.8	NS	74.4	73	NS	59.5	47.4	NS	81.6	70.2	NS	60.9	54.3	NS	45.6	37.2	NS
Lee <i>et al</i> [7]	86.9	98	NS	81.8	80.6	NS	76	76.1	NS	78.8	69.2	NS	51	55.9	NS	45.3	55.9	NS
Ahn <i>et al</i> [8]							80.1	85.7	NS							67.8	54.8	NS
Memeo <i>et al</i> [9]	88	63	NS				59	44	NS	80	60	NS				19	23	NS
Lee <i>et al</i> [10]	95.3	93.9	NS	89.7	89.5	NS	89.7	87.3	NS	60.5	81.5	NS	60.3	66.7	NS	60.3	58.6	NS
Yoon <i>et al</i> [11]	95	98	NS	86	84	NS				82	88	NS	63	62	NS			
Xiao <i>et al</i> [12]	95.1	89.5	NS	78	76.7	NS				87.8	82.6	NS	70.7	68.6	NS			
Sposito <i>et al</i> [13]				75	79	NS	38	46	NS				41	44	NS	25	11	NS
Cheung <i>et al</i> [14]	100	93	NS	85.6	84.1	NS	69.1	77.6	NS	95	69.2	NS	72.8	61.5	NS	51.8	61.5	NS
Ryu <i>et al</i> [15]	89.9	89.9	NS	84.7	68	NS	70.9	63.1	NS	79.5	72.4	NS	58	56.1	NS	42.5	50.4	NS
Rhu <i>et al</i> [16]	96.8	96.8	NS	94.5	94.5	NS	94.5	94.5	NS	77.8	77.8	NS	68.3	68.3	NS	62.5	62.5	NS
Guro <i>et al</i> [17]							77.3	60.2	NS							50.8	40.1	NS
El-Gendi <i>et al</i> [18]										88	84	NS	58.7	54	NS			
Inoue <i>et al</i> [19]	97.8	87.9	NS	78.8	70.6	NS				83.8	75	NS	57.5	54.8	NS			
Kim <i>et al</i> [20]				93.9	93.8								79.6	91.1	NS			
Deng <i>et al</i> [21]	96.2	96.8	NS	72.6	73.4	NS	45.3	46.9	NS	90.5	91.7	NS	53.7	54.4	NS	24.6	19.9	NS
Wu <i>et al</i> [22]	93	81.4	NS	81.4	75.5	NS	69.8	62.8	NS	75.6	69.8	NS	60.5	53.5	NS	44.2	38.4	NS
Tsai <i>et al</i> [23]	90.3	85	0.002	82.9	63.6	0.002	78.1	57.6	0.002	72.9	60.8	NS	49.2	43	NS	37.9	31	NS
Di Sandro <i>et al</i> [24]				68	76								44	44	NS			
Li <i>et al</i> [25]	96.3	95.3	NS	68.4	90.5	NS				84	87.2	NS	36	59.7	NS			
Kim <i>et al</i> [26]	94.4	100	NS	94.4	92.9	NS				93.8	76.5	NS	56.3	41.3	NS			
Chen <i>et al</i> [27]				69.8	74	NS							51.6	57.8	NS			
Untereiner <i>et al</i> [28]				78	79	NS							72	58.6	NS			
Yoon <i>et al</i> [29]	98.1	93.8	NS	87	90.8	NS	78.6	84.3	NS	81	85.3	NS	62	64.7	NS	49.1	56.2	NS

Peng <i>et al</i> [30]	95.8	92.8		77	77	NS				71.9	79.1	NS	51.4	46.2	NS			
Yamamoto <i>et al</i> [31]				82	78.4	NS	58.9	62.3	NS				52.6	40.3	NS	24	24.1	NS
Lee <i>et al</i> [32]	96.6	92.8	NS	73.3	93.1	NS	88.8	76.1	NS	84.4	64	NS	60.2	93.1	NS	67.4	63.9	NS
Navarro <i>et al</i> [33]							90	90	NS							58	40	NS
Delvecchio <i>et al</i> [34]	100	95	NS	100	88	NS	77	75	NS	67	79	NS	44	54	NS	29	46	NS
Ho <i>et al</i> [35]	95.6	87.5	0.036	84.9	70.3	0.036	84.9	61.1	0.036	80.0	73.3	NS	40.0	41.1	NS	20.0	22.2	NS

DFS: Disease-free survival; LLR: Laparoscopic liver resection; NS: Statistically not significant; OLR: Open liver resection; OS: Overall survival.

Two observations were made from the current review of meta-analyses and recent comparative studies. Firstly, the non-inferiority in long-term oncological outcome of LLR *vs* OLR has been repeatedly shown by pooling of various combinations of studies, patient populations and LLR procedures. This should partially address the concern of selection bias, as such outcomes are now widely reproducible worldwide. Secondly, while the studies on LLR for HCC are increasingly heterogenous in terms of disease spectrum included and type of procedure performed, the study methodologies adopted are more and more standardized. Thus, future publications are likely to reflect the advanced practice of difficult procedures of high-volume centers, while the diffusion of the technique among lower-volume centers may be underrepresented in the medical literature. This echoes the need of a broad-based prospectively collected registry database for the purpose of ongoing consolidation of evidence and monitoring of the development of LLR.

CONCLUSION

The current review has updated the findings on long-term oncological outcomes of LLR for HCC. Depicted is also a phenomenal development of LLR, in which there is a widespread adoption of an innovative invasive technique long before the availability of level 1 evidence. Complicated surgical procedures, heterogenous diseases presentation and a long learning curve are the main hurdles of conducting a widely generalizable randomized controlled trial. Given the heterogeneity of the data and the lack of randomized controlled trial, it may still be too bold to prioritize LLR in long-term survival, its advantage being more evident in the perioperative period. A broad-based prospective LLR registry keeping safety and oncological outcomes in check may be a better solution to the need of stronger evidence in the field.

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