

Surgical and oncological outcomes after laparoscopic *vs.* open major hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis

Qian Lu¹, Nannan Zhang¹, Feiran Wang², Xiaojian Chen¹, Zhong Chen²

¹Department of General Surgery, Tongzhou People's Hospital, Nantong 226300, China; ²Department of General Surgery, Affiliated Hospital of Nantong University, Nantong 226001, China

Contributions: (I) Conception and design: Q Lu, Z Chen; (II) Administrative support: Z Chen; (III) Provision of study materials or patients: Q Lu, N Zhang; (IV) Collection and assembly of data: Q Lu, N Zhang, F Wang; (V) Data analysis and interpretation: Q Lu, N Zhang, F Wang, X Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Zhong Chen. Department of General Surgery, Affiliated Hospital of Nantong University, No. 20, Xisi Road, Nantong 226001, China. Email: chenz9806@163.com.

Background: The short- and long-term prognoses are unclear following laparoscopic major hepatectomy (LMH) for hepatocellular carcinoma (HCC). We performed a meta-analysis to compare the surgical and oncological outcomes of LMH *vs.* open major hepatectomy (OMH) in patients with HCC.

Methods: All studies comparing LMH with OMH for HCC published until April 2019 were identified independently by searching PubMed, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials. We analyzed data for surgical and oncological outcomes, namely, operative time, intraoperative blood loss, blood transfusion rate, postoperative morbidity, major complications, mortality, hospital stay, margin distance, negative margin rate, long-term overall survival, and corresponding disease-free survival (DFS).

Results: We included 13 studies involving 1,225 patients with HCC (LMH: 534 patients; OMH: 691 patients) in the meta-analysis. Regarding short-term outcomes, the pooled data showed that LMH was associated with longer operative time [weighted mean difference (WMD): 72.14 min; 95% confidence interval (CI): 43.07–101.21; P<0.00001], less blood loss (WMD: –102.32 mL; 95% CI: –150.99 to –53.64; P<0.0001), shorter hospital stay (WMD: –3.77 d; 95% CI: –4.95 to –2.60; P<0.00001), lower morbidity [risk difference (RD): –0.01; 95% CI: –0.16 to –0.06; P<0.00001], and lower major complication rates (RD: –0.08; 95% CI: –0.11 to –0.05; P<0.00001). However, the need for blood transfusion (RD: –0.01; 95% CI: –0.06 to 0.05; P=0.78), mortality (RD: –0.01; 95% CI: –0.02 to 0.01; P=0.57), margin distance (WMD: 0.05 mm; 95% CI: –0.1 to 0.19; P=0.52), and negative margin rate (RD: 0.01; 95% CI: –0.03 to 0.05; P=0.65) were significantly comparable between the two groups. Regarding long-term outcomes, there was no difference in 3-year DFS [hazard ratio (HR): 0.99; 95% CI: 0.72–1.37; P=0.95], 3-year overall survival (HR: 1.25; 95% CI: 0.70–2.21; P=0.45), 5-year DFS (HR: 0.94; 95% CI: 0.64–1.38; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95% CI: 0.74–1.39; P=0.76), and 5-year overall survival (HR: 0.94; 95%

Conclusions: LMH can be performed as safely as OMH in select patients and provides improved short-term surgical outcomes without affecting long-term survival. However, confirming our results requires more evidence from high-quality and prospective randomized controlled trials.

Keywords: Laparoscopy; major hepatectomy; hepatocellular carcinoma (HCC); outcomes; meta-analysis

Submitted Oct 10, 2019. Accepted for publication Mar 12, 2020. doi: 10.21037/tcr.2020.04.01 View this article at: http://dx.doi.org/10.21037/tcr.2020.04.01

Introduction

Hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer, the sixth most commonly diagnosed cancer, and fourth dominating cause of cancer deaths worldwide according to 2018 global cancer statistics (1). Currently, the management of HCC depends mainly on multidisciplinary comprehensive treatment, of which surgical resection remains the prime therapeutic method for patients without distant metastasis (2).

Since the first laparoscopic liver resection (LLR) was reported in 1991 by Reich (3), the number of publications discussing LLR has increased, particularly over the past 10 years in Asia and Europe (4,5). With accumulated surgical experience and continuous improvements in laparoscopic devices and techniques, laparoscopic minor hepatectomy for tumors located in the anterolateral liver segments has become the standard practice (6). However, major resection for tumors located in the posterosuperior part of the liver (segments 1, 7, 8, and the superior part of segment 4) remain a laparoscopic challenge because of the limited visibility and difficulty controlling bleeding. Therefore, laparoscopic major hepatectomy (LMH) was deemed experimental in the Second International Consensus Conference Statement (7).

The precise definition of major hepatectomy is controversial, although most scholars define it as resection of greater or equal to 3 liver segments (8), namely, right hemihepatectomy, left hemihepatectomy, expanded hemihepatectomy, and central bisectionectomy. Furthermore, some experts recommended laparoscopic right posterior sectionectomy as part of LMH in the 2008 Louisville statement because this procedure is technically difficult (6). Recently, a number of clinical reports comparing LMH with open major hepatectomy (OMH) for HCC have been published, and the minimally invasive advantages of LMH have been recognized by some medical centers (9,10). However, most studies were retrospective or propensityscore-matched studies, and no high-quality randomized controlled trials have been conducted. Therefore, we carried out this meta-analysis by pooling the available nonrandomized comparative studies to compare the surgical and oncological outcomes of LMH vs. OMH for HCC in order to supply high-quality data for clinical practice.

Methods

This research was conducted according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (11).

Data sources and search strategy

Two reviewers (Qian Lu and Nannan Zhang) implemented a systematic review of the literature independently. All studies published until April 2019 were identified by searching PubMed, Web of Science, Embase and the Cochrane Central Register of Controlled Trials, with the language limited to English. The keywords [("laparoscopic" or "laparoscopy") and ("major hepatectomy" or "major liver resection" or "right hepatectomy" or "right hemihepatectomy" or "right liver resection" or "left hepatectomy" or "left hemihepatectomy" or "left liver resection" or "right posterior sectionectomy" or "central hepatectomy" or "central bisectionectomy") and ("hepatocellular carcinoma" or "primary liver cancer")] were selected to identify all documents possibly associated with "LMH for HCC". The reference lists of the identified studies were manually searched for extra studies.

Study selection and eligibility criteria

The inclusion criteria were: (I) studies with a clear definition of surgery as major hepatectomy, namely, right hepatectomy, left hepatectomy, central hepatectomy, or right posterior sectionectomy in accordance with the Brisbane 2000 Nomenclature 29 (12); (II) studies with a clear definition of the indications for HCC; and (III) studies reporting a clear description of the short- and long-term survival outcomes. The exclusion criteria were: (I) case reports, comments, letters, conference abstracts, review articles, non-English language studies, and nonhuman studies; (II) studies assessing outcomes of LMH alone or including less than 10 patients; (III) studies with similar patient data repeatedly published by the same author or institution; and (IV) studies including other minimally invasive approaches like laparoscopic-assisted, handassisted, hybrid techniques, single-site incision, robotic, or donor hepatectomies. Original data from the included studies were checked, analyzed, and combined.

Data extraction

All surgical and oncological outcomes of interest were collected, including operative time, intraoperative blood loss volume, blood transfusion rate, postoperative overall

3326

morbidity, major complications, postoperative mortality, hospital stay, margin distance, negative margin (R0) rate, 3- and 5-year DFS, and 3- and 5-year overall survival. Postoperative morbidity was graded by the Clavien classification model (13), and major complications were graded from III-V and were considered any condition requiring surgical, endoscopic, or radiological intervention, and any life-threatening complication (including central nervous system complications) requiring intermediate care or intensive care unit management and death of a patient. The following baseline characteristics were summarized: age, sex, sample size, operation type, study period, and conversion. Significant independent variables and external validity comparisons were summarized, namely, cirrhosis, Child-Pugh class, the retention rate of indocyanine green 15 min after administration (ICG-R15), microvascular invasion, and maximum tumor size.

Quality evaluation

The quality of every included study was evaluated using the Newcastle-Ottawa Quality Assessment Scale (14), which was developed for nonrandomized studies. Each study can be awarded up to 9 stars, consisting of 4 stars in patient selection, 2 stars in group comparability, and 3 stars in outcomes assessment. The total number of stars for all three components was assessed to evaluate the quality of the included studies. Studies with ≥ 6 total stars were considered high-quality.

Statistical analysis

Statistical analyses were implemented using Review Manager version 5.3.5 software (Cochrane Collaboration, Center, The Nordic Center, Copenhagen, Denmark). Risk differences (RD) with 95% confidence intervals (CIs) were used to assess the dichotomous variables, while weighted mean differences (WMD) with 95% CIs were used for continuous variables. If the study provided only medians and ranges, the means and standard deviations were estimated as depicted by Hozo et al. (15). The hazard ratio (HR) was utilized as a summary statistic for long-term survival outcomes. If the study data did not include HRs and 95% Cis, log HR and its standard error were estimated using Tierney et al.'s method (16). Cochran's Q test was used to evaluate statistical heterogeneity, and severity of heterogeneity was assessed by I² values, as recommended in the Cochrane Handbook (17) (0-40%: likely minimal;

30–60%: likely moderate; 50–90%: likely substantial; 75– 100%: likely considerable). The random effects model was adopted if the I² value was larger than 50% according to the DerSimonian-Laird method, otherwise, we used a fixedeffects model. Lastly, funnel plots were constructed to assess publication bias using informal visual inspection. Two-tailed P<0.05 was considered statistically significant.

Results

Search results and selection processes

According to our search formula, a total of 638 relevant published studies were initially identified. Among these studies, we excluded 621 articles based on their titles and abstracts because they didn't satisfy our eligibility criteria. A comprehensive examination of the remaining 17 studies was conducted, and four were excluded (18-21) because they involved liver diseases other than HCC. Then remaining 13 studies were subjected to further quality assessment (22-34), and all were included in the final meta-analysis because their Newcastle-Ottawa scale scores were more than 6 points (*Table 1*). A flow chart of the selection processes is shown in *Figure 1*, which contains the reasons for excluding studies.

Study characteristics and significant independent variables

Patients' characteristics in the 13 included researches are summarized in Table 2. The studies involved a total of 1,225 cases from Italy, France, South Korea, and China, with 534 undergoing LMH (46.8%) and 691 undergoing OMH (53.2%). Studies were well-matched for age, sex, and surgical extension, and all were retrospective studies or propensity-score-matched studies. Of the 13 studies, three evaluated right hemi-hepatectomy, three evaluated right posterior sectionectomy, two evaluated left hemihepatectomy, and the remaining five studies evaluated both right and left hemi-hepatectomy or central bisectionectomy. The conversion rate to laparoscopy-assisted or open surgery ranged from 0-31.6% in eight studies, with 33 conversions totally (9.5%). In accordance with the principle of intention-to-treat, all converted patients were included in the LMH group.

The significant independent variables of the included studies, namely, cirrhosis, Child-Pugh class A, ICG-R15, microvascular invasion, and maximum tumor size, are summarized in *Table 3*. The results of

Translational Cancer Research, Vol 9, No 5 May 2020

Authory		Selection	n		O a mark a mark i lith a		Outcome		Tatal stars
Author -	(I)	(11)	(111)	(IV)	Comparability —	(V)	(VI)	(VII)	 Total stars
Chen <i>et al.</i> (22)	*	*	*	*	**	*	_	_	7
Chen <i>et al</i> . (23)	*	*	*	*	**	*	*	*	9
Cho <i>et al</i> . (24)	*	*	*	*	**	*	*	-	8
Guro <i>et al</i> . (25)	*	*	*	*	**	*	*	-	8
Kim <i>et al.</i> (26)	*	*	*	*	**	*	*	-	8
Kim e <i>t al</i> . (27)	*	*	*	*	**	*	*	-	8
Komatsu <i>et al</i> . (28)	*	*	*	*	**	*	*	-	8
Rhu <i>et al.</i> (29)	*	*	*	*	**	*	*	-	8
Tarantino <i>et al.</i> (30)	*	*	*	*	**	*	-	-	7
Ku <i>et al</i> . (31)	*	*	*	*	**	*	*	*	9
Yoon <i>et al</i> . (32)	*	*	*	*	**	*	*	*	9
Zhang <i>et al.</i> (33)	*	*	*	*	**	*	*	-	8
Zhang <i>et al</i> . (34)	*	*	*	*	**	*	*	-	8

Table 1 Quality assessment based on the Newcastle-Ottawa Quality Assessment Scale

(I) Representativeness of the laparoscopic group; (II) selection of the open group; (III) exposure; (IV) outcome of interest not present at the start; (V) assessment of outcome; (VI) follow-up; (VII) adequacy of follow-up of the cohort; *, one score; **, two score.

the pooled variables are summarized in *Table 4*, and additional details can be found in *Figure S1*. Results indicated no significant difference except for maximum tumor size. Only one study not report tumor size, and the pooled data showed that the maximum tumor size in patients undergoing LMH was smaller than in patients undergoing OMH (WMD: -0.84 cm; 95% CI: -1.43 to -0.25 cm; P=0.005), with substantial heterogeneity (I²=76%; P<0.00001).

Meta-analysis for surgical outcomes

The pooled results of surgical outcomes are summarized in *Table 4*. Regarding intraoperative influences, operative time was recorded in all studies, and the pooled data showed a longer operative time in the LMH group (WMD: 72.14 minutes; 95% CI: 43.07–101.21 minutes; P<0.00001), with substantial heterogeneity between the studies (I²=88%; P<0.00001) (*Figure 2A*). In addition, blood loss data was available for eleven studies, and the pooled results indicated that LMH was related to less intraoperative blood loss *vs*. OMH (WMD: –102.32 mL; 95% CI: –150.99 to –53.64 mL; P<0.0001), with substantial heterogeneity between the studies (I²=73%; P<0.0001) (*Figure 2B*). Eight

studies recorded the perioperative blood transfusion rate, and the pooled data indicated that the transfusion rate was not markedly different between LMH and OMH (RD: -0.01, 95% CI: -0.06 to 0.05, P=0.78), with substantial heterogeneity (I²=61%; P=0.01) (*Figure 2C*).

Regarding patients' postoperative clinical course, hospital stay was pooled for all studies, and the pooled data indicated a significantly shorter hospital stay in the LMH group (WMD: -3.77 d; 95% CI: -4.95 to -2.60 d; P<0.0001), with substantial heterogeneity ($I^2=76\%$; P<0.00001) (Figure 3A). Eleven studies reported overall morbidity data; postoperative morbidity was 16.9% (90/534) after LMH and 30.1% (208/691) after OMH, and the pooled data showed a significantly lower postoperative overall morbidity in the LMH group (RD: -0.11; 95% CI: -0.16 to -0.06; P<0.0001) (Figure 3B), with minimal heterogeneity $(I^2=39\%; P=0.09)$. Similar to overall morbidity, the pooled results for ten studies revealed that patients in the LMH group suffered fewer major complications (RD: -0.08; 95% CI: -0.11 to -0.05; P<0.00001) (Figure 3C), with minimal heterogeneity ($I^2=10\%$; P=0.35). Eight studies reported postoperative mortality, and the pooled results indicated no significant difference between LMH and OMH (RD: -0.01; 95% CI: -0.02 to 0.01; P=0.57), with minimal heterogeneity

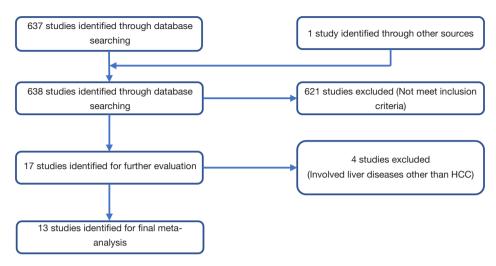


Figure 1 Flow chart of the screening and selection process for the included studies.

Authory	0	Surgical	Oturalu a suis al	Study	No. of	patients	Age (y), (n	nean ± SD)	Sex (ma	le/female)	Conversion,
Author	Country	extension	Study period	design	LMH	OMH	LMH	ОМН	LMH	OMH	n (%)
Chen <i>et al</i> . (22)	China	Mixed	2015–2016	R	126	133	50.8±10.6	50.3±11.9	93/33	108/25	3 (1.3)
Chen <i>et al</i> . (23)	China	RHH	2007–2018	PSM	38	38	56.0±10.3	55.2±11.1	31/7	32/6	7 (18.4)
Cho et al. (24)	Korea	RPH	2003–2012	R	24	19	53.9±12.6	60.0±8.9	17/7	16/3	3(12.5)
Guro <i>et al.</i> (25)	Korea	Mixed	2004–2015	R	67	110	57.7±11.1	59.1±12.3	49/18	93/17	NA
Kim <i>et al.</i> (26)	Korea	LHH	2012–2016	PSM	37	37	57.6±11.3	54.8±11.8	30/7	31/6	NA
Kim <i>et al</i> . (27)	Korea	Mixed	2013–2015	PSM	18	36	55.7±13.2	54.6±12.8	13/5	22/14	NA
Komatsu <i>et al.</i> (28) France	Mixed	2006–2014	PSM	38	38	61.5±12.2	61.7 ±16.1	34/4	33/5	12 (31.6)
Rhu <i>et al</i> . (29)	Korea	RPH	2009–2016	PSM	53	97	58.0±8.8	58.2±9.4	43/10	81/16	5 (8.6)
Tarantino <i>et al.</i> (30)) Italy	RPH	2000–2014	R	13	51	65.0±13.0	65.5±9.0	37/14	7/6	3 (23.1)
Xu <i>et al</i> . (31)	China	Mixed	2015–2017	PSM	32	32	52.2±10.6	51.7±11.4	28/4	28/4	NA
Yoon <i>et al</i> . (32)	Korea	RHH	2007–2015	PSM	33	33	56.0±7.0	57.3 ±6.9	23/10	26/7	NA
Zhang <i>et al</i> . (33)	China	RHH	2010–2015	R	35	42	58.0±9.5	63.0 ±10.5	10/25	16/26	0 (0.0)
Zhang <i>et al</i> . (34)	China	LHH	2012–2014	R	20	25	47.0±8.5	52.0 ±10.5	8/12	10/15	0 (0.0)

Table 2 Patient characteristics from the included studies

LHH, left hemi-hepatectomy; RHH, right hemi-hepatectomy; RPS, right posterior sectionectomy; LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; PSM, propensity score matching study; R, retrospective study; SD, standard deviation; NA, not applicable.

 $(I^2=0\%; P=0.99)$ (Figure 3D).

Meta-analysis for oncological outcomes

The pooled results of oncological outcomes are summarized in *Table 4*. Only five studies discussed the distance from the tumor margin, and margin distance was comparable between the two groups after pooling the results (WMD: 0.05 cm; 95% CI: -0.10 to 0.19 cm; P=0.52), with moderate heterogeneity (I²=43%; P=0.12) (*Figure 4A*). R0 resections was reported in three studies, and the pooled results indicated comparable outcomes between the two groups

Translational Cancer Research, Vol 9, No 5 May 2020

3329

Author	Cirrhosis	s, n (%)	Child A	N, n (%)		%) (mean ± D)	Microvascu n (lar invasion, %)		rumor size (cm) an ± SD)
	LMH	OMH	LMH	OMH	LMH	OMH	LMH	OMH	LMH	OMH
Chen <i>et al</i> . (22)	NA	NA	124 (98.4)	127 (95.5)	5.1±2.5	4.5±2.4	NA	NA	6.5±2.2	7.3±4.3
Chen <i>et al</i> . (23)	34 (89.5)	34 (89.5)	38 (100.0)	38 (100.0)	6.9±3.2	6.9±3.3	14 (36.8)	12 (31.6)	7.3±3.4	7.6±4.2
Cho et al. (24)	NA	NA	NA	NA	8.2±7.3	6.4±4.2	NA	NA	3.7±1.8	4.8±2.5
Guro <i>et al.</i> (25)	36 (54.5)	61 (55.5)	79 (95.2)	92 (82.8)	9.1±8.3	9.5±5.9	NA	NA	4.1±2.4	6.3±3.8
Kim <i>et al</i> . (26)	15 (41.7)	20 (54.1)	NA	NA	11.8±7.5	8.7±3.3	23 (63.9)	25 (67.6)	3.5±2.5	3.4±2.1
Kim <i>et al</i> . (27)	NA	NA	NA	NA	10.4±3.8	12.8±3.4	4 (22.2)	10 (27.8)	2.9±2.0	3.7±3.5
Komatsu <i>et al.</i> (28)	NA	NA	38 (100.0)	38 (100.0)	NA	NA	4 (10.5)	3 (7.9)	5.7±2.5	8.9±3.7
Rhu <i>et al.</i> (29)	20 (37.7)	36 (37.1)	NA	NA	11.5±5.1	10.7±4.0	30 (56.6)	57 (58.8)	3.1±1.8	3.1±1.7
Tarantino <i>et al.</i> (30)	13 (100.0)	49 (96.0)	9 (69.2)	46 (90.0)	NA	NA	0 (0.0)	2 (3.9)	2.6±0.9	3.7±2.3
Xu <i>et al</i> . (31)	NA	NA	NA	NA	5.0±2.1	5.1±2.0	11 (34.4)	12 (37.5)	4.3±2.2	6.1±2.1
Yoon <i>et al.</i> (32)	29 (87.9)	28 (80.7)	NA	NA	11.6±4.7	13.7±5.5	NA	NA	3.3±1.7	3.0±1.5
Zhang et al. (33)	NA	NA	35 (100.0)	42 (100.0)	NA	NA	NA	NA	6.7±4.2	5.9±3.0
Zhang et al. (34)	NA	NA	20 (100.0)	25 (100.0)	NA	NA	NA	NA	NA	NA

Table 3 Significant independent variables and external validity comparisons from the included studies

LMH, laparoscopic major hepatectomy; OMH, open major hepatectomy; Child A, Child–Pugh class A; ICG-R15, the retention rate of indocyanine green 15 min after administration; SD, standard deviation; NA, not applicable.

(RD: 0.01; 95% CI: -0.13 to 0.05; P=0.65), with minimal heterogeneity (I²=0%; P=0.40) (*Figure 4B*).

Regarding long-term outcomes, nine studies reported postoperative survival, and none found significant differences between the LMH and OMH groups in survival. Among the nine studies, 3- and 5-year survival rates were available in eight studies and three studies, respectively. The pooled results showed comparable 3-year DFS (HR: 0.99; 95% CI: 0.72–1.37; P=0.95) (*Figure 5A*), 3-year OS (HR =1.25; 95% CI: 0.70–2.21; P=0.45) (*Figure 5B*), 5-year DFS (HR: 0.94; 95% CI: 0.64–1.38; P=0.76) (*Figure 5C*), and 5-year OS (HR: 0.94; 95% CI: 0.45–1.99; P=0.88) (*Figure 5D*); heterogeneity was minimal (I²=0%; P>0.05).

Publication bias

Funnel plots for each perioperative outcome was drawn to evaluate symmetry (*Figure 6*). The drawn funnel plots were not asymmetrical, which suggested no or limited publication bias.

Discussion

Following the second International Laparoscopic Liver Surgery Expert Consensus Meeting (6,7), minor or nonanatomical LLR was the recommended standard practice, and some centers started to explore difficult major and anatomical LLR. Because of the complex biliary and vascular anatomy within the liver parenchyma and findings in diseases such as hepatitis and cirrhosis, it is especially difficult to perform major resection laparoscopically. However, with surgical experience and technical advances, some centers have achieved satisfactory surgical outcomes (35,36). Our meta-analysis revealed advantages with a laparoscopic approach regarding certain intraoperative and postoperative clinical measurements, but not regarding operative duration. In addition, our results highlighted that overall and disease-free survival (DFS) rates following LMH were comparable with those following OMH.

Regarding any surgical approach, patient safety is the most important issue, and our meta-analysis revealed no

Variables	NO. 01				11-4-11-11-12			
	studies	Effect model -	LMH	HMO	meterogeneity (F, I)	Overall effect size	95% Cl of overall effect	P value
Cirrhosis	9	Fixed	246	402	0.71, 0%	RD =0.00	(-0.07, 0.08)	0.9
Child A	7	Random	353	438	0.05, 51%	RD =-0.002	(-0.02, -0.05)	0.36
ICG-R15	6	Random	433	571	0.02, 55%	WMD =0.09	(-0.69, 0.88)	0.81
Microvascular invasion	7	Fixed	236	333	0.71, 0%	RD =0.03	(-0.05, 0.10)	0.53
Maximum tumor size	12	Random	514	666	<0.00001, 76%	WMD =-0.84	(-1.43, -0.25)	0.005*
Operative time (min)	13	Random	534	691	<0.00001, 88%	WMD =72.14	(43.07, 101.21)	<0.00001*
Blood loss (mL)	1	Random	457	575	<0.0001, 73%	WMD =-102.32	(-150.99, -53.64)	<0.0001*
Blood transfusion	80	Random	424	518	0.01, 61%	RD =-0.01	(-0.06, 0.05)	0.78
Hospital stay (d)	13	Random	481	594	<0.00001, 76%	WMD =-3.77	(-4.95, -2.60)	<0.00001*
Morbidity	1	Fixed	479	624	0.09, 39%	RD =-0.01	(-0.16, -0.06)	<0.00001*
Major complications	10	Fixed	440	602	0.35, 10%	RD =-0.08	(-0.11, -0.05)	<0.00001*
Mortality	8	Fixed	375	438	0.99, 0%	RD =-0.01	(-0.02, 0.01)	0.57
Margin distance (mm)	9	Fixed	178	273	0.12, 43%	WMD =0.05	(-0.1, 0.19)	0.52
R0 rate	ю	Fixed	172	162	0.40, 0%	RD =0.01	(-0.03, 0.05)	0.65
3-y disease-free survival	8	Fixed	308	408	0.98, 0%	HR =0.99	(0.72, 1.37)	0.95
3-y overall survival	8	Fixed	308	408	0.58, 0%	HR =1.25	(0.70, 2.21)	0.45
5-y disease-free survival	ю	Fixed	144	226	0.83, 0%	HR =0.94	(0.64, 1.38)	0.76
5-y overall survival	က	Fixed	144	226	0.84, 0%	HR =0.94	(0.45, 1.99)	0.88

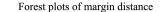
А				F	orest	plots	of op	erative time		
		LMH			омн			Mean Difference		Mean Difference
Study or Subgroup	Mean		Total	Mean	SD	Total	Weight	IV, Random, 95		IV, Random, 95% Cl
Chen JH et al	248.9	99.8	126	236	76	133	8.7%	12.90 [-8.79, 34		
Chen K et al	255.5	93.4	38	225.9	39.8	38	8.2%	29.60 [-2.68, 61	1.88]	
Cho JY et al	567.4	212.4	24	316.1	63	19	4.9%	251.30 [161.73, 340	0.87]	
Guro H et al	416.6	166.9	67	332.5	105.4	110	7.5%	84.10 [39.55, 128	3.65]	
Kim JM et al	279.3	86.6	37	262.2	117.6	37	7.4%	17.10 [-29.96, 64	4.16]	
Kim WJ et al	330		18	215.35	48.73	36	7.5%	114.65 [68.96, 160		
Komatsu S et al	370	98	38	304	50	38	8.1%	66.00 [31.02, 100		
Rhu J et al	381	149	53	220	91	97		161.00 [116.99, 205		
Tarantino G et al	234	57	13	216	73	51	8.0%	18.00 [-18.90, 54		
Xu HW et al	262	85	32	201	19	32	8.3%	61.00 [30.82, 91		
Yoon Yi et al	297 309	113 108	33 35	176 223	60 110	33 42	7.6% 7.3%	121.00 [77.35, 164		
Zhang Yetal Zhang Yetal	309 143	35.6	35 20	137	29.8	42 25	7.3% 8.8%	86.00 [37.14, 134		1
Zhang retai	145	30.0	20	157	29.0	25	0.070	6.00 [-13.49, 25	J.49J	
Total (95% CI)			534			691	100.0%	72.14 [43.07, 101	1.211	•
Heterogeneity: Tau ² =	= 2398.0	7; Chi ² =	103.78	3, df = 12	(P < 0.0	00001); I	²= 88%	. ,		
Test for overall effect										-200 -100 Ó 100 200 Favours (LMH) Favours (OMH)
				-						
В				F	orest	plots	of bl	ood loss		
2		LMH			омн			Mean Differend	-	Mean Difference
Study or Subgroup	Mean) Total	Mear		D Total	Weight			IV, Random, 95% Cl
Chen JH et al	302									
Chen K et al	372.5	257.5	5 38	624.3	3 421	.3 38	6.2%	-251.80 [-408.79,	-94.81]	
Guro H et al	1,543.3	2,641.8	367	1,248.1	1,402	.8 110			979.94]	
Kim JM et al	413.1	458.7		426.3						
Kim WJ et al	152.13									
Komatsu Set al	174.6	208								
Tarantino Getal Xu HW etal	125 351.6									
Yoon Yi et al	125.5									4
Zhang Yetal	293									+
Zhang Y et al	180	20.5								•
Total (95% CI)			457				100.0%	-102.32 [-150.99,	-53.64]	▼
Heterogeneity: Tau ² = Test for overall effect: J				= 10 (P <	< 0.0001); F= 739	%			-1000 -500 0 500 1000
restion overall ellect.	2 - 4.12 ((F < 0.00	01)							Favours (LMH) Favours (OMH)
				Г		1.	C1 1	1		
С				F	orest	plots	of blo	ood transfutio	on	
U		LMH		OMH			Ris	k Difference		Risk Difference
Study or Subgroup) Eve	ents T	otal E	vents	Total	Weight	M-H, I	Random, 95% Cl		M-H, Random, 95% Cl
Chen JH et al		6	126	22	133	15.4%	-0	.12 [-0.19, -0.04]		
Chen K et al		4	38	9	38	6.9%		0.13 [-0.30, 0.04]		
Guro H et al		29	67	45	110	7.9%	. (0.02 [-0.13, 0.17]		_
Kim JM et al		2	37	2	37	12.0%	. (0.00 [-0.10, 0.10]		_ + _
Komatsu S et al		2	38	1	38	13.7%		0.03 [-0.06, 0.11]		 _
Rhu J et al		7	53	2	97	12.8%		0.11 [0.02, 0.21]		
Xu HW et al		1	32	1	32	13.9%		0.00 [-0.09, 0.09]		_
Yoon YI et al		, 0	33	Ó	33	17.4%		0.00 [-0.06, 0.06]		+
.con nota			55			11.47		5.00 [0.00, 0.00]		
Total (95% CI)			424		518	100.0%	-0	.01 [-0.06, 0.05]		
Total events		51		82						
Heterogeneity: Tau	ı ² = 0.00); Chi ² =	: 18.17	. df = 7	(P = 0.0	01); I ² =	61%		<u> </u>	
Test for overall effe									-1	-0.5 0 0.5 1
			-,							Favours (LMH) Favours (OMH)

Figure 2 Forest plots of the meta-analysis for intraoperative outcomes. (A) Operative time; (B) intraoperative blood loss; (C) blood transfusion rates.

significant difference in postoperative mortality between two groups. Furthermore, our results showed that the laparoscopic approach achieved similar or better surgical outcomes compared with open surgery in major liver resection. Hemorrhage occurs easily during hepatectomy because hepatic vascular anatomy is complex, contains multiple blood sinuses, has abundant blood flow, and because the hepatic parenchyma is fragile. Therefore, effectively preventing intraoperative hemorrhage is an important factor in patient safety in laparoscopic surgery, and is the key to reducing rates of conversion to open surgery (37). Blood loss has a reported detrimental impact on postoperative death and liver dysfunction; therefore, the need for perioperative transfusion could indicate a worse poor prognosis (38). Our results showed less blood loss and similar transfusion rates with LMH for HCC, and the main reason may be that intra-abdominal pressure secondary to pneumoperitoneum plays an effective role in hemostasis. Additionally, the local magnified view helps surgeons precisely recognize the tiny blood vessels and bile ducts

		LMH			OMH	hosp		Mean Differend	e	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean		Total V	Veight	IV, Random, 95		IV, Random, 95% Cl	
Chen JH et al	6.58	3.49	126	9.58	8.08		10.9%	-3.00 [-4.50, -1			
Chen K et al	14	10.5	38	20	23	38	1.8%	-6.00 [-14.04, 2			
Cho JY et al	10.6	4.8	24	11.1	3.2	19	8.5%	-0.50 [-2.90, 1			
Guro H et al	11.3	8.3	67	18	21.4	110	4.5%	-6.70 [-11.17, -2			
Kim JM et al	9.8	3.8	37	15.6	9.2	37	6.7%	-5.80 [-9.01, -2		_ -	
Kim WJ et al	9.5	3.41	18	11.8	4.41	36	9.2%	-2.30 [-4.43, -0			
Komatsu S et al	11.5	11.2	38	13.9	11.2	38	3.8%	-2.40 [-7.44, 2	2.64]		
Rhu J et al	56.13	34.13	53	86.39	30.79	97		Not estim			
Tarantino G et al	5.7	3	13	10.7	5	51	9.2%	-5.00 [-7.13, -2			
Xu HW et al	8.65	4.11	32	9.46	2.9	32	10.3%	-0.81 [-2.55, 0		-+	
Yoon YI et al	9.97	3.02	33	13.94	3.37	33	10.8%	-3.97 [-5.51, -2	2.43]		
Zhang Yetal	9	2	35	15	3	42	11.8%	-6.00 [-7.12, -4		-	
Zhang Y et al	7	1	20	12	2	25	12.3%	-5.00 [-5.90, -4	.10]	-	
Total (95% Cl) Heterogeneity: Tau ² = Test for overall effect: .					< 0.000(594 1)1); I² = 7		-3.77 [-4.95, -2	. 60] -20	-10 0 10 Favours (LMH) Favours (OMH)	
В			For	est pl	ots of	mort	oidity				
	1	LMH		OMH	1		Risk	Difference		Risk Difference	
Study or Subgroup			otal F			Weight		Fixed, 95% Cl		M-H, Fixed, 95% Cl	
Chen JH et al	2.00		126	36	133	24.6%)5 [-0.15, 0.06]			
Chen Ketal		20 7	38	10	38	7.2%					
								08 [-0.27, 0.11]			
Cho JY et al		2	24	4	19	4.0%		3 [-0.34, 0.09]			
Guro H et al		17	67	43	110	15.9%		4 [-0.28, 0.00]			
Kim JM et al		3	37	8	37	7.0%		4 [-0.29, 0.02]			
Kim WJ et al		3	18	10	36	4.6%		1 [-0.34, 0.11]			
Komatsu S et al		12	38	23	38	7.2%	-0.2	9 [-0.50, -0.08]			
Rhu J et al		5	53	8	97	13.1%	0.0	01 [-0.08, 0.11]		_ + _	
Tarantino G et al		2	13	27	51	3.9%		8 [-0.61, -0.14]			
Xu HW et al		10	32	12	32	6.1%		06 [-0.29, 0.17]			
Yoon YI et al		1	33	7	33	6.3%		8 [-0.33, -0.03]		_ -	
			479								
Total events Heterogeneity: Chi² Test for overall effec		90), df = 1	10 (P = < 0.00	01)	l² = 399	6		l [-0.16, -0.06]		-0.5 -0.25 0 0.25 0.5 Favours (LMH) Favours (OMH)	
Total events Heterogeneity: Chi²		90), df = 1	10 (P = < 0.00	0.09); 01)	l² = 399	6		nplications			
Total events Heterogeneity: Chi² Test for overall effec	:t: Z = 4.	90), df = 1	10 (P = < 0.00	0.09); 01)	P= 399	6	r con			Favours (LMH) Favours (OMH)	
	:t: Z = 4.	90), df = ⁻ .33 (P LMH	10 (P = < 0.00 Fore	0.09); 01) est plo 0MF	I [≈] = 399 ots of	6 îmajo	r con Risk	nplications		Favours (LMH) Favours (OMH) Risk Difference	
Total events Heterogeneity: Chi ² Test for overall effec C Study or Subgroup	:t: Z = 4.	90),df= .33 (P LMH nts T	10 (P = < 0.00 Fore	0.09); 01) est plo OMF	1 ² = 399 Ots of I <u>Total</u>	% `majo <u>Weight</u>	r con Risk M-H,	nplications Difference Fixed, 95% Cl		Favours (LMH) Favours (OMH)	
Total events Heterogeneity: Chi ² Test for overall effec C <u>Study or Subgroup</u> Chen JH et al	:t: Z = 4.	90), df = ⁻ .33 (P LMH n <u>ts T</u> 2	10 (P = < 0.00 Fore	0.09); 01) est plo 0M⊩ <u>events</u> 8	1 ² = 399 ots of I <u>Total</u> 133	6 majo <u>Weight</u> 26.2%	r con Risk <u>M-H,</u>	nplications Conference Fixed, 95% CI 14 (-0.09, 0.00)		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effec C Study or Subgroup Chen JH et al Chen K et al	:t: Z = 4.	90), df = 1 .33 (P LMH n <u>ts T</u> 2 4	10 (P = < 0.00 Fore otal E 126 38	0.09); 01) est plo 0MF <u>events</u> 8 7	F = 399 Dts of I <u>Total</u> 133 38	6 majo <u>Weight</u> 26.2% 7.7%	r con Risk <u>M-H.</u> -0.0	nplications Conference <u>Fixed, 95% CI</u> 04 [-0.09, 0.00] 08 [-0.24, 0.08]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effec C Study or Subgroup Chen JH et al Guro H et al Guro H et al	:t: Z = 4.	90), df = 1 .33 (P LMH <u>nts T</u> 2 4 7	10 (P = < 0.00 For <u>otal E</u> 126 38 67	0.09); 01) est plo omr <u>events</u> 8 7 27	I ² = 399 Dts of I <u>Total</u> 133 38 110	6 majo <u>Weight</u> 26.2% 7.7% 16.8%	r con Risk <u>M-H.</u> -0.0	nplications Difference Fixed, 95% CI 14 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al	:t: Z = 4.	90), df = 1 .33 (P LMH nts T 2 4 7 1	10 (P = < 0.00 Fore 0tal E 126 38 67 18	: 0.09); 01) est plo omr <u>events</u> 8 7 27 4	I ² = 399 Dts of I <u>Total</u> 133 38 110 36	6 Weight 26.2% 7.7% 16.8% 4.9%	r con Risk <u>M-H.</u> -0.0 -0.1 -0.1	nplications (Difference Fixed, 95% CI 14 [-0.09, 0.00] 18 [-0.24, 0.08] 14 [-0.25, -0.03] 16 [-0.20, 0.09]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi [≇] Test for overall effec C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al	:t: Z = 4.	90), df = ⁻ .33 (P LMH <u>nts T</u> 2 4 7 1 5	10 (P = < 0.00 Fore 0tal E 126 38 67 18 38 38	: 0.09); 01) est plo om- twents 8 7 27 4 7	I ² = 399 ots of I <u>Total</u> 133 38 110 36 38	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7%	r con Risk <u>M-H.</u> -0.0 -0.1 -0.1	nplications Difference Fixed, 95% CI 14 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.20, 0.09] 15 [-0.22, 0.11]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al	:t: Z = 4.	90), df = ⁻ .33 (P LMH <u>mts T</u> 2 4 7 1 5 1	10 (P = < 0.00 Fore 126 38 67 18 38 53	: 0.09); 01) est plo OMH Events 7 27 4 7 4	F = 399 ots of I 133 38 110 36 38 97	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9%	r con Risk M-H, -0.0 -0.1 -0.1 -0.0 -0.0	nplications Difference Fixed, 95% CI 14 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.22, 0.11] 15 [-0.22, 0.11] 12 [-0.08, 0.03]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect Chen JH et al Chen JH et al Guro H et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al Tarantino G et al	:t: Z = 4.	90), df = ⁻ .33 (P LMH <u>mts T</u> 2 4 7 1 5 1 5 1 0	10 (P = < 0.000 Fore 126 38 67 18 38 53 13	: 0.09); 01) est plo OMH <u>ivents</u> 8 7 27 4 7 4 6	P = 399 ots of I 133 38 110 36 38 97 51	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2%	r con Risk M-H. -0.0 -0.1 -0.1 -0.0 -0.0 -0.0	nplications Conference Fixed, 95% C1 14 [-0.09, 0.00] 16 [-0.20, 0.09] 16 [-0.20, 0.09] 15 [-0.22, 0.11] 12 [-0.08, 0.03] 12 [-0.25, 0.01]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect Chen JH et al Chen H et al Guro H et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al Tarantino G et al	:t: Z = 4.	90), df = - .33 (P LMH <u>mts T</u> 2 4 7 1 5 1 5 0 0	10 (P = < 0.00) Ford 126 38 67 18 38 53 13 32	: 0.09); 01) est plo om- <u>vents</u> 8 7 27 4 7 4 7 4 5	1 ² = 399 Dts of 1 133 38 110 36 38 97 51 32	6 majo 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 6.5%	r con Risk -0.0 -0.1 -0.1 -0.0 -0.1 -0.0 -0.0	nplications Difference Fixed, 95% CI 14 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.22, 0.11] 15 [-0.22, 0.11] 12 [-0.08, 0.03]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Rhu J et al Tarantino G et al Xu HW et al	:t: Z = 4.	90), df = ⁻ .33 (P LMH <u>mts T</u> 2 4 7 1 5 1 5 1 0	10 (P = < 0.000 Fore 126 38 67 18 38 53 13	: 0.09); 01) est plo OMH <u>ivents</u> 8 7 27 4 7 4 6	P = 399 ots of I 133 38 110 36 38 97 51	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2%	r con Risk -0.0 -0.1 -0.1 -0.0 -0.1 -0.0 -0.0	nplications Conference Fixed, 95% C1 14 [-0.09, 0.00] 16 [-0.20, 0.09] 16 [-0.20, 0.09] 15 [-0.22, 0.11] 12 [-0.08, 0.03] 12 [-0.25, 0.01]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Rhu J et al Tarantino G et al Zu HW et al Zhang Y et al	:t: Z = 4.	90), df = - .33 (P LMH <u>mts T</u> 2 4 7 1 5 1 5 0 0	10 (P = < 0.00) Ford 126 38 67 18 38 53 13 32	: 0.09); 01) est plo om- vents 8 7 27 4 7 4 7 4 5	1 ² = 399 Dts of 1 133 38 110 36 38 97 51 32	6 majo 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 6.5%	r con Risk -0.0 -0.1 -0.1 -0.0 -0.1 -0.0 -0.1 -0.1	nplications x Difference Fixed, 95% CI 4 [-0.9, 0.00] 18 [-0.24, 0.08] 16 [-0.20, 0.09] 15 [-0.22, 0.11] 12 [-0.08, 0.03] 2 [-0.25, 0.01] 6 [-0.29, -0.02]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al	:t: Z = 4.	90), df = - .33 (P	10 (P = < 0.00) Fore 0 tal E 126 38 67 18 38 53 13 32 35 20	: 0.09); 01) est plo om- <u>events</u> 8 7 27 4 7 4 6 5 5	P = 399 Dts of 133 38 110 36 38 97 51 32 42 25	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 6.5% 7.7% 4.5%	r con Risk M-H. -0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.	nplications c Difference Fixed, 95% CI b4 [-0.09, 0.00] b6 [-0.20, 0.09] b5 [-0.22, 0.11] b2 [-0.28, 0.03] c2 [-0.25, 0.01] b6 [-0.29, -0.02] c2 [-0.23, -0.01] b8 [-0.21, 0.05]		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi [≇] Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kom 45 et al Kom 45 et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total (95% CI)	:t: Z = 4.	90), df = ' 33 (P LMH 1 2 4 7 1 5 1 0 0 0 0	10 (P = < 0.00) Ford 126 38 67 18 38 53 13 32 35	0.09); 01) est plo 0MI- vents 8 7 27 4 7 4 6 5 5 2	P = 399 Dts of 133 38 110 36 38 97 51 32 42 25	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 6.5% 7.7% 4.5%	r con Risk M-H. -0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.	nplications Difference Fixed, 95% CI 4 (-0.08, 0.00) 18 (-0.24, 0.08) 4 (-0.25, -0.03) 16 (-0.20, 0.09) 15 (-0.22, 0.11) 12 (-0.08, 0.03) 2 (-0.25, 0.01) 2 (-0.23, -0.02) 2 (-0.23, -0.01)		Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Chen K et al Chen K et al Guro H et al Kim WJ et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total (95% CI) Total events	t Z= 4.	90), df = : .33 (P LMH 2 4 7 1 5 1 5 1 0 0 0 0 0 0 20	10 (P = < 0.00) Ford 126 38 67 18 38 53 13 32 35 20 440	: 0.09); 01) est ple OMF <u>vents</u> 8 7 27 4 7 4 7 4 6 5 5 2 2 75	P = 399 ots of I Total 133 38 97 51 32 42 25 602	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 6.5% 7.7% 4.5%	r con Risk M-H. -0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.	nplications c Difference Fixed, 95% CI b4 [-0.09, 0.00] b6 [-0.20, 0.09] b5 [-0.22, 0.11] b2 [-0.28, 0.03] c2 [-0.25, 0.01] b6 [-0.29, -0.02] c2 [-0.23, -0.01] b8 [-0.21, 0.05]		Favours [LMH] Favours [OMH]	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al	t Z = 4.	90), df = : .33 (P LMH 2 4 7 1 5 1 5 1 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00 Ford 0 tal E 126 38 67 18 38 53 13 32 35 20 440 9 (P = 1	: 0.09); 01) est plo OMI- vents 7 27 4 7 4 7 4 5 5 5 2 2 75 0.35); I ² 001)	P ² = 399 Dts of Total 133 38 110 36 38 110 36 38 97 51 32 42 25 602 = 10%	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 4.9% 6.5% 7.7% 4.5% 100.0%	r con Risk -0.0 -0.0 -0.0 -0.0 -0.0 -0.0 -0.0 -0.	nplications c Difference Fixed, 95% CI b4 [-0.09, 0.00] b6 [-0.20, 0.09] b5 [-0.22, 0.11] b2 [-0.28, 0.03] c2 [-0.25, 0.01] b6 [-0.29, -0.02] c2 [-0.23, -0.01] b8 [-0.21, 0.05]	-0.5	Favours (LMH) Favours (OMH) Risk Difference M-H, Fixed, 95% Cl	0
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effect	t Z = 4.	90), df = : .33 (P LMH 2 4 7 1 5 1 5 1 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00 Ford 0 tal E 126 38 67 18 38 53 13 32 35 20 440 9 (P = 1	: 0.09); 01) est plo OMI- vents 7 27 4 7 4 7 4 5 5 5 2 2 75 0.35); I ² 001)	P ² = 399 Dts of Total 133 38 110 36 38 110 36 38 97 51 32 42 25 602 = 10%	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 6.5% 7.7% 4.5%	r con Risk -0.0 -0.0 -0.0 -0.0 -0.0 -0.0 -0.0 -0.	nplications c Difference Fixed, 95% CI b4 [-0.09, 0.00] b6 [-0.20, 0.09] b5 [-0.22, 0.11] b2 [-0.28, 0.03] c2 [-0.25, 0.01] b6 [-0.29, -0.02] c2 [-0.23, -0.01] b8 [-0.21, 0.05]	-0.5	Favours [LMH] Favours [OMH]	0
Total events Heterogeneity: Chi ² Test for overall effect C C Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi ²	t: Z = 4. Even = 10.04 t: Z = 4.	90), df = : .33 (P LMH 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00 Ford 0 tal E 126 38 67 18 38 53 13 32 35 20 440 9 (P = 1	0.09); (; 0.09); est ple 0MI- vents 8 7 27 4 7 4 7 4 6 5 5 2 75 5 0.35); (° 001) est ple 0010	I* = 399 I 133 38 110 36 97 51 32 25 602 = 10% bots of	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 4.9% 6.5% 7.7% 4.5% 100.0%	r con Risk - 0.0 - 0.0 - 0.1 - 0.0 - 0.0 - 0.0 - 0.1 - 0.1 - 0.1 - 0.0 -	nplications c Difference Fixed, 95% CI 14 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.22, 0.01] 16 [-0.22, 0.01] 10 [-0.08, 0.03] 2 [-0.25, 0.01] 16 [-0.29, -0.02] 18 [-0.21, 0.05] 8 [-0.11, -0.05]	-0.5	Favours [LMH] Favours [OMH]	0
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effect	t: Z = 4.	90), df = : 33 (P LMH nts T 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00 Ford 126 38 67 18 38 53 13 32 35 20 440 9 (P = 1 Ford Ford	0.09); ;; 01) 011 004 004 004 004 005 005 005 005	P ² = 399 Total 1 133 38 110 36 38 97 51 32 42 25 602 = 10% I	6 Weight 26.2% 7.7% 16.8% 4.9% 7.7% 4.9% 6.5% 7.7% 4.5% 100.0%	r con Risk M-H, - 0.0 -	nplications c Difference Fixed, 95% CI b4 [-0.09, 0.00] b6 [-0.20, 0.09] b5 [-0.22, 0.11] b2 [-0.28, 0.03] c2 [-0.25, 0.01] b6 [-0.29, -0.02] c2 [-0.23, -0.01] b8 [-0.21, 0.05]	-0.5	Favours [LMH] Favours [OMH]	0
Total events Heterogeneity: Chi [≇] Test for overall effec C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kom XJ et al Kom XJ et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi [₹] Test for overall effec D Study or Subgroup	t: Z = 4.	90), df = : 33 (P LMH 2 4 7 1 5 1 0 0 0 0 0 0 20 4, df = : 64 (P LMH nts T	10 (P = < 0.00 Ford 126 38 67 18 38 53 32 35 20 440 9 (P = 1 < 0.00 Ford Ford otal E	0.09); ;; 01) 011 004 004 004 004 005 005 005 005	I ² = 399 I Total 133 38 110 36 38 97 51 32 42 25 602 = 10% Dots of I Total	6 majo 26.2% 16.8% 4.9% 7.7% 4.2% 6.5% 7.7% 4.5% 100.0% mort Weight	r com Risk - 0.0 - 0.0 - 0.0 - 0.0 - 0.1 - 0.0 - 0.1 - 0.1 - 0.1 - 0.1 - 0.1 - 0.1 - 0.1 - 0.0 - 0.1 - 0.0 - 0.1 - 0.0 - 0.0 - 0.1 - 0.0 -	nplications Difference Fixed, 95% CI 4 [-0.29, 0.03] 8 [-0.24, 0.08] 4 [-0.25, -0.03] 05 [-0.20, 0.03] 12 [-0.08, 0.03] 2 [-0.25, 0.01] 12 [-0.23, -0.02] 2 [-0.23, -0.01] 18 [-0.21, 0.05] 8 [-0.11, -0.05] 8 [-0.11, -0.05]		Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total events Heterogeneity: Chi ² Test for overall effect D Study or Subgroup Chen JH et al	t: Z = 4.	90), df = : 33 (P LMH mts T 2 4 7 1 5 1 0 0 0 0 0 20 1, df = : 4 7 1 5 1 0 0 0 0 LMH 1 5 1 1 0 0 0 1 1 5 1 1 1 1 1 1 1 1 1 1 1 1 1	10 (P = < 0.00 Ford 126 67 18 38 53 13 32 35 20 440 9 (P = 1 < 0.00 Ford 50 Contained 53 13 32 35 20 410 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 35 20 53 13 20 53 13 20 53 13 20 53 13 20 53 13 20 53 53 13 20 53 50 50 50 50 50 50 50 50 50 50	0.009); () est ple omi- vents 8 7 27 7 4 7 4 6 5 5 2 75 5 2 75 5 2 75 5 2 001) est ple 001) 010 010 010 010 010 010 01	I 133 1 133 1 133 36 51 32 42 25 602 = 10% obts of 1 I 1 I 1 10 1 38 97 602 602 I 1 Total 1 133 1	6 majo 26.2% 26.2% 16.8% 4.9% 4.9% 4.2% 6.5% 4.5% 13.9% 4.5% 100.0% mort <u>Weighth</u>	r con Risk -0.0 -0.0 -0.0 -0.1 -0.0 -0.0 -0.0 -0.0	nplications Difference Fixed, 95% CI 4 (-0.03, 0.00) 18 (-0.24, 0.08) 4 (-0.25, -0.03) 16 (-0.20, 0.03) 2 (-0.25, 0.01) 12 (-0.08, 0.03) 2 (-0.25, 0.01) 18 (-0.29, -0.02) 3 (-0.11, -0.05) 3 (-0.12, -0.02) 3 (-0.12,	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen JH et al Chen JH et al Chun JH et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effect D Study or Subgroup Chen JH et al Chen K et al	t: Z = 4.	90), df = : 33 (P LMH nts T 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00 Ford 126 38 67 18 38 53 13 32 35 20 440 9 (P = 1 < 0.00 Ford 0 tal E 126 38	0.009); () est pld OMH Vents 8 7 27 4 7 4 7 4 7 4 6 5 2 2 75 5 2 2 75 5 2 2 75 5 2 0.35); ² () 001 001 001 001 001 001 001 00	I* = 39? I Total 133 38 110 36 71 32 42 25 602 = 10% Dots of I Total I Total 133 38 38	6 majo 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 4.5% 100.0% mort <u>Weight</u> 32.5% 9.6%	r con Risk <u>M-H,</u> -0.0 -0.0 -0.0 -0.1 -0.1 -0.1 -0.1 -0.0 k k k k k k k k	nplications c Difference Fixed, 95% CI 14 [-0.09, 0.00] 14 [-0.25, -0.03] 16 [-0.22, -0.03] 16 [-0.22, 0.01] 15 [-0.22, 0.01] 15 [-0.22, 0.01] 12 [-0.08, 0.03] 12 [-0.25, -0.01] 16 [-0.29, -0.02] 10 [-0.02, 0.02] 10 [-0.02, 0.02] 10 [-0.02, 0.05]		Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi [≇] Test for overall effect C Study or Subgroup. Chen JH et al Chen K et al Guro H et al Kim WJ et al Kim WJ et al Komatsu S et al Rhu J et al Zhang Y et al Zhang Y et al Total events Heterogeneity: Chi [≅] Test for overall effect D Study or Subgroup. Chen JH et al Chen K et al Cho JY et al	t: Z = 4.	90), df = : 33 (P LMH nts T 2 4 7 1 5 1 0 0 0 0 0 1 64 (P LMH nts T 0 0 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00) Ford otal E 126 53 13 32 53 13 32 20 440 9 (P = 1 < 0.00) Ford otal E 126 38 440 9 (P = 1 20 53 20 440 9 (P = 1 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 53 53 20 50 50 50 50 50 50 50 50 50 5	0.009); () est ple omi- omi- est ple omi- est ple omi- omi	P = 399 I Total 133 38 110 36 37 51 32 42 25 602 = 10% otts of I 133 38 100 133 38 100	6 Weight 26.2% 7.7% 16.8% 4.9% 4.9% 4.9% 7.7% 4.5% 6.5% 100.0% Weight 32.5% 9.6% 5.3%	r con Risk M-H, -0.0 -0.1 -0.0	nplications Difference Fixed, 95% CI 4 (-0.9, 0.00) 18 (-0.24, 0.08) 4 (-0.25, -0.03) 15 (-0.22, 0.01) 12 (-0.08, 0.03) 2 (-0.25, 0.01) 12 (-0.08, 0.03) 2 (-0.23, -0.01) 18 (-0.21, 0.05) 8 (-0.21, 0.05) 8 (-0.11, -0.05) 8 (-0.11, -0.05) 8 (-0.11, -0.05) 8 (-0.11, -0.05) 8 (-0.11, -0.05) 10 (-0.02, 0.02) 10 (-0.05, 0.05) 10 (-0.05, 0.05)		Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total events Heterogeneity: Chi ² Test for overall effect D Study or Subgroup Chen JH et al Chen K et al Chen JH et al Guro H et al	t: Z = 4.	90), df = - 3.33 (P LMH 1 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00) Ford 126 67 18 38 67 18 38 63 13 32 35 20 440 9 (P = 1 440 9 (P = 1 6 7 126 38 24 67	0.09); ;; est ple OMI- vents 8 7 27 4 7 7 4 6 5 2 2 75 2 75 2 2 75 2 2 75 2 2 75 5 2 0001) 1 0 0 0 0 0 0 0 0 0 0 0 0 0	Image: Control of the second state of the s	 ⁶ majo <u>Weight</u> 7.7% 16.8% 4.9% 7.7% 13.9% 4.2% 7.7% 4.5% 100.0% ⁶ mort <u>Weight</u> 32.5% 9.6% 5.3% 20.9% 	r con Risk -0.0 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.1 -0.0	nplications Difference Fixed, 95% CI 4 [-0.28, -0.03] 16 [-0.20, 0.09] 16 [-0.20, 0.03] 12 [-0.08, 0.03] 12 [-0.08, 0.03] 12 [-0.28, -0.02] 12 [-0.23, -0.01] 18 [-0.21, 0.05] 3 [-0.11, -0.05] 3 [-0.11, -0.05] 5 Difference Fixed, 95% CI 10 [-0.02, 0.02] 10 [-0.05, 0.05] 11 [-0.05, 0.03]	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen JH et al Chen K et al Guro H et al Kim WJ et al Tarantino G et al Xu HW et al Zhang Y et al Total events Heterogeneity: Chi ² Test for overall effect D Study or Subgroup Chen JH et al Cho JY et al Chen K et al Cho JY et al Cho JY et al Cho JY et al	t: Z = 4.	90), df = : 1.33 (P LMH 1 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 (P = < 0.00) Ford otal E 126 38 67 18 38 53 13 32 35 20 440 9 (P = 1 440 9 (P = 1 Ford 53 20 Ford 67 126 38 20 440 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 67 13 20 Ford 70 13 20 Ford 70 13 20 Ford 70 70 70 70 70 70 70 70 70 70	0.009); 01) est ple OMI- vents 8 7 7 4 6 5 5 2 7 4 6 5 5 2 7 5 2 7 5 5 2 7 5 5 2 7 5 5 5 2 001) 0 0 0 0 0 0 0 0 0 0 0 0 0	I* = 39? Total 133 38 110 36 97 51 32 25 602 = 10% Dts of 133 38 97 51 322 602 10% Total 133 38 19 110 37	6 majo 26.2% 7.7% 16.8% 4.9% 4.9% 4.2% 6.5% 4.5% 100.0% mort Weighth 32.5% 9.6% 5.3% 20.9% 9.3%	r con Risk <u>M-H.</u> -0.0 -0.	nplications Difference Fixed, 95% CI 4 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.22, 0.01] 16 [-0.22, 0.01] 12 [-0.08, 0.03] 2 [-0.25, 0.01] 16 [-0.29, -0.02] 10 [-0.21, 0.05] 8 [-0.11, -0.05] 8 [-0.11, -0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05]	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	C
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen JH et al Chen JH et al Chen JH et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effect D Study or Subgroup Chen JH et al Chen JH et al Chen JH et al Chon JY et al Guro H et al Chor JY et al Guro H et al Chor JY et al Guro H et al Kim WJ et al Kim WJ et al	t: Z = 4.	90), df = - 3.33 (P LMH nts T 2 4 7 1 5 1 5 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 ($P = < 0.00$) Ford total E 126 38 67 18 38 53 13 32 20 440 9 ($P = 1$ 440 9 ($P = 1$ 126 53 35 20 440 Ford 67 38 440 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 53 35 20 53 53 53 53 55 35 20 57 50 50 50 50 50 50 50 50 50 50	0.09); ;; 01) est ple omi- vents 8 7 27 4 7 4 7 4 6 5 5 27 7 4 7 4 7 4 6 5 5 27 7 4 7 4 7 4 7 4 6 5 5 27 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 7 7 7 7 7 8 7 7 7 8 7 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 7 8 7 7 7 8 7 7 8 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 9 8 7 9 8 8 8 8 8 8 8 8 8 8 8 8 8	P = 399 Total 1 1 1 3 3 1 1 3 3 8 97 51 32 25 602 = 10% 0 ts of 1 Total 1 3 8 97 51 32 42 25 602 = 10% 0 1 3 8 1 1 3 8 1 1 3 8 1 1 3 2 2 5 6 02 1 1 3 1 3 1 3 1 3 2 5 6 02 1 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 1 3 1 3 1 3 1 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1	6 majo 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 4.5% 100.0% mort Weighth 32.5% 9.6% 5.3% 9.6% 6.0%	r con Risk -0.0 -0.0 -0.0 -0.0 -0.0 -0.0 -0.0 -0.	nplications c Difference Fixed, 95% CI 14 [-0.09, 0.00] 14 [-0.25, -0.03] 16 [-0.24, 0.08] 4 [-0.25, -0.03] 15 [-0.22, 0.01] 15 [-0.22, 0.01] 15 [-0.22, 0.01] 12 [-0.08, 0.03] 2 [-0.23, -0.01] 18 [-0.21, 0.05] 8 [-0.11, -0.05] 8 [-0.11, -0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.13, 0.13]		Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi [≇] Test for overall effec C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Kim WJ et al Koratsu S et al Rhu J et al Zhang Y et al Zhang Y et al Zhang Y et al Zhang Y et al Chen (95% Cl) Total events Heterogeneity: Chi [≇] Test for overall effec D Study or Subgroup Chen JH et al Chen K et al Cho JY et al Guro H et al Kim WJ et al Kim WJ et al	t: Z = 4.	90), df = : ILMH mts T 2 4 7 1 5 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	10 ($P = < 0.00$) Ford 126 38 67 18 33 13 32 35 20 440 9 ($P = 1$ < 0.00 Ford 0 ($P = 1$ 20 440 9 ($P = 1$ 20 440 9 ($P = 1$ 20 440 9 ($P = 1$ 21 21 21 21 21 21 21 21 21 21	0.09); ;; est ple omi- vents 8 7 4 7 4 6 5 2 2 7 5 2 2 7 5 2 2 7 5 2 2 7 5 5 2 2 7 5 5 2 0 001) 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	Image: second	6 majo Weight 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 100.0% mort Weight 32.5% 9.6% 20.9% 9.3% 6.0% 8.0%	r con Risk <u>M-H</u> , -0.0 -0.1. -0.1. -0.1. -0.1. -0.1. -0.1. -0.1. -0.1. -0.0 -0.1. -0.0 -0.1. -0.0 -0.1. -0.0 -0.1. -0.0 -0.1. -0.0. -0.1. -0.0. -0.1. -0.0. -0.0. -0.0. -0.0. -0.0.0.0 -0.0.0 -0.0.0 -0.0.0 -0.0.0 -0.0.0 -0.	nplications Difference Fixed, 95% CI 4 [-0.29, 0.03] 8 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.20, 0.03] 2 [-0.25, 0.01] 12 [-0.08, 0.03] 2 [-0.25, 0.01] 18 [-0.21, 0.05] 2 [-0.23, -0.01] 18 [-0.21, 0.05] 3 [-0.11, -0.05] 3 [-0.11, -0.05] 3 [-0.11, -0.05] 10 [-0.02, 0.02] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.13, 0.13] 13 [-0.11, 0.05]	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	C
Total events Heterogeneity: Chi [≇] Test for overall effec C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kim WJ et al Kornatsu S et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Total (95% Cl) Total events Heterogeneity: Chi [≇] Test for overall effec D Study or Subgroup Chen JH et al Chen K et al Chen K et al Guro H et al Kim JM et al Kim WJ et al	t: Z = 4.	90), df = - 3.33 (P LMH nts T 2 4 7 1 5 1 5 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 ($P = < 0.00$) Ford total E 126 38 67 18 38 53 13 32 20 440 9 ($P = 1$ 440 9 ($P = 1$ 126 53 35 20 440 Ford 67 38 440 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 35 20 53 53 35 20 53 53 53 53 55 35 20 57 50 50 50 50 50 50 50 50 50 50	0.09); ;; 01) est ple omi- vents 8 7 27 4 7 4 7 4 6 5 5 27 7 4 7 4 7 4 6 5 5 27 7 4 7 4 7 4 7 4 6 5 5 27 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 4 7 7 7 7 7 7 7 8 7 7 7 8 7 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 7 7 8 7 7 7 8 7 7 8 7 7 8 7 7 7 8 7 7 7 8 7 7 7 8 7 7 9 8 7 9 8 8 8 8 8 8 8 8 8 8 8 8 8	P = 399 Total 1 1 1 3 3 1 1 3 3 8 97 51 32 25 602 = 10% 0 ts of 1 Total 1 3 8 97 51 32 42 25 602 = 10% 0 1 3 8 1 1 3 8 1 1 3 8 1 1 3 2 2 5 6 02 1 1 3 1 3 1 3 1 3 2 5 6 02 1 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 3 1 1 3 1 3 1 3 1 1 3 1 1 1 1 1 1 1 1 1 1 1 1 1	6 majo 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 4.5% 100.0% mort Weighth 32.5% 9.6% 5.3% 9.6% 6.0%	r con Risk <u>M-H</u> , -0.0 -0.1. -0.1. -0.1. -0.1. -0.1. -0.1. -0.1. -0.1. -0.0. -0.1. -0.0. -0.1. -0.0. -0.1. -0.0. -0.1. -0.0. -0.1. -0.1. -0.1. -0.1. -0.0. -0.	nplications c Difference Fixed, 95% CI 14 [-0.09, 0.00] 14 [-0.25, -0.03] 16 [-0.24, 0.08] 4 [-0.25, -0.03] 15 [-0.22, 0.01] 15 [-0.22, 0.01] 15 [-0.22, 0.01] 12 [-0.08, 0.03] 2 [-0.23, -0.01] 18 [-0.21, 0.05] 8 [-0.11, -0.05] 8 [-0.11, -0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.13, 0.13]	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	
Total events Heterogeneity: Chi ² Test for overall effect C Study or Subgroup Chen JH et al Chen JH et al Chen JH et al Chen JH et al Kim WJ et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Total (95% CI) Total events Heterogeneity: Chi ² Test for overall effect D Study or Subgroup Chen JH et al Chen JH et al Chen K et al Cho JY et al Guro H et al Kim WJ et al Kim WJ et al Kim WJ et al Xu HW et al Yoon Yi et al	t: Z = 4.	90), df = - , 33 (P LMH nts T 2 4 7 1 5 1 0 0 0 0 0 20 20 20 20 4 4 7 1 0 0 0 0 0 1 0 0 0 1 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 ($P = < 0.00$) Ford 126 38 67 18 33 13 32 35 20 440 9 ($P = 1$ < 0.00 Ford 0 ($P = 1$ 20 440 9 ($P = 1$ 20 440 9 ($P = 1$ 20 440 9 ($P = 1$ 21 21 21 21 21 21 21 21 21 21	0.09); ;; est ple omi- vents 8 7 4 7 4 6 5 2 2 7 5 2 2 7 5 2 2 7 5 2 2 7 5 5 2 2 7 5 5 2 0 001) 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	F = 39° Total 133 38 110 36 97 51 32 25 602 = 10% bts of 133 38 97 602 = 10% bts of 1 133 38 19 110 37 36 32 33	6 majo Weight 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 100.0% mort Weight 32.5% 9.6% 20.9% 9.3% 6.0% 8.0%	r con Risk -0.0 -0.0 -0.1 -0.0 -0.1 -0.1 -0.0 -0.1 -0.0	nplications c Difference Fixed, 95% CI 4 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.20, 0.09] 15 [-0.22, 0.01] 16 [-0.25, 0.01] 16 [-0.25, 0.01] 16 [-0.25, 0.01] 18 [-0.11, -0.05] 8 [-0.11, -0.05] 8 [-0.11, -0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.13, 0.13] 13 [-0.11, 0.05] 10 [-0.06, 0.06]	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	C
Total events Heterogeneity: Chi [≇] Test for overall effec C Study or Subgroup, Chen JH et al Chen K et al Guro H et al Kim WJ et al Komatsu S et al Rhu J et al Tarantino G et al Xu HW et al Zhang Y et al Total (95% Cl) Total events Heterogeneity: Chi [≇] Test for overall effec D Study or Subgroup, Chen JH et al Chen K et al Cho JY et al Guro H et al Kim JM et al Kim WJ et al Xu HW et al Xu HW et al Yoon YI et al Total (95% Cl)	t: Z = 4.	90), df = : LIMH Ints T 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0	10 ($P = < 0.00$) Ford otal E 126 38 67 18 38 53 13 32 20 440 9 ($P = 1$ 440 Ford Ford 0 ($P = 1$ 24 67 35 20 440 Ford 67 18 32 35 20 440 Ford 67 18 32 35 20 440 Ford 67 18 32 35 20 53 53 35 20 53 53 53 53 53 53 53 53 53 53	0.09); 01) est ple omi- vents 8 7 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 4 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 2 7 5 5 2 7 5 5 2 0 001) 0 0 0 0 0 0 0 0 0 0 0 0 0	F = 39° Total 133 38 110 36 97 51 32 25 602 = 10% bts of 133 38 97 602 = 10% bts of 1 133 38 19 110 37 36 32 33	6 majo 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 4.5% 100.0% mort Weight 32.5% 9.6% 5.3% 5.3% 8.0% 8.3%	r con Risk -0.0 -0.0 -0.1 -0.0 -0.1 -0.1 -0.0 -0.1 -0.0	nplications Difference Fixed, 95% CI 4 [-0.29, 0.03] 8 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.20, 0.03] 2 [-0.25, 0.01] 12 [-0.08, 0.03] 2 [-0.25, 0.01] 18 [-0.21, 0.05] 2 [-0.23, -0.01] 18 [-0.21, 0.05] 3 [-0.11, -0.05] 3 [-0.11, -0.05] 3 [-0.11, -0.05] 10 [-0.02, 0.02] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.05, 0.03] 10 [-0.13, 0.13] 13 [-0.11, 0.05]		Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0
Total events Heterogeneity: Chi [≇] Test for overall effec C Study or Subgroup Chen JH et al Chen K et al Guro H et al Kom 45 et al Kom 45 et al Kom 45 et al Tarantino G et al Xu HW et al Zhang Y et al Zhang Y et al Total (95% Cl) Total events Heterogeneity: Chi [≇] Test for overall effec D Study or Subgroup	= 10.04 Ever tt Z = 4.	90), df = : IMH 1 2 4 7 1 5 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	10 ($P = < 0.00$) Ford otal E (126) 38 67 18 53 13 32 20 440 9 ($P = 1$) < 0.00 Ford otal E (126) 38 24 67 37 18 24 67 37 33 375	0.09); ;; est ple OMH- vents 8 7 7 7 4 6 5 5 2 7 7 4 6 5 2 7 7 7 4 6 5 2 7 7 7 4 6 5 2 7 7 7 4 6 5 2 7 7 7 4 7 7 7 4 6 5 5 2 7 7 7 4 7 7 7 4 7 7 7 7 4 7 7 7 7 7 7 7 7 7 7 7 7 7	F = 39° Tots of 133 38 110 36 97 51 322 602 = 10% Dots of 133 38 110 38 12 5002 = 10% Dots of 1 133 38 10 37 38 110 37 38 438	6 majo 26.2% 7.7% 16.8% 4.9% 4.2% 6.5% 4.5% 100.0% mort Weight 32.5% 9.6% 5.3% 5.3% 8.0% 8.3%	r con Risk -0.0 -0.0 -0.1 -0.0 -0.1 -0.1 -0.0 -0.1 -0.0	nplications c Difference Fixed, 95% CI 4 [-0.09, 0.00] 18 [-0.24, 0.08] 4 [-0.25, -0.03] 16 [-0.20, 0.09] 15 [-0.22, 0.01] 16 [-0.25, 0.01] 16 [-0.25, 0.01] 16 [-0.25, 0.01] 18 [-0.11, -0.05] 8 [-0.11, -0.05] 8 [-0.11, -0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.05, 0.05] 10 [-0.13, 0.13] 13 [-0.11, 0.05] 10 [-0.06, 0.06]	-0.5	Favours [LMH] Favours [OMH] Risk Difference M-H, Fixed, 95% CI 	0

Figure 3 Forest plots of the meta-analysis for postoperative outcomes. (A) Hospital stay; (B) overall morbidity; (C) major complications; (D) mortality.



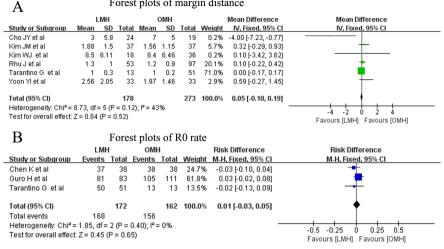


Figure 4 Forest plots of the meta-analysis for oncologic outcomes. (A) Margin distance; (B) R0 rate.

inside the liver parenchyma and more easily ligate or stop bleeding (39). Other significant factors for the lower blood loss with LMH are the ability to control blood flow, the choice of instruments and methods for liver transection, and the skilled manipulation secondary to extensive experience and the steep learning curve (40,41). Despite these factors, significant heterogeneity in blood loss and transfusion rates was documented in our meta-analysis. Therefore, we cannot exclude the fact that the advantages of a laparoscopic approach may be underestimated regarding blood loss and transfusion rates, or the reverse.

Regarding operation duration for LMH, which differs from similar or even reduced time with laparoscopic nonanatomical or minor resection (42,43), we found longer operative times with LMH for HCC, in our meta-analysis. The main reason may be the longer times required for the following with LMH: porta hepatis dissection, duct and vessel isolation, parenchymal resection, and bleeding control (10,44). In our pooled results, LMH operation duration was approximately 72 minutes longer than that for open procedures; a difference that is believed to have a little impact on patients' postoperative outcomes. However, we found significant heterogeneity between LMH and OMH; therefore, a standardized surgical procedure throughout the learning curve is required. Furthermore, the average conversion rate was 9.5% (range, 0-31.6%) in our included studies, which was clearly higher than that reported in laparoscopic minor liver resection and reflects the higher technical demands during LMH. Generally, cirrhosis and intraoperative bleeding were the principal causes of conversion in most LMH processes (45). Moreover, preoperative treatments that warrant particular technical modifications, such as transarterial chemoembolization or portal vein embolization, are continued significant risk factors for conversion (28). Experience from large research centers showed that comprehensive patient assessment using preoperative imaging studies and intraoperative ultrasonography, determining tumor characteristics, and evaluating patients' underlying liver condition could help lower the rate of conversion (22). Other studies have emphasized that a stepwise approach is appropriate to avoid conversions when performing laparoscopic liver surgery and recommend early conversion when encountering technical difficulties (37,46). Without doubt, the technical difficulty of LMH is a challenge for hepatobiliary surgeons; requiring sufficient experience and patience.

The ultimate goal of laparoscopic surgery highlights minimal invasiveness characterized by faster recovery and less complications. As expected, our pooled data showed better short-term postoperative outcomes. Compared with OMH, LMH for HCC was related to lower postoperative overall morbidity as well as fewer major complications. As with other laparoscopic procedures, LMH involves small abdominal incisions that minimize damage to the collateral circulation of the abdominal wall and lymphatic flow to the diaphragm; thus, reducing the incidence of refractory ascites (47). Moreover, the clearer surgical view provided by laparoscopy allows surgeons to ligate or stop bleeding more accurately; thus, reducing the incidence of postoperative hemorrhage and bile leakage. In addition to liver-specific

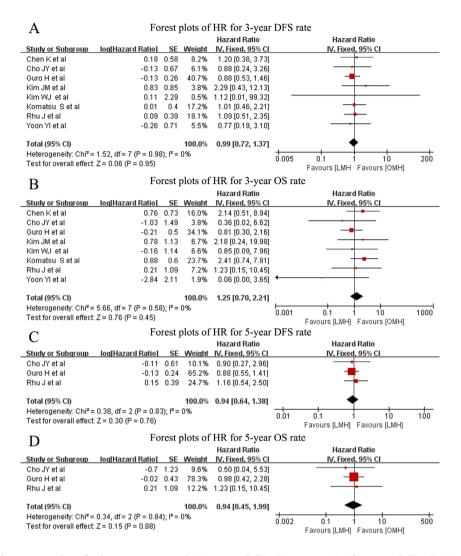


Figure 5 Forest plots of the meta-analysis for long-term survival. (A) 3-year DFS; (B) 3-year OS; (C) 5-year DFS; (D) 5-year OS.

complications, major liver resection has a damaging effect on respiratory function. However, we found in several included reports that pulmonary complications rate in patients undergoing LMH was lower than that in patients undergoing OMH (22,31). In addition, the minimally invasive advantage of LMH is reflected in patients' lower postoperative pain, which facilitates early return to normal activities and gastrointestinal function recovery (48). We also saw a shorter hospitalization duration after LMH, in our meta-analysis, although significant heterogeneity was present between studies, possibly because of differences in medical insurance policies or postoperative management in different countries and institutions.

Surgical margins are an important factor affecting the

prognosis of HCC patients. Because it is impossible to directly touch the liver or tumors located within the liver parenchyma, surgeons have difficulty visually judging the tumor boundaries with a laparoscopic approach, which stresses the need for preoperative and intraoperative imaging assessments such as three-dimensional reconstruction and intraoperative ultrasound (49,50). However, the ideal surgical margin is controversial. The Japanese guidelines recommend no tumor exposure (51), but some studies found that a margin >1 cm can reduce the recurrence rate of HCC (52). In our meta-analysis, the surgical margin and R0 rate for LMH were comparable to those for OMH, and the average surgical margin for all included reports was >1 cm, and was even >8 cm in the

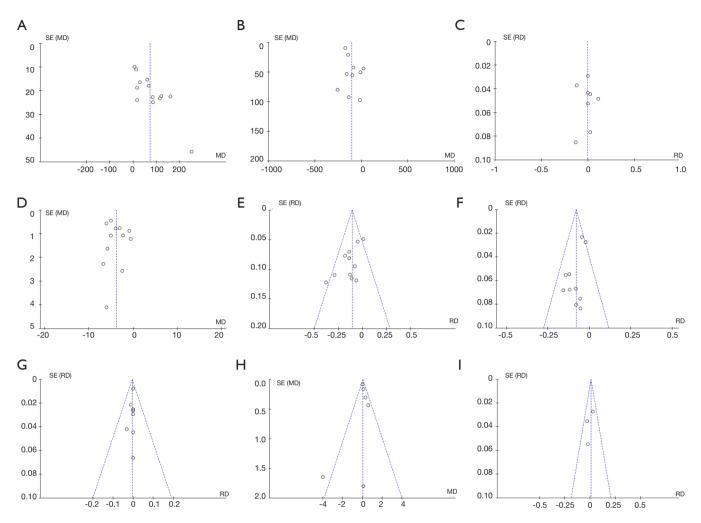


Figure 6 Funnel plots of each outcome reported in the included studies. (A) Operative time; (B) blood loss; (C) blood transfusion; (D) hospital stay; (E) morbidity; (F) major complications; (G) mortality; (H) margin distance; (I) R0 rate.

report by Kim (27). Consequently, our results showed no effect on the surgical margin using a laparoscopic approach, and the best surgical margin remains an important topic for discussion.

The long-term survival rate is conclusive for assessing LMH for HCC as a radical tumor surgery. As with previous studies of minor LLR (53,54), our study confirmed similar results for LMH, as we found no differences between LMH and OMH regarding long-term survival. Therefore, we believe that using laparoscopic techniques is not a direct factor, but that intraoperative hemorrhage, tumor exposure, and dissemination caused by a laparoscopic approach are the key factors affecting tumor recurrence and survival in HCC patients. Skilled laparoscopic techniques and extensive hepatectomy experience are prerequisites for LMH.

This meta-analysis included 13 studies published in the last 10 years and was based on a previous study (10); however, certain limitations warrant consideration. First, in our study, the tumor diameters in the LMH group were smaller than those in the OMH group, suggesting that some researchers were more conservative in selecting patients during the LMH learning phase, which may have underestimated the difficulty of LMH. Additionally, selection bias and unmeasured confounding factors were present in this meta-analysis because of deficiencies in retrospective studies, which may have impacts on outcomes. Second, the clinical heterogeneity caused by the perioperative management in different institutions may have influenced perioperative outcomes, especially reflected in operative time and hospital stay. Clinical

3336

heterogeneity caused by surgeons' skill level also had reasonably influenced for perioperative outcomes, reflected in the intraoperative blood loss volume. Third, this metaanalysis compared a limited number of postoperative indicators. However, other perioperative outcomes that would have been useful in this meta-analysis varied in the majority of included studies, namely, the duration of patients' intensive care unit stay, and readmission rates. Fourth, several studies showed that surgeons must perform LMH in 45-60 patients to overcome the learning curve (55,56). Unluckily, the number of cases in majority of the included studies are within the surgeons' learning curve, and therefore our outcomes represent outcomes following LMH only during the learning period. In addition, although LMH has several advantages, the current research only included high-volume laparoscopic liver surgery centers; low-volume liver surgery centers may require a steeper learning curve.

Conclusions

Our meta-analysis results suggested that LMH can be carried out as safely as OMH in select patients and was associated with improved short-term outcomes, namely, less blood loss, lower postoperative morbidity, and shorter hospital stay, without affecting long-term survival. However, our results require confirmation in studies with high-quality designs and in prospective randomized controlled trials.

Acknowledgments

We thank Jane Charbonneau, DVM, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding: This work was supported by National Natural Science Foundation of China (81871927).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi. org/10.21037/tcr.2020.04.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were

appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

- 1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
- Gadsden MM, Kaplan DE. Multidisciplinary Approach to HCC Management: How Can This Be Done? Dig Dis Sci 2019;64:968-75.
- Reich H, Mcglynn F, Decaprio J, et al. Laparoscopic excision of benign liver lesions. Obstet Gynecol 1991;78:956-8.
- 4. Kaneko H, Otsuka Y, Kubota Y, et al. Evolution and revolution of laparoscopic liver resection in Japan. Ann Gastroenterol Surg 2017;1:33-43.
- Yan Y, Cai X, Geller DA. Laparoscopic Liver Resection: A Review of Current Status. J Laparoendosc Adv Surg Tech A 2017;27:481-6.
- Buell JF, Cherqui D, Geller DA, et al. The international position on laparoscopic liver surgery: The Louisville Statement 2008. Ann Surg 2009;250:825-30.
- Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-29.
- Mullen JT, Ribero D, Reddy SK, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg 2007 204:854-62; discussion 862-4.
- 9. Kasai M, Cipriani F, Gayet B, et al. Laparoscopic versus open major hepatectomy: a systematic review and meta-analysis of individual patient data. Surgery 2018;163:985-95.
- Chen K, Pan Y, Hu GY, et al. Laparoscopic Versus Open Major Hepatectomy for Hepatocellular Carcinoma: A Meta-Analysis. Surg Laparosc Endosc Percutan Tech

2018;28:267-74.

- 11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
- 12. Strasberg SM, Phillips C. Use and dissemination of the brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg 2013;257:377-82.
- Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified Clavien classification. Ann Surg 2009;250:798-807.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
- Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into metaanalysis. Trials 2007;8:16.
- Higgins JPT, Green S. editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration;2011. Available online: http://handbook.cochrane.org, accessed March 7, 2018.
- Cho HD, Kim KH, Hwang S, et al. Comparison of pure laparoscopic versus open left hemihepatectomy by multivariate analysis: a retrospective cohort study. Surg Endosc 2018;32:643-50.
- Ratti F, Cipriani F, Ariotti R, et al. Laparoscopic major hepatectomies: current trends and indications. A comparison with the open technique. Updates Surg 2015;67:157-67.
- Medbery RL, Chadid TS, Sweeney JF, et al. Laparoscopic vs open right hepatectomy: a value-based analysis. J Am Coll Surg 2014;218:929-39.
- Kang SH, Kim KH, Shin MH, et al. Surgical outcomes following laparoscopic major hepatectomy for various liver diseases. Medicine (Baltimore) 2016;95:e5182.
- Chen J, Li H, Liu F, et al. Surgical outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma for various resection extent. Medicine (Baltimore) 2017;96:e6460.
- Chen K, Pan Y, Wang YF, et al. Laparoscopic Right Hepatectomy for Hepatocellular Carcinoma: A Propensity Score Matching Analysis of Outcomes Compared with

Conventional Open Surgery. J Laparoendosc Adv Surg Tech A 2019;29:503-12.

- 24. Cho JY, Han HS, Yoon YS, et al. Outcomes of laparoscopic right posterior sectionectomy in patients with hepatocellular carcinoma in the era of laparoscopic surgery. Surgery 2015;158:135-41.
- Guro H, Cho JY, Han HS, et al. Outcomes of major laparoscopic liver resection for hepatocellular carcinoma. Surg Oncol 2018;27:31-5.
- 26. Kim JM, Kwon CHD, Yoo H, et al. Which approach is preferred in left hepatocellular carcinoma? Laparoscopic versus open hepatectomy using propensity score matching. BMC Cancer 2018;18:668.
- Kim WJ, Kim KH, Kim SH, et al. Laparoscopic Versus Open Liver Resection for Centrally Located Hepatocellular Carcinoma in Patients With Cirrhosis: A Propensity Score-matching Analysis. Surg Laparosc Endosc Percutan Tech 2018;28:394-400.
- Komatsu S, Brustia R, Goumard C, et al. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. Surg Endosc 2016;30:1965-74.
- Rhu J, Kim SJ, Choi GS, et al. Laparoscopic Versus Open Right Posterior Sectionectomy for Hepatocellular Carcinoma in a High-Volume Center: A Propensity Score Matched Analysis. World J Surg 2018;42:2930-7.
- Tarantino G, Magistri P, Serra V, et al. Laparoscopic Liver Resection of Right Posterior Segments for Hepatocellular Carcinoma on Cirrhosis. J Laparoendosc Adv Surg Tech A 2017;27:559-63.
- Xu HW, Liu F, Li HY, et al. Outcomes following laparoscopic versus open major hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a propensity score-matched analysis. Surg Endosc 2018;32:712-9.
- 32. Yoon YI, Kim KH, Kang SH, et al. Pure Laparoscopic Versus Open Right Hepatectomy for Hepatocellular Carcinoma in Patients With Cirrhosis: A Propensity Score Matched Analysis. Ann Surg 2017;265:856-63.
- Zhang Y, Chen XM, Sun DL. Short-term Outcomes of Laparoscopic Versus Open Right Hemihepatectomy for Hepatocellular Carcinoma. Surg Laparosc Endosc Percutan Tech 2016;26:e157-e160.
- Zhang Y, Huang J, Chen XM, et al. A Comparison of Laparoscopic Versus Open Left Hemihepatectomy for Hepatocellular Carcinoma. Surg Laparosc Endosc Percutan Tech 2016;26:146-9.
- Takahara T, Wakabayashi G, Konno H, et al. Comparison of laparoscopic major hepatectomy with

Lu et al. Outcomes after laparoscopic major hepatectomy for HCC

propensity score matched open cases from the National Clinical Database in Japan. J Hepatobiliary Pancreat Sci 2016;23:721-34.

- Palanisamy S, Sabnis SC, Patel ND, et al. Laparoscopic Major Hepatectomy-Technique and Outcomes. J Gastrointest Surg 2015;19:2215-22.
- Cauchy F, Fuks D, Nomi T, et al. Risk factors and consequences of conversion in laparoscopic major liver resection. Br J Surg 2015;102:785-95.
- Yang JH, Gu J, Dong P, et al. Isolated complete caudate lobectomy for hepatic tumor of the anterior transhepatic approach: surgical approaches and perioperative outcomes. World J Surg Oncol 2013;11:197.
- Cipriani F, Shelat VG, Rawashdeh M, et al. Laparoscopic Parenchymal-Sparing Resections for Nonperipheral Liver Lesions, the Diamond Technique: Technical Aspects, Clinical Outcomes, and Oncologic Efficiency. J Am Coll Surg 2015;221:265-72.
- 40. Farges O, Goutte N, Dokmak S, et al. How surgical technology translates into practice: the model of laparoscopic liver resections performed in France. Ann Surg 2014;260:916-21; discussion 921.
- Jia C, Li H, Wen N, et al. Laparoscopic liver resection: a review of current indications and surgical techniques. Hepatobiliary Surg Nutr 2018;7:277-88.
- Sotiropoulos GC, Prodromidou A, Machairas N. Metaanalysis of laparoscopic vs open liver resection for hepatocellular carcinoma: The European experience. J BUON 2017;22:1160-71.
- 43. Ciria R, Cherqui D, Geller DA, et al. Comparative Shortterm Benefits of Laparoscopic Liver Resection: 9000 Cases and Climbing. Ann Surg 2016;263:761-77.
- 44. Cho W, Kwon CHD, Choi JY, et al. Impact of technical innovation on surgical outcome of laparoscopic major liver resection: 10 years' experience at a large-volume center. Ann Surg Treat Res 2019;96:14-8.
- 45. Abu Hilal M, Aldrighetti L, Dagher I, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Ann Surg 2018;268:11-8.
- 46. Halls MC, Cipriani F, Berardi G, et al. Conversion for Unfavorable Intraoperative Events Results in Significantly Worse Outcomes During Laparoscopic Liver Resection: Lessons Learned From a Multicenter Review of 2861 Cases. Ann Surg 2018;268:1051-7.
- 47. Morise Z, Ciria R, Cherqui D, et al. Can we expand

the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci 2015;22:342-52.

- Komatsu S, Brustia R, Goumard C, et al. Clinical impact of laparoscopic hepatectomy: technical and oncological viewpoints. Surg Endosc 2017;31:1442-50.
- 49. He YB, Bai L, Aji T, et al. Application of 3D reconstruction for surgical treatment of hepatic alveolar echinococcosis. World J Gastroenterol 2015;21:10200-7.
- Robu MR, Ramalhinho J, Thompson S, et al. Global rigid registration of CT to video in laparoscopic liver surgery. Int J Comput Assist Radiol Surg 2018;13:947-56.
- Nakashima Y, Nakashima O, Tanaka M, et al. Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type. Hepatol Res 2003;26:142-7.
- 52. Shi M, Guo RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg 2007;245:36-43.
- 53. Yoon SY, Kim KH, Jung DH, et al. Oncological and surgical results of laparoscopic versus open liver resection for HCC less than 5 cm: case-matched analysis. Surg Endosc 2015;29:2628-34.
- 54. Cheung TT, Dai WC, Tsang SH, et al. Pure Laparoscopic Hepatectomy Versus Open Hepatectomy for Hepatocellular Carcinoma in 110 Patients With Liver Cirrhosis: A Propensity Analysis at a Single Center. Ann Surg 2016;264:612-20.
- 55. Chan FK, Cheng KC, Yeung YP, et al. Learning Curve for Laparoscopic Major Hepatectomy: Use of the Cumulative Sum Method. Surg Laparosc Endosc Percutan Tech 2016;26:e41-5.
- Brown KM, Geller DA. What is the Learning Curve for Laparoscopic Major Hepatectomy? J Gastrointest Surg 2016;20:1065-71.

Cite this article as: Lu Q, Zhang N, Wang F, Chen X, Chen Z. Surgical and oncological outcomes after laparoscopic *vs.* open major hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. Transl Cancer Res 2020;9(5):3324-3338. doi: 10.21037/tcr.2020.04.01

Forst plots of cirrhosis

			Fors	t plo	ts of ci	rrhosis	
Study or Subgroup	LN Events		OM Events		Weight	Risk Difference M-H, Fixed, 95% Cl	Risk Difference M-H, Fixed, 95% Cl
Chen Ketal	34		34	38			
Guro H et al	36		61	110			
Kim JM et al	16		20	37			
Rhu J et al	20	58	36	133	27.6%	0.07 [-0.07, 0.22]	- +=
Tarantino G et al	13	13	49	51	7.1%	0.04 [-0.07, 0.15]	- -
Yoon YI et al	29	33	28	33	11.3%		_
					100.00		
Fotal (95% CI) Fotal events	147	246	228	402	100.0%	0.00 [-0.07, 0.08]	Ť
Heterogeneity: Chi²:	= 2.91, df	= 5 (P =	0.71); l²	= 0%		H	1 -0.5 0 0.5
Test for overall effec	t: Z = 0.13	(P = 0.9					Favours [LMH] Favours [OMHI]
В			Fors	t plo	ts of C	hild A	
Church and Carls are any	LM		OMH		18/	Risk Difference	Risk Difference
Study or Subgroup			Events			M-H, Random, 95% Cl	M-H, Random, 95% Cl
Chen JH et al	124	126	127	133	21.2%	0.03 [-0.01, 0.07]	T
Chen K et al	38	38	38	38	18.6%	0.00 [-0.05, 0.05]	
Guro H et al	79	83	92	111	10.8%	0.12 [0.04, 0.21]	
<omatsu al<="" et="" s="" td=""><td>38</td><td>38</td><td>38</td><td>38</td><td>18.6%</td><td>0.00 [-0.05, 0.05]</td><td>+</td></omatsu>	38	38	38	38	18.6%	0.00 [-0.05, 0.05]	+
Tarantino G et al	9	13	46	51	1.6%	-0.21 [-0.47, 0.05]	
	35	35	40	42	18.6%		_
Zhang Yetal Zhang Yetal	35 20	35 20	42	42 25	10.8%	0.00 [-0.05, 0.05]	_ _
Zhang Y et al	20	20	25	25	10.070	0.00 [-0.08, 0.08]	l
Fotal (95% CI)		353	400	438	100.0%	0.02 [-0.02, 0.05]	†
Fotal events Heterogeneity: Tau² :	343 - 1 חחח =	j² = 12 २	408 5 df = 6	(P = 0)	05): I ² = 5	1%	
Test for overall effect				(F = 0.)	03),1 = 3	1 20	-0.5 -0.25 0 0.25 0.5 Favours (LMH) Favours (OMH)
C			Fors	t plo	ts of IC	CG-R15	· · · · · · · · · · · · · · · · · · ·
	LN	н		мн		Mean Difference	Mean Difference
Study or Subgroup		D Total			otal We	ight IV, Random, 95% C	
Chen JH et al		.5 126				.4% 0.60 [0.00, 1.20	
Chen Ketal							
	6.9 3					.1% 0.00 [-1.48, 1.48	
Cho JY et al	8.2 7					.2% 1.80 [-1.68, 5.28	
Guro H et al	9.1 8					.0% -0.40 [-2.67, 1.87	
<im al<="" et="" jm="" td=""><td>11.8 7</td><td>.5 37</td><td></td><td>3.3</td><td></td><td>.5% 3.10 [0.46, 5.74</td><td></td></im>	11.8 7	.5 37		3.3		.5% 3.10 [0.46, 5.74	
<im al<="" et="" td="" wj=""><td>10.4 3</td><td>.8 18</td><td>12.8</td><td>3.4</td><td>36 9</td><td>.0% -2.40 [-4.48, -0.32</td><td></td></im>	10.4 3	.8 18	12.8	3.4	36 9	.0% -2.40 [-4.48, -0.32	
	10.4 3 11.5 5					.0% -2.40 [-4.48, -0.32 .1% 0.80 [-0.68, 2.28	i <u> </u>
Rhu J et al		.1 58	10.7		133 13		
Rhu Jetal Ku HW etal	11.5 5	.1 58 .1 32	10.7 5.1	4 2	133 13 32 17	.1% 0.80 [-0.68, 2.28	
Rhu J et al Xu HW et al Yoon YI et al	11.5 5 5 2	.1 58 .1 32 .7 33	10.7 5.1 13.7	4 2 5.5	133 13 32 17 33 7	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37	
Kim WJ et al Rhu Jet al Xu HW et al Yoon YI et al Total (95% CI) Heterogeneity: Tau ² =	11.5 5 5 2 11.6 4	.1 58 .1 32 .7 33 433	10.7 5.1 13.7	4 2 5.5	133 13 32 17 33 7 571 100	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88	
Rhu J et al Ku HW et al Yoon YI et al Fotal (95% CI)	11.5 5 5 2 11.6 4 0.66; Chi	.1 58 .1 32 .7 33 433 *= 17.69,	10.7 5.1 13.7	4 2 5.5	133 13 32 17 33 7 571 100	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88	
Rhu J et al Ku HW et al Yoon YI et al Total (95% CI) Heterogeneity: Tau ² =	11.5 5 5 2 11.6 4 0.66; Chi	.1 58 .1 32 .7 33 433 *= 17.69,	10.7 5.1 13.7 df = 8 (F	4 2 5.5 = 0.02	133 13 32 17 33 7 571 100); I ² = 559	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88	1 -4 -2 0 2 4 Favours [LMH] Favours [OMH]
Rhu J et al Ku HW et al Yoon YI et al Fotal (95% CI) Heterogeneity: Tau [#] = Test for overall effect: D	11.5 6 5 2 11.6 4 0.66; Chř Z = 0.23 (1 58 1 32 7 33 433 *= 17.69, P = 0.81)	10.7 5.1 13.7 df = 8 (F Fors OM	4 2 5.5 = 0.02 t plo	133 13 32 17 33 7 571 100); I ² = 559 ts of m	.1% 0.80 (-0.68, 2.28 .5% -0.10 (-1.10, 0.90 .2% -2.10 (-4.57, 0.37 .0% 0.09 (-0.69, 0.88 .5 icrovascular inva Risk Difference	1 -4 Favours [LMH] Favours [OMH] Sion Risk Difference
Rhu Jetal (u HW etal (voon Yi etal Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup	11.5 6 5 2 11.6 4 0.66; Chir Z = 0.23 (LN Events	1 58 1 32 7 33 433 1 17.69, P = 0.81) H <u>1 Total</u>	10.7 5.1 13.7 df=8 (F Fors OM Events	4 2 5.5 = 0.02 t plo H <u>Total</u>	133 13 32 17 33 7 571 100); I ^z = 559 ts of m <u>Weight</u>	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .5 icrovascular inva Risk Difference t. M-H, Fixed, 95% Cl	1 -4 Favours [LMH] Favours [OMH] Ision
Rhu Jetal Ku HW etal Yoon Yietal Fotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: D Study or Subgroup Chen K etal	11.5 5 5 2 11.6 4 0.66; Chř Z = 0.23 (LIV Events 14	1.1 58 1.1 32 1.7 33 433 1 433 1 43 1 4	t 10.7 5.1 13.7 df = 8 (F Fors OM <u>Events</u> 12	4 2 5.5 t plo H <u>Total</u> 38	133 13 32 17 33 7 571 100); I [≠] = 559 ts of m <u>Weight</u> 15.9%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .5 icrovascular inva Risk Difference <u>Risk Difference</u> <u>0.05 [-0.16, 0.27]</u>	1 -4 Favours [LMH] Favours [OMH] Sion Risk Difference
Rhu Jetal Ku HW etal Yoon Yi etal Fotal (95% CI) Heterogeneity: Tau [®] = Fest for overall effect D Study or Subgroup Chen K et al Kim JM et al	11.5 5 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23	1.1 58 1.1 32 1.7 33 433 1 433 1 431	t 10.7 5.1 13.7 df = 8 (F Fors OM Events 12 25	4 2 5.5 t plo H <u>Total</u> 38 37	133 13 32 17 33 7 571 100); I ² = 559 ts of m <u>Weight</u> 15.9% 15.5%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .5 icrovascular inva Risk Difference <u>M-H, Fixed, 95% Cl</u> 0.05 [-0.16, 0.27] -0.05 [-0.17, 0.16]	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal Ku HW etal Yoon Yi etal Fotal (95% CI) Heterogeneity: Tau [®] = Fest for overall effect D Study or Subgroup Chen K et al Kim JM et al	11.5 5 5 2 11.6 4 0.66; Chi [*] Z = 0.23 (LN <u>Events</u> 14 23	1 56 1 32 7 33 433 ² = 17.69, ² = 0.81) H <u>5 Total</u> 38 37 5 18	10.7 5.1 13.7 df = 8 (F Fors OM <u>Events</u> 12 25 10	4 5.5 t plo H <u>Total</u> 38 37 36	133 13 32 17 33 7 571 100 571 100 (); ² = 559 ts of m <u>1 Weight</u> 15.9% 15.5% i 10.1%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.70, 0.71] .00% [-0.16, 0.27] .00% [-0.30, 0.19] .00% [-0.30, 0.19]	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal (u HW etal (voon YI etal Fotal (95% CI) Heterogeneity: Tau ^s = Fest for overall effect: D Study or Subgroup Chen K etal (im JW etal Kim WJ etal	11.5 5 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23	1 56 1 32 7 33 433 ² = 17.69, ² = 0.81) H <u>5 Total</u> 38 37 5 18	t 10.7 5.1 13.7 df = 8 (F Fors OM Events 12 25	4 2 5.5 t plo H <u>Total</u> 38 37	133 13 32 17 33 7 571 100 571 100 (); ² = 559 ts of m <u>1 Weight</u> 15.9% 15.5% i 10.1%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.70, 0.71] .00% [-0.16, 0.27] .00% [-0.30, 0.19] .00% [-0.30, 0.19]	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal (u HW etal (von Yietal Fotal (95% CI) Heterogeneity: Tau [≆] = Fest for overall effect: D Study or Subgroup Chen K etal Kim VJ etal Komatsu S etal	11.5 5 5 2 11.6 4 0.66; Chi [*] Z = 0.23 (LN <u>Events</u> 14 23	1 56 1 32 7 33 ² = 17.69, ² = 0.81) H <u>5 Total</u> 38 37 18 38 38	10.7 5.1 13.7 df = 8 (F Fors OM <u>Events</u> 12 25 10	4 5.5 t plo H <u>Total</u> 38 37 36	133 13 32 17 33 7 571 100 571 100 (); ² = 559 ts of m 1 <u>Weight</u> 3 15.9% 1 15.5% 1 0.1% 3 15.9%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.69, 0.88 .5 .00% 0.09 [-0.69, 0.88 .00% 0.09 [-0.69, 0.88 .00% 0.00 [-0.10, 0.16] .0.05 [-0.16, 0.27] .0.05 [-0.27, 0.16] .0.03 [-0.10, 0.16]	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal (u HW etal (oon Yietal Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JW et al Rhu J et al	11.5 5 5 2 11.6 4 0.66; Chi [*] Z = 0.23 (LIN Events 14 23 2 4	1 56 1 32 7 33 ² = 17.69, ² = 0.81) H <u>5 Total</u> 38 37 18 38 38 58	t 10.7 5.1 13.7 df = 8 (F Fors 0M Events 12 25 10 3	4 2 5.5 t plo H <u>Total</u> 38 37 36 38	133 13 32 17 33 7 571 100 (); ² = 559 ts of m Weight 15.5% 10.1% 10.1% 15.9% 33.9%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .00% 0.09 [-0.69, 0.88 .00% 0.06 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16]	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal (u HW etal (voon YI etal Fotal (95% CI) Heterogeneity: Tau [∞] = Fest for overall effect: D Study or Subgroup Chen K etal (im WJ etal Kim WJ etal Kim WJ etal Komatsu S etal Rhu Jetal Tarantino G etal	11.5 5 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23 4 23 30	.1 58 .1 32 .7 33 .7 33 .1 12 .1 12 .1 18 .1 18 .1 18 .1 18 .1 18 .1 18 .1 13 .1 13	t 10.7 5.1 13.7 df = 8 (F Fors OM Events 12 25 10 3 57	4 2 5.5 t plo H <u>Total</u> 38 37 36 38 133	133 13 32 17 33 7 571 100); F = 559 ts of m Weight 15.9% 15.5% 15.5% 10.1% 33.9% 8.7%	.1% 0.80 [-0.68, 2.28 .5% -0.10 [-1.10, 0.90 .2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 .00% 0.09 [-0.69, 0.88 .00% 0.06 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16]	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu J et al (xu HW et al (xon YI et al Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al (Xim JM et al (Xim JM et al (Xim JW et al Rhu J et al Rhu J et al Farantino G et al (xu HW et al	11.5 5 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23 4 30 30 (.1 58 .1 32 .7 33 433 ≥ 17.69, > = 0.81) H Total 38 38 38 38 38 58 38 34 34	10.7 5.1 13.7 df = 8 (F Fors 0M Events 12 25 10 3 57 2	4 2 5.5 t plo H <u>Total</u> 38 37 36 38 133 51 0	133 13 32 17 33 7 571 100 (); ² = 559 ts of m Weight 15.9% 15.5% 10.1% 15.5% 3.9% 8.7%	1% 0.80[-0.68, 2.28 5% -0.10 [-1.10, 0.90 2.2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 0.09 [-0.69, 0.88 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.06, 0.24] -0.04 [-0.15, 0.07] Not estimable	1 -4 Favours [LMH] Favours [OMH] Sion Risk Difference
Rhu Jetal Ku HW etal Yoon YI etal Total (95% CI) Heterogeneity: Tau ^s = Test for overall effect: D Study or Subgroup Chen K etal Kim VJJ etal Kim VJJ etal Kim VJJ etal Kanu Jetal Tarantino G etal Ku HVY etal Tarantino G etal Ku HVY etal	11.5 5 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23 4 30 30 (.1 58 .1 32 .7 33 433 2 = 17.69, P = 0.81) H Total 38 38 37 18 38 38 38 38 38 38 33 4 236	10.7 5.1 13.7 df = 8 (F Fors 0M Events 12 25 10 3 57 2	4 2 5.5 t plo H <u>Total</u> 38 37 36 38 133 51 0	133 13 32 17 33 7 571 100); F = 559 ts of m Weight 15.9% 15.5% 15.5% 10.1% 33.9% 8.7%	1% 0.80[-0.68, 2.28 5% -0.10 [-1.10, 0.90 2.2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 0.09 [-0.69, 0.88 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.06, 0.24] -0.04 [-0.15, 0.07] Not estimable	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal (u HW etal (von YI etal Fotal (95% CI) Heterogeneity: Tau ^s = Fest for overall effect: D Study or Subgroup Chen K et al (im VU etal Komatsu S etal Rhu J etal Rhu J etal Farantino G etal (u HW etal Fotal (95% CI) Total events	11.5 5 5 2 11.6 4 0.66; Chi Z = 0.23 (Events 14 23 4 30 (11 86	.1 58 .1 32 .7 33 .7 33 .= 17.69, > = 0.81) 	10.7 5.1 13.7 off= 8 (F Fors 0M Events 12 25 10 3 57 2 12 12	4 2 5.5 t plo H <u>Total</u> 38 37 36 38 133 51 0 333	133 13 32 17 33 7 571 100 (); ² = 559 ts of m Weight 15.9% 15.5% 10.1% 15.5% 3.9% 8.7%	1% 0.80[-0.68, 2.28 5% -0.10 [-1.10, 0.90 2.2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 0.09 [-0.69, 0.88 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.06, 0.24] -0.04 [-0.15, 0.07] Not estimable	i i -4 Favours [LMH] Favours [OMH] ision Risk Difference M-H, Fixed, 95% Cl
Rhu J et al Ku HW et al Yoon YI et al Fotal (95% CI) Heterogeneity: Tau [®] = Test for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JM et al Rhu J et al Rhu J et al Tarantino G et al Xu HW et al Total (95% CI) Total events	11.5 5 5 2 11.6 4 0.66; Chii Z = 0.23 (Events 14 23 4 4 33 (0 11 11 58 5 52 14 23 14 23 14 23 14 23 14 23 14 23 14 23 24 24 24 24 24 24 24 24 24 24 24 24 24	.1 58 .1 32 .7 33 433 ² = 17.69, ² = 0.81) H <u>5</u> 37 18 38 58 58 58 58 58 34 236 = 5 (P =	t 10.7 5.1 13.7 df = 8 (F Fors 0M Events 25 10 3 57 2 12 12 121 0.71); F	4 2 5.5 t plo H <u>Total</u> 38 37 36 38 133 51 0 333	133 13 32 17 33 7 571 100 (); ² = 559 ts of m Weight 15.9% 15.5% 10.1% 15.5% 3.9% 8.7%	1% 0.80[-0.68, 2.28 5% -0.10 [-1.10, 0.90 2.2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 0.09 [-0.69, 0.88 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.06, 0.24] -0.04 [-0.15, 0.07] Not estimable	a -4 Favours [LMH] Favours [OMH] sion Risk Difference
Rhu Jetal Ku HW etal Yoon YI etal Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	11.5 5 5 2 11.6 4 0.66; Chii Z = 0.23 (Events 14 23 4 4 33 (0 11 11 58 5 52 14 23 14 23 14 23 14 23 14 23 14 23 14 23 24 24 24 24 24 24 24 24 24 24 24 24 24	1 58 1 32 1 32 1 33 433 1 17.69, P = 0.81) H 1 13 1 8 1 38 1 58 1 38 1 58 1 38 1 38 1 38 1 38 1 38 1 38 1 38 1 38 1 38 1 58 1 32 58 1 32 58 1 58 1 38 1 58 1 38 1 58 1 58	t 10.7 5.1 5.1 13.7 6 Fors 0M Events 25 10 3 577 2 12 12 121 0.71); I [≥] 3)	4 2 5.5 H Total 38 37 36 38 37 36 38 37 36 38 37 36 38 37 38 37 38 38 38 38 38 38 51 0 333 3 51 0 333 3	133 13 32 17 33 7 571 100 (); P = 559 ts of m <u>Weight</u> 15.9% 15.5% 10.1% 15.9% 10.1% 33.9% 8.7%	1% 0.80[-0.68, 2.28 5% -0.10 [-1.10, 0.90 2.2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 0.09 [-0.69, 0.88 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.06, 0.24] -0.04 [-0.15, 0.07] Not estimable	ision Risk Difference M-H, Fixed, 95% Cl -0.5 -0.25 0 0.25 0.5 Favours [LMH] Favours [OMH]
Rhu J et al (xu HW et al (xon YI et al Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al (xim JM et al (xim JM et al (xim JW et al Fotal (95% CI) Total events Heterogeneity: Chi ² : Test for overall effect E	11.5 6 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23 4 30 (11 11 86 = 2.90, df t; $Z = 0.63$	(1 566 (1 37) (1 37	10.7 1: 5.1 1.2 1.2 1.2 1.2 1.2 1.2 1.2 1.2 1.2 1	4 2 5.5 t plo H Total 38 37 38 38 133 51 0 333 51 0 333 51 0 0 333 51 0 0 333 8 133 51 0 0 333 8 133 51 0 0 333 8 133 51 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	133 13 32 17 33 7 571 100); P= 559 ts of m <u>Weight</u> 15.5% 15.5% 10.1% 5 15.9% 5 15.9% 5 10.1% 5 33.9% 8 .7% 5 100.0%	1% 0.80 [-0.65, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 icrovascular inva Risk Difference M-H, Fixed, 95% CI 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.03 [-0.00, 0.24] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] aximum tumor si Mean Difference	A contract of the second secon
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneily: Tau [#] = Fest for overall effect: D Study or Subgroup Chen K et al Kim WJ et al Kim WJ et al Kim WJ et al Tarantino G et al (u HW et al Total (95% CI) Total events Heterogeneily: Chi [#] : Fest for overall effect E Study or Subgroup	11.5 6 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 22 4 33 0 (11 2 4 2 4 33 11 5 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2 4 2	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 t plo H Total 38 37 36 38 33 133 51 0 333 51 0 333 51 0 0 333 51 0 0 333 51 0 0 333 51 0 0 333 51 0 0 333 51 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	133 13 32 17 33 7 571 100); F= 559 ts of m <u>Weighth</u> 15.5% 10.1% 15.5% 10.1% 33.9% 8.7% 100.0% 100.0%	1% 0.80 [-0.66, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 5 icrovascular inva Risk Difference <u>M-H, Fixed, 95% Cl</u> 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.10, 0.16] 0.03 [-0.06, 0.24] 0.03 [-0.06, 0.24] 0.03 [-0.05, 0.10] Not estimable 0.03 [-0.05, 0.10] aximum tumor si Mean Difference ight M.Random, 95% Cl	i i i i i i i i i i i i i i
Rhu J et al (xu HW et al (xon YI et al Fotal (95% CI) Heterogeneity: Tau ²² = Festfor overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JM et al Kim JM et al Rhu J et al Fotal (95% CI) Total events Heterogeneity: Chi ²² : Fest for overall effect E Study or Subgroup Chen JH et al	11.5 6 5 2 11.6 4 0.66; Chi ² Z = 0.23 (Events 23 4 14 23 4 23 4 23 4 24 23 4 24 23 4 24 23 4 24 23 4 24 24 25 25 26 26 26 26 26 26 26 26 26 26	(1 566 (1 37) (1 1 37) (1 1 37) (1 1 37) (1 1 37) (1 1 1 57) (1 1 1 57) (1 1 1 1 1 57) (1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	10.7 10.7	4 2 5.5 H Total 38 37 36 38 133 51 0 3333 = 0% t plo MH 50 T 4.3	133 13 32 17 33 7 571 100); P= 559 ts of m <u>Weight</u> 15.5% 15.5% 15.5% 15.5% 15.5% 33.9% 33.9% 15.9% 1	1% 0.80[-0.68, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 icrovascular inva Risk Difference M-H, Fixed, 95% CI 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.05 [-0.10, 0.16] 0.09 [-0.06, 0.24] 0.00 [-0.10, 0.16] 0.09 [-0.06, 0.24] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.05, 0.10] aximum tumor si Mean Difference ight IV, Random, 95% C 5% -0.80 [-1.63, 0.03	A constraints of the second se
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JM et al Kim JW et al Tarantino G et al Ku HW et al Fotal (95% CI) Total events Heterogeneity: Chi ² : Test for overall effect E Study or Subgroup Chen JH et al Chen JH et al	11.5 6 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23 4 33 (11 24 24 33 (11 24 24 33 (11 24 24 33 (11 11 24 24 33 (11 11 24 24 33 (11 11 24 24 24 33 (11 11 24 24 24 24 24 24 24 24 24 24	(1 566 (1 1 32 (7 3) (1 1 7 3) (1 1 7 3) (1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	10.7 10.7	4 2 5.5 = 0.02 t ploo H Total 38 37 36 37 37 36 37 37 36 37 37 36 37 37 36 37 37 36 37 37 37 36 37 37 37 36 37 37 37 37 37 37 37 37 37 37	133 13 32 17 33 7 571 100); F= 559 ts of m 15.5% 15.5% 15.5% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 15.5% 100.0% 100.0%	1% 0.80 [-0.6; 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 10% 0.09 [-0.69, 0.88 5 0.09 [-0.69, 0.88 6 0.09 [-0.69, 0.88 10 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.03 [-0.06, 0.24] 0.03 [-0.06, 0.24] 0.03 [-0.10, 0.16] 0.03 [-0.05, 0.10] Not estimable 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] aximum tumor si Mean Difference 10H, N, Random, 95% C 5% -0.80 [-1.63, 0.03 -0.30 [-2.02, 1.42	A constraint of the second sec
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneity: Tau ^s = Fest for overall effect: D Study or Subgroup Chen K et al (im WJ et al Kim WJ et al Kim WJ et al Tarantino G et al (u HW et al Total events Heterogeneity: Chi ² : Fest for overall effect Chen K et al Chen V et al	11.5 6 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 22 4 33 0 11 2 4 2 4 33 0 11 2 4 2 4 33 0 11 5 2 4 4 2 4 3 3 11 5 4 4 2 4 4 2 4 4 2 4 4 2 4 4 2 4 4 2 4 4 3 3 6 5 2 4 4 4 2 4 4 2 4 4 2 4 4 2 4 4 2 4 4 4 2 4 4 4 2 4 4 4 4 4 4 3 3 6 5 2 4 4 4 4 4 2 4 4 4 4 4 5 6 5 2 4 4 4 4 5 6 5 2 4 4 4 5 6 5 2 7 5 5 2 7 7 5 5 5 2 7 7 5 5 5 2 7 7 5 5 5 7 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7 7 5 7 7 7 5 7 7 7 5 7 7 7 7 7 7 7 7 7 7 7 7 7	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 t ploo H <u>Total</u> 38 37 36 38 37 37 36 38 37 36 38 37 37 36 38 37 37 36 38 37 37 36 38 37 37 36 38 37 37 37 37 38 37 37 38 37 37 37 37 37 37 37 37 37 37	133 13 32 17 33 7 571 100); F= 559 ts of m Weighting 15.5% 15.5% 10.1% 15.9% 15.5% 10.1% 15.9% 10.1% 15.9% 10.0% 10.0% 13.3 9 38 5 19 7	1% 0.80 [-0.68, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 5 icrovascular inva Risk Difference <u>M-H, Fixed, 95% Cl</u> 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.21] 0.03 [-0.06, 0.24] 0.03 [-0.06, 0.24] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] aximum tumor si Mean Difference ight N, Random, 95% C 5% -0.30 [-2.02, 1.42 3% -1.10 [-2.44, 0.24	A construction of the second s
Rhu J et al Ku HW et al Yoon YI et al Total (95% CI) Heterogeneity: Tau ²⁷ = Test for overall effect: D Study or Subgroup Chen K et al Kim WJ et al Kim WJ et al Rhu J et al Tarantino G et al Ku HW et al Total (95% CI) Total events Heterogeneity: Chi ²⁷ : Test for overall effect E Study or Subgroup Chen JH et al Chen K et al Cho JY et al Suro H et al	11.5 6 5 2 11.6 4 0.66; Chi ² Z = 0.23 (Events 23 4 23 24 24 25 24 25 26 25 26 25 26 26 27 27 27 27 27 27 27 27 27 27	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 t ploo H Total 38 37 36 38 37 36 38 37 36 38 37 36 38 37 36 38 37 36 38 37 36 38 37 36 38 37 36 51 0 33 33 35 10 0 33 35 10 0 33 35 10 0 35 10 0 10 10 10 10 10 10 10 10	133 13 32 17 33 7 571 100); P= 559 ts of m <u>Weight</u> 15.5% 1	1% 0.80 [-0.6; 2.26 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 .0% 0.09 [-0.69, 0.88 icrovascular inva Risk Difference M.H. Fixed, 95% CI 0.05 [-0.16, 0.27] -0.05 [-0.27, 0.16] 0.05 [-0.10, 0.16] 0.09 [-0.06, 0.24] -0.04 [-0.15, 0.07] Not estimable 0.03 [-0.05, 0.10] aximum tumor si Mean Difference 1M. V. Random, 95% CI -0.80 [-1.63, 0.27] -0.05 [-0.27, 0.16] -0.05 [-0.27, 0.16] -0.05 [-0.27, 0.16] -0.05 [-0.27, 0.16] -0.05 [-0.10, 0.16] 0.03 [-0.05, 0.10] Mean Difference IM. V. Random, 95% CI -0.30 (-2.2, 1.42 -3% -1.10 [-2.44, 0.24 -1.10 [-2.44, 0.24	A constraint of the second sec
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JW et al Fotal (95% CI) Fotal events Heterogeneity: Chi ² : Test for overall effect Chen JH et al Chen JH et al Chen JH et al Chen K et al	11.5 6 5 2 11.6 4 0.66; Chi Z = 0.23 (LN Events 14 23 4 33 6 5 2 14 14 23 4 23 4 24 33 6 5 2 14 14 23 33 11 11 14 14 23 14 14 23 11 11 14 14 14 14 14 14 14 14	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 H Total 38 37 38 133 51 0 333 = 0% t plo 0 3333 = 0% t plo 0 3333 = 0%	133 13 32 17 33 7 571 100); I*= 559 ts of m 10.1% 15.5% 10.1% 15.5% 10.1% 13.5% 10.1% 10.1% 10.1% 10.0% 10.1% 10.0% 10.	1% 0.80 [-0.68, 2.28, 5% -0.10 [-1.10, 0.90, 2% -2.10 [-4.57, 0.37, 2.10 [-4.57, 0.37, 0.09 [-0.69, 0.88, 5] [CTOVASCULAT INVA Risk Difference [A constraint of the second sec
Rhu J et al Ku HW et al Yoon YI et al Fotal (95% CI) Heterogeneity: Tau ²⁷ = Test for overall effect: D Study or Subgroup Chen K et al Kim WJ et al Kim WJ et al Kim WJ et al Rhu J et al Tarantino G et al Ku HW et al Total events Heterogeneity: Chi ²⁷ Test for overall effect E Study or Subgroup Chen JH et al Chen K et al Chen JH et al Guro H et al Guro H et al Kim VJ et al	$\begin{array}{c} 11.5 \\ 5 \\ 5 \\ 11.6 \\ 4 \\ \end{array}$ 0.66; Chi Z = 0.23 (LN Events 14 22 4 33 0 11 24 24 33 0 11 24 25 4 24 25 24 25 24 25 25 25 25 25 25 25 25 25 25	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 t ploo H Total 38 37 38 37 38 37 38 37 38 37 38 37 38 37 38 38 37 38 38 37 38 38 37 38 38 38 38 38 37 38 38 38 38 38 38 38 38 38 38	133 13 32 17 33 7 571 100); F= 559 ts of m Weighting 15.5% 15.5% 10.1% 15.9% 15.5% 10.1% 15.9% 10.1% 15.9% 10.1% 10.0% 10.0% 13.3 9 38 5 19 7 100 9 37 8 36 8	1% 0.80 [-0.68, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 icrovascular inva Risk Difference <u>M-H, Fixed, 95% Cl</u> 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.09 [-0.06, 0.24] 0.09 [-0.06, 0.24] 0.09 [-0.10, 0.16] 0.09 [-0.10, 0.16] 0.09 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.24] 0.03 [-0.25, 0.10] aximum tumor si Mean Difference 10 M V. Random, 95% C 5% -0.80 [-1.63, 0.03 9% -0.30 [-2.24, 2.42 1% -2.20 [-3.11, -1.28 5% 0.10 [-0.95, 1.15 1% -0.88 [-1.95, 0.15]	A construction of the second s
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JW et al Fotal (95% CI) Fotal events Heterogeneity: Chi ² : Test for overall effect Chen JH et al Chen JH et al Chen JH et al Chen K et al	$\begin{array}{c} 11.5 \\ 5 \\ 11.6 \\ 2 \\ 11.6 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 t plo H Total 38 37 36 38 37 36 38 37 0 3333 = 0% t plo 3333 = 0% t plo 4.3 4.2 2.5 3.8 2.1 2.3 .7	133 13 32 17 33 7 571 100); P= 559 ts of m <u>Weight</u> 15.5% 1	1% 0.80 [-0.6; 2.26 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 10% 0.09 [-0.69, 0.88 6 0.09 [-0.69, 0.88 6 0.09 [-0.69, 0.88 6 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.03 [-0.06, 0.24] 0.03 [-0.06, 0.24] 0.03 [-0.05, 0.19] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.20 [-1.42, 0.24] 0.03 [-0.30, [-2.31, 112] -2.20 [-3.11, -1.22, -3.12] 0.03 [-0.30, [-1.95, 0.35] 0.30 [-2.31, 0.12] 0.03 [-1.95, 0.35] <td>A construction of the second s</td>	A construction of the second s
Rhu J et al (20 HW et al (20 m Y1 et al Fotal (95% C1) Heterogeneity: Tau ²⁷ = Festfor overall effect: D Study or Subgroup Chen K et al Kim WJ et al Kim WJ et al Kim WJ et al Fotal (95% C1) Total events Heterogeneity: Chi ²⁷ : Test for overall effect E Study or Subgroup Chen JH et al Chen K et al Chen JH et al Suro H et al Gim VJ et al Gim	$\begin{array}{c} 11.5 \\ 5 \\ 11.6 \\ 2 \\ 11.6 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 t plo H Total 38 37 36 38 37 36 38 37 0 3333 = 0% t plo 3333 = 0% t plo 4.3 4.2 2.5 3.8 2.1 2.3 .7	133 13 32 17 33 7 571 100); P= 559 ts of m <u>Weight</u> 15.5% 15.5% 15.5% 15.5% 33.9% 8.7% 100.0% ts of m <u>otal We</u> 133 9 133 9 38 5 19 7 110 9 37 8 36 8 38 5	1% 0.80 [-0.68, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 icrovascular inva Risk Difference <u>M-H, Fixed, 95% Cl</u> 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.09 [-0.06, 0.24] 0.09 [-0.06, 0.24] 0.09 [-0.10, 0.16] 0.09 [-0.10, 0.16] 0.09 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.10, 0.16] 0.03 [-0.24] 0.03 [-0.25, 0.10] aximum tumor si Mean Difference 10 M V. Random, 95% C 5% -0.80 [-1.63, 0.03 9% -0.30 [-2.24, 2.42 1% -2.20 [-3.11, -1.28 5% 0.10 [-0.95, 1.15 1% -0.88 [-1.95, 0.15]	A construction of the second s
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneity: Tau [®] = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JW et al Fotal (95% CI) Total events Heterogeneity: Chi [®] : Test for overall effect Chen JH et al Chen JH et al Chen JH et al Chen JH et al Chen JH et al Sudy or Subgroup Chen JH et al Survey	$\begin{array}{c} 11.5 \\ 5 \\ 11.6 \\ 2 \\ 11.6 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 t plo H Total 38 37 36 37 36 37 36 37 36 37 36 37 36 37 36 37 36 37 36 37 37 4.2 2.5 4.2 2.1 2.1 3.7 1.7	133 13 32 17 33 7 571 100); I*= 559 ts of m <u>Weight</u> 15.5% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 15.9% 15.5% 10.1% 15.9% 10.1% 10.0%	1% 0.80 [-0.68; 2.28; 5% -0.10 [-1.10, 0.90; 2% -2.10 [-4.57, 0.37] 100 0.09 [-0.69; 0.88; 5 0.09 [-0.69; 0.88; 6 0.09 [-0.69; 0.88; 6 0.05 [-0.16; 0.27] 0.05 [-0.16; 0.27] 0.05 [-0.16; 0.27] 0.05 [-0.16; 0.27] 0.03 [-0.00; 0.16] 0.03 [-0.04; 0.01; 0.16] 0.03 [-0.05; 0.10] 0.03 [-0.05; 0.01; 0.10] 0.03 [-0.05; 0.01] 0.03 [-0.05; 0.10] 0.03 [-0.27; 0.16] 0.03 [-0.27; 0.16] 0.03 [-0.05; 0.10] 9 0.03 [-0.10; 0.16] 0.03 [-0.25; 0.16] 0.03 [-0.26; 0.42] 9 0.03 [-0.25; 0.16] 9 0.03 [-0.25; 0.16] 9 0.30 [-2.02; 1.42] 9 0.30 [-2.02; 1.44] 9 0.30 [-2.02; 1.44] 9 0.30 [-2.02; 1.44] 9 0.30 [-2.02; 1.44] 9 0.30 [-2.02; 1.44] 10 [-2.02; 1.14] -2.20 [-3.11, 1.29] 5% 0.00 [-0.59, 0.55] 9% <	A construction of the second s
Rhu J et al (xu HW et al (xu HW et al (xu HW et al (xu HW et al (xu HY et al Chen K et al (xu HW et al (xu	$\begin{array}{c} 11.5 \\ 6 \\ 5 \\ 11.6 \\ 4 \\ \end{array}$ $\begin{array}{c} 0.66; Chi^{2} \\ Z = 0.23 \\ (0 \\ 11 \\ 23 \\ 24 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 11 \\ 23 \\ 5 \\ 11 \\ 12 \\ 35 \\ 2 \\ 2 \\ 31 \\ 1 \\ 12 \\ 35 \\ 2 \\ 31 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 2.8 \\ 5.7 \\ 2 \\ 3.1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 2.8 \\ 5.7 \\ 2 \\ 3.1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 t plo H Total 38 37 36 38 133 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 333 51 0 7 36 38 133 3 51 0 7 36 38 133 3 51 0 7 38 133 3 51 0 333 51 0 7 1 1 1 1 1 1 1 1 1 1	133 13 32 17 33 7 571 100;); P= 559 ts of m <u>Weight</u> 5 15.9% 5 15.5% 5	1% 0.80 [-0.68, 2.28 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 0.09 [-0.69, 0.88 icrovascular inva Risk Difference <u>M-H, Fixed, 95% C1</u> 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.09 [-0.06, 0.24] 0.09 [-0.06, 0.24] 0.09 [-0.06, 0.24] 0.03 [-0.10, 0.16] 0.09 [-0.05, 0.10] 0.33 [-0.05, 0.10] aximum tumor si <u>Mean Difference</u> int <u>V. Random, 95% C</u> 5% -0.80 [-1.63, 0.03 9% -0.30 [-2.02, 1.42 3% -1.10 [-1.92, 4.0, 24 1% -2.20 [-3.11, -1.29 5% 0.10 [-1.92, -1.78 5% 0.00 [-1.90, 0.59 6% -1.10 [-1.90, -0.38	A construction of the second s
Rhu J et al (xu HW et al (xon YI et al Fotal (95% CI) Heterogeneily: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JW et al Rhu J et al Rhu J et al Rhu J et al Rhu J et al Fotal (95% CI) Heterogeneily: Chi ² : Test for overall effect E Study or Subgroup Chen JH et al Chen K et al Chen JH et al Chen K et al Chen JH et al Chen K et al Chen JH et al Chen	11.5 6 5 2 11.6 4 0.66; Chi Z = 0.23 (Events 14 23 4 30 (11 24 30 (11 24 23 4 23 4 23 24 24 30 (11 24 24 30 (11 24 24 24 24 24 24 24 24 24 24	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 H Total 38 37 36 8 333 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 0 51 1 51 1 51 0 51 1 51 1 51 1 51 1 51 1 51 5	133 13 32 17 33 7 571 100); P= 559 ts of m <u>Weight</u> 15.5% 15.5% 15.5% 10.1% 33.9% 10.1% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 10.0% 1	1% 0.80 [-0.6; 2.26 5% -0.10 [-1.10, 0.90 2% -2.10 [-4.57, 0.37 10% 0.09 [-0.69, 0.88 6 0.09 [-0.69, 0.88 6 0.09 [-0.69, 0.88 6 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.05 [-0.27, 0.16] 0.05 [-0.27, 0.16] 0.005 [-0.16, 0.27] 0.03 [-0.00, 0.24] 0.03 [-0.06, 0.24] 0.03 [-0.05, 0.19] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.20 [-0.30, 0.50, 0.50] 0.00 [-0.30, 0.50, 0.50] 0.00 [-0.50, 0.50] 0.00 [-0.50, 0.50] 0.00 [-0.50, 0.50] 0.00 [-0.50, 0.50] <td< td=""><td>A constraint of the second sec</td></td<>	A constraint of the second sec
Rhu J et al (u HW et al (von YI et al Fotal (95% CI) Heterogeneity: Tau [®] = Fest for overall effect: D Study or Subgroup Chen K et al (im JM et al Fotal (95% CI) Total events Heterogeneity: Chi [®] : Test for overall effect B Study or Subgroup Chen JH et al Chon JY et al Chon JY et al Surdy or Subgroup Chen JH et al (im JM et al (im JM et al (im JM et al (im JM et al (im MW et al (im MW et al (im MW et al (im JM et al	$\begin{array}{c} 11.5 \\ 6 \\ 5 \\ 11.6 \\ 4 \\ \end{array}$ $\begin{array}{c} 0.66; Chi^{2} \\ Z = 0.23 \\ (0 \\ 11 \\ 23 \\ 24 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 23 \\ 4 \\ 11 \\ 23 \\ 5 \\ 11 \\ 12 \\ 35 \\ 2 \\ 2 \\ 31 \\ 1 \\ 12 \\ 35 \\ 2 \\ 31 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 2.8 \\ 5.7 \\ 2 \\ 3.1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 2.8 \\ 5.7 \\ 2 \\ 3.1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 2.6 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ $	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 t plo H Total 38 37 36 37 36 38 38 38 38 38 39 33 3 51 0 333 3 51 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 333 3 51 0 0 3 333 2 1 1 0 1 0 1 0 1 1 1 1 1 1 1 1 1 1 1 1	133 13 32 17 33 7 571 100); I*= 559 ts of m <u>Weight</u> 15.5% 15.5% 10.1% 15.9% 15.5% 10.1% 15.9% 10.1% 15.9% 10.1% 10.0%	1% 0.80 [-0.68, 2.28, 5%, -0.10 [-1.10, 0.90, 2%, -2.10 [-4.57, 0.37] .5% -0.10 [-1.0, 0.90, 2.88, 5] icrovascular inva Risk Difference M.H. Fixed, 95% CI -0.05 [-0.60, 0.27] -0.05 [-0.16, 0.27] -0.05 [-0.16, 0.27] -0.05 [-0.16, 0.27] -0.06 [-0.30, 0.19] -0.05 [-0.16, 0.27] -0.06 [-0.30, 0.19] -0.03 [-0.05, 0.01] Not estimable 0.03 [-0.05, 0.10] -0.05 [-0.16, 0.24] -0.04 [-0.15, 0.07] Not estimable 0.03 [-0.05, 0.10] -0.05 [-0.16, 0.24] -0.04 [-0.15, 0.07] Not estimable 0.03 [-0.05, 0.10] -0.06 [-0.30, 0.10] -0.04 [-0.15, 0.07] Not estimable 0.03 [-0.05, 0.10] -0.05 [-0.16, 0.24] -0.04 [-0.15, 0.05] -0.80 [-1.63, 0.03] -0.05 [-0.16] -0.80 [-1.63, 0.03] -0.06 [-1.30, 0.10] -0.80 [-1.63, 0.03] -0.80 [-1.63, 0.03] -0.80 [-1.65, 0.56] -1.10 [-2.40, -2.4] -1.10 [-2.40, -2.4] -1.10 [-2.40, -2.4] -3.20 [-4.62, -1.76] -5% -0.80 [-1.65, 0.56] -1.10 [-1.	A construction of the second s
Rhu J et al (20 HW et al (20 nY I et al Fotal (95% CI) Heterogeneity: Tau ² = Festfor overall effect: D Study or Subgroup Chen K et al (21 m JM et al (21 m M et al (2	11.5 \leq 5 2 11.6 \leq 2 \leq 2 \leq 0.23 (2	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 H Total 333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 3333 51 0 51 1 51 0 51 1 51 0 51 0 51 1 51 0 51 51 0 51 51 51 51 51 51 51 51 51 51	133 13 32 17 33 7 571 100); I*= 559 ts of m 15.5% 15.5% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 15.5% 10.1% 15.5% 10.0% 13.3 9 38 5 19 7 110 9 37 8 36 8 36 8 36 8 33 97 10 51 9 32 8 33 97 10 51 9 32 8 33 97 42 6	1% 0.80 [-0.68; 2.28; 5% -0.10 [+1.0, 0.90; 2% -2.10 [+4.57, 0.37; 10% 0.09 [-0.69; 0.88; 5 0.09 [-0.69; 0.88; 6 0.05 [-0.69; 0.88; 6 0.05 [-0.16; 0.27]; 0.05 [-0.16; 0.27]; 0.05 [-0.16; 0.27]; 0.05 [-0.16; 0.27]; 0.03 [-0.06; 0.24]; 0.03 [-0.06; 0.24]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.27; 0.16]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.05; 0.10]; 0.03 [-0.27; 1.44; 0.24	A constraint of the second sec
Rhu J et al (xu HW et al (xon YI et al Fotal (95% CI) Heterogeneily: Tau ² = Fest for overall effect: D Study or Subgroup Chen K et al Kim JM et al Kim JM et al Kim JW et al Rhu J et al Rhu J et al Rhu J et al Rhu J et al Fotal (95% CI) Heterogeneily: Chi ² : Test for overall effect E Study or Subgroup Chen JH et al Chen K et al Chen JH et al Chen K et al Chen JH et al Chen K et al Chen JH et al Chen	$\begin{array}{c} 11.5 \\ 5 \\ 5 \\ 11.6 \\ 4 \\ 2 \\ 2 \\ 11.6 \\ 2 \\ 11.6 \\ 2 \\ 1.6$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	10.7 10.7	4 2 5.5 = 0.02 t ploo H Total 333 51 0 333 333 51 0 333 333 51 0 333 333 51 0 333 333 51 0 333 333 51 0 333 335 10 333 333 51 0 333 32 11 32 32 32 32 3 3 3 3 3 3 3 3 3 3 3 3 3	133 13 32 17 33 7 571 100); F= 559 ts of m Weight 15.9% 15.5% 10.1% 15.9% 10.1% 15.9% 10.1% 15.9% 10.1% 10.0% 10.1% 10.0% 10.	1% 0.80 [-0.68, 2.28, 5%, -0.10 [-1.10, 0.90, 2%, -2.10 [-4.57, 0.37] 2% -2.10 [-4.57, 0.37] 100 0.09 [-0.69, 0.88 5 0.00 [-0.69, 0.88 6 0.05 [-0.69, 0.88 100 0.05 [-0.16, 0.27] 0.005 [-0.16, 0.27] 0.05 [-0.16, 0.27] 0.005 [-0.16, 0.27] 0.03 [-0.00, 0.24] 0.03 [-0.00, 0.24] 0.03 [-0.06, 0.24] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.05, 0.10] 0.03 [-0.03, 0.22, 1.42] 0.03 [-0.04, 2, 1.76] 0.30 [-1.95, 0.35] 0.30 [-1.92, 1.76] 0.30 [-0.47, 1.07] 0.80 [-1.80, 0.38, 0.45] 0.30 [-0.47, 1.07] 0.80 [-1.82, 0.75] 0.30 [-0.47, 1.07] 0.80 [-0.86, 2.46] 0.30 [-0.47, 1.07	A constraint of the second sec

Figure S1 Forest plots of the meta-analysis for significant independent variables. (A) Cirrhosis; (B) child A; (C) ICG-R15; (D) microvascular invasion; (E) maximum tumor size.