Ann Surg Oncol (2019) 26:252–263
https://doi.org/10.1245/s10434-018-6926-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CrossMark

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

A Systematic Review and Meta-Analysis Comparing the Short- and Long-Term Outcomes for Laparoscopic and Open Liver Resections for Hepatocellular Carcinoma: Updated Results from the European Guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017

Ruben Ciria, MD, PhD[1], Irene Gomez-Luque, MD[1], Sira Ocaña, MD[2], Federica Cipriani, MD, PhD[3,4], Mark Halls, MBBS[4], Javier Briceño, MD, PhD[1], Yukihiro Okuda, MD, PhD[1,5], Roberto Troisi, MD, PhD[6], Fernando Rotellar, MD, PhD[2], Olivier Soubrane, MD, PhD[7], and Mohammed Abu Hilal, MD, PhD[4]

[1]Unit of Hepatobiliary Surgery and Liver Transplantation, CIBER-EHD, IMIBIC, University Hospital Reina Sofía, University of Cordoba, Cordoba, Spain; [2]Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University Clinic, University of Navarra, Pamplona, Spain; [3]Hepatobiliary Surgery Division, San Raffaele Hospital, Milan, Italy; [4]Department of Hepato-Biliary and Pancreatic Surgery, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [5]Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [6]Department of Clinical Medicine and Surgery, "Federico II" University, Naples, Italy; [7]Department of HPB Surgery and Liver Transplant, Beaujon Hospital, University Paris 7, Clichy, AP-HP, France

ABSTRACT

Background. The laparoscopic approach to liver resection has experienced exponential growth in recent years; however, its application is still under debate and objective, evidence-based guidelines for its safe future progression are needed.

Objective. The aim of this study was to perform a systematic review and meta-analysis comparing the short- and long-term outcomes of laparoscopic and open liver resections for hepatocellular carcinoma (HCC).

Methods. To identify all the comparative manuscripts reporting on laparoscopic and open liver resection for HCC, all published English-language studies with more than 10 cases were screened. In addition to the primary meta-analysis, four specific subgroup analyses were performed on patients with Child–Pugh A cirrhosis, resections for solitary tumors, and those undergoing minor and major resections. The quality of the studies was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) methodology and the Newcastle–Ottawa Scale.

Results. From the initial 361 manuscripts, 28 were included in the meta-analysis. Five of these 28 manuscripts were specific to patients with Child–Pugh A cirrhosis (321 cases), 11 focused on solitary tumors (1003 cases), 16 focused on minor resections (1286 cases), and 3 focused on major resections (164 cases). Three manuscripts compared 1079 cases but could not be assigned to any of the above subanalyses. In general terms, short-term outcomes were favorable when using a laparoscopic approach, especially in minor resections. The only advantage seen with an open approach was reduced operative time during major liver

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-018-6926-3) contains supplementary material, which is available to authorized users.

Ruben Ciria and Irene Gomez-Luque contributed equally to the development of this manuscript.

Manuscript and research performed in the context of the European Guidelines Meeting on Laparoscopic Liver Surgery held in Southampton, UK, from 9 to 11 February 2017.

© Society of Surgical Oncology 2018

First Received: 29 April 2018;
Published Online: 2 November 2018

R. Ciria, MD, PhD
e-mail: rubenciria@gmail.com; rubenciria@hotmail.com

M. Abu Hilal, MD, PhD
e-mail: abuhilal9@gmail.com

resections. No differences in long-term outcomes were observed between the approaches.
Conclusions. Laparoscopic liver resection for HCC is feasible and offers improved short-term outcomes, with comparable long-term outcomes as the open approach.

Liver resection is a first-line option in very early- and early-stage disease, and a secondary option in intermediate-stage hepatocellular carcinoma (HCC).[1–4] In 1995 and 1996, the first minimally invasive liver resection series for HCC was reported.[5,6] Since then, a minimally invasive approach to liver resections has been used in the treatment of a myriad of conditions, and exponential dissemination has been experienced.[7] However, at the last Consensus Conference held in Morioka in 2014,[8] the laparoscopic approach for HCC was still considered in need of standardization to allow for its safe development.

A laparoscopic approach to liver resections offers improved short-term outcomes compared with the traditional open approach.[7] Recent meta-analyses specific to HCC have reported that a laparoscopic approach is associated with improved outcomes, however these studies have considered all resections and lesions as a single homogenous group, which may result in potential bias and hence inaccuracies in the conclusions.[9–12] In addition, these studies have only considered either short- or long-term outcomes, leaving a need for a detailed, holistic assessment of the role of laparoscopic liver resection (LLR) in the management of HCC. A recent multicenter study by Cipriani et al.[13] demonstrated that a laparoscopic approach provided the same short-term outcomes in patients with both Child–Pugh A and Child–Pugh B cirrhosis, and suggested that the current guidelines regarding resections in cirrhosis could be expanded using a laparoscopic approach.

In the context of the European Guidelines Meeting on Laparoscopic Liver Surgery (EGMLLS) held in Southampton, UK, from 9 to 11 February 2017, an updated meta-analysis was prepared in which five sub-meta-analyses were performed after assessing the patterns of all available studies comparing the laparoscopic and open approaches in the management of HCC.

PATIENTS AND METHODS

Aims of the Study

Our primary aim was to amalgamate, weigh, and summarize the current evidence regarding the short- and long-term outcomes of laparoscopic and open liver resections for the management of HCC, by systematic review and meta-analysis, while our secondary aims were to assess the distribution of available studies with regard to disease stage and resection type, and perform secondary subgroup meta-analyses by grouping like studies in order to increase the level of evidence for specific disease stages and resection types.

Search Strategy and General Considerations

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The Pubmed, Embase, Cochrane Library, and Web of Science electronic databases were searched using the following search strategy: ((hepatocellular[Title] OR HCC) AND (laparoscopic[Title] OR laparoscopy[Title] OR minimally[Title] OR hybrid[Title])) and their associated combinations of controlled vocabulary (Medical Subject Heading [MeSH]) terms. The final search was performed on 20 June 2017.

Study Selection

Inclusion criteria were human comparative studies written in English that included only laparoscopic versus open procedures from the last 15 years and selected the last largest series in case of detection of duplicates. Reviews, editorials, case reports, or letters were excluded, as were manuscripts in which radiofrequency, chemoembolization, liver transplant, and robotic or hybrid procedures were performed. Review articles were examined for potential additional references, and duplicates were identified by matching both author names and publication centers. After initial screening, full-text versions of the selected manuscripts were obtained. Two reviewers (RC and IG-L), as well as an independent third reviewer (MH or FC) in cases where consensus could not be reached, individually assessed each manuscript and rejected those that failed to meet the inclusion criteria.

Definitions

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

1. Resection type was based on the proposal from the Louisville Consensus meeting in 2008 [15], with minor resections involving two or fewer Couinaud segments and major resections involving three or more continuous Couinaud segments.
2. Each manuscript was assessed to establish if results reported could be applicable to more than one of the subgroups. If so, the results were separated and individually analyzed within their subgroups.

3. Combined series were defined as those reporting a mixture of minor/major resections that could not be separated and analyzed separately, and hence could not be included within the above subgroups.

Variables and Endpoints (endpoints shown in bold).

1. Short-term outcomes (intraoperative parameters): operative time (minutes), operative blood loss (mL), and number of patients requiring blood transfusion (%).
2. Short-term outcomes (postoperative parameters): total number of early (< 30 days) complications (%), duration of postoperative hospital stay (days), mean resection margin (mm), post-hepatectomy liver failure (PHLF) [and subcategories as defined by the International Study Group of Liver Surgery (ISGLS) in 2011[16] and perioperative (30-day, 90-day, or undefined) mortality.
3. Long-term outcomes. 1-, 3-, and 5-year overall survival (OS); 1, 3-, and 5-year disease-free recurrence.

Quality Assessment of the Studies Included in the Meta-Analysis

First Quality Assessment The first quality assessment was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN).[17]

Second Quality Assessment The second quality assessment was performed in accordance with the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort and case–control studies (Ottawa Hospital Research Institute; available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The criteria for 'representativeness of cases' were considered as consecutive, or representative series of cases without potential selection bias. Specifically, no star was given if cases included were not matched by year of inclusion (due to potential selection bias) and/or different surgeons and/or an inclusion period > 10 years (due to potential technical bias). Similarly, equal distribution of type and severity of underlying liver disease was an exclusion criteria that was given a star. For the 'control for important factor' rating, two stars were given if laparoscopic and open cases were matched by age, sex, American Society of Anesthesiologists (ASA) score, body mass index, type of resection, Child–Pugh score, and number and size of the lesions. If any of these factors were not specifically mentioned or were not correctly matched, only one star was given. If two or more of these factors were not correctly matched or were not mentioned, no stars were given.

Statistical Analysis

Analyses were performed using log odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous variables, and weighted mean differences (WMD) with 95% CIs for continuous variables. For dichotomous variables in which any observed value was 0, it may not be possible to calculate the OR, and thus rate differences were used. The standard heterogeneity test used was the *I*-square statistic. Based on the method reported by DerSimonian and Laird,[18] substantial significance was set when the p value was < 0.10 and a random-effects model was used.[19] An *I*-square value of < 25% was defined to represent low heterogeneity, between 25 and 50% was defined as moderate heterogeneity, and > 50% was defined as high heterogeneity. Publication bias was also assessed visually using a funnel plot for standard error by effect size. Each calculation for every group had a specific funnel plot. Data that were not significantly heterogeneous ($p > 0.1$) were calculated using a fixed-effects model using the Mantel–Haenszel method.[20] OpenMEE software, based on Open MetaAnalyst Software, was used for statistical analyses.[21,22]] To perform meta-analyses, means and standard deviations (SDs) were needed, and estimations of means and SDs were performed to avoid discarding important studies. According to a recent publication from Wan et al.[23], in the event that a manuscript reported data in different measures other than mean and SD, two different scenarios were considered, as reported in our previous meta-analysis.[7] For the meta-analysis, the authors decided to perform calculations only if at least three series could be identified for each variable, avoiding results derived from analyses of two reports.

RESULTS

Eligible Studies and Final Count

From the initial 361 manuscripts identified in the searches, 34 comparative studies remained after the inclusion and exclusion criteria were applied (electronic supplementary material [ESM] 1). Six manuscripts[24–29] did not reach a minimum requirement of acceptable quality (by SIGN scoring) or 6 points (by NOS) and were subsequently discarded (Table 1), resulting in 28 manuscripts being considered for the systematic review and meta-analysis. Five of these 28 manuscripts were specific to patients with Child–Pugh A cirrhosis (321 cases),[30–34] 16 focused on minor resections (1286 cases),[3,32–46] three focused on major resections (164 cases),[30,47,48] and 11 focused on solitary tumors (1003 cases).[31,34,36,45,49–54] The remaining three manuscripts (comparing 1079 cases) could not be individually classified as they were propensity score or 2:1

TABLE 1 Overall quality analysis from all comparative studies including NOS and SIGN scores

Characteristics of the studies included in the meta-analysis for HCC patients															
Author (city/province, country)	Year	*N* lap	*N* open	Etiology	Conversion	Quality assessment by NOS									SIGN
						Selection				Comparability	Exposure			Quality judgment (maximum nine stars)	
						Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate		
Child–Pugh A															
Zhang et al.[30] (China)	2016	20	25	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Ahn et al.[31] (Daegu, Korea)	2014	52 (51)	150 (51)	HCC	Excluded	✠	✠	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠✠✠	++ High
Kim et al.[49] (Seoul, Korea)	2014	29	29	HCC	23.3%	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Truant et al.[33] (Lille, France)	2011	36	53	HCC	7 (19.4%)	−	−	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Lee et al.[24] (Hong Kong, China)	2011	33	50	HCC	6 (18.2%)	−	−	−	✠	✠	✠	✠	✠	✠✠✠✠✠	+ Acceptable
Laurent et al.[34] (Créteil, France)	2003	13	14	HCC	2 (15%)	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Minor - only															
Sposito et al.[3] (Italy)	2016	43 (43)	226 (43)	HCC	Excluded	✠	✠	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠✠✠	++ High
Zhang et al.[35] (China)	2016	31	33	HCC	0 (0%)	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Luo et al.[36] (Chengdu, China)	2015	53	53	HCC	Excluded	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Beppu et al.[37] (Kumamoto, Japan)	2015	89 (52)	180 (52)	HCC	2 (2.2%)	✠	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠✠	++ High
Xiao et al.[25] (China)	2015	41	86	HCC	3 (7.32%)	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠	++ High
Cheung et al.[38] (Hong Kong, China)	2015	24	29	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Yamashita et al.[39] (Fukuoka, Japan)	2014	63	99	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Memeo et al.[40] (Créteil, France)	2014	45	45	HCC	0	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Kim et al.[32] (Seoul, Korea)	2014	29	29	HCC	23.3%	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Kanazawa et al.[41] (Osaka, Japan)	2013	28	28	HCC	5/23 hybrid (21.73%)	−	−	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Cheung et al.[42] (Hong Kong, China)	2013	32	64	HCC	6 hand-assist (18.8%)	−	−	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Kobayashi et al.[43] (Osaka, Japan)	2013	24	27	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Hu et al.[26] (Jiangsu, China)	2011	30	30	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	− Low
Truant et al.[33] (Lille, France)	2011	36	53	HCC	7 (19.4%)	−	−	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable

TABLE 1 continued

Lee et al.[24] (Hong Kong, China)	2011	33	50	HCC	6 (18.2%)	−	−	−	✠	✠	✠	✠	✠	✠✠✠✠✠	+ Acceptable
Ker et al.[27] (Kaohsiung, China)	2011	116	208	HCC	6 (5.2%)	−	−	−	✠	−	✠	✠	✠	✠✠✠✠	+ Acceptable
Aldrighetti et al.[28] (Milan, Italy)	2010	16	16	HCC	1 (6.25%)	−	−	−	✠	−	✠	✠	✠	✠✠✠✠	+ Acceptable
Endo et al.[29] (Oita, Japan)	2009	10	11	HCC	Lap-assisted	−	−	−	✠	−	✠	✠	✠	✠✠✠✠	+ Acceptable
Belli et al.[44] (Naples, Italy)	2007	23	23	HCC	1 (4.3%)	−	−	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠	++ High
Kaneko et al.[45] (Tokyo, Japan)	2005	30	28	HCC	3.3%	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Laurent et al.[34] (Créteil, France)	2003	13	14	HCC	2 (15%)	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Shimada et al.[46] (Fukuoka, Japan)	2001	17	38	HCC	0	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Major- only															
Zhang et al.[30] (China)	2016	20	25	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Komatsu et al.[47] (France)	2016	38	38	HCC	–	–	✠	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠✠	+ Acceptable
Cho et al.[48] (Seoul, Korea)	2015	24	19	HCC	3 (12.5%)	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Solitary tumors															
Luo et al.[36] (Chengdu, China)	2015	53	53	HCC	Excluded	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Xiao et al.[25] (China)	2015	41	86	HCC	3 (7.32%)	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠	++ High
Ahn et al.[31] (Daegu, Korea)	2014	52 (51)	150 (51)	HCC	Excluded	✠	✠	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠✠✠	++ High
Kim et al.[49] (Seoul, Korea)	2014	70	76	HCC	6 (8.57%)	✠	✠	−	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠✠✠	++ High
Ai et al.[50] (Putian, China)	2013	97	178	HCC	9.3%	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Hu et al.[26] (Jiangsu, China)	2011	30	30	HCC	–	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	− Low
Kim et al.[51] (Gwangju, Korea)	2011	26	29	HCC	3 (10.3%)	–	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Nguyen et al.[52] (Pittsburgh, USA)	2011	17	20	HCC	–	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Ker et al.[27] (Kaohsiung, China)	2011	116	208	HCC	6 (5.2%)	−	−	−	✠	−	✠	✠	✠	✠✠✠✠	+ Acceptable
Tranchart et al.[53] (Paris, France)	2010	42	42	HCC	2 (4.7%)	−	✠	−	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Aldrighetti et al.[28] (Milan, Italy)	2010	16	16	HCC	1 (6.25%)	−	−	−	✠	−	✠	✠	✠	✠✠✠✠	+ Acceptable
Endo et al.[29] (Oita, Japan)	2009	10	11	HCC	Lap-assisted	−	−	−	✠	−	✠	✠	✠	✠✠✠✠	+ Acceptable

TABLE 1 continued

Lai et al.[54] (Chai Wan, Hong Kong)	2009	25	33	HCC	1 (4%)	–	✠	–	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Kaneko et al.[45] (Tokyo, Japan)	2005	30	28	HCC	3.3%	–	✠	–	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Laurent et al.[34] (Créteil, France)	2003	13	14	HCC	2 (15%)	–	✠	–	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Shimada et al.[46] (Fukuoka, Japan)	2001	17	38	HCC	0	–	✠	–	✠	✠	✠	✠	✠	✠✠✠✠✠✠	+ Acceptable
Combined															
Takahara et al.[55] (Japan)	2015	436 (387)	2969 (387)	HCC	25 (6.5%)	✠	✠	–	✠	✠✠	✠	✠	✠	✠✠✠✠✠✠✠✠	++ High
Han et al.[56] (Seoul, Korea)	2015	232 (88)	157 (88)	HCC	8 (9.1%)	✠	✠	–	✠	✠	✠	✠	✠	✠✠✠✠✠✠✠	++ High
Lee et al.[57] (Toronto, Canada)	2015	43	86	HCC	6 (14%)	–	✠	–	✠	✠	✠	✠	✠	✠✠✠✠✠✠	++ High

Studies marked in bold were discarded because they had NOS < 7 stars or low scoring in the SIGN analysis

SIGN Scottish Intercollegiate Guidelines Network, *NOS* Newcastle–Ottawa Scale, *HCC* hepatocellular carcinoma, *lap* laparoscopic surgery, *open* open surgery

matched, and hence independent results could not be obtained;[55–57] these were analyzed as 'combined' resections. All baseline results are depicted in ESM 2 and 3.

Solitary Tumors

A total of 11 studies were identified, including 562 open resections and 441 LLRs for solitary HCC. Operative times were equal between the groups, but all other short-term outcomes, including complication rates (heterogeneity p value = 0.095; I-squared = 38%; OR 2.42 [95% CI 1.695–3.456]; $p < 0.001$), blood loss (heterogeneity p value ≤ 0.001; I-squared = 78%; standardised mean difference [SMD] -0.476 [95% CI -0.828 to -0.124]; $p < 0.008$), transfusions (heterogeneity p value = 0.75; I-squared = 0%; OR 1.703 [95% CI 1.067–2.717]; $p < 0.026$), hospital stay (heterogeneity p value ≤ 0.001; I-squared = 78%; SMD -0.786 [95% CI -1.089 to -0.483]; $p < 0.001$), and resection margins (heterogeneity p-value = 0.88; I-squared = 0%; SMD 0.218 [95% CI 0.064–0.371]; $p = 0.005$), favored a laparoscopic approach (Figs. 1, 2). Mortality and PHLF were not significantly different between the groups (ESM 4), and there were no significant differences in 1-, 3-, and 5-year OS and DFS (Figs. 3, 4).

Child–Pugh A Resections

Five studies including 172 open procedures and 149 laparoscopic procedures were analyzed. Both complication rates (heterogeneity p value < 0.001; I-squared = 81%; OR 0.256 [95% CI 0.066–0.446]; $p = 0.008$) and hospital stay (heterogeneity p value ≤ 0.001; I-squared = 87%; SMD -1.037 [95% CI -1.718 to -0.357]; $p = 0.003$) favored a laparoscopic approach (Figs. 1, 2). Perioperative mortality was equivalent in both the open and laparoscopic approaches (ESM 4). Long-term outcomes were insufficiently reported, and hence only three manuscripts were analyzed. These demonstrated no difference in OS and disease-free survival (DFS) between the two groups (Figs. 3, 4).

Minor-Only Liver Resections

Sixteen manuscripts were identified that included 628 open procedures and 658 laparoscopic procedures. The short-term outcomes for complication rates (heterogeneity p value < 0.001; I-squared = 75%; OR 0.175 [95% CI 0.093–0.257]; $p < 0.001$), blood loss (heterogeneity p value ≤ 0.001; I-squared = 85%; SMD -0.685 [95% CI -1.012 to -0.357]; $p < 0.001$), transfusion rate (heterogeneity p value = 0.13; I-squared = 20%; OR 0.027 [95% CI 0.001–0.053]; $p < 0.001$), and hospital stay (heterogeneity p value ≤ 0.001; I-squared = 75%; SMD -0.837 [95% CI -1.083 to -0.590]; $p < 0.001$) all favored a laparoscopic approach (Figs. 1, 2), with no difference in operative time and resection margin (Fig. 3). As with solitary resections, mortality and PHLF were not different between the groups (ESM 4). Long-term outcomes

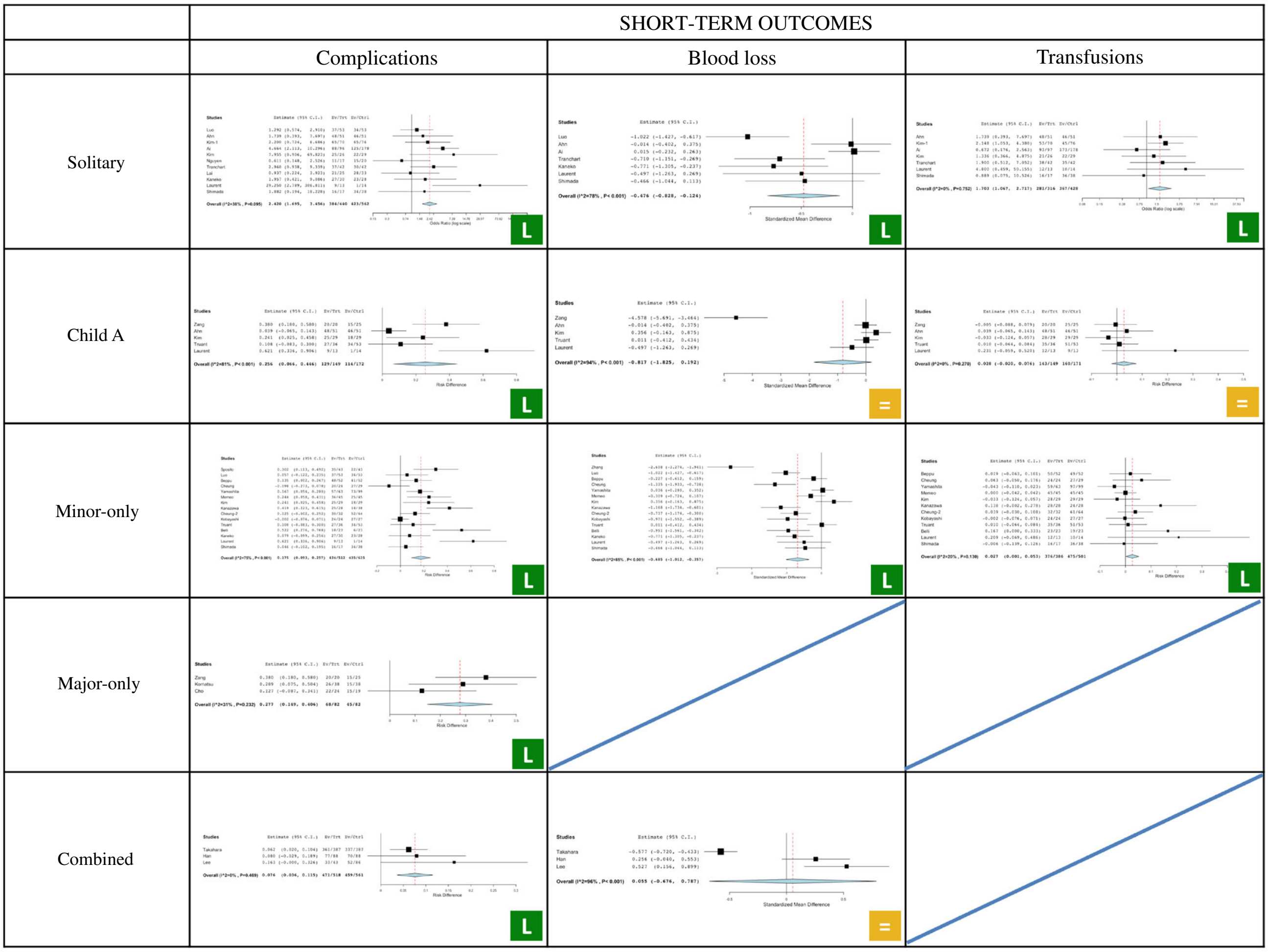

FIG. 1 Meta-analysis of short-term outcomes (I)

(Figs. 3, 4) were similar between both approaches, except for the 1-year DFS (heterogeneity p value = 0.019; I-squared = 66%; OR 0.133 [95% CI 0.001–0.265]; $p < 0.048$), which was in favor of the laparoscopic approach.

Major-Only Liver Resections

Only limited data were available for major liver resections and no long-term data could be retrieved. Regarding short-term outcomes, the complication rate was lower when using a laparoscopic approach (heterogeneity p value = 0.232; I-squared = 31%; OR 0.277 [95% CI 0.149–0.406]; $p < 0.001$) [Fig. 1]. However, operative time was shorter for OLR (heterogeneity p value = 0.015; I-squared = 76%; SMD 0.835 [95% CI 0.155–1.516]; $p = 0.016$) [Fig. 2]. There was a trend towards a shorter hospital stay in the laparoscopic group, but this did not reach statistical significance.

Combined Studies

The three manuscripts that contained combined studies did not have any long-term data available. Regarding short-term outcomes, the rate of complications (heterogeneity p value = 0.469; I-squared = 0%; OR 0.076 [95% CI 0.036–0.115]; $p < 0.001$) [Fig. 1] and hospital stay (heterogeneity p value $\leq$ 0.001; I-squared = 92%; SMD -0.788 [95% CI -1.339 to -0.237]; $p = 0.005$) favored a laparoscopic approach, but the remaining short-term outcomes (operative time and blood loss) were not different.

Publication Bias Analysis

All the series allocated to each subanalysis were independently assessed for bias in each variable (ESM 5, 6, 7, and 8).

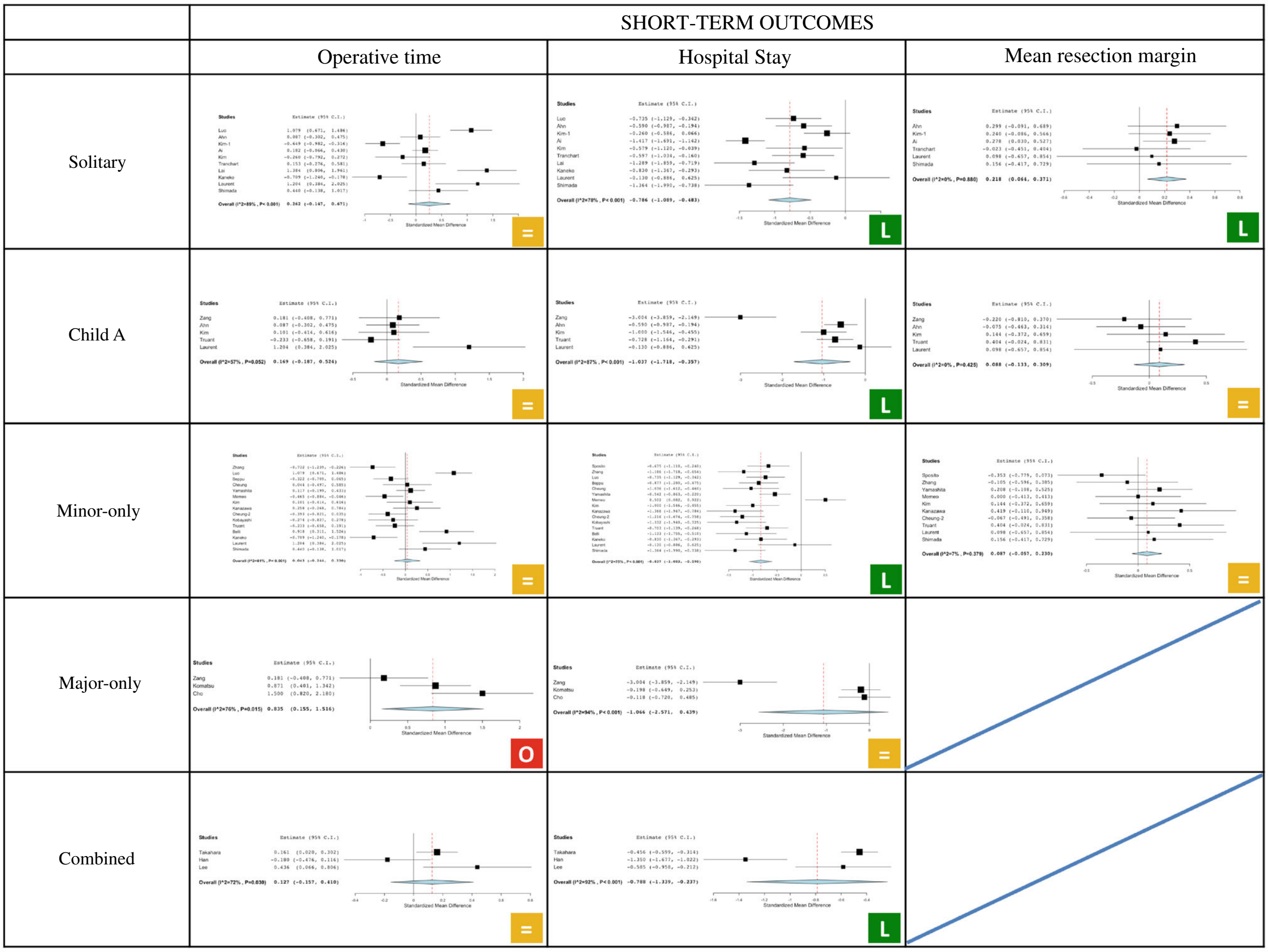

FIG. 2 Meta-analysis of short-term outcomes (II)

DISCUSSION

The largest meta-analysis to date suggests that a significant proportion of LLRs are performed for the management of HCC, as 3072 of 6190 LLRs for malignancies were performed for HCC [7]. In 2017, Southampton hosted the EGMLLS, with the specific aim of presenting and validating the first set of evidence-based guidelines for laparoscopic liver surgeons [58]. In this setting, the aim of our study was to perform a high-quality meta-analysis examining the short- and long-term outcomes after LLR for HCC. The results of our meta-analysis demonstrate that for most short-term outcomes, a laparoscopic approach provides better results than an open approach.

During and after liver resection, blood loss and transfusions are important factors that impact not only early postoperative outcomes but also long-term results with an increased risk of cancer recurrence and decreased patient survival [59,60]. When it came to these variables (blood loss and transfusions), our meta-analysis showed that the laparoscopic approach did better than the open route, especially within the subgroup analyses for solitary tumors and minor resections. Similarly, the complication rate was favorable for a laparoscopic approach in all analyses. These results suggest that a laparoscopic approach is similar, if not better than, the open approach for the management of HCC in patients with Child–Pugh A cirrhosis, solitary tumors, and those undergoing minor resections in terms of short-term outcomes.

It should be remarked that limited information was available for specific postoperative variables such as mortality (not clearly defined as perioperative, or 30- or 90-days) and PHLF. Because of this, perioperative mortality was all put together in our analysis. Similarly, PHLF could not be individually screened by the ISGLS groups and was thus analyzed as a single category. It should be encouraged that all research teams perform statistics for their manuscripts using currently validated classifications rather than institutional or self-raised criteria. In addition, limited information was available for long-term outcomes

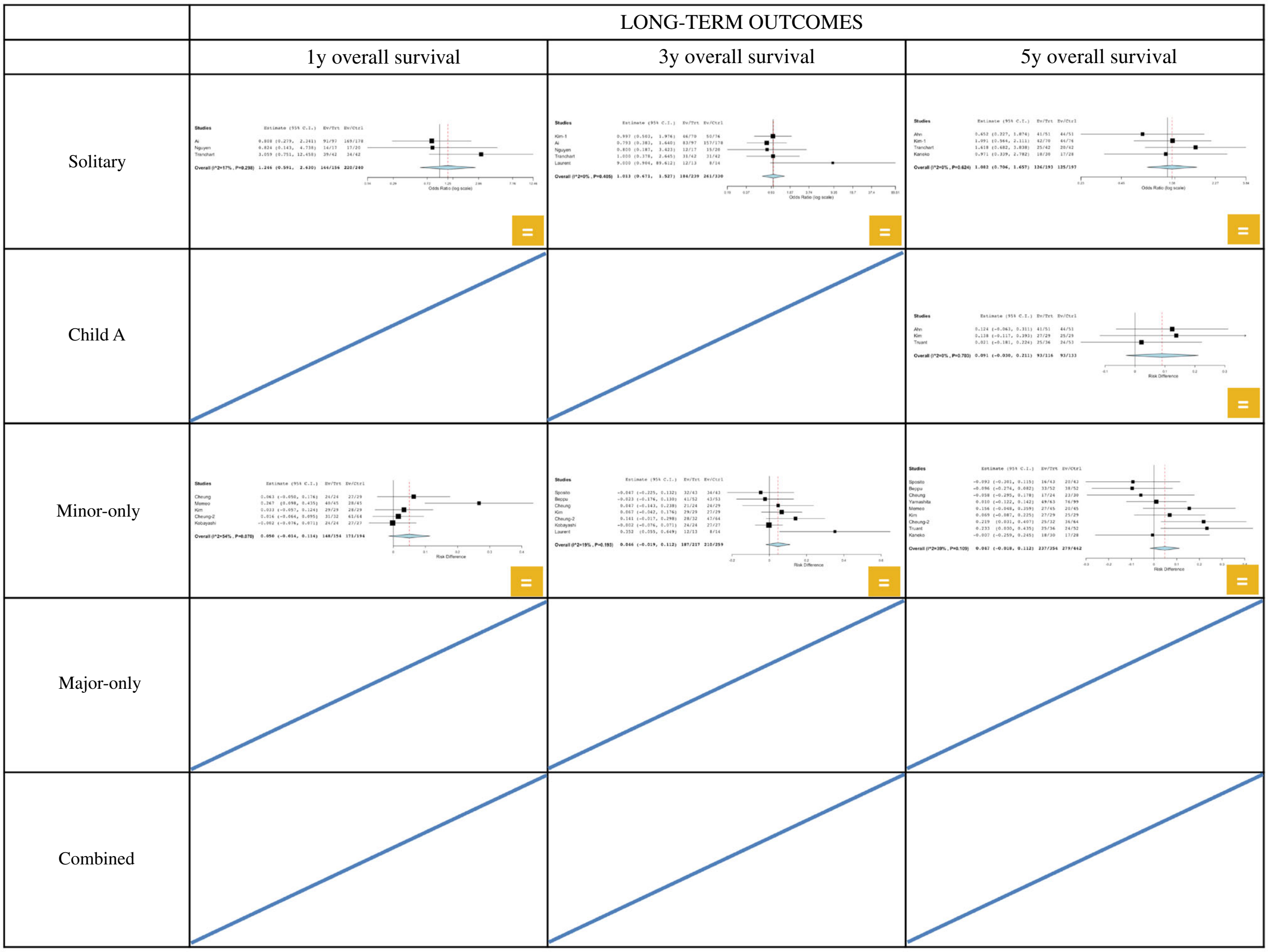

FIG. 3 Meta-analysis of long-term outcomes (I)

of the surgical management of HCC. Only data for 3- and 5-year survival provided sufficient detail for analysis. For this, a trend towards improved survival was associated with a laparoscopic approach, however this did not reach statistical significance. DFS followed a similar pattern, with the noteworthy exception of an improved rate at 1 year for laparoscopic minor resections. Although statistically significant, this difference should be considered with caution and no strong conclusions should be drawn from this finding as only five studies with a slight dispersion were included in the analysis.

Previous meta-analyses have already reported the results of open resection versus LLR for HCC;[10–13,61] however, most of them focused only on short-term outcomes. Only the studies by Zhou et al.[10] and Fancellu et al.[11] analyzed long-term OS and DFS (both in 2011), including few reports in which different types of resection were mixed. To give stronger evidence to the results currently available, we put together short- and long-term outcomes in each category that we could identify. It should be noted that the I2 score was high in many of the comparisons and thus decreased confidence in the estimates may be considered a limitation to our manuscript. In order to minimize this heterogeneity, our meta-analysis included several steps that tried to minimize biases. As per the EGMLLS methodology, we initially performed an extensive literature review with strong quality discrimination. For this purpose, we used two well-validated quality assessment tools to obtain the best quality of evidence—the SIGN methodology and the NOS. Manuscripts that were rated as low quality in the SIGN and/or received less than six stars in the NOS were discarded. Second, we performed subgroup meta-analyses specifically examining patients with Child–Pugh A cirrhosis, solitary tumors, and those undergoing minor and major liver resections. Additional literature searches were performed for ‘portal hypertension’ (using platelet count and/or esophageal varices), multicentric HCC, Barcelona Liver Clinic (BCLC)-A or -B, or severe cirrhosis, but no comparative series were available. Finally, all meta-analyses performed to date used the methodology of Hozo

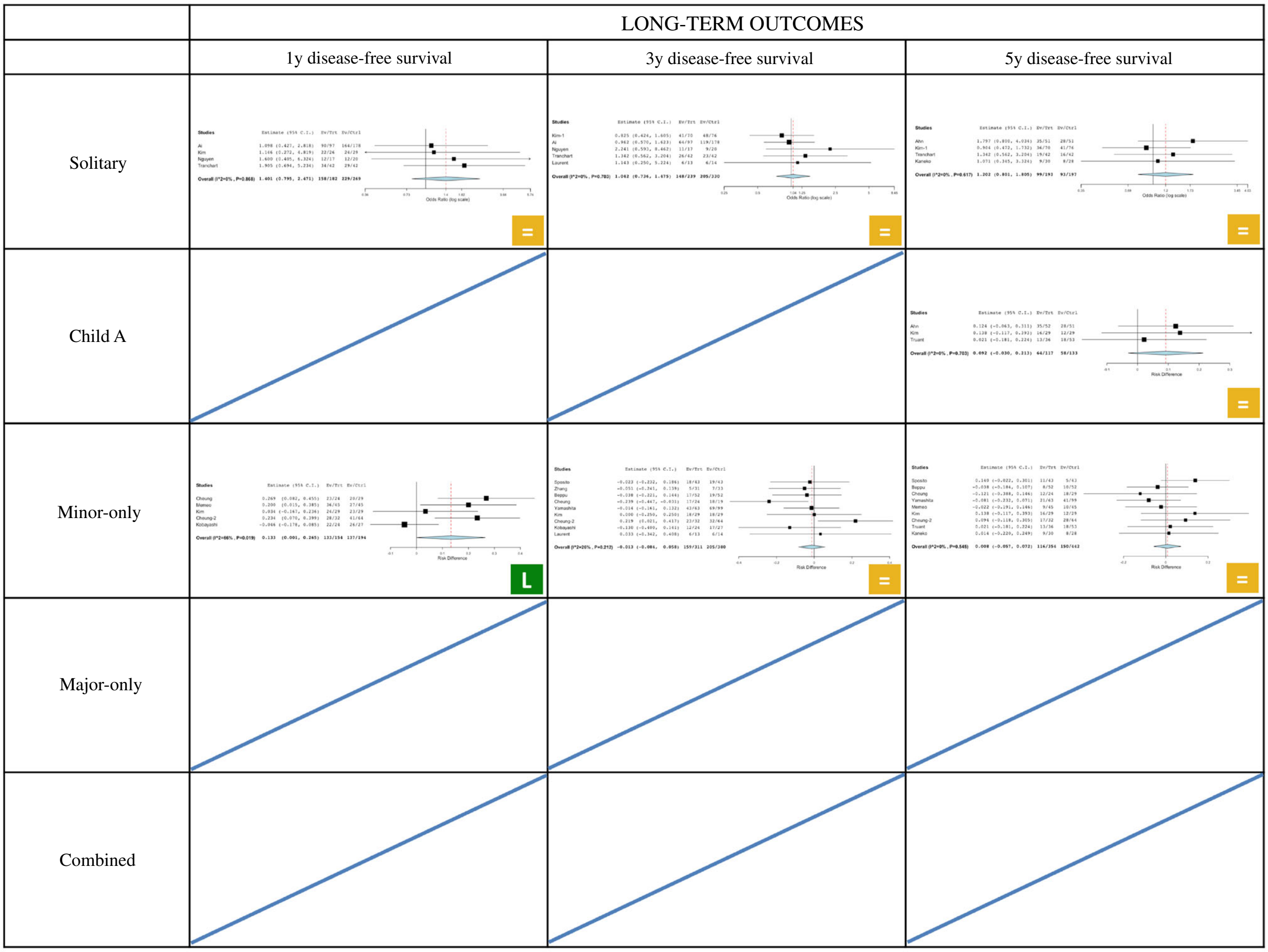

FIG. 4 Meta-analysis of long-term outcomes (II)

et al.[62], however we have chosen to use the methodology of Wan et al.[23], which has recently been demonstrated to achieve more precise calculations of mean and SD, and which in turn allows for more accurate conclusions.

CONCLUSIONS

Liver surgery for HCC in cirrhotic patients is considered more dangerous due to the potential for increased morbidity, especially liver decompensation, and higher postoperative mortality. Due to refinements in surgical technique, anesthetic management, and perioperative care, liver resections are now considered a standard practice for early-stage tumors in cirrhotic patients with well-compensated liver function. The results of the present meta-analysis demonstrate that a minimally invasive approach may be superior to an open approach with respect to short-term outcomes for patients with Child–Pugh A cirrhosis, solitary tumors, and minor resections. In the long-term setting, the results demonstrate that a minimally invasive approach is comparable to an open approach in terms of overall and DFSs. Considering the current evidence, it may be concluded that LLRs for HCC are safe and may be considered a standard practice in specific settings.

REFERENCES

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med.* 2011;365(12):1118–27.
2. Clavien P-A, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol.* 2012;13(1):e11–e22.
3. Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. *Br J Surg.* 2016;103(7):871–80.
4. Ciria R, López-Cillero P, Gallardo AB, Cabrera J, Pleguezuelo M, Ayllón MD et al. Optimizing the management of patients with BCLC stage-B hepatocellular carcinoma: modern surgical resection as a feasible alternative to transarterial chemoemolization. *Eur J Surg Oncol.* 2015;41(9):1153–61.

5. Hashizume M, Takenaka K, Yanaga K, Ohta M, Kajiyama K, Shirabe K et al. Laparoscopic hepatic resection for hepatocellular carcinoma. *Surg Endosc.* 1995;9(12):1289–91.
6. Kaneko H, Takagi S, Shiba T. Laparoscopic partial hepatectomy and left lateral segmentectomy: technique and results of a clinical series. *Surgery.* 1996;120(3):468–75.
7. Ciria R, Cherqui D, Geller DA, Briceño J, Wakabayashi G. Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. *Ann Surg.* 2016;263(4):761–77.
8. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han H-S et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg.* 2015;261(4):619–29.
9. Chang L, Wang Y, Zhang J, Guo T. The best strategy for HCC patients at each BCLC stage: a network meta-analysis of observational studies. *Oncotarget.* 2017;8(12):20418–27.
10. Zhou Y-M, Shao W-Y, Zhao Y-F, Xu D-H, Li B. Meta-analysis of laparoscopic versus open resection for hepatocellular carcinoma. *Dig Dis Sci.* 2011;56(7):1937–43.
11. Fancellu A, Rosman AS, Sanna V, Nigri GR, Zorcolo L, Pisano M et al. Meta-analysis of trials comparing minimally-invasive and open liver resections for hepatocellular carcinoma. *J Surg Res.* 2011;171(1):e33–45.
12. Morise Z, Ciria R, Cherqui D, Chen K-H, Belli G, Wakabayashi G. 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(5):342–52.
13. Cipriani F, Fantini C, Ratti F, Lauro R, Tranchart H, Halls M et al. (2017) Laparoscopic liver resections for hepatocellular carcinoma. Can we extend the surgical indication in cirrhotic patients? *Surg Endosc*. 30(suppl 3):61–70.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
15. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I et al. The international position on laparoscopic liver surgery: the Louisville statement, 2008. *Ann Surg.* 2009;250(5):825–30.
16. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery.* 2011;149(5):713–24.
17. Petrie JC, Grimshaw JM, Bryson A. The Scottish intercollegiate guidelines network initiative: getting validated guidelines into local practice. *Health Bull (Edinb).* 1995;53(6):345–8.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controll Clin Trials.* 1986;7(3):177–88.
19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–60.
20. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst.* 1959;22(4):719–48.
21. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw.* 2010;36(3):1–48.
22. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49(5):1–15.
23. Wan X, Wang W, Lui J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
24. Lee KF, Chong CN, Wong J, Cheung YS, Wong J, Lai P. Long-term results of laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma: a case-matched analysis. *World J Surg*. 2011;35(10):2268–74.
25. Xiao L, Xiang L-J, Li J-W, Chen J, Fan Y-D, Zheng S-G. Laparoscopic versus open liver resection for hepatocellular carcinoma in posterosuperior segments. *Surg Endosc.* 2015;29(10):2994–3001.
26. Hu B-S, Chen K, Tan HM, Ding X-M, Tan JW. Comparison of laparoscopic vs open liver lobectomy (segmentectomy) for hepatocellular carcinoma. *World J Gastroenterol*. 2011;17(42):4725–8.
27. Ker CG, Chen JS, Kuo KK, Chuang SC, Wang SJ, Chang WC et al. Liver surgery for hepatocellular carcinoma: laparoscopic versus open approach. *Int J Hepatol.* 2011;2011:596792.
28. Aldrighetti L, Guzzetti E, Pulitanò C, Cipriani F, Catena M, Paganelli M et al. Case-matched analysis of totally laparoscopic versus open liver resection for HCC: short and middle term results. *J Surg Oncol.* 2010;102(1):82–6.
29. Endo Y, Ohta M, Sasaki A, Kai S, Eguchi H, Iwaki K et al. A comparative study of the long-term outcomes after laparoscopy-assisted and open left lateral hepatectomy for hepatocellular carcinoma. *Surg Laparosc Endosc Percutan Tech*. 2009;19(5):e171–4.
30. Zhang Y, Huang J, Chen X-M, Sun D-L. A comparison of laparoscopic versus open left hemihepatectomy for hepatocellular carcinoma. *Surg Laparosc Endosc Percutan Tech*. 2016;26(2):146–9.
31. Ahn KS, Kang KJ, Kim YH, Kim T-S, Lim TJ. A propensity score-matched case-control comparative study of laparoscopic and open liver resection for hepatocellular carcinoma. *J Laparoendosc Adv Surg Tech*. 2014;24(12):872–7.
32. Kim H, Suh K-S, Lee K-W, Yi N-J, Hong G, Suh S-W et al. Long-term outcome of laparoscopic versus open liver resection for hepatocellular carcinoma: a case-controlled study with propensity score matching. *Surg Endosc.* 2014;28(3):950–60.
33. Truant S, Bouras AF, Hebbar M, Boleslawski E, Fromont G, Dharancy S et al. (2011) Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a case-matched study. *Surg Endosc.* 25(11):3668–77.
34. Laurent A, Cherqui D, Lesurtel M, Brunetti F, Tayar C, Fagniez PL. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. *Arch Surg.* 2003;138(7):763–9. **(discussion 769)**.
35. Zhang J, Zhou Z-G, Huang Z-X, Yang K-L, Chen J-C, Chen J-B et al. Prospective, single-center cohort study analyzing the efficacy of complete laparoscopic resection on recurrent hepatocellular carcinoma. *Chin J Cancer*. 2016;35(1):25.
36. Luo L, Zou H, Yao Y, Huang X. Laparoscopic versus open hepatectomy for hepatocellular carcinoma: short- and long-term outcomes comparison. *Int J Clin Exp Med.* 2015;8(10):18772–8.
37. Beppu T, Hayashi H, Okabe H, Imai K, Nitta H, Masuda T et al. Hybrid-including endoscopic versus open hepatic resection for patients with hepatocellular carcinoma meeting the Milan criteria: a propensity case-matched analysis. *Anticancer Res.* 2015;35(3):1583–90.
38. Cheung TT, Poon RTP, Dai WC, Chok KSH, Chan SC, Lo CM. Pure Laparoscopic versus open left lateral sectionectomy for hepatocellular carcinoma: a single-center experience. *World J Surg*. 2016;40(1):198–205.
39. Yamashita Y-I, Ikeda T, Kurihara T, Yoshida Y, Takeishi K, Itoh S et al. Long-term favorable surgical results of laparoscopic hepatic resection for hepatocellular carcinoma in patients with cirrhosis: a single-center experience over a 10-year period. *J Am Coll Surg*. 2014;219(6):1117–23.
40. Memeo R, de'Angelis N, Compagnon P, Salloum C, Cherqui D, Laurent A et al. (2014) Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case–control study. *World J Surg*. 38(11):2919–26.
41. Kanazawa A, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S et al. Impact of laparoscopic liver resection for

hepatocellular carcinoma with F4-liver cirrhosis. *Surg Endosc*. 2013;27(7):2592–7.
42. Cheung TT, Poon RTP, Yuen WK, Chok KSH, Jenkins CR, Chan SC et al. Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. *Ann Surg*. 2013;257(3):506–11.
43. Kobayashi S, Nagano H, Marubashi S, Kawamoto K, Wada H, Eguchi H et al. Hepatectomy based on the tumor hemodynamics for hepatocellular carcinoma: a comparison among the hybrid and pure laparoscopic procedures and open surgery. *Surg Endosc*. 2013;27(2):610–7.
44. Belli G, Fantini C, D'Agostino A, Cioffi L, Langella S, Russolillo N et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in patients with histologically proven cirrhosis: short- and middle-term results. *Surg Endosc*. 2007;21(11):2004–11.
45. Kaneko H, Takagi S, Otsuka Y, Tsuchiya M, Tamura A, Katagiri T et al. Laparoscopic liver resection of hepatocellular carcinoma. *Am J Surg*. 2005;189(2):190–4.
46. Shimada M, Hashizume M, Maehara S, Tsujita E, Rikimaru T, Yamashita Y et al. Laparoscopic hepatectomy for hepatocellular carcinoma. *Surg Endosc*. 2001;15(6):541–4.
47. Komatsu S, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. *Surg Endosc*. 2016;30(5):1965–74.
48. Cho JY, Han H-S, Yoon Y-S, Choi Y, Lee W. Outcomes of laparoscopic right posterior sectionectomy in patients with hepatocellular carcinoma in the era of laparoscopic surgery. *Surgery*. 2015;158(1):135–41.
49. Kim S-J, Jung H-K, Lee DS, Yun SS, Kim HJ. The comparison of oncologic and clinical outcomes of laparoscopic liver resection for hepatocellular carcinoma. *Ann Surg Treat Res*. 2014;86(2):61–7.
50. Ai J-H, Li J-W, Chen J, Bie P, Wang S-G, Zheng S-G. Feasibility and safety of laparoscopic liver resection for hepatocellular carcinoma with a tumor size of 5–10 cm. *PLoS ONE*. 2013;8(8):e72328.
51. Kim HH, Park EK, Seoung JS, Hur YH, Koh YS, Kim JC et al. Liver resection for hepatocellular carcinoma: case-matched analysis of laparoscopic versus open resection. *J Korean Surg Soc*. 2011;80(6):412–9.
52. Nguyen KT, Marsh JW, Tsung A, Steel JJL, Gamblin TC, Geller DA. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. *Arch Surg*. 2011;146(3):348–56.
53. Tranchart H, Di Giuro G, Lainas P, Roudie J, Agostini H, Franco D et al. Laparoscopic resection for hepatocellular carcinoma: a matched-pair comparative study. *Surg Endosc*. 2010;24(5):1170–6.
54. Lai ECH, Tang CN, Ha JPY, Li MKW (2009) Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. *Arch Surg*. 144(2):143–7. **(discussion 148)**.
55. Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N et al. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. *J Hepatobiliary Pancreat Sci*. 2015;22(10):721–7.
56. Han H-S, Shehta A, Ahn S, Yoon Y-S, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: case-matched study with propensity score matching. *J Hepatol*. 2015;63(3):643–50.
57. Lee JJ, Conneely JB, Smoot RL, Gallinger S, Greig PD, Moulton C-A et al. Laparoscopic versus open liver resection for hepatocellular carcinoma at a North-American Centre: a 2-to-1 matched pair analysis. *HPB (Oxford)*. 2015;17(4):304–10.
58. Abu HM. Why do we need guidelines in laparoscopic liver surgery? HPB (Oxford). 2017;19(4):287–8.
59. Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg*. 2009;249(4):617–23.
60. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, DeMatteo RP et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg*. 2003;237(6):860–9. **(discussion 869–70)**.
61. Twaij A, Pucher PH, Sodergren MH, Gall T, Darzi A, Jiao LR. Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis. *World J Gastroenterol*. 2014;20(25):8274–81.
62. 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.