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A systematic review and meta-analysis comparing the short- and long-term outcomes for laparoscopic and open liver resections for liver metastases from colorectal cancer

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Abstract

Background The laparoscopic approach to liver resection has experienced exponential growth in recent years. However, evidence-based guidelines are needed for its safe future progression. The main aim of our study was to perform a systematic review and meta-analysis comparing the short- and long-term outcomes of laparoscopic and open liver resections for colorectal liver metastases (CRLM).

Methods To identify all the comparative manuscripts between laparoscopic and open liver resections for CRLM, all published English language studies with more than ten cases were screened. In addition to the primary meta-analysis, 3 specific subgroup analyses were performed on patients undergoing minor-only, major-only and synchronous resections. The quality of the studies was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) methodology and Newcastle–Ottawa Score.

Results From the initial 194 manuscripts identified, 21 were meta-analysed, including results from the first randomized trial comparing open and laparoscopic resections of CRLM. Five of these were specific to patients undergoing a synchronous resection (399 cases), while six focused on minor (3 series including 226 cases) and major (3 series including 135 cases) resections, respectively. Thirteen manuscripts compared 2543 cases but could not be assigned to any of the above sub-analyses, so were analysed independently. The majority of short-term outcomes were favourable to the laparoscopic approach with equivalent rates of negative resection margins. No differences were observed between the approaches in overall or disease-free survival at 1, 3 or 5 years.

Conclusion Laparoscopic liver resection for CRLM offers improved short-term outcomes with comparable long-term outcomes when compared to open approach.

Keywords Minimally · Colorectal · Cancer · Metastases · Resection · Hepatectomy · Liver

Colorectal cancer (CRC) is one of the most common tumours worldwide and its incidence is increasing [1]. It is estimated that 30% of patients with CRC will present with liver metastases and a further 20% will develop metastases during their follow-up [2]. Resection of both the liver metastases and the primary tumour has been demonstrated to improve survival [3, 4]; hence, optimization of the management of colorectal liver metastases (CRLM) is essential.

A minimally invasive approach to the resection of CRLM and the primary colonic tumour(s) is now widely practised [5, 6], with recent meta-analyses demonstrating that a laparoscopic approach to liver resections offers improved short-term outcomes with comparable long-term outcomes [7]. However, these studies have all considered differing histopathological lesions as a single homogenous group, which

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Table 1 Exclusion and inclusion criteria. TACE: transarterial chemoembolization

Inclusion criteria	Exclusion criteria
Human studies	Animal/experimental studies
Comparative studies	Review/editorial/case report/letter
English language	Radiofrequency/TACE/Other ablations
Only laparoscopic versus open	Liver transplant involved
Only last 15 years	Robotics/hybrid cases
Duplicated data, most recent included	Other metastases non-CRLM

may result in a potential bias and hence inaccuracies in the drawn conclusions.

In the absence of specific evidence-based guidance to the optimal approach for resection of CRLM, an up-to-date meta-analysis incorporating all relevant studies, including data from the first randomized control trial [8] comparing open and laparoscopic liver resections for CRLM, is required. In preparation for The European Guidelines Meeting of Laparoscopic Liver Surgery (EGMLLS), Southampton, 2017 [9], an updated meta-analysis taking into account patterns of resections was prepared to compare open and laparoscopic resections for CRLM.

Patients and methods

a. Aims of the study.

  i. Primary aim: 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 CRLM by systematic review and meta-analysis.
  ii. Secondary aims: to assess the distribution of available studies with regard to resection type and perform secondary subgroup meta-analyses by grouping similar studies in order to increase the level of evidence for specific resection types.

b. Search strategy and general considerations: Pubmed, Embase, the Cochrane Library and Web of Science were searched, using the following search strategy ((colorectal[Title] OR colon[Title] OR colonic[Title] OR rectal[Title] OR bowel[Title]) AND (laparoscopic[Title] OR laparoscopy[Title] OR minimally[Title] OR hybrid[Title]) AND (liver[Title] OR hepatic[Title] OR hepatectomy[Title])) and their associated combinations of medical subject heading-MeSH terms. The final search was performed on 20 May 2017. Data from the Oslo laparoscopic versus open liver resection for colorectal metastases (OSLO-COMET) trial were made available by the COMET team (BE and AAF). No IRB approval nor written consent was necessary for this study.

c. Study selection: the inclusion and exclusion criteria are shown in Table 1. Review articles were examined for potential additional references. Duplications were identified by matching author's names and publication centres. Two reviewers (R.C and I.G-L.) and an independent third one (M.H. or F.C.) in case of match individually assessed each manuscript and rejected those that failed to meet the inclusion criteria.

d. Definitions: considering the aims of our study, the following definitions and patterns were considered:

  i. The resection type was based upon the proposal from the Louisville Consensus meeting in 2008 [10] considering minor or major a resection involving ≤ 2 or > 2 Couinaud segments, respectively. Resections including simultaneous colorectal and liver resections were also individually analysed.
  ii. 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 analysed within their subgroups.
  iii. Combined series were defined as those reporting a mixture of minor/major resections that could not be separated and analysed separately and hence could not be included within the above subgroups.

e. Variables and endpoints (endpoints in italics).

  i. Short-term outcomes (intraoperative parameters): *operative time (minutes), operative blood loss (ml) and number of patients requiring blood transfusion (%).*
  ii. Short-term outcomes (post-operative parameters): *total number of early (< 30 days) complications (%), duration of post-operative hospital stay (days), mean resection margin (mm).*
  iii. Long-term outcomes: *1-, 3- and 5-year overall survival; 1-, 3- and 5-year disease-free recurrence.*

f. Quality assessment of the studies included in the meta-analysis.

  i. First quality assessment: the first quality assessment was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN) [11].
  ii. Second quality assessment. The second quality assessment was performed in accordance with the Newcastle–Ottawa Quality Assessment Scale (NOS) available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. The criteria for "representativeness of cases" were considered as consecutive or obviously representative series of cases without a potential selection bias. Specifically, no star was given if cases included were not matched by year of inclusion (due to potential selection bias) and/or different surgeons and/or > 10 years of inclusion period (due to potential technical bias). Similarly, equal distribution of type and severity of underlying liver disease was an exclusion criterion to be given a star. For the rating of "Control for important factor", two stars were given if lap and open cases were matched by age, gender, ASA score, Body mass index, type of resection, number of lesions and size of the lesions. If any of these factors was not specifically mentioned or not correctly matched, only 1 star was given. If 2 or more of these factors were not correctly matched or non-mentioned, no stars were given.

g. Statistical analysis: analyses were performed using log odds ratios (OR) with a 95% confidence interval (95% CI) for dichotomous variables and weighted mean differences (WMD) with a 95% CI for continuous variables. For dichotomous variables in which any observed value was 0, OR may be not possible to calculate, and thus, rate differences were used. The standard heterogeneity test, the I-square statistic, was used to assess the consistency of the effect sizes. Based on method reported by DerSimonian and Laird [12], substantial significance was set when $p < 0.10$ and a random effect model was used [13]. In addition, an I^2 value < 25% was defined as low heterogeneity; between 25 and 50% as moderate heterogeneity; and > 50% as high heterogeneity. Publication bias was also assessed visually using a funnel plot. Every 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 by the Mantel–Haenszel method [14]. OpenMEE software based on OpenMetaAnalyst Software was used for statistical analyses [15, 16]. To perform meta-analyses, mean and Standard deviation (SD) were needed and estimations of mean and SD were performed to avoid discarding important studies. According to a recent publication from Wan et al. [17], in the event that a manuscript reported data in different measures 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, 3 series could be identified for each variable, avoiding results obtained derived from analyses of 2 reports.

Results

Eligible studies and final count

From the initial 194 manuscripts identified in the searches, 36 comparative studies remained after the inclusion and exclusion criteria were applied. Quality assessment was then performed in accordance to SIGN and NOS scales (Table 2). Fifteen manuscripts [18–32] did not reach a minimum requirement of acceptable quality (by SIGN scoring) or 6 points (by NOS) and were discarded (Fig. 1) resulting in 21 manuscripts to be considered for the systematic review and meta-analysis. Six of these were specific to patients undergoing minor [33–35] or major liver resections [33, 36, 37], including 226 and 140 cases, respectively. Five series [38–42] focused on synchronic colorectal and liver resection and included 399 patients. The remaining reports include 13 manuscripts [5, 6, 33, 36, 43–51] accounting for 2543 cases that could not be allocated to none of the previous categories and were analysed as "combined" resections. Each of the subgroups underwent separate secondary meta-analyses. All baseline results are depicted in Supplementary Digital Content 1.

Minor-only liver resections

Three manuscripts including 146 laparoscopic and 80 open cases were analysed. Overall complication rate and operative time were similar between both open and laparoscopic groups. Intraoperative blood loss (Het. p value = 0.080; $I^2 = 60\%$. SMD = −0.538 [−1.003 to −0.074]; $p = 0.023$) and hospital stay (Het. p value = 0.728; $I^2 = 0\%$. SMD = −0.363 [−0.641 to −0.085]; $p = 0.01$) were favourable with a laparoscopic approach (Figs. 2 and 3). None of the manuscripts reported data for long-term outcomes (Figs. 4 and 5).

Major-only liver resections

Three manuscripts including 45 laparoscopic and 95 open cases were analysed. With the exception of inpatient stay, which favoured an open approach (Het. p value = 0.150; $I^2 = 47\%$. SMD = −0.545 [0.148–0.943]; $p = 0.007$), there were no differences in the short-term outcomes between open and laparoscopic approaches (Figs. 2 and 3). Only one

Table 2 Overall quality analysis from all comparative studies including Newcastle–Ottawa and SIGN scores

CHARACTERISTICS OF THE STUDIES INCLUDED IN THE meta-analysis FOR CRLM PATIENTS															
Author Country	Year	N lap	N open	Etiology	Conversion	Quality assessment by Newcastle-Ottawa Scale									
						Selection				Comparability	Exposure			Quality judgment (máximum 9 stars)	SIGN
						Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factor	Ascertainment of exposure	Same method to ascertain for cases and controls	Non-response rate		
MINOR															
Nachmany Tel-Aviv-Israel	2015	37	82	CRLM	5 (13,5%)	–	–	–	★	★★	★	★	★	★★★★ ★★	+ Acceptable
Cheung Hong Kong-China	2013	20	40	CRLM	0	–	–	–	★	★★	★	★	★	★★★★ ★★	++ High Quality
Inoue Osaka-Japan	2013	23	24	CRLM	1(4,3%)	–	★	–	★	★	★	★	★	★★★★ ★★	++ High Quality
Mala Oslo-Norway	2002	13	14	CRLM	0	–	–	–	★	–	★	★	★	★★★★	- Low quality
MAJOR															
Hasegawa Morioka-Japan	2015	20	25	CRLM	1 (5%)	–	–	–	★	★★	★	★	★	★★★★ ★★	+ Acceptable
Nachmany Tel-Aviv-Israel	2015	5	50	CRLM	0	–	–	–	★	★★	★	★	★	★★★★ ★★	+ Acceptable
Topal Leuven-Belgium	2012	20	20	CRLM	0	–	★	–	★	★★	★	★	★	★★★★ ★★★	++ High Quality
SYNCHRONIC															
Tranchart Clamart - France	2016	89	89	CRLM	6 (7%)	★	–	–	★	★★	★	★	★	★★★★ ★★★	++ High Quality
Ratti Milan - Italy	2016	25	50	CRLM	1 (4%)	★	–	–	★	★★	★	★	★	★★★★ ★★★	++ High Quality
QiLin Shanghai - China	2015	36	36	CRLM	–	★	–	–	★	★★	★	★	★	★★★★ ★★★	++ High Quality
Jung Seoul-Korea	2014	24	24	CRLM	0	–	★	–	★	★★	★	★	★	★★★★ ★★★	+ Acceptable
Hu Beijing-China	2012	13	13	CRLM	0	–	★	–	★	★★	★	★	★	★★★★ ★★★	+ Acceptable
Huh Jeonnam-Korea	2011	20	20	CRLM	0	–	–	–	★	★★	★	★	★	★★★★ ★	+ Acceptable
CHEN Kai-yun Guangdong - China	2011	23	18	CRLM	0	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
COMBINED															
Fretland	2017	129	144	CRLM	9 (6,9%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	++ High quality
Martínez-Cecilia	2016	225	225	CRLM	17 (7.6%)	★	–	–	★	★	★	★	★	★★★★ ★★	++ High quality
Untereiner	2016	18	18	CRLM	1 (5.6%)	★	–	–	★	★	★	★	★	★★★★ ★★	++ High quality
Lewin Australia	2016	147	139	CRLM	15 (10.5%)	★	–	–	★	★	★	★	★	★★★★ ★★	+ Acceptable
Karagkounis Cleveland-OH	2016	65	65	CRLM	5 (7.7%)	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Cipriani Shouthampton-UK	2016	133	133	CRLM	13 (9.8%)	★	★	–	★	★	★	★	★	★★★★ ★★★	++ High quality
Allard Strasbourg-France	2015	153	153	CRLM	-	★	–	–	★	–	★	★	★	★★★★ ★	+ Acceptable
Tohme Pittsburgh-USA	2015	66	66	CRLM	3 (4%)	–	–	–	★	★	★	★	★	★★★★ ★	- Low quality
Beppu Kumamoto-Japan	2015	171	342	CRLM	-	★	–	–	★	★★	★	★	★	★★★★ ★★★	++ High quality
Hasegawa Morioka-Japan	2015	102	69	CRLM	1 (5%)	–	–	–	★	★★	★	★	★	★★★★ ★★	+ Acceptable
Nachmany Tel-Aviv-Israel	2015	42	132	CRLM	5 (13,5%)	–	–	–	★	★★	★	★	★	★★★★ ★★	+ Acceptable
Langella Turin-Italy	2015	37	37	CRLM	-	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
De´Angelis Créteil-France	2015	52	52	CRLM	3 (5.8%)	★	★	–	★	★★	★	★	★	★★★★ ★★★★	++ High quality
Iwahashi Tokushima-Japan	2014	21	21	CRLM	-	–	★	–	★	–	★	★	★	★★★★ ★	+ Acceptable
Qiu China	2014	24	25	CRLM	2 (8.3%)	–	–	–	★	★★	★	★	★	★★★★ ★★	+ Acceptable

Table 2 (continued)

Montalti Ghent-Belgium	2014	57	57	CRLM	15,8%	–	★	–	★	★★	★	★	★	★★★★ ★★★	++ High quality
Kubota Tokyo -Japan	2014	43	62	CRLM	-	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Guerron Cleveland-USA	2013	40	40	CRLM	5%	–	★	–	★	–	★	★	★	★★★★ ★	+ Acceptable
Doughtie Louisville-USA	2013	8	76	CRLM	0	–	–	–	★	★	★	★	★	★★★★ ★	+ Acceptable
Qiu Sichuan-China	2013	30	30	CRLM	2 (6.66%)	–	★	–	★	★★	★	★	★	★★★★ ★★★	++ High quality
Cannon Louisville-USA	2012	35	140	CRLM	-	–	–	–	★	★	★	★	★	★★★★ ★	+ Acceptable
Topal B. Leuven-Belgium	2012	81	193	CRLM		–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Nguyen Pittsburgh-USA	2011	24	25	CRLM	-	–	★	–	★	★	★	★	★	★★★★ ★★	+ Acceptable
Abu Hilal Southampton-UK	2010	50	85	CRLM	6 (12%)	–	–	–	★	–	★	★	★	★★★★	- Low quality
Castaing Paris-France	2009	60	60	CRLM	6 (10%)	–	–	–	★	★	★	★	★	★★★★ ★	+ Acceptable

Italics marked studies were the discarded ones because of NOS < 7 stars or Low scoring in the SIGN analysis

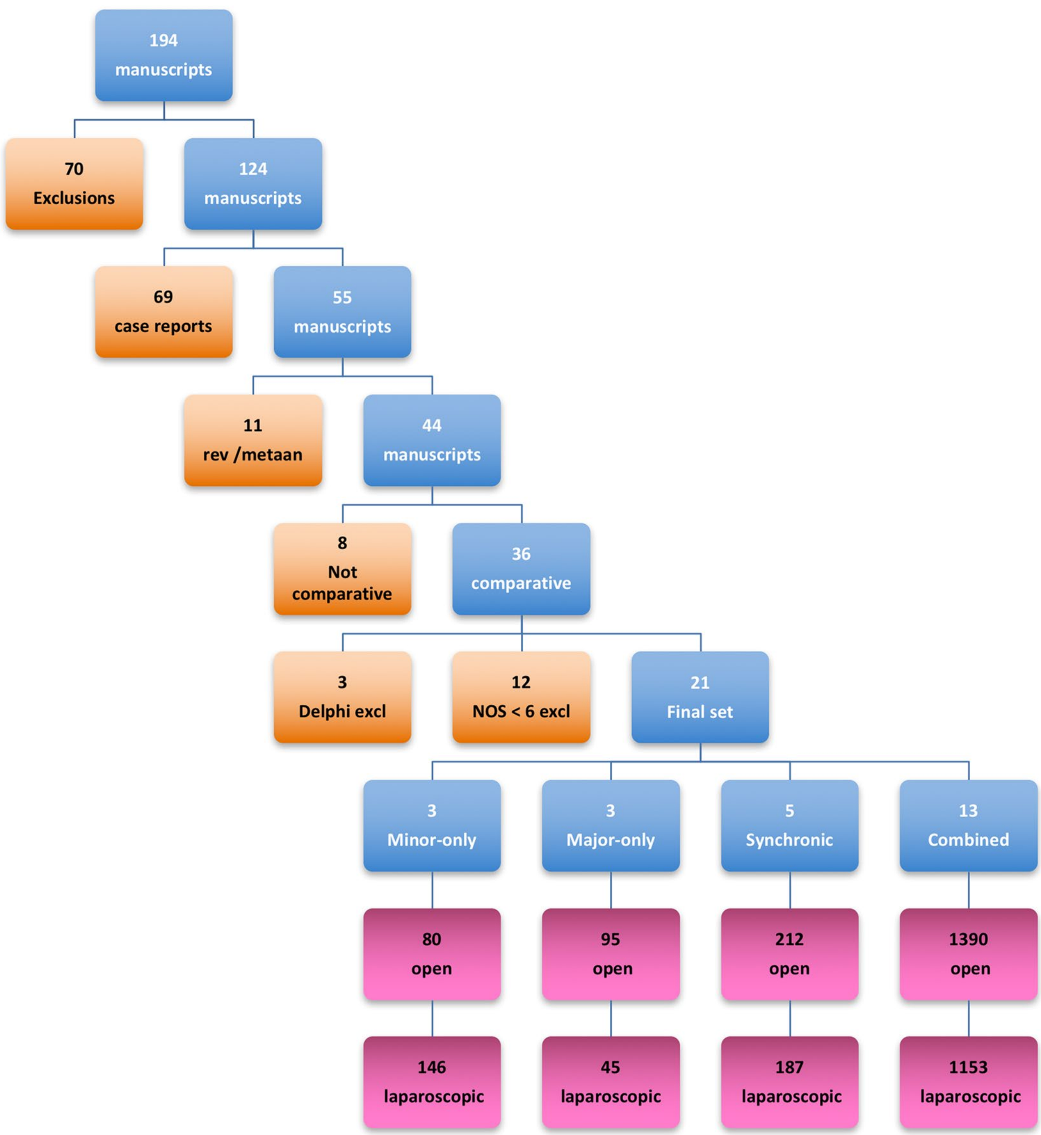

Fig. 1 PRISMA model flow chart of eligible studies

manuscript reported results on survival, so no further statistical analyses were performed (Figs. 4 and 5).

Synchronic colorectal and liver resections

Five manuscripts were identified including 212 open versus 187 laparoscopic synchronic colorectal–liver resections. All short-term outcomes were comparable between the groups except for a reduced inpatient stay in the laparoscopic group (Het. p value = 0.184; $I^2 = 75\%$. SMD = − 0.709 [− 1.156 to − 0.263]; $p = 0.002$) (Figs. 2 and 3). Regarding long-term outcomes, only 1-year overall survival had sufficient numbers to allow for meta-analysis, with no significant differences between the approaches (Figs. 4 and 5).

Combined studies

Thirteen manuscripts could not be allocated to any of the three previous subcategories and included 2543 patients (1390 open and 1153 laparoscopic). Short-term outcomes including blood loss, operative time and positive resection margins were not significantly different. However, the rates of complications (Het $p = 0.230$; $I^2 = 21.7\%$. OR = 1.906 [1.504–2.415]; $p < 0.001$), transfusions (Het $p = 0.001$; $I^2 = 0\%$. OR = 1.653 [1.163–2.349]; $p = 0.005$) and hospital stay (Het. $p = 0.001$; $I^2 = 92.864\%$. SMD = − 0.3.843 [− 5.533 to − 2.153]; $p < 0.001$) all favoured a laparoscopic approach (Figs. 2 and 3). Contrary to the previous categories, there were a considerable number of studies reporting long-term outcomes. There were no significant differences observed in the 1-, 3- or 5-year overall and disease-free survival between open and laparoscopic groups (Figs. 4 and 5). In this specific point, we analysed the ratio of minor/major resections in open and laparoscopic approaches. From the 1247 open resections included, 876 were reported as minor, while in the laparoscopic group, 795 out of the 1025 analysed were considered as minor. There was a significant higher rate of minor resections in the laparoscopic group ($I^2 = 69.22\%$. OR = 1.804 [1.180–2.760]; $p < 0.001$) compared to the open groups (Fig. 6).

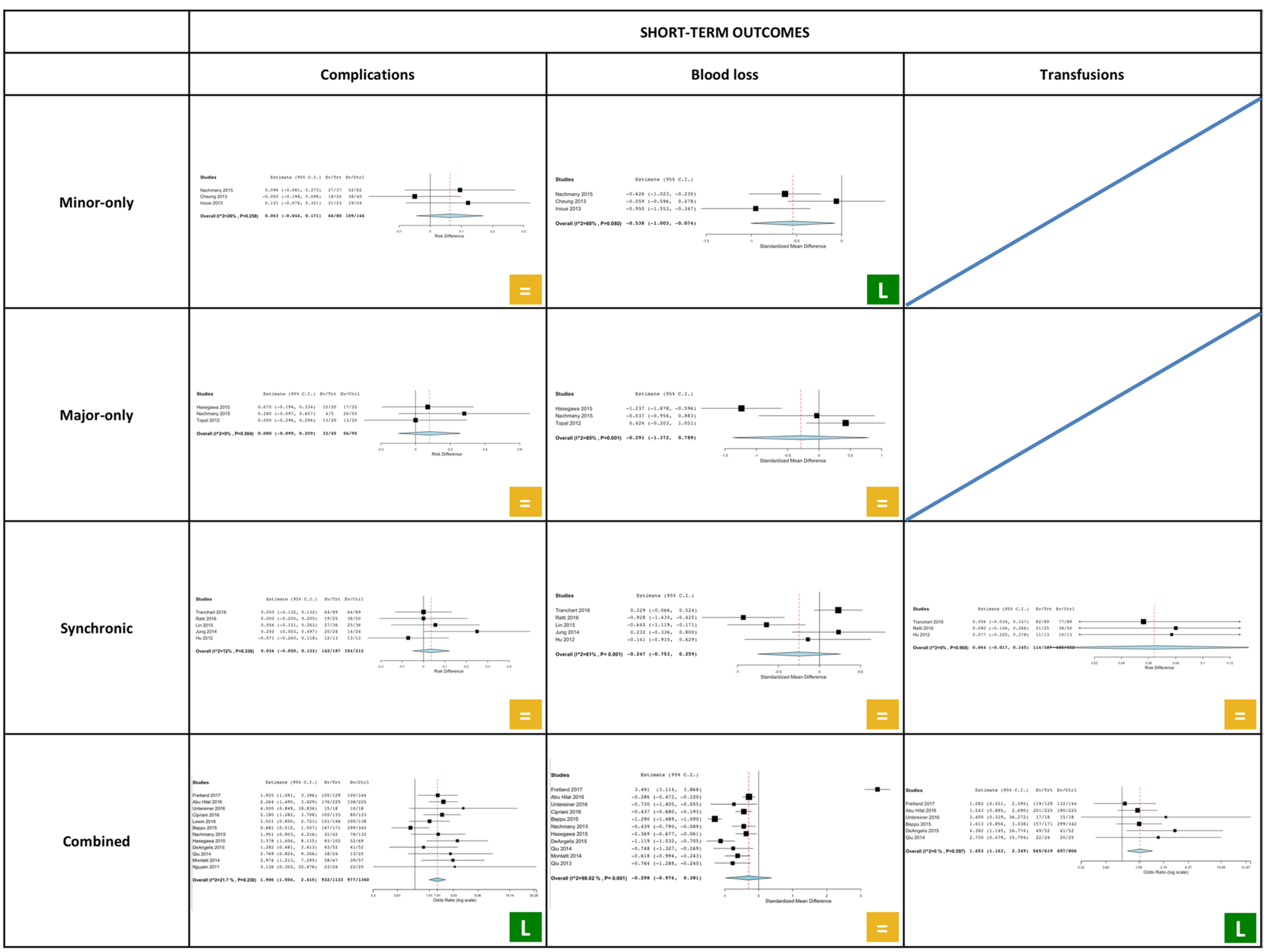

Fig. 2 Meta-analysis of short-term outcomes (I)

Fig. 3 Meta-analysis of short-term outcomes (II)

Bias analysis

Each sub-analysis was independently assessed for bias in each variable. All the resulting funnel plots are graphically depicted in Supplementary Digital Content 2, 3, 4 and 5.

Discussion

The initial implementation of a laparoscopic approach to liver resections was met with skepticism as to the oncological efficiency of the approach. These concerns have been addressed by small studies [30, 52, 53] but there remains limited high quality evidence provided by randomized controlled trials and meta-analysis to support this. The current study represents the most up-to-date and comprehensive analysis of the differing approaches to liver resection for CRLM and is the first meta-analysis to include data from a randomized controlled trial (OSLO-COMET) [43] specific to this subject.

The results of the current study demonstrate that, in general, the short-term outcomes are in favour of a laparoscopic approach. Regarding long-term outcomes, there are no differences in overall or disease-free survival in any of the series analysed thereby dispelling the concerns of an inferior oncological efficiency of a laparoscopic approach. It is noteworthy that post-operative complications have been suggested to worsen the oncological outcomes of a liver resection and may be even more influential than KRAS status [54]. Hence, a laparoscopic approach may even offer an oncological advantage by reducing post-operative complications. It has also traditionally been argued that laparoscopic liver surgery may not adequately balance the resection margin in CRLM leading to higher rates of R1-positive margins or unnecessary major liver resections. We performed meta-analyses for both resection margin rate and ratio of minor/major resections. Regarding the rate of positive resection margins, there were no differences between laparoscopic and open approaches. Regarding the rate of minor/major resections, there was a higher rate of minor resections in

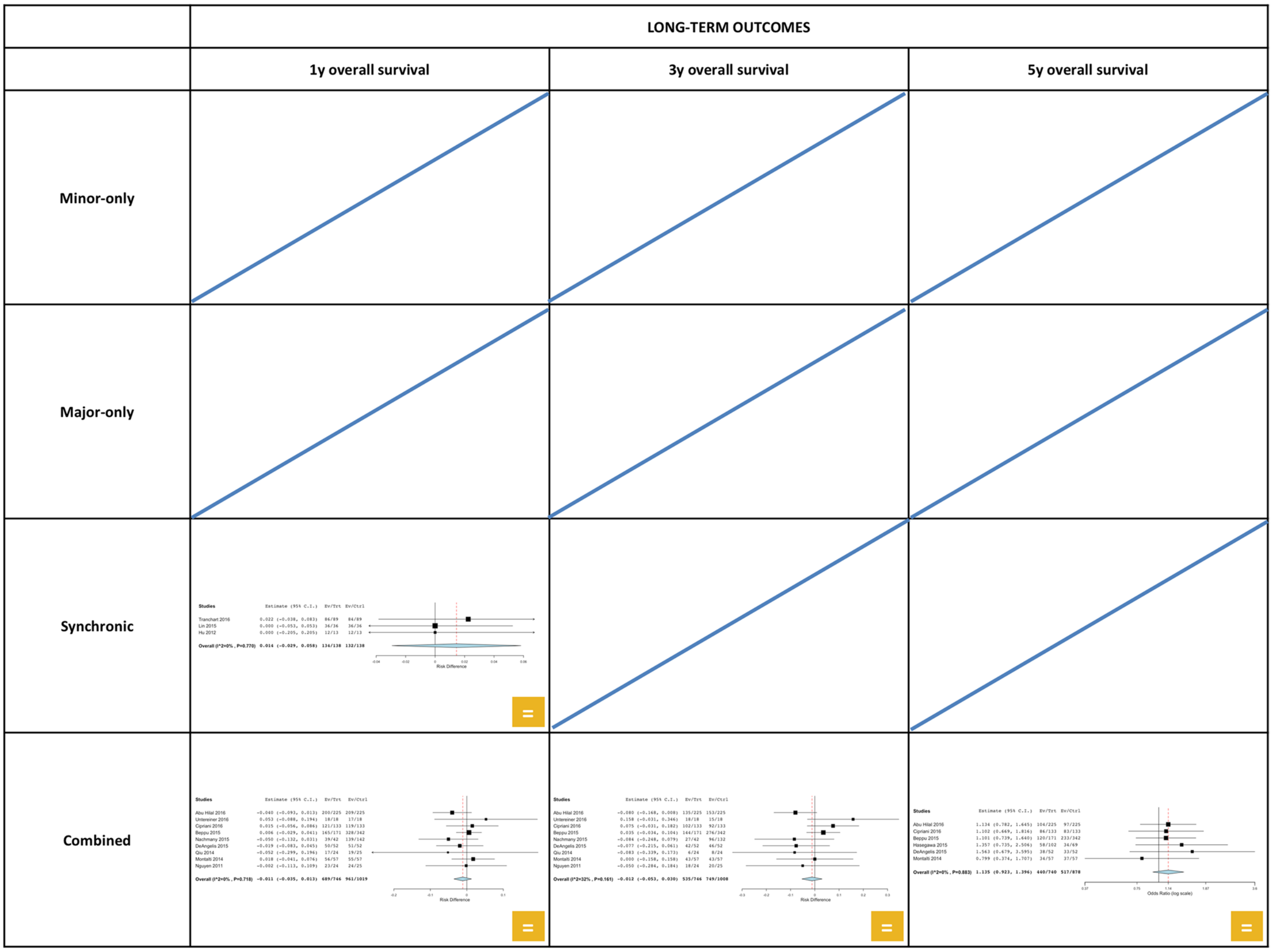

Fig. 4 Meta-analysis of long-term outcomes (I)

the laparoscopic group. We cannot discriminate from the analysed manuscripts if more complex cases were allocated to open groups, even though the matching was adequate in most of them.

The potential benefits of laparoscopic liver resections have already been demonstrated in smaller studies [5–7, 22, 37, 55, 56]. The results of this meta-analysis suggest that for the majority of resection classifications a laparoscopic approach produces better short-term outcomes with equivalent long-term outcomes to an open approach. However, this simplification overlooks important clinical advantages that may be associated with a laparoscopic approach. The reduced complication rate may allow an increased number of patients to have chemotherapy in a timely fashion, while the theoretical reduction in adhesions may allow for an increased number of repeat resections should recurrence occur. Similarly, reduced hospital stay has been found to be lower (not in major liver resections). This finding may also help administration of early chemotherapy with lower probabilities of complications that may delay its use leading to worse oncological prognosis. Finally, technical tools that are exclusive to a laparoscopic approach, such as Indocyanine green (ICG) fluorescence, may help achieve "anatomical parenchymal sparing" resections that may in turn contribute to a reduced ischemic residual that has been reported as a risk factor for recurrence [57].

A meta-analysis of retrospective studies should be approached with caution as several biases must be anticipated and controlled. Several manuscripts with a high quality of evidence could be identified in our search. Actually, excellent propensity score matching analyses [5] and the first RCT [8] could be enrolled in the search and the statistical analysis. This latter manuscript should be the basis of future RCT to be performed in LLR, as the inclusion criteria, statistical analysis and cost-effectiveness results were clearly defined and meticulously analysed. Unfortunately, long-term results were not included among the objectives of the study, which could have made the results of our study stronger.

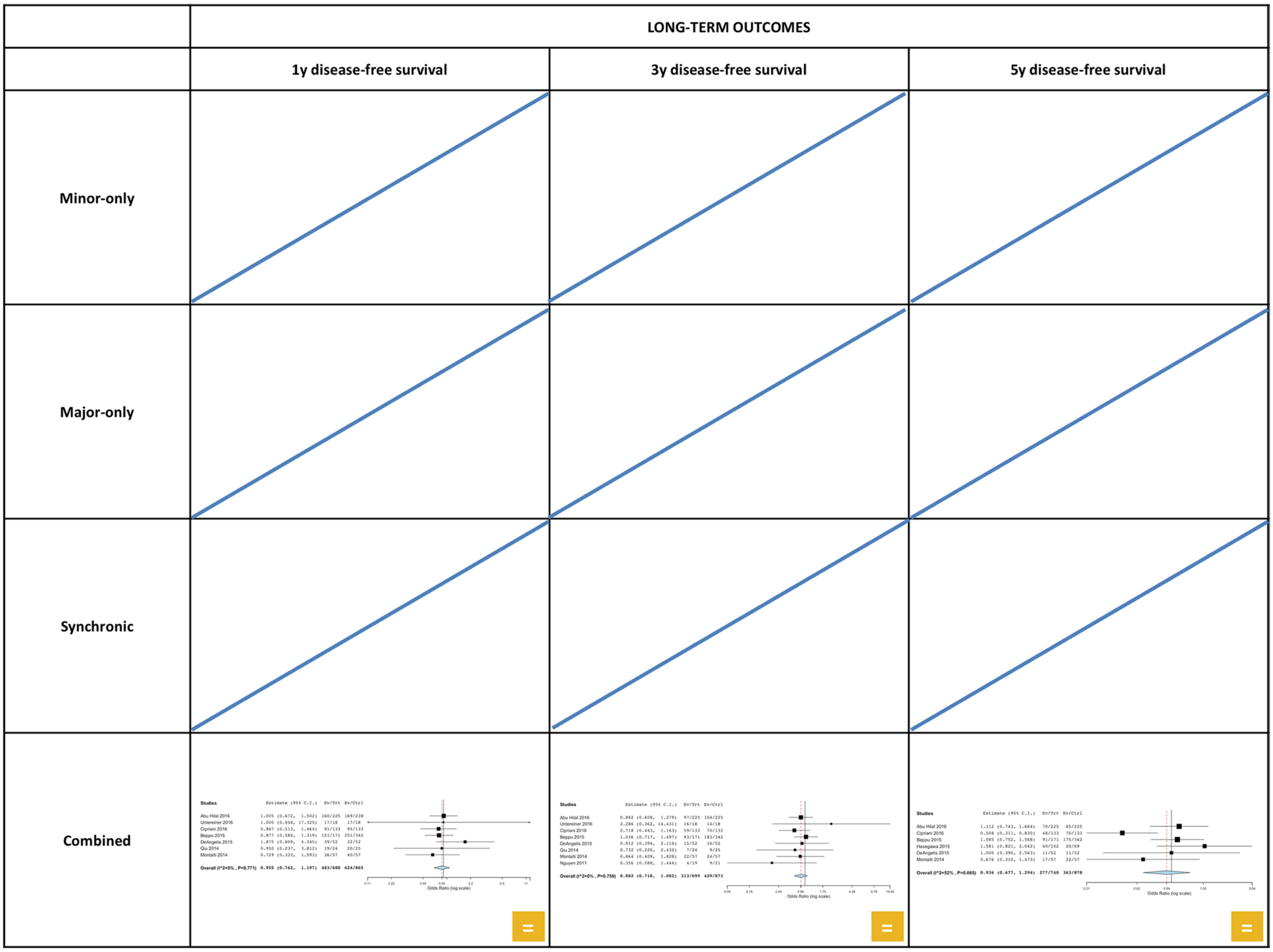

Fig. 5 Meta-analysis of long-term outcomes (II)

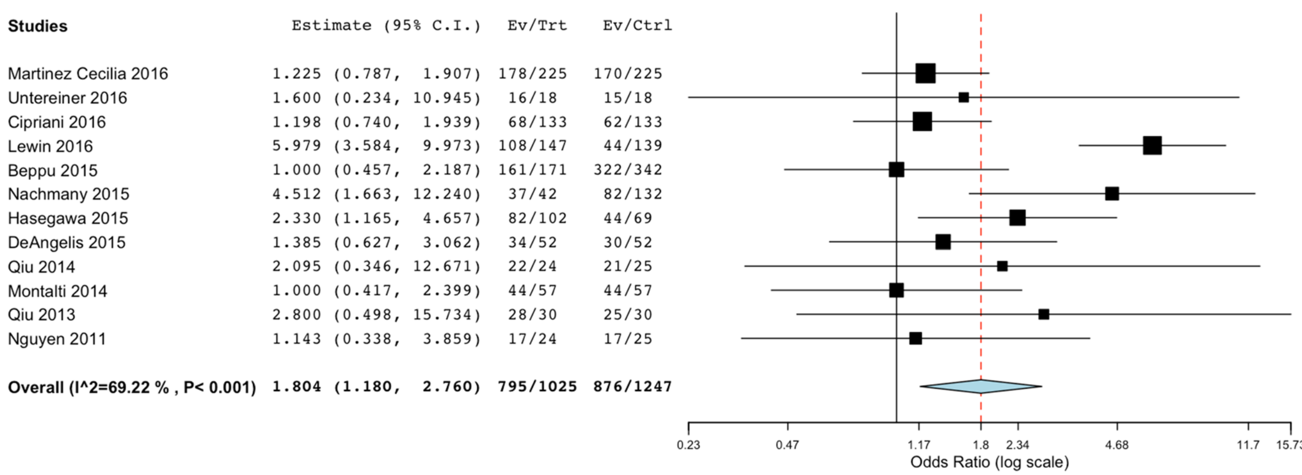

Fig. 6 Number of minor versus major resections in each of the studies included in the combined groups

After reviewing the current literature, and despite the fact that several good quality manuscripts were identified, from our point of view it would be desirable that specific comparisons should be reported. We strongly advocate for split results in future publications that may, at least, consider the difficulty of resection.

In order to increase the quality of evidence reported by this meta-analysis, several steps were taken to improve the analyses. The use of resection categories permitted sub-analyses that allow for more homogeneous groups for comparison, while the division of outcomes into short- and long-term enabled the specific examination of the intra- and post-operative period and the oncological efficiency of the approaches. Finally, the current 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 method and/or received less than 6 stars in the NOS were discarded. Finally, all meta-analyses performed to date use the methodology of Hozo et al. [58]; however, we have chosen to use the methodology of Wan et al. [17], which has recently been demonstrated to achieve more precise calculations of mean and standard deviation that in turn allows for more accurate conclusions to be drawn.

The results of this meta-analysis support the use of a minimally invasive approach for the resection of CRLM. A laparoscopic approach has no detrimental impact on long-term outcomes and provides improved short-term outcomes for the majority of resection classifications.

Compliance with ethical standards

Disclosures Drs. Ciria, Ocaña, Gómez-Luque, Cipriani, Halls, Fretland, Okuda, Aroori, Briceño, Aldrighetti, Edwin and Abu Hilal have no conflicts of interest or financial ties to disclose.

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