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Synchronous colorectal liver metastasis: A network meta-analysis review comparing classical, combined and liver-first surgical strategies

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Abstract

Background: In recent years, the management of synchronous colorectal liver metastasis has changed significantly. Alternative surgical strategies to the classical colorectal-first approach have been proposed. These include the liver-first and combined resections approaches. The objectives of this review were to compare the short and long-term outcomes for all three approaches.

Methods: A systematic review of comparative studies was performed. Evaluated endpoints included surgical outcomes(5-year overall survival, 30-day mortality, and post-operative complications). Pair-wise and network meta-analysis(NMA) were performed to compare survival outcomes.

Results: 18 studies were included in this review, reporting on 3,605 patients. NMA and pair-wise meta-analysis of the 5-year overall survival did not show significant difference between the three surgical approaches: combined vs. colorectal-first, mean odds- ratio 1.02(95% CI 0.8-1.28, p=0.93); liver-first vs. colorectal-first, mean odds-ratio 0.81(95% CI 0.53-1.26, p=0.37); liver-first vs. combined, mean odds-ratio 0.80(95% CI 0.52-1.24, p=0.41). In addition NMA of the 30-day mortality among the three approaches also did not observe statistical difference. Analysis of variance showed that mean post-operative complications of all approaches were comparable(p=0.51).

Conclusion: There are considerable differences in the peri-operative management of synchronous CLM patients. This meta-analysis demonstrated no clear statistical surgical outcome or survival advantage towards any of the three approaches.

Introduction

Colorectal cancer is the second most common cause of cancer-related deaths in the United States and in the United Kingdom. [1-2] The most common metastatic site is the liver,[3] with 15-25% of patients having colorectal liver metastasis (CLM) at the time of diagnosis,[4-5] and another 30-50% of patients developing CLM during their treatment course.[5-7] The presence of CLM is a poor prognostic factor conferring a median survival of 6-12 months in untreated patients. [8] A complete surgical resection is considered the best chance for long term survival, however unfortunately only 20% of patients with CLM are eligible for radical resection. [9-10] Recently, with advances in chemotherapy regiments and liver-directed therapy, as well as with the improvement of operative techniques, the 5-year survival of patients who underwent surgical resection for CLM has risen to 40-58%.[11-13]

The optimal surgical management of patients with colorectal cancer and synchronous liver metastasis is still controversial. Traditionally, colorectal cancer patients with synchronous liver metastasis would undergo a staged approach,[14] consisting of the resection of the primary tumor followed by hepatectomy at a later date (colorectal-first approach). The rationale is that the primary neoplasm should be managed first because it is both the source of further metastasis and potential complications, including intestinal obstruction, perforation or massive gastrointestinal bleeds.[15] The staged approach also provides the opportunity for recovery after the initial surgery and for commencing chemotherapy earlier. In addition, this approach enables a "natural selection" of patients. Those with "less favorable" disease typically have either progression of metastasis or significant morbidities after their primary surgery, and therefore are deemed unsuitable for hepatic resection. [16] More recently, in order to prevent delays in liver-directed therapy or in systemic treatment, some authors have advocated the liver-first approach. [15]

Alternatively, when technically feasible and clinical applicable, some centers have shifted to a combined approach. The potential benefit of performing a combined resection of both the primary colorectal and the liver metastatic tumor includes a single operation and anesthetic induction with an overall reduction in the total hospital length of stay.[1,17] In contrast, this approach may increase the complexity of the surgical procedure and the length of the operation, raising concern on safety and the long-term outcomes.[1,5]

Several studies have compared the different surgical approaches in an effort to identify whether one confers a survival advantage over the others, but the evidence so far has been inconclusive. [18-21] In this context, we sought to systematically review the existing evidence relating to clinical outcomes of patients with synchronous CLM depending on the surgical approach, and synthesize the data using the methodology of meta-analysis.

Methods

A systematic review was performed according to the guidelines and recommendations from the preferred reporting items for systematic reviews and meta-analyses checklist (PRISMA). [22] Institutional review board approval was not required.

Search strategy

An electronic search for relevant publications was performed using the following resources: PubMed, Embase, Ovid and the Cochrane collaboration database from January 1998 to November 2013. The following search headings were used: "colorectal liver metastasis surgery", "resectable synchronous colorectal liver metastasis", "synchronous colorectal liver metastasis surgery", "liver first approach surgery synchronous colorectal liver metastasis", "staged surgery synchronous colorectal liver metastasis", and "combined surgery synchronous colorectal liver metastasis". Subsequently, we repeated the search on PubMed using the following medical subject headings (MeSH); "surgical procedures, operative" AND "colorectal neoplasm" AND "neoplasm, synchronous". All titles were initially screened and appropriate abstracts were reviewed. Each of the relevant publication reference section and Google scholar was also screened for other applicable publications. The last date of search was November 12th, 2013.

Inclusion criteria

To be included in the analysis, the studies had to meet the following criteria: a) report on patients with synchronous colorectal liver metastasis (CLM); b) compare the approaches for synchronous CLM (either colorectal-first approach vs. combined, combined vs. liver-first approach or compare all three approaches); c) report on surgical and outcomes measures mentioned below; d) have a clear research methodology; e) have the longest follow-up or the largest sample size when two or more studies were reported by the same institution.

Exclusion criteria

Studies were excluded from the analysis if: a) they did not specify that CLM were synchronous to primary disease; b) they did not compare the surgical approaches; c) outcomes of interest were not reported; d) the methodology was not clearly reported; e) the data were overlapping among authors; f) the patients in the studies had a planned two stage hepatectomy or hybrid approach to define the CLM diagnosis.

Data extraction

Two reviewers (MK, GS) independently reviewed the literature according to the above predefined strategy and criteria. Each reviewer extracted the following data variables: title and reference details (first author, journal, year, country), study population characteristics (number in study, number treated by each approach, gender and age), disease characteristics (location of the primary lesion, location of hepatic metastasis, number and size of CLM), type and approach of surgical intervention, and outcome data. All data were recorded independently by both literature reviewers in separate databases and were compared at the end of the reviewing process to limit selection bias. The database was also reviewed by a third person (DW). Duplicates were removed and any disparities were clarified.

Outcomes of interest

The following outcomes were used in the meta-analysis to compare the three approaches in management of synchronous CLM:

Primary outcome:

1. Survival outcome: 5-year overall survival

Secondary outcome:

2. Surgical outcomes: Post-operative complications and 30-day mortality

Other areas of interest, but not included in the meta-analysis were: length of hospital stay, duration of surgery, volume of blood loss and transfusion requirements.

Statistical analysis

Descriptive statistic was used to report the characteristics of all eligible trials, describing the types of surgical modalities, total patients numbers, mean age, duration of surgery, amount of blood loss, and median length of stay.
Statistical analysis was conducted using STATA software (Version 13, StataCorp LP, USA). Analysis of dichotomous variables was performed using odds ratio (OR), reported with 95% confidence interval (CI). First, we utilized pair-wise meta-analysis to compare the overall 5-year survival between the three surgical approaches, using the random-effects model with the assumption that there is a variation between studies. The test for heterogeneity was investigated

by visual inspection of the forest plots and I^2 statistic, which provides the percentage of variability attributed to heterogeneity rather than sampling error. The odds-ratio (OR) was considered to be statistically significant at the $p < 0.05$ level if the 95% CI did not include the value of 1.

Second, we performed a network meta-analysis (NMA) using STATA to compare the three surgical approaches simultaneously. NMA synthesizes data from a network of trials involving multiple interventions and therefore has the potential to rank the treatments according to the studied outcome. [23] This method integrates direct and indirect comparisons of interventions. In NMA, a common heterogeneity variance is assumed across all pair-wise comparisons. The NMA results are represented graphically in a forest plot with the mean odds-ratios together with their 95% confidence and predictive intervals. The predictive intervals provide an estimated interval within which the results of future studies are expected to be. Within the framework of NMA, we ranked the evaluated surgical interventions based on the mortality outcome. The surface under the cumulative ranking curve (SUCRA) was used to provide ranking probabilities. The larger the SUCRA value, the better the rank of the intervention. We also performed a network meta-regression accounting for small-study effects (using the variance of the log-odds ratios as covariate).[23] This was graphically represented together with the SUCRA.

One-way analysis of variance (ANOVA) was used to analyze the differences between the mean numbers of complications of each surgical approach. The F-ratio was used as a test for the null hypothesis of equality of the means. A statistically significant result is denoted by $p < 0.05$.

The quality of the studies included in this systematic review was assessed by the Newcastle-Ottawa scale (NOS),[24] to evaluate patient selection methodology, comparability and assessments of outcomes. The quality score rating was determined for each publication, with eight or more stars representing studies of higher quality.

Results

Eligible studies

A total of 1,929 articles were initially identified using the aforementioned search strategy. On full text screening, 18 publications that met the inclusion criteria were included in the meta-analysis (Figure 1). All studies were retrospective, and were published between January 1998 and November 2013. All studies were comparative, reporting on at least two surgical approaches for synchronous CLM. On review of the extracted data, there was 100% agreement between the two reviewers. Numbers, characteristics and quality of the studies assessed by the Newcastle-Ottawa scale (NOS) are outlined in Table 1.

Demographics

Analysis was performed on 3,605 patients, of which 2,439 (67.7%) had classical colorectal-first resection, 133 (3.7%) had liver-first resection and 1,033 (28.6%) had combined resections. The studies spanned a mean time period of 14.3 years, with patients operated from 1982 to 2012 (Table 1). Across all studies, male gender was more common, accounting for 58.9%, 60.1% and 54.7% of all patients treated as colorectal-first, liver-first and combined approach respectively (Table 2).

Sixteen studies reported colorectal distribution of primary tumor. Colorectal first approach had 71.2% (n=1696) colonic primaries and 23.8% (n=684) rectal primaries. Liver-first approach had less colonic primaries at 50.4% (n=57) and more rectal primaries at 49.6% (n=56). Combined approach had 67.8% (n=652) colonic primaries and 32.2% (n=309) rectal.

Fourteen studies reported hepatic distribution of CLM. The colorectal-first approach had 48.3% (n=1091) unilobar and 51.7% (n=1167) bilobar CLM. The liver-first approach had 33.9% (n=38) unilobar and 66.1% (n=74) bilobar CLM. The combined approach had 64.7% (n=623) unilobar and 35.3% (n=340) bilobar CLM. (Table 2)

Surgical outcomes

There was a considerable heterogeneity in the methods of reporting surgical outcomes and complications among the studies. Only 9 studies reported on the duration of surgery with no information pertaining to liver-first strategy. Seven studies reported the median blood loss, and 8 studies reported on blood transfusion requirements. Sixteen studies reported post-operative

complications, with only 7 actually specifying the types of complication. Ten studies reported on the length of stay, including only 1 study from liver-first strategy (Table 3).

Overall results of meta-analysis

Meta-analysis of 5-year overall survival (Primary outcome)

Fifteen studies reported on the 5-year overall survival (OS). However, only 3 studies compared the 5-year OS for all 3 approaches; while 11 studies included 5-year OS for combined vs. colorectal-first, and 1 study reported 5-year OS for colorectal-first vs. liver-first. Pair-wise meta-analysis did not show significant difference between the three treatment approaches ($p = 0.93$ for combined vs. colorectal-first; $p = 0.37$ for liver-first vs. colorectal-first; $p = 0.41$ for liver-first vs. combined) (Figure 2). There was significant heterogeneity amongst the studies involving the liver-first vs. colorectal-first approaches ($p = 0.019$, $I^2 = 69.8\%$). This significance was due to one study finding higher OS in the liver-first group.

The finding of no significant difference between the 3 treatment approaches was concurred by the network meta-analysis. The forest plot depicting the estimated summary effects in the form of mean odds-ratios along with their confidence intervals and corresponding predictive intervals is presented in Figure 3. All confidence intervals crossed the line of no effect (combined vs. colorectal-first: mean odds- ratio 1.02 (95% CI 0.8-1.28); liver-first vs. colorectal-first: mean odds-ratio 0.81 (95% CI 0.53-1.26); liver-first vs. combined: mean odds-ratio 0.80 (95% CI 0.52-1.24). Within the frame-work of this network meta-analysis, the SUCRA probability was highest for combined approach at 69.8%. However, when adjustment for small-study effects was made, the liver-first approach was preferred at 78.9%.

Meta-analysis of post-operative outcomes

Only 5 studies reported 30-day mortality for the different surgical approaches. Network meta-analysis did not find significant difference amongst the three groups as all confidence intervals crossed the line of no effect (combined vs. colorectal-first: mean odds- ratio 1.26 (95% CI 0.53-2.99); liver-first vs. colorectal-first: mean odds-ratio 0.56 (95% CI 0.03-11.22); liver-first vs. combined: mean odds-ratio 0.44 (95% CI 0.02-8.91) (Figure 4).

Sixteen studies reported the post-operative complications. From ANOVA, there was no difference found between the mean number of complication events of the three surgical

approaches (colorectal-first mean 37.4 (SD 19.0), combined mean 33.0 (SD 17.9), liver-first mean 22.1 (SD 21.1), p = 0.51). For the colorectal-first group, the complication rate was 29.3% (n = 489), within which respiratory events (sepsis and pleural effusions, 12.2%, n=60), bile leak (7.9%, n=39), and intra-abdominal collection/abscess (5.9%, n=29) were the most common. The complication rate of the combined group was 30.7% (n = 294) with the most common types of complications being intra-abdominal collection/abscess (9.8%, n=29), wound infection (7.8%, n=23) and respiratory sepsis/pleural effusions (6.8%, n=20). Comparison of high-quality studies (NOS ≥ 8) to those of lower quality (NOS < 8) yielded similar complication rates. For the colorectal-first group, eleven high-quality studies that reported complication events had an overall rate of 27.8%, while the rate of the five low-quality studies was 31.1%. Similarly in the combined group, the complication rates for the high and low quality-studies were 30.6% and 31.0%, respectively. As for the liver-first group, only 2 studies reported complications with an overall rate of 16.5% (n = 12).

Discussion

This systematic review and meta-analysis compared the three surgical approaches in the management of patients with synchronous colorectal liver metastasis, with a specific aim to assess which approach conferred the best chance for long term survival. Despite the advancements in chemotherapy regimens and the use of biological agents, no treatment other than surgery has shown a survival plateau for the management of synchronous CLM. [25] There is clear evidence from randomized control trials that resection of hepatic metastasis has significant value in improving survival outcomes and quality of life with 5-year survival between 25-40% post CLM resection in selected patients. [25,27,28] The timing of surgery for patients with synchronous CLM is currently a hot topic, since there is no consensus on the approach strategy or contraindications to resection of CLM yet. Moreover, studies have observed that the potential for CLM resection is often under-estimated,[26] with many patients deemed unresectable too soon without being referred to specialized hepato-biliary centers.[1] This lack of consensus emphasizes the need for clear international guidelines and referral pathways to optimize long term clinical outcomes in patients with CLM.

Those in favor of the classical colorectal-first or delayed approach postulate that the interval between primary resection and CLM resection provides the opportunity to delineate those patients with unfavorable cancer biology, and therefore prevent them from undergoing major surgical resection with potential related morbidity.[10] In addition, there is the worry that delaying primary resection may increase the rate of complications from the primary including perforation, obstruction and bleeding. Studies have reported this rate as high as 20% but some argue that this may be over-stated.[29-30]

Alternatively, proponents of both combined or liver-first (reverse) strategies argued that the presence of synchronous CLM already indicates that the patients have poor cancer biology. Therefore it is reasonable that these patients should receive chemotherapy upfront, and then be reassessed to determine which surgical approach is appropriate if at all. Colorectal cancer is predominantly chemo-sensitive, and therefore early chemotherapy is logical. *Lam et al.* had shown that neoadjuvant chemotherapy resulted in down-staging and conversion of unresectable disease in 22.5% of patients.[31] Centers that strongly favor this approach contend that a post-immunodeficiency state occurs after primary resection which drives the rate of metastatic growth, and that chemo-therapy is typically delayed due to recovery from the primary

resection.[32-33] Advocates of combined resection assert that its greatest advantage is that patients receive one general anesthetic, and one operation. This approach offers reduction in total hospital length of stay, risk of morbidity and healthcare cost overall.[10, 19, 34] Liver-first (reverse strategy) is invariably a misleading term as patients undergo neoadjuvant treatment prior to surgical resection. This strategy does facilitate early control CLM by early hepatic resection hoping to optimize patient's survival.[35] However, studies reporting on this treatment strategy have been highly selective, and therefore are not representative of the spectrum of synchronous CLM patients. Moreover, concerns over the adverse effects of neoadjuvant chemotherapy have been raised. Reports of liver changes including steatosis, non-alcoholic steatohepatitis, sinusoidal changes and centrilobular necrosis have been cited, potentially delaying surgery.[36] Despite these reports, recent studies had observed and speculated that bevacizumab may protect the liver from sinusoidal damage from chemotherapy agents such as oxaliplatin.[37]

Of note, there was a considerable heterogeneity in the 5-year overall survival rates reported for patients treated with the liver-first approach, ranging from 39% to 67% in this review. Many surgeons consider that liver-first strategy is a highly selective strategy, which should be reserved for patients with a high burden of CLM, but with low risk of the primary neoplasm causing complications.[38] Our review observed that liver-first patients had the highest number of bilobar disease at 66.1%, compared to that of the combined resection group at 35.3%. This was expected as the rationale for the liver-first approach is to facilitate early control of CLM in the hope to offer patients down-staging therapy and curative resections. In addition, the colorectal-first approach had substantially more colonic primaries (71.2%) whereas, the liver-first approach had an evenly distribution between colonic and rectal neoplasm (50.4% and 49.6% respectively). This was likely due to a traditional emphasis for early resection of colonic neoplasm to prevent complication, whereas in recent years the role of neo-adjuvant therapy for rectal tumors had been strongly advocated.

Though 15 studies reported on 5-year overall survival, only 3 studies compared all three surgical approaches. *Broquet et al.* were the first authors to retrospectively compare all three treatment strategies for management of synchronous CLM.[21] They found comparable surgical outcomes, morbidity and mortality between all three treatment approaches. In concordance, our systematic review and meta-analyses found no significant difference between those surgical approaches. Interestingly though, upon further analysis, our network meta-analysis surface under the

cumulative ranking curve showed a tendency towards better outcomes in patients treated with the liver-first approach (78.9%) when adjusted for small-study effects. This finding could be attributed to the highly selective nature of the liver-first patient cohort and small sample size. We also noted that the combined surgical approach had a higher, though not statistically significant, rate of intra-abdominal collection/abscess most likely due to the fact that this approach evolves more extensive resection.

This study is the first systematic review and meta-analysis comparing all three surgical approaches for synchronous CLM, and as such it bears important clinical implications. Unfortunately, due to non-availability of more detailed time-to-event data in the original studies, it was impossible to use the ideal method of survival meta-analysis to compare hazard ratios instead of odds ratios of 5-year survival; however standard meta-analysis has been routinely used for comparison of survival data when detailed time-to-event data are not available. Our review also highlighted several limitations to the current data available. Currently, there are no randomized control trials comparing all three surgical approaches; instead, there are only limited retrospective studies that have mostly compared 2 surgical approaches. In addition, there remain vast differences in chemotherapy regimens, especially in relation to the role and use of biological agents. The evolution of surgical and anesthetic technology has added more variation over recent years. Current studies have considerable disparity in the age of patients, site of primary neoplasm, size, number and distribution of hepatic metastasis. All these aspects add substantial heterogeneity to the current data skewering any possible inference. Therefore, there is a need for prospective comparative trials (ideally randomized and including all three approaches) with standardized reporting of surgical outcomes including the length of surgery, blood transfusion and intensive care requirements, associated morbidities, length of hospital stay and both three and five-year disease free and overall survival to properly assess the superiority of one surgical approach over the others.

Nevertheless, our review and meta-analysis suggests that all surgical approaches have comparable outcomes. Therefore, the aim of surgical care could be to assess each case individually with multi-disciplinary input and select the appropriate approach available to each patient. Those patients with a high burden of liver disease may be more likely to benefit from early surgical intervention via liver-first approach, whereas the classical colorectal-first approach may be more appropriate for patients who do not require down-staging therapy.

Conclusion

The management of colorectal cancer with synchronous CLM is evolving. The decision for timing of the primary and CLM resection should be individualized for each patient based on technical, oncological and patient considerations, with multi-disciplinary team input. Our network meta-analysis showed no significant difference in the 5-year overall survival of the three surgical approaches. There is growing need for randomized controlled trials to further investigate differences in clinical outcomes of the 3 different approaches.

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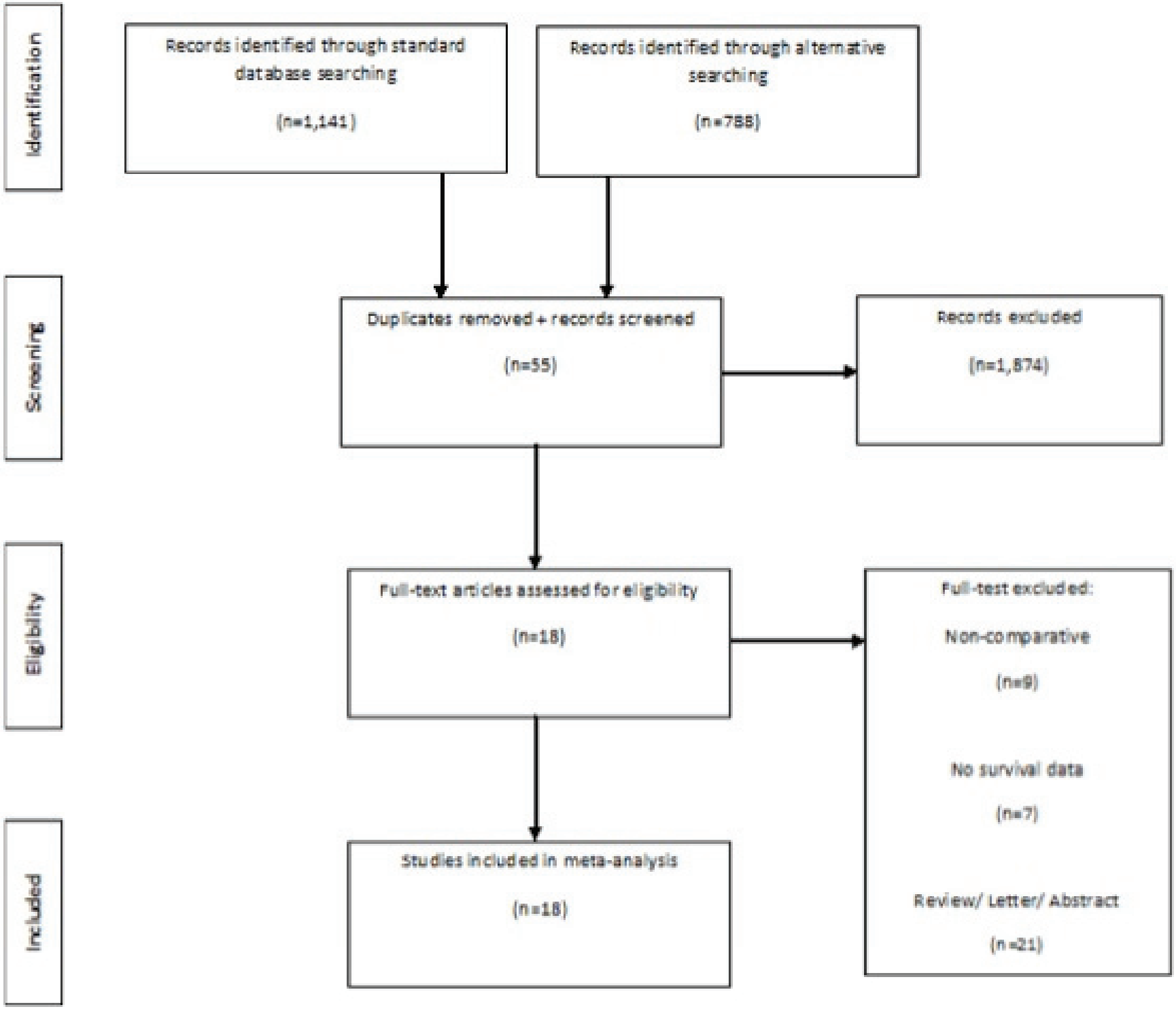
Figure Legends:

Figure 1. PRISMA flow diagram demonstrating results of literature search.

Figure 2. Forest plots of pair-wise standard meta-analysis of the 3 surgical approaches. OR = odds ratio, CI = confidence interval

Figure 3. A) Network meta-analysis predictive interval plot for the 3 surgical approaches. The black lines represent the confidence interval (CI) for mean odds-ratio (OR) for each comparison. The red lines are the predictive intervals (PrI). The blue line denotes the line of no effect (OR = 1). B) Plots of the surface under the cumulative ranking curves (SUCRA) for 3 treatments. The table presents the SUCRA hierarchical values (in percentage) for each surgical approach. The graphs show that small-study effects alter the ranking of treatments putting liver-first as the most favorable approach.

Figure 4. Network meta-analysis for 30-day mortality of the 3 surgical approaches. The black lines represent the confidence interval (CI) for mean odds-ratio (OR) for each comparison. The red lines are the predictive intervals (PrI). The blue line denotes the line of no effect (OR = 1).


Identification
Screening
Eligibility
Included
Records identified through standard database searching
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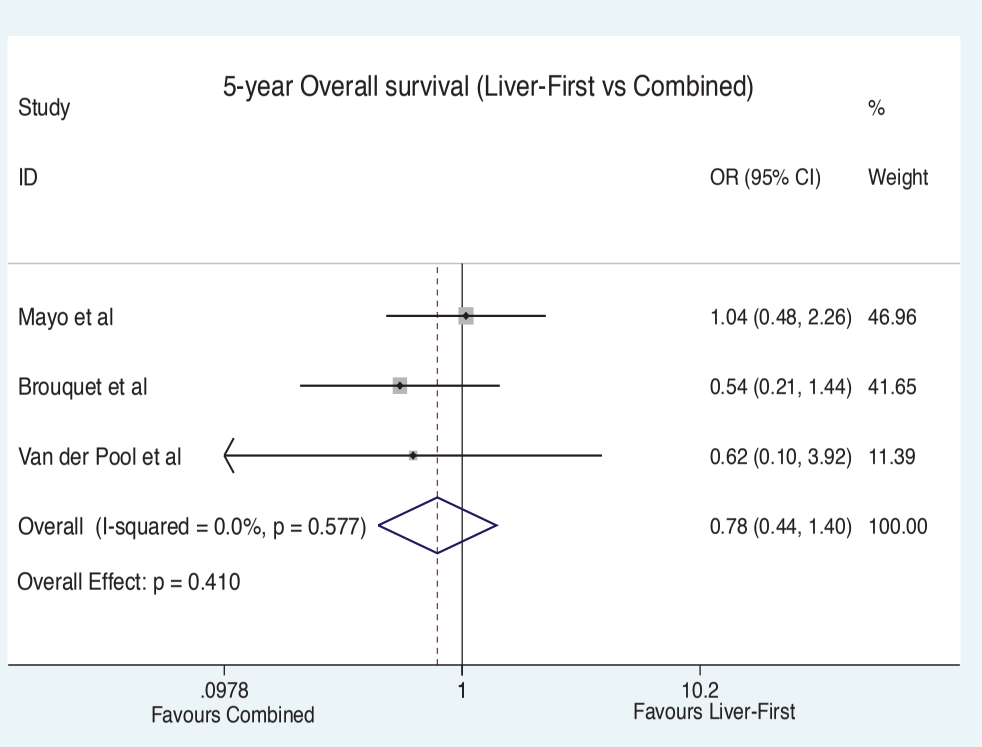
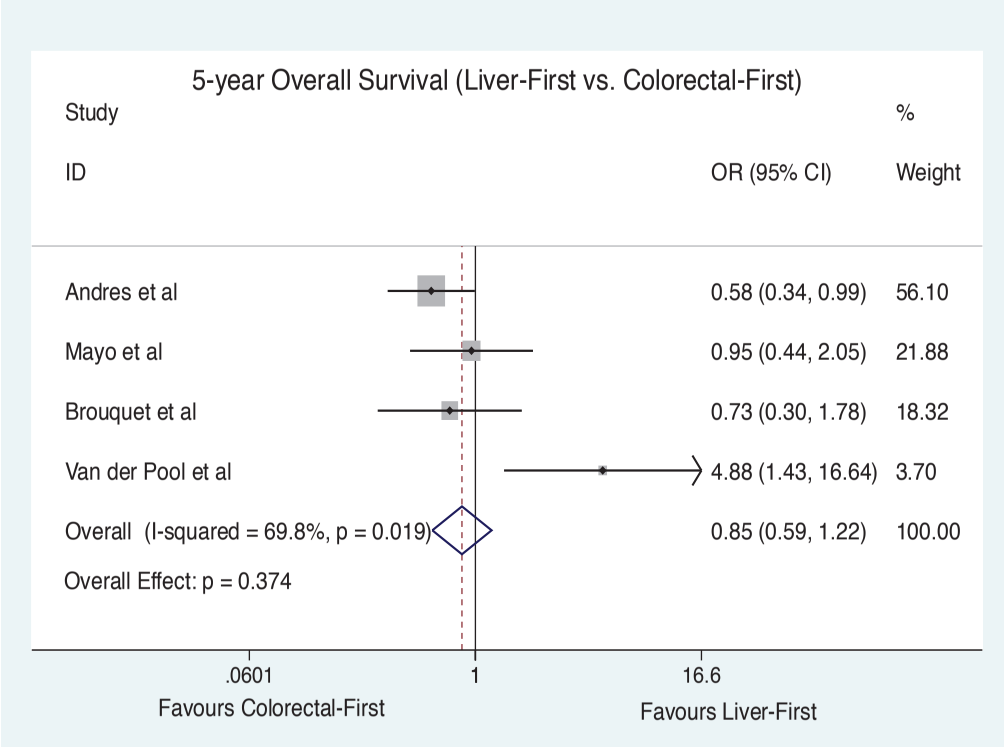
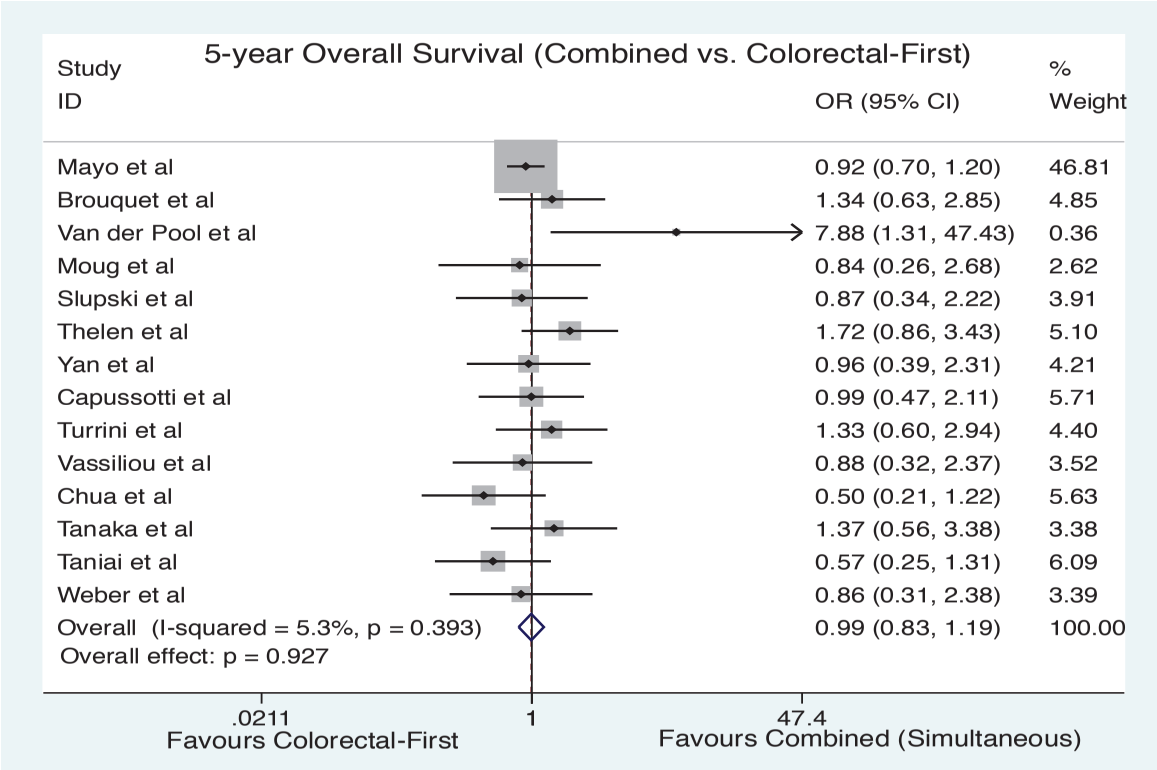
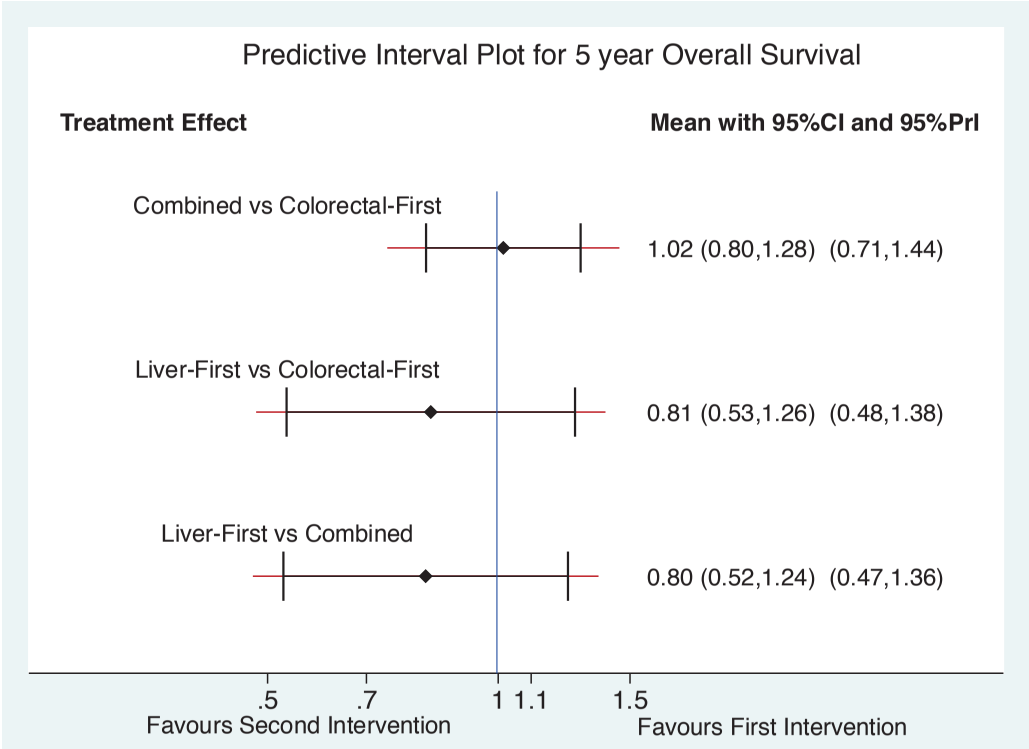
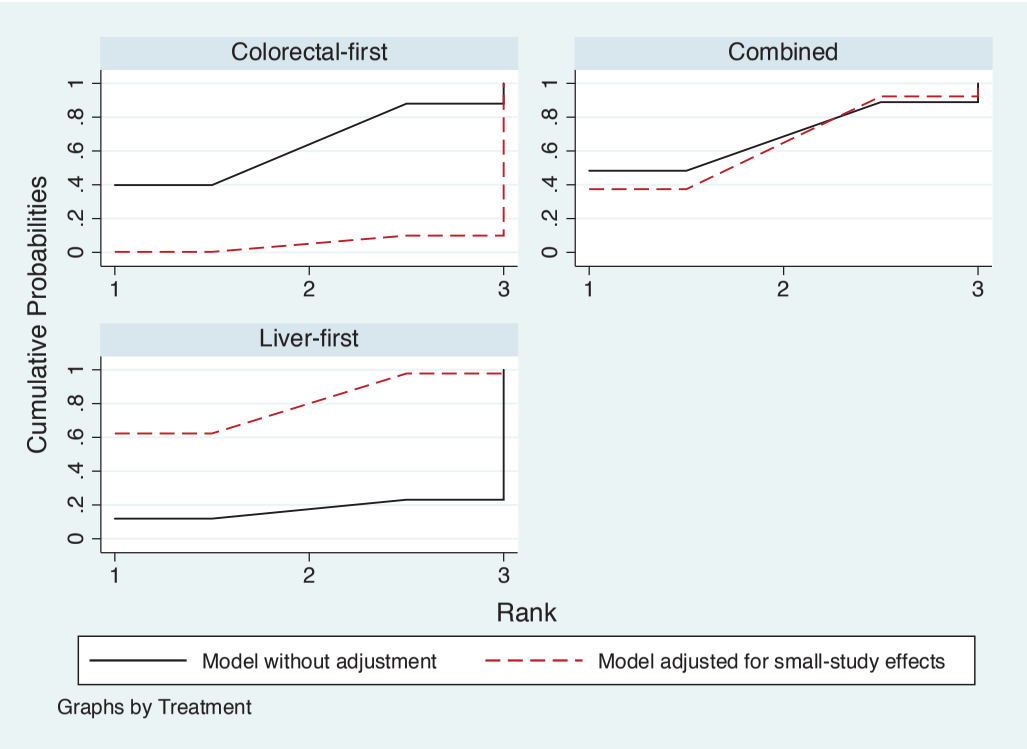
Records identified through alternative searching
(n=788)
Duplicates removed + records screened
(n=55)
Records excluded
(n=1,874)
Full-text articles assessed for eligibility
(n=18)
Full-test excluded:
Non-comparative
(n=9)
No survival data
(n=7)
Review/ Letter/ Abstract
(n=21)
Studies included in meta-analysis
(n=18)


5-year Overall survival (Liver-First vs Combined)
Study
ID
OR (95% CI)
%
Weight
Mayo et al
1.04 (0.48, 2.26)
46.96
Brouquet et al
0.54 (0.21, 1.44)
41.65
Van der Pool et al
0.62 (0.10, 3.92)
11.39
Overall (I-squared = 0.0%, p = 0.577)
0.78 (0.44, 1.40)
100.00
Overall Effect: p = 0.410
.0978
1
10.2
Favours Combined
Favours Liver-First

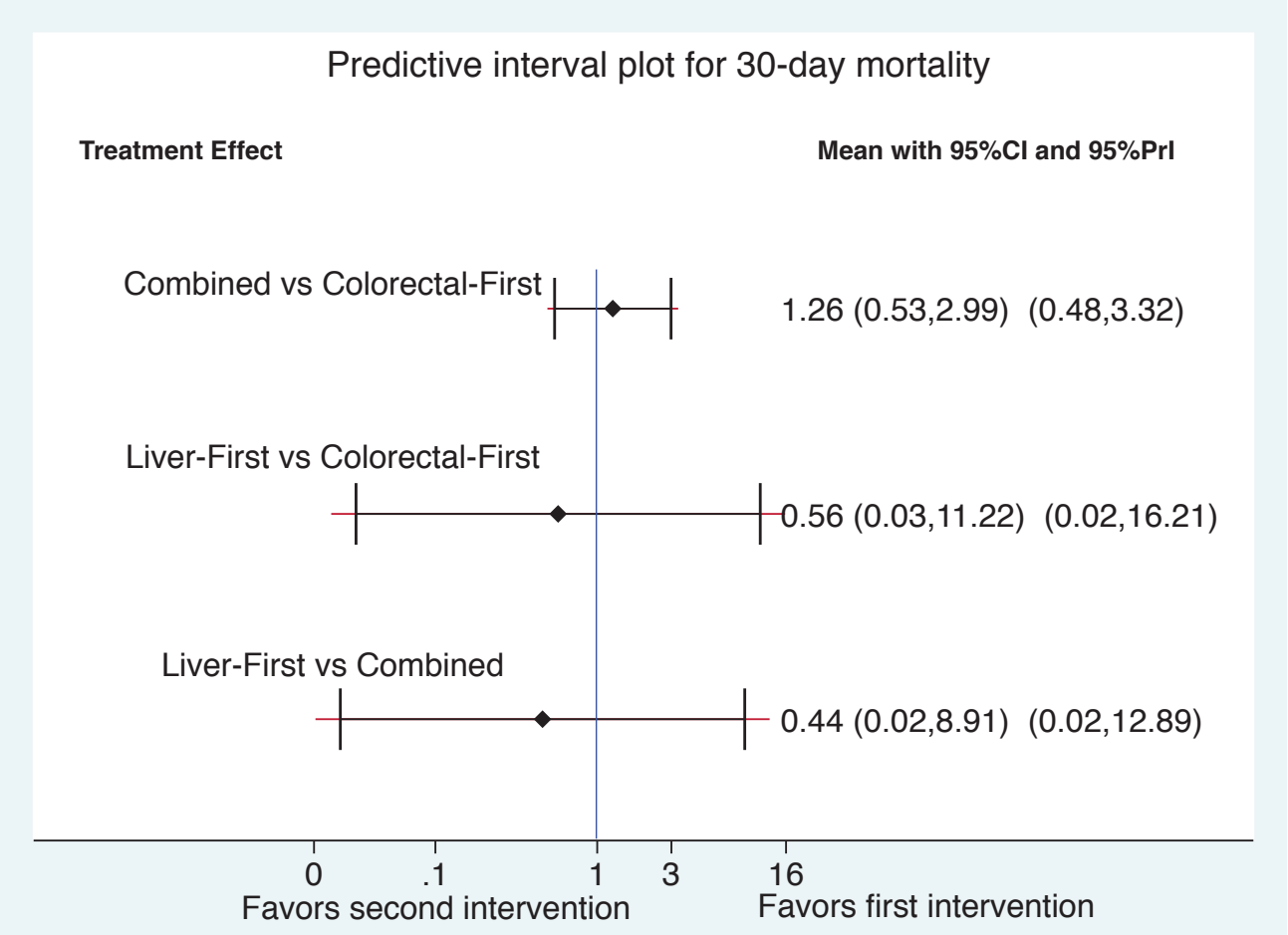

5-year Overall Survival (Liver-First vs. Colorectal-First)
Study
ID
OR (95% CI)
%
Weight
Andres et al
0.58 (0.34, 0.99)
56.10
Mayo et al
0.95 (0.44, 2.05)
21.88
Brouquet et al
0.73 (0.30, 1.78)
18.32
Van der Pool et al
4.88 (1.43, 16.64)
3.70
Overall (I-squared = 69.8%, p = 0.019)
0.85 (0.59, 1.22)
100.00
Overall Effect: p = 0.374
.0601
1
16.6
Favours Colorectal-First
Favours Liver-First


5-year Overall Survival (Combined vs. Colorectal-First)
Study
ID
OR (95% CI)
%
Weight
Mayo et al
0.92 (0.70, 1.20)
46.81
Brouquet et al
1.34 (0.63, 2.85)
4.85
Van der Pool et al
7.88 (1.31, 47.43)
0.36
Moug et al
0.84 (0.26, 2.68)
2.62
Slupski et al
0.87 (0.34, 2.22)
3.91
Thelen et al
1.72 (0.86, 3.43)
5.10
Yan et al
0.96 (0.39, 2.31)
4.21
Capussotti et al
0.99 (0.47, 2.11)
5.71
Turrini et al
1.33 (0.60, 2.94)
4.40
Vassiliou et al
0.88 (0.32, 2.37)
3.52
Chua et al
0.50 (0.21, 1.22)
5.63
Tanaka et al
1.37 (0.56, 3.38)
3.38
Taniai et al
0.57 (0.25, 1.31)
6.09
Weber et al
0.86 (0.31, 2.38)
3.39
Overall (I-squared = 5.3%, p = 0.393)
0.99 (0.83, 1.19)
100.00
Overall effect: p = 0.927
.0211
1
47.4
Favours Colorectal-First
Favours Combined (Simultaneous)





Surgical Approach	SUCRA (without adjustment)	SUCRA (adjusted for small-study effects)
Colorectal-First	61.6	4.4
Simultaneous	69.8	66.6
Liver-First	18.6	78.9


Predictive interval plot for 30-day mortality
Treatment Effect
Mean with 95%CI and 95%PrI
Combined vs Colorectal-First
1.26 (0.53,2.99) (0.48,3.32)
Liver-First vs Colorectal-First
0.56 (0.03,11.22) (0.02,16.21)
Liver-First vs Combined
0.44 (0.02,8.91) (0.02,12.89)
0
.1
1
3
16
Favors second intervention
Favors first intervention