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Synchronous Colorectal Liver Metastasis: A Network Meta-Analysis Review Comparing Classical, Combined, and Liver-First Surgical Strategies

M.E. KELLY, BA, MB, BCh, BAO, MRCS,[1]* G. SPOLVERATO, MD,[2] G.N. LÊ, BA, MB, BCh, BAO, MRCP,[1]
M.N. MAVROS, MD,[2] F. DOYLE, PhD,[3] T.M. PAWLIK, MD, PhD FACS,[2] AND D.C. WINTER, MD, FRCS[1]
[1]Department of Surgery, St Vincent's University Hospital, Dublin, Ireland
[2]Department of Surgery, Johns Hopkins, Baltimore, Maryland
[3]Division of Population Health Sciences, Royal College of Surgeons Ireland, Dublin, Ireland

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: Eighteen 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 versus colorectal-first, mean odds ratio (OR) 1.02 (95% CI 0.8–1.28, $P = 0.93$); liver-first versus colorectal-first, mean OR 0.81 (95% CI 0.53–1.26, $P = 0.37$); liver-first versus combined, mean OR 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.
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KEY WORDS: **surgical strategies; surgical outcomes; long-term survival; surgical oncology; colorectal resection; hepatobiliary resections; synchronous colorectal liver metastases**

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.

All authors have seen, edited and approved the final version of this paper.

*Correspondence to: Mr. M.E. Kelly, BA, MB, BCh, BAO, MRCS, Department of Surgery, St Vincent's University Hospital, Dublin, Ireland. Fax: 0035312214001. E-mail: kellym11@tcd.ie

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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 (M.K. and G.S.) 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 (D.W.). 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, TX). 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 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 ORs 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-ORs 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

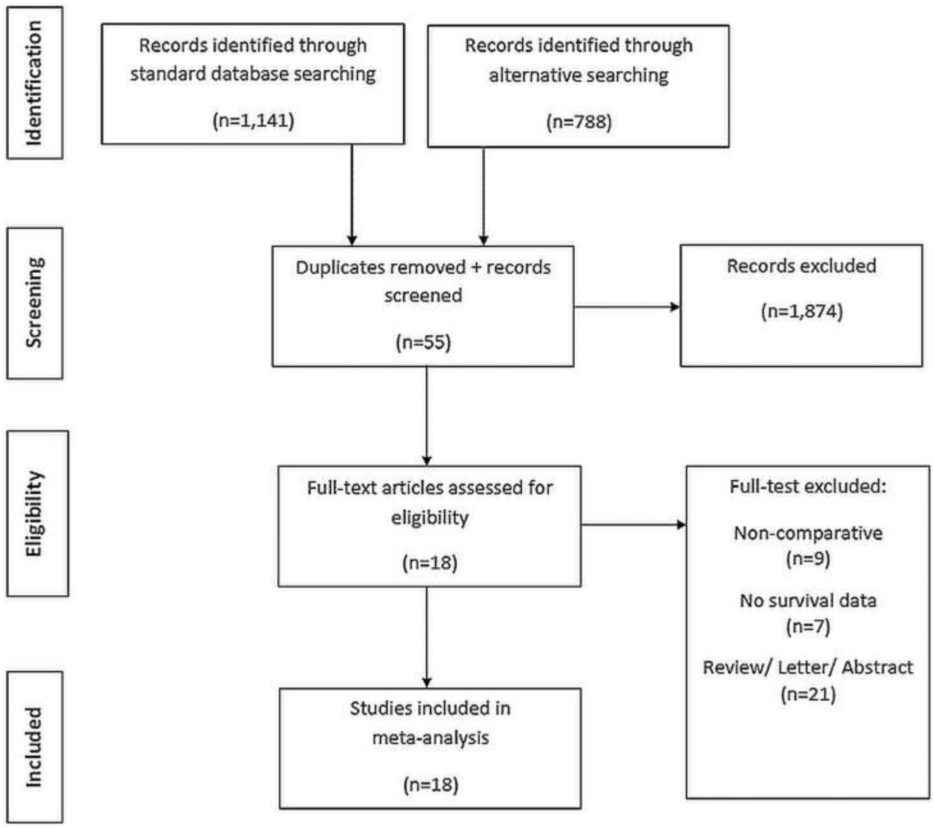


Fig. 1. PRISMA flow diagram demonstrating results of literature search.

publications that met the inclusion criteria were included in the meta-analysis (Fig. 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 I.

TABLE I. Demographic and Study Characteristics of the Studies Included in the Meta-Analysis

Study	Journal	Year	Study period	Country	Total number	Classical group	Combined group	Liver first group	Quality score (NOS)
Slesser et al. [39]	Eur J Surg Oncol	2013	2000–2012	UK	112	76	36	0	8
Andres et al. [40]	Annals of Surg	2012	2000–2010	59 Countries	787	729	0	58	8
Mayo et al. [20]	J Am Coll Surg	2012	1982–2011	USA, Italy, Portugal, Switzerland	1,004	647	329	28	8
Brouquet et al. [21]	J Am Coll Surg	2010	1992–2009	USA	142	72	43	27	8
van der Pool et al. [41]	Br J Surg	2010	2000–2007	Netherlands	57	29	8	20	6
Kaibori et al. [42]	Dig Dis Sci	2010	1993–2007	Japan	74	42	32	0	9
Moug et al. [43]	Eur J Oncol	2010	NS	UK	64	32	32	0	9
de Haas et al. [32]	Br J Surg	2010	1990–2006	France, Netherlands	228	173	55	0	8
Slupski et al. [44]	Can J Surg	2009	1997–2006	Poland	89	61	28	0	7
Thelan et al. [45]	Int J Colorectal Dis	2007	1988–2005	Germany	219	179	40	0	7
Yan et al. [46]	World J Surg	2007	NS	Australia	103	30	73	0	8
Capussotti et al. [47]	Ann Surg Oncol	2007	1985–2004	Italy	127	57	70	0	8
Turrini et al. [33]	Eur J Surg Oncol	2007	1994–2005	France	119	62	57	0	9
Vassiliou et al. [48]	World J Gastroenterol	2007	1996–2004	Greece	103	78	25	0	7
Chua et al. [49]	Dis Colon Rectum	2004	1986–1999	USA	96	32	64	0	9
Tanaka et al. [50]	Surgery	2004	1992–2003	Japan	76	37	39	0	7
Taniai et al. [51]	J Nippon Med Sch	2006	1990–2004	Japan	108	41	67	0	6
Weber et al. [52]	Br J Surg	2003	1987–2000	France	97	62	35	0	8

TABLE II. Clinicopathological and Operative Characteristics of the Patients Included in the Meta-Analysis

	No. of patients			Mean age (median)			Gender breakdown (male, female)			Colorectal distribution (colon, rectum)			Hepatic distribution (unilobar, bilobar)			Median no. of CLM (mean)			Type of liver resection		
Study	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L
Slesser et al.	76	36	[a]	NS (62)	NS (55.5)	[a]	52, 24	23, 13	[a]	46, 30	17, 19	[a]	48, 26	15, 19	[a]	NS	NS	[a]	30 right hep, 7 ext. R-hep, 13 left hep, 4 ext. L-hep, 2 caudate, 4 segm, 7 section, 6 trisegm, 3 wedge	12 right hep, 4 ext R-hep, 6 left hep, 4 segm, 4 section, 1 trisegm, 5 wedge	[a]
Andres et al.	729	[a]	58	60	[a]	59	440, 289	[a]	41, 17	558, 169	[a]	25, 33	199, 521	[a]	16, 41	NS (4.8)	[a]	NS (4.2)	NS	[a]	NS
Mayo et al.	647	329	28	NS (61)	NS (60)	NS (58)	396, 251	185, 144	17, 11	475, 170	238, 91	13, 15	407, 240	205, 124	12, 16	2.0	2	3	353 bisegm, 145 hemihep, 105 ext. hep, 44 NS	230 bisegm, 53 hemihep, 25 ext. hep, 21 NS	13 bisegm, 6 hemihep, 4 ext. Hep, 5 NS
Brouquet et al.	72	43	27	NS (56)	NS (58)	NS (48)	44, 28	23, 20	10, 17	37, 35	25, 18	19, 8	29, 43	30, 13	10, 17	3.0	2	3	NS	NS	24 >triseg, 3 NS
van der Pool et al.	29	8	20	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	2.0	1	3	NS	NS	NS
Kaibori et al.	42	32	[a]	62.3	62.3	[a]	27, 15	17, 15	[a]	28, 14	27, 5	[a]	22, 20	25, 7	[a]	NS	NS	[a]	NS	NS	[a]
Moug et al.	32	32	[a]	67	69	[a]	21, 11	18, 14	[a]	20, 12	20, 12	[a]	NS	NS	[a]	NS	NS	[a]	7 subsegm, 9 segm, 9 bisegm, 6 left hep, 1 right hep	7 subsegm, 9 monosegm, 9 bisegm, 6 left hep, 1 right hep	[a]
de Haas et al.	173	55	[a]	58	56	[a]	107, 66	28, 27	[a]	140, 29	43, 12	[a]	91, 75	37, 18	[a]	NS	NS	[a]	NS	NS	[a]
Slupski et al.	61	28	[a]	60.2	59.4	[a]	34, 27	18, 10	[a]	47, 14	18, 10	[a]	NS	NS	[a]	NS (3.8)	NS (2.9)	[a]	13 right hep, 2 ext. R-hep, 12 ext. L-hep, 2 trisegm, 15 bisegm, 9 segm, 8 non-anat	4 right hep, 4 ext. L-hep, 1 trisegm, 2 bisegm, 6 monosegm, 11 non-anat	[a]
Thelan et al.	179	40	[a]	59.7	60.5	[a]	96, 84	24, 16	[a]	107, 72	34, 6	[a]	91, 88	25, 15	[a]	NS	NS	[a]	60 right hep, 28 ext. R-hep, 17 left hep, 17 ext. L-hep, 12 right trisect, 3 left trisect, 5 bisegm, 7 segm, 6 left-lat, 24 non-anat	9 right hep, 2 left hep, 2 ext. R-hep, 2 R-trisect, 6 left-Lat, 19 non-anat	[a]
Yan et al.	30	73	[a]	59	60	[a]	15, 15	33, 40	[a]	18, 12	58, 15	[a]	20, 10	23, 50	[a]	NS (3)	NS (4)	[a]	17 hep, 6 ext. hep, 7 segm	25 hep, 28 ext. hep, 20 segm	[a]
Capussotti et al.	57	70	[a]	60.8	64.9	[a]	35, 22	40, 30	[a]	37, 20	43, 27	[a]	41, 16	55, 15	[a]	NS	NS	[a]	NS	NS	[a]
Turrini et al.	62	57	[a]	59	60	[a]	28, 34	25, 32	[a]	42, 20	33, 24	[a]	25, 37	43, 14	[a]	NS	NS	[a]	NS	NS	[a]
Vassiliou et al.	78	25	[a]	61	63	[a]	47, 31	15, 10	[a]	70, 8	22, 3	[a]	66, 12	23, 2	[a]	NS	NS	[a]	23 $\geq$ 3 segments, 55 $<$ 3 segments	7 >trisegm, 18 $<$trisegm	[a]
Chua et al.	32	64	[a]	61	63	[a]	18, 14	39, 25	[a]	NS	NS	[a]	19, 13	48, 16	[a]	2.0	1.5	[a]	10 right hep, 2 ext. R-hep, 1 left hep, 2 left-lat, 12 wedge, 5 non-anat	35 wedge, 9 right hep, 1 left hep, 7 left-lat, 12 non-anat	[a]
Tanaka et al.	37	39	[a]	NS (63)	NS (64)	[a]	NS	20, 19	[a]	19, 18	24, 15	[a]	13, 24	25, 14	[a]	4 (5.3)	NS (2.2)	[a]	14 right hep, 3 left hep, 3 segm, 6 section, 2 trisegm, 3 partial	23 partial, 3 segm, 8 section, 4 left hep, 1 right hep	[a]

TABLE II. (Continued)

Study	No. of patients			Mean age (median)			Gender breakdown (male, female)			Colorectal distribution (colon, rectum)			Hepatic distribution (unilobar, bilobar)			Median no. of CLM (mean)			Type of liver resection		
	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L
Taniai et al.	41	67	[a]	63.3	63	[a]	25, 16	35, 32	[a]	14, 27	25, 42	[a]	NS	42, 25	[a]	NS (1.86)	NS (2.36)	[a]	NS	NS	[a]
Weber et al.	62	35	[a]	60	58	[a]	31, 31	18, 17	[a]	38, 34	25, 10	[a]	20, 42	27, 8	[a]	NS (3.7)	NS (1.9)	[a]	12 right hep, 5 ext. R-hep, 7 left hep, 11 trisegm, 17 bisegm, 8 segm, 2 non-anat	6 right hep, 2 ext. R-hep, 1 left hep, 2 trisegm, 8 bisegm, 6 monosegm, 10 non-anat	[a]

C, colorectal-first; S, simultaneous/combined; L, liver-first; Hep/Hemi-hep, hepatectomy/hemi-hepatectomy; Ext. hep, extended hepatectomy; Segm, segmentectomy; Triseg, tri-segmentectomy; Section, sectionectomy; Lat, lateral; Non-anat, non-anatomical resection; NS, not-specified.

[a]No results.

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 I). 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 II).

Sixteen studies reported colorectal distribution of primary tumor. Colorectal first approach had 71.2% (n = 1,696) 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 = 1,091) unilobar and 51.7% (n = 1,167) 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 II).

Surgical Outcomes

There was a considerable heterogeneity in the methods of reporting surgical outcomes and complications among the studies. Only nine studies reported on the duration of surgery with no information pertaining to liver-first strategy. Seven studies reported the median blood loss, and eight 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 III).

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 three approaches; while 11 studies included 5-year OS for combined versus colorectal-first, and one study reported 5-year OS for colorectal-first versus 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; Fig. 2). There was significant heterogeneity amongst the studies involving the liver-first versus 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 (Table IV).

The finding of no significant difference between the three treatment approaches was concurred by the network meta-analysis. The forest plot depicting the estimated summary effects in the form of mean ORs 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 OR 1.02 (95% CI 0.8–1.28); liver-first vs. colorectal-first: mean OR 0.81 (95% CI 0.53–1.26); liver-first vs. combined: mean OR 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 five 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 OR 1.26 (95% CI 0.53–2.99); liver-first vs. colorectal-first: mean OR 0.56 (95% CI 0.03–11.22); liver-first vs. combined: mean OR 0.44 (95% CI 0.02–8.91; Fig. 4)].

TABLE III. Operative Outcomes and Complications After Combined Versus Staged Resection for Synchronous Colorectal Liver Metastasis

	Median (range) duration of surgery in minutes (mean)			Median (range) blood loss (ml)			No. of patients transfused (%)			Complication rate and type			Median (range) length of stay in days		
Study	C	S	L	C	S	L	C	S	L	C	S	L	C	S	L
Slesser et al.	420 (380–473)	400 (350–480)	[a]	900 (600–1,200)	1,200 (400–2,000)	[a]	16 (21.1%)	8 (22.2%)	[a]	34 complications—NS	9 complications—NS	[a]	18.5 (16–23)	14 (12–18)	[a]
Andres et al.	NS	[a]	NS	NS	[a]	NS	NS	[a]	NS	NS	[a]	NS	NS	[a]	NS
Mayo et al.	NS	NS	NS	NS	NS	NS	NS	NS	NS	124 complications—NS	78 complications—NS	2 complications—NS	NS	NS	NS
Brouquet et al.	NS	NS	NS	600 (100–3,300)	300 (50–3,300)	500 (200–2,200)	2 (2.7%)	7 (16.2%)	2 (7.4%)	37 complications—NS	20 complications—NS	10 complications—NS	NS	NS	NS
van der Pool et al.	NS	NS	NS	NS	NS	NS	NS	NS	NS	14 complications—NS	NS	NS	18 (13–95)	9 (7–15)	15 (7–30)
Kaibori et al.	NS	NS	[a]	NS	NS	[a]	15 (35.7%)	11 (34.3%)	[a]	6 complications—1 bile leak, 3 intra-abdominal abscess, 1 pneumonia, 1 pleural effusion	12 complications—3 bile leak, 4 intra-abdominal abscess, 3 acute colitis, 2 pleural effusion	[a]	NS	NS	[a]
Moug et al.	NS	NS	[a]	425 (50–1,700)	475 (150–850)	[a]	NS	0	[a]	19 complications—5 LRTI, 3 UTI, 3 ileus, 2 wound, 2 bile leak, 1 A. Fib, 1 myocardial infarction, 1 renal impairment, 1 transfusion	9-complications—2 bile leak, 2 wound infections, 1 ileus, 1 urinary infection, 3 new-onset A. Fib	[a]	20 (7–51)	12 (8–21)	[a]
de Haas et al.	NS	NS	[a]	NS	NS	[a]	0	0	[a]	44 complications—9 bile leak, 4 hematoma, 3 ascites, 5 abdominal collection, 3 transient liver failure, 12 sepsis, 4 LRTI, 1 bronchitis, 1 UTI, 1 delirium, 1 cholecystitis	6 complications—1 hematoma, 1 bile leak, 1 hepatic failure, 1 sepsis, 1 pneumonia, 1 LRTI	[a]	NS	NS	[a]
Slupski et al.	200 (140–260)	250 (160–360)	[a]	620 (0–1,170)	950 (0–3,000)	[a]	NS	NS	[a]	8 complications—NS	4 complications—NS	[a]	6 (5–14)	12 (10–26)	[a]
Thelan et al.	NS (208.6)	NS (260.4)	[a]	NS	NS	[a]	38 (21%)	14 (35%)	[a]	45 complications—16 bile leaks, 10 transient hepatic failure, 10 wound infection, 4 pleural effusion, 2 pneumonia, 1 reintubation, 1 stroke, 1 PE	7 complications—1 bile leak, 3 wound infections, 1 transient liver impairment, 1 pneumonia	[a]	NS	NS	[a]
Yan et al.	NS (180)	NS (300)	[a]	NS	NS	[a]	NS	NS	[a]	20 complications—7 wound infection, 3 peri-hepatic collections, 5 other abdominal collection, 3 respiratory issues, 1 bile leak, 1 sepsis	41 complications—14 wound infections, 9 intra-abdominal collections, 10 hepatic collections, 5 LRTI, 1 sepsis, 1 cardiac complication, 1 bile leak	[a]	15 (9–27)	7 (5–19)	[a]
Capussotti et al.	NS	NS	[a]	NS	NS	[a]	NS	NS	[a]	21 complications—NS	24 complications—NS	[a]	NS	NS	[a]
Turrini et al.	NS (256)	NS (325)	[a]	NS	NS	[a]	NS	2 (3.5%)	[a]	19 complications—NS	12 complications—NS	[a]	15	18	[a]
Vassiliou et al.	NS (340)	NS (260)	[a]	NS	NS	[a]	NS	NS	[a]	59 complications—3 wound, 20 LRTI, 18 pleural effusion, 7 bile leak, 8 subphrenic collection, 1 splenic bleed E, 1 anastomotic leak, 1 intra-abdominal bleed	19 complications—2 bile leak, 2 wound infections, 3 subphrenic collections, 4 LTRI, 5 pleural effusions, 1 bleed (NS)	[a]	NS	NS	[a]
Chua et al.	392 (427)	370 (430)	[a]	NS	NS	[a]	NS	NS	[a]	13 complications—NS	34 complications—NS	[a]	17 (11–107)	10 (5–40)	[a]
Tanaka et al.	480 (220–845)	510 (170–865)	[a]	1,070 (300–5,000)	1,300 (70–6,300)	[a]	NS	NS	[a]	6 complications—3 biliary fistula, 1 post-operative bleed, 1 transient liver failure, 1 intestinal obstruction	11 complications—2 bile leak, 2 wound infections, 1 intra-abdominal abscess, 2 subphrenic abscess, 2 transient liver impairment, 1 biliary fistula, 1 pneumonia	[a]	20 (11–48)	22 (12–58)	[a]
Taniai et al.	NS	NS	[a]	NS	NS	[a]	NS	NS	[a]	NS	NS	[a]	NS	NS	[a]
Weber et al.	NS (290)	NS (313)	[a]	NS	NS	[a]	35 (56%)	NS	[a]	20 complications—NS	8 complications—NS	[a]	NS	NS	[a]

C, colorectal-first; S, simultaneous/combined; L, liver-first; NS, not-specified; UTI, urinary tract infection; LRTI, lower respiratory tract infection; PE, pulmonary embolism; A. Fib, new-onset atrial fibrillation.

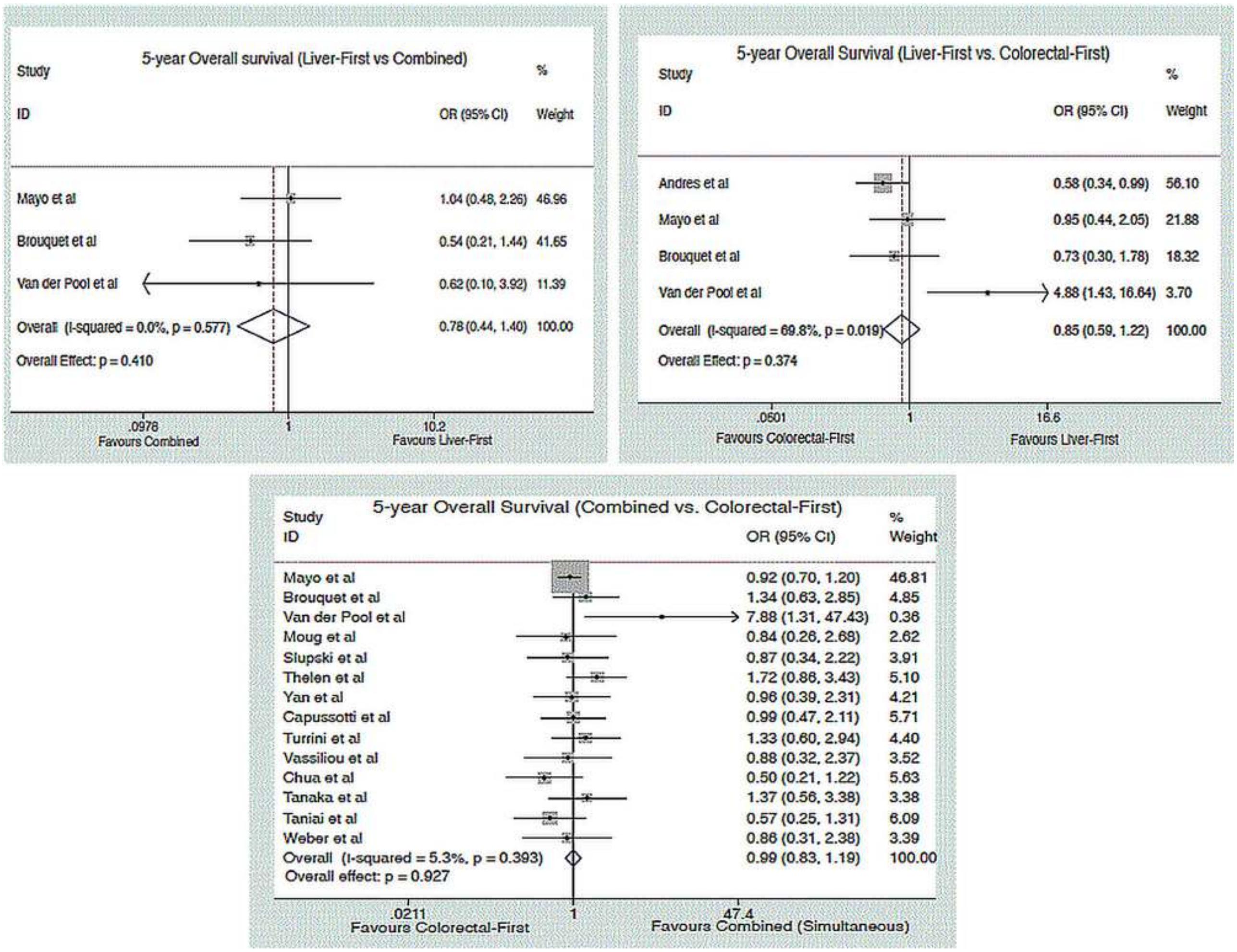
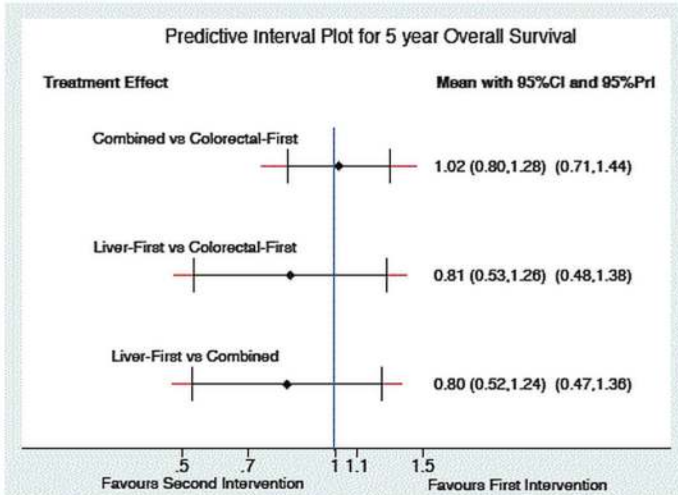


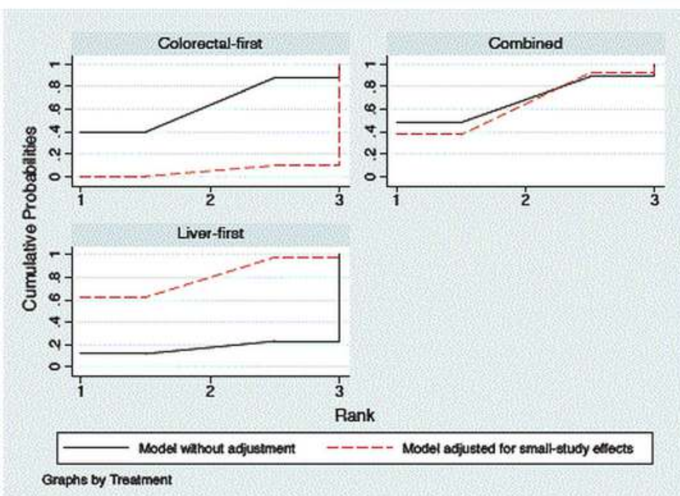
Fig. 2. Forest plots of pair-wise standard meta-analysis of the three surgical approaches. OR, odds ratio; CI, confidence interval.

TABLE IV. Overall Survival After Combined Versus Staged Resection for Synchronous Colorectal Liver Metastasis

	30-day mortality (%)			Median follow-up in months (Mean)			5-year overall survival (%)			Median survival in months		
Study	C	S	L	C	S	L	C	S	L	C	S	L
Slesser et al.	1 (1.3%)	2 (5.5%)	*	NS	NS	*	NS	NS	*	NS	NS	*
Andres et al.	NS	*	NS	NS	*	NS	55%	*	42%	NS	*	NS
Mayo et al.	NS	NS	0	34	34	34	44%	42%	44%	NS	NS	40.9
Brouquet et al.	2 (2.7%)	2 (4.6%)	0	25.1	25.1	25.1	48%	55%	39%	55	95	50
van der Pool et al.	NS	NS	NS	40	34	28	28%	73%	67%	NS	NS	NS
Kaibori et al.	NS	NS	*	31	NS	*	NS	NS	*	NS	NS	*
Moug et al.	0	0	*	NS	NS	*	24%	21%	*	42	39	*
de Haas et al.	0	0	*	NS (39)	NS (45)	*	NS	NS	*	56.4	52.8	*
Slupski et al.	1 (1.6%)	0	*	NS	NS	*	38%	45%	*	NS	51.2	*
Thelan et al.	NS	NS	*	65.4	90.8	*	39%	53%	*	NS	NS	*
Yan et al.	0	0	*	NS	NS	*	37%	36%	*	36	37	*
Capussotti et al.	0	1 (1.4%)	*	33.7	38.2	*	32%	30.80%	*	NS	NS	*
Turrini et al.	3 (5%)	2 (3.5%)	*	66	66	*	25%	32%	*	NS	NS	*
Vassiliou et al.	NS	0	*	NS	NS	*	31%	28%	*	NS	NS	*
Chua et al.	0	0	*	NS	NS	*	42.90%	28.90%	*	34	27	*
Tanaka et al.	0	0	*	21	21	*	47%	53%	*	NS	NS	*
Taniai et al.	0	0	*	19 (31)	19	*	39.20%	26.70%	*	NS	NS	*
Weber et al.	0	0	*	NS (32)	NS (37)	*	22%	21%	*	33	35	*

* - Not assessed.





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

Fig. 3. **A**: Network meta-analysis predictive interval plot for the three 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 three 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.

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 $\geq$ 8) to those of lower quality (NOS < 8) yielded similar complication rates. For the colorectal-first group, 11 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 two 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% and 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

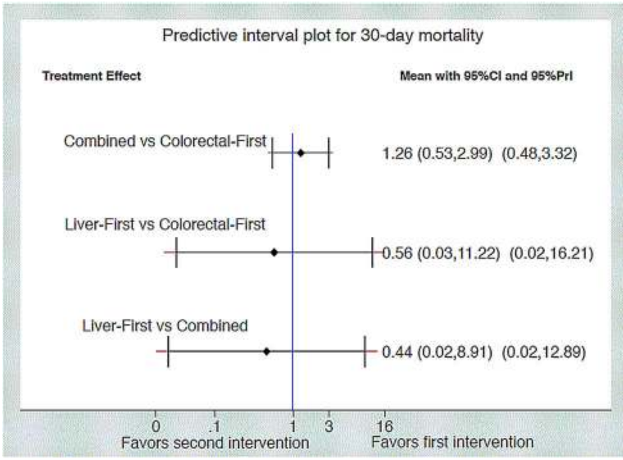


Fig. 4. Network meta-analysis for 30-day mortality of the three surgical approaches. The black lines represent the confidence interval (CI) for mean odds ratio (OR) for each comparison. The red lines are the predictive intervals (PrI). The blue line denotes the line of no effect (OR = 1).

have observed that the potential for CLM resection is often underestimated [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. [31] had shown that neoadjuvant chemotherapy resulted in down-staging and conversion of unresectable disease in 22.5% of patients. 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. Brouquet et al. [21] were the first authors to retrospectively compare all three treatment strategies for management of synchronous CLM. 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 ORs 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 two 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 3- and 5-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 three different approaches.

REFERENCES

1. Qureshi MS, Goldsmith PJ, Maslekar S, et al.: Synchronous resection of colorectal cancer and liver metastases: Comparative views of colorectal and liver surgeons. Colorectal Dis 2012;14: e477–e485.
2. Jemal A, Siegel R, Ward E, et al.: Cancer statistics 2007. Cancer J Clin 2007;57:43–66.
3. Leporrier J, Maurel J, Chiche L, et al.: A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. Br J Surg 2006;93:465–474.
4. McMillan DC, McArdle CS: Epidemiology of colorectal liver metastases. Surg Oncol 2007;16:3–5.
5. Van Cutsem E, Nordlinger B, Adam R, et al.: Towards a pan-european consensus on the treatment of patients with colorectal liver metastases. Eur J Cancer 2006;42:2212–2221.
6. Boyle P, Ferlay J: Cancer incidence and mortality in Europe 2004. Ann Oncol 2005;16:481–488.
7. Haddad AJ, Hani MB, Pawlik TM, et al.: Colorectal liver metastases. Int J Surg Oncol 2011;2011:285840.doi: 10.1155/2011/285840. Epub2011 Jun 6
8. Bird NC, Mangnall D, Majeed AW: Biology of colorectal liver metastases: A review. J Surg Oncol 2006;94:68–80.
9. Kopetz S, Chang GJ, Overman MJ, et al.: Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009;27:3677–3683.
10. Slesser AAP, Simillis C, Goldin R, et al.: A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases. Surg Oncol 2013;22:36–47.
11. deJong MC, Pulitano C, Ribero D, et al.: Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: An international multi-institutional analysis of 1669 patients. Ann Surg 2009;250:440–448.
12. Abdalla EK, Vauthey JN, Ellis LM, et al.: Recurrence and outcomes following hepatic resection, radiofrequency ablation and combined resection/ablation for colorectal liver metastasis. Ann Surg 2004;239:818–825.
13. Mavros MN, de Jong M, Dogeas E, et al.: Impact of complications on long-term survival after resection of colorectal liver metastases. Br J Surg 2013;100:711–718.
14. Vassiliou I, Arkadopoulos M, Theodosopoulos T, et al.: Surgica approaches of resectable synchronous colorectal liver metastases: Timing considerations. World J Gastroenterol 2007;13:1431–1434.
15. Jegatheeswaran S, Mason JM, Hancock HC, et al.: The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases. JAMA Surg 2013;148:385–392.
16. Mentha G, Majno PE, Andres A, et al.: Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before the treatment of the primary. Br J Surg 2006;93:872–878.
17. Hillingso JG, Wille-Jorgensen P: Staged or simultaneous resection of synchronous liver metastases from colorectal cancer—A systematic review. Colorectal Dis 2008;11:3–10.
18. Lyass S, Zamir G, Matot I, et al.: Combined colon and hepatic resection for synchronous colorectal liver metastases. J Surg Oncol 2001;78:17–21.
19. Martin R, Paty P, Fong Y, et al.: Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg 2003;197:233–241.
20. Mayo SC, Pulitano C, Marques H, et al.: Surgical management of patients with synchronous colorectal liver metastasis: A multicenter international analysis. J Am Coll Surg 2013;216:707–716.
21. Brouquet A, Morthenson MM, Vauthey JN, et al.: Surgical strategies for synchronous colorectal liver metastasis in 156 consecutive patients: Classic, combined or reverse strategy? J Am Coll Surg 2010;210:934–941.
22. Liberati A, Altman DG, Tetzlaff J, et al.: The PRISMA statement for reporting systematic reviews, meta-analyses of studies that evaluate healthcare interventions: Explanation, elaboration. Br Med J 2009; 339:b2700.
23. Chaimani A, Higgins JPT, Mavridis D, et al.: Graphical tools for network meta-anlaysis in STATA. PLoS ONE 2013;8:e76654.
24. Wells GA, Shea B, O'Connell D, et al.: The Newcastle-Ottawa scale for assessing the quality of nonrandomized studies in meta-analyses. Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
25. Lam VW, Laurence JM, Pang T, et al.: A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases. HPB 2014;16:101–108.
26. Bilchik AJ, Poston G, Curley SA, et al.: Neoadjuvant chemotherapy for metastatic colon cancer: A cautionary note. J Clin Oncol 2005;23:9073–9078.
27. Simmonds PC, Primrose JN, Colquitt JL, et al.: Surgical resection of hepatic metastases from colorectal cancer: A systematic review of published studies. Br J Cancer 2006;94:982–999.
28. Pawlik TM, Choti MA: Surgical therapy for colorectal metastases to the liver. J Gastrointest Surg 2007;11:1057–1077.
29. McCahill LE, Yothers G, Sharif S, et al.: Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: Definitive analysis of NSABP trial C-10. J Clin Oncol 2012;30:3233–3238.
30. Poultisides GA, Servais EL, Saltz LB, et al.: Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol 2009;27:3379–3384.
31. Lam VWT, Spiro C, Laurence JM, et al.: A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases. Ann Surg Oncol 2012; 19:1292–1301.
32. de Haas RJ, Adam R, Wicherts DA, et al.: Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases. Br J Surg 2010;97:1279–1289.
33. Turrini O, Viret F, Guiramand J, et al.: Strategies for the treatment of synchronous liver metatstases. Eur J Surg Oncol 2007;33:735–740.
34. Reddy SK, Pawlik TM, Zorzi D, et al.: Simultaneous resections of colorectal cancer and synchronous liver metastases: A multi-institutional analysis. Ann Surg Oncol 2007;14:3481–3491.
35. Pawlik TM, Schulick RD, Choti MA: Expanding criteria for resectability of colorectal liver metastases. Oncologist 2008;13:51–64.
36. Nordlinger B, Benoist S: Benefits and risks of neoadjuvant therapy for liver metastases. J Clin Oncol 2006;24:4954–4955.
37. Zalinski S, Bigourdan JM, Vauthey JN: Does bevacizumab have a protective effect on hepatotoxicity induced by chemotherapy? J Chir 2010;147:S18–S24.
38. Gonzalez HD, Figueras J: Practical questions in liver metastases of colorectal cancer: General principals of treatment. HPB 2007; 9:251–258.
39. Slesser AA, Chand M, Goldin R, et al.: Outcomes of simultaneous resections for patients with synchronous colorectal liver metastases. Eur J Surg Oncol 2013;39:1384–1393.

40. Andres A, Toso C, Adam R, et al.: A Survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases. Ann Surg 2012;256:772–779.
41. van der Pool AE, de Wilt JH, Lalmahomed ZS, et al.: Optimizing the outcomes of surgery in patients with rectal cancer and synchronous liver metastases. Br J Surg 2010;97:383–390.
42. Kaibori M, Iwamoto S, Ishizaki M, et al.: Timing of resection for synchronous liver metastasis from colorectal cancer. Dig Dis Sci 2010;55:3262–3270.
43. Moug SJ, Smith D, Leen E, et al.: Evidence for a synchronous operative approach in the treatment of colorectal cancer with hepatic metastasis: A case matched study. Eur J Surg Oncol 2010;36:365–370.
44. Slupski M, Wlodarczyk Z, Jasinski M, et al.: Outcomes of simultaneous and delayed resections of synchronous liver metastases. Can J Surg 2009;52:241–244.
45. Thelan A, Jonas S, Benckert C, et al.: Simultaneous versus staged liver resection of synchronous liver metastases from colorectal cancer. Int J Colorectal Dis 2007;22:1269–1276.
46. Yan TD, Chu F, Black D, et al.: Synchronous resection of colorectal primary cancer and liver metastases. World J Surg 2007;31:1496–1501.
47. Capussotti L, Vigano L, Ferrero A, et al.: Timing of resection of liver metastases synchronous to colorectal tumor; proposal of prognosis-based decisional model. Ann Surg Oncol 2006; 14: 1143–1150.
48. Vassiliou I, Arkadopoulos N, Theodosopoulos T, et al.: Surgical approaches of resectable synchronous colorectal liver metastases: Timing considerations. World J Gastroenterol 2007;13:1431–1434.
49. Chua HK, Sondenaa K, Tsiotos GG, et al.: Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Colon Rectum 2004;47:1310–1316.
50. Tanaka K, Shimada H, Matsuo K, et al.: Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery 2004;136:650–659.
51. Taniai N, Yoshida H, Mamada Y, et al.: Outcome of surgical treatment of synchronous liver metastases from colorectal cancer. J Nippon Med Sch 2006;73:82–88.
52. Weber JC, Bachellier P, Oussoultzoglou E, et al.: Simultaneous resection of colorectal primary tumour and synchronous liver metastases. Br J Surg 2003;90:956–962.