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REVIEW

Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors

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Background: Hepatic metastases develop in approximately 50% of colorectal cancer (CRC) cases. We performed a review and meta-analysis to evaluate survival after resection of CRC liver metastases (CLMs) and estimated the summary effect for seven prognostic factors.

Methods: Studies published between 1999 and 2010, indexed on Medline, that reported survival after resection of CLMs, were reviewed. Meta-relative risks for survival by prognostic factor were calculated, stratified by study size and annual clinic volume. Cumulative meta-analysis results by annual clinic volume were plotted.

Results: Five- and 10-year survival ranged from 16% to 74% (median 38%) and 9% to 69% (median 26%), respectively, based on 60 studies. The overall summary median survival time was 3.6 (range: 1.7–7.3) years. Meta-relative risks (95% confidence intervals) by prognostic factor were: node positive primary, 1.6 (1.5–1.7); carcinoembryonic antigen level, 1.9 (1.1–3.2); extrahepatic disease, 1.9 (1.5–2.4); poor tumor grade, 1.9 (1.3–2.7); positive margin, 2.0 (1.7–2.5); >1 liver metastases, 1.6 (1.4–1.8); and >3 cm tumor diameter, 1.5 (1.3–1.8). Cumulative meta-analyses by annual clinic volume suggested improved survival with increasing volume.

Conclusion: The overall median survival following CLM liver resection was 3.6 years. All seven investigated prognostic factors showed a modest but significant predictive relationship with survival, and certain prognostic factors may prove useful in determining optimal therapeutic options. Due to the increasing complexity of surgical interventions for CLM and the inclusion of patients with higher disease burdens, future studies should consider the potential for selection and referral bias on survival.

Keywords: metastatic colorectal cancer, liver resection, survival, meta-analysis

Introduction

Hepatic metastases develop in approximately 50% of colorectal cancer cases,[1,2] with 20%–25% of newly diagnosed metastatic colorectal cancer (mCRC) patients presenting with liver metastases at the time of primary diagnosis, and up to 50% of all CRC patients developing metastatic liver disease after resection of primary CRC.[2–4] Among those with liver-limited colorectal metastases, it has been reported that 10%–30% of patients have potentially resectable disease that can be treated with curative intent at the time of detection.[5–9] Among those patients with successful resection of all evident metastatic disease, long-term survival appears to be improving, with 5-year survival reported to be over 50% in recent studies.[2,3,10–14]

The purpose of this review was to evaluate studies published in the past decade (1999–2010) that report survival of patients with liver resections for colorectal liver

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metastases (CLMs). The current analysis updates information on survival from a published review of these data in 2006.[15] We estimated the association between seven prognostic factors reported to be predictors of survival[2,4,16,17] in this patient population, using meta-analysis techniques. Our analysis also sought to evaluate the impact of annual clinic volume on the association between prognostic factors and survival.

Materials and methods

Literature search strategy

Peer-reviewed English-language papers published between January 1, 1999 and May 31, 2010 that reported survival after surgical resection of CLM were identified using Medline, accessed through PubMed. No review protocol is available. All overlapping studies reported in the Simmonds et al[15] review that met the basic inclusion criteria of the current analysis were also included. The main search strategy used the following keywords: surgery, resection, hepatectomy, colon cancer, colorectal cancer, rectal cancer, metastatic, mestastases, mortality, and survival. The full search strategy is included in the Supplementary material. The bibliographies of identified articles were examined to identify additional literature. Reviews, meta-analyses, and case reports were excluded, although their reference lists were reviewed for additional studies. Case series were included, but were required to report on at least ten patients.

Inclusion criteria

Our inclusion criteria were:

1. original publication (no reviews or commentaries);
2. clinical trials, case-control or cohort observational studies;
3. case series of at least ten patients;
4. study populations aged at least 18 years;
5. patients with CLM;
6. patients with surgical liver resection;
7. median or mean follow-up time of at least 24 months; and
8. reported outcome measures of overall and disease-free survival.

If multiple publications reported results for survival after liver resection in the same population, the most recent report or the most comprehensive data were included. If an older publication contained more comprehensive data than a more recent one, the more comprehensive study was included. In addition, if an older study contained unique prognostic factor data, then this publication would also be included in the prognostic-factor analysis. Data were extracted from published papers by one reviewer using a standard data-extraction database and then verified independently by a second reviewer. For the meta-analysis, hazard ratios for overall survival and 95% confidence intervals (CIs) were extracted for each prognostic factor.

Summary of survival data

The following were identified and summarized for all included studies: median disease-free interval between diagnosis of primary cancer and diagnosis of metastasis; reported 3-, 5-, and 10-year disease-free survival (DFS) rates; and reported 3-, 5-, and 10-year overall survival rates. Wherever possible, survival information was summarized by the following patient subgroups, which were determined a priori to be potentially important determinants of survival (and as reported in the literature):[4,15,18] (1) isolated CLM (any number); (2) solitary CLM; (3) extrahepatic disease; (4) initially unresectable receiving preoperative chemotherapy; (5) initially resectable; (6) synchronous liver metastases (metastases identified at time of primary CRC diagnosis); and (7) metachronous liver metastases (metastases occurring at a time period defined by study authors after primary CRC diagnosis). All extracted data were based on analyses from the first CLM resection. Median survival rates were calculated for the overall patient population, as well as for patient subgroups with specific prognostic indications.

Median survival

To calculate a summary value of median survival time, studies that reported information on survival rates only in terms of calendar intervals (eg, 1- or 3-year survival) were converted using a simple interpolation to create a crude median survival time. It was assumed that median survival time fell within reported calendar-specific survival times, and that the survival line between the two time points that crossed the 50% mark was linear. Summary medians and standard deviations were calculated based on the reported or estimated median values from each individual study.

Trends in survival by prognostic factors

We assessed the association between survival and seven prognostic factors that previously had been reported in the literature as predictors of survival.[2,4,16,17] The prognostic factors included number of hepatic metastases, node-positive compared to node-negative primary, poorly differentiated compared to well or moderately primary, extrahepatic disease compared to liver-only disease, tumor diameter, carcinoembryonic antigen (CEA) level, and positive compared

to negative resection margins. For this study, we set the following cutoff points (cutoffs based on those reported in the original articles) for the following prognostic factors in which categories were required: CEA level ≥ 200, number of liver metastases > 1, and tumor diameter > 3 cm. Median survival time for each prognostic factor was plotted by published study dates (1999–2010) separately, and, in addition, was stratified by the seven prognostic factors.

Meta-analysis

Random-effects meta-analysis models were used to calculate meta-relative risks (mRRs), 95% CIs, and corresponding *P*-values for heterogeneity for the seven prognostic factors. The presence of significant heterogeneity ($P < 0.10$) indicates that statistical variation between studies in a particular meta-analysis model may invalidate data summaries;[19] however, lack of statistically significant heterogeneity may not be sufficiently sensitive to indicate underlying variation between studies. Further, a significant test for heterogeneity will not indicate the source of variations among studies. Accordingly, subgroup analyses were conducted by stratifying study size and estimated patient volume per study center (termed "annual clinic volume" herein) to identify potential sources of between-study heterogeneity. The estimated annual clinic volume was calculated as: initial patient population/number of years over which patients were recruited/number of centers participating in the study. Stratifications by study size and annual clinic volume were based on the median number of patients per center (n = 236) and median annual clinic volume (n = 21) of all studies included in the meta-analysis. We therefore stratified using values of 200 (≥ and <) and 20 (≥ and <), respectively. To visualize the mRR distribution by annual clinic volume, cumulative meta-analysis plots by each prognostic factor were created, adding each study one at a time from low to high annual clinic volume. Sensitivity analyses were conducted to determine the relative influence that a particular study had on a meta-analysis model. Specifically, the "one study removed" sensitivity analysis was used to assess the relative influence of each study on the model-specific mRR. This was performed by generating an mRR based on all studies, followed by the removal of one study at a time to compare the overall mRR with mRRs from models with one study removed.

Because study size is likely to be related directly to the annual volume of patients seen at a liver-resection center (eg, see[20]), and with the volume of patients seen annually related to survival, a cumulative meta-analysis based on annual clinic volume size by study center per year (ie, number of patients treated per year per center) was performed. This analysis was conducted to determine whether clinic volume had an impact on overall survival after CLM resection.

We examined the effect of publication bias, examined visually by producing funnel plots that measure the standard error as a function of effect size, as well as performing Begg's adjusted-rank correlation test[21] and Egger's regression asymmetry test.[22] All analyses were conducted with the Comprehensive Meta-Analysis (CMA) version 2 (BioStat, Englewood, NJ) statistical package.

Results

Our initial literature search identified 1493 articles published between 1999 and May 2010. Among these, 1377 articles were excluded because they did not meet inclusion criteria. Of the studies identified, six included in our analyses[23–28] were also included in the earlier literature review by Simmonds et al,[15] published in 2006. A total of 116 articles were identified that reported survival after liver resection in adults with mCRC and the modifying effect (if any) of other personal and clinical factors on survival.[3,4,10–14,16,17,23–127] After accounting for overlap of multiple publications reporting on patients from the same center (34 articles), our review included a total of approximately 20,745 patients (range: 21–1600 patients per study). Fifty-four of these studies were included in the meta-analysis. Seventy-five studies (64.7%) reported median follow-up times of 24–36 months, with the remainder reporting longer follow-up times. Figure 1 provides a diagram illustrating the study selection and exclusion process.

Survival for metastatic colorectal cancer following liver resection

Ninety-three studies reported overall survival after liver resection in adults with CLM, with varying numbers of studies by patient subgroup (Table 1). Of these, 64 reported 3-year survival (median 57.5%, range 29.7%–80.0%), 86 studies reported 5-year survival (median 38.0%, range 16.0%–74.0%), and 20 studies reported 10-year overall survival (median 26.0%, range 9.0%–69.0%). Ten studies reported median disease-free interval (median 15.9 months, range 9.2–23.7 months). Twenty-six studies reported 5-year DFS (median 24.7%, range 7.4%–48.0%), whereas six studies reported 10-year DFS (median 20%, range 15.0%–33.7%). Survival rates stratified by patient subgroups were reported in 27 studies (Table 1); however, no studies reported 10-year survival by subgroup. When evaluating CLM, median survival was highest in patients with solitary CLM, followed by isolated CLM then CLM with extrahepatic disease. Median

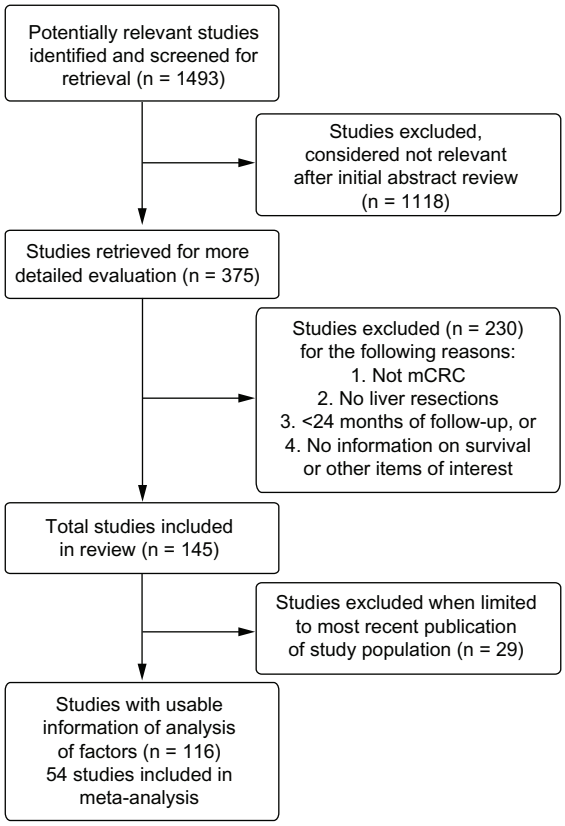


Figure 1 A diagram illustrating the study selection and exclusion process.

survival was higher in patients with metachronous compared to synchronous disease, though data were limited. Patients receiving preoperative chemotherapy had similar median survival as those patients with initially resectable disease without the need for chemotherapy, though again data were limited.

Sixty-one studies were included in the summary of median survival (Table 1). Of these, median survival times were reported in 41 studies and were estimated for the additional 20 studies that reported survival rates that overlapped 50% but did not report median survival times. For patients in all 61 studies, the overall summary median of the median survival time was 3.6 (range 1.7–7.3) years. Comparison of median survival by publication date from most recent (2010) to oldest (1999) did not suggest an improvement in median survival in more recent years (data not shown); however, as some of the more recent publications reported survival from patients diagnosed decades earlier, it was not possible to make accurate approximations between publication date and date of treatment and subsequent survival. The median survival varied by the prognostic factor studied (Figure 2). Median survival was better in patients with CEA level < 200 than in those with CEA level ≥ 200. In patients with a negative

Table 1 Summary of survival by patient group (3- and 5-year overall and median[a])

Patient group	Number of studies	Overall survival (3-year)	Number of studies	Overall survival (5-year)	Number of studies	Mean survival (years)	Median survival (range)
All patients	64	Mean: 57.6%	86	Mean: 40.3%	61	3.8	3.6 (1.7–7.3)
		Median: 57.5% (range 29.7%–80.0%)		Median: 38.0% (range 16.0%–74.0%)			
Solitary CLM	14	Mean: 61.0%	21	Mean: 47.4%	14	3.6	3.6 (1.8–4.8)
		Median: 66.1% (range 33.4%–79.0%)		Median: 44.6% (range 27.0%–71.0%)			
Extrahepatic CLM	10	Mean: 39.8%	14	Mean: 23.5%	8	2.5	2.5 (1.4–3.8)
		Median: 43.0% (range 9.0%–75.0%)		Median: 22.5% (range 0%–48.0%)			
Isolated CLM	10	Mean: 53.6%	15	Mean: 38.5%	11	3.5	3.2 (2.5–5.3)
		Median: 52.5% (range 33.0%–78.0%)		Median: 38.0% (range 16.0%–73.0%)			
Preoperative chemotherapy[b]	14	Mean: 54.6%	13	Mean: 36.6%	16	3.2	3.3 (1.5–5.2)
		Median: 52.5% (range 20.8%–79.0%)		Median: 37.0% (range 7.8%–79.0%)			
Initially resectable without the need for chemotherapy[c]	12	Mean: 54.6%	10	Mean: 40.7%	12	3.3	3.3 (1.9–5.4)
		Median: 54.8% (range 40.6%–71.0%)		Median: 38.1% (range 30.0%–68.0%)			
Synchronous[d]	15	Mean: 46.3%	27	Mean: 36.5%	16	3.1	3.2 (1.7–4.2)
		Median: 46.1% (range 19.3%–81.3%)		Median: 34.2% (range 11.2%–74.0%)			
Metachronous	14	Mean: 57.6%	26	Mean: 42.6%	20	3.3	3.3 (1.5–4.2)
		Median: 57.8% (range 34.4%–91.0%)		Median: 41.9% (range 23.0%–73.0%)			

Notes: [a]Summary of median survival reported or estimated from the studies included, see methods for details on estimation; [b]includes three studies of patients with preoperative chemotherapy only (Gallagher et al,[111] Kishi et al,[123] Neumann et al[84]); [c]includes studies that compared preoperative chemotherapy to no preoperative chemotherapy only; [d]one study in synchronous patient populations only (de Santibañes et al[105]).
Abbreviation: CLM, colorectal cancer liver metastasis.

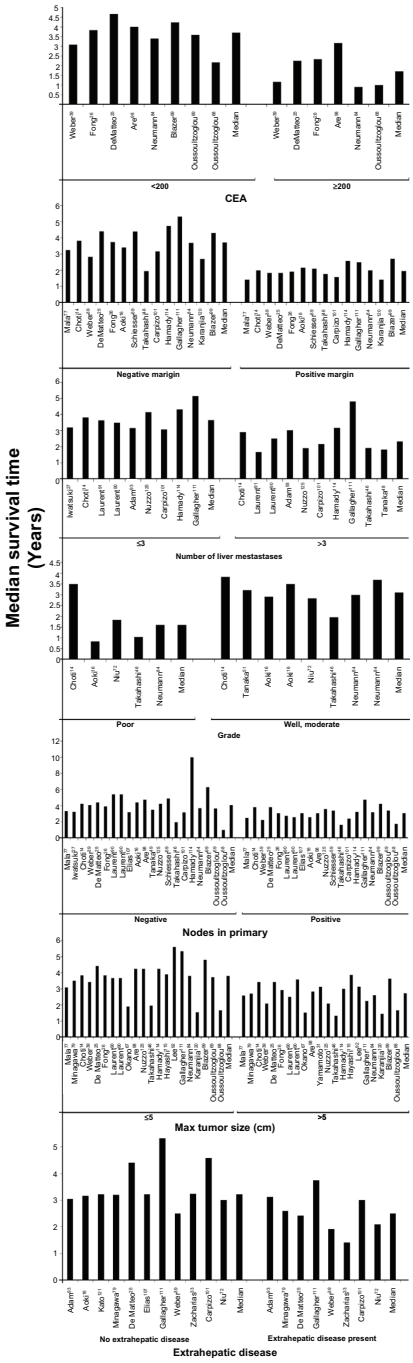


Figure 2 Meta-analysis forest plots of the relative risk and 95% confidence intervals of survival after liver resection in metastatic colorectal cancer reported in the literature for each of the seven identified prognostic factors.
Abbreviation: CEA, carcinoembryonic antigen.

tumor margin, survival was better than in those with a positive margin, as was survival in patients with fewer than three liver metastases compared to those with at least three liver metastases. Patients with poor grade had poorer median survival than those with good or moderate grade reported, as did those with negative nodes compared to patients with positive nodes (Figure 2).

Meta-analysis

Risk estimates from multivariate analyses estimating survival were obtained from each study and meta-analyzed for the seven prognostic factors. All prognostic factors were found to be statistically significantly associated with lower survival (Figure 3). Table 2 summarizes the mRRs for each of the prognostic factors overall, by study size and by annual clinic volume. mRRs were elevated for each of the prognostic factors and ranged from the lowest mRR of 1.52 (95% CI, 1.28–1.80) for ≥3-cm tumor diameter to the highest of 2.02 (95% CI, 1.65–2.48) for positive resection margin. The test for heterogeneity was significant for all our analyses of prognostic factors, except for the analysis of positive primary nodal status ($P = 0.55$). However, all individual studies, with few exceptions, observed elevated hazard ratios for each prognostic factor. Thus, even though statistical heterogeneity was observed, the directionality of the individual studies was virtually uniform. Study characteristics for the 54 studies included in the meta-analysis are shown in Table 3.

Plots for publication bias were created for each of the prognostic factors (results not shown). In general, the plots showed symmetry around the plotted summary log-relative risk, suggesting that publication bias was not large and was unlikely to drive the conclusions; however, all of the log-hazard ratios were greater than zero, with few studies reporting null or protective estimates for the prognostic factors.

Stratification by study size of 200 study subjects or fewer and stratification by annual clinic volume (<20 vs ≥20 patients) resulted in marked differences in mRRs for some of the prognostic factors (CEA level, extrahepatic disease, tumor grade and positive resection margin). Each prognostic factor listed in Table 2 was associated with stronger mRRs in studies of greater than 200 subjects (vs < 200) and in studies of annual volume per study center of 20 or more patients (vs < 20), with the exception of 1+ liver metastases in the clinic volume analysis. Cumulative meta-analyses generally indicated better prognosis by annual clinic volume within the categories of prognostic factors analyzed for positive resection margin, extrahepatic disease, CEA level, tumor diameter, and node-positive status, but this trend was not apparent for 1+ liver metastases or tumor grade (Figure 4).

Sensitivity analysis

We conducted several sensitivity analyses to determine the relative impact or influence that each study had on the overall model-specific mRR. For CEA level, one study[96] had a very different point estimate and CI from the other studies, but contributed only <1% of the relative weight; therefore,

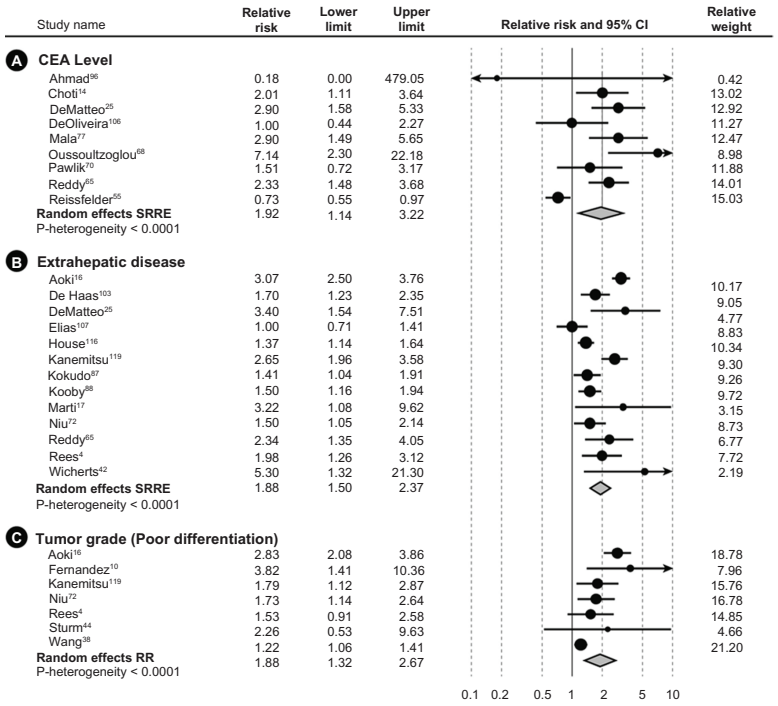


Figure 3 (*Continued*)

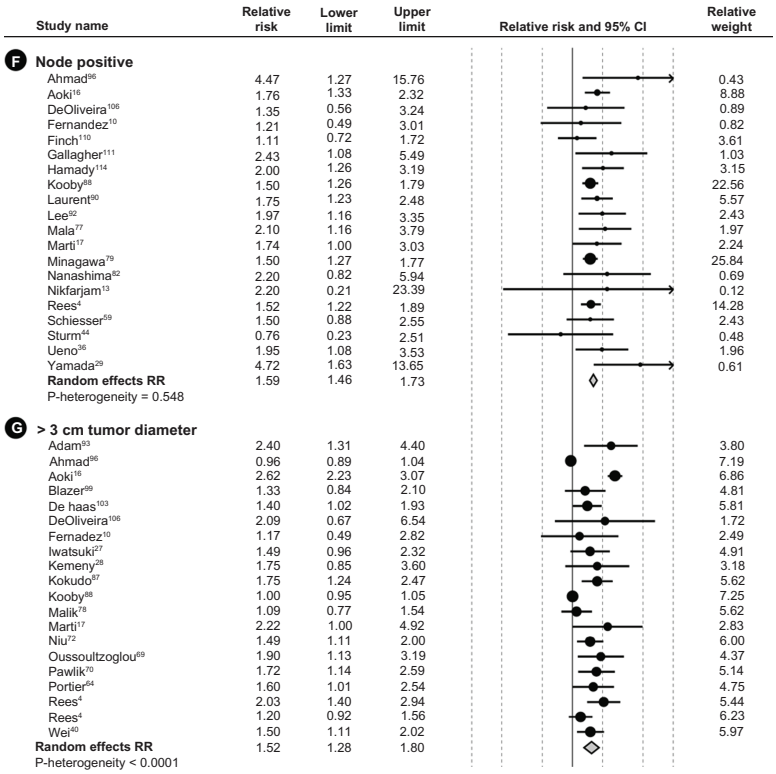


Figure 3 Summary of median survival after liver resection for metastatic colorectal cancer reported or estimated from the studies included.
Note: Results are shown by date of publication as well as the seven identified prognostic factors.
Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval.

keeping or removing this study did not appreciably change the mRR for CEA level. In the studies reporting extrahepatic disease, one study[107] also reported metastases to the lung; however, no effect was seen on the mRR when this study was removed from the analysis. Overall, the meta-analysis models were generally robust to study removal and replacement, indicating little appreciable influence at the individual study level.

Discussion

Observed median 5-year survival after liver resections for CLM in this review was 38% (range 16%–74%), compared to 30% (range 15%–67%) reported in an earlier review of studies published before 2001.[15] After resection of CLM, median 5- and 10-year survival rates were 38% and 26%, respectively. Comparison of change in median survival over study time period did not show a trend of increasing survival, and this was also true when looking at the prognostic factors individually. Some of the more recent publications included in this review reported survival from patients diagnosed decades earlier; therefore, it may not be possible to make accurate approximations between publication date and date of treatment and subsequent survival. It may also be difficult to show trends in survival given the increasing role of surgical intervention in CLM.[2,128,129] In addition, more complicated cases such as patients with multiple metastases or extrahepatic disease are now considered standard surgical candidates.[2,128,129] Inclusion of complicated cases may improve survival on a patient-by-patient basis, although the incremental gain across a larger patient population with a wider range of patient severity may not yet be observed when those with more severe disease are included.[128] The instrumentation to evaluate the degree of hepatic involvement and surgical technique has also improved, allowing surgeons to make more informed decisions when selecting surgical candidates.[2,128]

All the mRRs for the prognostic factors reviewed and meta-analyzed were statistically significantly associated with poorer survival. All seven factors exceeded unity on the forest plots (Figure 3). Significant heterogeneity was observed for all but one prognostic factor, which may be partially attributable to variation in clinic volume or study center size, patient selection, or clinical parameters. Our cumulative meta-analyses by annual clinic volume suggested improved survival with increasing clinic volume for each prognostic factor, consistent with observations by others.[128] Associations for the prognostic factors were stronger in magnitude among studies of 200 or more subjects (vs < 200) and among studies of annual clinic volume of 20 or more patients (vs < 20).

Table 2 Summary of calculated meta-relative risks (mRRs) for the seven prognostic factors of interest, including mRRs stratified by study size and annual patient volume[a]

Prognostic factor	Number of studies	Overall mRR (95% CI)	*P*-value[b]	Number of studies	mRR (95% CI) by study size	*P*-value	Number of studies[c]	mRR (95% CI) by patient volume per study center	*P*-value
CEA level (≥200)	9	1.92 (1.14–3.22)	<0.0001	<200: 4	<200: 2.49 (0.96–6.49)	<200: 0.034	<20: 4	<20: 2.19 (1.64–2.9)	<20: 0.616
				≥200: 5	≥200: 1.68 (0.90–3.14)	≥200: <0.0001	≥20: 4	≥20: 1.23 (0.51–2.96)	≥20: 0.001
Extrahepatic disease (yes vs no)	13	1.88 (1.50–2.37)	<0.0001	<200: 3	<200: 2.43 (1.22–4.83)	<200: <0.0001	<20: 5	<20: 2.35 (1.66–3.34)	<20: 0.001
				≥200: 10	≥200: 1.74 (1.41–2.15)	≥200: 0.001	≥20: 8	≥20: 1.55 (1.28–1.88)	≥20: 0.032
Tumor grade (poor differentiation)	7	1.88 (1.32–2.67)	<0.0001	<200: 3	<200: 2.88 (2.15–3.84)	<200: 0.808	<20: 4	<20: 2.51 (1.91–3.29)	<20: 0.356
				≥200: 4	≥200: 1.43 (1.15–1.78)	≥200: 0.195	≥20: 2	≥20: 1.65 (1.19–2.29)	≥20: 0.713
Positive resection margin (yes vs no)	20	2.02 (1.65–2.48)	<0.0001	<200: 9	<200: 2.52 (1.73–3.66)	<200: 0.044	<20: 10	<20: 2.53 (1.77–3.61)	<20: 0.044
				≥200: 11	≥200: 1.82 (1.44–2.30)	≥200: <0.0001	≥20: 10	≥20: 1.79 (1.41–2.27)	≥20: <0.0001
I+ liver metastases[d]	36	1.57 (1.39–1.78)	<0.0001	<200: 17	<200: 1.74 (1.29–2.34)	<200: <0.0001	<20: 16	<20: 1.46 (1.20–1.79)	<20: <0.0001
				≥200: 19	≥200: 1.52 (1.34–1.71)	≥200: <0.0001	≥20: 19	≥20: 1.66 (1.40–1.96)	≥20: <0.0001
Node positive (yes vs no)	20	1.59 (1.46–1.73)	0.548	<200: 13	<200: 1.84 (1.55–2.19)	<200: 0.626	<20: 13	<20: 1.64 (1.47–1.84)	<20: 0.632
				≥200: 7	≥200: 1.52 (1.38–1.67)	≥200: 0.645	≥20: 7	≥20: 1.55 (1.33–1.79)	≥20: 0.309
>3 cm tumor diameter	20	1.52 (1.28–1.80)	<0.0001	<200: 11	<200: 1.57 (1.24–1.98)	<200: <0.0001	<20: 5	<20: 2.00 (1.51–2.64)	<20: 0.058
				≥200: 9	≥200: 1.43 (1.24–1.64)	≥200: 0.754	≥20: 13	≥20: 1.32 (1.15–1.51)	≥20: <0.0001

Notes: [a]The estimated annual clinic volume was calculated as: initial patient population/number of years over which patients were recruited/number of centers participating in the study. Stratifications by study size and annual clinic volume were based on the median number of patients per center (n = 236) and median annual clinic volume (n = 21) of all studies included in the meta-analysis, thus the stratifications were performed using values of 200 (≥ and <) and 20 (≥ and <), respectively; [b]*P*-value is for heterogeneity of meta-analysis for all columns; [c]number of studies included in the analysis by patient volume not equal to total number of studies; data were not reported in some studies to calculate a patient volume; [d]includes variety of categories: "multiple" and various iterations of more than one metastasis.

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval.

Long-term survival of all patients with mCRC, both operable and inoperable, has been improving significantly over the last two decades.[121,130,131] Increased use of liver resection has played some part in these improving outcomes, but wide variations in its use persist.[130] Still, for the approximately 20% of patients with liver-limited metastases whose disease is determined to be resectable,[132] hepatectomy with curative intent is now the standard of care. To be more clinically useful, long-term survival after liver resection for mCRC should report 10-year survival. Of the 93 studies we identified that reported survival, only 20 (22%) reported 10-year survival rates, whereas the majority reported 3- or 5-year survival. Throughout the 1990s, if studies reported long-term survival, these outcomes consistently examined 3- or 5-year disease-free and/or overall survival; however, disease can still recur,[133] and in line with our results, published results show 40% survival after 5 years posthepatectomy, and slightly less than 30% after 10 years. Therefore, disease will recur in 70% of patients following CLM, with the majority in the first 2 years but continuing to occur up to 10 years after such surgery.

Several confounders need to be considered when evaluating survival after resection of CLM. Patient characteristics may play a role, and advanced age has been considered a barrier to offering liver resection.[26] The issue of patient selection has already been discussed, where surgical intervention is now offered to patients presenting with multiple metastases, large tumor size, and extrahepatic or other underlying liver disease.[2,128] Recent data[134,135] from large single centers and international registries demonstrate an association of disease-free and overall survival in older patients with higher operative mortality (4.7% for those over 70, compared to 1.2% for those under 70); however, subsequent disease-free and overall survival are the same, regardless of age.

When analyzing resection data over the study period, the definition of surgical resectability of CLM is not always defined. In the late 1990s, such surgery was offered only to patients with liver-limited disease that was (1) ideally detected metachronously after a previous potentially curative resection of the primary tumor; (2) confined to only one lobe of the liver; (3) showed no more than three metastases, the largest of which was no greater than 5 cm in diameter; or (4) could be resected on intention to treat with at least a >1 cm margin of healthy liver tissue.[8,136] Based on these criteria, the option of liver surgery would be restricted to the small portion (<10%)[136] of all patients with liver-limited disease. At present, the definition of resectability is disease within the liver, even in the presence of resectable extrahepatic disease, that can be resected, leaving two disease-free

Table 3 Study characteristics for the 54 studies included in the meta-analysis

Study	Country	Study type	Study dates	Age at surgery, median years (range)	Number resected	Follow-up (months)	Prognostic factors reported
Adam[93]	France	Cohort	1993–2000	59.5 (32–78)	138	48.7	Number of metastases Tumor size
Ahmad[96]	US	Cohort	1997–2003	63 (28–85)	64	10	CEA level Number of metastases Positive primary node Tumor size
Aoki[16]	Japan	Cohort	1988–2005	64 (27–83)	187	25	Extrahepatic disease Primary tumor grade Positive margin Number of metastases
Blazer[99]	US	Cohort	1997–2007	57 (26–85)	305	25	Positive margin Number of metastases Tumor size
Capussotti[100]	Italy	Cohort	1985–2004	mean Syn (n = 70): 64.9 (37–83) mean Meta (n = 57): 60.8 (39–83)	127	38.2	Number of metastases
Chiu[102]	Taiwan	Case series	1977–2004	58 (SD 11)	166	24.6	Positive margin
Choti[14]	US	Case series	1984–1999	62 (32–87)	226	121	CEA level Positive margin
de Haas[104]	France	Case series	1990–2006	–	806	>40	Extrahepatic disease Tumor size
DeMatteo[25]	US	Case series	1985–1998	65 (28–87)	267	25	CEA level Extrahepatic disease Positive margin
DeOliveira[106]	US	Case series	1998–2004	64 (22–87)	84	26.2	CEA level Positive margin Number of metastases Positive primary node Tumor size
Elias[107]	France	Cohort	1987–2000	58 (18–86)	308	99	Extrahepatic disease Number of metastases
Farid[109]	UK	Case series	1993–2007	46 (23–91)	705	38	Number of metastases
Fernandez[10]	US	Cohort	1995–2002	61.1 (23–86)	100	31	Primary tumor grade Number of metastases Positive primary node Tumor size
Finch[110]	UK	Cohort	1993–2003	61 (23–84)	484	33	Positive margin Number of metastases Positive primary node

(*Continued*)

Table 3 (*Continued*)

Study	Country	Study type	Study dates	Age at surgery, median years (range)	Number resected	Follow-up (months)	Prognostic factors reported
Gallagher[111]	US	Cohort	1995–2003	61 (27–85)	111	63	Positive margin Positive primary node
Hamady[114]	UK	Case series	1993–2001	61 (38–80)	293	29	Positive margin Positive primary node
Hayashi[115]	Japan	Case series	1993–2006	60 (33–80)	53	27.9	Positive margin
House[116]	US	Cohort	1985–2004	1985–1998 (n = 1037): 63.1 (20–87) 1999–2004 (n = 563): 61.5 (23–89)	1600	36	Extrahepatic disease Positive margin
Iwatsuki[27]	US	Case series	1981–1996	60 (26–82)	305	36	Number of metastases Positive margin
Kaibori[118]	Japan	Cohort	1993–2007	Syn (n = 32): 62.3 (SD 9.3) Meta (n = 42): 65.0 (S 9.9)	74	31	Positive margin
Kanemitsu[119]	Japan	Cohort	1990–1998	61 (28–88)	578	55.2	Extrahepatic disease Primary tumor grade
Kemeny[28]	US	Clinical trial	NR	Combined therapy (n = 74): 59 (28–79) Monotherapy (n = 82): 59 (30–77)	156	62.7	Tumor size
Kishi[123]	US	Cohort	1997–2007	57 (23–86)	200	29	Positive margin Number of metastases
Kokudo[87]	Japan	Case series	1980–2000	59.0 (35–82)	194	29.1	Extrahepatic disease Number of metastases Tumor size
Kooby[88]	US	Cohort	1986–2001	–	1351	35	Extrahepatic disease Positive margin Number of metastases Positive primary node Tumor size
Korita[89]	Japan	Cohort	1990–2004	64 (32–80)	105	124	Positive margin
Laurent[90]	France	Case series	1985–2000	63 (31–86)	311	29	Number of metastases Positive primary node
Lee[92]	Korea	Cohort	1994–2005	59 (26–79)	138	47.2	Number of metastases Positive primary node
Mala[77]	Norway	Case series	1977–1999	61 (23–79)	137	27	CEA level Positive primary node
Malik[78]	UK	Case series	1993–2006	64 (23–87)	687	34	Positive margin Number of metastases Tumor size
Marti[17]	Spain	Case series	1994–2006 (Split periods: 1994–2000; 2000–2006)	1994–2000 (n = 93): 63.9 (40–81) 2000–2006 (n = 143): 62.5 (36–81)	236	69.6	Extrahepatic disease Number of metastases Positive primary node Tumor size

Minagawa[79]	Japan	Case series	1980–2002	–	369	47.4	Number of metastases Positive primary node
Nanashima[82]	Japan	Case series	1990–2006	63 (24–85)	130	56	Positive primary node
Nikfarjam[13]	US	Case series	2002–2007	66 (44–86)	65	24	Positive margin Number of metastases Positive primary node
Niu[72]	Australia	Case series	1990–2006	Mean 62 (SD 11)	415	25	Extrahepatic disease Primary tumor grade Tumor size
Oussoultzoglou[69]	France	Case series	2000–2004	Mean 63.7 (39.7–84.2)	213	34.7	Number of metastases Tumor size
Oussoultzoglou[68]	France	Case series	2000–2006	58.4 (29–78)	45	25.5	CEA level
Pawlik[70]	US Italy Switzerland	Cohort	1990–2004	60 (19–88)	557	29	CEA level Positive margin Number of metastases Tumor size
Petrowsky[63]	Germany	Case series	1985–1995	61 (20–75)	41	39	Number of metastases
Portier[64]	France Switzerland	Clinical trial	1991–2001	–	171	87.4	Number of metastases Tumor size
Reddy[65]	US	Cohort	1985–2005	57 (49–66)	449	48	CEA Extrahepatic disease Number of metastases
Rees[4]	UK	Case series	1987–2005	62 (25–86)	929	26.4	Extrahepatic disease Primary tumor grade Positive margin Number of metastases Positive primary node Tumor size
Reissfelder[55]	Germany	Cohort	2002–2008	63 (30–88)	281	36	CEA level
Sasaki[58]	Japan	Case series	1985–2003	Mean 64.0	103	24	Number of metastases
Schiesser[59]	Australia	Case series	1992–2005	64 (22–92)	197	54	Positive margin Number of metastases Positive primary node
Shah[61]	Canada	Cohort	1996–2004	64 (23–90)	841	24	Number of metastases
Sturm[44]	Germany	Case series	1985–1995	61 (20–75)	40	40	Primary tumor grade Number of metastases Positive primary node
Ueno[36]	Japan	Case series	1985–1996	Average 60.2 (33–79)	85	52	Number of metastases Positive primary node

(*Continued*)

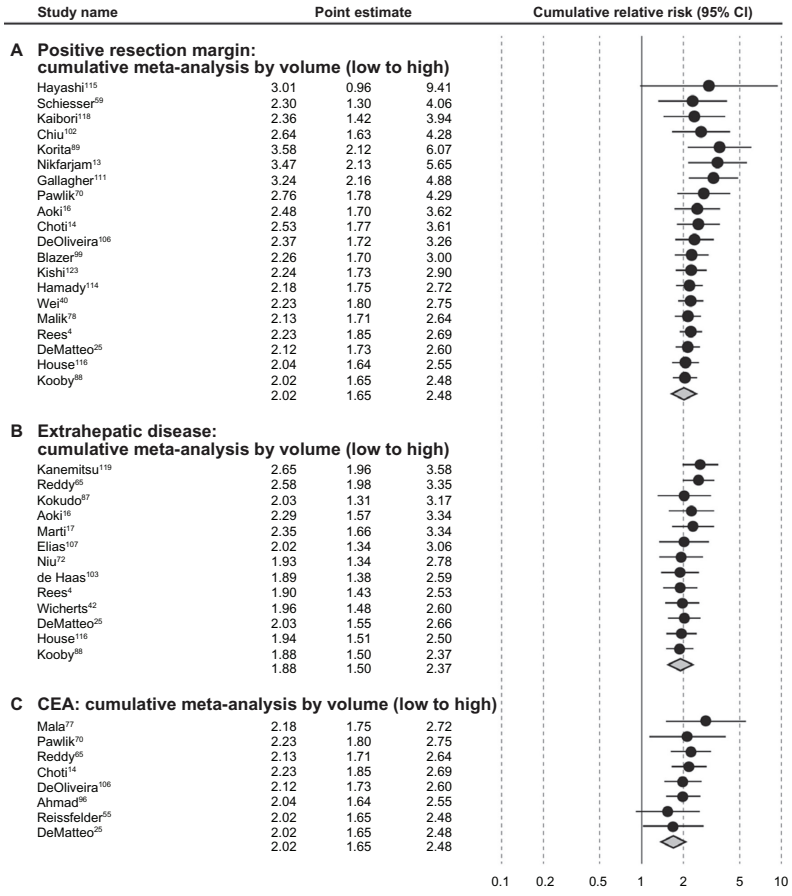
Table 3 (*Continued*)

Study	Country	Study type	Study dates	Age at surgery, median years (range)	Number resected	Follow-up (months)	Prognostic factors reported
van der Pool[34]	Netherlands	Case series	2000–2008	62 (28–84)	272	25	Number of metastases
Wang[38]	US	Cohort	1991–2003	–	923	26	Primary tumor grade
Wei[40]	Canada	Case series	1992–2002	62.7 (23–88)	395	31	Positive margin Number of metastases Tumor size
Wicherts[42]	France	Case series	1992–2007	58.2 (32.8–83.7)	59	24.4	Extrahepatic disease Number of metastases
Yamada[29]	Japan	Case series	1988–1995	(42–82)	90	26.8	Positive primary node
Yamamoto[31]	Japan	Case series	1992–1994	–	96	37.6	Number of metastases

Abbreviations: CEA, carcinoembryonic antigen; Meta, metachronous; NR, not reported; SD, standard deviation; Syn, synchronous.

viable contiguous liver segments with a future liver remnant volume of at least 25%–30% and with a viable vascular inflow and viable biliary and vascular outflow.[131] This new definition of resectability means that at least 20% of patients with liver-limited disease can now be considered candidates for surgery with long-term survival. It is clear from our analyses that many of the patients who now fulfill the new criteria for such liver surgery also fall into those high-risk prognostic factor groups that are associated with poorer outcomes. As noted above, this observation may partially explain why no definitive overall improvement in survival over time was seen in the studies evaluated, and is supported by observations by others.[2,128]

There are limitations in this review. Our meta-analyses were limited by the availability of risk estimates for the prognostic factors of interest. Multivariate model results were reported inconsistently in studies: some reported only significant factors, others reported all factors, and model covariates usually were not reported. Studies varied by the number of prognostic factors reported in their multivariate analyses, thus we were unable to address the risk for patients with more than one of the prognostic factors in multivariate modeling. Our analysis suggested that publication bias, examined visually by producing funnel plots measuring the standard error as a function of effect size, as well as performing Begg's adjusted-rank correlation test[21] and Egger's regression asymmetry test[22] was likely not a factor in our analysis. Due to the missing information in several studies of prognostic factors that were not statistically significant, reporting bias by the study authors may have influenced the calculated summary risk estimates. If there was a reporting bias, however, it would likely result in attenuation of the mRR. Due to the missing information in several studies of prognostic factors that were not statistically significant, reporting bias by the study authors may have influenced the calculated summary risk estimates. If there was a reporting bias, however, it would also likely result in attenuation of the mRR. In calculating the estimated annual clinic volume, we assumed that each center had uniform patient accrual. Referral bias to specialized study centers or selection bias of patients in certain study populations may also have influenced associations, although we were not able to account for these potential limitations based on the available data.[128,129] Among the studies we included, there was a wide range of 5- and 10-year survival reported. This is, in part, due to the number of articles included (total of 86 studies for 5-year survival and 20 for 10-year survival). The wide range also likely reflects differences in study design of the



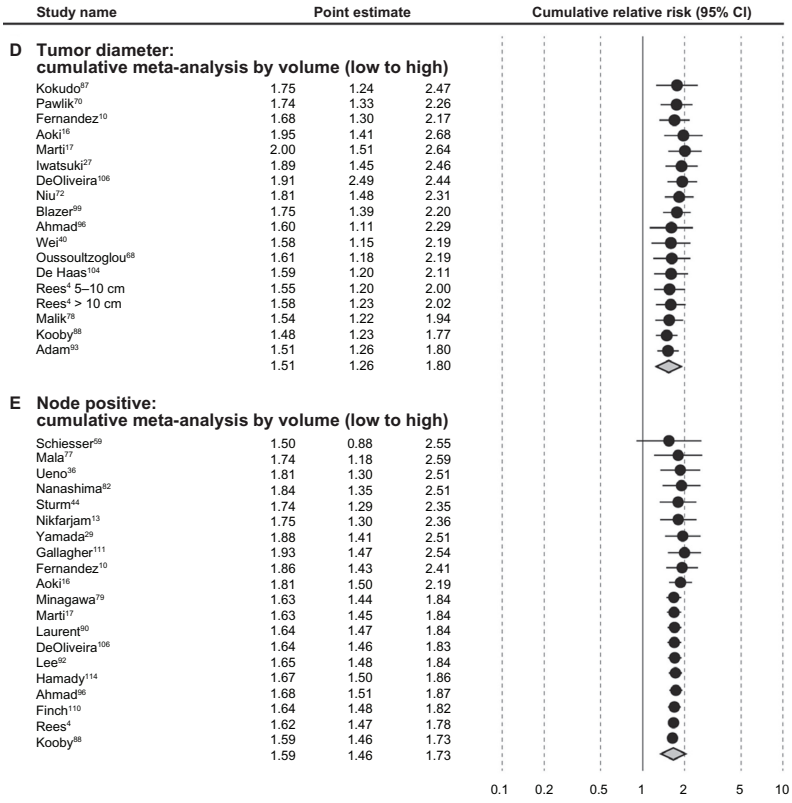


Figure 4 (*Continued*)

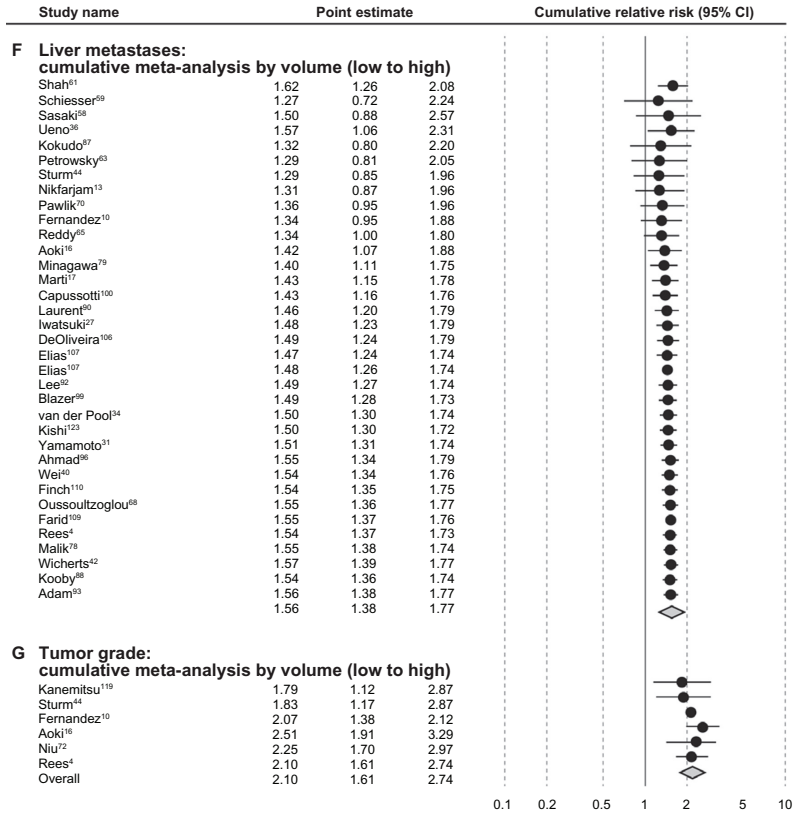


Figure 4 Cumulative meta-analysis of meta relative risks by patient volume and seven prognostic factors identified.
Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval.

included articles and differences in follow-up period and patient-selection criteria. Overall, this systematic review has shown that the 5-year survival rate following CLM resection in patients with mCRC was approximately 38%. Only 22% of the studies we included reported 10-year survival, thus our conclusions regarding 10-year survival following CLM resection are limited. In the future, as follow-up time is accrued among CLM resection patients, we expect that 10-year survival results will be published to aid in evaluating long-term survival in patients undergoing CLM resection.

Conclusion

The overall median survival in mCRC patients following CLM liver resection was 3.6 years. All seven investigated prognostic factors showed a modest but significant predictive relationship with survival. In addition, certain prognostic factors may prove useful in clinical practice when assessing optimal therapeutic options.

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Supplementary material

Search strategy

The PubMed literature search included the following query: liver and (surgery OR resection OR hepatectomy) AND (metastatic OR metastases) AND (colon cancer OR rectal cancer OR colorectal cancer OR colon neoplasm OR rectal neoplasm OR colorectal neoplasm) AND (mortality OR mortalities OR death* OR survival).

Discussion of clinical management of patients with colorectal liver metastases

Patients who present with CLM can generally be divided into three groups: (1) those with resectable disease, (2) those whose metastases may become resectable, and (3) patients who are never going to become resectable.[133] For the latter group, palliative chemotherapy is the main form of treatment, and these patients have poor long-term outcomes. A clear understanding of chemotherapy use is important when reporting long-term outcomes in patients undergoing hepatectomy, and the benefit of perioperative chemotherapy with surgery for good prognosis of liver disease (solitary, easily resectable metachronous tumors) remains controversial.[133] The management of patients with CLM should be determined by a multidisciplinary team.[128] A series of studies in liver-limited metastases patients observed a difference in resection by type of multidisciplinary team that managed the patients, with improvement in survival among patients with resection managed with a liver surgeon on the team.[128,136–139]

We were not able to study in detail the effect of chemotherapy on survival. Preoperative chemotherapy has the potential to improve long-term survival after liver surgery for resectable disease.[2,27,140–142] The use of hepatic arterial floxuridine has been reproduced in only one other study,[143] whereas the use of peri- and postoperative chemotherapy remains controversial.[133] Adam et al[144] also reported on the use of "induction" chemotherapy to convert borderline resectable or unresectable liver-limited disease to surgical resectability with curative intent.[6] Kopetz et al reported that with the approval of new drugs such as oxaliplatin, bevacizumab, and cetuximab in 2004, significant increases in survival overall were observed following use of these drugs.[127] We identified 21 studies[13,14,49,50,52,59,63,67,68,71,73,83,92,100,110,122,123,125,145–147] that reported survival information for patients treated with induction chemotherapy, primarily treated with a combination of folinic acid, fluorouracil, and oxaplatin or folinic acid, fluorouracil, and irinotecan. When compared to the patients who did not receive preoperative chemotherapy, survival was the same in the chemotherapy-treated groups (median 3.3 years in both groups).