Effect of Adding Bevacizumab to Chemotherapy on Pathologic Response to Preoperative Systemic Therapy for Resectable Colorectal Liver Metastases: A Systematic Review and Meta-analysis

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Abstract

Background: Liver-limited metastatic colorectal cancer is a potentially curable disease. Pathologic response (pR) to preoperative chemotherapy (CT) for colorectal liver metastases (CLM) is a surrogate endpoint for overall survival (OS). We conducted the first meta-analysis of observational studies to estimate the overall effect of bevacizumab on pR in preoperative systemic therapy for CLM. **Methods:** We systematically searched PubMed, Cochrane Library, CINAHL, Web of Science, Embase, and LILACS for studies published between January 2004 and August 2019 that compared the pR of CT plus bevacizumab to CT alone as preoperative therapy for CLM. The primary endpoint was pathologic complete response (pCR). Secondary endpoints were pathologic major (pMaR) and minor (pMiR) response. Overall effects were expressed by odds ratios (ORs) and 95% confidence intervals (CIs) using a random-effects model. **Results:** Of the 1,452 studies yielded by the search, 9 were eligible, totaling 1,202 patients (516 CT plus bevacizumab and 686 CT alone). The addition of bevacizumab to CT increased the pCR rate without reaching statistical significance (OR: 1.24, 95% CI 0.81 to 1.92, $P = .32$). However, pMaR was significantly higher (OR: 2.45, 95% CI 1.85 to 3.25, $P < .001$), and pMiR was significantly lower (OR: 0.41, 95% CI 0.31 to 0.54, $P < .001$), in the bevacizumab group. The analyses showed a low level of heterogeneity ($I^2 = 0\%$ to 6%). Publication bias was not found. **Conclusions:** This meta-analysis demonstrates that bevacizumab plus preoperative CT is associated with higher rates of pR in CLM. Antiangiogenics might improve the OS of CLM patients and should be evaluated in randomized clinical trials. **MicroAbstract:** The benefit of perioperative chemotherapy for colorectal liver metastases (CLM) is uncertain, but pathologic response (pR) to preoperative chemotherapy is a strong prognostic factor. Our meta-analysis of observational studies compared the pR of bevacizumab plus chemotherapy to chemotherapy alone as preoperative systemic therapy in the management of CLM. The addition of bevacizumab was associated with significantly higher rates of pR.

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Introduction

Colorectal cancer (CRC) is the fourth most common cancer worldwide, accounting for ~1,100,000 new cases and 550,000 deaths in 2018.[1] In the United States, ~20% of patients present with metastatic disease,[2] and ~20% of patients with stage II disease and 35% of patients with stage III disease have distant metastasis within 5 years, despite the use of adjuvant chemotherapy.[3-5]

The liver is the most common site of metastatic disease. In patients with liver-limited disease, surgical resection offers the greatest likelihood of long-term disease control, with a 5-year overall survival (OS) rate of 40%,[6-8] contrasting with 10% to 15% in patients who undergo systemic therapy only.[9, 10] The largest series suggests that liver resection is curative, since ~15% of CRC patients who undergo liver resection do not have disease recurrence at the 10-year follow-up.[11, 12] Unfortunately, most patients succumb to the disease.

The hypothesis that perioperative systemic therapy might improve the clinical outcomes in the management of CRC liver metastases (CLM) has been tested in recent years. The pivotal phase III EORTC 40983 trial compared the use of perioperative 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) to surgery alone in 364 patients with resectable CLM.[13] At a median follow-up of 8.5 years, statistically significant improvement in neither progression-free survival (PFS) (hazard ratio [HR]14: 0.81, 95% confidence interval [CI] 0.64 to 1.02, $P = .068$) nor OS

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(HR: 0.88, 95% CI 0.68 to 1.14, $P = .34$) has been demonstrated in the intention-to-treat population. Perioperative chemotherapy conferred a statistically significant increase in PFS only in the eligible patients (HR: 0.78, 95% CI 0.78 to 0.99, $P = .035$). Based on these findings, the National Comprehensive Cancer Network and the European Society for Medical Oncology consider oxaliplatin-based perioperative chemotherapy as a therapeutic option in the management of resectable CLM.[15]

The addition of anti-epidermal growth factor receptor monoclonal antibodies to preoperative chemotherapy is not recommended, even in patients with RAS wild type, since the addition of cetuximab to perioperative FOLFOX was associated with a significantly worse OS in patients with resectable CLM (HR: 1.45, 95% CI 1.02 to 2.05, $P = .036$).[16] Although antiangiogenic therapy has an established role in the palliative setting, no randomized controlled trials have assessed its efficacy in the management of resectable CLM.

Retrospective studies have suggested that pathologic response is an independent prognostic factor and a surrogate endpoint for OS in CRC patients who have undergone liver resection and preoperative chemotherapy. In a study of 181 CRC patients who underwent liver resection, the 5-year OS rate was 41% in patients with pathologic major response (pMaR) compared with 9% in patients with no response ($P = .0003$).[17] Another study of 305 patients who underwent preoperative chemotherapy for CLM reported 5-year OS rates of 75%, 56%, and 33% in patients who reached pathologic complete response (pCR), pMaR, and pathologic minor response (pMiR), respectively ($P < 0.05$ in the 3 comparisons).[18] A larger study of 767 patients reported a 5-year OS rate of 76% in patients with pCR versus 45% in patients with no pCR ($P = .004$).[19]

The comparison between bevacizumab plus chemotherapy versus chemotherapy alone in observational studies[18, 20, 21] and a nonrandomized clinical trial[22] have suggested that the addition of antiangiogenic therapy to preoperative chemotherapy is associated with higher rates of pathologic response, irrespective of treatment duration. In addition, further analyses, predominantly with oxaliplatin-based chemotherapy, have demonstrated that bevacizumab attenuates chemotherapy-related hepatotoxicity, with lower rates of sinusoidal obstruction and oxaliplatin-related nodular regenerative hyperplasia.[20, 21, 23, 24]

Because no randomized clinical trials have systematically compared the pathologic response of bevacizumab plus chemotherapy to chemotherapy alone as preoperative therapy for resectable CLM, we conducted the first meta-analysis of observational studies to estimate the overall effect of bevacizumab on pathologic response to preoperative systemic therapy for CLM. Therapeutic modalities that improve pathologic response should be urgently pursued, and the demonstration of a positive effect of bevacizumab might foster the conception of randomized studies to address this issue, with the potential to improve recurrence rates and OS in metastatic CRC.

Methods

Search Strategy

We systematically searched for studies in PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, Web of Science, EMBASE, CINAHL, and LILACS, using the following search strategy: ("colon*" OR "rectal" OR "colorectal" OR "large bowel" All Fields) AND ("cancer" OR "carcinoma" OR "adenocarcinoma" OR "tumor" OR "tumour" OR "malignant" OR "neoplasm" All Fields) AND ("bevacizumab" OR "avastin" All Fields) AND ("pathologic response" OR "pathologic complete response" OR "histopathologic response" All Fields). Reference lists from studies selected by electronic searching were hand searched to identify additional relevant studies. The search was performed between August 2019 and November 2019.

The study was conducted according to the MOOSE (Meta-analyses of Observational Studies in Epidemiology) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[25, 26] The study is registered at PROSPERO with ID CRD42020150715.

Selection Criteria

Articles were included if they were retrospective studies that compared the pathologic response of preoperative chemotherapy to that of preoperative chemotherapy plus bevacizumab in the surgical treatment of colorectal cancer with liver metastases. We searched for studies published between January 2004 and August 2019, with no language restriction. The start date of 2004 was based on the publication of the first phase III trial of bevacizumab as systemic therapy for metastatic CRC.[27] Studies were excluded if they used chemotherapy regimens that did not contain fluoropyrimidines, used monoclonal antibodies other than bevacizumab, or included patients who had not undergone liver resection.

To select studies for further assessment, 3 independent reviewers (AAJ, FOA, FL) scanned the title, abstract, and keywords of every record retrieved. Full articles were further assessed if the information given suggested that the study was retrospective and compared the pathologic response of preoperative chemotherapy to preoperative chemotherapy plus bevacizumab in patients with CRC who had undergone resection of liver metastases.

Data Extraction

Each database was assessed independently by 2 of 3 authors (AAJ, FOA, FL), who analyzed the quality of the eligible studies. Disagreements were resolved by a fourth reviewer (JPSNL) until consensus was obtained. Data were extracted using an assessment form that was designed especially for the topic of this review. The following data were extracted: first author; year of study; chemotherapy regimens; number of patients who had pCR, pMaR, and pMiR; and total number of patients in each group.

The primary endpoint was pCR, which was defined as the absence of residual cancer cells in the liver specimen. pMaR and pMiR were secondary endpoints. pMaR was defined as ≤50% residual cancer cells or tumor regression grade (TRG) 1 to 3 in the liver specimen, and this category included patients who had achieved pCR. pMiR was defined as >50% residual cancer cells or TRG 4 or 5.[17, 18] Postoperative endpoints, such as adjuvant therapy, disease-free survival, and OS, were not assessed in the present study.

Statistical Analysis and Synthesis

The likelihood of preoperative therapy being associated with pCR, pMaR, or pMiR was expressed by odds ratios (ORs) and 95%

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Table 1 Summary of the Studies Selected

Reference	*N*		pCR (%)		pMaR (%)		pMiR (%)		Regimen	
	CT + Bev	CT	CT + Bev	CT	CT + Bev	CT	CT + Bev	CT	CT + Bev (*n*)	CT (*n*)
Ribero et al., 2007[20]	62	43	11	12					FOLFOX (62)	FOLFOX (43)
Blazer et al., 2008[18]	108	163	9	9	57	37	43	63	FOLFIRI (27); FOLFOX (81)	FOLFIRI (113); FOLFOX (50)
Kishi et al., 2010[21]	102	117	10	7	70	45	30	55	FOLFOX (102)	FOLFOX (117)
Klinger et al., 2010[22]	50	50	20	6	66	34	33	66	XELOX (30); FOLFOX (20)	XELOX (50); FOLFOX (0)
Loupakis et al., 2013[31]	24	18	16	11	63	28	27	72	FOLFOXIRI (24); XELOXIRI (0)	FOLFOXIRI (24); XELOXIRI (0)
Brouquet et al., 2013[32]	71	82	5	7	65	54	35	46	FOLFOX (66); FOLFIRI (9)	FOLFOX (38); FOLFIRI (40)
Constantinidou et al., 2013[33]	42	52	12	12					XELOX (14); FOLFOX (1); FOLFIRI (10); XELIRI (2); Xeloda (2); Others (1)	XELOX (18); FOLFOX (4); FOLFIRI (4); XELIRI (0); Xeloda (4); Others (3)
Eefsen et al., 2016[34]	35	47			80	49	20	51	FOLFOX (35)	FOLFOX (47)
Wang et al., 2017[35]	22	114			68	62	32	38	5FU (0); FOLFOX (13); FOLFIRI (9); FOLFOXIRI (0)	5FU (2); FOLFOX (83); FOLFIRI (26); FOLFOXIRI (3)

Abbreviations: pCR: pathologic complete response, pMaR: pathologic major response, pMiR: pathologic minor response, CT: chemotherapy, Bev: Bevacizumab.

CIs using a random-effects model and presented in forest plots. The pooled OR, symbolized by a solid diamond at the bottom of the forest plot (the width of which represents the 95% CI) is the best estimate of the true (pooled) outcome. The effect of treatment for each study was expressed as a ratio of the chemotherapy-plus-bevacizumab group to the chemotherapy-alone group. Statistical heterogeneity in the results of the trials was assessed by the χ^2 test[28] and was expressed by the I^2 index, as described by Higgins et al.[29] Publication bias was evaluated with Egger's test.[30] Statistical analysis of summary data was performed with RevMan version 5.3.

Results

Of the 1,452 studies yielded by the search, 234 were duplicates. The titles and abstracts of the 1,218 remaining studies were analyzed using the exclusion criteria, and 1,194 were removed. Of the 24 studies selected for full-text analysis, only 9 were retained (Figure 1; Table 1).

Of the 9 studies retained, 5 reported pCR, pMaR, and pMiR rates,[18, 21, 22, 31, 32] 2 reported only pCR,[20, 33] and 2 reported only pMaR and pMiR[34, 35] (Table 1). Thus, 7 studies were evaluated for the estimation of the overall treatment effect on pCR, and 7 studies were analyzed for the treatment effect on pMaR and pMiR.

The 9 studies comprised 1,202 patients, of whom 516 received chemotherapy plus bevacizumab and 686 received chemotherapy alone. All the patients underwent fluoropyrimidine-based chemotherapy regimens. Oxaliplatin-based regimens were the most frequent in both groups of patients. However, a higher percentage of patients underwent oxaliplatin-based regimens in the bevacizumab group than in the chemotherapy-alone group (84% versus 68%, $P < .001$), whereas irinotecan-based regimens were more common in the chemotherapy-alone group (11% versus 28%, $P < .001$) (Table 1).

The addition of bevacizumab to chemotherapy increased the pCR rate, but the increase did not reach statistical significance (OR: 1.24, 95% CI 0.81 to 1.92, $P = .32$), with a low level of heterogeneity among studies ($I^2 = 0\%$) (Figure 2). However, pMaR was significantly higher in the bevacizumab group (OR: 2.45, 95% CI 1.85 to 3.25, $P < .001$) (Figure 3), and pMiR was significantly lower in the same group (OR: 0.41, 95% CI 0.31 to 0.54, $P < .001$) (Figure 4). Both endpoints presented a low level of heterogeneity among studies ($I^2 = 6\%$). No evidence of publication bias was found (Figure 5).

Discussion

In our systematic review and meta-analysis of observational studies, we found that the addition of bevacizumab to fluoropyrimidine-based preoperative chemotherapy increased the rate of pathologic response in the treatment of CLM. The rates of pCR were not significantly improved by the addition of bevacizumab, but the rates of both pMaR and pMiR were significantly influenced by the antiangiogenic.

No standard criteria exist for the classification of pathologic response to preoperative systemic therapy in the management of CLM. pCR is the most standardized and reproductible category. The definitions of pMaR and pMiR vary among studies, but there are similarities between the 2 most-used criteria: TRG and the percentage of neoplastic cells in the surgical specimen. TRG categorizes pathologic response in 5 categories, taking into account the relative predominance of fibrotic tissue over neoplastic cells.[17] The second criterion categorizes responses according to the percentage

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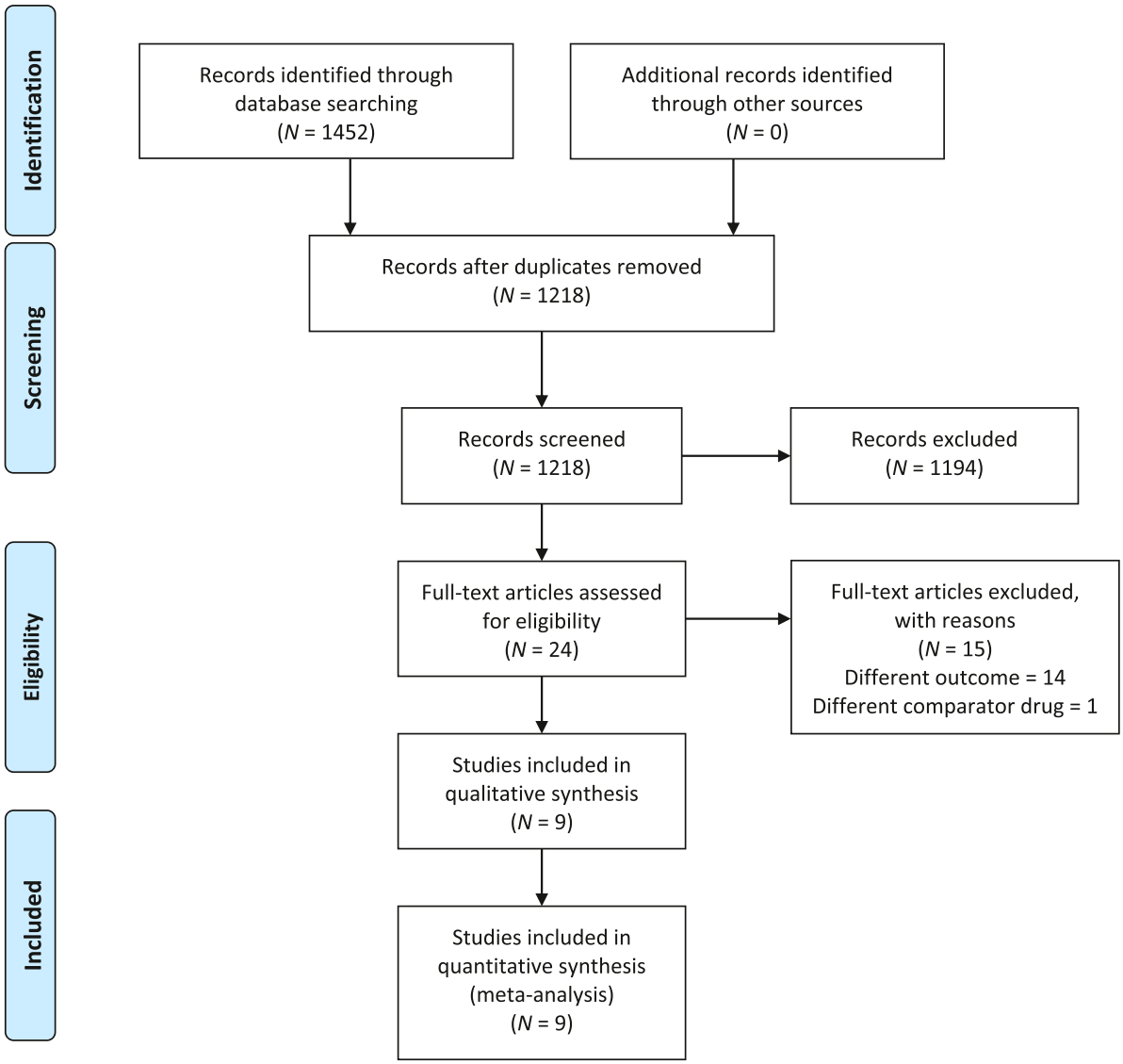
Figure 1 PRISMA flow diagram.



of neoplastic cells in the surgical specimen: pCR if 0% of residual cancer cells; pMaR if 1% to 49%; and pMiR if ≥50%.[18] Because both TRG 1 to 3 and <50% of residual cancer cells mean that fibrosis predominates over neoplastic cells, we considered the 2 definitions to be pMaR in our study, and we considered TRG 4 or 5 and >50% residual cancer cells to be pMiR. In addition, both criteria adopted in our study (TRG and the percentage of residual cancer cells) have been demonstrated to be prognostic factors in the management of CLM.[17, 18, 22]

Because no randomized controlled trials have systematically evaluated the pathologic response to antiangiogenics as preoperative therapy for CLM, we opted to include only observational studies that methodically compared pathologic response to chemotherapy plus bevacizumab to decrease the level of heterogeneity in our meta-analysis. The inclusion of single-arm or nonrandomized prospective studies might have led to a larger imbalance between sample sizes, as well as to a more heterogeneous population of patients and standard practices among studies.

Pathologic response to neoadjuvant therapy has been consistently demonstrated as a prognostic factor for both PFS and OS in other solid tumors, such as breast,[36, 37] esophageal,[38, 39] and rectal[40, 41] cancers. In addition, when added to neoadjuvant chemotherapy for breast cancer, bevacizumab was associated with higher rates of pCR.[42, 43] Pathologic response is the standard endpoint in the neoadjuvant setting. In randomized clinical trials, the positive effect of therapeutic interventions on pathologic response does not necessarily translate to an improvement in survival, even when pathologic response is a prognostic factor. Owing to the low rates of

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Figure 2 Overall treatment effect on pathologic complete response. Abbreviations: CT, chemotherapy; M-H, Mantel-Haenszel.

Study or Subgroup	Bevacizumab + CT Events	Total	CT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Blazer 2008	10	108	15	163	26.6%	1.01 [0.43, 2.33]
Kishi 2010	10	102	8	117	20.0%	1.48 [0.56, 3.91]
Brouquet 2013	5	71	7	82	13.2%	0.81 [0.25, 2.68]
Ribero 2007	7	62	5	43	12.6%	0.97 [0.29, 3.28]
Constantinidou 2013	5	42	6	52	11.8%	1.04 [0.29, 3.66]
Klinger 2010	10	50	3	50	10.2%	3.92 [1.01, 15.22]
Loupakis 2012	4	24	2	18	5.7%	1.60 [0.26, 9.88]
Total (95% CI)		**459**		**525**	**100.0%**	**1.24 [0.81, 1.92]**
Total events	51		46			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.93$, df = 6 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 0.99 (P = 0.32)

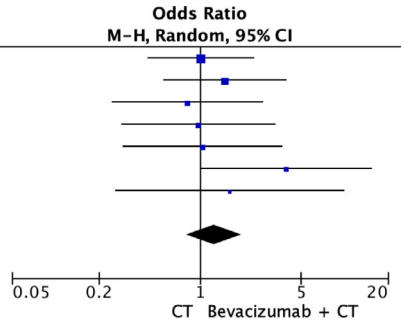


Figure 3 Overall treatment effect on pathologic major response. Abbreviations: CT, chemotherapy; M-H, Mantel-Haenszel.

Study or Subgroup	CT Events	Total	CT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Blazer 2008	62	108	60	163	28.3%	2.31 [1.41, 3.80]
Kishi 2010	71	102	53	117	23.1%	2.77 [1.58, 4.83]
Brouquet 2013	46	71	44	82	17.3%	1.59 [0.83, 3.05]
Klinger 2010	33	50	17	50	11.1%	3.77 [1.65, 8.62]
Wang 2017	15	22	71	114	8.1%	1.30 [0.49, 3.44]
Eefsen 2016	28	35	23	47	7.6%	4.17 [1.53, 11.42]
Loupakis 2012	15	24	5	18	4.5%	4.33 [1.16, 16.25]
Total (95% CI)		**412**		**591**	**100.0%**	**2.45 [1.85, 3.25]**
Total events	270		273			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.39$, df = 6 (P = 0.38); $I^2 = 6\%$
Test for overall effect: Z = 6.21 (P < 0.00001)

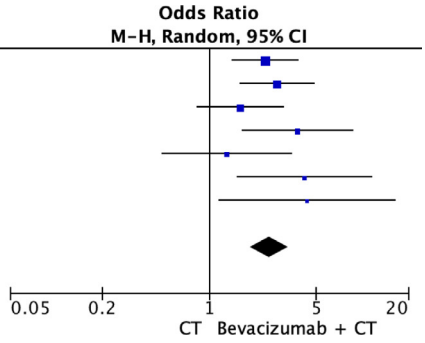
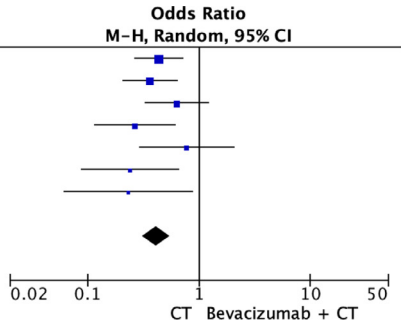


Figure 4 Overall treatment effect on pathologic minor response. Abbreviations: CT, chemotherapy; M-H, Mantel-Haenszel.

Study or Subgroup	Bevacizumab + CT Events	Total	CT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Blazer 2008	46	108	103	163	28.3%	0.43 [0.26, 0.71]
Kishi 2010	31	102	64	117	23.1%	0.36 [0.21, 0.63]
Brouquet 2013	25	71	38	82	17.3%	0.63 [0.33, 1.21]
Klinger 2010	17	50	33	50	11.1%	0.27 [0.12, 0.61]
Wang 2017	7	22	43	114	8.1%	0.77 [0.29, 2.04]
Eefsen 2016	7	35	24	47	7.6%	0.24 [0.09, 0.66]
Loupakis 2012	9	24	13	18	4.5%	0.23 [0.06, 0.87]
Total (95% CI)		**412**		**591**	**100.0%**	**0.41 [0.31, 0.54]**
Total events	142		318			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.39$, df = 6 (P = 0.38); $I^2 = 6\%$
Test for overall effect: Z = 6.21 (P < 0.00001)



pCR and the varying degrees of pathologic response not represented in a dichotomized analysis (pCR and no pCR), treatment arms usually have similar survival rates, even if the interventional arm is associated with higher pathologic response rates, such as neoadjuvant taxanes in breast cancer[44] and fluoropyrimidines in rectal cancer.[45] Nevertheless, the therapeutic principles applied to neoadjuvant therapy for locally advanced disease, as aforementioned, do not necessarily apply to metastatic disease, which is the population in our study. The paucity of data correlating pathologic response and survival does not allow definitive conclusions about the role of

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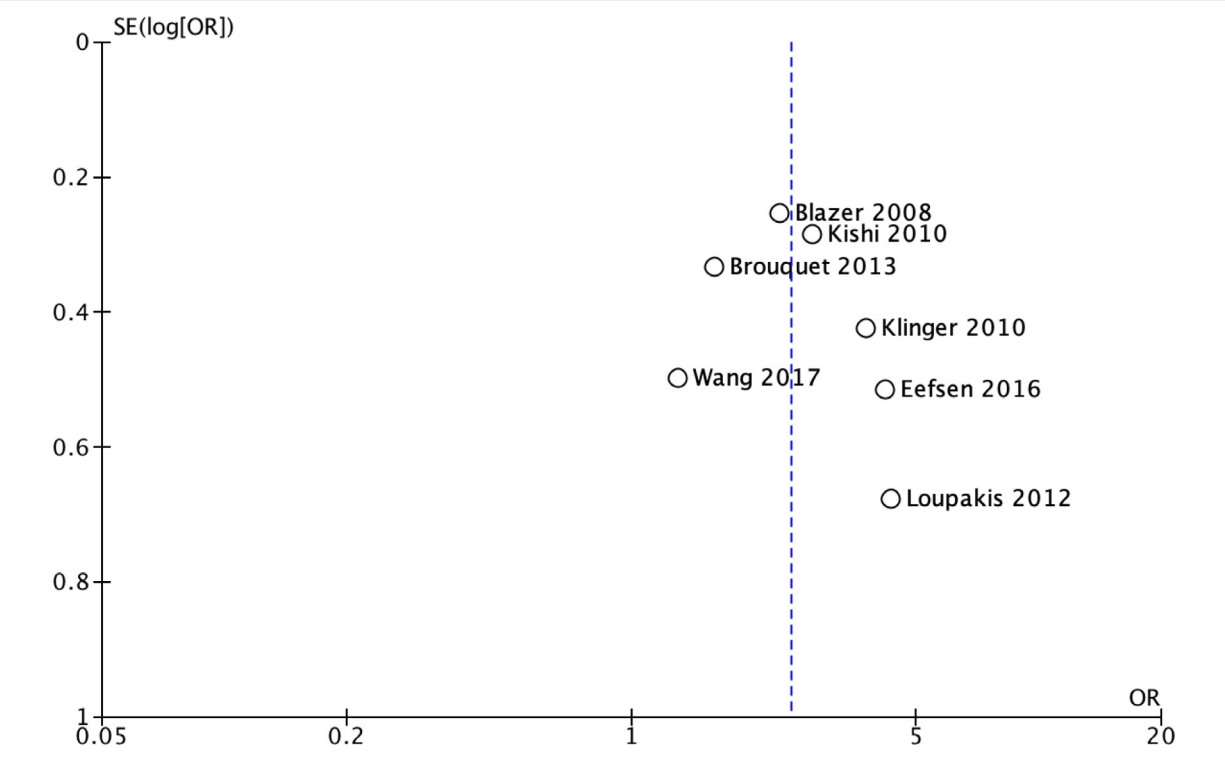
Figure 5 Funnel plot for the data from pathologic major response rates. The *x*-axis is the odds ratio (OR), and the *y*-axis is the standard error (SE) of the log of the odds ratio. Each circle represents the respective OR of each study included in the meta-analysis. The vertical dashed line is the funnel axis, which represents the overall OR (2.45) of pathologic major response. All the studies are scattered close to the funnel axis, with a symmetrical distribution, which means that there is no evidence of publication bias.



pathologic response as a surrogate endpoint in the management of CLM.

Because anti-VEGF therapy has the potential to impair wound healing and liver regeneration, the impact of bevacizumab before liver resection for CLM on postoperative complications has been extensively evaluated. Retrospective studies did not show significant difference in the rate of postoperative morbidity of patients treated versus those not treated with preoperative bevacizumab.[14, 46, 47] However, a nonsignificant increase in the rate of overall complications was seen when liver resection was performed within 8 weeks after the last antiangiogenic dose.[46] Meta-analysis of nonrandomized studies and a recent randomized study also did not demonstrate an increase in mortality or in the rate of bevacizumab-related complications, including wound healing, thromboembolic and bleeding events, and gastrointestinal perforation, in the group of patients treated with preoperative bevacizumab.[48, 49] There is no consensus on the recommended interval time between the discontinuation of bevacizumab and liver resection, but given that the drug half-life is ~21 days (range 11 to 50), an interval time of 6 to 8 weeks is recommended.[14, 46-49]

We must be prudent when drawing conclusions about the role of bevacizumab in increasing the pathologic response, since the 2 groups of patients included were not randomized, and thereby, occult factors imbalanced between the groups might also influence the endpoints. Likewise, despite including a high number of databases and the absence of bias suggested by the funnel plot, our search did not include abstracts from meeting proceedings and unpublished studies.

In summary, our study demonstrates that the addition of bevacizumab increases the pathologic response to preoperative chemotherapy in the management of CLM. Liver-limited metastatic CRC is a potentially curable disease, and randomized clinical trials in this setting must be urgently pursued to improve pathologic response rates, recurrence-free survival, and OS.

Clinical Practice Points

Liver-limited metastatic colorectal cancer (mCRC) is a potentially curable disease. The resection of colorectal liver metastases (CLM) substantially improves recurrence-free survival and overall survival (OS) so that ~15% of CRC patients remain disease-free at a 10-year follow-up. The benefit of perioperative chemotherapy is uncertain. However, pathologic response (pR) to preoperative chemotherapy is a strong prognostic factor. Therefore, therapeutic strategies that might potentially increase the rates of pR should be pursued. Bevacizumab improves the overall response rate, progression-free survival, and OS of the patients with mCRC,

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and retrospective studies demonstrate that antiangiogenic therapy attenuates chemotherapy-related hepatotoxicity and improves the pR to chemotherapy. Nevertheless, there are no randomized clinical trials addressing the effect of the combination of bevacizumab with chemotherapy on the pR in the liver specimen in patients with resectable CLM. We performed an original meta-analysis of observational studies that systematically compared the pR of bevacizumab plus chemotherapy to chemotherapy alone as preoperative systemic therapy in the management of CLM. We found that the addition of bevacizumab to chemotherapy was associated with significantly higher rates of pR. These findings corroborate the hypothesis that the combination of preoperative chemotherapy plus anti-angiogenics might potentially improve OS of the patients with CLM and, thereby, should be evaluated in randomized clinical trials.

Authorship

AJ: conception, search strategy, data extraction, analysis of data, manuscript writing, manuscript review.

FAO: search strategy, data extraction, manuscript review.

FL: search strategy, data extraction, manuscript review.

JPSNL: conception, analysis of data, manuscript review.

Conflict of interest

The authors declare no conflict of interest.

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