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OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL OMPARISON OF BEVACIZUMAB PLUS CHEMOTHERAPY COMBINATION REGIMENT VERSUS CHEMOTHERAPY ONLY REGIMENT IN METASTATIC COLORECTAL CANCER: A COMPARATIVE META-ANALYSIS AND SYSTEMATIC REVIEW

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ABSTRACT
Bevacizumab's role in enhancing chemotherapy's efficacy by inhibiting tumor vasculature has led to its incorporation in both first-line and second-line treatment protocols for mCRC. This meta-analysis and systematic review aim to provide a comprehensive comparison of the overall survival (OS) and progress-free survival (PFS) of bevacizumab plus chemotherapy versus chemotherapy alone in patients with metastatic colorectal cancer. A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines using the PICO framework. Rigorous screening, data extraction, risk of bias assessment, and statistical analysis were performed to investigate the OS and PFS of bevacizumab plus chemotherapy versus chemotherapy alone in patients with metastatic colorectal cancer. A total of 79 articles were retrieved from online databases (PubMed, SagePub, Nature and Cochrane) using combinations terms such as "metastatic colorectal cancer," "bevacizumab," "chemotherapy," "overall survival," and "progression-free survival." After three rounds of screening, seven articles directly relevant to the meta-analysis were selected for full-text reading and analysis. The pooled OS across all studies is 0.79 (95% CI: [0.68, 0.93]), indicating a statistically significant overall survival benefit for bevacizumab plus chemotherapy. The pooled PFS across studies was 0.68 (95% CI: 0.54–0.87), strongly favoring the combination therapy for improved PFS. Bevacizumab plus chemotherapy offers survival benefits for metastatic colorectal cancer, especially in overall survival. However, increased risks of hypertension and bleeding require careful patient selection and monitoring. Ongoing research is needed to optimize treatment protocols and safety.

Keywords: bevacizumab; chemotherapy; metastatic colorectal cancer; overall survival; progression-free survival

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INTRODUCTION

Metastatic colorectal cancer (mCRC) remains one of the most challenging malignancies to manage, with advanced stages presenting a significant therapeutic hurdle. Despite the progress made in the field of oncology, survival outcomes for mCRC patients are still unsatisfactory, highlighting the need for more effective treatment regimens. (Van Cutsem et al., 2020; Aranda et al., 2018). Over the past decade, the combination of targeted therapies with chemotherapy has become a cornerstone of treatment strategies, with bevacizumab—an anti-vascular endothelial growth factor (VEGF) monoclonal antibody—emerging as a key player. Bevacizumab's role in enhancing chemotherapy's efficacy by inhibiting tumor vasculature has led to its incorporation in both first-line and second-line treatment protocols for mCRC. However, its exact benefits, include in the second-line setting, are still under debate (Loupakis et al., 2014; Qu et al., 2015; Rosen et al., 2017).

Chemotherapy regimens used for mCRC are generally are oxaliplatin or irinotecan-based in combination with 5-Fluorouracil (5-FU), leucovorin or capecitabine (Qu et al., 2015; Baraniskin et al., 2019). Combination with bevacizumab has shown promising results in terms of progression-free survival (PFS) and overall survival (OS). This combination approach aims to improve outcomes by providing additional therapeutic benefits through anti-angiogenic effects. However, the comparative efficacy of bevacizumab plus chemotherapy versus chemotherapy alone remains controversial, with studies showing mixed results (Baraniskin et al., 2019; Prager et al., 2023).

The existing body of evidence is heterogeneous, with studies varying in patient demographics, chemotherapy regimens, and the specific dose and schedule of bevacizumab. While some trials have demonstrated a significant improvement in PFS and OS, others have highlighted a less pronounced benefit. These disparities underscore the complexity of assessing bevacizumab's true value in metastatic disease, particularly in later stages of treatment where resistance to chemotherapy often develops (Rinaldi et al., 2022; Venook et al., 2017; Botrel et al., 2016). Moreover, the safety profile of bevacizumab remains a critical consideration. While it has proven effective in many cases, the addition of bevacizumab to chemotherapy regimens is associated with increased risks of adverse events, such as hypertension, bleeding, proteinuria, and thromboembolic events. These side effects can compromise patient quality of life and may limit the broader application of this combination therapy. Therefore, understanding the balance between clinical benefit and safety is essential when considering bevacizumab as a treatment option for therapy in mCRC patients (Baraniskin et al., 2019; Yamazaki et al., 2016; Heinemann et al., 2014). This meta-analysis and systematic review aim to provide a comprehensive comparison of the overall survival (OS) and progress-free survival (PFS) of bevacizumab plus chemotherapy versus chemotherapy alone in patients with untreated metastatic colorectal cancer or who had previously undergone first-line treatment.

METHOD

This systematic review and meta-analysis was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analysis) guidelines. This study utilized the PICO (Population, Intervention, Comparator, and Outcomes) framework. The population included adult patients diagnosed with untreated metastatic colorectal cancer (mCRC) who had previously undergone first-line treatment. The intervention was therapy with bevacizumab in combination with chemotherapy, compared to chemotherapy-only regimens. The outcomes of interest were overall survival (OS) and progression-free survival (PFS).

Eligibility Criteria

The inclusion criteria for this study required studies to focus on adult patients with mCRC to compare bevacizumab plus chemotherapy with chemotherapy alone. Studies reporting data on OS and/or PFS were eligible, provided they were randomized controlled trials (RCTs), cohort studies, or case- control studies published in peer-reviewed journals. Studies were excluded if they excluded bevacizumab from the intervention group, lacked comparative data on OS or PFS, or were non-peer-reviewed articles, conference abstracts, case reports, or studies with fewer than 10 participants. Additionally, studies involving non-human subjects or conditions unrelated to mCRC were excluded.

Data Sources and Search Strategy

Authors utilized various data sources and search strategies, including the Medical Subject Headings (MeSH) database. A comprehensive search was conducted across PubMed, SagePub, Nature, and Cochrane to identify relevant studies. Keywords were combined with Boolean operators to include terms such as “metastatic colorectal cancer,” “bevacizumab,” “chemotherapy,” “overall survival,” and “progression-free survival.” Filters were applied to include studies published in English and involving human participants. To enhance the search, manual screening of reference lists and

relevant reviews was also performed. The selection of studies followed a two-step process. Initially, titles and abstracts were independently screened by two reviewers to exclude studies that did not meet the inclusion criteria. Full-text articles of potentially eligible studies were then retrieved and evaluated against the eligibility criteria. Any disagreements during this process were resolved through discussion or consultation with a third reviewer. The study selection process was summarized using a PRISMA flow diagram.

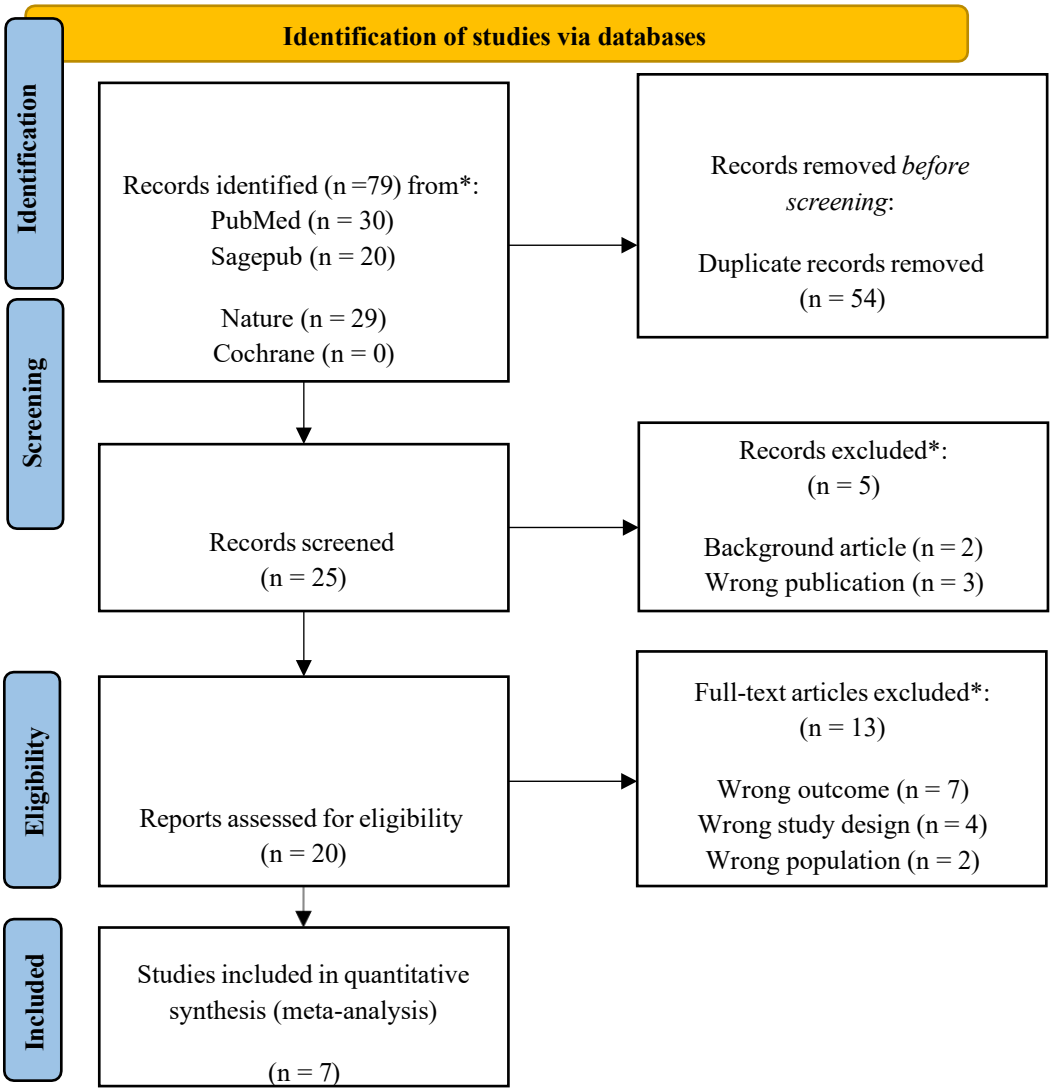

Figure 1. Search strategy and selection of studies for the meta-analysis.

Data extraction was conducted independently by two reviewers using a standardized form. Extracted data included study characteristics (e.g., design and sample size), patient demographics, treatment regimens, and outcomes (OS and PFS). The reviewers cross-verified the extracted data to ensure accuracy and consistency. The risk of bias in each trial was assessed across six domains using the RevMan 5.4 tool (Cochrane, UK). These domains included sequence generation, allocation concealment, blinding, attrition bias, selective outcome reporting, and other potential sources of bias. Trials were categorized as having high, low, or unclear bias in each domain, with detailed justifications provided for each determination.

Data synthesis and analysis were performed using Review Manager (RevMan) version 5.4. Hazard ratios (HRs) for OS and PFS were pooled using a random-effects model, and 95% confidence intervals (CIs) were calculated. Forest plots were generated to visually present the comparative effectiveness of bevacizumab plus chemotherapy versus chemotherapy-only regimens. Heterogeneity was assessed using the I^2 statistic, and subgroup analyses were conducted to explore

differences based on factors such as study design, patient age, and prior treatments. Sensitivity analyses were performed to test the robustness of the findings, and publication bias was evaluated using funnel plots and Egger's test. The statistical analyses, including the forest plot generation, are conducted using Review Manager Software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).

RESULT

A total of 79 articles were retrieved from online databases (PubMed, SagePub, Nature and Cochrane). After three rounds of screening, seven articles directly relevant to the systematic review were selected for full-text reading and analysis. The characteristics of the studies are showed in Table 1 and 2

Table 1.
Characteristics of studies included in the systematic review

Author	Origin	Study Design	Sample Size	Result
Aparicio et al., 2017	France	RCT	102	In this study, 102 patients (median age 80 years, range 75–91) were randomized equally into two groups: bevacizumab plus chemotherapy (BEV) and chemotherapy alone (CT). Efficacy was achieved in 50% of BEV patients and 58% of CT patients, while safety endpoints were met in 61% and 71%, respectively. Median progression-free survival (PFS) was longer in the BEV group (9.7 months) compared to the CT group (7.8 months). Similarly, median overall survival (OS) was higher in the BEV group (21.7 months) compared to the CT group (19.8 months), with a 36- month OS rate of 27% in BEV and 10.1% in CT. Severe grade 3/4 toxicities were predominantly non- hematologic and more frequent in the BEV group (80.4%) than in the CT group (63.3%).
Cunningham et al., 2013	UK	RCT	280	Between July 2007 and December 2010, 280 patients (median age 76 years, range 70–87) were recruited from 40 sites across ten countries and randomized to receive either bevacizumab plus capecitabine (n=140) or capecitabine alone (n=140). Progression-free survival (PFS) was significantly longer in the combination group compared to capecitabine alone (median 9.1 months [95% CI 7.3–11.4] vs. 5.1 months [4.2–6.3]; HR 0.53 [0.41–0.69]; p<0.0001). Grade 3 or worse treatment- related adverse events were more frequent in the combination group (40%) than in the capecitabine group (22%), with serious adverse events reported in 14% and 8% of patients, respectively. Common grade 3 or worse adverse events of special interest included hand-foot syndrome (16% vs. 7%), diarrhoea (7% in both groups), and venous thromboembolic events (8% vs. 4%). Treatment-related deaths occurred in five patients in the combination group and four in the capecitabine group. Haemorrhage was the most frequent any-grade adverse event associated with bevacizumab (25% vs. 7%).
				The study demonstrated that adding bevacizumab to mIFL significantly improved outcomes for Chinese patients with metastatic colorectal cancer (mCRC). Median progression-free survival (PFS) was longer in the bevacizumab plus mIFL group (8.3 months) compared to the mIFL group (4.2 months, **P<0.001**), with a higher 6- month PFS rate (62.6% vs. 25.0%, **P < 0.001**). Median overall survival also increased (18.7 months vs. 13.4

Author	Origin	Study Design	Sample Size	Result
Guan et al., 2011	China	RCT	214	months, **P = 0.014**), and the response rate improved (35% vs. 17%, **P =0.013**). Grades 3 and 4 adverse events included diarrhea (26% vs. 21%) and neutropenia (33% vs. 19%). No cases of wound-healing complications or congestive heart failure were reported. The results suggest that bevacizumab plus mIFL is an effective and well-tolerated first-line treatment, with clinical benefits and safety profiles consistent with phase III trials in predominantly Caucasian populations.
Khakoo et al., 2019	UK	RCT	714	The study included 714 patients recruited between August 30, 2012, and February 4, 2014, with a median follow- up of 16.4 months. The median duration of first-line chemotherapy was 5.6 months, most commonly capecitabine/oxaliplatin (37.1%). The median total chemotherapy duration was 8.1 months, with no geographic variation in the UK. Median progression-free survival (PFS) was 8.7 months (95% CI: 8.2–9.1), and median overall survival (OS) was 17.8 months (95% CI: 16.1–19.3). No significant differences in efficacy were observed between chemotherapy regimens. After disease progression, 13.9% of patients received bevacizumab, with a safety profile consistent with previous studies.
Passardi et al., 2015	Italy	RCT	376	The study randomized 376 patients between November 2007 and March 2012, with 60% receiving FOLFOX4 and 40% receiving FOLFIRI. After a median follow-up of 36 months, 343 progressions and 275 deaths were recorded. Median progression-free survival (PFS) was 9.6 months (95% CI: 8.2–10.3) in arm A and 8.4 months (95% CI: 7.2– 9.0) in arm B, with a hazard ratio of 0.86 (95% CI: 0.70–1.07; P = 0.182). No significant differences in overall survival (OS) or overall response rate (ORR) were found. B-containing regimens were linked to higher rates of hypertension, bleeding, proteinuria, and asthenia.
Tahover et al., 2014	Israel	RCT	308	Bevacizumab-related adverse effects caused 1.9% mortality, all in patients <70 years old. In patients ≥70, grade 3–5 adverse events included hypertension (37.0%), bleeding (7.6%), venous thromboembolism (6.5%), and proteinuria (14.1%). Older patients had more baseline hypertension and ischemic heart disease and were treated less with FOLFOX. Despite higher proteinuria (p=0.012) and marginally higher hypertension rates (p=0.053), OS and PFS were similar across age groups, confirming bevacizumab's safety and efficacy in older and younger patients.
Tang et al., 2020	China	RCT	241	In a study of 241 patients, the addition of bevacizumab to mFOLFOX6 (arm A) significantly improved outcomes compared to mFOLFOX6 alone (arm B). Arm A showed higher R0 resection rates (22.3% vs. 5.8%; *P* < .01), better response rates (54.5% vs. 36.7%; *P* < .01), longer median progression-free survival (9.5 vs. 5.6 months; *P* < .01), and longer median overall survival (25.7 vs. 20.5 months; *P* = .03). Bevacizumab was associated with increased proteinuria (9.9% vs. 3.3%; *P* = .04) and hypertension (8.3% vs. 2.5%; *P* < .05). Bevacizumab improved resectability and survival in patients with unresectable RAS mutant colorectal liver metastases.

Table 2.
Characteristics of studies included in the meta-analysis assessing the use of bevacizumab combined with chemotherapy as the initial treatment for patients with metastatic colorectal cancer

No.	Author	Country	Study Design	Total Sample	First Line Chemotherapy	Overall Survival (OS)	Progression-free Survival (PFS)
						HR (RE, 95%CI)	HR (RE, 95%CI)
1.	Aparicio et al., 2017	France	RCT	102	Simplified LV5FU2, modified FOLFOX6, modified FOLFIRI	0.73 [0.48, 1.11]	0.79 [0.53, 1.18]
2.	Cunningham et al., 2013	UK	RCT	280	Capecitabine	0.79 [0.57, 1.09]	0.53 [0.41, 0.69]
3.	Guan et al., 2011	China	RCT	214	mIFL	0.62 [0.41, 0.94]	0.44 [0.31, 0.62]
4.	Khakoo et al., 2019	UK	RCT	714	Capecitabine or oxaliplatin	0.70 [0.51, 0.96]	1.00 [0.80, 1.25]
5.	Passardi et al., 2015	Italy	RCT	376	FOLFOX4 or FOLFIRI	1.13 [0.89, 1.43]	0.86 [0.70, 1.06]
6.	Tahover et al., 2015	Israel	RCT	308	FOLFOX, FOLFIRI, CapeOx, 5FU/LV, Capecitabine	0.81 [0.62, 1.06]	0.85 [0.65, 1.11]
7.	Tang et al., 2020	China	RCT	241	mFOLFOX6	0.71 [0.52, 0.97]	0.49 [0.38, 0.63]

The risk of bias analysis for studies comparing overall survival (OS) and progression-free survival (PFS) outcomes of first-line and second-line bevacizumab plus chemotherapy regimens versus chemotherapy alone in metastatic colorectal cancer revealed a varied risk profile across key domains. Random sequence generation was well-addressed in most studies, including Aparicio et al. (2017), Cunningham et al. (2013), and Guan et al. (2011), which utilized robust randomization methods, ensuring a low risk of bias in this domain. Similarly, allocation concealment was adequately reported in most studies, reducing selection bias and strengthening internal validity.

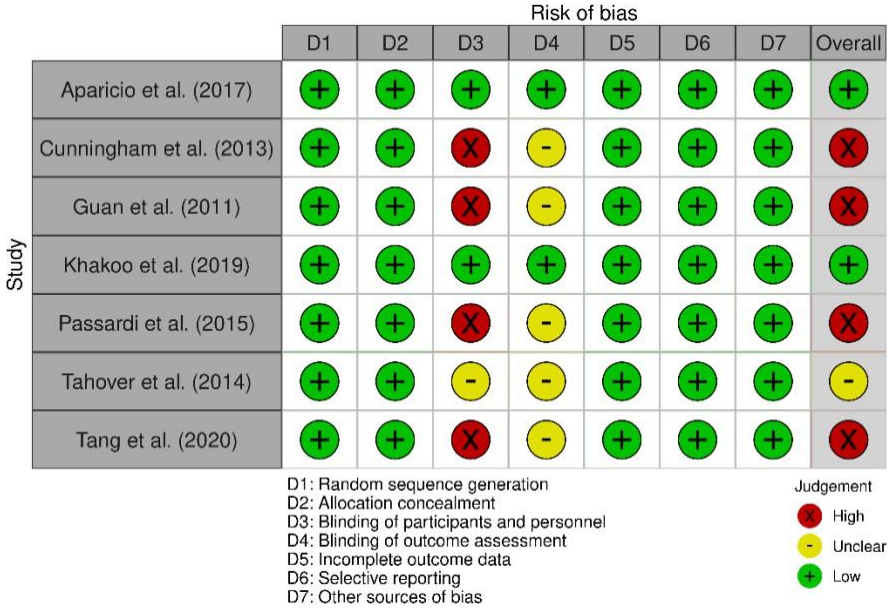

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

However, a high risk of bias was noted for the blinding of participants and personnel in several trials, including Cunningham et al., Passardi et al. (2015), and Tang et al. (2020). Due to the nature of the interventions, complete blinding was often unfeasible, potentially introducing performance bias. Blinding of outcome assessment was inadequately reported in some studies, leading to an unclear risk of bias. Despite this, objective outcomes such as OS and PFS mitigate the impact of potential measurement bias to some extent.

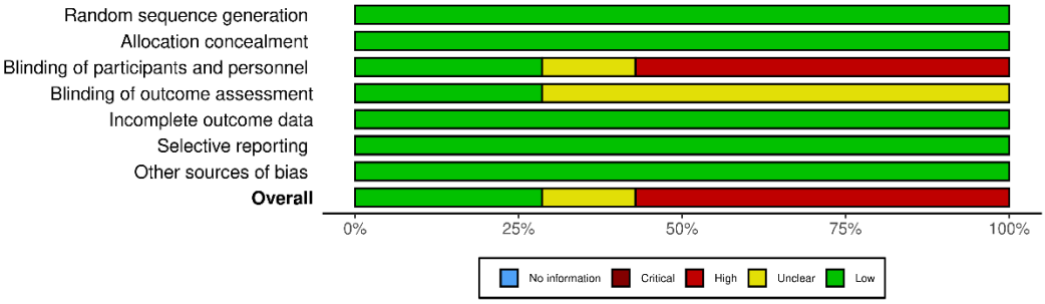

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Incomplete outcome data were well-managed in the majority of studies, with low risk observed due to comprehensive reporting of follow-ups and clearly defined outcomes. Selective reporting was uncommon, as most studies adhered to their pre-specified outcomes, ensuring consistency and transparency. Other sources of bias, such as imbalances in baseline characteristics and geographic variations, were noted in specific studies like Tahover et al. (2014) and Guan et al., which slightly affected the overall risk assessment.

Overall, while the studies demonstrated strong methodologies in certain areas, such as randomization and reporting completeness, the lack of adequate blinding in many trials contributed to a moderate to high risk of bias. The use of objective outcomes like OS and PFS adds reliability to the findings, but caution is warranted when interpreting the results. Future research should prioritize improved blinding techniques and standardized protocols to minimize bias and enhance the robustness of findings.

Overall Survival Comparison of Bevacizumab Plus Chemotherapy Combination Regiment Versus Chemotherapy Only Regiment

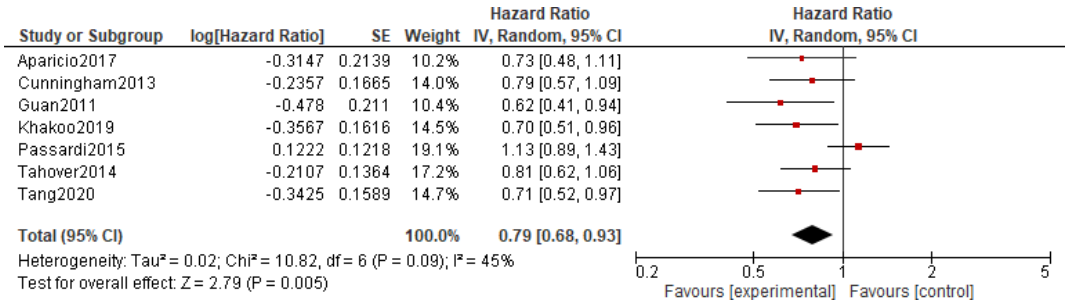

Figure 4. Forest Plot: Overall survival comparison

The forest plot compares the overall survival (OS) between bevacizumab plus chemotherapy combination regimens and chemotherapy-only regimens, using hazard ratios (HR) and 95% confidence intervals (CI) from seven studies. Each study provides a measure of the treatment effect, allowing for a comprehensive comparison of the two approaches.

Aparicio et al. (2017) reported an HR of 0.73 (95% CI: [0.48, 1.11]), indicating a non-significant trend favoring the bevacizumab combination therapy. Similarly, Cunningham et al. (2013) showed an HR of 0.79 (95% CI: [0.57, 1.09]), which also did not achieve statistical significance but

suggested a slight survival advantage for the experimental group. Guan et al. (2011), however, demonstrated a significant improvement in survival with an HR of 0.62 (95% CI: [0.41, 0.94]). This benefit was consistent with the findings from Khakoo et al. (2019), who reported a significant HR of 0.70 (95% CI: [0.51, 0.96]).

In contrast, Passardi et al. (2015) presented an HR of 1.13 (95% CI: [0.89, 1.43]), which favored the control group but was not statistically significant. Tahover et al. (2014) reported an HR of 0.81 (95% CI: [0.62, 1.06]), indicating a non-significant trend in favor of the combination regimen. Tang et al. (2020) demonstrated a significant survival benefit with an HR of 0.71 (95% CI: [0.52, 0.97]), supporting the efficacy of bevacizumab plus chemotherapy.

When pooled, the overall HR was 0.79 (95% CI: [0.68, 0.93]), reflecting a statistically significant survival advantage for the combination therapy compared to chemotherapy alone. The heterogeneity across studies was moderate ($I^2 = 45\%$), suggesting some variability in the observed effects. Overall, these findings support the use of bevacizumab in combination with chemotherapy treatment for improved overall survival in metastatic colorectal cancer patients.

Progression-Free Survival Comparison Bevacizumab Plus Chemotherapy Combination Regiment Versus Chemotherapy Only Regiment

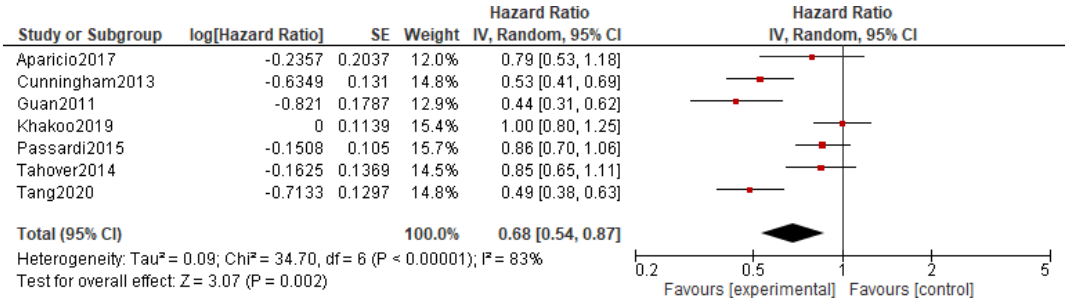

Figure 5. Forest Plot: Progression-free survival comparison

The forest plot evaluates the progression-free survival (PFS) outcomes for bevacizumab plus chemotherapy combination regimens compared to chemotherapy-only regimens, based on data from seven studies. Each study provides a hazard ratio (HR) with a 95% confidence interval (CI), enabling a comparison of the risk of disease progression or death between the two treatment approaches.

Aparicio et al. (2017) reported an HR of 0.79 (95% CI: 0.53–1.18), indicating a potential, though not statistically significant, benefit with bevacizumab. In contrast, Cunningham et al. (2013) demonstrated a strong reduction in the risk of progression or death, with an HR of 0.53 (95% CI: 0.41–0.69). Similarly, Guan et al. (2011) found a significant benefit, with an HR of 0.44 (95% CI: 0.31–0.62), strongly favoring the addition of bevacizumab.

Results from Khakoo et al. (2019) indicated no difference between the two regimens, with an HR of 1.00 (95% CI: 0.80–1.25). Passardi et al. (2015) and Tahover et al. (2014) reported HRs of 0.86 (95% CI: 0.70–1.06) and 0.85 (95% CI: 0.65–1.11), respectively, showing modest but non-significant trends favoring bevacizumab. On the other hand, Tang et al. (2020) found a significant reduction in progression or death risk, with an HR of 0.49 (95% CI: 0.38–0.63).

The pooled analysis across all studies revealed an overall HR of 0.68 (95% CI: 0.54–0.87), indicating a significant improvement in PFS with the combination therapy. However, the analysis identified substantial heterogeneity ($I^2 = 83\%$, $Tau^2 = 0.09$, $Chi^2 = 34.70$, $P < 0.00001$), suggesting variability in the study results.

Despite this, the test for overall effect (Z = 3.07, P = 0.002) confirms the significant benefit of bevacizumab in prolonging PFS. In conclusion, bevacizumab plus chemotherapy demonstrates a statistically significant improvement in PFS compared to chemotherapy alone. Nonetheless, the observed heterogeneity underscores the need for further investigation to identify factors contributing to the variability in treatment outcomes.

DISCUSSION

This systematic review and meta-analysis aims to evaluate the comparison of overall survival (OS) and progression-free survival (PFS) between first-line and second-line bevacizumab plus chemotherapy regimens versus chemotherapy-only regimens in metastatic colorectal cancer (mCRC). The overall survival data across the included studies show a mix of non-significant and significant benefits for the combination regimen. In studies like Aparicio et al. (2017) and Cunningham et al. (2013), hazard ratios (HRs) for OS were 0.73 (95% CI: [0.48, 1.11]) and 0.79 (95% CI: [0.57, 1.09]), respectively, neither of which achieved statistical significance (Aparicio et al., 2018; Cunningham et al., 2013).

However, the trend pointed towards a potential benefit for the bevacizumab plus chemotherapy group, suggesting that while not definitive, the combination might offer a survival advantage over chemotherapy alone. On the other hand, studies such as Guan et al. (2011) and Tang et al. (2020) demonstrated statistically significant HRs (0.62 [95% CI: 0.41, 0.94] and 0.71 [95% CI: 0.52, 0.97], respectively), providing stronger evidence that bevacizumab enhances OS when added to chemotherapy (Guan et al., 2011; Tang et al., 2020).

Notably, the pooled data from all seven studies revealed an overall HR of 0.79 (95% CI: [0.68, 0.93]), indicating a statistically significant survival advantage for the bevacizumab plus chemotherapy regimen. This finding supports the use of bevacizumab in treatment of mCRC, providing a clear benefit for patients in terms of extended survival. The moderate heterogeneity (I^2 = 45%) observed across the studies suggests variability in the treatment effects, potentially due to differences in chemotherapy regimens, patient demographics, or geographical factors. Nonetheless, the consistent trend favoring the combination treatment reinforces its clinical relevance (Gao et al., 2021; Luo et al., 2016).

When focusing on progression-free survival (PFS), the evidence again demonstrates a mixed response. In the study by Cunningham et al. (2013), the combination regimen significantly reduced the risk of progression or death with an HR of 0.53 (95% CI: 0.41–0.69), indicating a meaningful benefit (Cunningham et al., 2013). Similarly, Guan et al. (2011) and Tang et al. (2020) found substantial improvements in PFS, with HRs of 0.44 (95% CI: 0.31, 0.62) and 0.49 (95% CI: 0.38, 0.63), respectively, both of which were statistically significant. These results suggest that the addition of bevacizumab to chemotherapy delays disease progression, providing a clinically relevant advantage in PFS (Guan et al., 2011; Tang et al., 2020).

However, in contrast to these significant findings, other studies like Aparicio et al. (2017) and Passardi et al. (2015) did not report significant improvements in PFS. Aparicio et al. (2017) found a non-significant HR of 0.79 (95% CI: 0.53–1.18), while Passardi et al. (2015) reported an HR of 0.86 (95% CI: 0.70–1.06), indicating no substantial benefit in progression-free survival for the combination regimen. This inconsistency highlights the need for further exploration of the factors that may influence the response to bevacizumab in different populations and settings (Aparicio et al., 2018; Passardi et al., 2015).

The safety profile of bevacizumab in combination with chemotherapy remains an important consideration in these trials. While the combination therapy provided some survival advantages, it also led to higher rates of adverse events. Studies consistently reported an increased incidence of

grade 3 or worse adverse events, such as hypertension, proteinuria, and gastrointestinal toxicities, in the bevacizumab arms compared to chemotherapy alone (Wang et al., 2018; Qu et al., 2023). For example, in the study by Cunningham et al. (2013), 40% of patients in the combination group experienced grade 3 or worse treatment-related adverse events, compared to 22% in the chemotherapy-alone group. Bevacizumab-related adverse effects, including hypertension and bleeding, were particularly prevalent, with 25% of patients experiencing any-grade hemorrhage, compared to 7% in the chemotherapy-only group (Cunningham et al., 2013).

Despite the increased toxicity, the incidence of serious adverse events and treatment-related deaths was relatively low, with no major differences between the two treatment groups in most studies. In fact, in the study by Khakoo et al. (2019), despite the higher incidence of toxicities, the overall treatment-related mortality was similar between groups. However, the higher rates of non-hematologic toxicities, such as hand-foot syndrome and venous thromboembolism, in the bevacizumab group underscore the need for careful monitoring and management of adverse events during treatment (Khakoo et al., 2019).

The heterogeneity in the outcomes of OS and PFS across the studies may be attributed to several factors, including differences in chemotherapy regimens, patient populations, and disease characteristics. For instance, while some studies used capecitabine-based regimens, others employed FOLFOX or mFOLFOX6, which might have different efficacy profiles (Ma et al., 2019). Additionally, variations in patient demographics, including age and comorbidities, may contribute to the observed differences in treatment outcomes. For example, studies like Tahover et al. (2014) specifically addressed outcomes in older patients, confirming that bevacizumab remains effective and safe even in this population, though with a higher incidence of adverse events such as hypertension (Tahover et al., 2015).

Overall, the findings of this meta-analysis provide a robust assessment of the efficacy of first-line or second-line bevacizumab plus chemotherapy in the treatment of metastatic colorectal cancer. While the data demonstrate a statistically significant improvement in OS and PFS for the combination regimen, the variability in treatment outcomes across studies highlights the complexity of optimizing treatment in mCRC. Future research should focus on identifying patient subgroups that benefit the most from bevacizumab, as well as exploring strategies to minimize its associated toxicities.

CONCLUSION

Administration bevacizumab plus chemotherapy either as first-line or second-line appears to offer a survival benefit in patients with metastatic colorectal cancer, particularly in terms of overall survival. However, the increased risk of adverse events, particularly hypertension and bleeding, necessitates careful patient selection and monitoring. The evidence supporting its use in clinical practice is compelling, but ongoing research is required to refine treatment protocols and optimize the balance between efficacy and safety.

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