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Overall Survival and Progression-Free Survival Comparison of Bevacizumab Plus Chemotherapy Combination Regiment versus Chemotherapy Only Regiment in Previously Untreated Metastatic Colorectal Cancer: Systematic Review and Meta-Analysis

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Abstract

BACKGROUND: Colorectal cancer is the third-most common cancer in the world, in which 15%–25% of patients already had metastatic colorectal cancer (mCRC) at the time of diagnosis. The overall survival (OS) of mCRC is poor with the use of chemotherapy.

AIM: This systematic review and meta-analysis aim to examine the outcomes of OS and progression-free survival (PFS) of adding bevacizumab to different chemotherapy regiments compared to chemotherapy regiments only in the treatment of untreated mCRC.

METHODS: Literature searching was done in databases such as PubMed, EBSCO, SCOPUS, and ScienceDirect. The primary outcome measured in this systematic review and meta-analysis was OS, while the secondary outcome was PFS. Hazard ratio (HR) was used as the main summary measure with 95% confidence interval (CI). Publication bias was measured using a funnel plot.

RESULTS: Literature searching resulted in 11 selected studies, 9 selected for meta-analysis. Addition of bevacizumab showed significant better results in OS (HR 0.83, CI 95% 0.74–0.93; p = 0.002; I^2 = 29%) and PFS (HR 0.62, 95% CI 0.51–0.75; p < 0.0001, I^2 = 78%).

CONCLUSION: The addition of bevacizumab to chemotherapy resulted in better OS and PFS in untreated mCRC. Further studies are needed to confirm PFS benefit from the combination of bevacizumab and chemotherapy due to significant heterogeneity.

Introduction

According to the International Agency for Research on Cancer reports, colorectal cancer is the third-most common cancer globally [1]. The global incidence of colorectal cancer is around 1.85 million cases per year, and the mortality is around 0.79 million deaths in 2016 [1]. In newly diagnosed colorectal cancer, around 15%–25% were metastatic colorectal cancer (mCRC) [2], [3], [4], [5].

In the management of mCRC, systemic therapy with chemotherapy agents has been the main choice. Chemotherapy regimens used for colorectal cancer are generally irinotecan or oxaliplatin-based in combination with 5-fluorouracil, leucovorin, or capecitabine [6], [7]. This first-line therapy produces a relatively good 1-year survival outcome. As many as 70%–75% of patients survived 1 year after diagnosis. However, survival in the following years decreased, ranging from 30% to 35% after 3 years and 20% after 5 years after diagnosis, with a median survival of 18 months' post diagnosis in patients receiving chemotherapy [7], [8].

Targeted therapy is now becoming a common therapeutic option for cancer treatment. One of the pathways for targeted therapy is angiogenesis pathway which influences tumor growth and metastasis. Several monoclonal antibodies have been studied and applied to target the process of angiogenesis in mCRC, one of which is bevacizumab [6], [7], [9], [10].

There are many randomized controlled trials (RCTs) comparing the addition of bevacizumab against chemotherapy alone in the management of mCRC. However, the studies were diverse in terms

of chemotherapy regimens and the results varied between one another; hence, a meta-analysis needs to be appropriately conducted to see the overall effect of bevacizumab addition in treatment of mCRC. Furthermore, there is a trend in all cancer where new treatments produce an increase of overall survival (OS) without an increase of progression-free survival (PFS). Thus, it is important to see whether bevacizumab combined with chemotherapy improves PFS.

Methods

This systematic review and meta-analysis aimed to evaluate the efficacy of bevacizumab added to chemotherapy compared to chemotherapy alone as first-line treatment in adult patients with untreated mCRC. Primary outcome in this study was OS, while the secondary outcome included PFS. The patient/population, intervention, comparison, and outcomes framework is as follows:

1. Patient: adult patients aged ≥18 years old with untreated mCRC
2. Intervention: bevacizumab + any type of chemotherapy
3. Comparator: any type of chemotherapy without bevacizumab
4. Outcomes: OS and PFS

This systematic review was registered on International Prospective Register of Systematic Reviews (PROSPERO) with ID of CRD42021230453.

Literature search

Electronic databases (PubMed, EBSCO, Scopus, and ScienceDirect) were searched up to December 12, 2021, using keywords of colorectal cancer, colorectal neoplasm, metastatic, bevacizumab, and chemotherapy. No filter and date restriction were applied. Boolean operators, MESH terms, and alternative spellings were used. Gray literatures on medRxiv were also searched. Reference citations were also examined for additional studies.

Study selection criteria

The inclusion criteria were randomized clinical trials enrolling patients with newly diagnosed mCRC aged ≥18 years old treated with chemotherapy and bevacizumab combination. The exclusion criteria were previously treated mCRC patients (chemotherapy, targeted therapy, immunotherapy), treatment with anti-vascular endothelial growth factor (VEGF) other than bevacizumab, non-RCTs, observational studies, review articles, duplicate studies, and conference abstracts.

Every record was screened by three independent reviewers. Abstract screening, continued by full-text screening was done by two independent reviewers, with discussion among the two reviewers following independent screening.

Data extraction

Data extracted from the studies were author and year of study, study design, number of participants, age group, chemotherapy regimens, median survival, OS, and PFS.

Selected full-text articles will be assessed for risk of bias by the Cochrane Risk of Bias Tool for RCTs, which assesses random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Agreement through consensus was conducted to resolve disagreements.

Statistical analysis

The main summary measure of this study is hazard ratio (HR), reported with 95% confidence intervals (CIs). Statistical analysis was performed using RevMan application version 5.4 (The Nordic Cochrane Center, Copenhagen). All analyses were conducted using random-effect model, and the effects estimates were conducted using generic inverse variance method.

Heterogeneity was evaluated using I^2 test, and $p < 0.05$ was interpreted as statistically significant. Low, moderate, and high heterogeneity were defined as $I^2 < 25\%$, 25%–49%, and ≥ 50%, respectively. Publication bias was analyzed using a funnel plot.

Results

Study selection

Literature searching was done through several databases, which include PubMed, EBSCO, SCOPUS, and ScienceDirect. A preliminary search from keywords resulted in 767 articles after duplicates were removed (Figure 1). Through further abstract screening, 14 articles were selected for full-text screening. After full-text screening, two articles were removed due to different study design (review of RCT and non-RCTs), and one article was removed due to the difference in chemotherapy used in experimental and control groups, which finally resulted in a total of 11 selected articles, all of which were RCT.

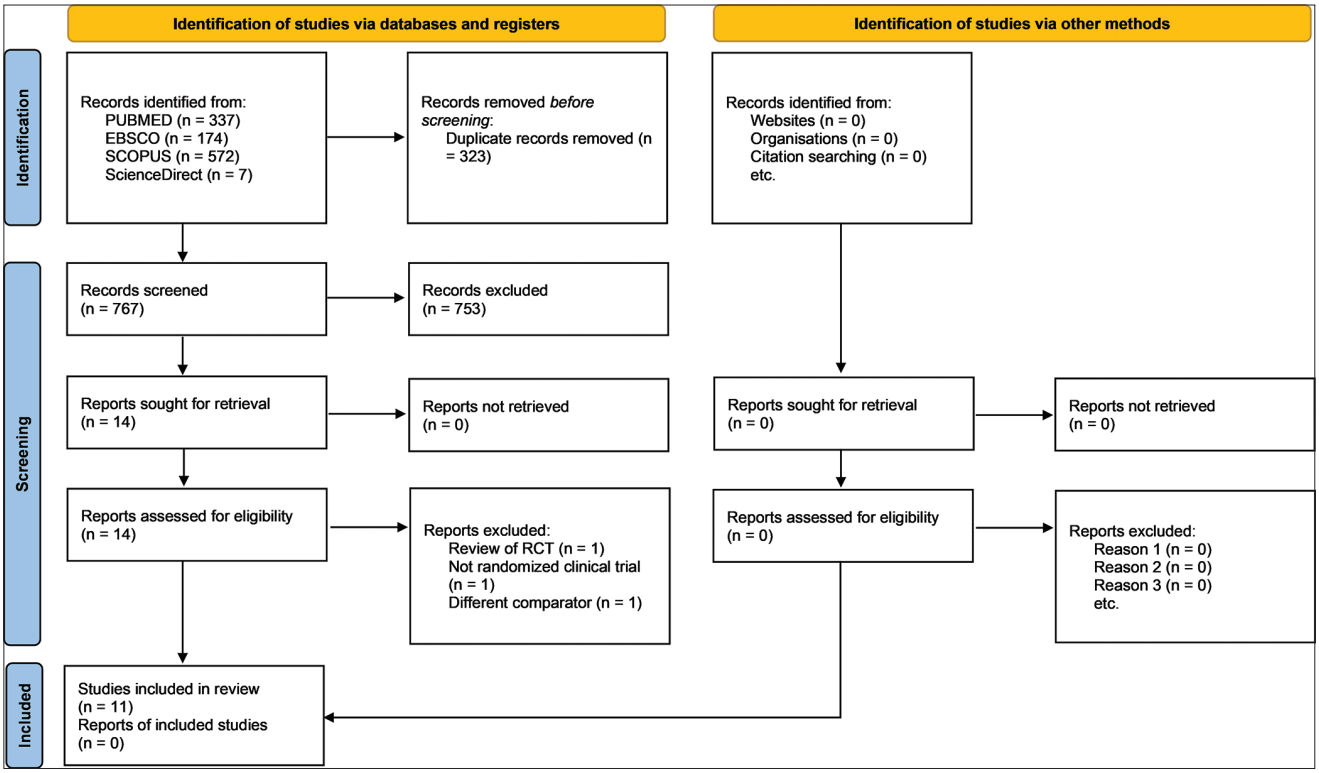

Figure 1: Flowchart of literature searching based on PRISMA 2020 diagram for systematic review.

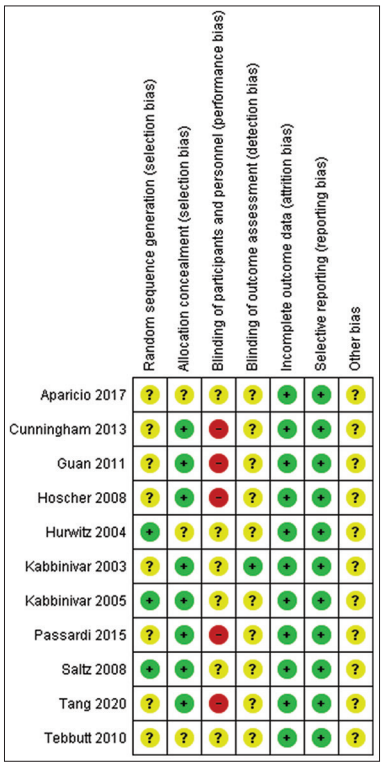

Figure 2: Risk of bias summary for each included study

Cochrane risk of bias assessment

All of 11 selected studies were assessed for risk of bias using the Cochrane Risk of Bias Tool for RCT (Figure 2). More than half of the studies did not describe the randomization sequence method. Furthermore, information on allocation concealment in 3 studies were unclear. Several studies had high bias in blinding of participants and personnel, which were studies by Cunningham *et al.*, Guan *et al.*, Hoscher *et al.*, Passardi *et al.*, and Tang *et al.*, as some of those studies were open-labeled trial, while others were unclear. However, all of the studies were assessed as low bias in reporting and outcome data. All studies follow intention to treat analysis.

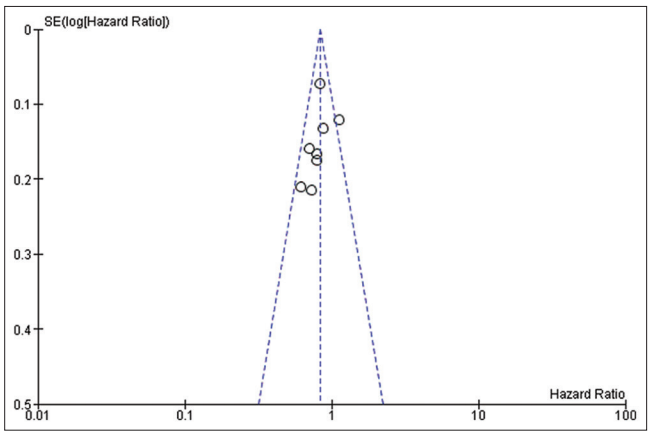

Figure 3: Funnel plot of overall survival analysis

Characteristics of included studies

From literature searching, 11 studies were included (Table 1). Studies were grouped into four subgroups for further analysis based on the chemotherapy regiment used. Studies by Tang *et al*. and Saltz *et al*. were based on oxaliplatin containing regiments [11], [12]. Studies by Kabbinavar *et al.*, Tebbutt *et al*., and Cunningham *et al*. were

capecitabine or fluorouracil/leucovorin (FU/LV) containing regiments [13], [14], [15], [16]. Irinotecan containing regiments study include studies by Guan *et al.* and Hurwitz *et al.*, while studies by Passardi *et al.*, Aparicio *et al.*, and Hochster *et al.* contained other unspecified regiments [17], [18], [19], [20], [21]. From 11 studies, 9 studies were included in meta-analysis for efficacy (8 studies for OS analysis and 9 studies for PFS analysis). Studies which were not included in meta-analysis due to incomplete HR data for calculation in Revman 5.4 were studies by Kabbinavar *et al*. OS, Hurwitz *et al*., and Hochster *et al*. [13], [18], [21]. All studies were RCT, and primary endpoints generally include OS or PFS. The funnel plot showed no indication of publication bias (Figures 3 and 4).

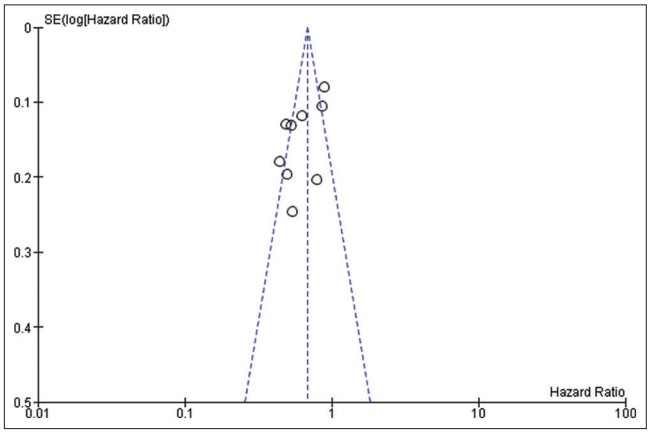

Figure 4: Funnel plot of progression-free survival analysis

Analysis of effect in bevacizumab containing therapy on OS

Results from a meta-analysis of all studies regardless of chemotherapy regiments showed a significant increase of OS in treatments with bevacizumab and chemotherapy compared with chemotherapy alone without heterogeneity (HR 0.83, CI 95% 0.74–0.93; p 0.002; I^2 = 29%) as shown in Figure 5.

In separate subgroup analysis (Figure 6) based on chemotherapy regiments, all chemotherapy regiments (oxaliplating containing regiments, FU/LV containing regiments, and irinotecan containing regiments) showed a significant increase in OS, with the exception of unspecified chemotherapy regiments by Passardi *et al*. and Aparicio *et al*. [19], [20]. Overall and subgroup analysis showed homogeneity of significant results across groups.

Analysis of effect in bevacizumab containing therapy on PFS

Results from meta-analysis (Figure 7) on PFS showed similar results with OS, which was a significant increase in PFS in adding bevacizumab to chemotherapy (HR 0.62, 95% CI 0.51–0.75; p < 0.0001). However, the results were heterogeneous (I^2 = 78%).

Further subgroup analysis showed significant results in FU/LV containing regiments (HR 0.57, 95% CI 0.49–0.66; p < 0.01) with homogeneous results in FU/LV containing regiments (I^2 = 0%). Only one study assessed irinotecan containing regiments (HR 0.44, 95% CI 0.31–0.62; p < 0.01). Nonsignificant results were observed in oxaliplatin-containing regiments and unspecified chemotherapy regiments (Figure 8). Through overall and subgroup analysis, significant and consistent increase in PFS was found in capecitabine or FU/LV containing regiments.

Discussion

Our study analyzed the previous 11 RCT studies through literature searching, in which 9 studies were included in meta-analysis of efficacy (OS and PFS), and all studies were included in safety analysis. A meta-analysis of efficacy was further divided into subgroups to test measure of effects between subgroup and heterogeneity.

Despite advances in chemotherapy regiment, surgical resection, and molecular-targeted therapy, most patients with mCRC still have a poor prognosis [7], [15]. Bevacizumab is a humanized

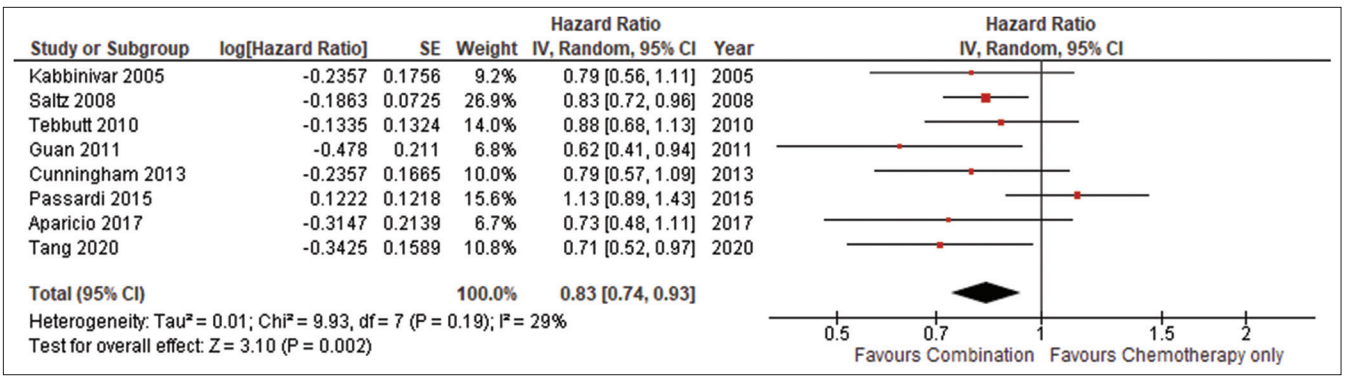

Figure 5: Comparative results of overall survival between bevacizumab plus chemotherapy against chemotherapy alone in all chemotherapy regiments

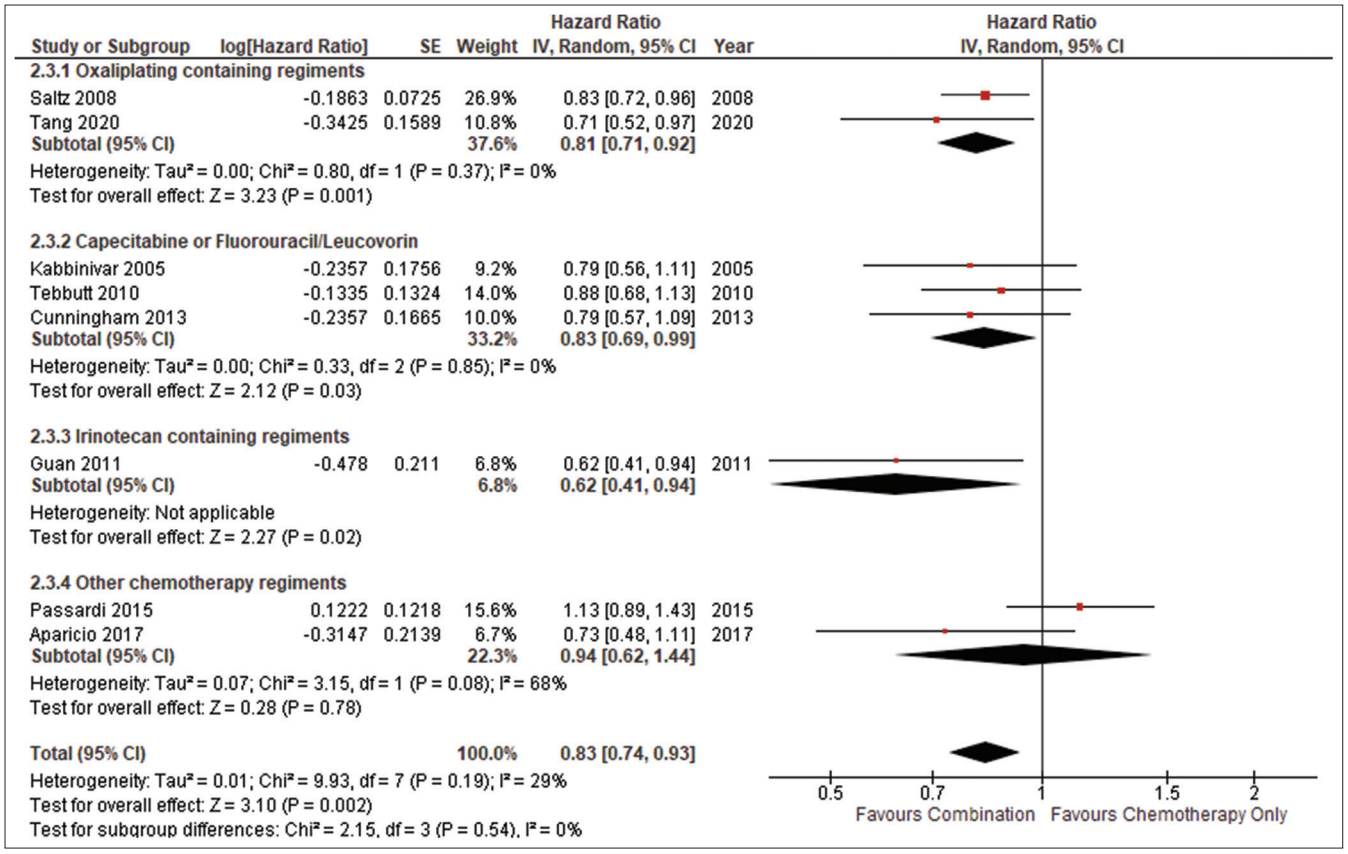

Figure 6: Comparative results of overall survival between bevacizumab plus chemotherapy against chemotherapy alone in all chemotherapy regiments

monoclonal antibody against VEGF-A. The binding of VEGF-A prevents the activation of angiogenesis through VEGF-A signaling, thus reducing tumor blood supply and normalize tumor vasculature for enhanced cytotoxic treatment [9], [22]. Bevacizumab also inhibits angiogenesis-independent effects of VEGF signaling, which include cancer cell proliferation, stemness promotion, and immunosuppression. However, the exact mechanism of action of bevacizumab is not completely understood [9]. Upregulation of VEGF and PIGF is associated with advanced metastasis in certain cancers, including colorectal cancer [22], [23]. mCRC tissues highly express VEGF and VEGF receptor, thus making it a strategic target for bevacizumab treatment [24].

The current mCRC guideline by (the National Comprehensive Cancer Network [NCCN]) in 2021 also recommended the use of bevacizumab as primary treatment in mCRC, preferably combined with chemotherapy of oxaliplatin containing regiments, such as FOLFOX, CAPOX, and also irinotecan containing regiments such as FOLFIRI [25]. Previous meta-analysis, we found also conducted a study on the effect of adding bevacizumab to chemotherapy in mCRC therapy [26, [27], [28], [29].

Our meta-analysis showed significant increase in OS (HR 0.83, CI 95% 0.74–0.93; p = 0.002; I^2 = 29%) and PFS (HR 0.62, 95% CI 0.51–0,75; p < 0.0001, I^2 = 78%) without heterogeneity in OS. Further subgroup

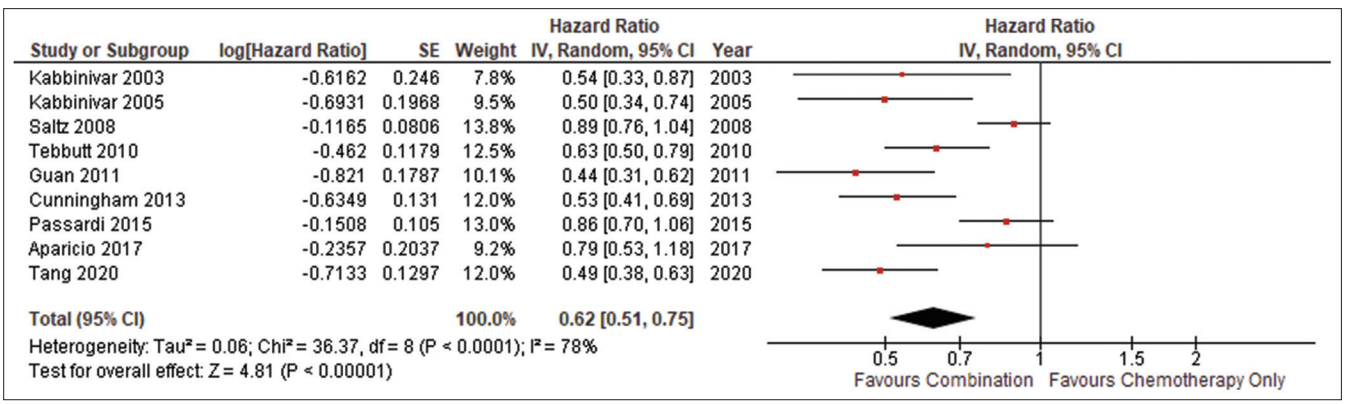

Figure 7: Comparative results of overall survival between bevacizumab plus chemotherapy against chemotherapy alone based on chemotherapy regiments

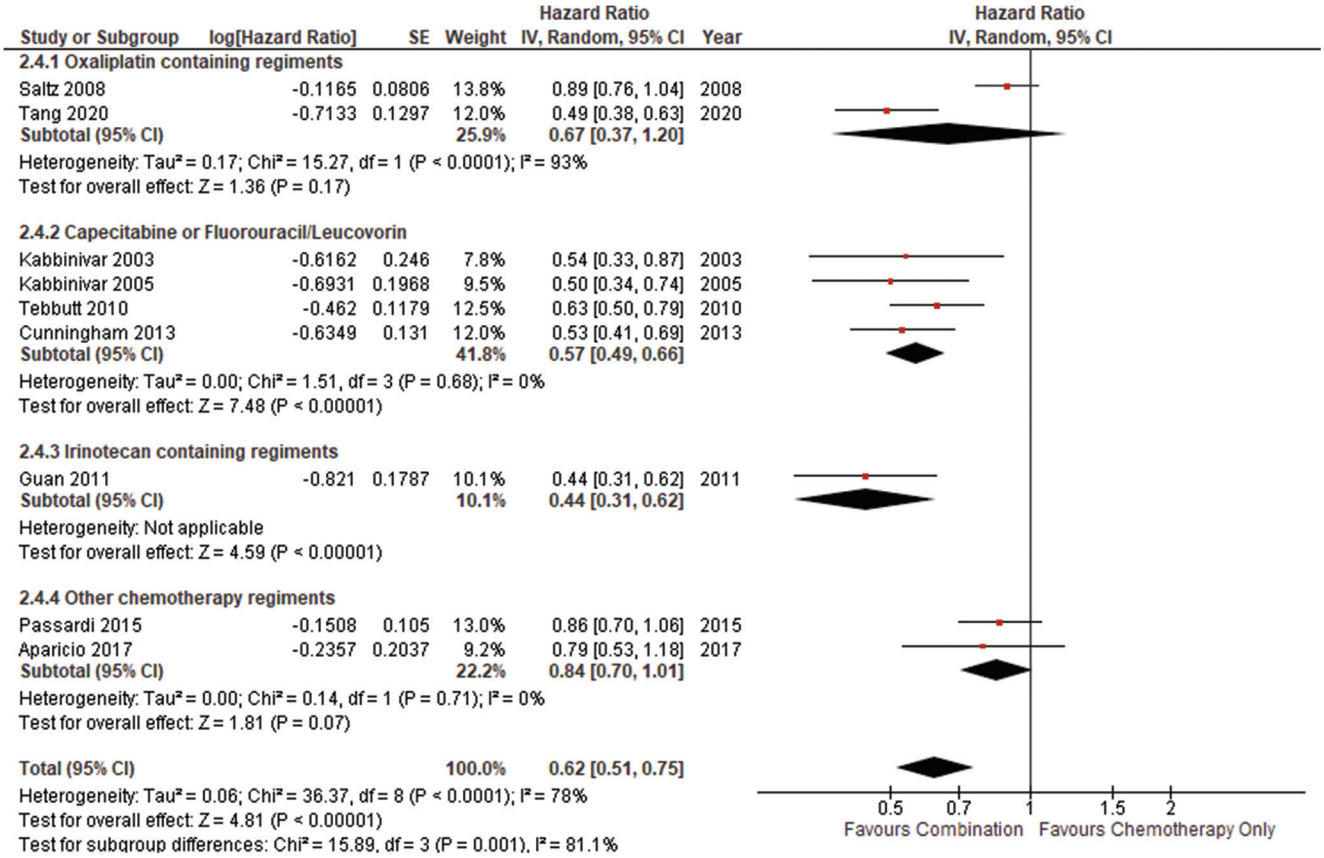

Figure 8: Comparative results of progression free survival between bevacizumab plus chemotherapy against chemotherapy alone based on chemotherapy regiments

analysis showed that while all subgroups showed significant results in OS, only capecitabine or FU/LV containing regiments and irinotecan-based regiments showed significant results in both OS and PFS without heterogeneity.

Although only one study fell into irinotecan containing regiments by Guan *et al*. (2011), the result was the most significant in OS (HR 0.62, 95% CI 0.41–0.94, p = 0.02) and PFS (HR 0.44, 95% CI 0.31–0.62, p < 0.01) [17]. However, the baseline characteristics should be noted in this single irinotecan-based study and used cautiously. The mean age in this study was 53 and 50 years old in bevacizumab and control groups, compared to ≥60 years old in other studies in other regiments. Based on previous studies, the age has been shown to impact the prognosis of mCRC. Age of ≥60 years old has a significant higher risk in mortality (HR 1.61, 95% CI 1.37–1.89, p < 0.01) compared to <60 years old in explorative analysis by Rumpold *et al.*, while population-based analysis by Wang *et al*. showed similar results in population ≥64 years old (HR 1.64 95% CI 1.59–1.69, p < 0.01) [30], [31].

Other baseline characteristics between irinotecan-containing regiments and other chemotherapy were similar. Other parameters, such as performance status (measured as eastern cooperative oncology group [ECOG]), number of organ and location of metastasis, mutation status, and other parameters had been shown to significantly affect prognosis and survival of mCRC [30], [31], [32]. All studies included in this meta-analysis provided ECOG as performance status in baseline characteristics, and ECOG score in all studies were similar (ECOG 0 50%–60%, ECOG 1 30%–40%, ECOG 2 and 3 < 10%). Based on these data, the heterogeneity in some regiments and superiority of results in subgroup analysis were not likely to be affected by difference in baseline characteristics, except the age difference in a study by Guan *et al*. (2011) as mentioned above.

Regiments containing oxaliplatin or irinotecan have been the main recommendation in most recent NCCN guidelines, with or without bevacizumab, in initial therapy of mCRC [25]. However, our subgroup analysis showed consistent significant results only in irinotecan-containing regiments and FU/LV containing regiments, while oxaliplatin containing regiments showed heterogeneity and non-significant results in PFS. Regarding irinotecan, previous trials also demonstrated that irinotecan combined with FU or LV regiments (IFL or FOLFIRI) demonstrated significant increase in survival, time to progression, and other parameters [33], [34]. Based on these data, irinotecan or FU/LV containing regiments might be the preferred chemotherapy to be combined with bevacizumab in mCRC. The authors also suggest the use of bevacizumab in a younger age group, preferably aged ≤60 years old, as better results were shown in irinotecan-based study by Guan *et al*. shown above, although more studies need to be conducted in those age groups [17].

Table 1: Characteristics of study included in systematic review and meta-analysis evaluating bevacizumab plus chemotherapy as first line therapy in metastatic colorectal cancer patients

Study	Study design	n	Age	Chemotherapy regiment	Primary endpoint	OS (months, median)	PFS (months, median)	Analysis included
Oxaliplatin containing regiments								
Tang *et al.* (2020)	RCT, phase not specified	241	58 (29–75) versus 59 (24–72)	mFOLFOX6	Conversion rate	25.7 versus 20.5 (HR, 0.71 [95% CI, 0.52–0.97], P < 0.031)	9.5 versus 5.6 (HR, 0.49 [95% CI, 0.38–0.65], P < 0.001)	Efficacy and safety analysis
Saltz *et al.* (2008)	Phase III randomized control trial	1400	60 (18–83) versus 60 (18–86)	FOLFOX4 or XELOX	PFS	21.3 versus 19.9 (HR 0.83 [97.5% CI, 0.72–0.95], P = 0.0023)	9.4 versus 8.0 (HR 0.89 [97.5% CI 0.76–1.03], P = 0.77)	Efficacy and safety analysis
Capecitabine or Fluorouracil/Leucovorin containing regiments								
Kabbinivar *et al.* (2003)	Phase II randomized controlled trial	104	N/A	FU/LV	PFS	N/A	7.4 versus 5.2 (HR 0.54)	Efficacy (PFS only) and safety analysis
Kabbinivar *et al.* (2005)	Phase II randomized controlled trial	209	71.3 versus 70.7 (mean)	FU/LV	OS	16.6 versus 12.9 (HR 0.79 (95% CI, 0.56–1.10), *P* = 0.16)	9.2 versus 5.5 (HR 0.50; 95% CI, 0.34– 0.73, *P* = 0.0002)	Efficacy and safety analysis
Tebbutt *et al.* (2010)	Phase III randomized control trial	313	67 (32–85) versus 69 (37–86)	Capecitabine	PFS	18.9 versus 18.9 (HR 0.875 (95% CI, 0.675–1.134), *P* = 0.314)	8.5 versus 5.7 (HR 0.63 (95% CI 0.50–0.79), *P* = 0.03)	Efficacy and safety analysis
Cunningham *et al.* (2013)	Phase III randomized open-label trial	280	76 (70–87) versus 77 (70–87)	Capecitabine	PFS	20.7 versus 16.8 (HR 0.79, 95% CI: 0.57–1.09, P = 0.18)	9.1 versus 5.1 (HR 0.53, 95% CI 0.41–069, P < 0.0001)	Efficacy and safety analysis
Irinotecan containing regiments								
Guan *et al.* (2011)	Phase III randomized open-label trial	203	53 (23–77) versus 50 (22–72)	mIFL	PFS	18.7 versus 13.4 (HR, 0.62; 95% CI, 0.410.95; P = 0.014)	8.3 versus 4.2 (HR), 0.44; 95% CI, 0.310.63; P < 0.001)	Efficacy and safety analysis
Hurwitz *et al.* (2004)	Phase III randomized controlled trial	813	59.5 versus 59.2 (mean)	IFL	OS	20.3 versus 15.6 (HR 0.66 [p < 0.001])	10.6 versus 6.2 (HR 0.62 [p = 0.001])	Safety analysis
Other unspecified chemotherapy regiments								
Passardi *et al.* (2015)	Phase III randomized control trial	370	66 (34–83) versus 66 (33–82)	FOLFOX4 or FOLFIRI	PFS	20.8 versus 21.3 (HR 1.13 [95% CI, 0.89–1.43], P = 0.317)	9.6 versus 8.4 (HR 0.86 (95% CI 0.70–1.07), P = 0.182)	Efficacy and safety analysis
Aparicio *et al.* (2017)	Phase II randomized non-comparative trial	91	80.9 (75.2–88.3) versus 80.1 (75.0–90.6)	Simplified LV5FU2, modified FOLFOX6, modified FOLFIRI	Tumor control	21.7 versus 19.8 (HR 0.73, 95% CI: 0.48–1.11)	9.7 versus 7.8 (HR 0.79, 95% CI 0.53–1.17)	Efficacy and safety analysis
Hoscher *et al.* (2008)	Open-label randomized controlled trial	360	64 versus 62 9 (mFOLFOX6), 57 versus 62 (bFOL), 62 versus 62.5 (CapeOX)	mFOLFOX6, bFOL, CapeOx	AE	23.7 versus 18.2 (HR not available)	9.5 versus 7.2 (HR not available)	Safety analysis

OS: Overall survival, PFS: Progression free survival, AE: Adverse events, FOLFOX: Leucovorin, fluorouracil, oxaliplatin, XELOX: Capecitabine plus oxaliplatin, FU: Fluorouracil, LV: Leucovorin, IFL: Irinotecan, fluorouracil, leucovorin, CAPIRI: Capecitabine and irinotecan, FOLFIRI: Leucovorin plus fluorouracil plus irinotecan, CapeOx: Capecitabine oxaliplatin, bFOL: Oxaliplatine plus 5 fluorouracil plus folinic acid, RCT: Randomized controlled trial, CI: Confidence interval, HR: Hazard ratio, N/A: Not available.

Although the addition of bevacizumab in improving survival and PFS is promising, the adverse events as consequences of adding bevacizumab need to be analyzed. Bevacizumab-related adverse effects are increased in patients treated with all types of chemotherapy regimens included in this meta-analysis. Commonly observed adverse effects of bevacizumab include hemorrhage, hypertension, proteinuria, and thromboembolism [26], [35], [36]. Hypertension and proteinuria are known to be the most common adverse effects in the studies we included. Hemorrhage and thromboembolism could be life-threatening, and the risk must be put to attention despite the low incidence. Thromboembolism must be warned in trousseau's syndrome and elderly [37]. Gastrointestinal perforation risk is also increased with the addition of bevacizumab [38]. Previous meta-analysis specifically evaluating safety profile of bevacizumab in advanced cancer patients showed that bevacizumab had slightly higher rates of Grade 3–4 adverse events compared with control [39]. Despite these possible adverse effects, a meta-analysis showed that patients treated with bevacizumab have no difference in the quality of life compared with patients treated with chemotherapy alone [40]. A study which specifically examine bevacizumab toxicity also showed that the adverse events were manageable, with recommendations of using irinotecan-based regiment (preferably FOLFIRI) [41]. Hence, with personalized benefit-risk assessment, the combination of bevacizumab and chemotherapy could be an effective regimen with minimal toxicity.

Colorectal cancer is the fourth-most common cancer in the world, and in about 20%–25% of cases already have metastasis at the time of diagnosis. Patients with Stage IV colorectal cancer (metastasis) only have 5-year survival of 12% [42], [43]. From the current data, the use of bevacizumab in addition to chemotherapy improves OS and PFS. However, the availability and further cost-effectiveness analysis of bevacizumab need to be analyzed based on each country or region. The difference in median OS and PFS of around a few months between the addition of bevacizumab and chemotherapy alone need to be taken into account as well. This is especially difficult in developing countries with low healthcare resource. Indeed, a cost-effectiveness study by Goldstein *et al.* in the year 2017 showed a lack of cost0effectiveness from bevacizumab in the U.S., U.K., Canada, Australia, and Israel [44]. For developing countries, the cost-effectiveness may be worse.

Through all risk and benefit mentioned above and results from our meta-analysis, the authors suggest the addition of bevacizumab with chemotherapy in untreated mCRC, preferably in irinotecan or FU/LV chemotherapy regiments, preferable in younger age group.

Conclusion

Bevacizumab combined with chemotherapy for first-line treatment of untreated mCRC showed better OS and PFS when compared with using chemotherapy only. Irinotecan and fluorouracil or leucovorin-based chemotherapy regimens were the most consistent and significant regimens to be combined with bevacizumab in both OS and PFS; hence, it is recommended to combine bevacizumab with those chemotherapy regiments.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

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