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Original Article

The efficacy and safety of adding bevacizumab to cetuximab- or panitumumab-based therapy in the treatment of patients with metastatic colorectal cancer (mCRC): a meta-analysis from randomized control trials

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Abstract: Objective: To estimate the efficacy and safety of adding bevacizumab to cetuximab- or panitumumab-based therapy in the treatment of patients with metastatic colorectal cancer (mCRC), using a meta-analysis of randomized controlled trials. Methods: A literature search for randomized clinical trials (RCTs) was performed through Pubmed, Embase, and Web of Science (up to May 22, 2014). The outcome measures were progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events. Two investigators identified eligible studies and extracted data independently. The quality of the included studies was assessed by the Jadad score. Hazard ratios (HR), risk ratio (RR), and 95% confidence intervals (CIs) were calculated and pooled. Results: A total of 4 RCTs with 2069 patients were included in this meta-analysis. The addition of bevacizumab to cetuximab- or panitumumab-based therapy did not significantly prolonged PFS, when compared with antibody alone. The subgroup analysis of adding bevacizumab to cetuximab-based therapy also suggested no significant benefit in PFS or in OS. Patients who received the combined therapy did not have a higher ORR (RR = 0.98, 95% CI: 0.89-1.07; P = 0.608). The incidence of grade 3/4 adverse events was not significantly higher in the bevacizumab and cetuximab/panitumumab group. Conclusion: The addition of bevacizumab to cetuximab- or panitumumab-based therapy did not improve PFS and OS resulting in better ORR. Thus, the combined therapy of bevacizumab with cetuximab or panitumumab is not recommended for the treatment of mCRC. However, larger scale RCTs are needed to confirm these findings.

Keywords: Olorectal cancer, bevacizumab, cetuximab, panitumumab, VEGF, EGFR, meta-analysis

Introduction

Colorectal cancer (CRC) ranks the second most common cancer in men and third in women worldwide [1]. Radical surgery is the initial treatment for CRC [2-4], however, about 40-60% patients had disease recurs or metastases owning to the presence of micrometastases at the time of surgery [5, 6]. Over the past decades, with the introduction of new active drugs, including multi-agent chemotherapy and biologic agents, the median overall survival (OS) of patients with mCRC has been improved greatly [7, 8].

Fluoropyrimidines (e.g., fluorouracil and capecitabine), irinotecan, and oxaliplatin are the standard cytotoxic drugs used in treating metastatic colorectal cancer (mCRC) [9, 10]. Bevacizumab, a humanized antibody against vascular endothelial growth factor (VEGF), has been shown an improvement in OS and progression-free survival (PFS), when combined with chemotherapy in the treatment of mCRC [11-13]. Panitumumab and cetuximab, antibodies against epidermal growth factor receptor (EGFR), also have activity in the treatment of mCRC both as monotherapy or in combination with chemotherapy [14-17].

The preclinical studies have suggested that the combination of anti-VEGF and anti-EGFR agents have synergy for the treatment of mCRC [18-21]. And in a randomized phase II trial, patients treated with bevacizumab and cetuximab had a promising objective response rate (ORR) of 20%

[22]. However, in another phase 3 trial [23], which assessed the effect of adding cetuximab to a combination of bevacizumab and Fluoropyrimidine-based chemotherapy for mCRC, the results indicated a detrimental effect that, these combinations had a significantly shorter PFS, when compared with these combinations without cetuximab. Therefore, we conducted this meta-analysis to estimate the efficacy and safety of adding bevacizumab to cetuximab- or panitumumab-based therapy in the treatment of mCRC.

Methods and material

Search strategy

We conducted this meta-analysis of randomized controlled trials (RCTs) in accordance with the preferred reported items for systematic reviews and meta-analyses guidelines [24]. We searched all relevant randomized controlled trials, which compared the effect of combination of anti-VEGF and anti-EGFR agents with antibody alone in mCRC patients. Two authors (Zixin Yang and Yingqian Lv) identified the database of Pubmed, Embase, and Web of Science for RCTs published before May 22, 2014. Keywords used for the searching process were as follows: bevacizumab, cetuximab, panitumumab, metastatic colorectal cancer, chemotherapy. The search had no language limitation, but confined to studies conducted on human subjects. The reference lists of included studies and related publications were screened iteratively until no new potential citations could be found. Abstracts and unpublished reports were not included. When the same population was included in several studies, only the most recent or complete study was included in this meta-analysis.

Inclusion and exclusion criteria

We included studies when the following inclusion criteria were met: (1) randomized controlled trials; (2) adult patients were old than 18 years diagnosed with colorectal cancer; (3) randomized allocation to the treatment group in which patients receiving anti-VEGF and anti-EGFR agents, or the control group in which patients receiving with just one targeted drug; (4) reporting the data on progression-free survival (PFS), overall survival (OS), and objective response rate (ORR). Exclusion criteria included age < 18 years old, single arm study, or randomized controlled trials with dual targeted drugs in both arms.

Data extraction

The following data were extracted onto standardized forms by two independently reviewers: (1) basic information of the included studies, such as the name of first author, country, publication year; (2) characteristics of the enrolled patients, such as age, number, drug administration; (3) information of the study design, such as type of blinding, type of controls, the methods for randomization allocation; (4) survival outcomes, such as PFS, OS, ORR, and adverse events. For the studies without directly available data in the paper, we firstly attempted to contact the authors for this information. If this strategy failed, we used the method described by Tierney to estimate the HR with 95% from the Kaplan-Meier curves [25]. Disagreements between the two authors were resolved by discussion and consensus.

Quality assessment

The methodological quality of each trial was assessed using the Jadad Scale [26], which consists of three items describing randomization (0-2 points), blinding (0-2 points), and drop-outs and withdrawals (0-1 points) in reported randomized controlled trials. A score of 1 is obtained for each of the points described. A further point is obtained where the method randomization and/or blinding is given and is appropriate; whereas it is inappropriate a point is deducted. Higher scores indicate better reporting. Studies with Jadad score ≥ 3 points are said to be of high quality [27].

Statistical analyses

The summary estimates were generated using a fixed-effect model (Mantel-Haenszel method) [28] or random-effect model (DerSimonian-Laird method) [29], depending on the absence or presence of heterogeneity. I^2 statistic, which quantitatively measured the degree of inconsistency across studies, was used to estimate the heterogeneity across the studies. $I^2 \geq 50\%$ indicates substantial heterogeneity, and thus a random-effect model is used to pool the results; otherwise, a fixed-effect model is used. For time-to-event variables, including PFS and

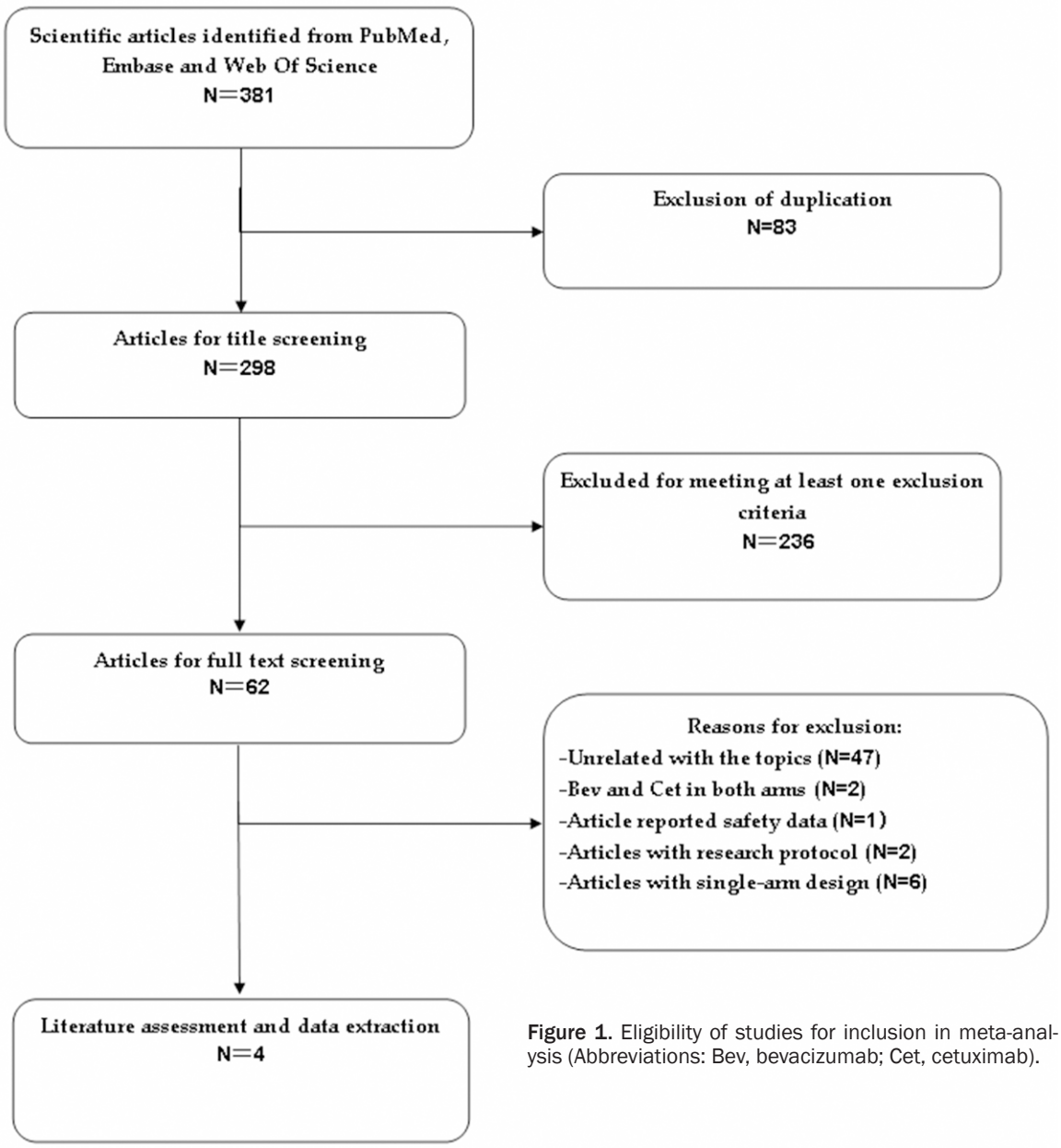

Figure 1. Eligibility of studies for inclusion in meta-analysis (Abbreviations: Bev, bevacizumab; Cet, cetuximab).

OS, hazard ratio (HR) with 95% confidence interval (95% CI) was calculated for each study; for dichotomous variables, including ORR, risk ratio (RR) with 95% CI was calculated for each study. HR less than 1, or RR more than 1 is a positive index of treatment effect, which indicates that the combination of anti-VEGF and anti-EGFR agents is better than the antibody alone. The publication bias was evaluated by using the Begg and Egger tests [30, 31]. A *P* value less than 0.05 was judged as statistically significant, except where otherwise specified. All statistical analyses were conducted by using of STATA software version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Identification of eligible studies

381 colorectal cancer-related citations from Pubmed, Embase, and Web of Science, were identified by the initial literature search. After the first excluding duplicate records (n = 83), 236 was excluded after screening of title/abstract, leaving 62 for full text information review. Of these 62 studies, 11 were excluded

Table 1. Characteristics of the studies included in the meta-analysis

Study	Treatment group	No. of patients	Median age (range)	Male/ Female	WHO performance status (0/1/2+)	Number of metastatic organs (1/2+)	Median follow up (mon)	Jadad score
Efrat Dotan [43]	Capecitabine,oxaliplatin, cetuximab,bevacizumab	12	59 (45-78)	8/4	3/9/0	9[a]/3[b]	18.14	4
	Capecitabine,oxaliplatin, cetuximab	11	58 (42-74)	10/1	10/1/0	9[a]/2[b]	33.53	
J.Randolph Hecht [44]	Pmab-Bev	528	61 (28-88)	289/239	321/207/0	250/278	20.7	3
	Bev	525	62 (22-89)	309/216	313/212/0	252/273	20.5	
Leonard Saltz [45]	FOLF-CB	123	63.2 (34.9-86.5)	73/50	59/64/0	100/23	21.3	3
	mFOLFOX6-B	124	61.2 (31.8-86.9)	70/54	68/56/0	102/22	19.5	
Jolien Tol [23]	CBC	368	62 (33-80)	233/135	240/126/2	163/205	23	4
	CB	368	62 (27-83)	205/163	219/149/0	167/201	23	

Abbreviations: Pmab, panitumumab; Bev, bevacizumab; mFOLFOX6-B, bevacizumab-5-fluorouracil, leucovorin (folinic acid), oxaliplatin; FOLF-CB, 5-fluorouracil, oxaliplatin, leucovorin, cetuximab, bevacizumab; [a]data from 1-2 metastatic sites; [b]data from > 3 metastatic sites.

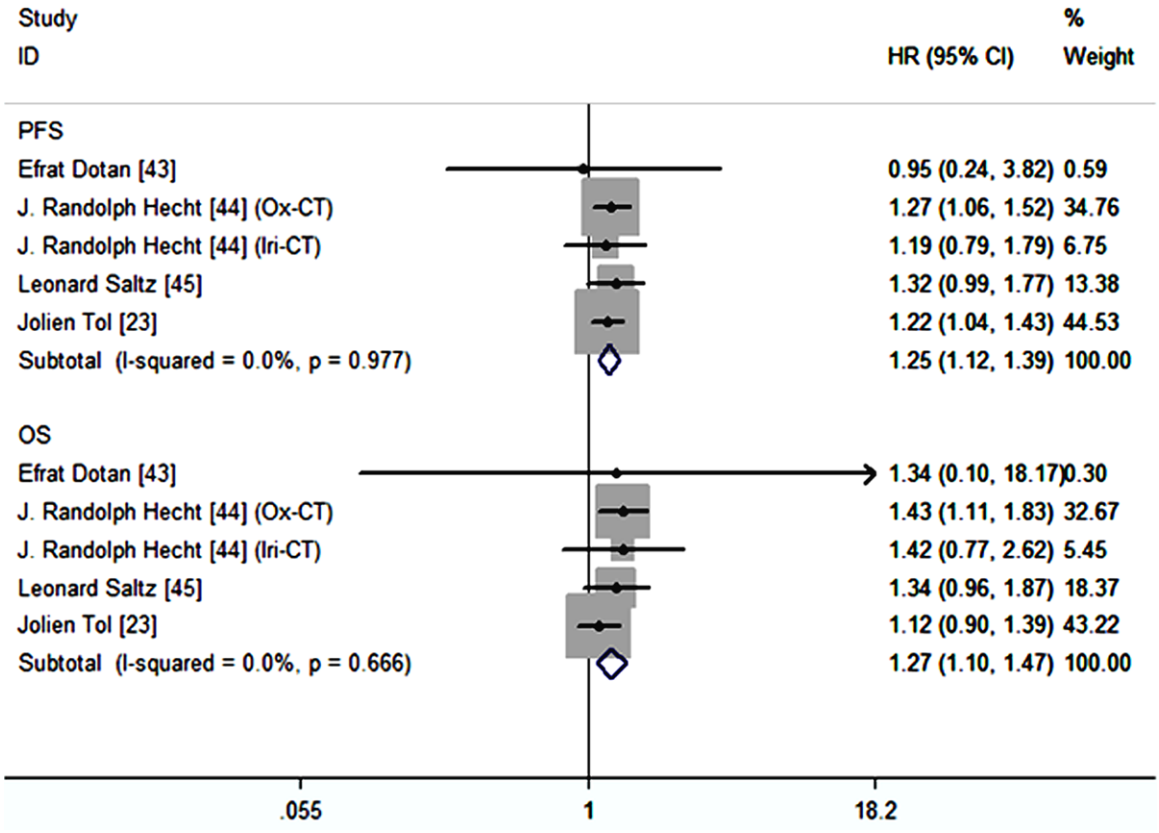

Figure 2. Meta-analysis exploring the effect of addition of bevacizumab to cetuximab- or panitumumab-based therapy on progression-free survival (PFS) and overall survival (OS).

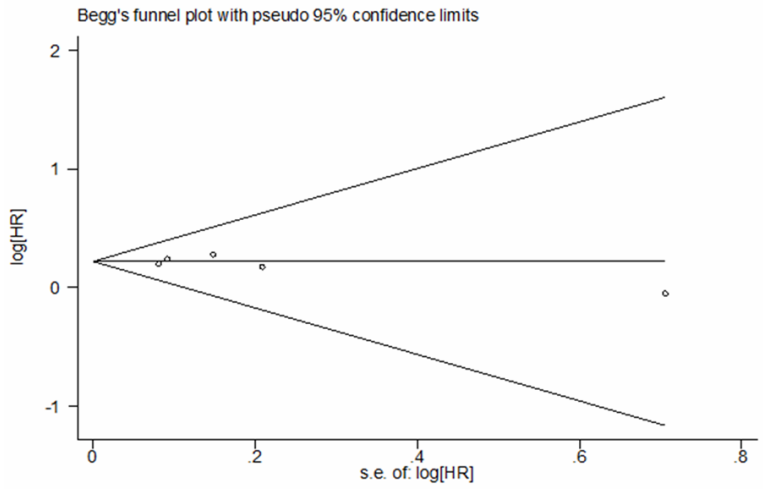

Figure 3. Test for publication bias for HR of progression-free survival (PFS).

for the reasons as following: two studies with bevacizumab and cetuximab in both arms [32, 33]; six studies with single-arm study design [34-39]; two studies were research protocols [40, 41]; one study only provided safety data of bevacizumab and cetuximab [42]. Finally, the remaining 4 RCTs [23, 43-45] that met our inclusion criteria were included in the pooled analysis. The flow chart of search strategy is shown in **Figure 1**.

Characteristics of eligible studies and quality assessment

The baseline characteristics of the included studies are listed in **Table 1**. The number of patients ranged from 33 to 1053. Of the 4 included studies, three were conducted in USA [43-45], and the rest one in Netherlands [23]. In three of the included studies [23, 43, 45], patients in the intervention group were administered bevacizumab and cetuximab. While in the rest one, patients were administered bevacizumab and pannitumumab [44]. The chemotherapeutic agents varied greatly, but most of them were oxaliplatin-based. The overall response rate ranged from 45.9% [44] to 54.5% [43]. The number of

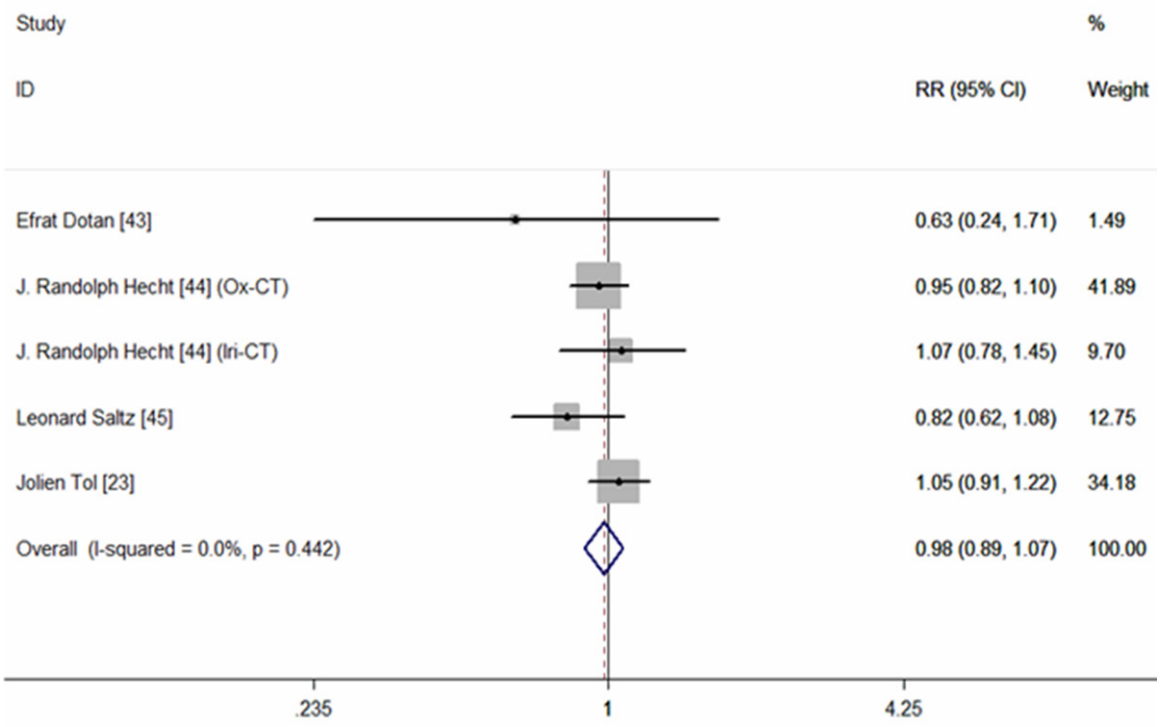

Figure 4. Meta-analysis exploring the effect of addition of bevacizumab to cetuximab- or panitumumab-based therapy on objective response rate (ORR).

patients that were allocated randomly into intervention group and control group, were 1031 and 1038, respectively. The Jadad score of the included studies ranged from 3 to 4.

PFS

PFS data were reported in all four studies [23, 43-45]. Meta-analysis of four studies using a fixed-effects model showed that the addition of bevacizumab to cetuximab- or panitumumab-based therapy did not significantly improve PFS (HR = 1.25, 95% CI: 1.12-1.39; P = 0.00) (**Figure 2**) compared with antibody alone, with no heterogeneity between the studies (I^2 = 0.0%, P = 0.977). The Begg's test (Z = 0.24, P = 0.806) and Egger's test (Z = -0.71, P = 0.529) (**Figure 3**) suggested that there was no significant publication bias. In the subgroup analysis of bevacizumab combination, the results showed no significant survival advantage in PFS (HR = 1.24, 95% CI: 1.08-1.42; P = 0.001) when bevacizumab was combined with cetuximab in the treatment of mCRC.

We also performed sensitivity analysis to identify the A trial conducted by Efrat Dotan [43] enrolled 12 patients in the combination group and 11 patients in the control group. We excluded this study for the pooled analysis, and the results didn't significantly change (HR = 1.25, 95%: 1.12-1.39; P = 0.000).

OS

Four studies [23, 43-45] reported the data of OS in mCRC patients. The pooled analysis using a fixed-effects model showed that the addition of bevacizumab to cetuximab- or panitumumab-based therapy did not significantly improve OS (HR = 1.27, 95% CI: 1.10-1.47; P = 0.001) (**Figure 2**) compared with antibody alone, with no heterogeneity between these studies (I^2 = 0.0%, P = 0.666). The Begg's test (Z = -0.24, P = 1.000) and Egger's test (Z = 0.53, P = 0.634) suggested that there was no significant publication bias.

In the subgroup analysis of bevacizumab combination, the results showed that combination of bevacizumab with cetuximab did not have survival advantage in OS (HR = 1.18, 95% CI: 0.99-1.42; P = 0.071), compared with antibody alone. Exclusion of the study conducted by Efrat Dotan [43] yielded similar results (HR = 1.27, 95% CI: 1.10-1.47; P = 0.001).

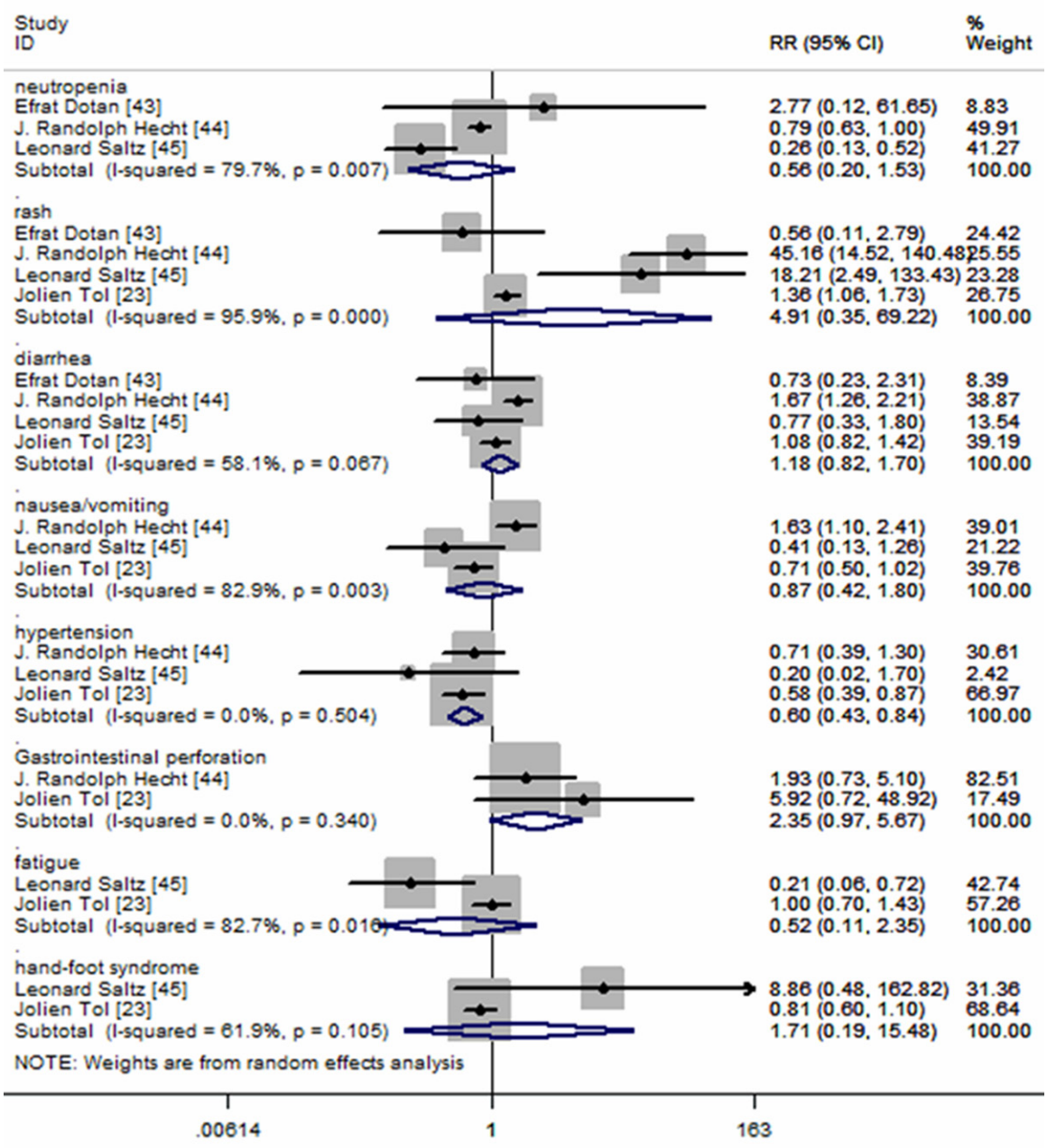

Figure 5. Meta-analysis exploring the risk ratio of Grade 3/4 adverse events in patients with addition of bevacizumab to cetuximab- or panitumumab-based therapy versus antibody alone.

ORR

Four studies [23, 43-45] provided ORR data in mCRC patients. The pooled analysis using a fixed-effects model showed that the addition of bevacizumab to cetuximab- or panitumumab-based therapy did not significantly increase ORR (RR = 0.98, 95% CI: 0.89-1.07; P = 0.608) (**Figure 4**) compared with antibody alone, with no heterogeneity between the studies (I^2 = 0.0%, P = 0.442). The Begg's test (Z = 0.73, P = 0.462) and Egger's test (Z = -1.71, P = 0.186) suggested that there was no significant publication bias.

Adverse events

Four studies reported the data of adverse events [23, 43-45]. The pooled analysis using a random-effects model showed that the incidence of grade 3/4 rash (RR = 4.91, 95% CI:

0.35-69.22; P = 0.239; I^2 = 95.9%, P = 0.000), neutropenia (RR = 0.56, 95% CI: 0.20-1.53; P = 0.258; I^2 = 79.7%, P = 0.522), diarrhea (RR = 1.18, 95% CI: 0.82-1.70; P = 0.363; I^2 = 58.1%, P = 0.068), nausea/vomiting (RR = 0.87, 95% CI: 0.42-1.80; P = 0.713; I^2 = 82.9%, P = 0.0.311), gastrointestinal perforation (RR = 2.35, 95% CI: 0.97-5.68; P = 0.058; I^2 = 0.0%, P = 0.00), fatigue (RR = 0.52, 95% CI: 0.11-2.35; P = 0.392; I^2 = 82.7%, P = 0.016), or hand-foot syndrome (RR = 1.04, 95% CI: 0.78-1.39; P = 0.631; I^2 = 61.9%, P = 0.105), were almost the similar in the two groups (**Figure 5**). Interestingly, the incidence of hypertension in the combination group was even lower than that in the antibody alone group (RR = 0.60, 95% CI: 0.43-0.84; P = 0.392; I^2 = 0.0%, P = 0.504).

Discussion

Our meta-analysis suggests that the combination of anti-EGFR and anti-VEGF antibodies did not improve PFS, OS or ORR in patients with mCRC, when compared with antibody alone. The dual antibodies have no significant survival advantage over single antibody (for PFS, HR = 1.25, 95% CI: 1.12-1.39; P = 0.00; for OS, HR = 1.27, 95% CI: 1.10-1.47; P = 0.001; for ORR, RR = 0.98, 95% CI: 0.89-1.07; P = 0.608). Moreover, subgroup analysis of bevacizumab in combination with cetuximab was conducted, and similar outcomes were found-no significant benefit in PFS (HR = 1.24, 95% CI: 1.08-1.42; P = 0.001), OS (HR = 1.18, 95% CI: 0.99-1.42; P = 0.071).

To the best of our knowledge, this is the first meta-analysis to assess the efficacy and safety of the combined use of anti-VEGF and anti-VGFR in the treatment of mCRC patients. Bevacizumab, is a humanized antibody against vascular endothelial growth factor (VEGF) [11-13]. Panitumumab and cetuximab, are antibodies against epidermal growth factor receptor (EGFR). The preclinical studies revealed that the combination of bevacizumab and cetuximab had synergy effects in the treatment of metastatic colorectal cancer [46, 47]. Thus, it is reasonable to apply these combinations into the clinical practice. However, in this meta-analysis, the combinations of VEGF and EGFR inhibition indicated worse rather than better survival benefits. These results might be explained by the followings: (1) The pharmacokinetic interactions between antibodies or between antibodies and chemotherapy. In the CAIRO2 [23] study, Jolien Tol et al. compared capecitabine, oxaliplatin, and bevacizumab (CB group) with the same regimen plus cetuximab (CBC group). According to a recently published study [48], hypertension, a common side induced by bevacizumab treatment, was correlated with clinical outcome in patients with colorectal cancer. Jolien Tol et al. found that hypertension was less frequent in the CBC group than in the CB group, which indicated decreased efficacy of bevacizumab in combination with cetuximab. Moreover, skin toxicity, one of the cetuximab-related adverse events, was considered as a clinical surrogate of therapeutic effectiveness for cetuximab [49]. However, for the patients with most severe cetuximab-related skin toxicity, the median PFS was not significantly longer than those treated without cetuximab. (2) The increased adverse events resulted in dose delays and reduction, and dose intensity decrease, thus increased the mortality in the combination group. The toxicity would be exacerbated by dual-pathway inhibition of EGFR and VEGF. The combination use of anti-EGFR and anti-VEGF could have increased the incidence of diarrhea and skin toxicity by inhibiting tissue repair, which would lead to dose delays and reduction. The reduced dose intensity may explain the similar response rates in the combination group and control group.

The KRAS status is regarded as a predictive marker for anti-EGFR treatment: patients with wild type KRAS tumors have longer PFS than those with mutation KRAS tumors [50-54]. In the PACCE study [44], J. Randolph Hecht et al. compared bevacizumab and chemotherapy with or without panitumumab. The authors found that the PFS among wild-type KRAS patients treated with panitumumab was even worse than those without. One possible hypotheses was postulated that the differential exposure to EGFR antibodies in later lines may have affected the survival outcomes in the wild-type KRAS group [44]. The similar results were also observed in the CAIRO2 study [23]. The combination use of bevacizumab and cetuximab with chemotherapy did not improve the survival effect in the wild-type KRAS group [23]. This observation may attributed to the negative interaction between anti-EGFR antibodies and

bevacizumab, even though the anti-EGFR antibodies could effectively inhibit the EGFR signaling [44].

This study had some limitations. First, our study is based on only four RCTs, and one of them had a relatively small sample size. It is assumed that clinical trials with small sample size would overestimate the treatment effect when compared with large trials. Thus, interpreting the conclusions should be with caution. Second, six phase II trials were excluded for lack of control groups, which may result in potential bias. Third, some of the included studies did not provide sufficient data of time-to-event outcomes for meta-analysis directly. We extracted data from survival curves using Engauge Digitizer, which may lead to inaccurate data. Finally, it was possible that some missing and unpublished data may lead to bias.

Despite of these limitations, our meta-analysis shows that combined use of anti-VEGF and anti-EGFR monoclonal antibodies in the treatment of mCRC patients has no beneficial effects in PFS, OS and ORR, and suggests that these combinations are not recommended for the treatment of mCRC in clinical practice. Much more well-designed, placebo-control clinical trials are needed to evaluate the efficacy of combination treatment.

Disclosure of conflict of interest

None.

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