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RESEARCH ARTICLE

Efficacy and toxicity of adding cetuximab to chemotherapy in the treatment of metastatic colorectal cancer: a meta-analysis from 12 randomized controlled trials

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Abstract Cetuxiamb, a monoclonal antibody against epidermal growth factor receptor (EGFR), has been used in combination with chemotherapy for patients with metastatic colorectal cancer (mCRC). However, the efficacy of combined therapies of cetuximab and different chemotherapy regimens remains controversial. Therefore, we conducted a meta-analysis to evaluate the efficacy and toxicity of adding cetuximab to oxaliplatin-based or irinotecan-based chemotherapeutic regimens for the treatment of patients with mCRC with wild-type/mutated *KRAS* tumors. Randomized controlled trials (RCTs), published in Pubmed and Embase were systematically reviewed to assess the survival benefits and toxicity profile mCRC patients treated with cetuximab plus chemotherapy. Outcomes included overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and toxicities. Results were expressed as the hazard ratio (HR) with 95 % confidence intervals (CI). Pooled estimates were generated by using a fixed-effects model or a randomized-effects model, depending on the heterogeneity among studies. A total of 12 trials involving 6,297 patients met the inclusion criteria and were included in this meta-analysis. All patients were administered oxaliplatin-based or irinotecan-based chemotherapy with or without cetuximab. Pooled results showed that the addition of cetuximab did not significantly improve the OS (HR=0.99, 95 % CI=0.89–1.09; Z=0.28, P=0.78) or PFS (HR=0.94, 95 % CI=0.81–1.10; Z=0.76, P=0.49), but did improve ORR (RR=1.34, 95 % CI=1.08–1.65; Z=2.72, P=0.00), when compared with chemotherapy alone. Subgroup analysis showed the highest PFS benefit in patients with wild-type *KRAS* tumors (HR=0.80, 95 % CI=0.65–0.99; Z=2.1, P=0.04) or wild-type *KRAS*/*BRAF* tumors (HR=0.64, 95 % CI=0.52–0.79; Z=4.15, P=0.00). When combined with cetuximab, irinotecan-based chemotherapy was significantly associated with prolonged PFS (HR=0.79, 95 % CI=0.66–0.96; Z=2.36, P=0.02) for all patients with differing gene-status. The incidence of grade 3/4 adverse events, including skin toxicity, diarrhea, hypertension, anorexia, and mucositis/stomatitis, was slightly higher in the combined therapy group than in the chemotherapy-only group. Based on the current evidence, the addition of cetuximab to chemotherapy significantly improves the PFS in patients with wild-type *KRAS* or wild-type *KRAS*/*BRAF* tumors as well as the ORR in all patients. In addition, irinotecan-based combination therapy showed a beneficial effect on the PFS in all patients. These findings confirm the use of cetuximab in combination with chemotherapy for the treatment of patients with mCRC with wild-type *KRAS* tumors. Further multi-center RCTs are needed to indentify these findings.

Keywords Colorectal cancer · Cetuximab · KRAS · Meta-analysis

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Introduction

Colorectal cancer (CRC) is the second most common cancer in women and the third in men, with approximately 50 % of patients developing metastatic disease (mCRC), leading to a half million deaths annually worldwide [1]. Although the incidence of CRC is high, its death rate in several western countries has decreased rapidly owing to advances in treatment and improvements in early detection [1].

Over the past decades, new therapeutic options have been introduced for the treatment of CRC, including new chemotherapeutic agents [2] and novel targeted drugs [3], which

have led to a significantly longer median survival of patients with mCRC [4, 5]. Chemotherapeutic agents, used widely for patients with mCRC [6–10], have been proved to prolong survival, palliate symptoms, and enhance the quality of life [6]. Oxaliplatin and irinotecan, acting as the foundation of chemotherapy backbone in the treatment of mCRC, showed beneficial effect in terms of median survival [11–13]. Furthermore, the results from the previous studies indicate that the addition of cetuximab to irinotecan-based chemotherapy may be more beneficial than addition of cetuximab to oxaliplatin-based chemotherapy. However, the interaction between cetuximab and oxaliplatin or irinotecan still remains unknown. Therefore, we conducted this meta-analysis to assess the survival benefits of combination therapies.

Epidermal growth factor receptor (EGFR) mediates stimulation of cellular proliferation, survival, and motility [14]. In addition, aberrant activation of EGFR may be associated with advanced stage of disease [15, 16], making it a promising target for anticancer therapies [17]. Cetuximab is a monoclonal immunoglobulin G1 antibody that targets EGFR, and it has been shown to improve progression-free survival (PFS) and overall survival (OS) when used in third-line therapy both as a monotherapy and in combination with irinotecan in irinotecan-refractory patients [18].

KRAS gene status is regarded as a predictive maker for outcome after anti-EGFR therapy in mCRC [19]. Patients with wild-type KRAS tumors would benefit from EGFR antibodies [20], while those with mutated KRAS may have a low response rate and poor outcome [21, 22]. The aim of this meta-analysis was to evaluate the efficacy and toxicity of adding cetuximab to oxaliplatin-based or irinotecan-based chemotherapy in the treatment of patients with mCRC with wild-type or mutated *KRAS* tumors.

Material and methods

Literature search

We identified studies on the use of cetuximab and chemotherapy in the treatment of mCRC, published before February 16 2014. Scientific articles published in English were searched, using the Pubmed and Embase databases. The following search items were used: (“colorectal neoplasms” [MeSH Terms] OR (“colorectal” [All Fields] AND “neoplasms” [All Fields]) OR “colorectal neoplasms” [All Fields]) AND (“cetuximab” [Supplementary Concept] OR “cetuximab” [All Fields]) AND (Clinical Trial [ptyp] AND “humans” [MeSH Terms]).

Review strategy

Endnote bibliographic software was used to create an electronic library of citations indentified in the database searches. Pubmed and Embase were performed using Endnote, and duplicate records were deleted. Two independent reviewers (Zhong-chuan Lv and Hong-bing Chen) first screened titles and abstracts and then reviewed full texts. Disagreements between reviewers were resolved by consensus and discussion or by contacting the author of the paper.

We used the Jadad scale to appraise the methodological quality of all studies included in this analysis. The Jadad scale consists of three items describing randomization (0–2 points), masking (0–2 points), and dropouts and withdrawals (0–1 points) in the report of a randomized controlled trial [23]. A score of 1 is given for each of the points described. A further point is given when the method of randomization or double-blinding is performed. The quality scale ranges from 0 to 5 points. The studies with a score≥3 are considered to be high quality [24].

Study inclusion and exclusion criteria

All studies published up until February 16, 2014, obtained from the database of Pubmed and Embase, were reviewed. Studies that met the following criteria were considered for inclusion: (1) randomized controlled trials; (2) the study population of patients aged ≥18 years; (3) eligible patients with histologically or cytologically confirmed mCRC; (4) randomized allocation to cetuximab plus chemotherapy group or chemotherapy group; and (5) results reported data on efficacy and safety. Reports were excluded from the final analysis if they described studies with a single-arm design or randomized controlled trials that assigned cetuximab into the two treatment arms.

Data extraction and quality assessment

A structured questionnaire was used for data extraction. Two investigators (Zhong-chuan Lv and Hong-bing Chen) independently extracted the following information from each study: first author, treatment regimen, number of patients in each treatment group, median age, male percentage, number of metastases, line of treatment, type of blinding, type of controls, hazard ratio (HR) with 95 % confidence interval (CI) of OS and PFS, overall response rate (ORR), and the incidence of toxic effects. In some studies, Kaplan–Meier curves were provided instead of HR and 95 % CI; in such cases, we used the method described by Tierney to estimate the HR with 95 % confidence from the Kaplan–Meier curves [25].

Statistical analysis

We assessed the overall efficacy of adding cetuximab to chemotherapy in the treatment of mCRC based on the data from randomized controlled trials. The OS and PFS were

treated as time-to-event variables, and they are thus expressed as HR with 95 % CI for each study. ORR and incidence of adverse events were treated as dichotomous variables, and they are expressed as risk ratio (RR) with 95 % CI for each study. Pooled estimates were calculated by using a fixed-effects model (Mantel–Haenszel method) [26] or a randomized-effects model (DerSimonian–Laird method) [27], depending on the heterogeneity between the included studies. Before the original data were synthesized, I^2 statistics were used to test the homogeneity [28]. If there was substantial heterogeneity among studies, the randomized-effects model was used; otherwise, the fixed-effects model was used to summarize the pool data. Studies with an I^2 of 25–50 %, 50–75 %, or >75 % were considered to have low, moderate, or high heterogeneity, respectively [29]. Subgroup analysis was conducted according to KRAS and BRAF gene type and different chemotherapeutic partners. Publication bias was assessed by using the Begg tests [30]. A P value less than 0.05 was considered statistical significant. All analyses were performed by using STATA version 12.0 (Stata Corporation, College Station, TX, USA).

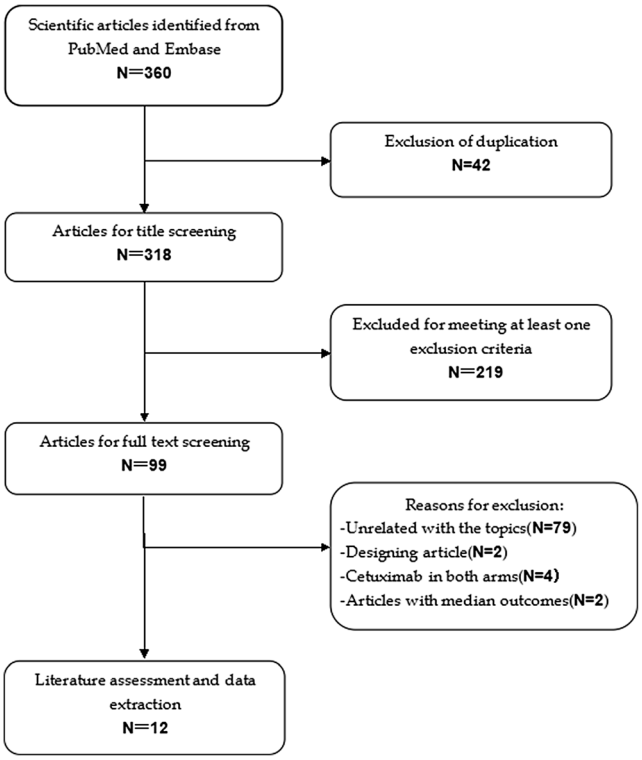

Fig. 1 Search strategy and flow chart for this meta-analysis

Results

Identification of eligible studies

The initial search yielded 360 relevant citations from Pubmed and Embase. Of these, 42 were excluded as duplicate records, and 219 and 79 were excluded after review of title/abstract and full text information, respectively (Fig. 1). Therefore, 20 potential studies were identified for the final analysis; however, two RCTs were excluded because of study design (trial protocol) and four were excluded because cetuximab was assigned in both treatment arms. In addition, four articles described outcome data at different stages of the same two trials; therefore, we excluded the two studies with incomplete data [31, 32] and retained the two latest studies [33, 34]. Finally, 12 RCTs (involving 6,297 patients) [33–44] that met the inclusion criteria were included in our meta-analysis.

Characteristics of eligible studies

The baseline patient characteristics of the included studies are presented in Table 1. All 12 included trials were well-performed, prospective randomized controlled trials. Clinical characteristics were matched for age, gender, and performance status in each study. Patients eligible for these studies had adequate liver and kidney function and Eastern Cooperative Oncology Group performance status of 0 to 2. Cetuximab was administered at an initial dose of 400 mg/m^2 followed by infusions of 250 mg/m^2. In the combination therapy of cetuximab with irinotecan-based chemotherapy, cetuximab was followed by irinotecan at an dose of 180 mg/m^2, day 1, infused over 30 to 90 min. In nine of the included studies, the chemotherapy regimen consisted of oxaliplatin [33, 35–37, 39–43], while irinotecan was administered in the remaining three studies [34, 38, 44].

In the Medical Research Council (MRC) COIN trial [36] and the NORDIC VII trial [42], patients were randomly assigned into the following three arms: oxaliplatin-based chemotherapy, same chemotherapy plus cetuximab, and intermittent chemotherapy. We excluded the intermittent chemotherapy group based on the settings of same regular administration in control groups. The median Jadad score of the included studies was 4 (range from 3 to 5).

Overall survival

Nine RCTs reported data of OS [33–35, 38, 39, 41–44]. The aggregated results suggest that there was no significant OS benefit from combination therapy of cetuximab and chemotherapy when compared with chemotherapy alone (HR=0.99, 95 % CI=0.89–1.09; Z=0.28, P=0.779; Fig. 2).

We also performed subgroup analyses based on different gene status of patients. For patients with mCRC with wild-type *KRAS* tumors (HR=0.94, 95 % CI=0.79–1.12; P=0.49), mutated *KRAS* tumors (HR=1.06, 95 % CI=0.94–1.19; P=0.34), wild-type *KRAS*/*BRAF* tumors

Table 1 Baseline characteristics of patients in the trials included in the meta-analysis

Author	Treatment regimen	No. of patients	Median age (range)	Male/female	WHO performance status (0/1/2)	Number of metastatic sites (1/2/>2)	Line of treatment	Jadad score
Bokemeyer et al. [33]	FOLFOX-4 + cetuximab	169	62 (24–82)	89/80	65/89/15	74/60/35	First line	4
	FOLFOX-4	168	60 (30–82)	92/76	75/76/17	69/63/35		
Van Cutsem et al. [34]	FOLFIRI + cetuximab	599	61 (22–82)	369/230	330/231/38	NR	First line	5
	FOLFIRI	599	61 (19–84)	356/243	318/260/21	NR		
Borner et al. [35]	CAPOX + cetuximab	37	60 (37–81)	23/14	22/15/0	NR	First line	4
	CAPOX	37	63 (47–80)	21/16	21/16/0	NR		
Maughan et al. [36]	Oxaliplatin + fluoropyrimidin + cetuximab	815	63 (58–70)	543/272	376/377/62	305/311/193	First line	4
	Oxaliplatin + fluoropyrimidine	815	63 (56–69)	525/290	375/378/62	283/326/199	NR	
Alberts et al. [37]	m FOLFOX6 + cetuximab							4
Stintzing et al. [38]	FOLFRI + cetuximab	50	65 (44–76)	32/18	28/19/3	19/14/17	First line	4
	FOLFRI + bevacizumab	46	63 (46–74)	30/16	25/19/2	20/14/12		
Tol et al. [39]	CBC	368	62 (33–80)	233/135	240/126/2	163/205	First line	4
	CB	368	62 (27–83)	205/163	219/149/0	167/201		
Ye et al. [40]	FOLFIRI or m FOLFOX6 + cetuximab	70	57 (26–75)	46/24	58/12/0	NR	First line	3
	mFOLFOX	68	59 (35–75)	42/26	54/14/0	NR		
Saltz et al. [41]	FOLF-CB	123	63.2 (34.9–86.5)	73/50	59/60/4	NR	First line	4
	mFOLFOX6-B	124	61.2 (31.8–86.9)	70/54	68/54/2	NR		
Tveit et al. [42]	FLOX + cetuximab	194	60.8 (24.1–74.4)	120/74	134/52/8	64/130	First line	4
	Nordic FLOX	185	61.2 (29.9–74.8)	100/85	122/54/9	52/133		
Dewdney et al. [43]	CAPOX + C	83	61 (31–75)	54/29	39/42/2	NR	NR	4
	CAPOX	81	65 (28–79)	47/34	39/41/1	NR		
Sobrero et al. [44]	Cetuximab + Irinotecan	648	61 (23–85)	405/243	608/35/5	214/431/3	Second line	4
	Irinotecan	650	62 (21–90)	411/239	611/35/4	201/440/9		

mFOLFOX6 the modified sixth version regimen of leucovorin, fluorouracil, and oxaliplatin, *FOLFRI* 5-fluorouracil, folinic acid, and irinotecan, *FOLFIRI* fluorouracil, leucovorin, and irinotecan, *FOLF-CB* bevacizumab, leucovorin, and 5-FU + cetuximab, *mFOLFOX6-B* modified, 5-FU L (folinic acid), oxaliplatin (O) + bevacizumab, *Nordic FLOX* fluorouracil/folinic acid and oxaliplatin, *CAPOX + C* capecitabine/oxaliplatin plus cetuximab, *CAPOX* capecitabine/oxaliplatin, *CBC* capecitabine, oxaliplatin, and bevacizumab + cetuximab, *CB* capecitabine, oxaliplatin, and bevacizumab, *NR* not reported

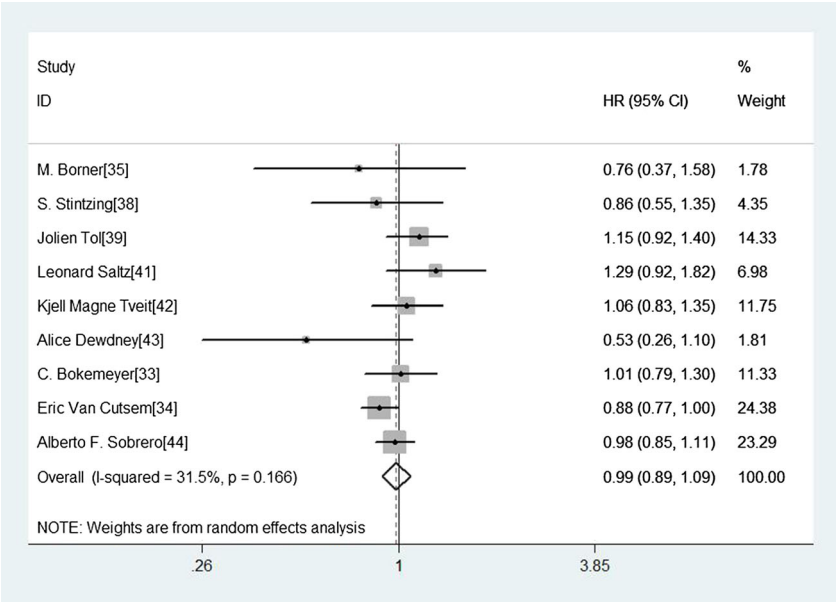

Fig. 2 Comparison of cetuximab plus chemotherapy with chemotherapy for mCRC patients in terms of the overall survival (OS)

Table 2 Summary of subgroup analysis based on different chemotherapy regimens in patients with different gene-status tumors

Event	Chemotherapy regimen	HR	95 % CI	*P* value
All patients				
OS	All	0.99	0.89–1.09	0.779
	Oxaliplatin -based	1.07	0.95–1.21	0.250
	Irinotecan-based	0.92	0.84–1.01	0.067
PFS	All	0.94	0.81–1.10	0.448
	Oxaliplatin-based	1.03	0.91–1.17	0.616
	Irinotecan-based	0.79	0.66–0.96	0.018
Wild-type KRAS				
OS	All	0.94	0.79–1.12	0.485
	Oxaliplatin-based	0.99	0.82–1.19	0.887
	Irinotecan-based	–	–	–
PFS	All	0.80	0.65–0.99	0.036
	Oxaliplatin-based	0.83	0.65–1.06	0.128
	Irinotecan-based	–	–	–
Mutated KRAS				
OS	All	1.06	0.94–1.19	0.339
	Oxaliplatin-based	1.07	0.93–1.23	0.348
	Irinotecan-based	–	–	–
PFS	All	1.23	0.82–1.84	0.317
	Oxaliplatin-based	1.28	0.67–2.46	0.461
	Irinotecan-based	–	–	–
Wild-type KRAS/BRAF				
OS	All	0.93	0.77–1.13	0.480
	Oxaliplatin-based	1.01	0.86–1.18	0.946
	Irinotecan-based	–	–	–
PFS	All	0.64	0.52–0.79	0.000
	Oxaliplatin-based	0.57	0.38–0.85	0.006
	Irinotecan-based	–	–	–
Wild-type KRAS/mutated BRAF				
OS	All	1.08	0.76–1.52	0.685
	Oxaliplatin-based	–	–	–
	Irinotecan-based	–	–	–

– No appropriate available data for meta-analysis performance

(HR=0.93, 95 % CI=0.77–1.13; *P*=0.48), or wild-type *KRAS*/mutated *BRAF* tumors (HR=1.08, 95 % CI=0.76–1.52; *P*=0.69), combination therapy of cetuximab and chemotherapy did not significantly improve OS compared to chemotherapy alone (Table 2).

Subgroup analyses were conducted based on different chemotherapeutic regimens: oxaliplatin-based chemotherapy and irinotecan-based chemotherapy. The results revealed that combination of cetuximab with oxaliplatin-based (HR=1.07, 95 % CI=0.95–1.21; *Z*=1.2, *P*=0.25) or irinotecan-based (HR=0.92, 95 % CI=0.84–1.01; *Z*=1.83, *P*=0.07) chemotherapy had no effect on OS in patients with mCRC (Table 2).

Progression-free survival

Nine RCTs reported data on PFS [33, 34, 36, 38, 39, 41–44]. The pooled results of these studies indicated that combination of cetuximab with chemotherapy did not prolong PFS when compared to chemotherapy alone (HR=0.94, 95 % CI=0.81–1.10; *Z*=0.76, *P*=0.49; Fig. 3).

In subgroup analyses, a significant benefit in PFS was seen for patients with wild-type *KRAS* tumors (HR=0.80, 95 % CI=0.65–0.99; *Z*=2.10, *P*=0.04) or wild-type *KRAS*/*BRAF* tumors (HR=0.64, 95 % CI=0.52–0.79; *Z*=4.15, *P*=0.00) following treatment with cetuximab plus chemotherapy. However, this benefit was not found in patients with mutated *KRAS* tumors (HR=1.23, 95 % CI=0.82–1.84; *Z*=1.00, *P*=0.32; Table 2).

In subgroup analyses, irinotecan-based chemotherapy when combined with cetuximab significantly improved the PFS in the treatment of all patients (HR=0.79, 95 % CI=0.66–0.96; *Z*=2.36, *P*=0.018; Table 2). However, this benefit was not seen in the combined treatment of oxaliplatin-based chemotherapy. We did not perform subgroup analysis of irinotecan-based chemotherapy based on the gene status of patients because only one RCT provided available data.

Overall response rate

Nine RCTs reported data on ORR [33–35, 38–40, 42–44]. The pooled results suggest that patients with mCRC treated with combined therapy have a higher RR when compared to those treated with chemotherapy alone (RR=1.34, 95 % CI=1.08–1.65; *Z*=2.72, *P*=0.006; Fig. 4). In subgroup analyses, a significantly high RR was found in patients with wild-type *KRAS* tumors (RR=1.17, 95 % CI=1.03–1.32; *Z*=2.35, *P*=0.019), but not in patients with mutated *KRAS* tumors (RR=0.91, 95 % CI=0.73–1.12; *Z*=0.89, *P*=0.374).

Adverse Events

All 12 RCTs reported adverse events [33–44]. The most frequently observed grade 3 or 4 adverse events are listed in Table 3. The pooled results show that the addition of cetuximab to chemotherapy induced a significantly higher rate of skin toxicity, diarrhea, hypertension, anorexia, and mucositis/stomatitis compared to chemotherapy alone.

Publication bias

We performed the Begg's test and funnel plots for OS, PFS, and ORR to assess the presence of any publication bias. No evidence of obvious publication bias was found according to the funnel plots (Figs. 5, 6, and 7) or Begg's test in OS (*Z*=0.52, *P*=0.602), PFS (*Z*=0.10, *P*=0.917), or ORR (*Z*=1.77, *P*=0.076).

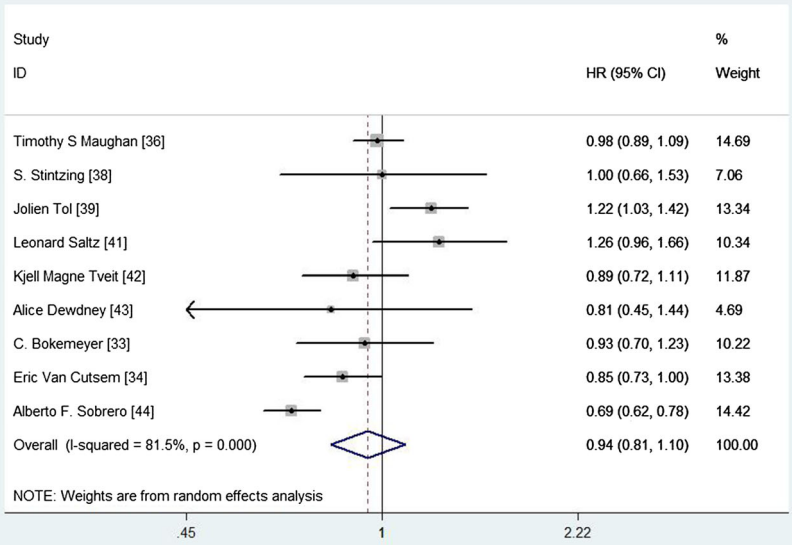

Fig. 3 Comparison of cetuximab plus chemotherapy with chemotherapy for mCRC patients in terms of progression free survival (PFS)

Discussion

The major purpose of this meta-analysis was to critically evaluate the efficacy and toxicity of the addition of cetuximab to chemotherapy in patients with mCRC. This meta-analysis suggests that combination therapy did not significantly prolong OS (HR=0.99, 95 % CI=0.89–1.09, *P*=0.779) or PFS (HR=0.94, 95 % CI=0.81–1.10, *P*=0.448), but did increase the ORR (RR=1.34, 95 % CI=1.08–1.65, *P*=0.006). Moreover, in subgroup analysis, the addition of cetuximab for patients receiving irinotecan-based chemotherapy significantly prolonged PFS compared to chemotherapy alone (HR=0.79, 95 % CI=0.66–0.96; *P*=0.02). Similarly, a PFS benefit was observed in patients with wild-type *KRAS* tumors (HR=0.80, 95 % CI=0.65–0.99, *P*=0.04) or wild-type *KRAS*/*BRAF* tumors (HR=0.64, 95 % CI=0.52–0.79, *P*=0.00). In contrast, in patients with mutated *KRAS* tumors, no statistically significant survival benefits were found for OS (HR=1.06, 95 % CI=0.94–1.19; *P*=0.34) or PFS (HR=1.23, 95 % CI=0.82–1.84; *P*=0.32).

To the best of our knowledge, this is the first comprehensive meta-analysis to assess the role of *KRAS*/*BRAF* and chemotherapy partners on the efficacy of cetuximab in patients with mCRC. Our results confirmed the use of combination therapy of cetuximab with chemotherapy in patients with wild-type *KRAS* tumors based on a significant benefit in PFS. In addition, data suggests a beneficial effect of cetuximab in

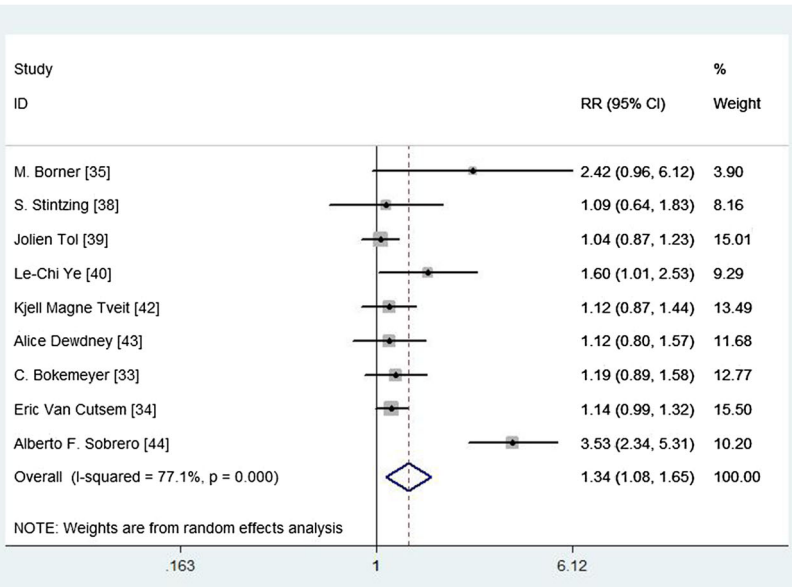

Fig. 4 Comparison of cetuximab plus chemotherapy with chemotherapy for mCRC patients in terms of overall response rate (*ORR*)

Table 3 Summary of the risk ratio (RR) of adverse events in patients with mCRC

Adverse events	RR	95 % CI	*P* value
Skin toxicity	20.76	3.87–111.33	0.000
Diarrhea	1.48	1.33–1.64	0.000
Hypertension	1.69	1.17–2.46	0.006
Anorexia	1.57	1.18–2.10	0.002
Mucositis/stomatitis	2.69	1.90–3.80	0.000
Fatigue	1.58	0.96–2.60	0.100
Anemia	0.91	0.53–1.54	0.718
Nausea/vomiting	1.07	0.92–1.24	0.372
Neutropenia	1.09	0.99–1.21	0.094
Sensory neuropathy	0.77	0.64–0.93	0.007
Thrombocytopenia	1.10	0.73–1.67	0.652

combination with irinotecan-based chemotherapy. However, a survival benefit from combined therapy was not found in patients with mutated *KRAS* tumors.

OS was set as the primary endpoint for incurable disease because it can be measured objectively and precisely. However, OS requires a long follow-up, and it may be influenced by crossover or sequential therapy. Meanwhile, PFS is accepted as direct measure of treatment benefit and can be applied universally without being affected by subsequent therapies. Therefore, PFS is a more accurate surrogate endpoint for survival in patients with mCRC. For these reasons, we emphasized our study on PFS rather than OS.

Of the included studies, only one RCT showed an OS benefit [34], and two RCTs showed a PFS benefit [34, 44]. Interestingly, these two RCTs were conducted by using irinotecan and infusional fluorouracil as the chemotherapy backbone. In contrast, the remaining trials, which used oxaliplatin-based regimens, did not indicate any survival benefit. This discrepancy between studies have raised the hypothesis that there may be a negative interaction between oxaliplatin and cetuximab [45–47]. However, the reason why oxaliplatin-based chemotherapy has a potential disadvantageous influence on the extent of treatment effect still remains unknown.

This meta-analysis showed that combination treatment of cetuximab plus chemotherapy increased the frequency of grades 3 and 4 toxicities including skin toxicity, diarrhea, hypertension, anorexia, and mucositis/stomatitis. Of these toxicities, skin toxicity is considered the most common adverse event and is associated with cetuximab. Although the exact mechanism of this relationship is not clear, skin toxicity may act as a clinical surrogate of the therapeutic effectiveness of cetuximab [48]. In fact, patients that develop rashes have a higher RR than those without rashes, and this significant correlations has been indicated in studies [18, 49, 50].

According to this meta-analysis, we found no OS benefit from combined therapy of cetuximab with oxaliplatin-based chemotherapy in the treatment of patients with mCRC with wild-type *KRAS* tumors. Our results are consistent with a recent published meta-analysis [51]. Of the four RCTs included in this study, patients received combined therapy of chemotherapy with cetuximab in three RCTs, while patients received panitumumab in the remaining one RCT. Subgroup analysis showed no significant benefit of cetuximab on OS (HR=1.02, 95 % CI=0.89–1.18; *P*=0.75) [51]. However, in another meta-analysis [52], a pooled analysis showed a significant OS benefit (HR=0.72, 95 % CI=0.56–0.93; *P*=0.01) for cetuximab in combination with chemotherapy in the treatment of patients with *KRAS* wild-type tumors. Interestingly, the outcome was derived from three RCTs, in which two were abstracts [53, 54] and the remaining one was a median-stage analysis [32]. In the present meta-analysis, all included studies were well performed with a randomized

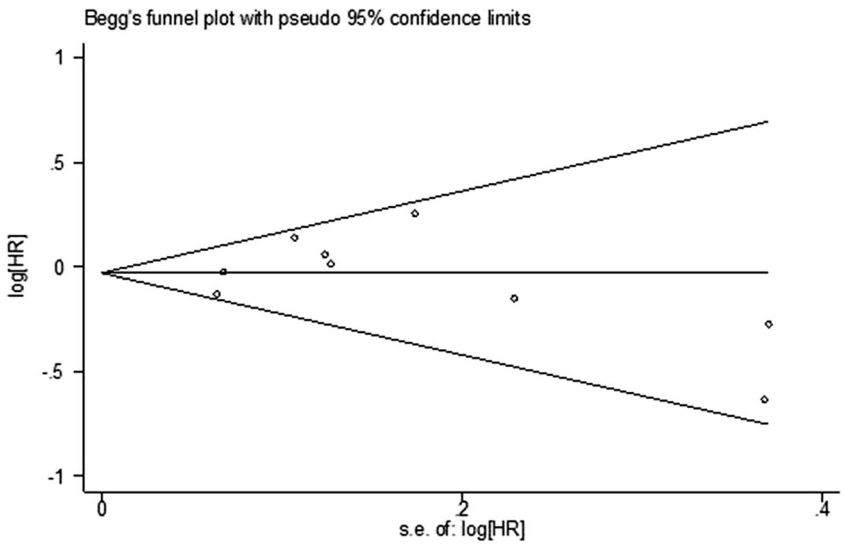

Fig. 5 Tests for publication bias for HR of the overall survival (OS) in patients with mCRC

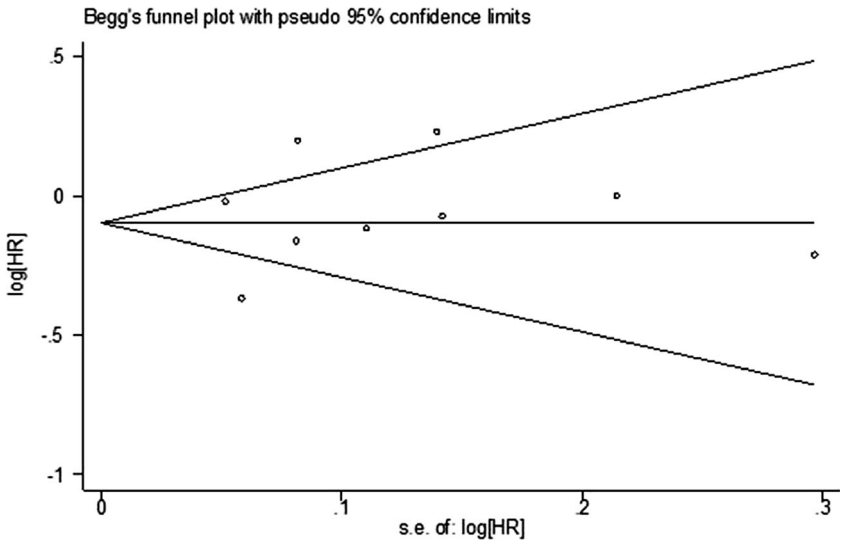

Fig. 6 Tests for publication bias for HR of progression-free survival (PFS) in patients with mCRC

controlled design and were high-quality trials (Jadad score≥3). Therefore, these enhanced statistical power would enable our effect estimates more precise and reliable than those of previous analyses.

However, this study has several limitations. Firstly, some of the included trials had relatively small sample size, which could have led to an overestimation of the treatment effect when compared with larger trials. Although the Begg's test and funnel plots revealed no evidence of publication bias, our conclusions should be interpreted with caution. Secondly, three of the 12 trials provided Kaplan–Meier curves for OS, but did not calculate the HRs with 95 % CIs. These missing data could have resulted in publication bias and influenced the finally pooled estimates. To address this issue, we contacted the investigators of these published studies. However, this strategy was unsuccessful, so we estimated the values of HRs with 95 % CI by using the method mentioned in the data extraction. The resulting data were in accordance with published outcomes, indicating that the results were not significantly modified by our manipulation of the data. Thirdly, inevitable variations existed among the studies, such as study design, basic therapy, follow-up intervals, and line of therapy. All of these factors could potentially affect our results. Finally, subgroup analyses of irinotecan-based chemotherapy were based on three studies. Therefore, applying this finding to clinical practice should be done with caution.

In conclusion, this meta-analysis indicates that the addition of cetuximab to chemotherapy significantly improved PFS for patients with wild-type *KRAS* or wild-type *KRAS*/*BRAF* tumors, but did not produce a benefit on OS. In terms of different chemotherapeutic partners, irinotecan-based chemotherapy when combined with cetuximab prolonged PFS in patients with all gene status. However, given the potential heterogeneity among studies, further prospective clinical trials

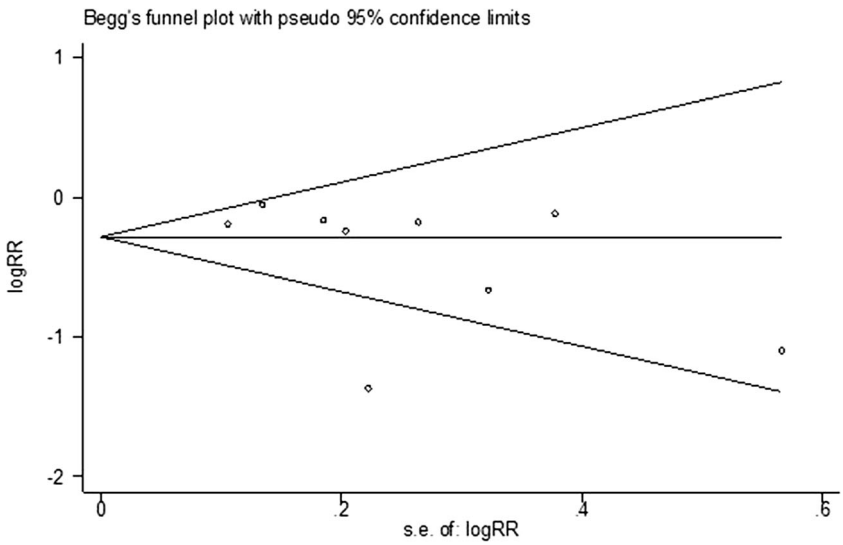

Fig. 7 Tests for publication bias for HR of overall response rate (*ORR*) in patients with mCRC

are needed to indentify these findings and investigate the efficacy of cetuximab with different chemotherapy partners in the treatment of patients with mCRC.

Conflicts of interest None.

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