

Overall survival of patients with KRAS wild-type tumor treated with FOLFOX/FOLFIRI±cetuximab as the first-line treatment for metastatic colorectal cancer

A meta-analysis

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Abstract

The addition of cetuximab to FOLFIRI or FOLFOX as the first-line treatment for metastatic colorectal cancer (mCRC) was shown to reduce the risk of disease progression and increase the chance of response in patients with *KRAS* wild-type disease. An updated systematic meta-analysis was undertaken to determine the efficacy of cetuximab plus FOLFIRI or FOLFOX.

Major databases were searched to identify RCTs investigating wild-type *KRAS* mCRC after the first-line treatment, and treatment with FOLFOX/FOLFIRI±cetuximab was compared. Data on clinical efficacy and safety were pooled and compared by ORs, HRs, and 95% CIs.

Five eligible trials with 1464 patients were included in the meta-analysis. Compared to FOLFOX/FOLFIRI, cetuximab as the first-line therapy has improved overall survival (OS) (hazard ratio [HR]=0.82, 95% confidence interval [CI]: 0.72–0.93, $P=0.003$), progression-free survival (PFS) (HR=0.66, 95% CI: 0.56–0.77, $P<0.00001$), and overall response rate (ORR) (odds ratio [OR]=2.12, 95% CI: 1.70–2.65, $P<0.00001$). However, Grade 3/4 AE was increased with the OR of 2.76 (95%CI: 2.01–3.78, $P<0.00001$). The most common grade 3/4 toxicity in the wild-type *KRAS* population was neutropenia and diarrhea. For cetuximab plus FOLFIRI, there was a higher incidence of grade 3 or 4 diarrhea (OR=1.76, 95% CI: 1.15–2.70, $P=0.01$), but there was no significant difference for neutropenia (OR=1.35, 95% CI: 1.00–1.83, $P=0.05$).

The addition of cetuximab in mCRC as the first-line treatment is a potential effective approach in the improved outcomes but associated with increased toxicity.

Abbreviations: EGFR = epidermal growth factor receptor, mCRC = metastatic colorectal cancer, ORR = overall response rate, OS = overall survival, PFS = progression-free survival.

Keywords: cetuximab, first-line, FOLFOX/FOLFIRI, meta-analysis, metastatic colorectal cancer, wild-type *KRAS*

1. Introduction

The efficacy of biologic agents plus systemic chemotherapy in the first-line treatment of metastatic colorectal cancer (mCRC) has been extensively investigated. Studies have reported that biologic agents with FOLFOX /FOLFIRI can significantly improve the therapeutic effect compared with FOLFOX /FOLFIRI alone.^[1–4]

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Their role in wild-type *KRAS* mCRC as the first-line therapy, however, has not been systematically examined. For this review, cetuximab was defined as a drug targeting a specific receptor of cancer cell growth factors, epidermal growth factor receptor (EGFR).

The purpose of this study was to evaluate and summarize the safety and efficacy of cetuximab combined with standard arm (FOLFOX/FOLFIRI) in treating patients with wild-type mCRC. Clinical strategies were needed: cetuximab in addition to FOLFOX/FOLFIRI compared with FOLFOX/FOLFIRI alone, and FOLFOX/FOLFIRI±cetuximab as the first-line treatment in patients with wild-type mCRC.^[5–9] The meta-analysis examined the survival benefit and the adverse effect of cetuximab including overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) as well as Grade 3/4 toxicity.

2. Materials and methods

2.1. Literature search

All studies that reported cetuximab plus FOLFOX/FOLFIRI as the first-line treatment for metastatic colorectal cancer were identified by comprehensive computer-based searches of PubMed (from 1950 to 2016), the Web of Science, Wanfang, the China Biological Medicine Database (SinoMed), and the China

National Knowledge Infrastructure (CNKI). These computer searches were limited to English and Chinese language articles published before 2016, and did not include reviews and editorials. The following all fields were used for the search: “wt-kras” OR “wild-type kras” AND “colorectal cancer” OR “mCRC” OR “metastatic colorectal cancer” AND “cetuximab” OR “erbitux” OR “cmab” OR “c225.”

2.2. Inclusion criteria

Studies involved patients with histologically confirmed mCRC. The inclusion criteria were as follows: (1) studies were limited to FOLFOX/FOLFIRI with or without cetuximab as the first-line treatment for metastatic colorectal cancer. (2) All studies which employed random control test using either a hospital-based or a population-based design. (3) Studies were selected using the literature research methods. (4) The existing literature provided us with a comprehensive statistical index and sufficient data for estimating overall survival, progression-free survival, and overall response rate as well as toxicity in patients with wild-type KRAS mCRC. Studies were excluded from analysis when (1) data could not be extracted from the published results, (2) the reported appropriate outcomes were excluded, or (3) the studies contained republished data.

2.3. Data extraction

Two authors (YFY and YNZ) independently extracted outcomes from the studies. Disagreement was resolved by reaching a consensus. The extracted data included the following items: the first author's name, the year of publication, the total number of cases and controls with wild-type KRAS mCRC, the population (country), the methods, overall survival (hazard ratio [HR], 95% confidence interval [CI]), progression-free survival (HR, 95%CI), and overall response rate (ORR) (odds ratio [OR], 95%CI) as well as toxicity (events and total).

2.4. Quality assessment

Two authors (YFY and YNZ) evaluated the methodological quality of the included studies using criteria developed by Jadad et al,^[10] which is a 4-point scale including a description of randomization, allocation concealment, double-blinded structure, and withdrawals/dropouts. Any disagreements were resolved by discussion.

2.5. Outcome measures and data analysis

The outcomes of OS, PFS, ORR, and toxicity were analyzed based on trial-level data. Data analysis was performed using Review Manager 5.3 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). For each trial, individual OR for ORR and 95% CI were pooled and analyzed using the general inverse variance fixed-effects method. Meta-analysis of the log hazard ratio and log upper and lower CIs for OS and PFS was performed. The toxicity was analyzed by the Mantel–Haenszel fixed-effects method.

2.6. OS and PFS

For each trial, the HR and corresponding standard error were calculated, which were computed by the software in all cases except for the studies of Bokemeyer et al^[7] or Bokemeyer et al^[5] in which OS or PFS was not available.

2.7. ORR

OR and 95% CI for response were pooled to give a clinically useful measure of the effect except for the literature,^[5] which did not include original data.

2.8. Toxicity

Data were extracted from Van Cutsem et al^[9] and Bokemeyer et al^[6] on incidence of Grade 3 and 4 toxicity and pooled difference in toxicity calculated as for OR. Detailed statistical analysis on the risk of toxicity and subgroup analyses were presented for the combined cohort.

Heterogeneity was assessed using χ^2 and I^2 test, with an I^2 of 25 to 50, and 50 to 75 or >75% was considered as low, moderate, or high heterogeneity, respectively.^[11] Studies with $P < 0.10$ and $I^2 > 25\%$ indicated substantial heterogeneity. If heterogeneity existed among the studies, the random effects model was used to estimate the pooled OR or HR (DerSimonian and Laird method).^[12] Otherwise, the fixed effects model was adopted (Mantel–Haenszel method).^[13] The Z test was used to determine the pooled OR or HR, and $P < 0.05$ indicated significant difference. Sensitivity analyses and funnel plots were undertaken to investigate possible bias.

3. Results

3.1. Literature search and description of studies

Our predefined search strategy identified a total of 4492 potentially relevant publications. Following screening of titles and abstracts, studies limited to FOLFOX/FOLFIRI with or without cetuximab treatment for wild-type KRAS mCRC were retrieved in full text, leaving 44 publications. Later, through the full text, we evaluated the experimental methods and results data to exclude studies (1) without RCTs or (2) without first-line treatment trials and (3) lack of comparative survival data or (4) with duplicate data, and 5 articles were finally enrolled, with 1464 patients entering the meta-analysis (Fig. 1). The Jadad scores showed that the methodological quality was generally good. The main characteristics of the studies are shown in Table 1.

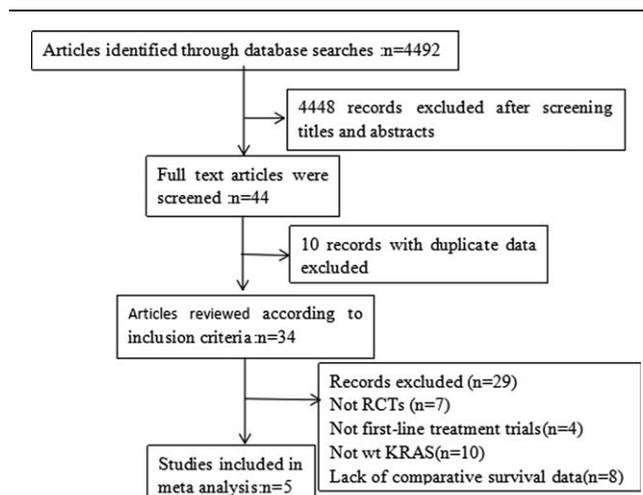


Figure 1. Flow chart of selection.

Table 1
Characteristics of studies.

Trial name	Author, y	country	Experimental arms	Control arms	Patients (KRAS wild type population)	Jadad score	OS	PFS	ORR	3/4 Grade toxicity
							HR (95%CI)	HR (95%CI)	OR (95%CI)	
OPUS	Bokemeyer and Bondarenko et al, 2011	Europe	Cetuximab + FOLFOX-4	FOLFOX-4	179	2	0.855 (0.599–1.219)	0.567 (0.375–0.856)	2.551 (1.380–4.717)	Anny, diarrhea, neutropenia, cardiac events
OPUS	Bokemeyer and Bondarenko et al, 2009	87 centers in 13 countries	Cetuximab + FOLFOX-4	FOLFOX-4	136	3	0.89 (0.60–1.34)	NA	NA	NA
CRYSTAL	Bokemeyer and Bondarenko et al, 2009	Europe	Cetuximab + FOLFOX-4	FOLFOX-4	134	4	NA	0.57 (0.36–0.91)	2.54 (1.24–5.20)	NA
CRYSTAL	Van Cutsem and Kohne et al, 2009	Europe and outside Europe	Cetuximab plus FOLFIRI	FOLFIRI Alone	348	5	0.84 (0.64–1.11)	0.68 (0.50–0.94)	1.91 (1.24–2.93)	Skin reactions, infusion-related reactions
CRYSTAL	Van Cutsem and Kohne et al, 2011	Europe and outside Europe	Cetuximab + FOLFIRI	FOLFIRI	666	3	0.796 (0.670–0.946)	0.696 (0.558–0.867)	2.069 (1.515–2.826)	Anny, diarrhea, Neutropenia, skin reactions, infusion-related reactions

CI=confidence interval, HR = hazard ratio, NA=not available, OR=odds ratio, ORR = overall response rate, OS = overall survival, PFS = progression-free survival.

3.2. Main results, heterogeneity, and sensitivity analysis overall survival

Five studies, involving 4 comparisons,^[5,6,8,9] reported OS and HRs. Using fixed-effects meta-analysis, the overall survival HR was 0.82 (95% CI 0.72–0.93, $P=0.003$, Fig. 2). As expected, *response5* there was no heterogeneity ($I^2=0$, $P=0.95$).

3.3. Progression-free survival

Five studies involving 4 comparisons^[6–9] proved the use of cetuximab was beneficial for PFS with the fixed-effects HR of 0.66 (95% CI 0.56–0.77, $P<0.00001$, Fig. 3) and fixed-effects analysis indicated no heterogeneity ($I^2=0$, $P=0.76$).

3.4. Overall response rate

Five studies involving 4 comparisons^[6–9] allowed fixed-effects meta-analysis, which demonstrated *response7* the benefits of FOLFOX/FOLFIRI with cetuximab treatment for wild-type KRAS mCRC with the pooled OR 2.12 (95% CI 1.70–2.65, $P<0.00001$, $I^2=0$, Fig. 4).

3.5. Toxicity

Two of the five publications^[6,9] which involved Grade 3/4 toxicity of cetuximab plus FOLFOX/FOLFIRI in wt-KRAS mCRC patients were analyzed, and it was demonstrated that the use of cetuximab increased the risk of Grade 3/4 toxicity with OR

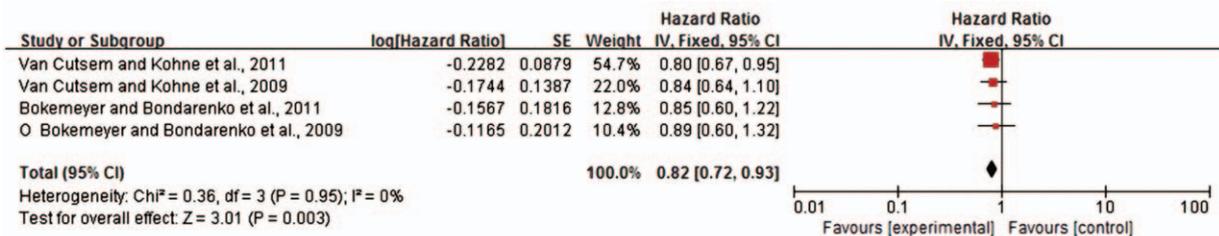


Figure 2. Forest plot for OS. Meta-analysis of overall survival associated with cetuximab plus FOLFIRI or FOLFOX versus FOLFIRI or FOLFOX alone in the fixed-effects model. OS=overall survival.

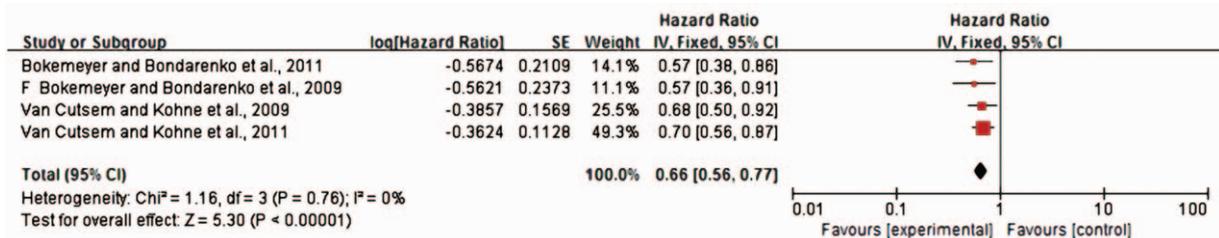


Figure 3. Forest plot for PFS. Meta-analysis of progression-free survival between cetuximab plus FOLFIRI or FOLFOX and FOLFIRI or FOLFOX alone. PFS= progression-free survival.

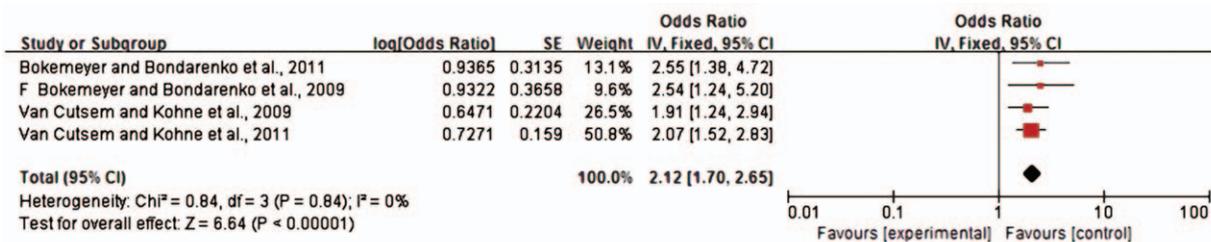


Figure 4. Forest plot for ORR. Meta-analysis of overall response rate associated with cetuximab plus FOLFIRI or FOLFOX versus FOLFIRI or FOLFOX alone in the fixed-effects model. ORR=overall response rate.

of 2.76 (95% CI 2.01–3.78, *P* < 0.00001, Fig. 5) in the fixed-effects model. Subgroup analyses of the most common adverse effects showed a higher incidence of grade 3 or 4 diarrhea (OR = 1.76, 95% CI 1.15–2.70, *P* = 0.01), without significant difference for neutropenia (OR = 1.35, 95% CI 1.00–1.83, *P* = 0.05).

3.6. Sensitivity analysis

The contribution of each study to the pooled estimate was assessed in the sensitivity analysis. We excluded 1 individual study every time and reevaluated the pooled HR or OR estimates for the remaining studies. Similarly, Van Cutsem et al^[9] had undue influences on the pooled OR /HR estimates for results. However, its data were excluded, producing the similar outcomes. Thus, our results were reliable.

3.7. Publication bias

The publication bias of the individual studies was evaluated by a funnel plot. The figure HR of OS and PFS and OR of ORR were also taken as the representative. No visual publication bias was

found in the funnel plot for the HR of OS (Fig. 6A), HR of FPS (Fig. 6B) or OR of ORR (Fig. 6C). This indicated that the publication bias was low in the current meta-analysis.

4. Discussion

Biologic agents have improved outcomes of patients with mCRC, which are integrated into treatment guidelines. Updated analysis from the CRYSTAL trial demonstrated that adding cetuximab to FOLFIRI improved OS of wt-KRAS metastatic colorectal patients, whereas mut-KRAS patients experienced no benefit in PFS or OS.^[1] KRAS mutation status is more powerful to predict the resistance to cetuximab than EGFR overexpression.^[14–19] The specific effect of the cetuximab with FOLFIRI or FOLFOX as the first-line treatment in wt-KRAS patients, however, remains unclear. This study was the first to systematically examine the effect of this chemotherapy backbone, including cetuximab, on the efficacy of FOLFIRI or FOLFOX treatment in wt-KRAS mCRC.

Considering the addition of cetuximab to chemotherapy in wt-KRAS patients, benefits of OS, PFS and ORR were found in the

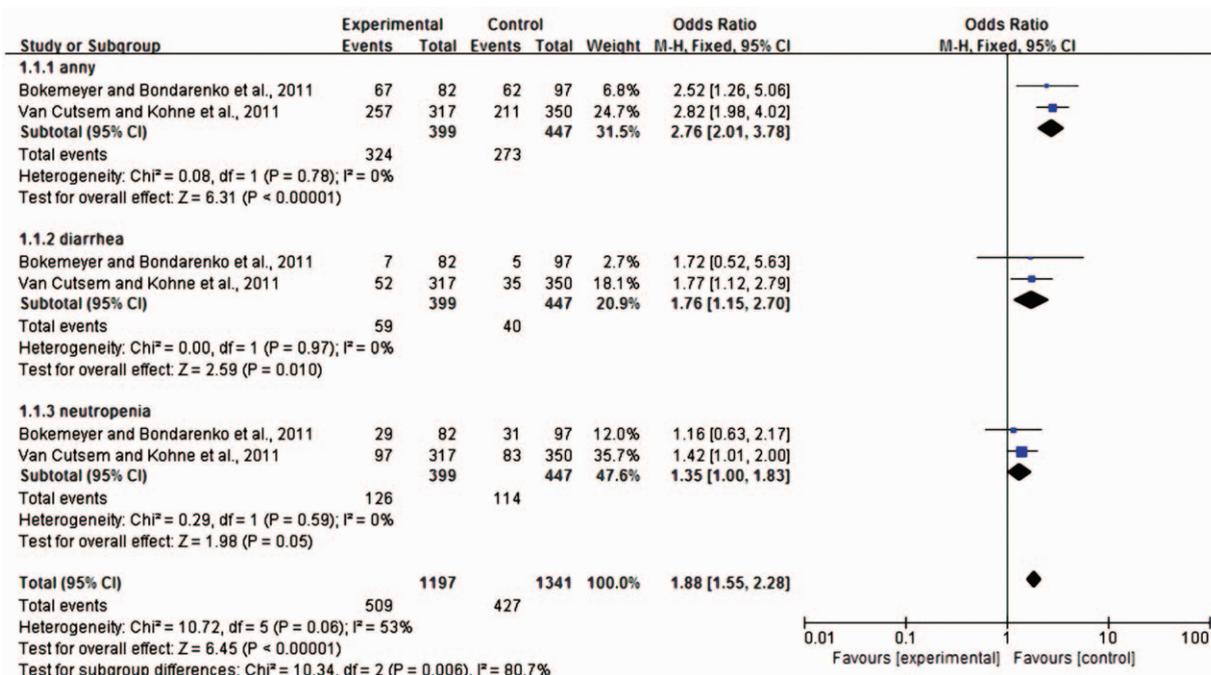


Figure 5. Forest plot for Grade 3/4 toxicity. Meta-analysis of Grade 3/4 toxicity on cetuximab plus FOLFIRI or FOLFOX versus FOLFIRI or FOLFOX alone.

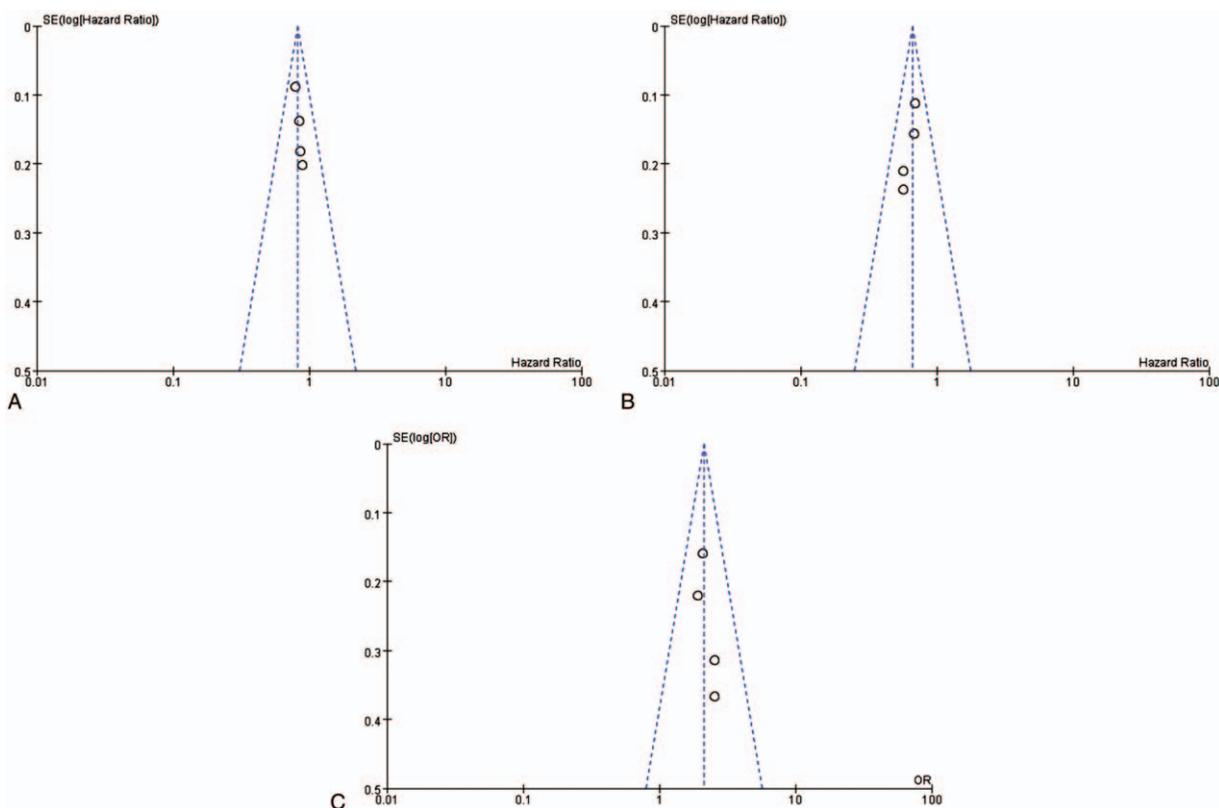


Figure 6. Funnel plot for the publication bias tests. (A) Funnel plot for the HR of OS; (B) funnel plot for the HR of FPS; (C) funnel plot for the OR of ORR. Each point represents a separate study for the indicated association. HR=hazard ratio, ORR=overall response rate, OS=overall survival, FPS=progression-free survival.

combined treatment of cetuximab plus fluorouracil.^[5–9,20,21] Investigating the cetuximab+chemotherapy more closely, superior efficacy was observed in trials using cetuximab with FOLFIRI or FOLFOX over those utilizing FOLFIRI or FOLFOX alone. Subsequent analysis was made about effects of cetuximab with/without FOLFIRI/FOLFOX on survival in wt-KRAS mCRC patients.

We found that the first-line treatment of metastatic colorectal cancer by cetuximab and FOLFIRI/FOLFOX reduced the risk of disease progression by 34% (hazard ratio, 0.66; $P < 0.00001$), compared with FOLFIRI/FOLFOX alone. The addition of cetuximab to FOLFIRI/FOLFOX also increased the overall response rate with the OR of 2.12 ($P < 0.00001$). There was significant difference between the treatment groups in overall survival (HR=0.82, 95%CI 0.72–0.93, $P = 0.003$). The safety of the cetuximab–FOLFIRI/FOLFOX treatment was evaluated. The incidence of grade 3 or 4 diarrhea and neutropenia was higher for cetuximab plus FOLFIRI/FOLFOX compared to FOLFIRI/FOLFOX alone, and the overall incidence of grade 3 or 4 adverse events was significantly higher for cetuximab, with the OR of 2.76 (95%CI 2.01–3.78, $P < 0.00001$). However, these adverse events were generally manageable. To better explain the results, other limitations of this meta-analysis were also considered. On one hand, some publication bias may be inevitable in the results. Only full text articles published in English and Chinese were assessed in this meta-analysis. Thus, some eligible studies that were unpublished or reported in other languages may be missed. Some cultural background may also affect the decision to publish, making researchers more likely not to report or edit negative results in some areas of research.

Furthermore, survival of mCRC was involved in complex reasons, including gene and potential disease factors, and so on. However, many eligible studies included in this meta-analysis failed to consider these factors, which could also influence the study results.

Despite these disadvantages, our meta-analysis did have some advantages. First, a systematic review of the benefits of cetuximab with FOLFIRI or FOLFOX as the first-line treatment in wt-KRAS patients was able to overcome the limitation of small sample size of the study population, thus generating more precise data. Second, the quality of the case-control studies included in our analysis was nearly satisfactory and met our inclusion criteria.

5. Conclusion

This systematic review provided evidence for the benefits from *response8* the addition of cetuximab, which included OS, PFS, and ORR, but the toxicity was also increased for the patients with mCRC. *Response9* When effects of FOLFIRI or FOLFOX with or without cetuximab were analyzed separately, it was found that progression was made in the use of cetuximab plus FOLFIRI or FOLFOX to prolong the life of patients with mCRC.

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