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META-ANALYSIS

# Standard chemotherapy with cetuximab for treatment of colorectal cancer

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Data sharing: Technical appendix, statistical code, and dataset available from the corresponding author at cai_sanjunsci@163.com.



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## Abstract

**AIM:** To review and assess the evidence related to cetuximab treatment in metastatic colorectal cancer (mCRC) with regard to *KRAS* status.

**METHODS:** PubMed, EMBASE, Cochrane database and American Society of Clinical Oncology meeting abstracts were searched for randomized controlled trials (RCTs) reporting the effect of *KRAS* status on efficacy of chemotherapy regimen with or without cetuximab in mCRC. Baseline information such as sex and age was summarized from the included studies. Hazard ratios of progression-free survival (PFS) and overall survival (OS) as well as objective response based on KRAS status were extracted for analysis.

**RESULTS:** A total of 8 RCTs with 6780 patients were included. The combined analysis showed that cetuximab failed to improve the OS and PFS in patients with mCRC. However, in subgroup analysis, the pooled data showed that addition of cetuximab to irinotecan containing chemotherapy regimen was sufficient to improve OS and PFS in wild-type *KRAS* mCRC patients, but not in patients with mutant-type *KRAS*. The addition of cetuximab increased the incidence of adverse events such as diarrhea, rash, skin toxicity/rash, and nausea and vomiting. There was no significant publication bias existing in the included studies.

**CONCLUSION:** The clinical benefit of cetuximab was only confirmed in patients with wild-type *KRAS*. *KRAS* status could be considered a biomarker of efficacy of cetuximab.

**Key words:** Cetuximab; KRAS; Standard chemotherapy; Metastatic colorectal cancer; Meta-analysis

**Core tip:** The addition of cetuximab to irinotecan containing chemotherapy regimen was sufficient to improve overall survival and progression-free survival in wild-type *KRAS* metastatic colorectal cancer patients, but not in patients with mutant-type *KRAS*.

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## INTRODUCTION

Colorectal cancer remains one of the most common cancers worldwide and its incidence was about 1.2 million in 2008[1]. In the past few years, progress has been achieved in improving outcome of metastatic colorectal cancer (mCRC), and this was mainly due to the application of novel molecular targeted agents[2,3]. However, recent evidence[4-6] showed that addition of cetuximab to chemotherapy did not improve the outcome for patients with mCRC, making the anti-tumor effect of cetuximab controversial, and indicating that cetuximab should be recommended based on individual information. Therefore, it is urgent to identify patients who could benefit from cetuximab treatment most and this relies on effective biomarkers in predicting efficacy of cetuximab in the treatment of mCRC.

Cetuximab is an IgG1 monoclonal antibody to the epidermal growth factor receptor (EGFR) and it exerts clinical activity in mCRC patients who are chemotherapy-resistant[6-8]. A phase Ⅲ trial in patients with oxaliplatin and fluoropyrimidines-refractory mCRC who were randomized to cetuximab plus irinotecan showed an improved outcome for the addition of cetuximab[9]. Cetuximab has been approved by United States Food and Drug Administration in 2004. However, not all the individuals are sensitive to cetuximab, and investigations about influencing factors of its effectiveness have emerged, with one of the best known being KRAS status[10].

The KRAS protein is one of the most important downstream effectors coupling EGFR to intracellular signaling cascades, leading to cell growth, division, motility, and inhibition of apoptosis[11,12]. Single-nucleotide point mutations in the *KRAS* gene are found in approximately 40% of patients with metastatic CRC, including mutations in codons 12 and 13 of exon 2[12,13]. These mutations of *KRAS* may contribute to the lack of response to anti-EGFR monoclonal antibodies in patients with mCRC[10-12]. A meta-analysis[14] of pooled data from the CRYSTAL[15] and OPUS[16] studies confirmed that in patients with *KRAS* wild-type tumours, adding cetuximab to chemotherapy led to a significant improvement in overall survival (OS), progression-free survival (PFS) and overall response rate (ORR). However, other trials demonstrated that *KRAS* status was not predictive of benefit when adding cetuximab to the first-line therapy[12,17,18]. Thus, it is essential to evaluate whether KRAS is a biomarker of effectiveness of cetuximab using pooled data.

In regard of issues mentioned above, the present meta-analysis was to investigate whether addition of cetuximab could improve treatment outcomes such as PFS and OS based on KRAS status in patients with mCRC, and whether *KRAS* status could be a useful indicator of benefit from cetuximab treatment.

## MATERIALS AND METHODS

### *Literature search strategy*

Population, intervention, control, and outcome (PICO) were defined prior to literature research. Then, electronic databases comprising PubMed, EMBASE, Cochrane, and American Society of Clinical Oncology meeting abstract (conference on colorectal cancer) were selected and used to search for randomized controlled trials (RCTs) comparing chemotherapy regimen with or without cetuximab in treatment of mCRC based on *KRAS* status. The search terms used were: ["colorectal neoplasms/therapy"(Mesh) or "carcinoma, colorectal " or "tumor, colorectal"] and ("cetuximab" or "erbitux" or "MAb C225" or "anti-EGFR agents") and ("stage Ⅲ" or "stage Ⅳ" or "metasta?" or "advanced") and ("KRAS" or "K-ras"). We also used a manual reference search for relevant articles, including original articles and reviews, to identify additional studies. If more than one article was published using the same case series, only the study with the latest data was included. The search was restricted to published English language papers. The literature search was updated on December 31, 2013. The detailed information of the search strategy for the eligible studies is presented in flow diagram provided by PRISMA (Figure 1).

### *Inclusion criteria*

Inclusion criteria were: (1) high quality RCTs performed in mCRC patients, either in form of a full article or a meeting abstract; (2) mCRC patients treated with traditional chemotherapy regimen with or without cetuximab; (3) RCTs comparing cetuximab + chemotherapy *vs* chemotherapy only, with regard to KRAS status; and (4) primary endpoints were PFS and/or OS, and secondary endpoints were OR and toxicity information.

### *Data extraction*

Information in each eligible study was carefully extracted and identified by two reviewers independently (Li XX and Liang L), and classical data collection methods were applied during extraction process.

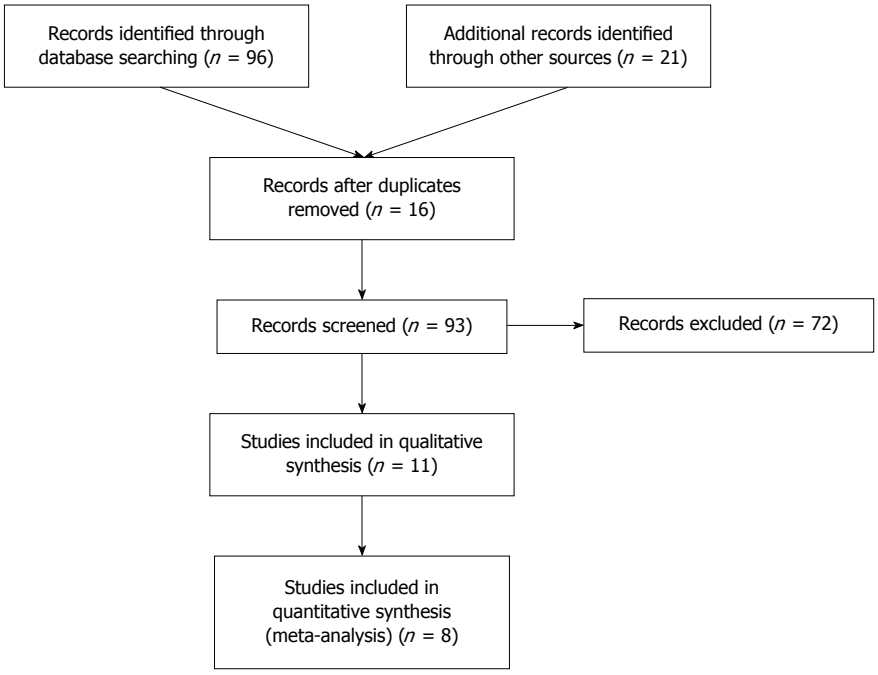



**Figure 1 Flow diagram of study selection.**

The following data were extracted from the included studies: numbers of patients enrolled, publication date, characteristics of patients such as age and gender, and other data such as clinical stage, method of randomization, chemotherapy regimen and details of first-line chemotherapy, doses of cetuximab, PFS, OS, and OR. If hazard ratio (HR) and its variance were not available directly from original article, the method of Parmar *et al*[19] was introduced to establish estimates of these information. For identification of each eligible study, the first author' name and publication year were used.

### *Quality control*

The protocols of GRADE were used to evaluate the quality of each RCT included for this meta-analysis. Quality control was performed independently by two reviewers. If there was a disagreement about quality of a certain study, another reviewer was involved to solve it. Funnel plots were also introduced to assess the publication bias.

### *Statistical analysis*

RevMan 5.2 software which was provided by the Cochrane Collaboration was applied to perform all of the statistical analyses, and introduction of the Cochrane Collaboration for meta-analysis was followed to ensure the accuracy of whole analysis process. We assessed the between-study heterogeneity by Cochran's $Q$ test and quantified by $I^2$ (a significance level of $P < 0.10$ and/or $I^2 \geqslant 50\%$). If the $P$-value of the $Q$ test is > 0.05, the summary OR estimate of each study was calculated using the fixed-effect model. Otherwise, the random-effect model was used. A funnel plot and Egger's linear regression test were used to investigate any possible publication bias[20]. For all analyses, a two-sided $P$-value less than 0.05 was considered to be statistically significant.

The statistical methods of this study were reviewed by San-Jun Cai from Department of Colorectal Surgery, Fudan University Shanghai Cancer Center.

## RESULTS

### *Characteristics of included studies*

A total of eight RCTs[17,21-27] were included for this meta-analysis involving a number of 6780 mCRC patients. Among these eligible trials, full articles are available from databases. The baseline information and adverse events of these studies are shown in Tables 1 and 2. Five of them[17,22,25-27] assessed oxaliplatin based chemotherapy regimen plus cetuximab in the first-line treatment of metastatic or advanced CRC, while two studies[21,24] evaluated the effect of cetuximab in combination with the FOLFIRI regimen on outcome of metastatic or advanced CRC patients, and only one trial[23] involved both FOLFIRI or oxaliplatin based regimen. All studies[17,21-26] reported the status of *KRAS* in mCRC except the study of Borner *et al*[27]. Data from these RCTs were sufficient to support the statistically pooled analysis of PFS and OS.

### *Analysis of OS*

**OS regardless of *KRAS* status:** Five RCTs[21,22,24,25,27] were included for the analysis of whether addition of cetuximab to standard chemotherapy could improve OS than chemotherapy alone. The result showed that the application of cetuximab failed to provide a

**Table 1 Included studies on efficacy of cetuximab plus chemotherapy *vs* chemotherapy alone in patients with metastatic or advanced colorectal cancer**

| Study | Type of article | Patients | Intervention | | Main endpoints | Mutation status reported | | Quality control |
|---|---|---|---|---|---|---|---|---|
| | | | Cetuximab + chemotherapy | Chemotherapy | (HR, 95%CI) | KRAS | BRAF | |
| Borner *et al*[27] | Full manuscript | 74 | Cetuximab + XELOX | XELOX | PFS: NR; OS: NR | No | No | Moderate |
| Bokemeyer *et al*[25] | Full manuscript | 337 | Cetuximab + FOLFOX-4 | FOLFOX-4 | PFS: 0.931, 0.705-1.230; OS: 1.015, 0.791-1.303 | Yes | Yes | Good |
| Van Cutsem *et al*[21] | Full manuscript | 1198 | Cetuximab + FOLFIRI | FOLFIRI | PFS: 0.851, 0.726-0.998; OS: 0.878, 0.774-0.995 | Yes | Yes | Good |
| Maughan *et al*[17] | Full manuscript | 1630 | Cetuximab + oxaliplatin + fluoropyrimidine | Oxaliplatin + fluoropyrimidine | PFS: 0.96, 0.82-1.12; OS: 1.04, 0.87-1.23 | Yes | Yes | Good |
| Tveit *et al*[22] | Full manuscript | 571 | Cetuximab + FLOX | FLOX | PFS: NR; OS: NR | Yes | Yes | Good |
| Alberts *et al*[26] | Full manuscript | 2686 | Cetuximab + mFOLFOX6 | mFOLFOX6 | PFS: NR; OS: NR | Yes | Yes | Good |
| Huang *et al*[24] | Full manuscript | 146 | Cetuximab + FOLFIRI | FOLFIRI | PFS: 0.53, 0.26-1.10; OS: 0.45, 0.2-1.2 | Yes | Yes | Good |
| Ye *et al*[23] | Full manuscript | 138 | Cetuximab + mFOLFOX6/ FOLFIRI | mFOLFOX6/ FOLFIRI | PFS: 0.60, 0.41-0.87; OS: 0.54, 0.33-0.89 | Yes | Yes | Good |

XELOX: Capecitabine and oxaliplatin regimen; FOLFOX-4: Oxaliplatin and folinic acid and 5-fluorouracil regimen; FOLFIRI: Fluorouracil and leucovorin and irinotecan regimen; FLOX: Fluorouracil/folinic acid and oxaliplatin regimen; mFOLFOX6: Oxaliplatin and leucovorin and fluorouracil regimen; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

**Table 2 Adverse events (grade 3 and 4)**

| Study | Neutropenia | | Nausea and vomiting | | Skin toxicity/rash | | Rash | | Diarrhea | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control group | Cetuximab group | Control group | Cetuximab group | Control group | Cetuximab group | Control group | Cetuximab group | Control group | Cetuximab group |
| Borner *et al*[27] | 3 | 0 | 6 | 10 | 0 | 16 | 0 | 8 | 16 | 22 |
| Bokemeyer *et al*[25] | 57 | 51 | NA | NA | 1 | 30 | 1 | 19 | 12 | 14 |
| Van Cutsem *et al*[21] | 150 | 169 | 30 | 28 | 1 | 117 | 0 | 49 | 63 | 94 |
| Maughan *et al*[17] | NA | NA | NA | NA | 14 | 114 | NA | NA | NA | NA |
| Tveit *et al*[22] | 47 | 95 | 3 | 14 | 1 | 51 | 1 | 51 | 10 | 33 |
| Alberts *et al*[26] | 89 | 110 | 59 | 70 | NA | NA | 3 | 186 | 83 | 148 |
| Huang *et al*[24] | 15 | 3 | 0 | 18 | NA | NA | 0 | 11 | 15 | 6 |
| Ye *et al*[23] | 6 | 8 | 3 | 3 | 1 | 2 | 2 | 9 | 3 | 4 |

GI: Gastrointestinal toxic effects; NA: Not available.


**Figure 2 Meta-analysis of effect of cetuximab plus chemotherapy on overall survival regardless of *KRAS* status.**

significant improvement of OS regardless of *KRAS* status (HR = 0.92, 95%CI: 0.83-1.01; $P$ > 0.05; Figure 2).

**OS based on wild-type *KRAS*:** To evaluate whether cetuximab plus chemotherapy could benefit OS in population harboring wild-type *KRAS*, seven studies were included[17,21-26]. As shown in Figure 3, though cetuximab plus chemotherapy seemed to provide a benefit in prolonging OS, there was no statistically significance (HR = 0.95, 95%CI: 0.86-1.05; $P$ > 0.05).

**OS based on mutated *KRAS*:** There was five studies[21,22,24-26] involved in the analysis of OS based on mutant *KRAS* in patients who received cetuximab combined with chemotherapy. A significant difference was not observed from the pooled analysis (HR = 1.10, 95%CI: 0.94-1.28; $P$ > 0.05; Figure 3).

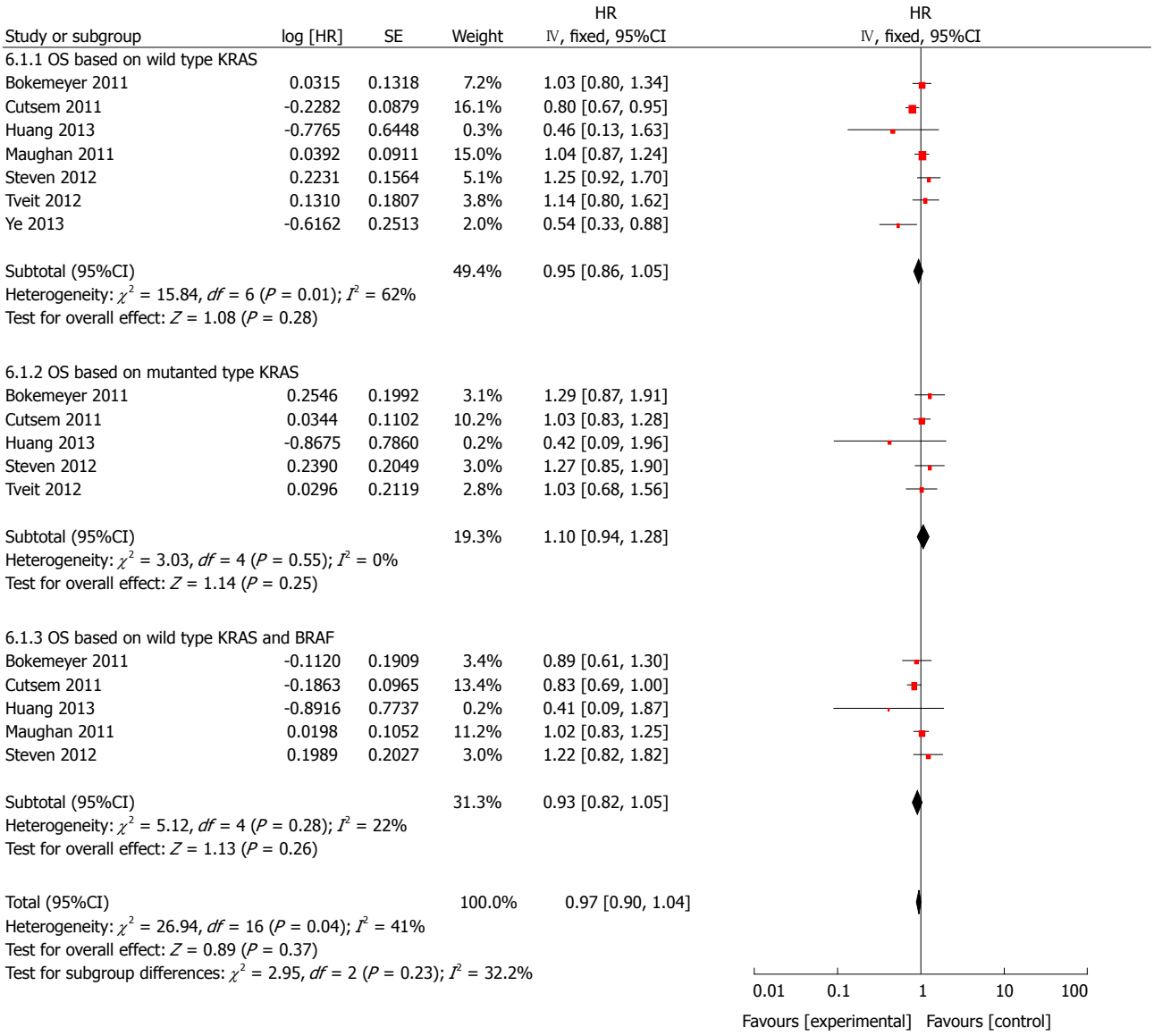



**Figure 3 Meta-analysis of effect of cetuximab plus chemotherapy on overall survival based on status of *KRAS*.**

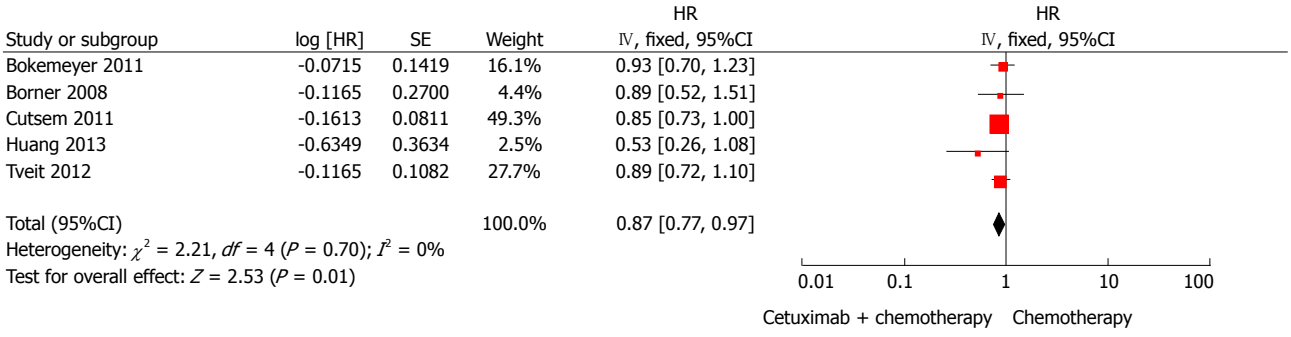



**Figure 4 Meta-analysis of effect of cetuximab plus chemotherapy on progression-free survival regardless of *KRAS* status.**

**OS based on wild-type KRAS and BRAF:** We also analyzed the effect of cetuximab on OS in patients with both wild-type *KRAS* and *BRAF* by using five studies[21,22,24-26]. Still, it showed that there was no significant improvement on OS (HR = 0.93, 95%CI: 0.82-1.05; *P* > 0.05; Figure 3), though in the setting

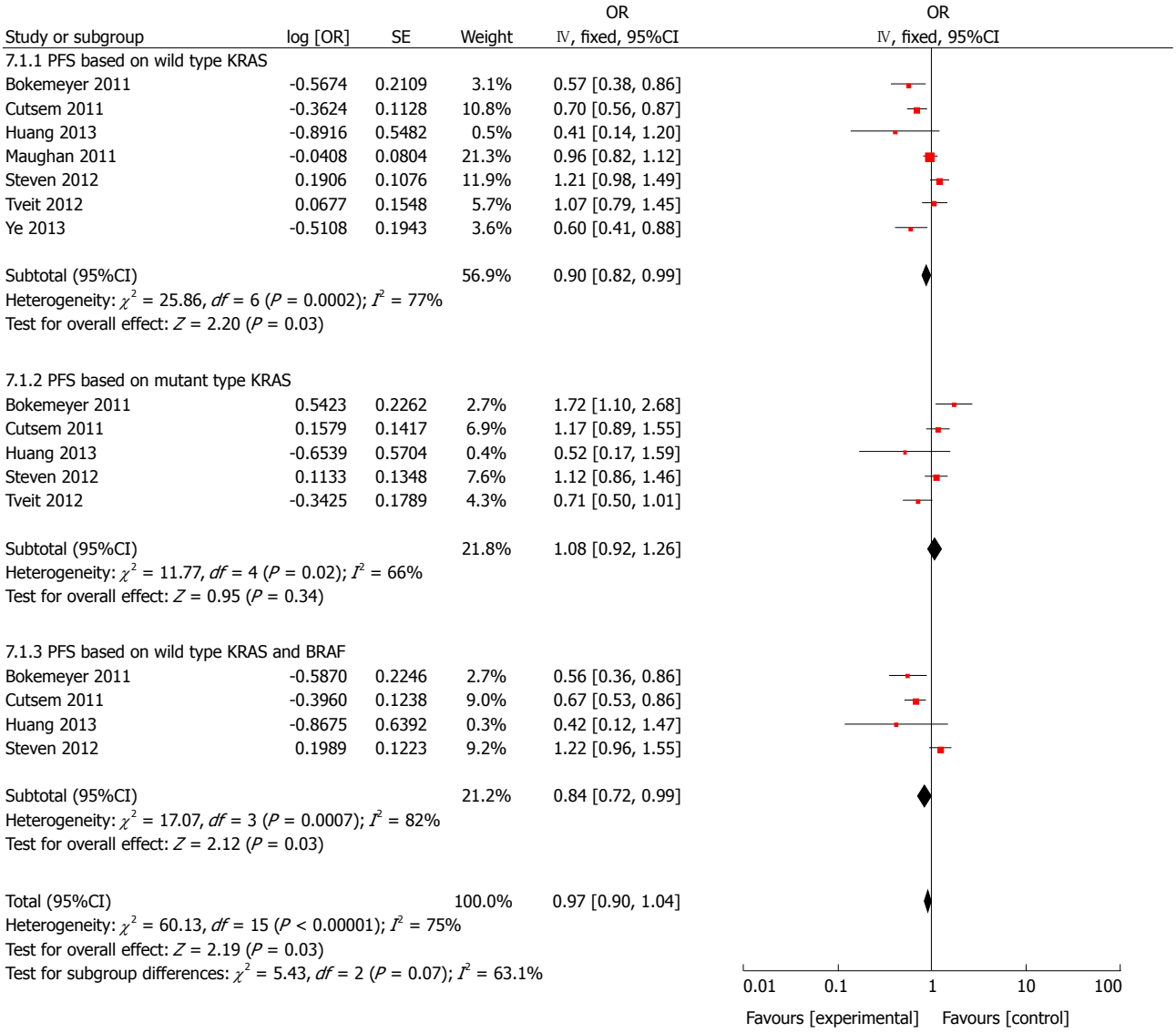



**Figure 5 Meta-analysis of effect of cetuximab plus chemotherapy on progression-free survival based on status of *KRAS*.**

of wild-type targeted genes.

### *Analysis of PFS*

**PFS regardless of *KRAS* status:** Five trials[21,22,24,25,27] were used to evaluate the improvement in PFS with cetuximab combined with chemotherapy *vs* chemotherapy alone. Compared with chemotherapy, there was a significantly prolonged PFS in patients treated with cetuximab (HR = 0.87, 95%CI: 0.77-0.97; *P* < 0.05; Figure 4).

**PFS based on wild-type *KRAS*:** We further performed a sub-group analysis of cetuximab combined with chemotherapy *vs* chemotherapy in patients having wild-type *KRAS*. As shown in Figure 5, cetuximab succeeded to provide a significant improvement in PFS (HR = 0.90, 95%CI: 0.82-0.99; *P* < 0.05).

**PFS based on mutated *KRAS*:** A total of five studies[21,22,24-26] were selected for the analysis of PFS based on mutant *KRAS* in patients who received cetuximab combined with chemotherapy. A significant difference was not observed from the result (HR = 1.08, 95%CI: 0.92-1.26; *P* > 0.05, Figure 5).

**PFS based on wild-type KRAS and BRAF:** Analysis of cetuximab plus chemotherapy *vs* chemotherapy was performed using data extracted from four RCTs[21,24-26]. A positive result was obtained and it presented that cetuximab therapy benefited PFS significantly in patients with wild-type *KRAS* and *BRAF* (HR = 0.84, 95%CI: 0.72-0.99; *P* < 0.05; Figure 5).

### *Analysis of PFS and OS based on chemotherapy regimen*

We performed another combined analysis based on different chemotherapy regimens. Whether the regimen contained irinotecan was used as the standard to group the included studies. Cetuximab added to irinotecan-

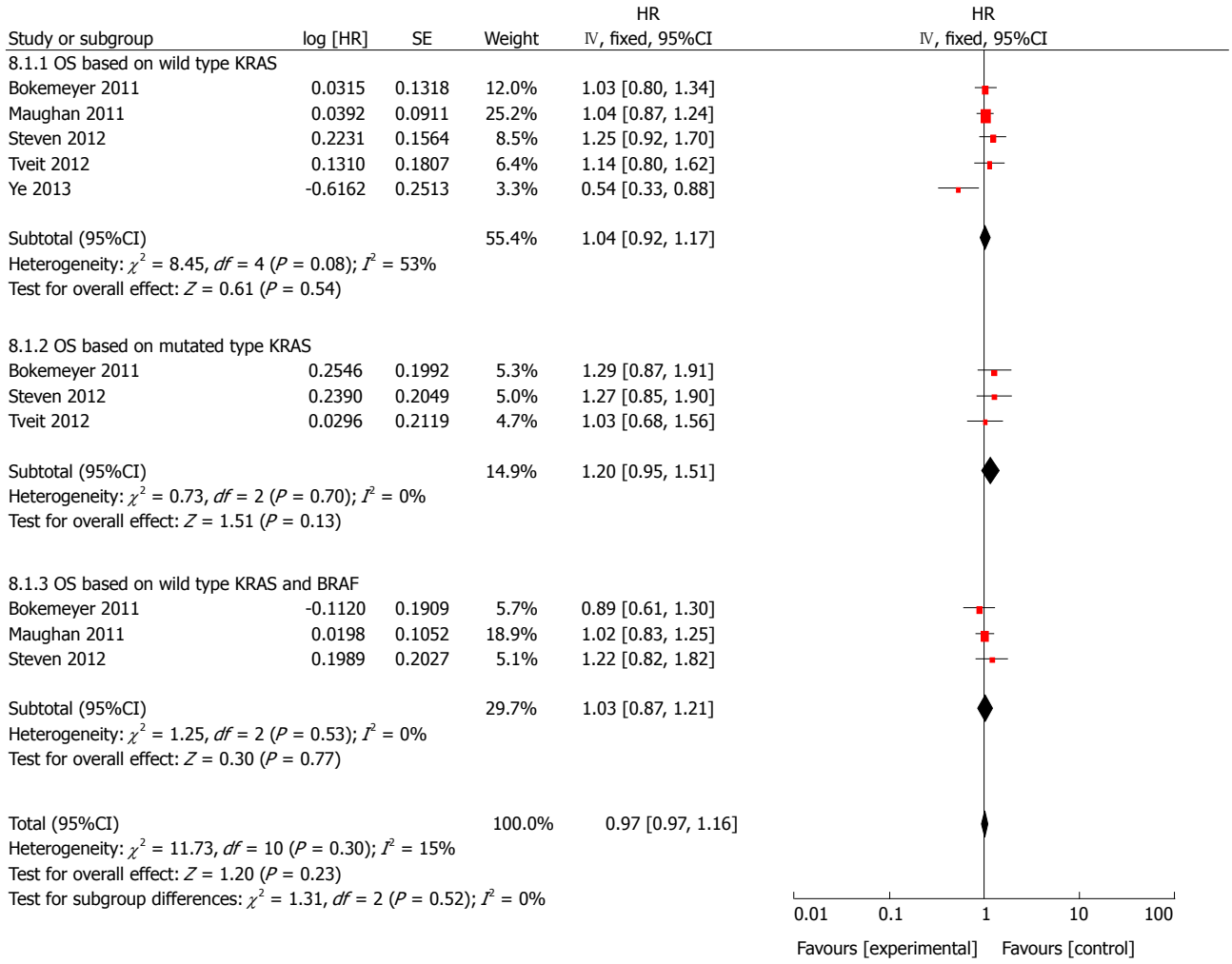
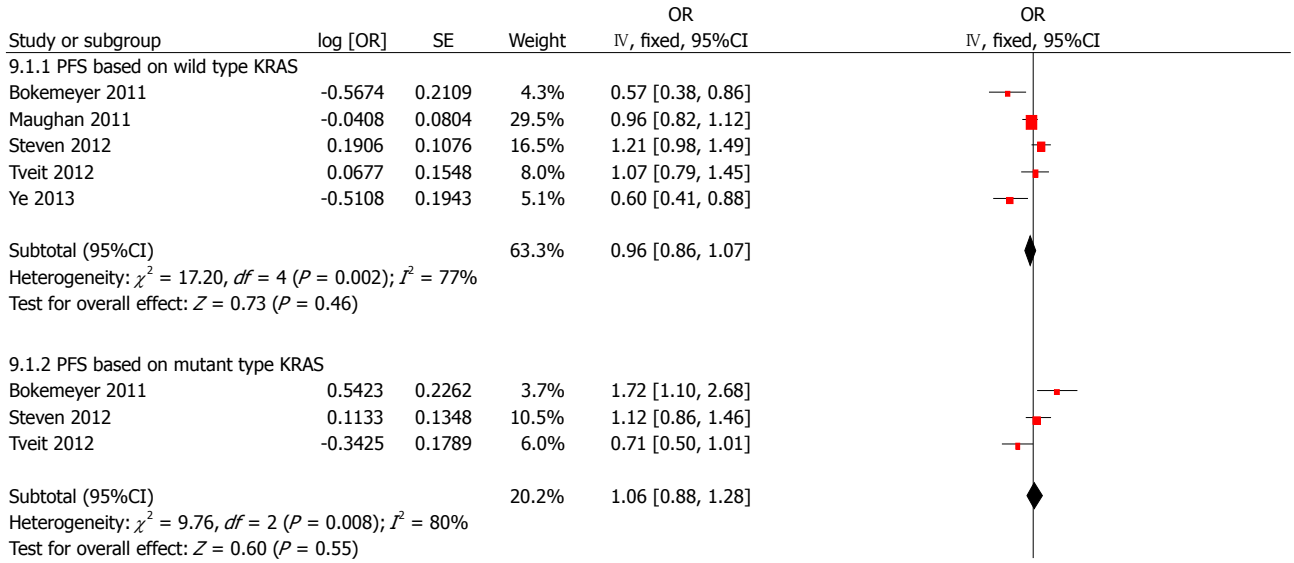



**Figure 6 Meta-analysis of effect of cetuximab plus irinotecan-free chemotherapy on overall survival based on status of *KRAS*.**



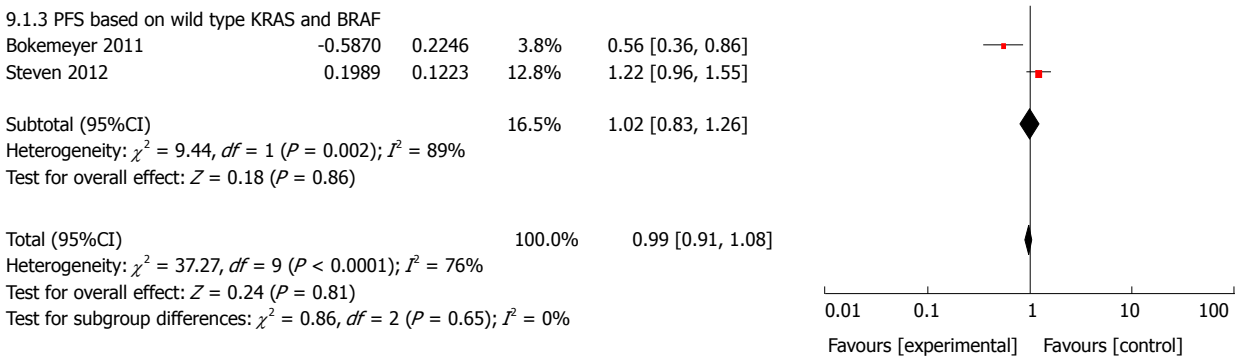



**Figure 7 Meta-analysis of effect of cetuximab plus irinotecan-free chemotherapy on progression-free survival based on status of *KRAS*.**

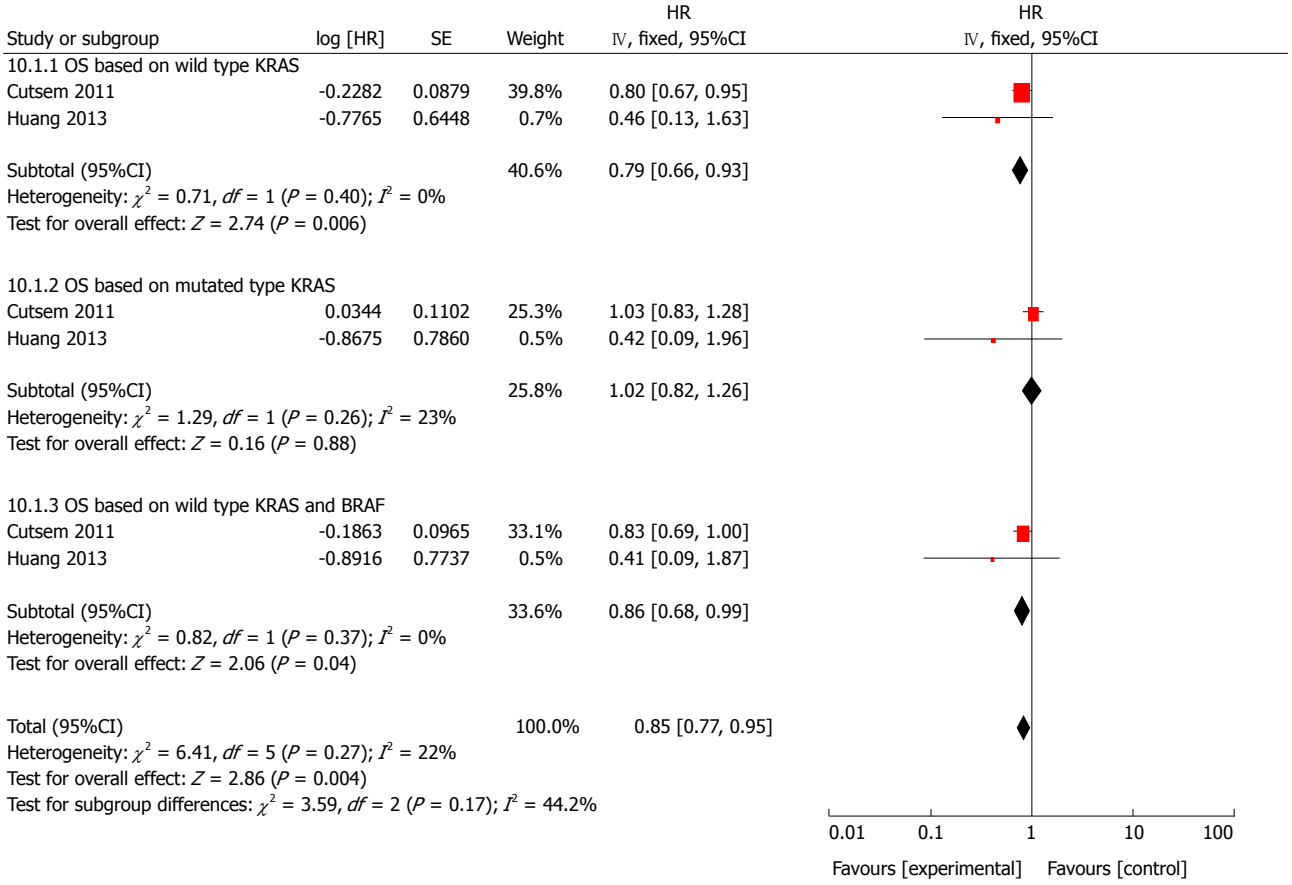



**Figure 8 Meta-analysis of effect of cetuximab plus irinotecan containing chemotherapy on overall survival based on status of *KRAS*.**

free regimen did not significantly improve the OS (HR = 1.06, 95%CI: 0.97-1.16; *P* = 0.23; Figure 6) or PFS (HR = 0.99, 95%CI: 0.91-1.08; *P* = 0.81; Figure 7) in patients with mCRC, regardless of status of *KRAS* and/or *BRAF*. Next, we compared the outcomes of patients receiving cetuximab and irinotecan, and the weighted results showed that cetuximab and irinotecan significantly improved OS (HR = 0.85, 95%CI: 0.77-0.95; *P* = 0.004; Figure 8) and PFS (HR = 0.77, 95%CI: 0.67-0.88; *P* = 0.0002; Figure 9) in mCRC patients with wild-type *KRAS*, but not in patients with mutant *KRAS*.

### *Analysis of adverse events*

As cetuximab is a targeted agent, we examined the effect of cetuximab on adverse events. The results determined that patients who received cetuximab suffered from more adverse events such as skin toxicity/rash (HR = 18.35, 95%CI: 11.28-29.86; *P* = 0.008, Figure 10), rash (HR = 43.27, 95%CI: 21.73-86.17; *P* = 0.0002; Figure 10), diarrhea (HR = 1.66, 95%CI: 1.37-2.02; *P* < 0.001; Figure 10), and nausea and vomiting (HR = 1.44, 95%CI: 1.11-1.87; *P* = 0.007; Figure 10), indicating that the application of cetuximab should be carefully considered not only

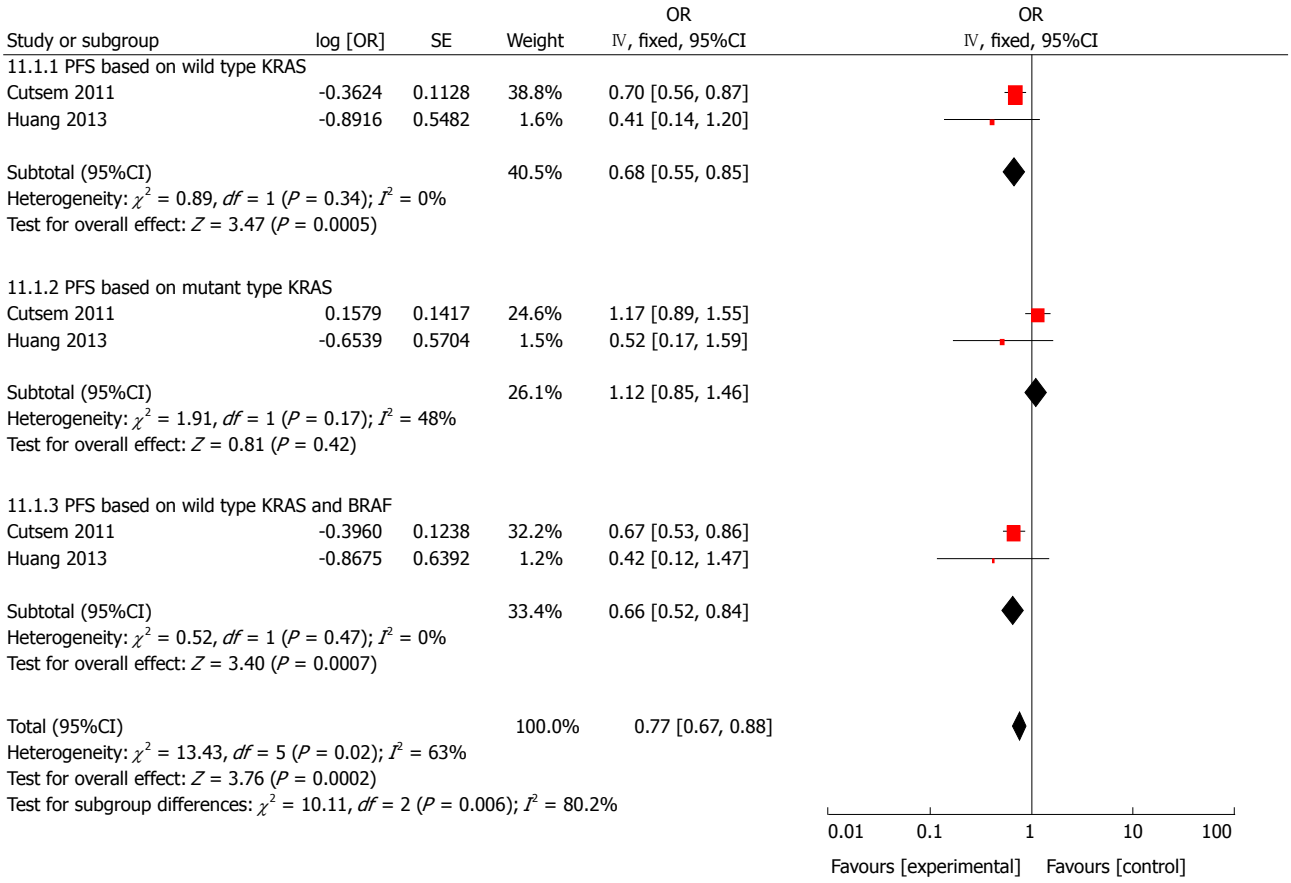
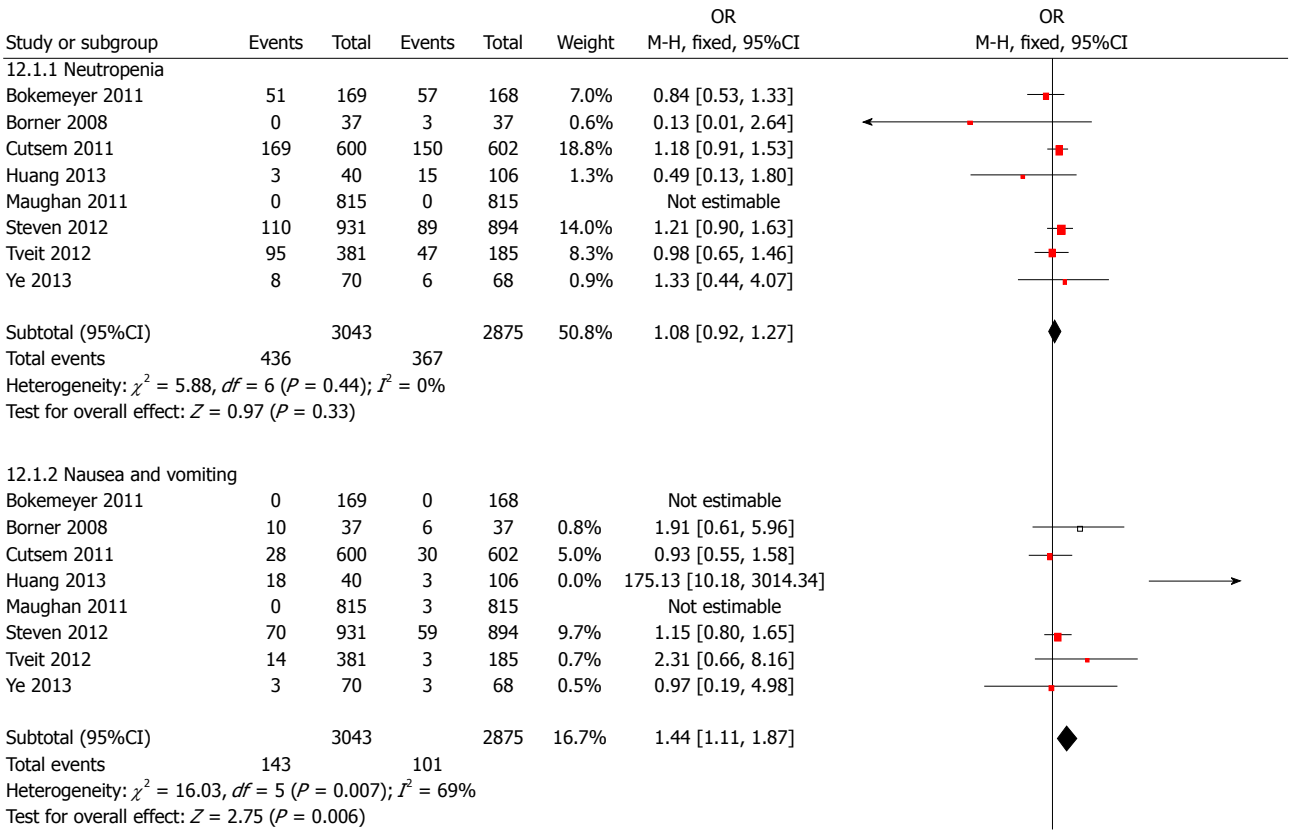



**Figure 9 Meta-analysis of effect of cetuximab plus irinotecan containing chemotherapy on progression-free survival based on status of *KRAS*.**



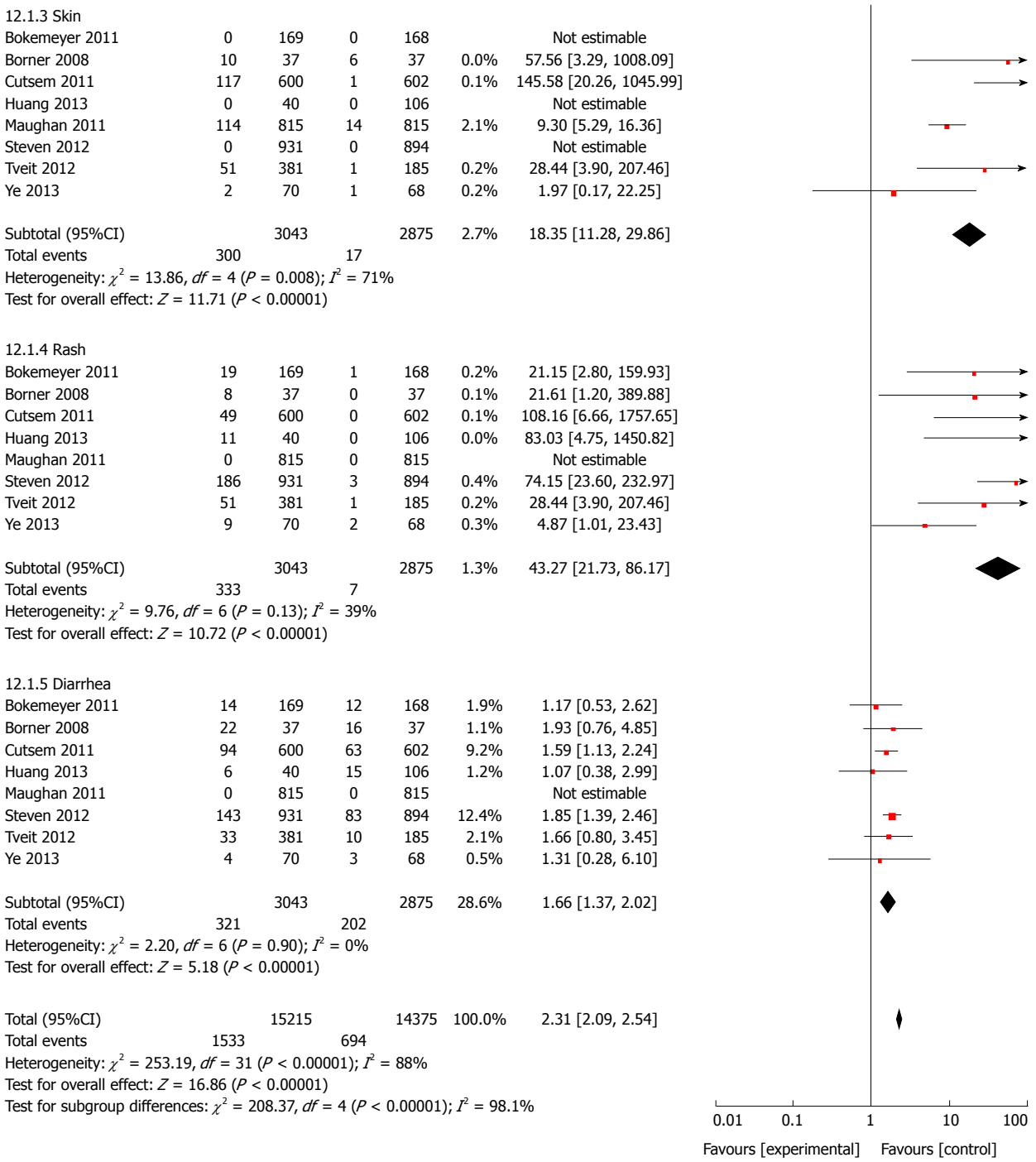



**Figure 10 Meta-analysis of adverse events in patients receiving cetuximab or not.**

based on status of targeted genes, but also the quality of life and safety.

### *Analysis of publication bias*

To evaluate the publication bias, we performed the Egger's test and funnel plot. As illustrated by Figure 11, only 2 studies exceeded the confidence interval and the Egger's test showed that there was no significant publication bias within the included studies ($P < 0.05$).

## DISCUSSION

Cetuximab, in combination with chemotherapy, has been approved for the treatment of mCRC patients[28]. Many clinical trials[14-18,28] have been published to evaluate the efficacy of cetuximab in mCRC, especially based on *KRAS* status. However, the outcomes from these studies were not consistent. Thus, it is essential to provide clinical evidence relating to the application of

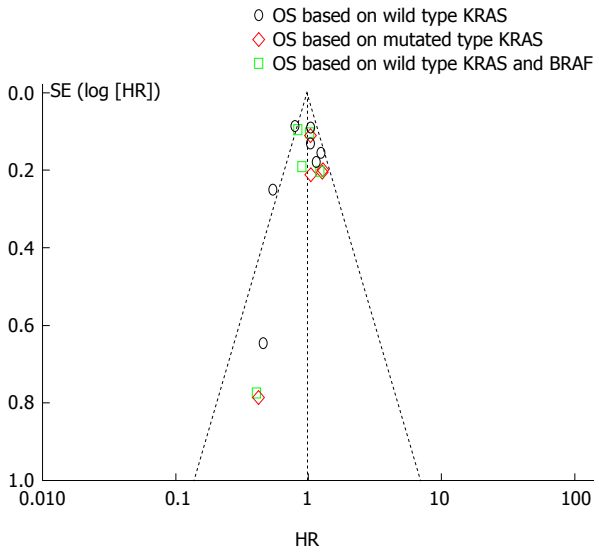



**Figure 11 Funnel plot for detecting publication bias.**

cetuximab in mCRC treatment. Indeed, several meta-analyses[29-33] have been published in recent years, but the arguments about whether cetuximab could benefit outcomes of mCRC patients with different *KRAS* status still exist. The present meta-analysis was performed to address the issues mentioned above, and to increase the statistical power of efficacy analysis of cetuximab in mCRC patients and further to identify what kind of population could benefit from treatment of cetuximab most.

The present meta-analysis confirms that adding anti-EGFR therapy to standard chemotherapy could result in clinical benefits in the treatment of mCRC containing wild-type *KRAS*, with a significantly prolonged PFS. For patients harboring wild-type *KRAS*, a statistically significant longer PFS was found when using cetuximab with traditional chemotherapy regimens. However, cetuximab treatment was associated with an impaired improvement in OS, and no statistical significance was achieved. Compared with the clinical benefit of addition of cetuximab to chemotherapy regimens in wild-type *KRAS* patients, mutation of *KRAS* is a predictor of less sensitivity to cetuximab in mCRC patients with regard to PFS and OS. The subgroup analysis demonstrated that cetuximab in combination with irinotecan containing regimen could improve OS and PFS in patients with wild-type KRAS and/or BRAF, but not in patients with mutant KRAS. These benefits were not observed in patients treated with irinotecan-free chemotherapy. Notably, the incidence of adverse events in the cetuximab group was much higher than that in patients without cetuximab treatment.

The results of this meta-analysis is in accordance with those of other meta-analyses[34]. In the study performed by Qiu *et al*[31], they compared the efficacy of cetuximab combined with chemotherapy *vs* chemotherapy for patients with mCRC, as well as the influence of *KRAS* mutation status on the outcomes, and the results showed that in wild-type *KRAS* patients, cetuximab plus chemotherapy significantly improved PFS when compared with chemotherapy alone, but not for OS, whereas in mutant *KRAS* patients, there was no significant benefit between those treated with cetuximab plus chemotherapy and those with chemotherapy alone regarding PFS and OS. In addition, Bokemeyer *et al*[14] enrolled CRYSTAL and OPUS studies for meta-analysis and by analyzing pooled data from the CRYSTAL and OPUS studies, they confirmed that adding cetuximab to first-line chemotherapy in patients with *KRAS* wild-type mCRC could obtain benefit in all efficacy end-points. Barni *et al*[32] conducted a meta-analysis evaluating the efficacy of cetuximab in patients with wild-type *KRAS* as second- or further-line therapy, and they demonstrated that treatment with cetuximab plus chemotherapy in mCRC patients with wild-type *KRAS* pretreated with one or more lines of therapy could improve survival outcomes, however, this meta-analysis did not include patients treated with chemotherapy alone and patients with mutant *KRAS* status.

In contrast to the results mentioned above, the meta-analysis of Zhou *et al*[29] showed that the addition of cetuximab or panitumumab to oxaliplatin-based chemotherapy in first-line treatment of mCRC in wild-type *KRAS* population did not improve survival benefit or response rate. They explained that the nature and interaction of drugs used in combination may be responsible for this observation[29]. Indeed, constitutive activation of the intracellular signaling pathway downstream of EGFR would counteract the effects of anti-EGFR agents[12], though it is in the setting of *KRAS* mutation status. In addition, another meta-analysis demonstrated that efficacy of cetuximab could be influenced by drugs used in combination[34]. Indeed, irinotecan has been widely used in the treatment of mCRC, but not all of the patients were treated with this agent. Our study proved that efficacy of cetuximab combined with irinotecan chemotherapy was much better those without irinotecan. These all demonstrated the complexity of tumor pathology and capacity of response to different chemotherapy. More elegant trials considering suitable drugs used in combination treatment are needed.

It seems that KRAS status is a good predictor of sensitivity to cetuximab treatment, making it reasonable to detect the exact mutation location in *KRAS* gene. In our study, we observed that patients with wild-type KRAS could benefit a lot from cetuximab treatment, while this did not happen in patients with mutant *KRAS*. However, several studies[30,35,36] reported that certain specific mutations in *KRAS* could gain a greater clinical response to anti-EGFR treatment than patients with other *KRAS* mutations. This again demonstrated the complexity in the treatment of mCRC patients regarding *KRAS* status.

There are a few limitations in the present meta-analysis. First, the randomization is not appropriately applied in some of the studies, and heterogeneity in trial protocols, age, sex, and endpoint variables is inevitable. Second, information about PFS and OS is not directly available from each included study. Finally, only a subset of specimens were available from all participants, despite that the initial trials were carefully designed. However, these limitations could be attenuated partly by using random effect model analysis. More elegant RCTs assessing efficacy of cetuximab in the treatment of mCRC patients with different *KRAS* status are warranted.

In conclusion, the results from this meta-analysis strength the evidence supporting the use of cetuximab treatment in combination with traditional chemotherapy in mCRC patients with wild-type *KRAS*. *KRAS* status should be explored prior to the initiation of adding cetuximab to treatment of mCRC patients in order to avoid ineffective and toxic therapies. For patients with unclear status of *KRAS* and/or *BRAF*, cetuximab should be initially considered. More challenges emerged in the search of better biomarkers of cetuximab in mCRC, in the setting that certain *KRAS* mutational status is also associated with an favorable outcome when encountering with other mutational status. It is expected to find that judicious application of biomarkers will provide more chances to optimize the use of cetuximab.

## COMMENTS

### Background

The application of novel molecular targeted agents prolongs the survival of patients with metastatic colorectal cancer (mCRC). However, some research showed that addition of cetuximab to chemotherapy did not improve the outcome of mCRC patients, making the anti-tumor effect of cetuximab controversial, and indicating that cetuximab should be recommended based on individual information. Therefore, it is urgent to identify patients who could benefit from cetuximab treatment most and this relies on effective biomarkers in predicting efficacy of cetuximab in the treatment of mCRC.

### Research frontiers

The KRAS protein is one of the most important downstream effectors coupling EGFR to intracellular signaling cascades. The mutations of *KRAS* may contribute to the lack of response to anti-EGFR monoclonal antibodies in patients with mCRC. Thus, it is essential to evaluate whether KRAS is a biomarker of effectiveness of cetuximab using pooled data.

### Innovations and breakthroughs

Pooled data from the CRYSTAL and OPUS studies confirmed that in patients with KRAS wild-type tumors, adding cetuximab to chemotherapy led to a significant improvement in overall survival (OS), progression-free survival (PFS) and overall response rate. However, other trials demonstrated that KRAS status was not predictive of benefit when adding cetuximab to the first-line therapy.

### Applications

The results from this meta-analysis strength the evidence supporting the use of cetuximab treatment in combination with traditional chemotherapy in mCRC patients with wild-type *KRAS*. *KRAS* status should be explored prior to the initiation of adding cetuximab to treatment of mCRC patients in order to avoid ineffective and toxic therapies. For patients with unclear status of *KRAS* and/or *BRAF*, cetuximab should be initially considered.

### Terminology

In this systematic review, the authors performed a series of subgroup analysis regarding not only FPS or OS of the patients, but also the mutation status of *KRAS* and/or *BRAF*, to compare the efficacy and safety of additional cetuximab to irinotecan containing chemotherapy under these different circumstances.

### Peer-review

This is a good systematic review in which the authors analyzed the cetuximab treatment in mCRC with regard to *KRAS* status. The results are clear and interesting and suggest that KRAS is a biomarker of effectiveness of cetuximab, and *KRAS* status should be explored prior to the initiation of adding cetuximab to treatment of mCRC patients in order to avoid ineffective and toxic therapies.

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