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ORIGINAL RESEARCH

Efficacy and safety of anti-epidermal growth factor receptor therapy compared with anti-vascular endothelial growth factor therapy for metastatic colorectal cancer in first-line and second-line therapies: a meta-analysis

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Aim: This study aimed to compare anti-epidermal growth factor receptor (anti-EGFR) therapy and anti-vascular endothelial growth factor therapy as first-line and second-line therapies in patients with KRAS exon 2 codon 12/13 wild-type (KRAS-WT) metastatic colorectal cancer (mCRC).

Methods: Major databases were systematically searched. The hazard ratio (HR), odds ratio (OR), and 95% confidence intervals (95% CIs) were used to estimate the effect measures. Review Manager software version 5.3 was used for statistical analysis.

Results: Seven trials including ten articles were eligible in the meta-analysis. The patients treated with anti-EGFR as first-line therapy showed a longer overall survival (OS) for KRAS-WT and all RAS wild-type (RAS-WT) mCRC (HR =0.81, 95% CI: 0.72–0.92, $P<0.01$, n=5; HR =0.78, 95% CI: 0.66–0.93, $P<0.01$, n=3, respectively). The objective response rate (ORR) was better with the anti-EGFR therapy for KRAS-WT and all RAS-WT mCRC (OR =1.32, 95% CI: 1.11–1.56, $P<0.01$, n=5; OR =1.55, 95% CI: 1.21–2.00, $P<0.01$, n=3, respectively). There was no difference in progression-free survival (PFS) for KRAS-WT mCRC and all RAS-WT mCRC between the two groups (HR =1.00; 95% CI: 0.92–1.09, $P=0.99$, n=4; HR =0.92, 95% CI: 0.71–1.19, $P=0.52$, n=3, respectively). In addition, two trials provided data on the second-line therapy; there was no significant difference in OS and PFS for the second-line therapy, but a significant improvement in ORR was found in the anti-EGFR group (OR =1.91, 95% CI: 1.16–3.16, $P=0.01$, n=2). No difference in the conversion therapy (OR =1.34; 95% CI: 0.91–1.99; $P=0.14$, n=4) was observed between the two therapies.

Conclusion: Our results indicate that anti-EGFR therapy is superior to anti-vascular endothelial growth factor therapy for OS and ORR as a first-line therapy for KRAS-WT mCRC. In the second-line therapy, there was no significant difference in the survival outcomes on the basis of OS and PFS between the two groups. However, ORR improved significantly in the anti-EGFR group.

Keywords: colorectal cancer, anti-EGFR, anti-VEGF, chemotherapy, meta-analysis

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Introduction

Colorectal cancer (CRC) is the third most common cancer among males and the second most common cancer among females, with an estimated death of 600,000 individuals in 2012 worldwide owing to advanced CRC.[1] Although the surgical approach has ensured

an improvement in the management of early and advanced CRC, the prognosis of patients with metastatic CRC (mCRC) is still poor.[2] The systemic therapeutic approach is the major choice of treatment for mCRC. In the past decade, combination chemotherapies, including 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and fluorouracil, folinic acid, and irinotecan (FOLFIRI), have improved the survival outcomes significantly in patients with mCRC.[3,4] More recently, studies have demonstrated that the addition of anti-epidermal growth factor receptor (anti-EGFR) or anti-vascular endothelial growth factor (anti-VEGF) to the conventional combination chemotherapy improved the survival outcomes compared with conventional combination chemotherapy.[5–7] Therefore, antibodies to EGFR/VEGF in combination with FOLFOX or FOLFIRI have become the first- and second-line treatment options for patients with mCRC.

However, anti-EGFR therapy predicted a negative outcome for mCRC patients with mutations in codons 12 and 13 of KRAS exon 2 (up to 40%).[8] In addition, recent studies have indicated that less frequent mutations in RAS protooncogenes HRAS, KRAS, and NRAS, including mutations in exons 3 or 4 of KRAS and exons 2–4 of NRAS, predicted a lack of effectiveness of anti-EGFR therapies in mCRC patients.[9,10] Therefore, the patients with such mutations who were excluded after RAS and KRAS analyses would have higher survival with anti-EGFR therapy combined with conventional combination therapy, compared with the conventional combination therapy alone.[10,11] However, at present, there is no predictive biomarker for anti-VEGF therapy.

Recent studies have demonstrated conflicting results for the types of antibody (anti-EGFR or anti-VEGF) that provide better clinical efficacy for mCRC patients.[12–15] A previous meta-analysis compared anti-EGFR and anti-VEGF therapies in the first-line setting on the basis of overall survival (OS), progression-free survival (PFS), and objective response rate (ORR).[16] However, it did not compare the two therapies based on toxicity, second-line therapy, and conversion therapy. Therefore, we conducted this meta-analysis including randomized clinical trials and retrospective studies so as to give an overview of the results comparing anti-EGFR and anti-VEGF therapies as first- and second-line therapies based on survival outcomes, toxicity, and conversion rate in conversion therapy in patients with KRAS exon 2 wild-type (KRAS-WT) mCRC.

Materials and methods

Search strategy

This meta-analysis was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[17] We conducted a systematic literature search for journals published until January of 2016 using PubMed, EMBASE, and the Cochrane databases. We also searched for abstracts from the American Society of Clinical Oncology and European Society for Medical Oncology. The main search terms were "cancer of colon", "colorectal carcinoma", "colorectal cancer", "cetuximab or panitumumab or anti-EGFR", and "bevacizumab or aflibercept or anti-VEGF". We also screened relevant abstracts, methods, and references of the retrieved articles. The search was limited to human studies, and the language of the searched publications was restricted to English.

Inclusion criteria

To ensure the accuracy and reliability of the analysis, the studies included in this meta-analysis met the following criteria: 1) studies involving patients diagnosed with KRAS-WT mCRC; 2) trials that compared anti-EGFR therapy and anti-VEGF therapy in association with combination chemotherapy as first-line or second-line chemotherapy for mCRC; and 3) studies that reported at least one of the following outcome measures: OS, PFS, ORR, toxicity, and conversion therapy.

Exclusion criteria

The exclusion criteria were as follows: 1) studies that evaluated fewer than 30 patients; 2) studies that lacked sufficient data necessary for analysis; 3) repeated studies that contained the same databases or patients; 4) letters, reviews, case reports, editorials, and expert opinions.

Quality assessment

Two independent reviewers (H. C. Wang and B. Ma) used the Jadad scale to assess the methodological quality of all eligible randomized controlled trials (RCTs) and the Newcastle–Ottawa Scale to evaluate the quality of the nonrandomized studies.[18,19] Any disagreements between the two reviewers were resolved by a third reviewer.

Data extraction

Two researchers (H. C. Wang and B. Ma) independently extracted data from all eligible studies. The outputs for this meta-analysis included first author's name, year of publication, country of origin of the studies, study design, participants (number of patients and mean age), study regimen, Eastern Cooperative Oncology Group performance status score, ORR, OS, PFS, toxicity, and conversion therapy. Any disagreements were resolved by a third reviewer.

Statistical analysis

The end points of this study were OS, PFS, ORR, toxicity, and conversion rate. ORR was defined as the sum of partial and complete response rates, according to the Response Evaluation Criteria in Solid Tumors.[20] Toxicity was assessed using the National Cancer Institution Common Toxicity Criteria (version 2.0, http://ctep.cancer.gov). This meta-analysis was conducted using Review Manager software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

Time-to-event data (OS, PFS) analyses were performed via calculation of the hazard ratio (HR) and 95% confidence intervals (CIs). The pooled HR was calculated using the inverse-variance-weighted average of the individual studies. Dichotomous data (ORR, toxicity, and conversion rate) were represented by pooled estimates of odds ratios (ORs) and 95% CIs. A test with a P-value of <0.05 was considered statistically significant. The heterogeneity between studies was tested using the Cochran Q-test and I^2 index. P-values <0.1 and/or $I^2 > 50\%$ indicated significant heterogeneity. A random-effects model was used in cases of significant heterogeneity. Otherwise, data were analyzed using a fixed-effects model.[21] Publication bias was assessed by Begg's and Egger's tests based on the Stata software, version 12.0 (2011; Stata Corp, College Station, TX, USA).[22,23] Subgroups analyses were performed considering the patient groups (KRAS-WT mCRC patients and all RAS-WT mCRC patients) and the chemotherapy backbones (FOLFOX and FOLFIRI).

Results

Eligible studies

We searched 3,090 studies (Figure 1), 61 of which were retrieved after the screening of titles and abstracts. Subsequently, 51 studies were excluded because of redundancy or the lack of an outcome of interest. Therefore, seven trials containing ten articles (the CALGB/SWOG80405 trial was found in meeting abstracts from four articles) were finally included in this meta-analysis. The baseline characteristics of the included trials are listed in Table 1. Eight eligible articles (the CALGB/SWOG80405 trial was found in meeting abstracts from four studies, all of which presented different outcomes) involving 1,117 patients in the anti-EGFR group and 1,193 patients in the anti-VEGF group compared two therapies used as the first-line setting (we accumulated the patients number from CALGB/SWOG80405 trial only once).[12–15,24–27] Two articles (including one meeting abstract) containing 160 patients in the anti-EGFR group and 147 patients in the anti-VEGF group, respectively, were eligible for our study in the second-line setting.[28,29] All the RCTs had Jadad scores of ≥3 and were considered to be high-quality studies. All the retrospective studies had Newcastle–Ottawa Scale score of 6 and were considered

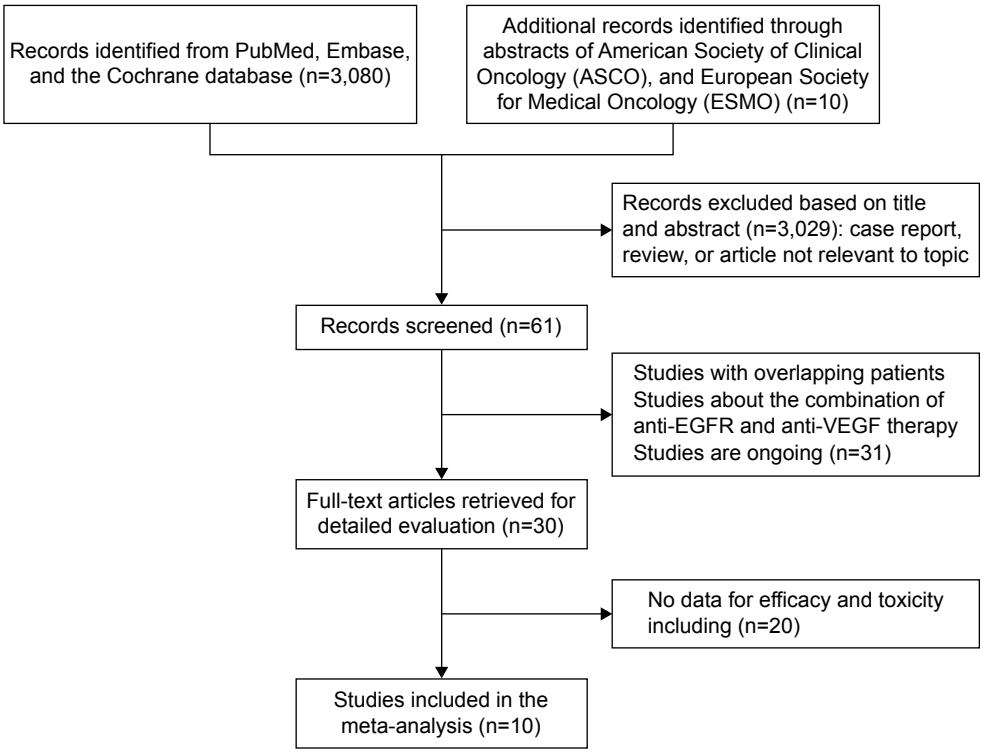

Figure 1 Flow chart of study selection.

Table 1 Characteristics of studies included in this meta-analysis

Study	Year	Country	Study design	Treatment groups	No of patients	Regimen	Age	PS
Heinemann et al[12]	2014	Germany	Randomized Phase III study	Group A	A=297	A: FOLFIRI + cetuximab	64 (38–79)	0–2
				Group B	B=295	B: FOLFIRI + bevacizumab	65 (27–76)	0–2
Schwartzberg et al[14]	2014	Spain	Randomized Phase II study	Group A	A=142	A: mFOLFOX6 + panitumumab	63 (23–82)	0–1
				Group B	B=143	B: mFOLFOX6 + bevacizumab	61 (28–82)	0–1
CALGB/ SWOG80405[13,15,24,26]	2014	USA	Randomized Phase III study	Group A	A=578	A: FOLFIRI/mFOLFOX6 + cetuximab	59 (NA)	0–1
				Group B	B=559	B: FOLFIRI/mFOLFOX6 + bevacizumab	59 (NA)	0–1
Stremitzer et al[25]	2015	Austria	Retrospective	Group A	A=37	A: Fluoropyrimidine only/irinotecan/oxaliplatin + cetuximab	63 (31–80)	NA
				Group B	B=101	B: irinotecan/irinotecan + oxaliplatin/oxaliplatin + bevacizumab	63 (31–80)	NA
Yang et al[27]	2014	Taiwan	Retrospective	Group A	A=63	A: irinotecan-based/oxaliplatin-based + cetuximab	NA	NA
				Group B	B=95	B: irinotecan-based/oxaliplatin-based + bevacizumab	NA	NA
Heinemann et al[29]	2015	Germany	Randomized Phase III study	Group A	A=69	A: FOLFIRI + cetuximab	NA	0–1
				Group B	B=56	B: FOLFIRI + bevacizumab	NA	0–1
Hecht et al[28]	2015	USA	Randomized Phase II study	Group A	A=91	A: FOLFIRI + panitumumab	60 (27–84)	0–1
				Group B	B=91	B: FOLFIRI + bevacizumab	60 (25–80)	0–1

Abbreviations: Irinotecan-based, irinotecan-based combination therapy; Oxaliplatin-based, oxaliplatin-based combination therapy; NA, not applicable; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; PS, performance status; mFOLFOX, modified, 5-fluorouracil, leucovorin, oxaliplatin.

to be moderate-quality studies (Tables S1 and S2). In our meta-analysis, we included five abstracts because only these provided the results without a detailed description of materials and methods. Hence, we did not assess the quality of the five abstracts.

Effectiveness of first-line therapy on the basis of OS, PFS, ORR, toxicity, and conversion therapy

Overall survival

Five articles provided data on OS for KRAS-WT mCRC.[12,14,15,25,27] An improvement in OS was observed in the anti-EGFR group compared with the anti-VEGF group (HR =0.81, 95% CI: 0.72–0.92, $P<0.01$, n=5) (Figure 2A). In addition, for all RAS-WT mCRC patients, the results of three studies on all RAS-WT mCRC corroborated the improvement in OS (HR =0.78, 95% CI: 0.66–0.93, $P<0.01$, n=3) (Figure 2B).[12–14] Furthermore, for all RAS-WT mCRC patients, we performed subgroup analyses on the basis of FOLFOX and FOLFIRI. No significant difference was observed between the two therapies (FOLFOX subgroup, HR =0.79, 95% CI: 0.60–1.04, $P=0.09$; FOLFIRI subgroup, HR =0.86, 95% CI: 0.55–1.34, $P=0.49$).[12,14,24] (Figure 2C). Publication bias was assessed by Begg's and Egger's test. There was no evidence of publication bias for pooled analysis of OS (P_{Begg} =0.806, P_{Egger} =0.295) (Figures S1 and S2).

Progression-free survival

Four articles on KRAS-WT mCRC[12,14,15,27] and three studies on all RAS-WT mCRC[12–14] provided data on PFS in the first-line therapy. There were no significant differences in PFS for KRAS-WT and all RAS-WT mCRC patients between the two therapies (HR =1.00, 95% CI: 0.92–1.09, $P=0.99$, n=4; HR =0.92, 95% CI: 0.71–1.19, $P=0.52$, n=3, respectively) (Figure 3A and B). In addition, for patients with all RAS-WT mCRC, we observed no significant difference in PFS between the two therapies based on the FOLFOX or FOLFIRI regimen (HR =0.87, 95% CI: 0.52–1.46, $P=0.60$; HR =0.98, 95% CI: 0.80–1.19, $P=0.83$, respectively)[12,14,24] (Figure 3C).

Toxicity

We evaluated the differences in Grade 3 toxicity or lower between the anti-EGFR and anti-VEGF groups. Three articles presented data on toxicity, and these studies are listed in Table 2.[12,14,27] The pooling analysis of relevant studies indicated a significant increase in the occurrence of skin disorders, hypomagnesemia, and hypokalemia in the anti-EGFR group compared with the anti-VEGF group (skin disorders: OR =20.35, 95% CI: 9.82–42.17, $P<0.01$, n=2; hypomagnesemia: OR =9.35, 95% CI: 2.52–34.69, $P<0.01$, n=2; hypokalemia: OR =2.43; 95% CI: 1.33–4.44, $P<0.01$, n=2). By contrast, there was a significant increase in hypertension in the anti-VEGF group (OR =0.12, 95% CI: 0.02–0.62, $P=0.01$, n=2). No significant differences in fatigue, stomatitis, dehydration, decreased appetite, nausea, and hypocalcemia were found between the two groups.

Objective response rate

For patients with KRAS-WT mCRC, data on ORR were available from five trials.[12,14,15,25,27] A total of 709 patients

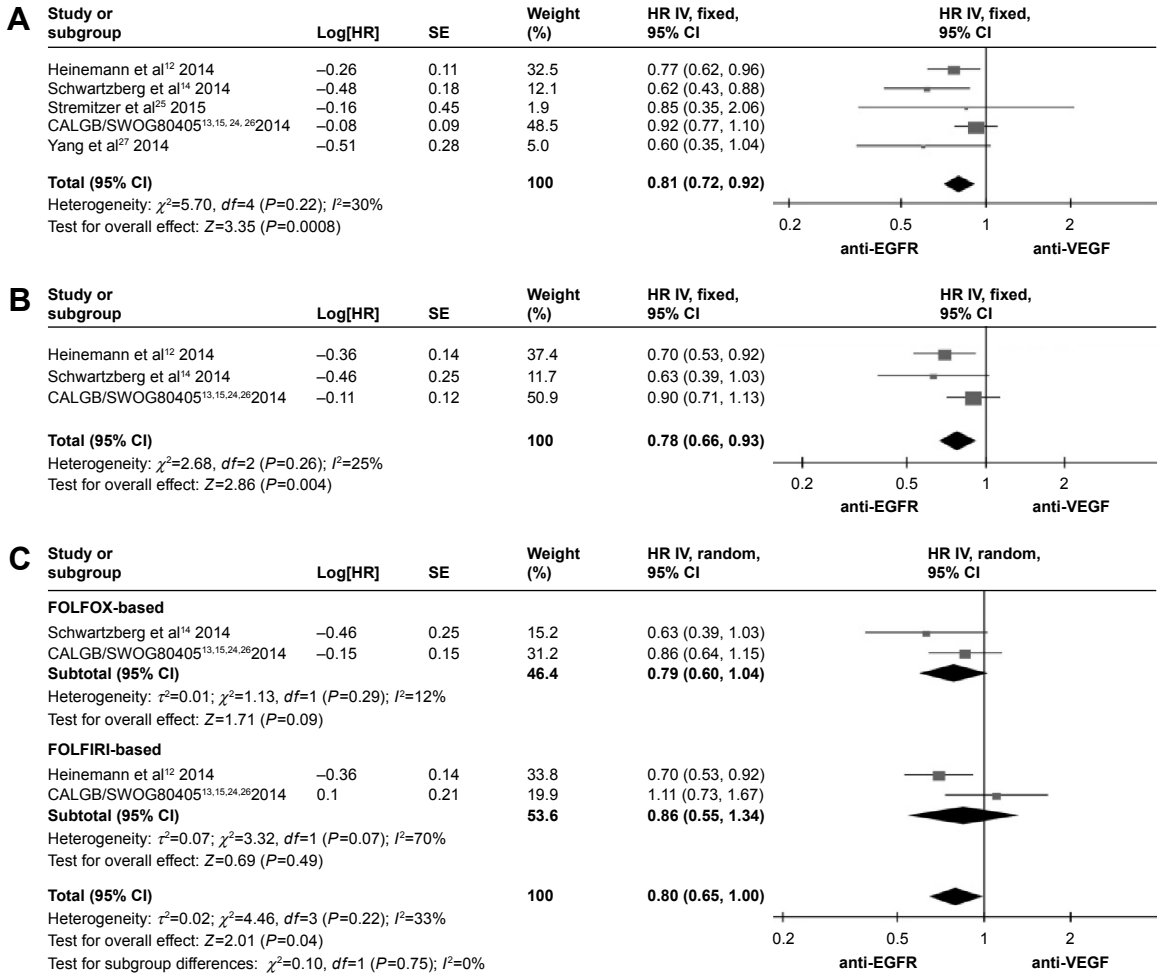

Figure 2 Forest plots and subgroup analysis.

Notes: (**A**) Forest plot of HR for OS in KRAS-WT mCRC patients; (**B**) Forest plot of HR for OS in all RAS-WT mCRC patients. (**C**) Subgroup analysis for OS based on FOLFIRI and FOLFOX.

Abbreviations: HR, hazard ratio; OS, overall survival; CI, confidence interval; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; WT, wild type; mCRC, metastatic colorectal cancer; anti-EGFR, anti-epidermal growth factor receptor; anti-VEGF, anti-vascular endothelial growth factor; SE, standard error; *df*, degrees of freedom.

(709/1,106, 64%) in the anti-EGFR group and 689 patients (689/1,169, 59%) in the anti-VEGF group achieved an objective response. A significant improvement in ORR was observed in the anti-EGFR group (OR =1.32, 95% CI: 1.11–1.56, $P<0.01$, n=5) (Figure 4A). In addition, three articles provided data on all RAS-WT mCRC.[12–14] A similar improvement in ORR was observed in all RAS-WT mCRC patients (OR =1.55, 95% CI: 1.21– 2.00, $P<0.01$, n=3) (Figure 4B).

Conversion therapy

Anti-EGFR and anti-VEGF therapies can improve metastasectomy outcomes by converting unresectable metastatic disease into resectable disease. Four studies presented data on conversion therapy.[12,14,26,27] A total of 183 patients (183/1,080) underwent surgical resection in the anti-EGFR group (17%) whereas 150 patients (150/1,092) underwent surgical resection in the anti-VEGF group (14%). There was no significant difference in this outcome between the two therapies (OR =1.34, 95% CI: 0.91–1.99, $P=0.14$, n=4) (Figure 4C). However, we found a clear tendency for conversion therapy in the anti-EGFR therapy compared with the anti-VEGF therapy.

Effectiveness of second-line therapy on the basis of OS, PFS, and ORR

Two articles (including one meeting abstract) provided data on the comparison between anti-EGFR and anti-VEGF therapies in combination with FOLFIRI for KRAS-WT mCRC when the disease progressed during oxaliplatin-based chemotherapy.[28,29] There was no significant difference in OS (HR =1.17, 95% CI: 0.88–1.56, $P=0.29$, n=2) (Figure 5A) and PFS (HR =1.12, 95% CI: 0.88–1.43, $P=0.36$, n=2) (Figure 5B) between the two therapies. However, there was a significant improvement in ORR in the anti-EGFR group

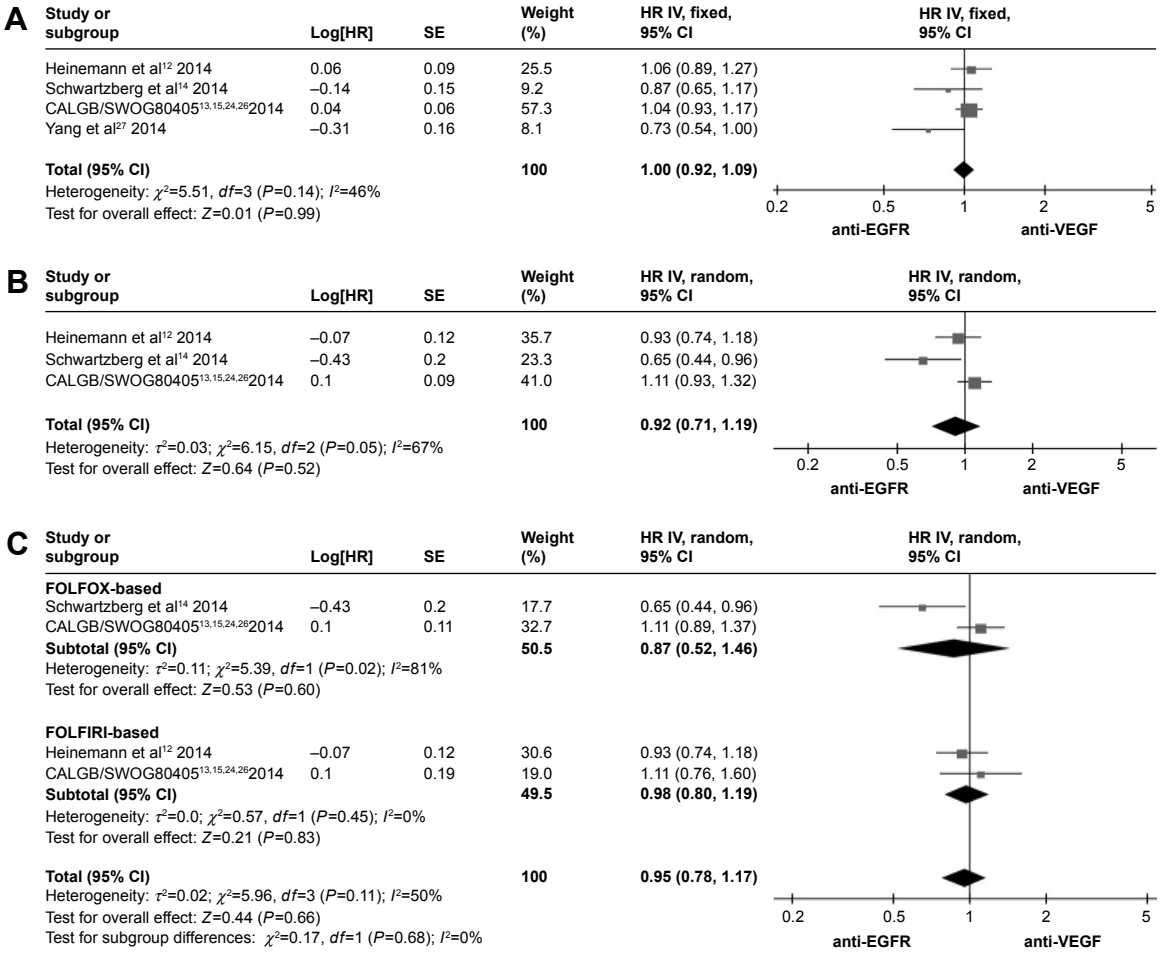

Figure 3 Forest plots.

Notes: (**A**) HR for PFS in KRAS-WT mCRC patients. (**B**) HR for PFS in all RAS-WT mCRC patients. (**C**) Subgroup analysis for PFS based on FOLFIRI and FOLFOX.

Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; WT, wild type; mCRC, metastatic colorectal cancer; anti-EGFR, anti-epidermal growth factor receptor; anti-VEGF, anti-vascular endothelial growth factor; SE, standard error; *df*, degrees of freedom.

when it was used as the second-line therapy (OR =1.91, 95% CI: 1.16–3.16, *P*=0.01, n=2) (Figure 5C).

Discussion

In recent years, molecularly targeted therapies, including anti-EGFR and anti-VEGF therapies, have been applied in the treatment of mCRC. Studies have reported that the inclusion of anti-EGFR or anti-VEGF agents to combination chemotherapy improved the survival outcomes in mCRC.[5,30,31] A recent review described the trials that compared the clinical efficacy and toxicity of anti-EGFR therapy and anti-VEGF therapy as a first-line therapy for KRAS-WT mCRC patients.[32]

Table 2 Toxicities (Grade 3 or lower) comparison between anti-EGFR therapy and anti-VEGF therapy

Toxicity	Trials	Anti-EGFR based (n)	Anti-VEGF based (n)	Heterogeneity *P*-value (I^2, %)	OR (95% CI)	*P*-value
Skin disorders	2	121	8	0.46 (0.0)	20.35 (9.82, 42.17)	<0.01
Hypomagnesemia	2	22	2	0.42 (0.0)	9.35 (2.52, 34.69)	<0.01
Fatigue	2	17	16	0.32 (0.0)	1.07 (0.52, 2.17)	0.86
Stomatitis	2	18	13	0.07 (71)	2.06 (0.27, 15.82)	0.49
Hypokalemia	2	37	16	0.86 (0.0)	2.43 (1.33, 4.44)	<0.01
Dehydration	2	8	5	0.07 (71)	1.61 (0.13, 19.83)	0.71
Hypocalcemia	2	7	7	0.23 (31)	0.99 (0.36, 2.76)	0.99
Decreased appetite	2	11	5	0.37 (0.0)	2.23 (0.77, 6.46)	0.14
Nausea	3	18	22	0.54 (0)	0.93 (0.49, 1.75)	0.81
Hypertension	2	1	14	0.23 (31)	0.12 (0.02, 0.62)	0.01

Abbreviations: anti-EGFR, anti-epidermal growth factor receptor; anti-VEGF, anti-vascular endothelial growth factor; OR, odds ratio; CI, confidence interval.

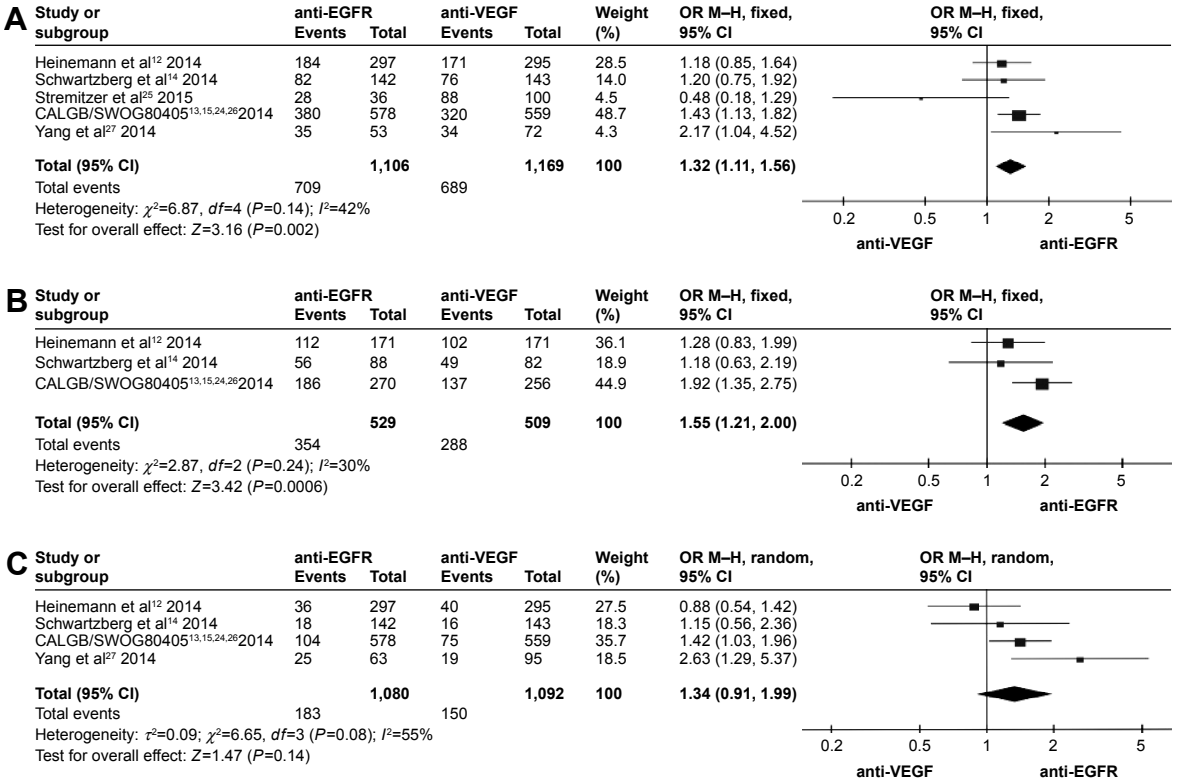

Figure 4 (**A**) OR for ORR in KRAS-WT mCRC patients, (**B**) OR for ORR in all RAS-WT mCRC patients, (**C**) OR for conversion therapy in KRAS-WT mCRC patients.
Abbreviations: OR, odds ratio; ORR, objective response rate; CI, confidence interval; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; WT, wild type; mCRC, metastatic colorectal cancer; anti-EGFR, anti-epidermal growth factor receptor; anti-VEGF, anti-vascular endothelial growth factor; SE, standard error; *df*, degrees of freedom.

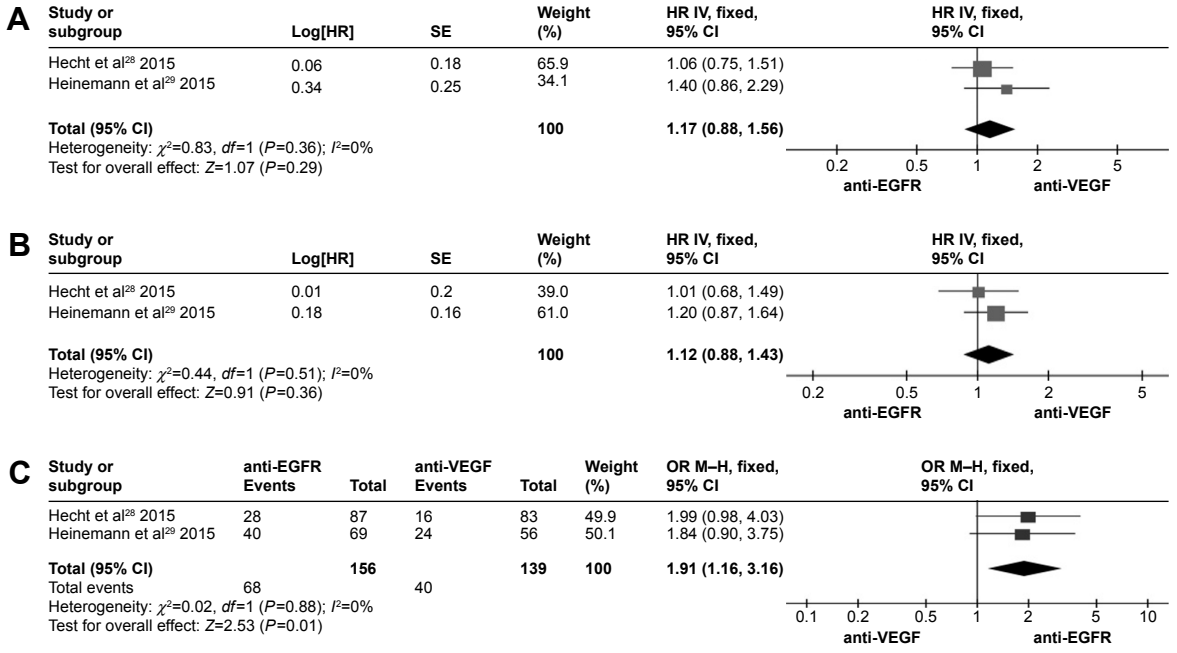

Figure 5 (**A**) HR for OS in KRAS-WT mCRC patients as a second-line therapy, (**B**) HR for PFS in KRAS-WT mCRC patients as a second-line therapy, (**C**) OR for ORR in KRAS-WT mCRC patients as a second-line therapy.
Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; OR, Odds ratio; ORR, objective response rate; CI, confidence interval; FOLFIRI, fluorouracil, folinic acid, and irinotecan; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; WT, wild type; mCRC, metastatic colorectal cancer; anti-EGFR, anti-epidermal growth factor receptor; anti-VEGF, anti-vascular endothelial growth factor; SE, standard error; *df*, degrees of freedom.

However, conflicting results between these trials were observed, and the optimal targeted combination chemotherapy as first-line and second-line treatments for mCRC patients is still unclear. A previous meta-analysis that evaluated the FIRE-3, PEAK, and CALGB/SWOG80405 trials concluded that ORR and OS were superior in the anti-EGFR therapy compared with anti-VEGF therapy for KRAS-WT mCRC, particularly in all RAS-WT mCRC patients; therefore, anti-EGFR therapy may be an alternative to anti-VEGF therapy as the initial treatment for mCRC.[16] However, the results of previous meta-analyses were restricted by the limited number of eligible studies, and it did not provide data on toxicity, conversion therapy, and second-line therapy between the two groups. Our meta-analysis added retrospective studies and provided a more comprehensive comparison between anti-EGFR and anti-VEGF therapies for KRAS-WT mCRC patients in the first-line therapy on the basis of OS, PFS, ORR, conversion therapy, and toxicity and in the second-line therapy on the basis of OS, PFS, and ORR. In our meta-analysis, eight eligible studies provided data on survival outcomes in the first-line therapy for mCRC patients, and three of the included studies were RCTs. These RCTs (CALGB 80405 trial was found in meeting abstracts from four studies) have reported conflicting results on OS, PFS, and ORR in KRAS-WT mCRC patients.[12,14,15] The analysis of the FIRE-3 and PEAK trials indicated a significant improvement in OS in the anti-EGFR group. By contrast, the randomized Phase III CALGB 80405 study found no significant difference in OS in KRAS-WT mCRC between the two therapies. In addition, the analysis of these RCTs indicated no significant difference in PFS between the two therapies. Similarly, the analysis of the FIRE-3 and PEAK trials indicated no significant difference in ORR between the two therapies. However, the CALGB 80405 study found a significant improvement in ORR in anti-EGFR therapy. Our meta-analysis indicated a significant improvement in ORR and OS in anti-EGFR therapy for KRAS-WT and all RAS-WT mCRC patients but no significant difference in PFS between the two therapies as the initial treatment for mCRC patients. The survival outcomes based on OS, PFS, ORR of our meta-analysis were consistent with the previous meta-analysis. These results allowed us to hypothesize the presence of a survival benefit in the anti-EGFR group compared with the anti-VEGF group as a first-line therapy for KRAS-WT mCRC patients.

It was a somewhat puzzling result that there was a significant difference in OS but no apparent difference in PFS between two groups in our meta-analysis and other eligible studies. There were some explanations. One explanation for this result is that a recent independent radiological review study demonstrated that higher early tumor shrinkage and higher depth of response were associated with improved OS. These effects were more pronounced in the anti-EGFR therapy compared with the anti-VEGF therapy, and this might explain the significant OS benefit of anti-EGFR associated with the combination chemotherapy.[33] Another explanation is the effect of the second-line treatment and other therapies. A study on subsequent therapies for mCRC patients suggested that anti-EGFR therapy followed by the second-line anti-VEGF therapy could result in higher survival compared with the second-line anti-VEGF therapy followed by anti-EGFR therapy.[34] The upregulation of VEGF associated with the resistance to cetuximab has been reported in experimental models and favors the use of the second-line anti-VEGF therapy after the first-line anti-EGFR therapy.[35,36] In addition, an eligible study in our meta-analysis found that the PFS benefit of anti-EGFR therapy relative to anti-VEGF therapy was only observed in patients with measurable tumor who achieved objective tumor response to biochemotherapy.[27] This result indicated that only some subpopulations could achieve a PFS benefit by the anti-EGFR therapy. However, the CALGB 80405 trial found no significant difference in OS. This result may be because 73.4% of the patients received first-line FOLFOX, which might not be the best chemotherapy drug in combination with anti-EGFR therapy.[37] Therefore, there was a selection bias in the chemotherapy backbones.

The prognosis of patients with mCRC is very poor, and a systemic therapeutic approach is the major choice of treatment for these patients. However, tumors of some patients might revert back to a resectable state in response to the conversion chemotherapy.[2] Our meta-analysis evaluated the difference in conversion therapy between anti-EGFR therapy and anti-VEGF therapy. We found a clear trend toward the use of anti-EGFR therapy despite the lack of a significant difference between the two groups. The response rate and early tumor shrinkage are short-term indicators in conversion therapy.[38] Our meta-analysis indicated a significant improvement in ORR in the anti-EGFR therapy. In addition, the FIRE-3 trial demonstrated that, for the population evaluated, anti-EGFR therapy improved ORR compared with the anti-VEGF therapy.[33] These results may indicate that the improved conversion therapy favors anti-EGFR therapy compared with anti-VEGF therapy.

We highlight the importance of toxicity of these two therapies in the first-line setting. A previous study has found that anti-EGFR therapy can cause infusion-related reactions

and skin alterations.[39] Moreover, anti-VEGF therapy can cause arterial hypertension, venous and arterial thromboembolic events, and gastrointestinal perforations.[40] Our meta-analysis indicated that, in the anti-EGFR group, there was a significant increase in Grade 3 toxicity or lower, including skin disorders, hypomagnesemia, and hypokalemia, whereas the patients in the anti-VEGF group experienced hypertension more often. Therefore, we should evaluate the toxicity profiles and patient preferences when choosing between these two therapies because toxicity may have an adverse influence on the physical and psychological status of the patients.

The inclusion of RAS testing of/in all patients with mCRC could identify those who are potentially sensitive to anti-EGFR therapy. In our study, the exclusion of the patients with mutant RAS mCRC increased the OS in the anti-EGFR therapy compared with the anti-VEGF therapy. In addition, trials demonstrated that mutations in *RAS* genes, in addition to mutations in KRAS exon 2, were negative predictive factors in anti-EGFR therapy.[41,42] Furthermore, retrospective analyses suggested that mutations in the *BRAF* gene might predict the efficacy of anti-EGFR therapy in mCRC.[43,44] It is important to extend RAS analysis and carry out BRAF analysis to identify differences in survival outcomes in anti-EGFR therapy. The merging of the data from the FIRE-3, PEAK, and CALGB/SWOG 80405 studies revealed that the chemotherapy backbone for all RAS-WT mCRC patients did not yield significant differences in OS and PFS between the two therapies in combination with FOLFOX or FOLFIRI regimen. However, our meta-analysis did not provide sufficient data and only made an indirect comparison regarding this issue. A previous meta-analysis reported the superior efficacy of anti-EGFR therapy when used in combination with an irinotecan-based regimen compared with an oxaliplatin-based chemotherapy.[45] However, the PRIME trial provided evidence of improvement in survival outcomes for KRAS-WT mCRC patients when the anti-EGFR agent was combined with FOLFOX chemotherapy.[30] These results indicate that these studies provided no definitively preferred backbone of chemotherapy and that additional studies are needed to elucidate this association.[46]

Trials have concluded that anti-EGFR and anti-VEGF therapies together with combination chemotherapy can improve survival outcomes in the second-line therapy for mCRC compared with combination chemotherapy alone.[47,48] Our meta-analysis compared two therapies in the second-line setting and indicated that anti-EGFR therapy significantly improved ORR, whereas no significant differences in OS and PFS were observed between these two therapies. However, we identified a trend toward improvement in the OS in anti-VEGF therapy. There are some explanations for this result. On one hand, more patients on anti-VEGF therapy received subsequent-line therapies. On the other hand, the SPIRITT trial reported that more patients on anti-EGFR therapy were older, had colon cancer, and two or more organs presented metastatic disease.[28] Our meta-analysis suggested that survival outcomes in anti-EGFR and anti-VEGF therapies were similar as second-line therapies. Therefore, the development of accurate biomarkers and further toxicological analyses in the second-line setting may help to identify the best therapy for individual patients.

Our meta-analysis had some limitations. First, the quality of the trials affected the results, and two of the eligible studies in our meta-analysis were not RCTs. Second, the sample size of the eligible studies was relatively small, leading to a relatively low statistical power. Third, our study included the CALGB/SWOG 80405 trial – presented in the abstracts from the American Society of Clinical Oncology and European Society for Medical Oncology conferences – and it did not provide sufficient data (such as toxicity) for analysis. Fourth, one of the included studies evaluated patients with mutations in KRAS codons 12 and 13 in anti-VEGF therapy, which might have caused bias.[27] Fifth, we could not control or avoid the occurrence of relevant bias (ie, age, sex, and treatment regimen) in the pooling analysis. Sixth, heterogeneity was observed across the studies, and we adjusted for this factor by using a random-effects model to make our results statistically credible.

Conclusion

Our results indicate that anti-EGFR therapy improved OS and ORR and caused the toxicity expected compared with anti-VEGF therapy as a first-line therapy for KRAS-WT and all RAS-WT mCRC. Furthermore, we found a clear tendency for conversion therapy in the anti-EGFR group. There was a significant improvement in ORR in the second-line setting in the anti-EGFR group. Therefore, more high-quality and well-designed studies are needed to provide further evidence.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Risk of bias of RCTs (the Jadad scale)

Study	Randomization	Blinding	Withdraw and dropout	Jadad's score	Quality
Heinemann et al[12]	2	1	2	5	High
Schwartzberg et al[14]	2	1	1	4	High
Hecht et al[28]	2	1	1	4	High

Notes: Randomization: randomization was described with appropriate method: 2 score; randomization was described without appropriate method: 1 score; no randomization: 0 score. Blinding: blinding was performed on all doctors and patients: 2 score blinding was partially performed on doctors and patients: 1 score; no blinding: 0 score. Withdraw and dropout: the reason of withdraw and dropout was described: 1 score; the reason of withdraw and dropout was not described: 0 score; Quality: high-quality trials should score ≥3.
Abbreviation: RCTs, randomized controlled trials.

Table S2 Risk of bias of retrospective studies (NOS)

Study	Selection				Comparability		Outcome			Total	Quality
	REC	SNEC	AE	DO	SC	AF	AO	FU	FUO		
Stremitzer et al[25]	1	0	1	1	0	0	1	1	1	6	Moderate
Yang et al[27]	1	0	1	1	0	0	1	1	1	6	Moderate

Abbreviations: REC, representativeness of the exposed cohort; SNEC, selection of the nonexposed cohort; AE, ascertainment of exposure; DO, demonstration that outcome of interest was not present at start of study; SC, study controls for age and sex; AF, study controls for any additional factors; AO, assessment of outcome; FU, follow-up long enough for outcomes to occur; FUO, adequacy of follow-up of cohorts; NOS, Newcastle–Ottawa Scale.

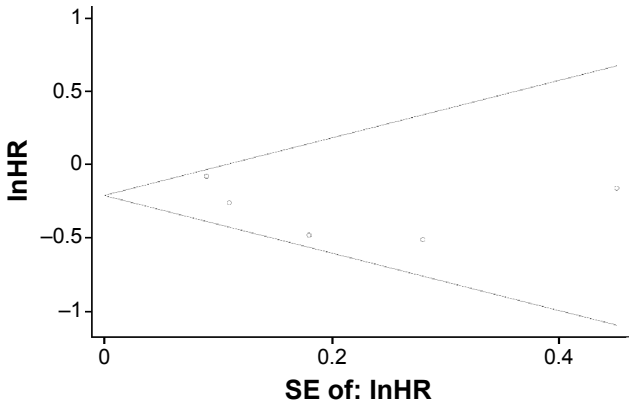

Figure S1 Begg's funnel plot with pseudo 95% confidence limits on OS.
Abbreviations: HR, hazard ratio; SE, standard error; OS, overall survival.

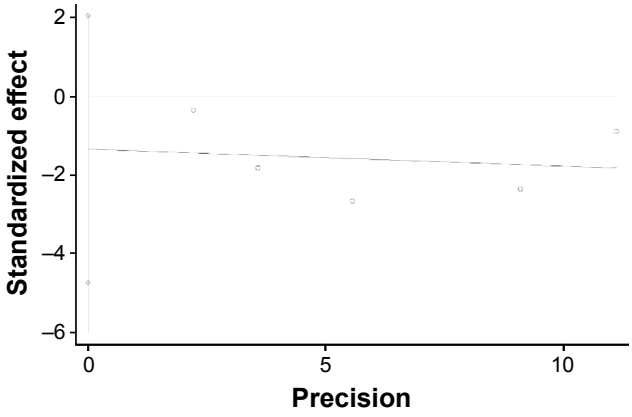

Figure S2 Egger's publication bias plot on OS.
Abbreviation: OS, overall survival.