Systematic Review and Meta-Analysis

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The efficacy and safety of panitumumab supplementation for colorectal cancer

A meta-analysis of randomized controlled studies

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Abstract

Background: The efficacy of panitumumab supplementation for colorectal cancer remains controversial. We conduct a systematic review and meta-analysis to explore the influence of panitumumab supplementation on treatment efficacy of colorectal cancer.

Methods: We search PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through June 2019 for randomized controlled trials (RCTs) assessing the efficacy of panitumumab supplementation for colorectal cancer. This meta-analysis is performed using the random-effect model.

Results: Five RCTs are included in the meta-analysis. Overall, compared with control group for colorectal cancer, panitumumab supplementation is associated with the increase in objective response for wild-type (WT) KRAS (RR = 1.70; 95% CI = 1.07–2.69; $P = .03$), but has no remarkable influence on objective response for mutant KRAS (RR = 0.92; 95% CI = 0.79–1.08; $P = .32$), objective response (RR = 1.35; 95% CI = 1.00–1.83; $P = 0.05$), progressive disease for WT KRAS (RR = 0.94; 95% CI = 0.85–1.02; $P = .15$), mortality (RR = 0.86; 95% CI = 0.69–1.08; $P = .20$), or mortality for WT KRAS (RR = 0.94; 95% CI = 0.84–1.05; $P = .28$). In addition, grade 3 and 4 adverse events are found to be higher in panitumumab group than those in control group (RR = 1.17; 95% CI = 1.08–1.27; $P = .0001$; Fig. 8).

Conclusions: Panitumumab supplementation can provide some improvement in objective response for colorectal cancer patients with WT KRAS, but results in the increase in grade 3 and 4 adverse events.

Abbreviations: CI = confidence interval, FOLFIRI = fluorouracil, leucovorin, and irinotecan, FOLFOX4 = fluorouracil, leucovorin, and oxaliplatin, MT = mutant, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, WT = wild-type.

Keywords: colorectal cancer, panitumumab supplementation, randomized controlled trials, treatment efficacy

1. Introduction

Colorectal cancer is known as the third most common cancer, and more than one million new cases are diagnosed annually worldwide.[1–3] Twenty-five percent of patients are estimated to have metastases at diagnosis, and eventually ~50% of patients would suffer from metastases.[4] Vascular endothelial growth factor A-targeted agents as adjunctive therapy to 5-fluorouracil (5-FU)-based chemotherapy are associated with the better outcomes in first- and second-line metastatic colorectal cancer.[5–7]

Epidermal growth factor receptor (EGFR)-targeted agents are also found to improve the outcomes when adding to chemotherapy in first- and second-line settings or serving as monotherapy in chemorefractory disease.[8–12] Tumor KRAS status is regarded as the important biomarker to predict the efficacy of anti-EGFR agents in colorectal cancer patients.[13,14] Panitumumab is a fully human monoclonal antibody targeting EGFR and shows the antitumor activity across multiple lines of therapy for non-mutated KRAS metastatic colorectal cancer.[9,13] Panitumumab should be administered at 6 mg/kg every 14 days as an intravenous infusion over 60 minutes (≤1000 mg) or 90 minutes (>1000 mg). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Although Panitumumab should be colorless, the solution may contain a small amount of visible translucent-to-white, amorphous, proteinaceous, panitumumab particulates (which will be removed by filtration). Do not shake. Do not administer Panitumumab if discoloration is observed. Withdraw the necessary amount of Panitumumab for a dose of 6 mg/kg. Dilute to a total volume of 100 mL with 0.9% sodium chloride injection. Doses higher than 1000 mg should be diluted to 150 mL with 0.9% sodium chloride injection. Do not exceed a final

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concentration of 10 mg/mL. Mix diluted solution by gentle inversion. Do not shake. Administer using a low-protein-binding 0.2 or 0.22 μm in-line filter. In an open-label, randomized, global, phase 3 trial, the addition of panitumumab to fluorouracil, leucovorin, and irinotecan (FOLFIRI) can significantly improve progression-free survival for colorectal cancer patients with wild-type (WT) KRAS tumors.[9]

Current evidence is insufficient for routine clinical use of panitumumab supplementation for colorectal cancer. Recently, several studies have investigated the efficacy and safety of panitumumab for colorectal cancer, but the results are conflicting.[8,9,15] This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to assess the efficacy of panitumumab supplementation for colorectal cancer with WT or mutant (MT) KRAS.

2. Materials and methods

This systematic review and meta-analysis are performed based on the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement and Cochrane Handbook for Systematic Reviews of Interventions.[16,17] No ethical approval and patient consent are required because all analyses are based on previous published studies.

2.1. Literature search and selection criteria

We systematically search several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library from inception to June 2019 with the following keywords: panitumumab, and colorectal cancer. The reference lists of retrieved studies and relevant reviews are also hand-searched and the process above is performed repeatedly in order to include additional eligible studies.

The inclusion criteria are presented as follows:

(1) study design is RCT,
(2) neonates are diagnosed with colorectal cancer, and
(3) intervention treatments are panitumumab supplementation versus standard therapy.

2.2. Data extraction and outcome measures

Some baseline information is extracted from the original studies, and they include first author, number of patients, age, female, WHO performance status, primary disease site and detail methods in two groups. Data are extracted independently by two investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary.

The primary outcomes are objective response for WT KRAS and MT KRAS. Secondary outcomes include objective response, progressive disease for WT KRAS, mortality, mortality for WT KRAS, grade 3 and 4 adverse events.

2.3. Quality assessment in individual studies

The methodological quality of each RCT is assessed by the Jadad Scale which consists of three evaluation elements: randomization (0–2 points), blinding (0–2 points), dropouts and withdrawals (0–1 points).[18] One point would be allocated to each element if they have been conducted and mentioned appropriately in the original article. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. The study is thought to be of high quality if Jadad score ≥ 3.[19]

2.4. Statistical analysis

We assess risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous outcomes (objective response for WT KRAS and MT KRAS, objective response, progressive disease for WT KRAS, mortality, mortality for WT KRAS, grade 3 and 4 adverse events). Heterogeneity is evaluated using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity.[20] The random-effects model is used for all meta-analysis. We search for potential sources of heterogeneity for significant heterogeneity. Sensitivity analysis is performed to detect the influence of a single study on the overall estimate via omitting one study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias is not assessed. Results are considered as statistically significant for $P < .05$. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

3. Results

3.1. Literature search, study characteristics and quality assessment

Figure 1 shows the detail flowchart of the search and selection results. Five hundred and sixty-seven potentially relevant articles are identified initially. Finally, five RCTs are included in the meta-analysis.[8,9,15,21,22]

The baseline characteristics of five included RCTs are shown in Table 1. These studies are published between 2007 and 2013, and the total sample size is 4155. Patients are divided into WT or MT KRAS. Panitumumab serves as the adjunctive therapy to irinotecan,[15] FOLFIRI,[9] fluorouracil, leucovorin, and oxaliplatin (FOLFOX4),[8] bevacizumab, oxaliplatin, or irinotecan.[21]

Four studies report objective response for WT KRAS,[8,9,15,21] three studies report objective response for MT KRAS,[8,9,21] five studies report objective response for objective response,[8,9,15,21,22] three studies report objective response for progressive disease for WT KRAS,[8,15,21] three studies report objective response for mortality,[9,15,22] two studies report objective response for mortality for WT KRAS,[9,15] and four studies report objective response for grade 3 and 4 adverse events.[8,9,15,22] Jadad scores of the five included studies vary from 3 to 5, and all five studies have high-quality based on the quality assessment.

3.2. Primary outcomes: objective response for WT KRAS and MT KRAS

The random-effect model is used for the analysis of primary outcomes. The results find that compared to control group for colorectal cancer, panitumumab supplementation can substantially increase the objective response for WT KRAS (RR = 1.70; 95% CI = 1.07–2.69; $P = .03$) with significant heterogeneity among the studies ($I^2 = 91\%$, heterogeneity $P < .00001$, Fig. 2), but shows no obvious impact on objective response for MT KRAS (RR = 0.92; 95% CI = 0.79–1.08; $P = .32$) with no

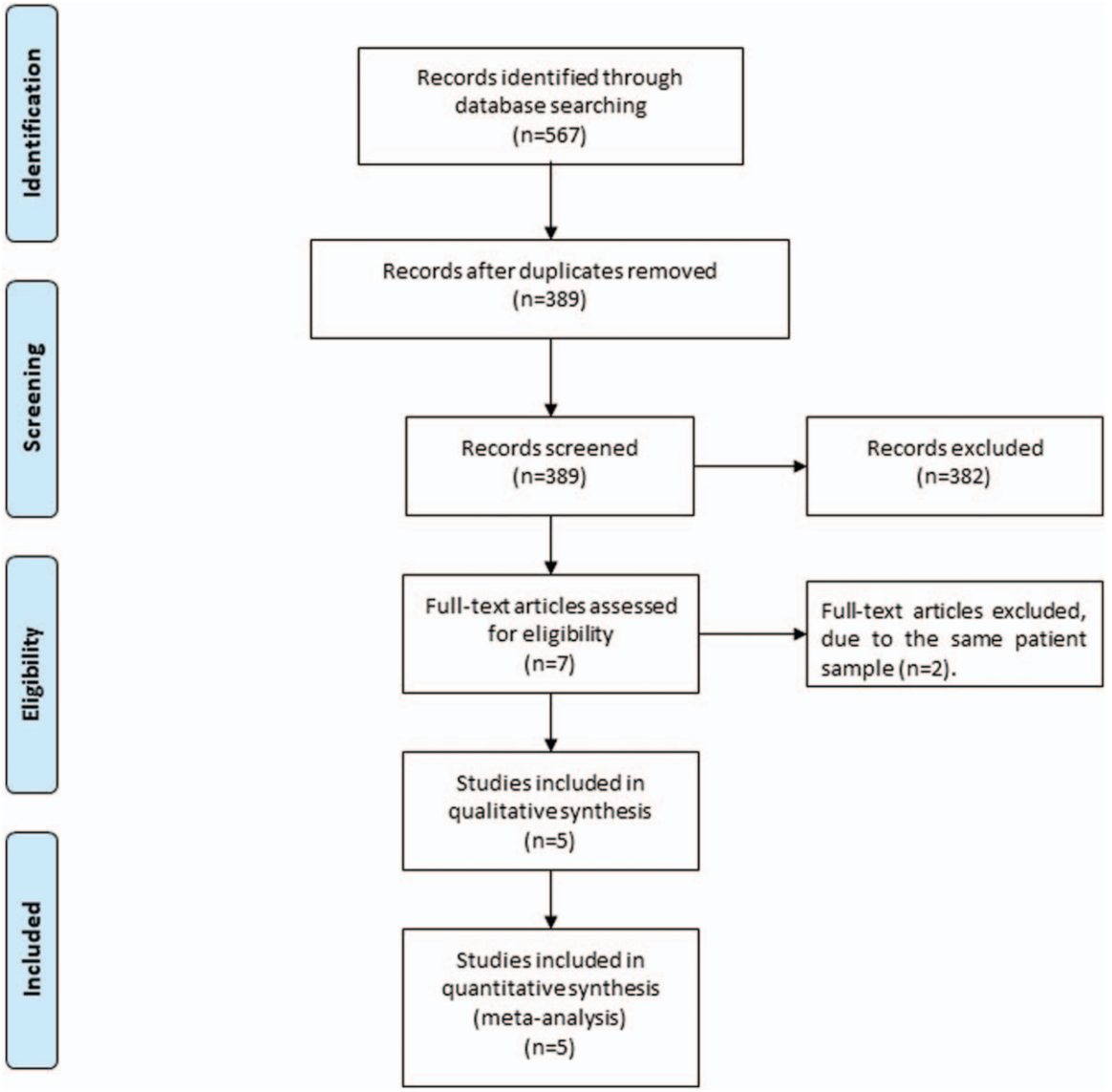

Figure 1. Flow diagram of study searching and selection process.

heterogeneity among the studies ($I^2=0\%$, heterogeneity $P=.58$, Fig. 3).

3.3. Sensitivity analysis

There is significant heterogeneity for objective response for WT KRAS, but significant heterogeneity remains when performing sensitivity analysis by omitting one study in each turn to detect the source of heterogeneity.

3.4. Secondary outcomes

In comparison with control intervention for colorectal cancer, panitumumab supplementation has no significant impact on objective response (RR=1.35; 95% CI=1.00–1.83; $P=.05$; Fig. 4), progressive disease for WT KRAS (RR=0.94; 95% CI=0.85–1.02; $P=.15$; Fig. 5), mortality (RR=0.86; 95% CI=0.69–1.08; $P=.20$; Fig. 6), or mortality for WT KRAS (RR=0.94; 95% CI=0.84–1.05; $P=.28$; Fig. 7), but results in the increase in grade 3 and 4 adverse events (RR=1.17; 95% CI=1.08–1.27; $P=.0001$; Fig. 8).

4. Discussion

The final analysis of the PRIME study confirms the efficacy of the addition of panitumumab to FOLFOX4 as first-line treatment of WT KRAS colorectal cancer.[8] Panitumumab–FOLFOX4 is associated with significantly improved progression-free survival (HR=0.80, $P=.01$), overall survival (HR=0.83, $P=.03$) and objective response rate (57% versus 48%; $P=.02$) compared to FOLFOX4.[23] Adding panitumumab to FOLFIRI as the second-line treatment of patients with WT KRAS tumors also demonstrated the benefits to progression-free survival, response rate, and overall survival.[9] Our meta-analysis suggests that panitumumab supplementation can substantially increase the objective response for WT KRAS colorectal cancer, but has no

Table 1

Characteristics of included studies.

No.	Author	Panitumumab group						Control group						Type	Jada scores
		Number	Age (yr)	Female (n)	WHO performance status (0-1/2)	Primary disease site (Colon/Rectal)	Methods	Number	Age (yr)	Female (n)	WHO performance status (0-1/2)	Primary disease site (Colon/Rectal)	Methods		
1	Seymour 2013	230	64 (57–70), median (IQR)	70	217/13	144/80	Intravenous panitumumab 9 mg/kg every 3 wks plus 350 mg/m^2 intravenous irinotecan every 3 wk	230	63 (56–69)	72	217/13	140/82	350 mg/m^2 intravenous irinotecan every 3 wk	WT KRAS	4
2	Peeters 2010 (1)	303	60, median	115	288/15	187/116	Panitumumab 6.0 mg/kg plus FOLFIRI	294	61, median	103	273/21	189/105	FOLFIRI every 2 wk	WT KRAS	5
	Peeters 2010 (2)	238	61	105	224/14	156/82		248	64	100	233/15	164/84		MT KRAS	
3	Douillard 2010 (1)	325	62 (27–85)	108	305/20	214/111	Intravenously over 1 h at 6 mg/kg every 2 wk-FOLFOX4	331	61 (24–82)	117	312/18	216/115	FOLFOX4	WT KRAS	5
	Douillard 2010 (2)	221	63 (33–83)	76	213/8	151/70		219	61 (27–82)	81	209/10	160/59		MT KRAS	
4	Hecht 2008 (1)	413	61 (28–88), median (range)	180	413/0	–	Panitumumab 6 mg/kg every 2 wk plus bevacizumab, oxaliplatin	410	62 (22–89)	172	410/0	–	Bevacizumab, oxaliplatin	Unknown	4
	Hecht 2008 (2)	115	60 (35–84)	59	115/0	–	Panitumumab 6 mg/kg every 2 wk plus bevacizumab, irinotecan	115	69 (23–80)	44	115/0	–	Bevacizumab, irinotecan		
5	Van Cutsem 2007	231	62, median	85	201/29	153/78	Panitumumab 6 mg/kg every 2 wk plus best supportive care	232	63, median	84	195/35	157/75	Best supportive care	Unknown	4

FOLFIRI = fluorouracil, leucovorin, and irinotecan, FOLFOX4 = fluorouracil, leucovorin, and oxaliplatin, MT = mutant, WT = wild-type.

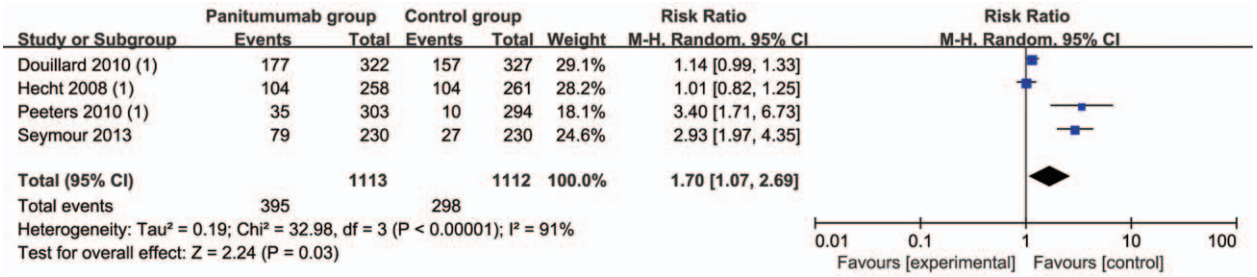

Figure 2. Forest plot for the meta-analysis of objective response for WT KRAS. WT = wild-type.

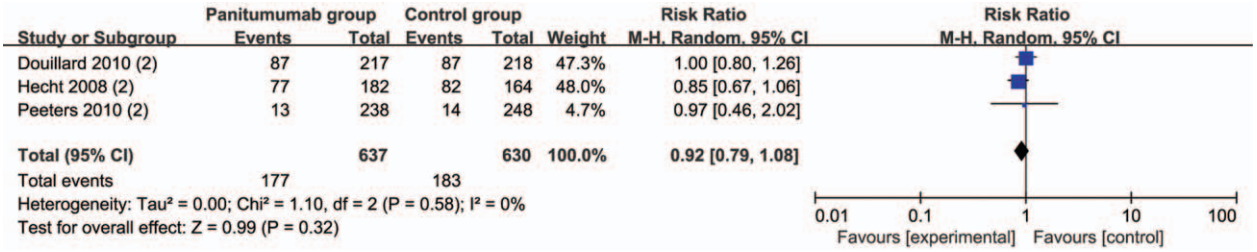

Figure 3. Forest plot for the meta-analysis of objective response for MT KRAS. MT = mutant.

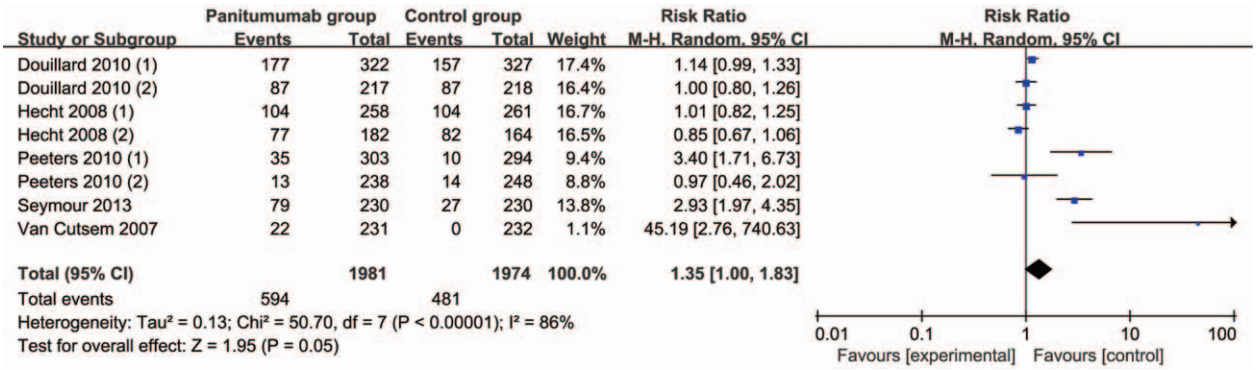

Figure 4. Forest plot for the meta-analysis of objective response.

obvious impact on objective response for MT KRAS, overall objective response, progressive disease for WT KRAS, mortality, and mortality for WT KRAS.

Skin toxicity is reported to be class effect of anti-EGFR treatment of both monoclonal antibodies and tyrosine kinase inhibitors, and is the an important parameter to predict the efficacy of panitumumab treatment.[24,25] Colorectal cancer patients with WT KRAS after panitumumab–FOLFOX4 treatment have grade 2 to 4 skin toxicity which is associated with longer progression-free survival, overall survival, and higher

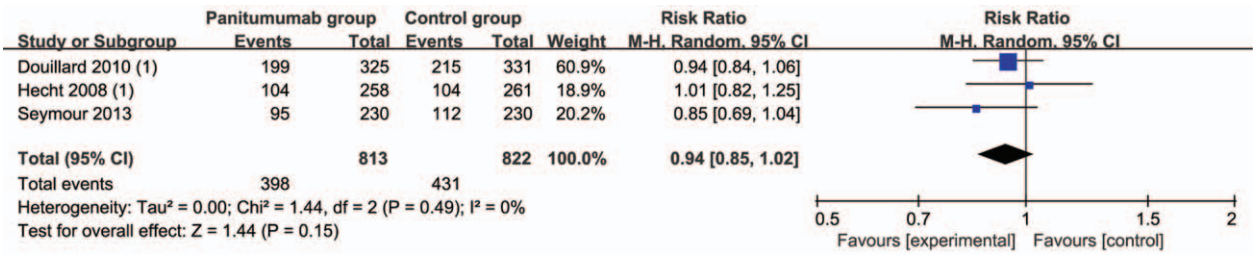

Figure 5. Forest plot for the meta-analysis of progressive disease for WT KRAS. WT = wild-type.

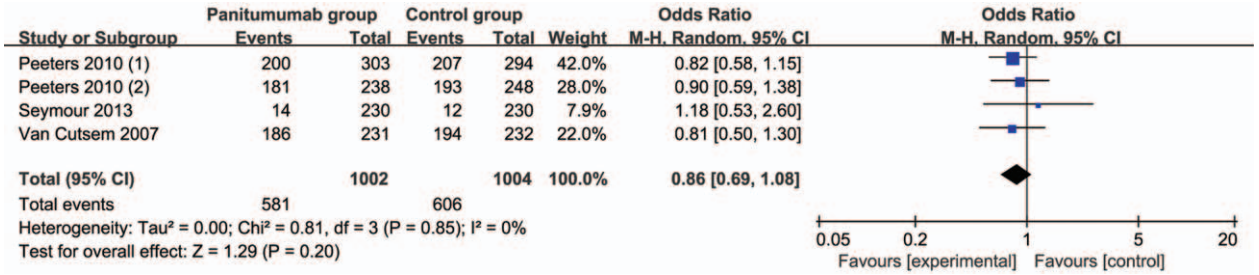

Figure 6. Forest plot for the meta-analysis of mortality.

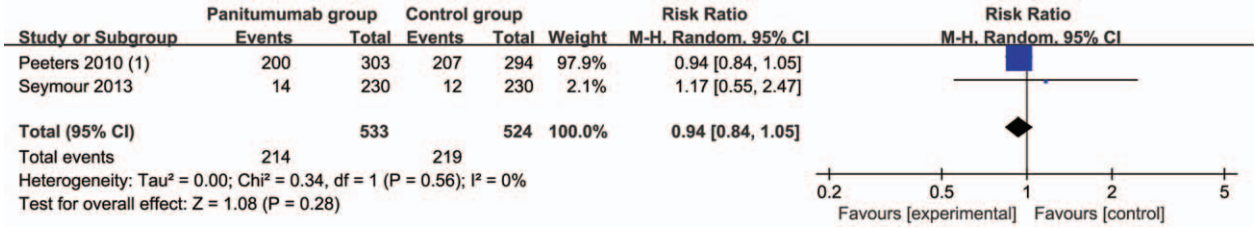

Figure 7. Forest plot for the meta-analysis of mortality for WT KRAS. WT = wild-type.

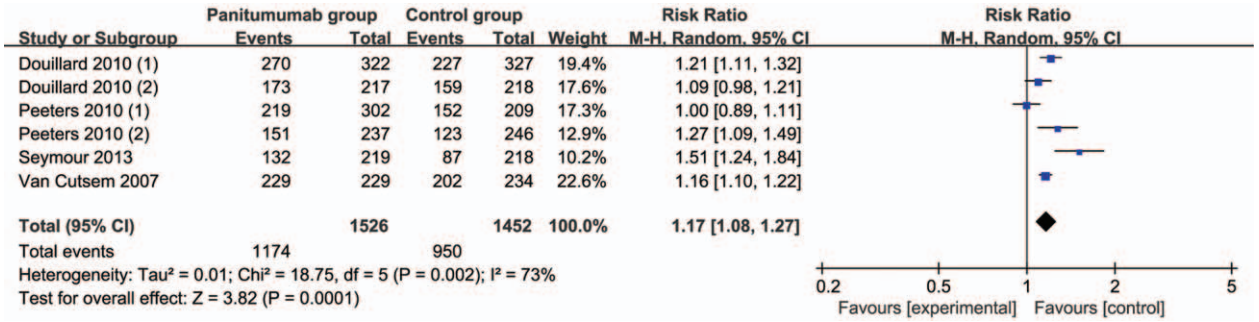

Figure 8. Forest plot for the meta-analysis of grade 3 and 4 adverse events.

response rate versus the overall patient population.[26] Furthermore, panitumumab supplementation treatment is associated with the increase in grade 3 and 4 adverse events for colorectal cancer patients based on the results of this meta-analysis, but the incidence of panitumumab infusion-related reactions is relatively low (grade 3–4 rate is <1%).[22]

The addition of panitumumab to FOLFOX4 is found to have a statistically significant detrimental effect and no improvement in outcomes in colorectal cancer patients with MT or unknown KRAS, and these indicate the a pharmacodynamics interaction between anti-EGFR agents and oxaliplatin.[27] In addition to KRAS exon 2 (codons 12 and 13), mutations in KRAS exon 3 (at codons 59 and 61), exon 4 (at codons 117 and 146), NRAS exon 2 (at codons 12 and 13), exon 3 (at codons 59 and 61), and exon 4 (at codons 117 and 146) have demonstrated to be negative predictive biomarkers for panitumumab treatment.[23]

Several limitations exist in this meta-analysis. Firstly, our analysis is based on only five RCTs, and more RCTs with large sample size should be conducted to explore this issue. Next, there is significant heterogeneity, which may be caused by different combination and duration of panitumumab supplementation. Finally, it is not feasible to perform the analysis of some important outcomes such as progression-free survival, and overall survival based on the KRAS status.

5. Conclusion

Panitumumab supplementation benefits the treatment of colorectal cancer patients with WT KRAS.

Author contributions

Chengchen Wang, Chunyan Tan, Xiaopin Chen and Shuangdong Chen contributed equally to this manuscript.

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