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The efficacy and safety of neoadjuvant nimotuzumab for gastric cancer
A meta-analysis of randomized controlled studies

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Abstract

Introduction: The efficacy of neoadjuvant nimotuzumab for gastric cancer remained controversial. We conducted a systematic review and meta-analysis to explore the efficacy of neoadjuvant nimotuzumab plus chemotherapy vs chemotherapy for gastric cancer.

Methods: We have searched PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases through May 2019, and included randomized controlled trials assessing the efficacy of neoadjuvant nimotuzumab plus chemotherapy vs chemotherapy for gastric cancer. This meta-analysis was performed using the random-effect model.

Results: Four randomized controlled trials were included in the meta-analysis. There were 128 patients included in intervention group and 131 patients included in control group. Overall, compared with chemotherapy for gastric cancer, neoadjuvant nimotuzumab plus chemotherapy showed no substantial influence on response rate (risk ratio [RR] = 1.22; 95% CI = 0.78–1.89; P = .38), disease control rate (RR = 2.22; 95% confidence interval [CI] = 0.32–15.40; P = .42), rash (RR = 1.26; 95% CI = 0.96–1.66; P = .10), neutropenia (RR = 1.26; 95% CI = 0.96–1.66; P = .10), anemia (RR = 1.08; 95% CI = 0.62–1.89; P = .78), or nausea (RR = 1.19; 95% CI = 0.96–1.48; P = .12), but might improve the incidence of vomiting (RR = 1.60; 95% CI = 1.03–2.50; P = .04).

Conclusions: Neoadjuvant nimotuzumab might provide no additional benefits to the treatment of gastric cancer.

Abbreviations: CI = confidence interval, RCTs = randomized controlled trials.

Keywords: efficacy, gastric cancer, nimotuzumab, randomized controlled trials, safety

1. Introduction

Gastric cancer is known as one of the most common causes of cancer-related death worldwide.[1–3] Combination chemotherapies were reported to improve the prognosis, and extends the median overall survival from 3–4 months to 10–13 months for patients with locally unresectable, recurrent, or metastatic disease, but the 5-year survival rate of these patients was still low (less than 10%).[4–6] Although no standard treatment has been widely accepted for advanced gastric cancer, several combination regimens (e.g., cisplatin-S-1, cisplatin–capecitabine) are recommended as first-line treatments.[7,8]

Molecular targeted drugs in combination with chemotherapies were developed to improve the poor outcomes of advanced gastric cancer.[9,10] Approximately 20%–30% of gastric cancers were reported to have the overexpression of epidermal growth factor receptor (EGFR), and gastric cancer with positive expression of EGFR was associated with poor prognosis[11,12] Several studies reported that nimotuzumab, in combination with irradiation or chemoradiotherapy, could improve the prognosis in patients with head and neck cancer, and esophagus squamous cell carcinoma.[13,14] The synergistic antitumor effect of anti-EGFR antibodies and S-1 was revealed in gastric cancer with the overexpression of EGFR.[15,16]

Recently, several studies have investigated the efficacy and safety of neoadjuvant nimotuzumab for gastric cancer, but the results were conflicting.[17–19] This systematic review and meta-analysis of randomized controlled trials (RCTs) aims to assess the efficacy and safety of neoadjuvant nimotuzumab plus chemotherapy vs chemotherapy in patients with gastric cancer.

2. Materials and methods

This systematic review and meta-analysis were 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.[20,21] No ethical approval and patient consent were required because all analyses were based on previous published studies.

2.1. Search strategy

We have systematically searched several databases including PubMed, EMbase, Web of science, EBSCO, and the Cochrane library from inception to May 2019 with the following keywords "nimotuzumab" AND "gastric cancer." The reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly in order to include additional eligible studies. We screened the studies by title, abstract, and then full-text.

2.2. Selection criteria and exclusion criteria

The inclusion criteria were presented as follows:

1. study design was RCT,
2. patients were diagnosed as gastric cancer, and
3. intervention treatments are neoadjuvant nimotuzumab plus chemotherapy vs chemotherapy.

Patients with significant comorbidities (e.g., diarrhea, interstitial pneumonia, and pulmonary fibrosis) were excluded.

2.3. Information sources, data extraction, and analysis

Some baseline information was extracted from the original studies, and they included first author, publication year, country, period, number of patients, age, female, weight, the number of Eastern Cooperative Oncology Group performance status 0/1, and detail methods etc. Data were extracted independently by 2 investigators, and discrepancies were resolved by consensus.

The primary outcome was response rate. Secondary outcomes included disease control rate, rash, neutropenia, anemia, nausea, and vomiting. We assessed risk ratio (RR) with 95% confidence
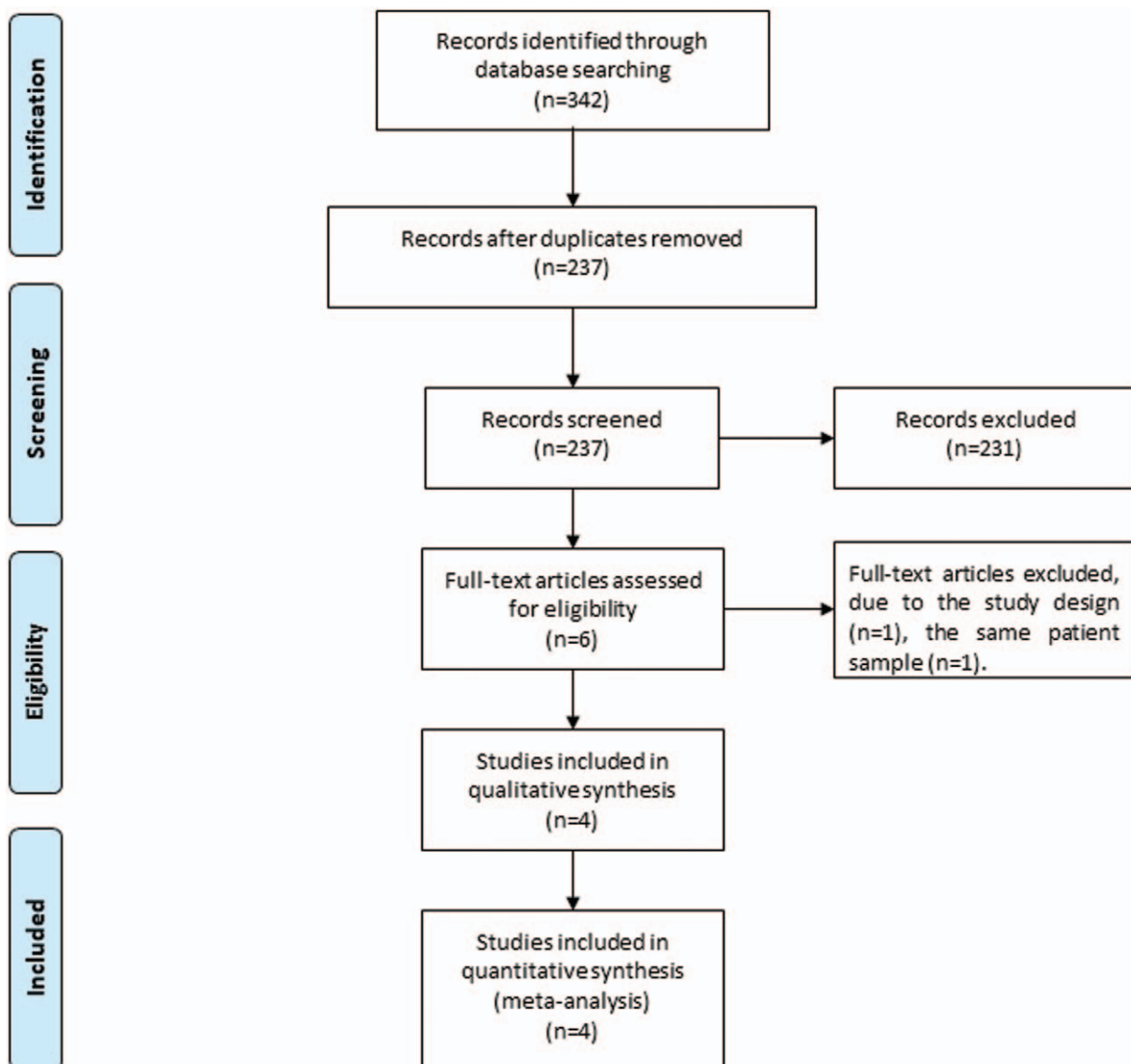

Figure 1. Flow diagram of study searching and selection process.
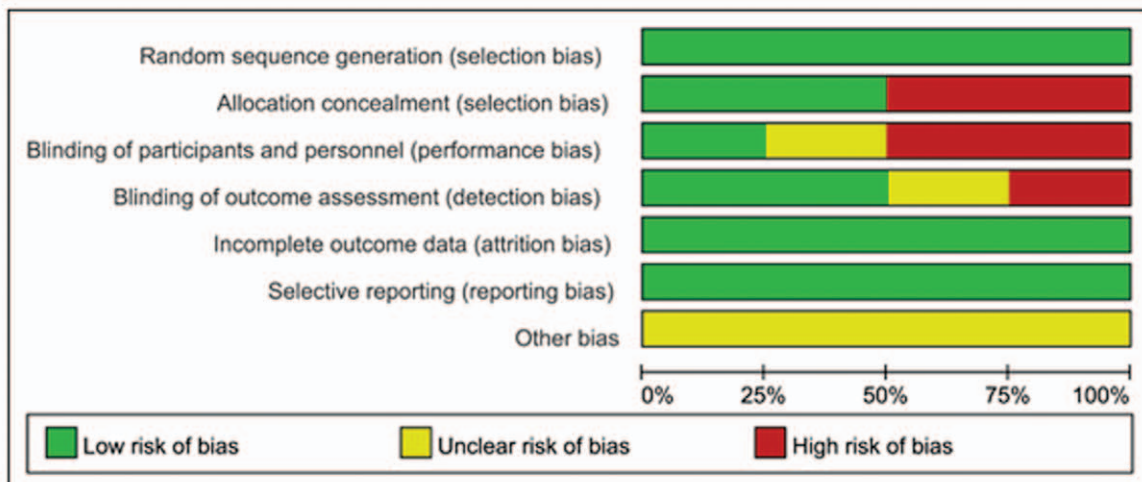
Table 1

Characteristics of included studies.

NO.	Author and year	Irinotecan group						Control group					
		Number	Age	Female (n)	Performance status 0/1/2 (n)	Primary tumor site, colon/rectum/both (n)	Methods	Number	Age	Female (n)	Performance status 0/1/2 (n)	Primary tumor site, colon/rectum/both (n)	Methods
1	Aparicio 2015 [13]	71	80.1 (74.7–90.3), median (range)	25	–	56/12/2	leucovorin 200 mg/m² as a 2-h intravenous infusion, fluorouracil 400 mg/m² intravenous bolus and fluorouracil 600 mg/m² as a 22-h continuous infusion on D1 and D2 every 2 weeks plus irinotecan at D1 as a 90-min intravenous perfusion 150 mg/m² and then 180 mg/m² after the second cycle	70	79.9 (75.1–91.3)	34	–	54/14/1	leucovorin 200 mg/m² as a 2-h intravenous infusion, fluorouracil 400 mg/m² intravenous bolus and fluorouracil 600 mg/m² as a 22-h continuous infusion on D1 and D2 every 2 wks
2	Van Cutsem 2009 [4]	1497	60 (21–76)	663	1222/272/0	–	leucovorin 200 mg/m² as a 2-h infusion, followed by fluorouracil as a 400 mg/m² bolus and then a 600 mg/m² continuous infusion over 22h, days 1 and 2, every 2 weeks for 12 cycles plus irinotecan (180 mg/m² as a 30- to 90-min infusion, day 1, every 2 wks	1485	60 (18–76)	659	1228/250/0	–	leucovorin 200 mg/m² as a 2-h infusion, followed by fluorouracil as a 400 mg/m² bolus and then a 600 mg/m² continuous infusion over 22h, days 1 and 2, every 2 wks for 12 cycles
3	Köhne 2005 [9]	216	60.5 (24–80), median (range)	84	126/81/9	101/114/1	leucovorin 500 mg/m² as a 2-h infusion and fluorouracil 2.3 or 2.0 g/m² by intravenous 24-h infusion, both administered weekly for 6 wks plus irinotecan 80 mg/m² administered over 30 min	214	61 (32–78)	78	120/84/10	118/96/0	leucovorin 500 mg/m² as a 2-hour infusion and fluorouracil 2.6 g/m² by intravenous 24-h infusion, both administered weekly for 6 wks, followed by a 2- wks rest
4	Saltz 2001 [14]	187	59 (24–75), median (range)	88	95/77/15	121/66	fluorouracil (2.3 gm/m²/wk × 6 wks, q 7 wks) and leucovorin (500 mg/m²/wk × 6 wks, q 7 wks) plus irinotecan (80 mg/m²/wk × 6 wks, q 7 wks) or fluorouracil (400 IV/600 CI mgm² dL, 2 q 2 wks) and leucovorin (200 mg/m² dL, 2 q 2 wks) plus irinotecan (180 mg/m² dL q 2 wks)	198	62 (27–75)	65	101/83/14	109/89	fluorouracil (2.6 gm/m²/wk × 6 wks, q 7 wks) and leucovorin (500 mg/m²/wk × 6 wks, q 7 wks) or fluorouracil (400 IV/ 600 CI mg/m² dL, 2 q 2 wks) and leucovorin (200 mg/m² dL, 2 q 2 wk)
5	Saltz 2000 [20]	226	61 (19–85)	101	93/102/29	192/31/-	irinotecan (125 mg/m² of body-surface area intravenously over a 90-min period), leucovorin (20 mg/m² as an intravenous bolus) and fluorouracil (500 mg/m² as an intravenous bolus), given weekly for 4 wks every 6 wks	231	62 (25–85)	79	89/106/35	188/38/-	leucovorin (20 mg/m² as an intravenous bolus) and fluorouracil (425 mg/m² as an intravenous bolus), given daily for 5 d (on days 1–5) every 4 wks

3

Risk of bias summary

A

Risk of bias graph

B

Figure 2. Risk of bias assessment. (A) Authors' judgments about each risk of bias item for each included study. (B) Authors' judgments about each risk of bias item presented as percentages across all included studies.

intervals (CI) for all dichotomous outcomes. Heterogeneity was evaluated using the I^2 statistic, and $I^2 > 50\%$ indicated significant heterogeneity.[22] The random-effects model was used for all meta-analysis. We searched for potential sources of heterogeneity when encountering significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting 1 study in turn or performing the subgroup analysis. Owing to the limited number (<10) of included studies, publication bias was not assessed. Results were

considered as statistically significant for $P < .05$. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

2.4. Assessment for risk of bias

The risk of bias tool was used to assess the quality of individual studies in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*,[23] and the following
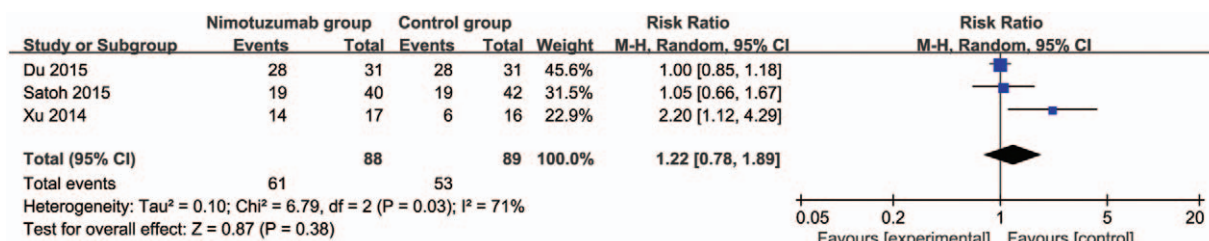
Figure 3. Forest plot for the meta-analysis of response rate.

sources of bias were considered: selection bias, performance bias, attrition bias, detection bias, reporting bias, and other potential sources of bias.[24] Two investigators independently searched articles, extracted data, and assessed the quality of included studies. Any discrepancy was solved by consensus.

2.5. Ethical approval

The ethical approval was not necessary because our study was a meta-analysis that belonged to secondary researches.

3. Results

3.1. Literature search, study characteristics, and quality assessment

Figure 1 showed the detail flowchart of the search and selection results. Three hundred forty two potentially relevant articles were identified initially, 105 duplicates, and 231 papers after checking the titles/abstracts were excluded. Two studies were removed because of the study design or the same patient sample. Finally, 3 RCTs and 1 abstract of RCT are included in the meta-analysis.[17–19,25]

The baseline characteristics of 4 included RCTs were shown in Table 1. These studies were published between 2011 and 2015, and the total sample size was 259. Among the included RCTs, nimotuzumab was regarded as the adjunctive therapy to irinotecan,[17,25] S-1, and cisplatin.[18] Patients were diagnosed with advanced gastric cancer,[17] untreated unresectable, reoccurrence, or metastatic gastric cancer.[18,19,25] Three studies reported response rate and disease control rate,[17–19] while 2 studies reported rash, neutropenia, anemia, nausea, and vomiting.[17,18]

3.2. Assessment of risk of bias

Risk of bias analysis (Fig. 2) showed that 3 studies had high risk of allocation concealment or blinding due to the open label,[17,18,25] but all RCTs generally had high quality.

3.3. Primary outcome: response rate

The random-effect model was used for the analysis of primary outcome. The results found that compared to control group for gastric cancer, neoadjuvant nimotuzumab had no obvious impact on response rate ($RR = 1.22$; 95% CI = 0.78–1.89; $P = .38$), with significant heterogeneity among the studies ($I^2 = 71\%$, heterogeneity $P = .03$, Fig. 3).

3.4. Sensitivity analysis

There was significant heterogeneity for the primary outcome. As shown in Figure 3, the study[18] showed results that were completely out of range of the others and probably contributed to the heterogeneity. After excluding this study, the results suggested that neoadjuvant nimotuzumab was associated with the significant increase in response rate ($RR = 2.26$; 95% CI = 1.11–4.64; $P = .03$). No evidence of heterogeneity was observed among the remaining studies ($I^2 = 0\%$).

3.5. Secondary outcomes

In comparison with control intervention for gastric cancer, neoadjuvant nimotuzumab had no notable impact on disease control rate ($RR = 2.22$; 95% CI = 0.32–15.40; $P = .42$; Fig. 4), rash ($RR = 1.26$; 95% CI = 0.96–1.66; $P = .10$; Fig. 5), neutropenia ($RR = 1.26$; 95% CI = 0.96–1.66; $P = .10$; Fig. 6), anemia ($RR = 1.08$; 95% CI = 0.62–1.89; $P = .78$; Fig. 7), or nausea ($RR = 1.19$; 95% CI = 0.96–1.48; $P = .12$; Fig. 8), but appeared to increase the incidence of vomiting ($RR = 1.60$; 95% CI = 1.03–2.50; $P = .04$; Fig. 9).

4. Discussion

EGFR signaling pathways is frequently disordered in gastric cancer, and may be a candidate therapeutic targets.[26–29] Nimotuzumab is known as one recombinant humanized monoclonal antibody against human EGFR, and has a prolonged
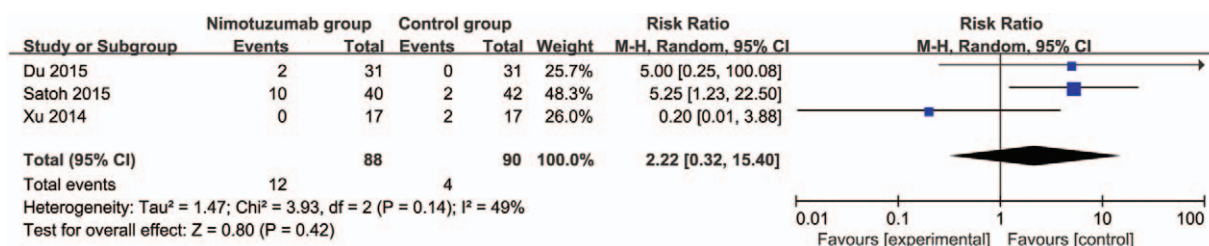

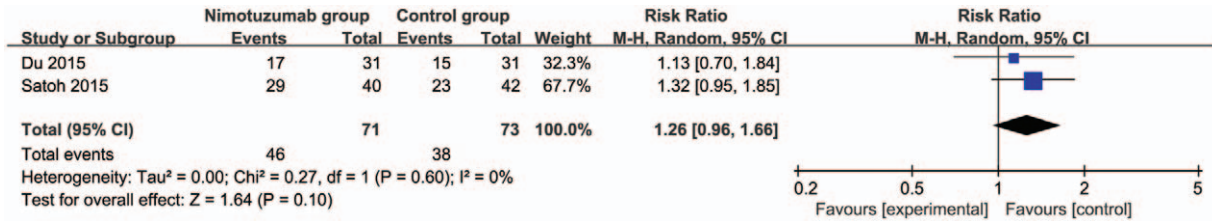**Figure 4.** Forest plot for the meta-analysis of disease control rate.

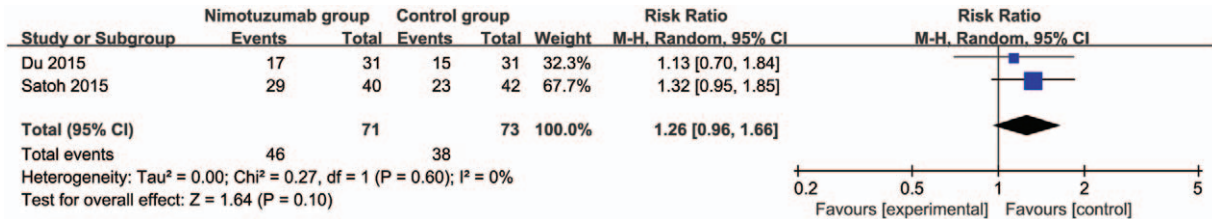**Figure 5.** Forest plot for the meta-analysis of rash.

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

half-life compared with other anti-EGFR antibodies such as cetuximab.[30] Two randomized phase III studies (EXPAND, REAL-3) reported anti-EGFR agents such as cetuximab and panitumumab in combination with chemotherapy failed to improve clinical outcome (e.g., response rate, progression-free survival, and overall survival) in advanced or metastatic gastric cancer, indicating the negative synergistic effect between anti-EGFR agents and capecitabine.[31,32]

Our meta-analysis suggests that neoadjuvant nimotuzumab plus chemotherapy showed no favorable impact on response rate or disease control rate for advanced gastric cancer as compared to chemotherapy. In addition, 1 RCT involving 62 patients with untreated unresectable or metastatic gastric cancer, neoadjuvant

nimotuzumab appears to be associated with the decrease in median progression-free survival (4.8 months vs 7.2 months) and overall survival (10.2 months vs 14.3 months) compared to control group.[18] These results are consistent with nimotuzumab as the adjunctive therapy to irinotecan in patient with advanced gastric cancer.[17] These also confirm the negative interaction between neoadjuvant nimotuzumab and chemotherapy.

EGFR expression may have some association with the candidate predictive factors of anti-EGFR antibody such as nimotuzumab. In patients with untreated unresectable or metastatic gastric cancer, neoadjuvant nimotuzumab obtain no additional benefit in EGFR2 +/3+ patients compared to only S-1 and cisplatin.[18] In contrast, nimotuzumab as an adjunctive therapy to irinotecan appears to
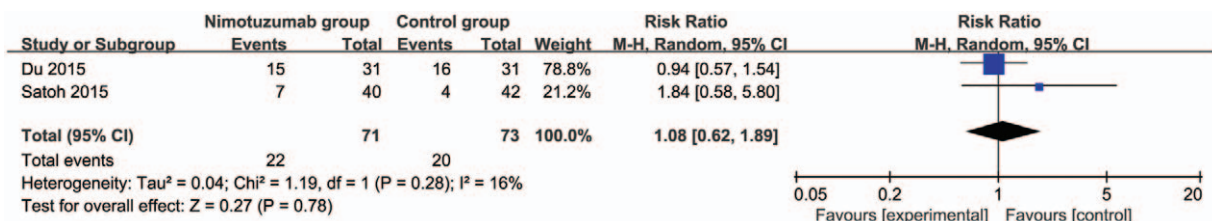

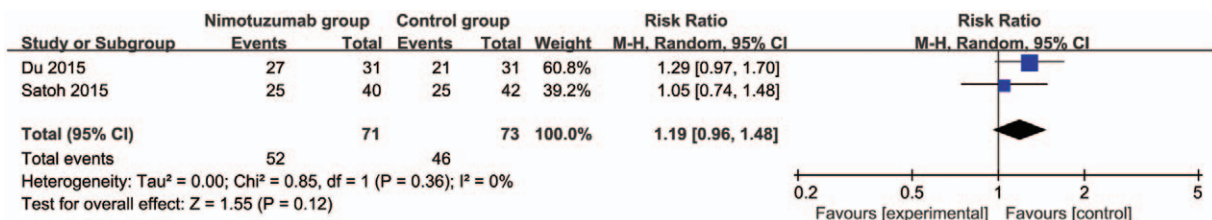**Figure 7.** Forest plot for the meta-analysis of anemia.

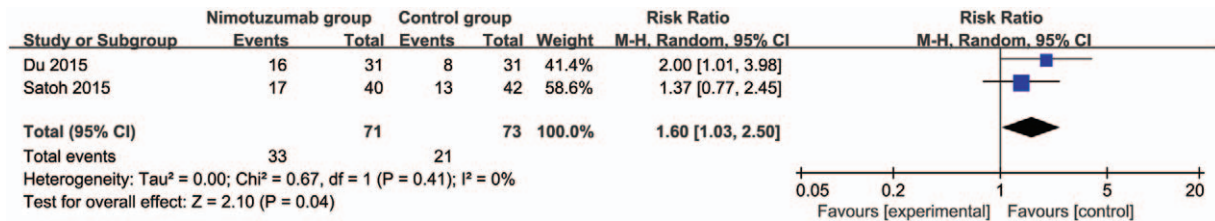**Figure 8.** Forest plot for the meta-analysis of nausea.

Figure 9. Forest plot for the meta-analysis of vomiting.

achieve improved progression-free survival and overall survival in patients with higher EGFR expression (EGFR 2+/3+).[17] Regarding the sensitivity analysis, significant heterogeneity is observed, and no heterogeneity remains after excluding 1 study.[18] The results reveal the benefits of neoadjuvant nimotuzumab to improve response rate for gastric cancer. This inconsistency may be caused by the different synergistic effect of neoadjuvant nimotuzumab to various chemotherapies, indicating that nimotuzumab in combination with docetaxel, cisplatin, and fluorouracil may have better efficacy than other combination methods.

Dermatological toxicity is found to be most common adverse events from cetuximab and panitumumab, but severe dermatological toxicity rarely occurs after using nimotuzumab.[13] Neoadjuvant nimotuzumab leads to no increase in rash, neutropenia, anemia, or nausea for patients with gastric cancer in this meta-analysis, but the incidence of vomiting appears to be improved. Several limitations exist in this meta-analysis. First, our analysis is based on only 4 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 methods of neoadjuvant nimotuzumab. Finally, it is not feasible to perform subgroup analysis based on EGFR expression status among current studies.

5. Conclusion

Neoadjuvant nimotuzumab may provide no additional benefits to treat gastric cancer, but more RCTs should be conducted to explore this issue.

Author contributions

Conceptualization: Bin Cao, Qian Wang, Hui-qing Zhang.
Data curation: Bin Cao, Qian Wang.
Formal analysis: Qian Wang, Hui-qing Zhang.
Investigation: Dairong Li.
Methodology: Xiao-li Fu, Pei-jun Zhang.
Resources: Guo-dong Wei.
Supervision: Qian Wang.
Visualization: Long Zhao.
Writing – original draft: Qi Zhang, Hui-qing Zhang.
Writing – review & editing: Qi Zhang, Hui-qing Zhang.

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