Systematic Review and Meta-Analysis

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Efficacy and safety of elemene combined with chemotherapy in advanced gastric cancer

A Meta-analysis

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Abstract

Background: Elemene is a natural compound extracted from Zingiberaceae plants, and is used in various cancer. However, the efficacy and safety elemene combined with chemotherapy in advanced gastric cancer (GC) are lack of systematic assessment.

Methods: we searched the PubMed, EMBASE, Web of Science, Cochrane Library, China Academic Journals (CNKI), Chinese Science and Technology Journals (CQVIP) and Chinese Biomedical Literature databases. Randomized controlled trials (RCTs) comparing elemene plus chemotherapy with chemotherapy alone in participants with advanced GC and reporting at least one of the following outcomes were selected and assessed for inclusion. JADAD scale was used to assess the quality. Data was screened and extracted by two independent investigators. The primary clinical outcome was overall response rate (ORR); the secondary outcomes were quality of life (QOL) and adverse events (AEs). Analysis was performed using Review Manager 5.3.

Results: Sixteen RCTs matched the selection criteria, which reported on 969 subjects. Risk ratios (RR) and corresponding 95% confidence intervals (CIs) were pooled for ORR, life quality based on KPS, and risk of AEs. Compared to chemotherapy alone, elemene combined with chemotherapy in the treatment of GC may increase the efficiency of ORR(RR: 1.41; 95% CI: 1.23–1.60; $P < .0001$), improve their life quality based on KPS (RR: 1.84; 95% CI: 1.45–2.34; $P < .00001$), and reduce the adverse reactions, including leukopenia(RR: 0.73; 95% CI: 0.62–0.85; $P < .00001$), neutropenia (RR: 0.75; 95% CI: 0.60–0.95; $P = .02$), anemia (RR: 0.76; 95% CI: 0.60–0.95; $P = .02$), thrombocytopenia (RR: 0.56; 95% CI: 0.43–0.73; $P < .00001$). Nausea and vomiting (RR: 0.84; 95% CI: 0.84–1.07; $P = .39$), diarrhea (RR: 0.69; 95% CI: 0.41–1.15; $P = .15$), neurotoxicity (RR: 0.77; 95% CI: 0.59–1.00; $P = .05$) and hepatic dysfunction (RR: 0.95; 95% CI: 0.58–1.54; $P = .83$) were similar between two groups.

Conclusions: Elemene may have the potential to improve the efficacy and reduce the AEs of chemotherapy for gastric cancer. However, the long-term, high-quality researches with a large sample size in different populations are required.

Abbreviations: 5-Fu = 5-fluorouracil, ADM = doxorubicin, AEs = adverse events, C = control, CF = calcium folinate, CIs = confidence intervals, CNKI = China Academic Journals, CQVIP = Chinese Science and Technology Journals, CR = complete response, Do = docetaxel, GC = gastric cancer, KPS = Karnofsky performance status, MMC = mitomycin, NCI-CTC = National Cancer Institute Common Toxicity Criteria, ORR = overall response rate, Ox = oxaliplatin, P = paclitaxel, PR = partial response,

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QOL = quality of life, RCTs = randomized controlled trials, RECIST = Response Evaluation Criteria in Solid Tumors, RRs = risk ratios, S-1 = tegafur, gimeracil, and oteracil potassium capsules, T = test, Xe = xeloda.

Keywords: chemotherapy, elemene, gastric cancer, meta-analysis, randomized control trials

1. Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer death worldwide.[1] In 2012, GC was diagnosed in approximately 951,600 individuals and led to 723,100 deaths worldwide. The incidence rates of GC vary widely across countries, with the highest in Eastern Asia and the lowest in Northern America and most parts of Africa.[2] The reasons for such differences are multiple and complex, included genetic susceptibility, *Helicobacter pylori* infection, socioeconomic conditions, and so on. A decline in GC incidence and mortality rates has been observed in the most developed countries.[3] China accounts for ~40% in the annual global new cases. Consistent with the global trends, despite a decline in incidence and mortality, the burden of GC remains high in China. For patients in advanced stages, systemic chemotherapy represented by a platinum-based or/and a fluoropyrimidine doublet is the conventional therapy.[4] However, the side effects and drug resistance still need to be resolved in clinical.

Elemene is a natural compound extracted from Zingiberaceae plants and has broad-spectrum antitumor effects. Currently, elemene has been approved for the treatment of a variety of respiratory and digestive tract tumors as well as malignant pleural effusions as an adjuvant. Several studies have shown that elemene may exert anticancer effects by inhibiting cell proliferation, arresting cell cycle, and inducing apoptosis.[5–7] In addition, reversing chemotherapy-associated multidrug resistance is one of the possible mechanisms. Many clinical trials have demonstrated that many kinds of cancer can benefit from elemene and indicated the combination therapy play a role in increasing clinical benefit and reducing side effects.[8–11] A meta-analysis has been published to evaluate the efficacy and safety of elemene injection combined with chemotherapy in GC.[12] However, due to the small amount of literature included and a single mode of administration, the efficacy and safety are lack of sufficient evidence. In this study, we performed a meta-analysis to summarize and evaluate the efficacy and safety of elemene combined with chemotherapy in inpatients with advanced GC.

2. Materials and methods

In the study, all the materials are published articles, ethical approval is not necessary.

2.1. Study selection

A systematical search of the PubMed, Web of Science, Cochrane Library, and EMBASE databases as well as China Academic Journals (CNKI), Chinese Science and Technology Journals (CQVIP), and Chinese Biomedical Literature databases was performed from inception to July 2019, which is in order to compare elemene and chemotherapy or with chemotherapy alone in the treatment of GC. The search strategy included a combination of the following MeSH term "stomach neoplasms" OR the keywords "stomach cancer*," "stomach tumor*," "gastric neoplasm*," "gastric cancer*," "gastric neoplasm*," "gastric tumor*" (* is a symbol for truncated search); the keywords "beta-elemene," "β-elemene," "elemene," "Traditional medicine," "Chinese herb." Further references were identified manually using the bibliographies of relevant papers and review articles. All relevant text, tables, and figures were reviewed for data extraction.

2.2. Inclusion criteria

Studies which fulfill the following criteria were included: all patients must be pathologically or cytologically confirmed as having GC at a clinically advanced stage; randomized controlled trials (RCTs) comparing Elemene plus chemotherapy with chemotherapy alone were deemed eligible; at least 1 of the following outcome measures were reported in the trials; if dual (or multiple) studies were reported by the same institution and/or authors, either the one of higher quality or the most recent publication was included in the analysis.

2.3. Outcomes of interest

The primary clinical outcome was overall response rate (ORR); the secondary outcomes were quality of life (QOL) and adverse events (AEs), including the blood system (leukopenia, neutropenia, anemia, and thrombocytopenia), hepatic dysfunction, nausea and vomiting, diarrhea, and neurotoxicity.

Based on Response Evaluation Criteria in Solid Tumors (RECIST 1.1), short-term treatment effectiveness was evaluated and classified as complete response (CR), partial response (PR), stable disease, and progressive disease.ORR include CR and PR. QOL was considered to improve when Karnofsky performance status (KPS) increased by more than 10 points after treatment. AEs was evaluated and graded as grades 0 through IV according to National Cancer Institute Common Toxicity Criteria (NCI-CTC).

2.4. Data extraction

Two investigators independently extracted data from the included studies. Discrepancies between the 2 reviewers were resolved by discussion and consensus. Parameters extracted from these trials included first author, year of publication, study population characteristics, number of subjects operated on with each group and lastly, therapeutic regimen, drug doses, and clinical outcome. Jadad scale was used to assess the quality.

2.5. Statistical analysis

A statistical analysis was performed using Review Manager 5.3. Risk ratios (RRs) and their 95% confidence interval (95% CI) were calculated for ORR, KPS, and toxicity as dichotomous outcomes. Heterogeneity between articles was assessed with Cochrane Chi-squared statistics and the inconsistency statistic (I^2). The pooled effect was calculated using either the fixed effects model or random effects model. We considered $I^2 < 50\%$ as low-level heterogeneity, which a fixed-effect model was suited to use.

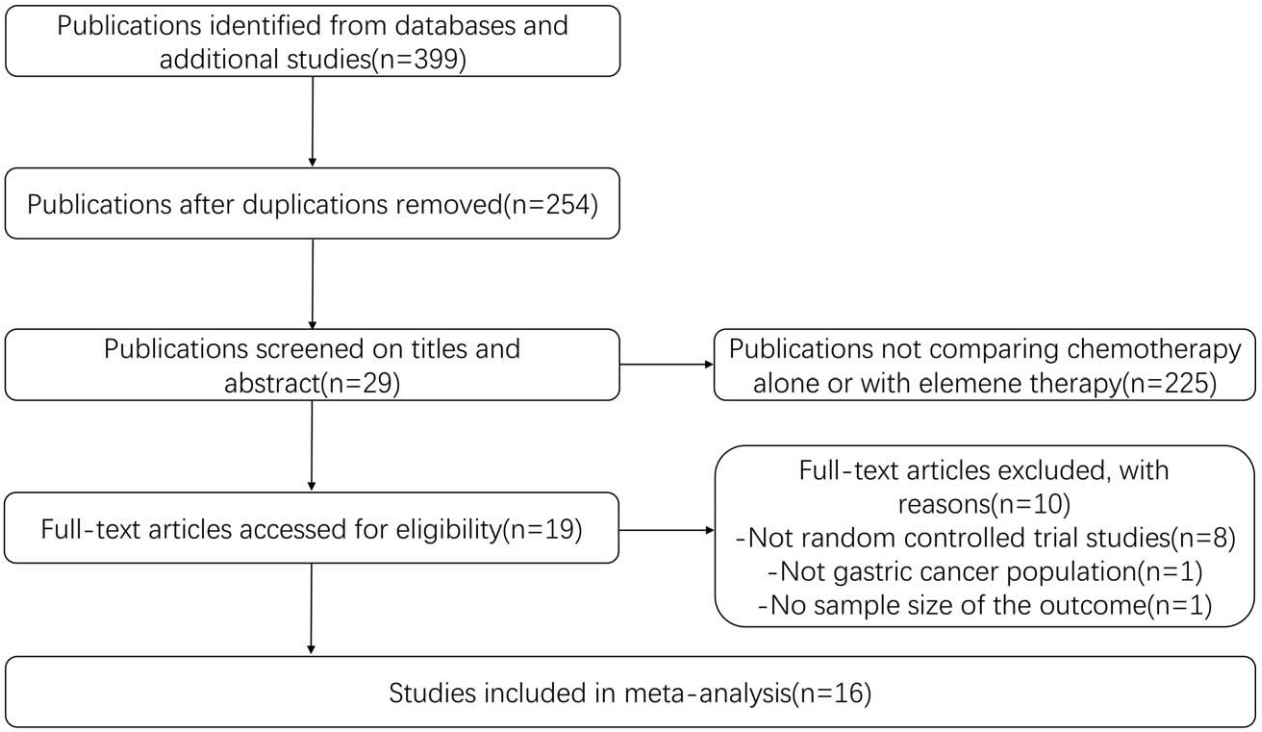

Figure 1. Flow diagram indicating the process of selecting articles for meta-analysis.

$I^2 > 50\%$ was considered as significant heterogeneity. A random-effect model was used when $I^2 > 50\%$. $P < .05$ were regarded as statistically significant in all included studies. When the same outcome was reported by more than 5 studies, publication bias was assessed using a funnel plot.

3. Results

There shows the flow chart of study selection (Fig. 1). The comprehensive search strategy identified 399 publications. One hundred forty-five duplications were excluded, and 254 articles were potentially eligible for inclusion, of which 225 were eliminated after reading the abstracts and titles. We reviewed the full texts of the remaining 29 articles, and 16 RCTs involving 969 patients were finally included in this meta-analysis, which characteristics are summarized in Table 1.[13–28] The sample size in the included trials ranged from 28 to 106, with 485 in the test groups and 484 in the controls. All 16 trials were conducted in China, of which 12 studies were administered intravenously, 2 trials were administered orally, and another 2 trials were administered by peritoneal perfusion. The elemene used in 16 clinical trials, whether oral or injectable, were prescription drugs approved for sale in China. The quality of the included trials was evaluated by the quantitative 5-point Jadad scale. Articles with more than 3 scores were defined as high-quality.

3.1. Quality assessment

The inverted funnel plot was used to assess publication bias and conducted for all comparisons. We checked its asymmetry visually to determine whether there was publication bias. The shapes of the funnel plots showed that a low potential for publication bias (Figure S1–6, http://links.lww.com/MD/D929, http://links.lww.com/MD/D931, http://links.lww.com/MD/D932, http://links.lww.com/MD/D933, http://links.lww.com/MD/D934, http://links.lww.com/MD/D935). There was no statistically significant heterogeneity of the trials ($I^2 < 50\%$ in all comparisons), so the fixed effects model was used.

3.2. Overall response rate

All 16 trials reported ORR. The pooled data showed that elemene plus chemotherapy resulted in superior ORR (RR: 1.41; 95% CI: 1.23–1.60; $P < .00001$, Fig. 2) compared with chemotherapy alone. Subgroup analysis of method of administration indicated that both intravenous administration and oral administration led to a statistically significant improvement in ORR (RR: 1.33; 95% CI: 1.13–1.57; $P = .0006$ and RR: 1.63; 95% CI: 1.12–2.37; $P = .01$, Fig. 3). In addition, we also observed the improvement in 4 high-quality studies (RR: 1.52; 95% CI: 1.20–1.93; $P = .0006$, Fig. 3).

3.3. Karnofsky performance status

Seven trials reported the number of patients whose QOL improved based on KPS. The meta-analysis indicated elemene combined with chemotherapy resulted in superior KPS improvement (RR: 1.84; 95% CI: 1.45–2.34; $P < .00001$, Fig. 4). Elemene combined with chemotherapy is significant to increase KPS score and improve QOL compared to chemotherapy alone.

3.4. Blood system toxicity

Eleven trials with 674 patients reported blood system toxicity, included leukopenia, neutropenia, anemia, and thrombocytopenia. Leukopenia was most reported and the pooled analysis of

Table 1

Study characteristics for the included studies.

References	TNM stage (patients)	Sample size (T/C, n)	Gender (M) (T/C, n)	Age (T/C)	Ethnic origin	Clinical status	Study arm	Elemene drug delivery	ORR (T/C)	KPS (T/C)	Jadad score
[13]	Advanced stage	64 (32/32)	17/18	62.3±5.1/ 61.5±7.3	Chinese	ECOG ≤1	(Ox+Do+5-Fu plus elemene) vs. (Ox+Do+5-Fu)	Orally	18/9	NR	3
[14]	Advanced stage	106 (53/53)	28/29	57.2±8.8/ 56.8±8.4	Chinese	NR	(Ox+5-Fu plus elemene) vs. (Ox+5-Fu)	Injection	32/19	Reported	3
[15]	Advanced stage	68 (34/34)	12/14	69/71	Chinese	Reported	(S-1 plus elemene) vs (S-1)	Orally	21/15	11/5	2
[16]	Advanced stage	52 (26/26)	16/15	64.32±2.85/ 65.82±3.09	Chinese	ECOG ≤2	(Ox+P plus elemene) vs. (Ox+P)	External	13/11	5/2	3
[17]	Advanced stage	56 (29/27)	35 (all)	54.2±5.3 (all)	Chinese	NR	(S-1 plus elemene) vs (S-1)	Injection	24/13	NR	2
[18]	III	38 (19/19)	11/10	52.6±7.4 (all)	Chinese	KPS ≥70	(S-1 plus elemene) vs (Ox+ CF+5-Fu+VP-16)	Injection	8/6	Reported	2
[19]	Advanced stage	65 (34/31)	18/18	56/54	Chinese	NR	(S-1 plus elemene) vs (S-1)	Injection	19/9	16/6	2
[20]	Advanced stage	61 (31/30)	36 (all)	42.5±7.2 (all)	Chinese	KPS >70	(Xe plus elemene) vs (Ox+ CF+5-Fu+VP-16)	Injection	23/17	Reported	3
[21]	III/IV	81 (41/40)	53 (all)	59 (all)	Chinese	KPS >60	(Ox+Xe plus Elemene) vs. (Ox+Xe)	Injection	24/19	NR	2
[22]	III/IV	49 (25/24)	14/14	52/53	Chinese	KPS ≥70	(FOLFOX4 plus elemene) vs (FOLFOX4)	Injection	15/10	12/6	2
[23]	Advanced stage	68 (34/34)	NR	71 (all)	Chinese	KPS ≥70	(Ox+CF+5-Fu plus elemene) vs (Ox+CF+5-Fu)	Injection	19/11	15/6	2
[24]	IV	40 (20/20)	25 (all)	58 (all)	Chinese	NR	(5-Fu plus elemene) vs 5-Fu	External	17/11	NR	2
[25]	Advanced stage	60 (30/30)	17/16	52.6/52.8	Chinese	KPS ≥50	(P+CF+5-Fu plus elemene) vs (P+CF+5-Fu)	Injection	17/15	24/16	2
[26]	III/IV	68 (32/36)	27/29	48.5/45	Chinese	NR	(5-Fu plus elemene) vs (ADM+MMC+5-Fu)	Injection	12/16	24/18	2
[27]	Advanced stage	28 (14/14)	NR	Reported	Chinese	KPS ≥50	(ELF plus elemene) vs ELF	Injection	4/0	NR	2
[28]	III/IV	65 (31/34)	26/28	46.5/48	Chinese	Reported	(5-Fu plus elemene) vs (MMC+5-Fu)	Injection	10/14	NR	2

Study quality was listed using the results of the Jadad scale.

5-Fu = 5-fluorouracil, ADM = doxorubicin, C = control, CF = calcium folinate, Do = docetaxel, M = male, MMC = mitomycin, NR = not reported, Ox = oxaliplatin, P = paclitaxel, S-1 = tegafur, gimeracil and oteracil potassium capsules, T = test, Xe = xeloda.

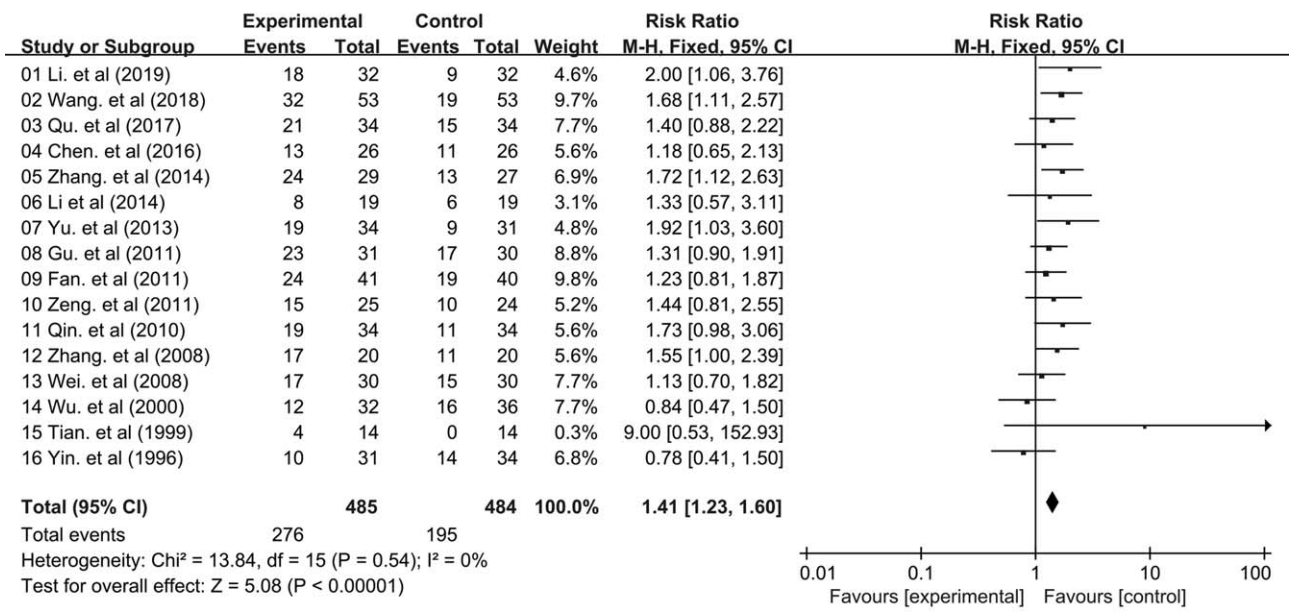

Figure 2. Forest plot displaying the results of the meta-analysis for overall response rate (ORR). CI = confidence interval.

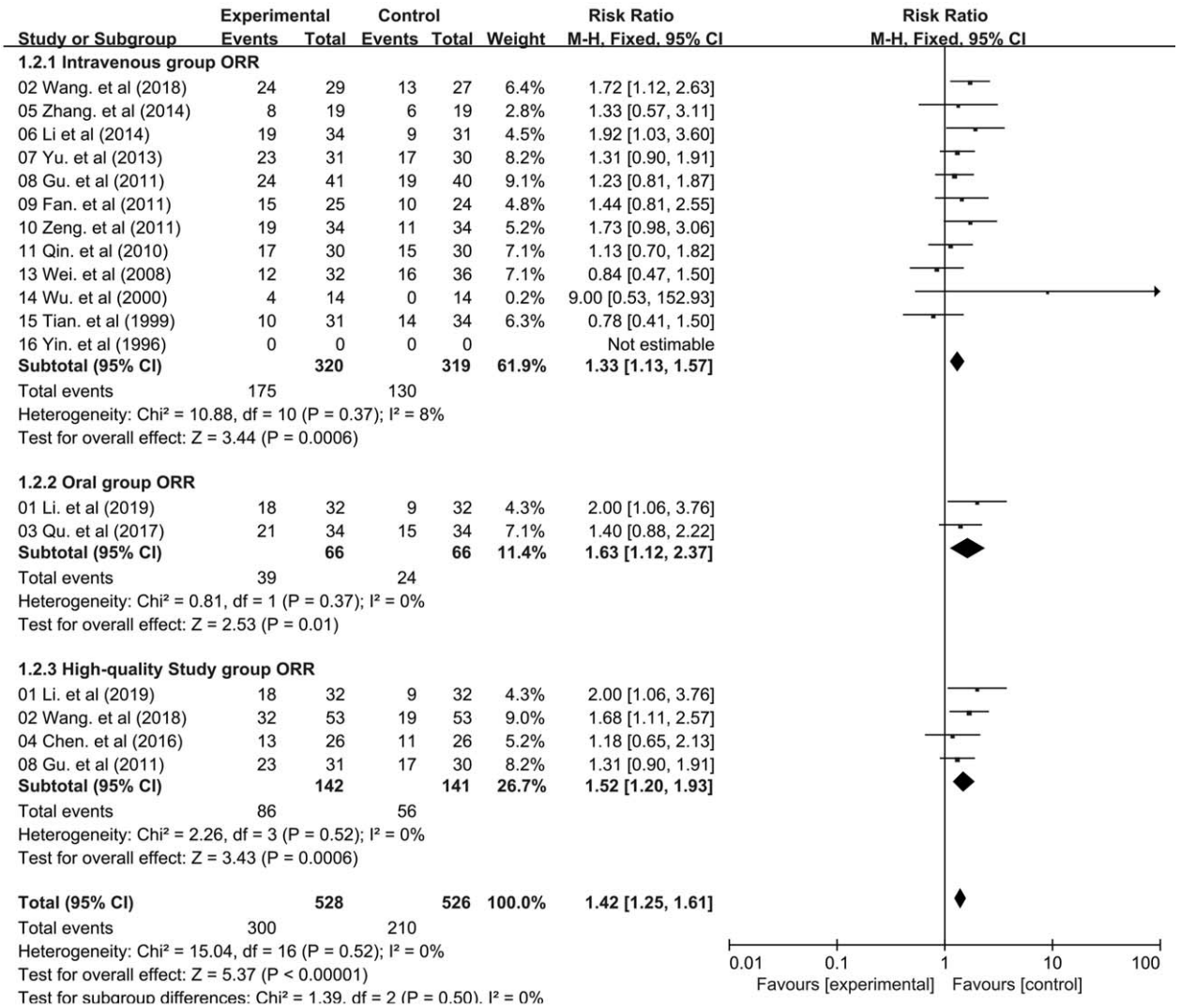

Figure 3. Forest plot displaying the results of the meta-analysis for overall response rate (ORR) of subgroup. CI = confidence interval, ORR = overall response rate.

8 trials showed statistically significant difference between the 2 treatment groups (RR: 0.73; 95% CI: 0.62–0.85; $P < .0001$, Fig. 5). Four trials reported neutropenia occurrence and the meta-analysis indicated elemene combined with chemotherapy group had lower occurrence of neutropenia (RR: 0.75; 95% CI: 0.60–0.95; $P = .02$, Fig. 5). In addition, anemia (RR: 0.76; 95% CI: 0.60–0.95; $P = .02$, Fig. 5) and thrombocytopenia (RR: 0.56; 95% CI: 0.43–0.73; $P < .0001$, Fig. 5) were significantly

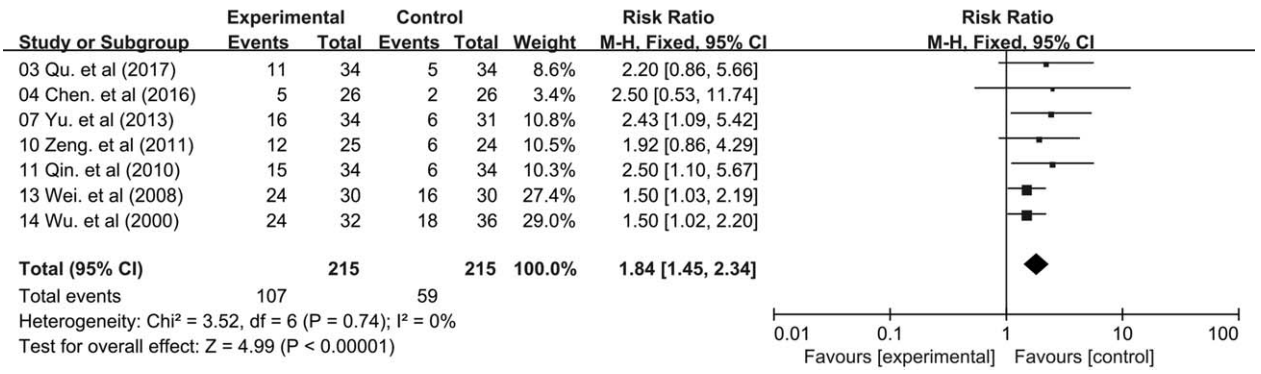

Figure 4. Forest plot displaying the results of the meta-analysis for Karnofsky performance status (KPS). CI = confidence interval.

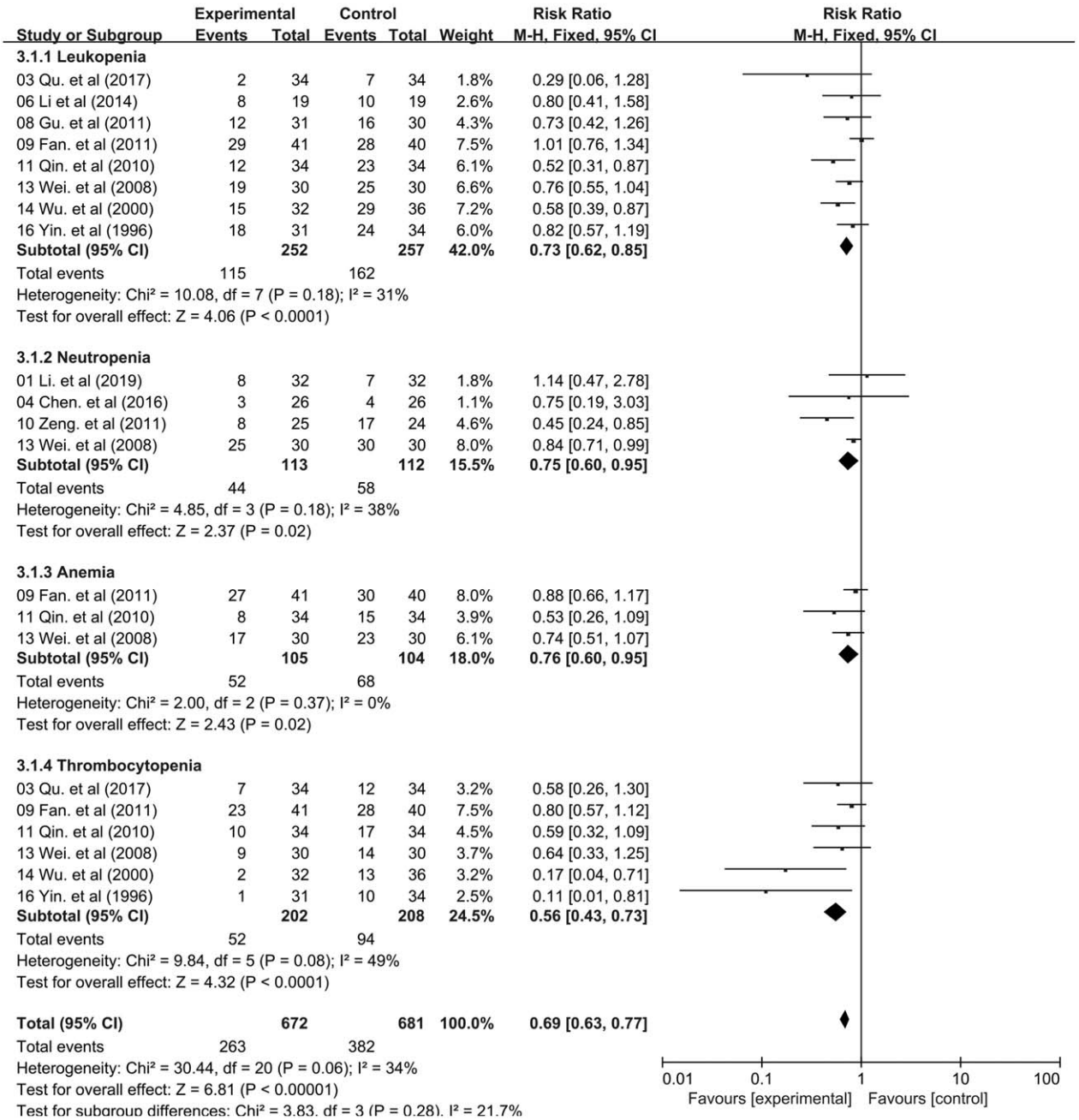

Figure 5. Forest plot displaying the results of the meta-analysis for the blood system toxicity. CI = confidence interval.

decreased in patients treated with elemene. Those results indicated that elemene with chemotherapy can significantly reduce the rate of leucopenia, neutropenia, anemia, and thrombocytopenia compared to chemotherapy alone for the treatment of advanced GC.

3.5. Nausea, vomiting, and diarrhea

Eleven trials with 730 patients reported nausea and vomiting, and there was no statistical difference between elemene plus chemotherapy group and chemotherapy alone group (RR: 0.95; 95% CI: 0.95–1.07; $P = .39$, Fig. 6). Similarly, no statistical difference was observed in the meta-analysis of diarrhea extracted from 4 trials (RR: 0.69; 95% CI: 0.41–1.15; $P = .15$, Fig. 6).

3.6. Hepatic dysfunction and neurotoxicity

Hepatic dysfunction and neurotoxicity were reported respectively in 4 different clinical trials. Disappointingly, neither hepatic dysfunction (RR: 0.95; 95% CI: 0.58–1.54; $P = .83$, Fig. 7) nor neurotoxicity (RR: 0.77; 95% CI: 0.59–1.00; $P = .05$, Fig. 7) had any improvement with the treatment of elemene plus chemotherapy compared to chemotherapy alone.

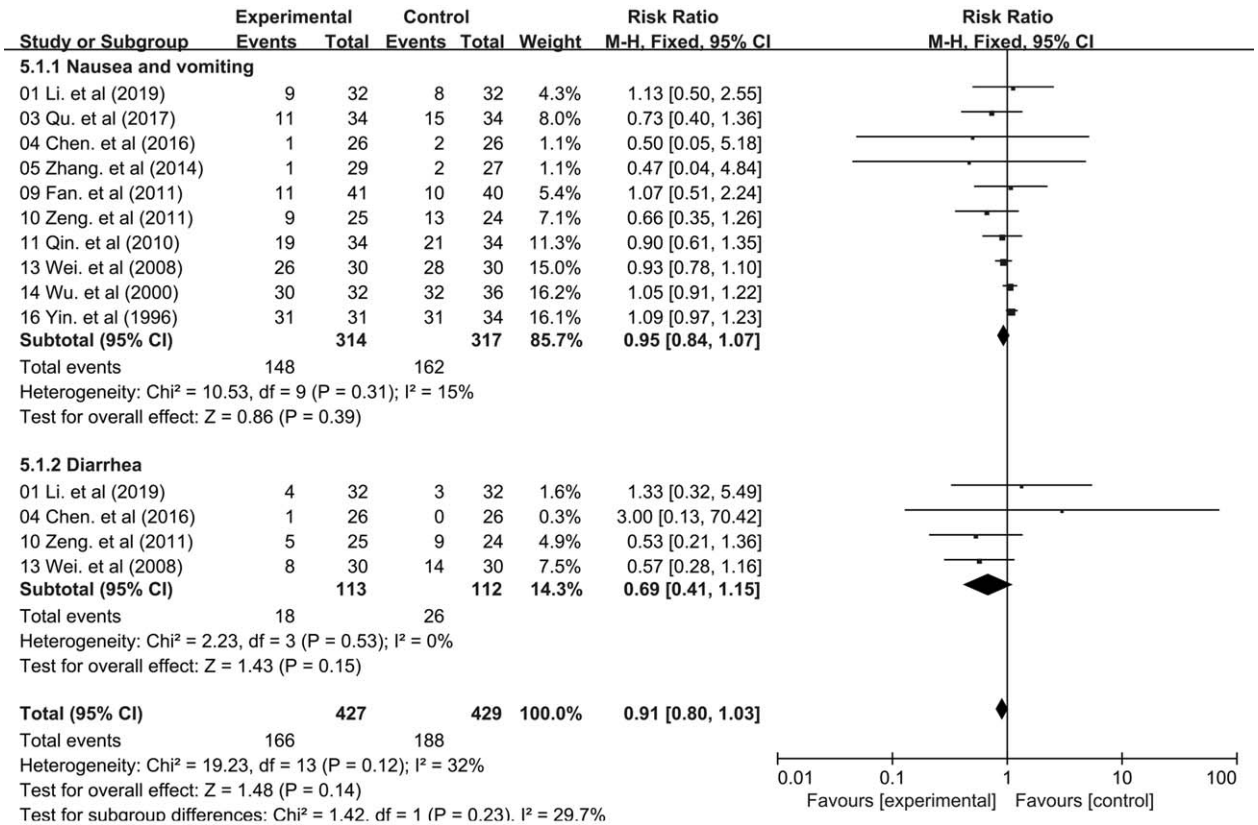

Figure 6. Forest plot displaying the results of the meta-analysis for nausea and vomiting, diarrhea. CI = confidence interval.

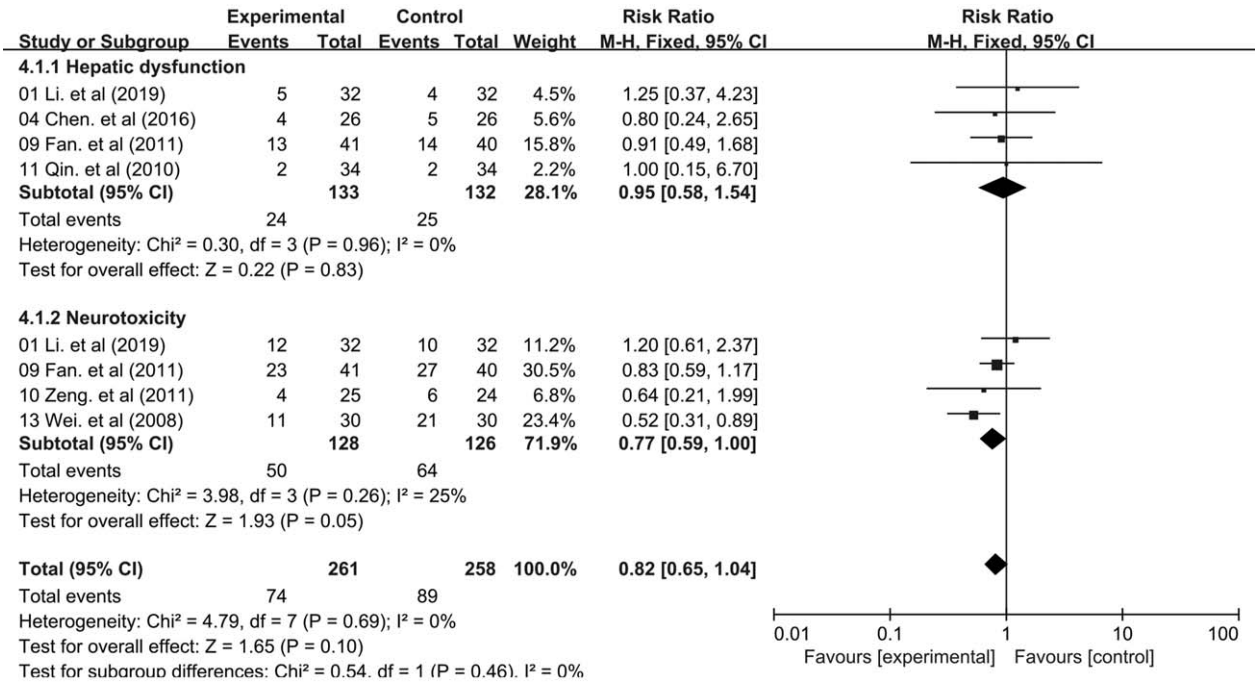

Figure 7. Forest plot displaying the results of the meta-analysis for hepatic dysfunction and neurotoxicity. CI = confidence interval.

4. Discussion

GC is one of the common malignant tumors of the digestive system worldwide. Over the past few decades, the incidence and mortality of GC worldwide has declined with the advancement of eating habits and treatment strategies and the reduction in chronic *H pylori* infection due to improved sanitation and antibiotics. However, due to the increase in the average life expectancy of the population and the aging of the population, GC is a main contributor to the global burden from cancer, especially in developing countries such as China. And the prognosis of GC is currently not optimistic. Currently, the main treatment strategy for advanced GC is chemotherapy. But the side effects and drug resistance problems that come with it cannot be ignored. Therefore, it is necessary to use adjuvant to reduce the toxicity, increase the tumor response rate, and improve the QOL of patients.

Compared with western medicine, traditional Chinese medicine emphasizes the overall concept and is better at whole body conditioning. It has always been regarded as an important adjuvant treatment in cancer treatment. Elemene is a sesquiterpene compound extracted from Zingiberaceae plants, which could exert anticancer effects by inhibiting cell proliferation, arresting cell cycle, and inducing apoptosis. Moreover, elemene did not report serious adverse reactions. Therefore, it attracted much attention for the clinical efficacy of elemene combined with chemotherapy. Several studies have shown that chemotherapy combined with elemene had synergistic clinical effectiveness with reduced the side effects.[13–28]

According to the results of the meta-analysis, regimens containing elemene combined with chemotherapy could increase the efficiency of ORR, improve the QOL, and reduce the AEs compared with regimens with chemotherapy alone. We conjecture that it may have synergistic clinical effectiveness with reduced the side effects in GC. However, the above conclusions need to be further verified by the long-term, high-quality researches with a large sample size in different populations.

There are many limitations in this meta-analysis. Firstly, the quality of the included literature was generally low. Although all included studies were RCTs, most of them did not describe random assignment methods, allocation concealment, and blinding in detail in strict accordance with the Consolidated Standards of Reporting Trials. Secondly, there was inconsistent baseline between studies, such as inconsistent chemotherapy regimens, different modes of administration and different courses of treatment, etc. Thirdly, reports in languages other than English and Chinese were excluded. The language bias had to be considered, but may not result in any notable bias in the assessment of interventional effectiveness. Finally, due to the limited number of studies included, it is so difficult to compare each chemotherapy combination regimen, elemene regimen, and mode of administration that recommends the best treatment for GC patients. Therefore, future research should focus on high-quality studies with a large sample size thus resulting in more accurate conclusions.

Author contributions

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Supervision: Ying Liu, Lili Yan, Ting Jin.
Validation: Ying Liu, Shuiping Liu.
Visualization: Ying Liu, Jiao Feng, Ting Duan.
Writing – original draft: Ying Liu, Liuxi Chen.
Writing – review & editing: Ying Liu, Tian Xie, Shuang Lin, Xinbing Sui.

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