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ABOUT COVER

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AIMS AND SCOPE

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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META-ANALYSIS

Efficacy and safety of perioperative therapy for locally resectable gastric cancer: A network meta-analysis of randomized clinical trials

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Abstract

BACKGROUND

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy worldwide, with over 1 million new cases per year, and the third leading cause of cancer-related death.

AIM

To determine the optimal perioperative treatment regimen for patients with locally resectable GC.

METHODS

A comprehensive literature search was conducted, focusing on phase II/III randomized controlled trials (RCTs) assessing perioperative chemotherapy and chemoradiotherapy in treating locally resectable GC. The R0 resection rate, overall survival (OS), disease-free survival (DFS), and incidence of grade 3 or higher nonsurgical severe adverse events (SAEs) associated with various perioperative regimens were analyzed. A Bayesian network meta-analysis was performed to compare treatment regimens and rank their efficacy.

RESULTS

Thirty RCTs involving 8346 patients were included in this study. Neoadjuvant XELOX plus neoadjuvant radiotherapy and neoadjuvant CF were found to significantly improve the R0 resection rate compared with surgery alone, and the former had the highest probability of being the most effective option in this context. Neoadjuvant plus adjuvant FLOT was associated with the highest probability of being the best regimen for improving OS. Owing to limited data, no definitive ranking could be determined for DFS. Considering nonsurgical SAEs, FLO has emerged as the safest treatment regimen.

CONCLUSION
This study provides valuable insights for clinicians when selecting perioperative treatment regimens for patients with locally resectable GC. Further studies are required to validate these findings.

Key Words: Gastric cancer; Perioperative treatment; Network meta-analysis; Efficacy and safety

Core Tip: This study provides an update of the literature on perioperative therapy for locally resectable gastric cancer (GC) as of April 21, 2023. This study aimed to provide a multidimensional approach to perioperative treatment regimens for resectable GC using Bayesian network meta-analysis.

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INTRODUCTION

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy worldwide, with over 1 million new cases per year, and is the third leading cause of cancer-related deaths[1]. It is highly prevalent in Asia, South America, Southern Africa, and Eastern Europe[2]. The incidence of GC is associated with various factors, with Helicobacter pylori infection being the most significant[3]. Other factors include dietary habits, smoking, heavy alcohol consumption, age, and genetic predisposition[4,5]. Gastroesophageal reflux disease is also linked to gastric-esophageal junction cancers[6]. Although the global incidence of GC has declined due to improved living conditions and early screening[2], the number of new cases and deaths remains significant, likely due to population growth and aging[7].

Surgical or endoscopic resection remains the only curative treatment for GC[8], especially in patients with resectable GC without distant metastases[9]. However, even after radical resection, the prognosis for node-positive patients remains poor, with a five-year survival rate of < 50%[8]. Consequently, the management of GC has shifted from a singular surgical approach to a multidisciplinary approach. Several clinical trials such as MAGIC[10], FNCLCC and FFCD[11], and FLOT [12] have established the therapeutic value of perioperative chemotherapy for locally resectable GC. Perioperative chemotherapy improves the survival of patients with GC of stage IB or higher[13]. However, guidelines such as the National Comprehensive Cancer Network[1], European Society for Medical Oncology (ESMO)[14], and Chinese Society of Clinical Oncology[14] offer varying recommendations regarding the choice of perioperative chemotherapy regimens for GC, leading to confusion among clinicians. Although perioperative radiotherapy has been shown to improve overall survival (OS) in patients with GC[15,16], its role in the treatment of resectable GC remains controversial[17].

Network meta-analysis (NMA) is an extension of traditional meta-analysis[18] that overcomes some of the limitations of pairwise meta-analysis by enabling indirect comparisons of multiple interventions and the sequencing of individual interventions[19]. Accordingly, it facilitates clinicians' decision-making regarding chemotherapy regimens[20]. This study aimed to conduct a systematic search for randomized controlled trials (RCTs) involving resectable GC treated with perioperative chemotherapy and/or radiotherapy and rank them based on R0 resection rate, OS, disease-free survival (DFS), and safety using Bayesian NMA. The ultimate goal of this study was to identify an optimal treatment regimen and provide valuable clinical guidance.

MATERIALS AND METHODS

Registration information

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement[21] (Supplementary Table 1) and was registered in the International Prospective Register of Systematic Reviews (CRD420-23420814).

Database selection and search strategy

PubMed, Embase, and the Cochrane Library were searched from their inception to April 21, 2023, without language restrictions, using the terms Stomach, Gastric, Cancer, Tumor, Neoplasm, Carcinoma, Neoadjuvant, Preoperative, Perioperative, Adjuvant, Chemoradiotherapy, Radiotherapy, Chemotherapy, and Random. The search was conducted by Kuang ZY, Sun QH, and Cao LC, and any disagreements were resolved through discussions with three other authors (Ma XY, Wang JX, and Liu KX). All articles were screened using Endnote 20, and the search details are provided in Supplementary material.

Eligibility criteria

Studies meeting the following criteria were included: (1) Type: Phase II or III RCTs, with or without blinding; (2) Participants: Participants with locally resectable GC and gastroesophageal junctions according to the eighth edition of the tumor–node–metastasis (TNM) classification issued by the International Union against Cancer were included if they met the criteria of stage IB-III or cT2-4NanyM0 and had not received treatment before joining the clinical trial. Pathologically, the tumor was an adenocarcinoma. No sex-related limitations were observed in this study; (3) Interventions: Neoadjuvant chemotherapy and/or radiotherapy combined with postoperative adjuvant chemotherapy and/or radiotherapy, neoadjuvant chemotherapy and/or radiotherapy, and adjuvant chemotherapy and/or radiotherapy. There were no restrictions on specific regimens, and the surgical approach involved D2 Lymph node dissection based on the patient's condition; and (4) Outcomes: At least one of the following clinical outcomes should be reported: R0 resection rate, OS, DFS, incidence of non-surgical grade 3 or higher nonsurgical severe adverse events (SAEs).

Studies meeting the following criteria were excluded: (1) Multiple cancer; (2) Studies involving targeted immunotherapy and alternative therapies; (3) Studies lacking detailed information on treatment regimens; and (4) Studies that were reported repeatedly, lacked full-text availability, or had unavailable data.

Data extraction

We documented literature information, including the first author, year of publication, demographic data, and interventions. Data extraction for outcomes, such as the R0 excision rate, OS, DFS, and nonsurgical SAEs, was performed independently by two authors (Wang JX and Liu KX), and Kuang ZY was involved in cases of disagreement. For articles lacking survival data but providing survival curves, we used Engauge Digitizer software to extract the hazard ratio (HR) value and 95% confidence interval (95%CI) from the survival curve, as described by Tierney *et al*[22].

Risk of bias

We assessed the risk of bias using Review Manager (5.4.1) following the guidelines provided in the Cochrane Handbook [23]. In the case of disputes, the assessment was carried out independently by two authors (Wang JX and Liu KX) and a third author (Kuang ZY).

Statistical analysis

The primary outcome of this review was OS, whereas the secondary outcomes were R0 resection rate, DFS, and non-surgical SAEs. The study was divided into two phases. For the R0 resection rate, we compared studies related to neoadjuvant treatment regimens, while the outcome measures, OS, DFS, and non-surgical SAEs, were analyzed in studies involving neoadjuvant therapy, surgery, and postoperative adjuvant treatment regimens simultaneously. We assessed the risk ratio (RR) and 95%CI for dichotomous outcomes (R0 excision rate and non-surgical SAE) and converted the HR and 95%CI to lnHR and selnHR for outcomes such as OS and DFS.

We assessed the heterogeneity between studies using the Q-test and I^2 statistics. Unless I^2 exceeded 50% and the P value was less than 0.05, a fixed-effects model was employed. Intervention network diagrams were generated using Stata 15.0, and the mapping of the dichotomous variable surface under the cumulative ranking (SUCRA) was conducted under a Bayesian framework using the "GeMTC" software package in R 4.3.0. A model convergence diagnosis, heterogeneity testing, and consistency testing were performed. For outcomes for which NMA was not feasible, pairwise direct comparisons were performed using the Review Manager software. Publication bias was assessed by plotting funnels and Egger's test.

There are three ways to assess convergence in an NMA. The trajectory graph depicts the fluctuation of the Markov Monte Carlo chain during iterative calculations. If the chains demonstrated stable fusion and substantial overlap, the convergence was considered satisfactory. The density map compares the distribution patterns of the posterior values with a preset distribution; a smaller bandwidth value indicates a closer match. The Brooks-Gelman-Rubin diagnosis plot combines graphical evaluation and quantitative analysis using the potential scale reduction factor (PSRF), with a value closer to 1 indicating satisfactory convergence.

SUCRA is an indicator of the cumulative ranking probability. A SUCRA value of 1 signifies absolute effectiveness, whereas a value of 0 indicates complete ineffectiveness. Interventions can be ranked according to their effectiveness based on SUCRA values.

RESULTS

Literature search

A total of 2426 articles were initially retrieved. Among them, 544 duplicate articles were identified and manually removed. Additionally, 1259 non-clinical studies, including reviews, systematic reviews, and protocols, and 593 articles that did not meet the inclusion criteria were excluded. As a result, a total of 30 RCTs were included in the analysis[10-12, 24-50] (Figure 1 and Supplementary Table 2).

Literature characteristics and quality evaluation

The characteristics of the 30 RCTs are summarized in Supplementary Table 3. The bias risk assessment of these studies is presented in Supplementary Figures 1 and 2.

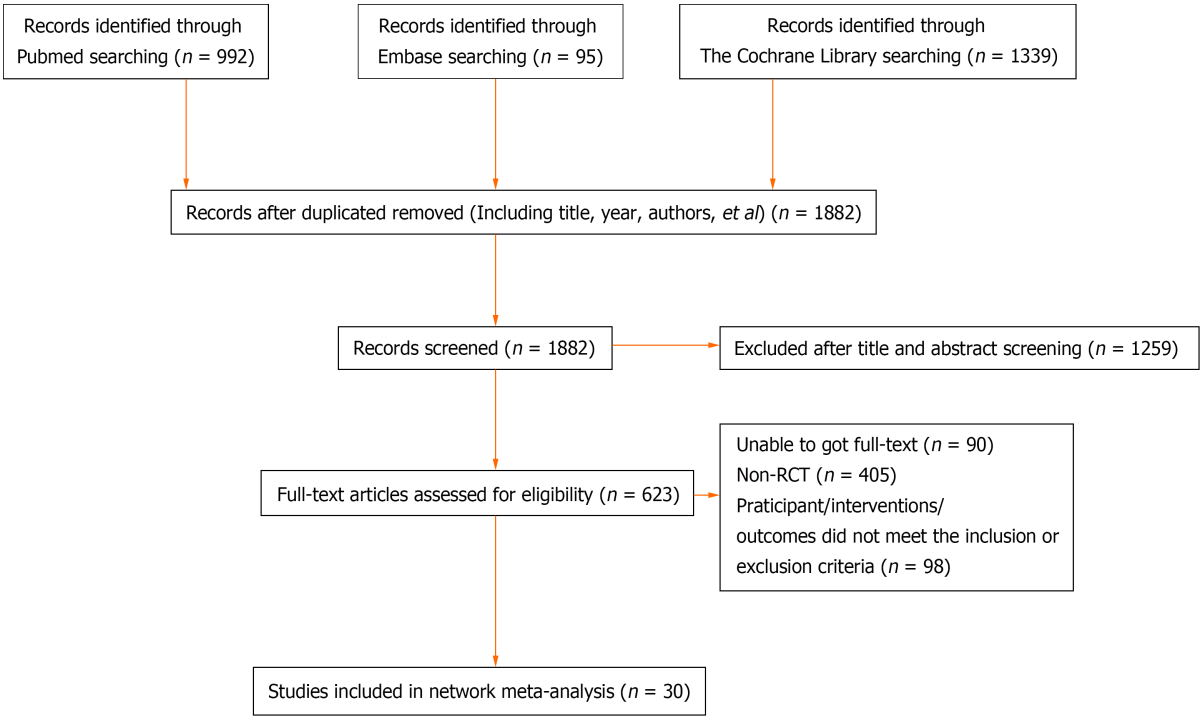


Figure 1 Flow diagram of article search and study selection.

R0 resection rate

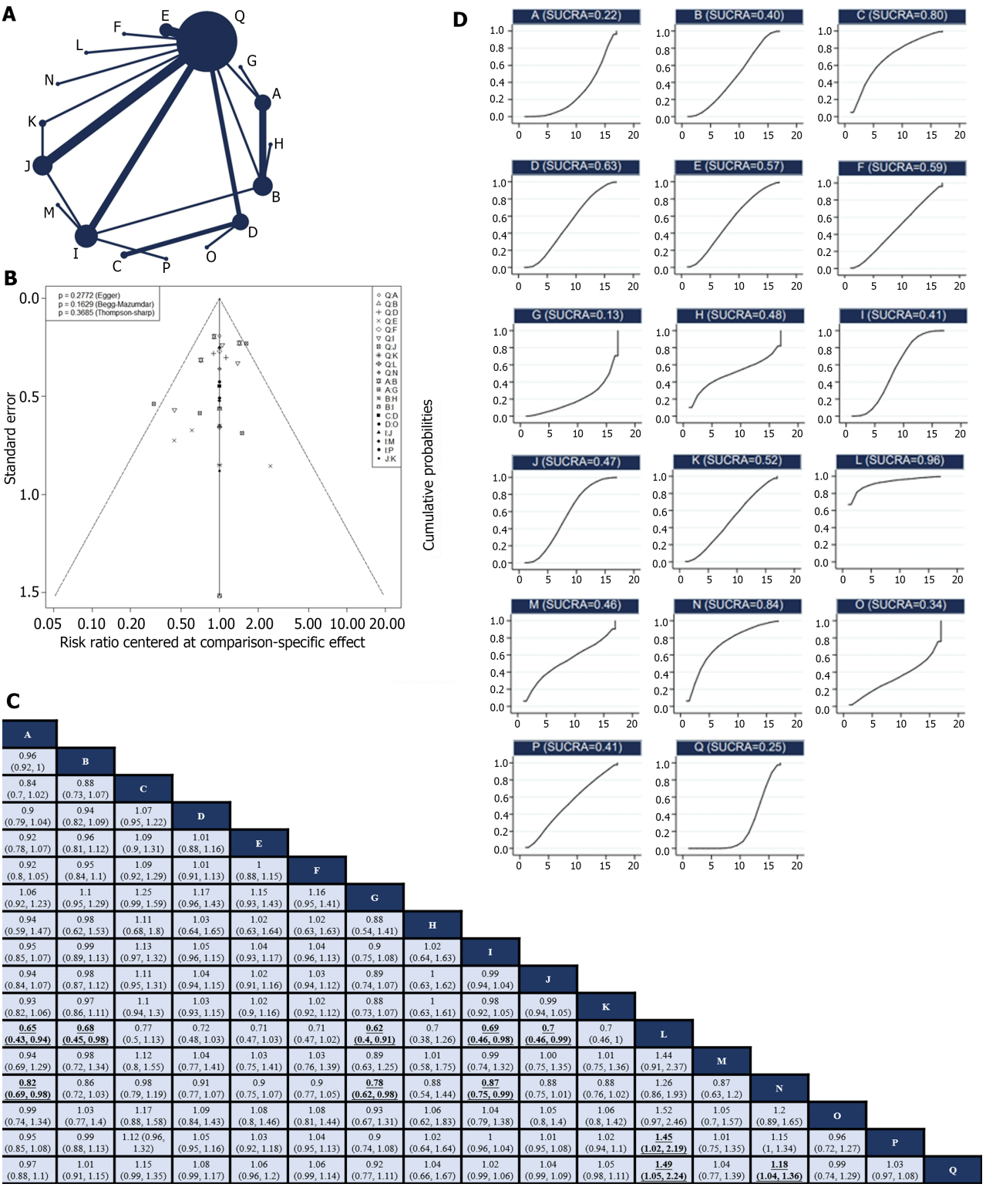
Of the 30 RCTs, 28[10-12,24-29,31-44,46-50] reported the R0 resection rate. Among them, there were 17 direct or indirect comparisons between the preoperative neoadjuvant regimens (Figure 2A). Some control groups where surgery was performed directly without neoadjuvant therapy were considered as the "surgery alone" group. Global inconsistency detection yielded an I^2 value of 34%. Accordingly, a fixed-effects model was used for effect size pooling. The trace plot, density plot, and Brooks-Gelman-Rubin diagnosis plot showed good convergence (Supplementary Figures 3 and 4), and the PSRF was 1, further indicating good convergence. Local inconsistencies were found between neoadjuvant SOX *vs* neoadjuvant FLOT, and neoadjuvant SOX *vs* surgery alone (Supplementary Figure 5). The Funnel plot indicated no evidence of publication bias (P = 0.2772; Figure 2B).

Pairwise comparisons between treatments showed that neoadjuvant XELOX plus neoadjuvant radiotherapy (RR: 1.49; 95%CI: 1.05–2.24) and neoadjuvant CF (RR: 1.18; 95%CI: 1.04–1.36) significantly improved the R0 resection rate compared with surgery alone. However, the remaining neoadjuvant regimens failed to improve the R0 resection rates. In addition, neoadjuvant ECF (RR: 0.65; 95%CI: 0.43–0.94), neoadjuvant FLOT (RR: 0.68; 95%CI: 0.45–0.98), neoadjuvant ECF plus neoadjuvant radiotherapy (RR: 0.62; 95%CI: 0.4–0.91), neoadjuvant SOX (RR: 0.69; 95%CI: 0.46–0.98), and neoadjuvant XELOX (RR: 0.7; 95%CI: 0.46–0.99) exhibited lower R0 resection rates compared to neoadjuvant XELOX plus neoadjuvant radiotherapy. Neoadjuvant ECF (RR: 0.82; 95%CI: 0.69–0.98), neoadjuvant ECF plus neoadjuvant radiotherapy (RR: 0.78; 95%CI: 0.62–0.98), and neoadjuvant SOX (RR: 0.87; 95%CI: 0.75–0.99) had inferior R0 resection rates compared to neoadjuvant CF. Notably, the R0 excision rate of neoadjuvant XELOX plus neoadjuvant radiotherapy was higher than that of neoadjuvant FOLFOX (RR: 1,45; 95%CI: 1.02–2.19; Figure 2C). Neoadjuvant XELOX combined with neoadjuvant radiotherapy resulted in the highest SUCRA value (0.96; Figure 2D). Taken together, neoadjuvant XELOX plus neoadjuvant radiotherapy appear to be the most effective neoadjuvant regimen.

OS

Fourteen RCTs[10-12,24-28,31,41,42,45,47,50] reported HR values for OS with corresponding 95%CIs for 14 interventions (Figure 3A). Global inconsistency detection yielded an I^2 value of 0%. Accordingly, the effect size was pooled using a fixed effects model. Convergence was confirmed by the trace plot, density plot, and Brooks-Gelman-Rubin diagnosis plot (Supplementary Figures 6 and 7), with a PSRF of 1, indicating good convergence. No local inconsistencies were detected in any study (Supplementary Figure 8). The Funnel plot showed no evidence of a publication bias (Figure 3B).

Pairwise comparisons of treatments revealed that neoadjuvant plus adjuvant FLOT (HR: 0.58; 95%CI: 0.44–0.75), neoadjuvant plus adjuvant ECF (HR: 0.75; 95%CI: 0.6–0.93), neoadjuvant plus adjuvant DCF (HR: 0.75; 95%CI: 0.6–0.93), neoadjuvant ECF plus adjuvant ECF and radiotherapy (HR: 0.74; 95%CI: 0.56–0.99), and neoadjuvant plus adjuvant CF (HR: 0.69; 95%CI: 0.5–0.95) significantly improved OS compared to surgery alone. In addition, neoadjuvant plus adjuvant FLOT outperformed neoadjuvant plus adjuvant ECF (HR: 0.77; 95%CI: 0.67–0.89), neoadjuvant ECF plus adjuvant ECF and radiotherapy (HR: 0.78; 95%CI: 0.61–0.98), and neoadjuvant CS plus adjuvant S-1 (HR: 0.63; 95%CI: 0.42–0.93) in terms of OS. Furthermore, neoadjuvant plus adjuvant XELOX showed superior OS compared with neoadjuvant plus adjuvant FOLFOX (HR: 0.43; 95%CI: 0.2–0.92). No statistically significant differences were observed in other intervention comparisons (Figure 3C). The neoadjuvant plus adjuvant FLOT group had the highest SUCRA value (0.91). Therefore,



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
A		0.96 (0.92, 1)	0.84 (0.7, 1.02)	0.9 (0.79, 1.04)	0.92 (0.78, 1.07)	0.92 (0.8, 1.05)	1.06 (0.92, 1.23)	0.94 (0.59, 1.47)	0.95 (0.85, 1.07)	0.94 (0.84, 1.07)	0.93 (0.82, 1.06)	**0.65 (0.43, 0.94)**	0.94 (0.69, 1.29)	**0.82 (0.69, 0.98)**	0.99 (0.74, 1.34)	0.95 (0.85, 1.08)	0.97 (0.88, 1.1)
B	0.88 (0.73, 1.07)		0.94 (0.82, 1.09)	0.96 (0.81, 1.12)	0.95 (0.84, 1.1)	1.1 (0.95, 1.29)	0.98 (0.62, 1.53)	0.99 (0.89, 1.13)	0.98 (0.87, 1.12)	0.97 (0.86, 1.11)	**0.68 (0.45, 0.98)**	0.98 (0.72, 1.34)	0.86 (0.72, 1.03)	1.03 (0.77, 1.4)	0.99 (0.88, 1.13)	1.01 (0.91, 1.15)
C	1.07 (0.95, 1.22)	1.09 (0.9, 1.31)		1.01 (0.88, 1.16)	1 (0.88, 1.15)	1.09 (0.92, 1.29)	1.25 (0.99, 1.59)	1.11 (0.68, 1.8)	1.13 (0.97, 1.32)	1.11 (0.95, 1.31)	1.1 (0.94, 1.3)	0.77 (0.5, 1.13)	1.12 (0.8, 1.55)	0.98 (0.79, 1.19)	1.17 (0.88, 1.58)	1.12 (0.96, 1.32)	1.15 (0.99, 1.35)
D	1.09 (0.91, 1.13)	1.01 (0.91, 1.13)	1.03 (0.64, 1.65)		1.02 (0.63, 1.64)	1.03 (0.64, 1.65)	1.17 (0.96, 1.43)	1.03 (0.64, 1.65)	1.05 (0.96, 1.15)	1.04 (0.94, 1.15)	1.03 (0.93, 1.15)	0.72 (0.48, 1.03)	1.04 (0.77, 1.41)	0.91 (0.77, 1.07)	1.09 (0.84, 1.43)	1.05 (0.95, 1.16)	1.08 (0.99, 1.17)
E	1.15 (0.93, 1.43)	1.02 (0.63, 1.64)	1.02 (0.63, 1.63)	1.02 (0.92, 1.12)		1.03 (0.94, 1.12)	1.15 (0.93, 1.43)	1.02 (0.63, 1.64)	1.04 (0.93, 1.17)	1.02 (0.91, 1.16)	1.02 (0.9, 1.16)	0.71 (0.47, 1.03)	1.03 (0.75, 1.41)	0.9 (0.75, 1.07)	1.08 (0.8, 1.46)	1.03 (0.92, 1.18)	1.06 (0.96, 1.2)
F	1.16 (0.95, 1.41)	1.02 (0.63, 1.63)	1.04 (0.63, 1.63)	1.03 (0.92, 1.12)	1.03 (0.94, 1.12)		1.16 (0.95, 1.41)	1.02 (0.63, 1.63)	1.04 (0.96, 1.13)	1.03 (0.94, 1.12)	1.02 (0.92, 1.12)	0.71 (0.47, 1.02)	1.03 (0.76, 1.39)	0.9 (0.77, 1.05)	1.08 (0.81, 1.44)	1.04 (0.95, 1.13)	1.06 (0.99, 1.14)
G	1.15 (0.93, 1.43)	0.88 (0.54, 1.41)	0.9 (0.75, 1.08)	0.89 (0.74, 1.07)	0.88 (0.73, 1.07)	**0.62 (0.4, 0.91)**		0.88 (0.54, 1.41)	0.9 (0.75, 1.08)	0.89 (0.74, 1.07)	0.88 (0.73, 1.07)	0.7 (0.38, 1.26)	0.89 (0.63, 1.25)	**0.78 (0.62, 0.98)**	0.93 (0.67, 1.31)	0.9 (0.74, 1.08)	0.92 (0.77, 1.11)
H	1.02 (0.64, 1.63)		1.02 (0.64, 1.63)	1 (0.63, 1.62)	1 (0.63, 1.61)	0.7 (0.38, 1.26)	1.01 (0.58, 1.75)	0.88 (0.54, 1.44)	1.06 (0.62, 1.83)	1.02 (0.64, 1.64)	1.04 (0.66, 1.67)						
I	0.99 (0.94, 1.04)	0.98 (0.92, 1.05)	**0.69 (0.46, 0.98)**	0.99 (0.79, 1.38)	1.04 (0.79, 1.38)	1.02 (0.99, 1.06)											
J	0.99 (0.94, 1.05)	**0.7 (0.46, 0.99)**	0.99 (0.75, 1.35)	0.88 (0.75, 1.01)	1.05 (0.8, 1.4)	1.04 (0.99, 1.09)											
K	0.7 (0.46, 1)	1.01 (0.75, 1.36)	0.88 (0.76, 1.02)	0.88 (0.8, 1.42)	1.06 (0.8, 1.42)	1.05 (0.98, 1.11)											
L	1.44 (0.91, 2.37)	1.26 (0.86, 1.93)	1.52 (0.97, 2.46)	**1.45 (1.02, 2.19)**	**1.49 (1.05, 2.24)**												
M	0.87 (0.63, 1.2)	1.05 (0.7, 1.57)	1.04 (0.77, 1.39)														
N	1.2 (0.89, 1.65)	**1.18 (1.04, 1.36)**															
O	0.99 (0.74, 1.29)																
P	1.03 (0.97, 1.08)																
Q																	

Figure 2 Network meta-analysis of R0 resection rate. A: Network diagram of R0 resection rate; B: The published biased funnel plot of R0 resection rate; C: Comparisons between each treatment; D: Surface under the cumulative ranking value of R0 resection rate of each intervention. Bold and underlined indicate statistically significant pairwise comparisons. A: Neoadjuvant ECF; B: Neoadjuvant FLOT; C: Neoadjuvant DCS; D: Neoadjuvant CS; E: Neoadjuvant DCF; F: Neoadjuvant DOS; G: Neoadjuvant ECF plus Neoadjuvant Radiotherapy; H: Neoadjuvant FLO; I: Neoadjuvant SOX; J: Neoadjuvant XELOX; K: Neoadjuvant DOX; L: Neoadjuvant XELOX plus Neoadjuvant Radiotherapy; M: Neoadjuvant SOX plus Neoadjuvant Radiotherapy; N: Neoadjuvant CF; O: Neoadjuvant PC; P: Neoadjuvant FOLFOX; Q: Surgery alone.

neoadjuvant plus adjuvant FLOT is likely to offer the best OS outcome (Table 1).

DFS

Six RCTs[11,12,25-27,50] reported the HR values and 95%CIs for DFS. Due to the limited number of included studies, only direct comparisons were conducted (Table 2). Neoadjuvant plus adjuvant FLOT demonstrated superior DFS compared to

Table 1 The SUCRA value of intervasion

Rank	Intervention	SUCRA value
1	Neoadjuvant plus adjuvant FLOT	0.91
2	Neoadjuvant plus adjuvant CF	0.74
3	Neoadjuvant DCS plus adjuvant S-1	0.67
4	Neoadjuvant ECF plus adjuvant ECF and radiotherapy	0.67
5	Neoadjuvant plus adjuvant DCF	0.66
6	Neoadjuvant plus adjuvant ECF	0.65
7	Neoadjuvant plus adjuvant XELOX	0.57
8	Neoadjuvant SOX and radiotherapy plus adjuvant SOX	0.46
9	Neoadjuvant CS plus adjuvant S-1	0.46
10	Surgery alone	0.37
11	Neoadjuvant plus adjuvant SOX	0.28
12	Adjuvant SOX	0.27
13	Neoadjuvant plus adjuvant FOLFOX	0.17
14	Adjuvant XELOX	0.11

Table 2 Direct comparison of disease-free survival of various interventions

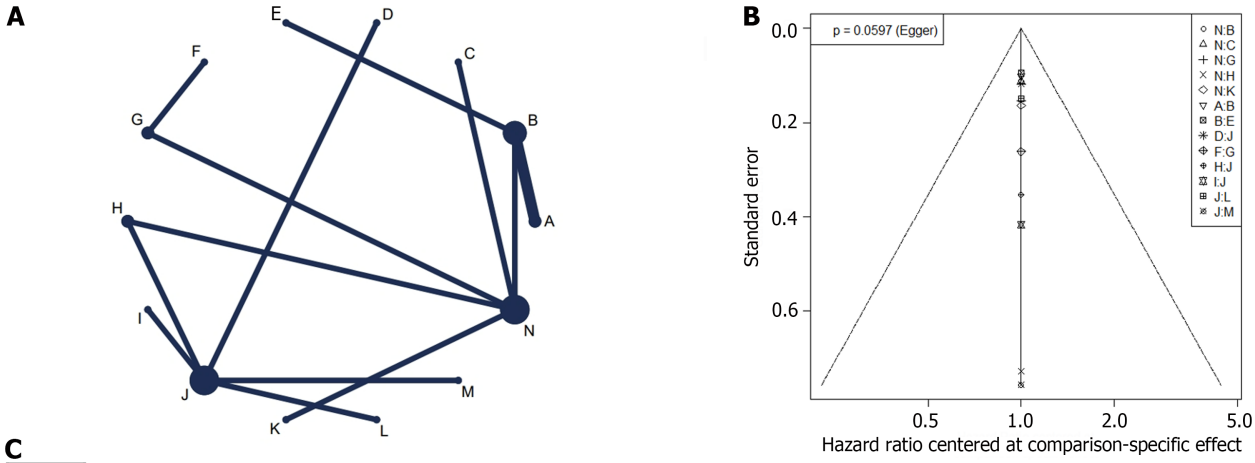
Intervention 1	Intervention 2	Study number	I^2	*P* value	HR/95%CI
Neoadjuvant plus adjuvant FLOT	Neoadjuvant plus adjuvant ECF	2	0	1.00	0.75 (0.65, 0.86)
Neoadjuvant plus adjuvant CF	Surgery alone	1	-	-	0.69 (0.50, 0.95)
Neoadjuvant plus adjuvant XELOX	Surgery alone	1	-	-	0.96 (0.25, 3.66)
Neoadjuvant plus Adjuvant SOX	Adjuvant SOX	1	-	-	1.28 (0.33, 4.93)
Neoadjuvant plus adjuvant SOX	Adjuvant XELOX	1	-	-	0.77 (0.61, 0.97)

neoadjuvant plus adjuvant ECF (HR: 0.75; 95%CI: 0.65–0.86). Neoadjuvant plus adjuvant CF outperformed surgery alone (HR: 0.69; 95%CI: 0.50–0.95). However, there was no statistically significant difference between Neoadjuvant plus adjuvant XELOX and surgery alone (HR: 0.96; 95%CI: 0.25–3.66). In addition, no significant difference was observed between the neoadjuvant plus adjuvant SOX and adjuvant SOX alone groups (HR: 1.28; 95%CI: 0.33–4.93). Neoadjuvant plus adjuvant SOX outperformed adjuvant XELOX (HR: 0.77; 95%CI: 0.61–0.97).

Non-surgical SAEs

Twelve RCTs[12,24,27,28,30-33,37,38,45,49] reported 12 treatments for nonsurgical SAEs (Figure 4A). Global inconsistency detection yielded an I^2 value of 6%. Accordingly, the effect size was pooled using a fixed effects model. Convergence was confirmed by the trace plot, density plot, and Brooks-Gelman-Rubin diagnosis plot (Supplementary Figures 9 and 10), with a PSRF of 1, suggesting good convergence, and no local inconsistencies were detected (Supplementary Figure 11). The Funnel plot indicated no evidence of a publication bias (P = 0.5483; Figure 4B).

Pairwise comparisons of interventions showed that neoadjuvant chemotherapy plus adjuvant ECF (RR: 3.6; 95%CI: 2–7.03), neoadjuvant chemotherapy plus adjuvant FLOT (RR: 3.53; 95%CI: 1.98–6.88), and neoadjuvant chemotherapy plus adjuvant ECF and radiotherapy (RR: 3.47; 95%CI: 1.93–6.8) were associated with a higher occurrence of non-surgical SAEs than neoadjuvant chemotherapy plus adjuvant FLO. Conversely, neoadjuvant plus adjuvant FLO (RR: 0.13; 95%CI: 0.02–0.74), neoadjuvant plus adjuvant SOX (RR: 0.24; 95%CI: 0.05–0.75), neoadjuvant DOX plus adjuvant SOX (RR: 0.29; 95%CI: 0.06–0.93), neoadjuvant plus adjuvant XELOX (RR: 0.29; 95%CI: 0.06–0.93), and adjuvant XELOX (RR: 0.25; 95%CI: 0.06–0.8) were associated with fewer non-surgical SAEs during treatment compared to neoadjuvant SOX and radiotherapy plus adjuvant SOX. Neoadjuvant plus adjuvant SOX had fewer non-surgical SAEs compared to neoadjuvant plus adjuvant XELOX (RR: 0.81; 95%CI: 0.69–0.96). Neoadjuvant plus adjuvant XELOX had more non-surgical SAEs compared to adjuvant SOX (RR: 1.26; 95%CI: 1.06–1.49). Neoadjuvant SOX and radiotherapy plus adjuvant SOX had a higher occurrence of non-surgical SAEs compared to adjuvant SOX (RR: 4.28; 95%CI: 1.35–19.41) and neoadjuvant plus adjuvant FOLFOX (RR: 4.07; 95%CI: 1.29–18.56; Figure 4C). The SUCRA value of the neoadjuvant plus adjuvant FLO regimen was the highest (0.91), indicating that this regimen had the lowest probability of nonsurgical SAEs. Conversely, the neoadjuvant SOX and radiotherapy plus adjuvant SOX regimens (SUCRA, 0.06) were associated with the highest



C

A												
0.77 (0.67, 0.89)	B											
0.77 (0.55, 1.08)	1 (0.73, 1.36	C										
0.23 (0.05, 1.17)	0.3 (0.06, 1.51)	0.3 (0.06, 1.51)	D									
0.78 (0.61, 0.98)	1.01 (0.84, 1.22)	1.01 (0.7, 1.45)	3.37 (0.66, 17.24)	E								
0.78 (0.41, 1.5)	1.02 (0.54, 1.92)	1.02 (0.54, 1.93)	3.41 (0.62, 18.89)	1.01 (0.52, 1.96)	F							
0.63 (0.42, 0.93)	0.82 (0.56, 1.18)	0.82 (0.56, 1.18)	2.72 (0.53, 13.94)	0.81 (0.53, 1.22)	0.8 (0.48, 1.33)	G						
0.58 (0.14, 2.49)	0.75 (0.18, 3.2)	0.75 (0.18, 3.2)	2.52 (1.21, 5.24)	0.75 (0.17, 3.21)	0.74 (0.16, 3.46)	0.93 (0.22, 3.97)	H					
0.41 (0.04, 4.16)	0.53 (0.05, 5.39)	0.53 (0.05, 5.4)	1.76 (0.32, 9.65)	0.52 (0.05, 5.36)	0.52 (0.05, 5.65)	0.65 (0.06, 6.66)	0.7 (0.11, 4.33)	I				
0.3 (0.06, 1.49)	0.39 (0.08, 1.93)	0.39 (0.08, 1.93)	1.3 (1.03, 1.64)	0.39 (0.08, 1.92)	0.38 (0.07, 2.07)	0.48 (0.09, 2.4)	0.52 (0.26, 1.03)	0.74 (0.14, 3.99)	J			
0.84 (0.55, 1.27)	1.09 (0.74, 1.6)	1.09 (0.74, 1.6)	3.62 (0.7, 18.72)	1.08 (0.7, 1.66)	1.07 (0.54, 2.1)	1.33 (0.86, 2.07)	1.44 (0.33, 6.21)	2.06 (0.2, 21.42)	2.79 (0.55, 14.2)	K		
0.25 (0.05, 1.29)	0.33 (0.06, 1.67)	0.33 (0.06, 1.65)	1.09 (0.75, 1.58)	0.32 (0.06, 1.66)	0.32 (0.06, 1.78)	0.4 (0.08, 2.07)	**0.43 (0.2, 0.92)**	0.62 (0.11, 3.45)	0.84 (0.63, 1.13)	0.3 (0.06, 1.55)	L	
0.27 (0.03, 2.41)	0.35 (0.04, 3.11)	0.35 (0.04, 3.14)	1.18 (0.26, 5.26)	0.35 (0.04, 3.1)	0.35 (0.04, 3.28)	0.43 (0.05, 3.85)	0.47 (0.09, 2.4)	0.67 (0.3, 1.53)	0.91 (0.21, 3.97)	0.33 (0.04, 2.9)	1.08 (0.24, 4.89)	M
0.58 (0.44, 0.75)	**0.75 (0.6, 0.93)**	**0.75 (0.6, 0.93)**	2.5 (0.5, 12.51)	**0.74 (0.56, 0.99)**	0.74 (0.41, 1.33)	0.92 (0.68, 1.24)	0.99 (0.24, 4.13)	1.42 (0.14, 14.42)	1.93 (0.39, 9.45)	**0.69 (0.5, 0.95)**	2.29 (0.46, 11.53)	2.12 (0.24, 18.66)	N

Figure 3 Network meta-analysis of overall survival. A: Network diagram of overall survival; B: The published biased funnel plot of overall survival; C: Comparisons between each treatment. Bold and underlined indicate statistically significant pairwise comparisons. A: Neoadjuvant plus adjuvant FLOT; B: Neoadjuvant plus adjuvant ECF; C: Neoadjuvant plus adjuvant DCF; D: Adjuvant CapeOX; E: Neoadjuvant ECF plus adjuvant ECF and radiotherapy; F: Neoadjuvant DCS plus adjuvant S-1; G: Neoadjuvant CS plus adjuvant S-1; H: Neoadjuvant plus adjuvant XELOX; I: Neoadjuvant SOX and radiotherapy plus adjuvant SOX; J: Neoadjuvant plus adjuvant SOX; K: Neoadjuvant plus adjuvant CF; L: Neoadjuvant plus adjuvant FOLFOX; M: Adjuvant SOX; N: Surgery alone.

probability of nonsurgical SAEs (Figure 4D).

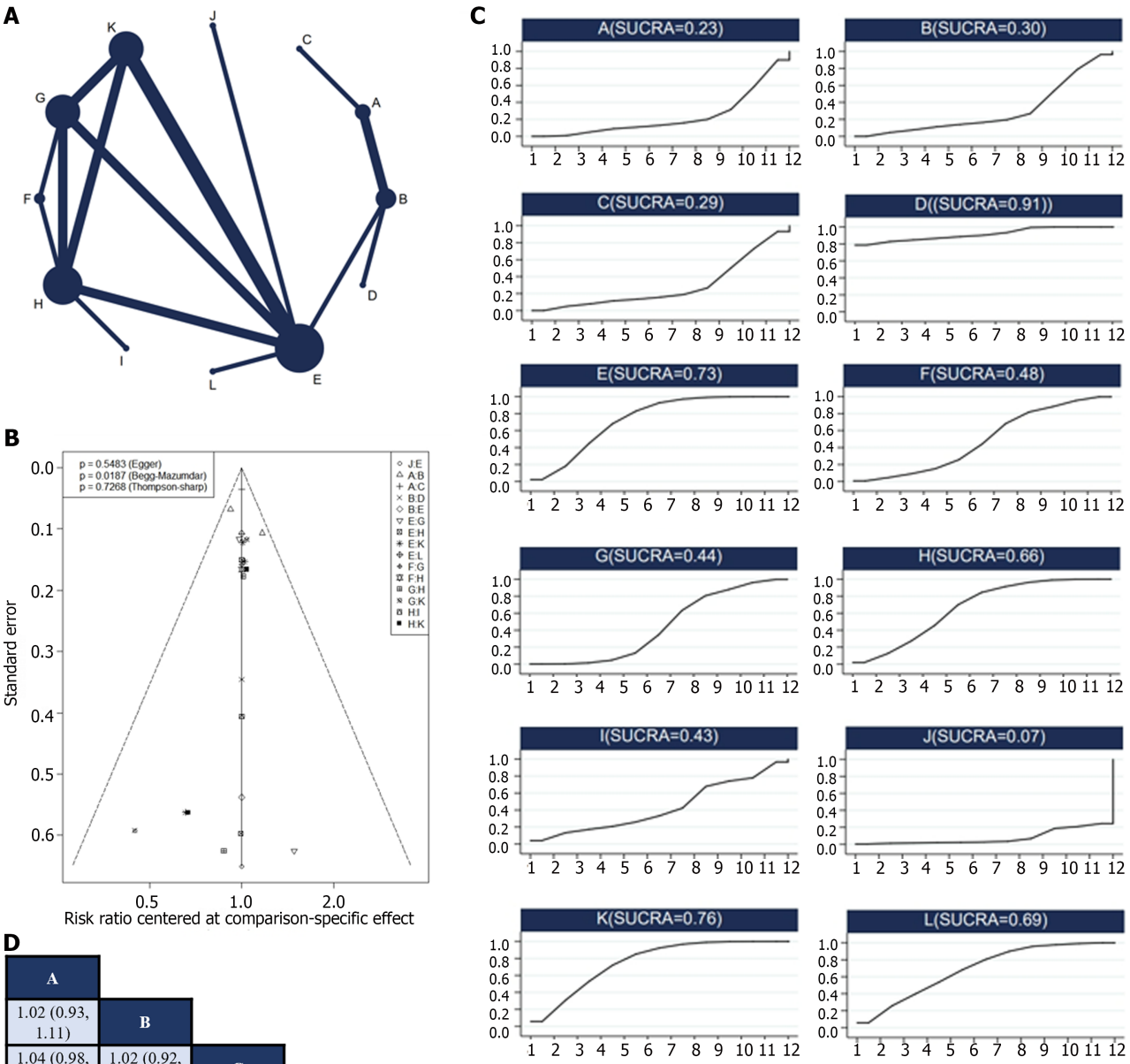
Evidence grade

We evaluated the R0 resection rate, OS, DFS, and nonsurgical SAEs using the GRADE assessment tool, and the results indicated that all four outcomes were assessed as low-quality evidence (Supplementary Table 4).

DISCUSSION

Advancements in biological science have deepened our understanding of GC characteristics[51,52]. Numerous biomarkers, such as HER2, PD-L1, MSI-H, and EBV, have emerged as therapeutic targets or predictors of treatment efficacy[53] and serve as the basis for selecting targeted therapy or immunotherapy drugs[54]. However, targeted therapy and immunotherapy currently have significant limitations, including drug resistance, strict eligibility criteria, and high costs [55,56]. As a result, chemotherapy remains the most commonly used treatment during the perioperative period for GC[7, 57]. This study aimed to identify an optimal regimen for enhancing the survival outcomes of patients with locally resectable GC. We analyzed the R0 resection rate, OS, DFS, and safety profiles of various perioperative chemoradiotherapy regimens. Our findings will provide valuable guidance for clinical treatment decisions.

These results indicate that only the neoadjuvant XELOX plus neoadjuvant radiotherapy and neoadjuvant CF regimens effectively improved the R0 resection rate. However, this result was inconsistent with those of some of the included studies. For example, Zhao *et al*[25] reported that neoadjuvant XELOX increased the R0 resection rate (P = 0.04) compared to surgery alone, but indirect comparisons in NMA showed no significant difference. Similarly, Al-Batran *et al*[12] found



D

A										
1.02 (0.93, 1.11)	B									
1.04 (0.98, 1.09)	1.02 (0.92, 1.13)	C								
3.6 (2, 7.03)	**3.53 (1.98, 6.88)**	**3.47 (1.93, 6.8)**	D							
1.97 (0.72, 6.36)	1.93 (0.71, 6.22)	1.9 (0.69, 6.16)	0.55 (0.16, 2.01)	E						
1.64 (0.58, 5.43)	1.61 (0.57, 5.31)	1.58 (0.56, 5.24)	0.45 (0.13, 1.71)	0.83 (0.64, 1.08)	F					
1.6 (0.58, 5.24)	1.58 (0.57, 5.14)	1.55 (0.56, 5.07)	0.45 (0.13, 1.65)	**0.81 (0.69, 0.96)**	0.98 (0.78, 1.24)	G				
1.88 (0.67, 6.17)	1.85 (0.67, 6.05)	1.81 (0.65, 5.96)	0.52 (0.15, 1.94)	0.95 (0.79, 1.16)	1.15 (0.9, 1.47)	1.17 (0.96, 1.42)	H			
1.48 (0.43, 5.7)	1.45 (0.43, 5.58)	1.43 (0.42, 5.51)	0.41 (0.1, 1.77)	0.75 (0.37, 1.48)	0.9 (0.44, 1.81)	0.91 (0.46, 1.81)	0.78 (0.4, 1.5)	I		
0.47 (0.08, 2.43)	0.46 (0.08, 2.38)	0.45 (0.08, 2.35)	**0.13 (0.02, 0.74)**	**0.24 (0.05, 0.75)**	**0.29 (0.06, 0.93)**	**0.29 (0.06, 0.93)**	**0.25 (0.06, 0.8)**	0.32 (0.06, 1.23)	J	
2.02 (0.73, 6.59)	1.99 (0.72, 6.45)	1.95 (0.71, 6.37)	0.56 (0.17, 2.08)	1.03 (0.88, 1.2)	1.24 (0.95, 1.61)	**1.26 (1.06, 1.49)**	1.08 (0.88, 1.31)	1.38 (0.69, 2.76)	**4.28 (1.35, 19.41)**	K
1.93 (0.69, 6.29)	1.89 (0.68, 6.17)	1.86 (0.67, 6.09)	0.53 (0.16, 1.99)	0.98 (0.81, 1.18)	1.18 (0.85, 1.63)	1.2 (0.93, 1.54)	1.03 (0.78, 1.34)	1.31 (0.65, 2.68)	**4.07 (1.29, 18.56)**	0.95 (0.75, 1.22)	L

Figure 4 Network meta-analysis of non-surgical severe adverse events. A: Network diagram of higher nonsurgical severe adverse events (SAEs); B: The published biased funnel plot of non-surgical SAEs; C: Comparisons between each treatment. old and underlined indicate statistically significant pairwise comparisons; D: Surface under the cumulative ranking value of non-surgical SAEs of each intervention. A: Neoadjuvant plus adjuvant ECF, B: Neoadjuvant plus adjuvant FLOT, C: Neoadjuvant ECF plus adjuvant ECF and radiotherapy, D: Neoadjuvant plus adjuvant FLO, E: Neoadjuvant plus adjuvant SOX, F: Neoadjuvant DOX plus adjuvant SOX, G: Neoadjuvant plus adjuvant XELOX, H: Adjuvant XELOX, I: Neoadjuvant and radiotherapy plus adjuvant XELOX, J: Neoadjuvant SOX

and radiotherapy plus adjuvant SOX, K: Adjuvant SOX, L: Neoadjuvant plus adjuvant FOLFOX.

that preoperative FLOT chemotherapy was superior to preoperative ECF in terms of R0 resection rate (P = 0.0162), whereas indirect comparisons showed no significant difference. Based on the SUCRA values, we inferred that neoadjuvant XELOX plus neoadjuvant radiotherapy might be the most effective regimen for improving the R0 resection rate, supporting its short-term efficacy. However, there is insufficient data available to determine the long-term survival benefits. Moreover, recommendations for preoperative chemotherapy combined with radiotherapy for locally resectable GC remain unclear among various guidelines. Therefore, caution should be exercised when interpreting these results.

Neoadjuvant FLOT plus adjuvant FLOT showed the highest probability of being the most effective regimen for OS, which is consistent with the ESMO guidelines. FLOT is currently the mainstream three-drug perioperative chemotherapy regimen used in Europe and has been shown to effectively prolong OS and DFS[12,58]. However, its impact on the R0 resection rate appears to be minimal and requires further investigation. Interestingly, neoadjuvant therapy plus adjuvant SOX did not show a survival benefit compared to surgery alone. The SOX regimen is widely used as a perioperative chemotherapy regimen for GC in Asia, and several phase III clinical trials conducted in Asia have established its role in locally resectable GC[27,59]. However, the results of this study suggest that perioperative SOX regimens may not confer a survival benefit compared to surgery alone. This discrepancy could be attributed to the limited number of available studies and the uncertainties associated with indirect comparisons. Further clinical studies involving direct comparisons are required to validate these findings.

Unfortunately, we could not rank the regimens based on DFS because of insufficient data. Only direct head-to-head comparisons were made between the regimens, and further clinical studies are required to gain a better understanding. Therefore, the safety of this regimen is crucial, particularly in the context of radical GC resection. This study suggests that FLO may be the safest perioperative treatment option, whereas neoadjuvant SOX and radiotherapy plus adjuvant SOX may be associated with a higher risk of adverse effects, presumably owing to the increased toxicity of this combination.

This study has several limitations. First, most of the included studies were open-label studies, which may have introduced some degree of bias into the conclusions. Second, there is ongoing controversy regarding the classification of malignant tumors[60]. Although classified as a distinct type of malignant tumor, gastroesophageal junction tumors are often combined with gastric or esophageal cancers in clinical studies. However, their unique pathological characteristics require caution when combined with general oncological principles[61]. Another limitation of this study was the limited number of direct comparisons between interventions, with most comparisons being indirect. Then, SUCRA values have limitations and do not necessarily imply statistical differences, so caution is needed when interpreting intervention rankings based on SUCRA values. Finally, caution must be exercised when applying findings from Eastern countries to Western countries and vice versa, as the biology of patients with GC may vary from country to country.

CONCLUSION

In this study, perioperative chemoradiotherapy regimens for locally resectable GC were analyzed and ranked using a Bayesian NMA. Our findings may guide clinicians in selecting appropriate treatment regimens. However, it is important to consider the limitations of this study and exercise caution when interpreting its conclusions. Future RCTs with rigorous designs and large sample sizes are needed to validate these findings. Given the advancements in targeted therapy and immunotherapy, it would be valuable to further explore the potential survival benefits of combining basic chemotherapy with targeted therapies and immunotherapy for locally resectable GC in future research.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy worldwide, with over 1 million new cases per year, and the third leading cause of cancer-related death.

Research motivation

To conduct a systematic search for randomized controlled trials (RCTs) involving resectable GC with perioperative chemotherapy and/or radiotherapy and rank them based on R0 resection rate, overall survival (OS), disease-free survival (DFS), and safety using Bayesian NMA. The ultimate goal was to identify the optimal treatment regimen and provide valuable clinical guidance.

Research objectives

To determine the optimal perioperative treatment regimen for locally resectable GC.

Research methods

A comprehensive literature search was conducted focusing on phase II/III RCTs assessing perioperative chemotherapy

and chemoradiotherapy in locally resectable GC. The R0 resection rate, OS, DFS, and incidence of grade 3 or non-surgical grade 3 or higher nonsurgical severe adverse events (SAEs) associated with various perioperative regimens were analyzed. Bayesian network meta-analysis was performed to compare the treatment regimens and rank their efficacy.

Research results

A total of 30 RCTs involving 8346 patients were included in this study. Neoadjuvant XELOX plus neoadjuvant radiotherapy and neoadjuvant CF were found to significantly improve the R0 resection rate compared to surgery alone, and the former had the highest probability of being the most effective option in this context. Neoadjuvant plus adjuvant FLOT was associated with the highest probability of being the best regimen for OS. Due to limited data, no definitive ranking could be determined for DFS. Considering non-surgical SAEs, FLO emerged as the safest regimen.

Research conclusions

A total of 30 RCTs involving 8346 patients were included in this study. Neoadjuvant XELOX plus neoadjuvant radiotherapy and neoadjuvant CF were found to significantly improve the R0 resection rate compared to surgery alone, and the former had the highest probability of being the most effective option in this context. Neoadjuvant plus adjuvant FLOT was associated with the highest probability of being the best regimen for OS. Due to limited data, no definitive ranking could be determined for DFS. Considering non-surgical SAEs, FLO emerged as the safest regimen.

Research perspectives

Our findings may provide some guidance to clinicians in selecting the appropriate treatment regimens. However, it is important to consider the limitations of this study and exercise caution when interpreting its conclusions. Future RCTs with rigorous designs and large sample sizes are needed to validate the findings. Given the advancements in targeted therapy and immunotherapy, it would be valuable to further explore the potential survival benefits of combining basic chemotherapy with targeted therapies and immunotherapy for locally resectable GC in future research.

FOOTNOTES

Co-first authors: Zi-Yu Kuang and Qian-Hui Sun.

Author contributions: Li L mainly conceived this manuscript and gave instructions. Kuang ZY, Sun QH, and Cao LC critically analyzed the current literature and wrote the original manuscript; Ma XY, Wang JX, and Liu KX were responsible for extracting data and drawing charts; all authors have read and agreed to the published version of the manuscript. Kuang ZY and Sun QH are the co-first authors of this study as this study was conceived by Kuang ZY and Sun QH.

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