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Multimodal treatments for resectable gastric cancer: A systematic review and network meta-analysis

Ji Cheng [a, b, *], Ming Cai [a], Xiaoming Shuai [a], Jinbo Gao [a], Guobin Wang [a], Kaixiong Tao [a, **]

[a] Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China
[b] Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, 02115, USA

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ABSTRACT

Different countries prefer particular types of multimodal treatments against resectable gastric cancer. Due to lacking of unified conclusions, we therefore conducted a network meta-analysis to rank all recommended strategies simultaneously and hierarchically. Record retrieval was conducted in PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Embase, ASCO and ESMO meeting libraries from inception to September 2018. Randomized controlled trials featuring comparisons between different preferred multimodal treatments against resectable gastric cancer were eligible. The Cochrane Risk of Bias Tool was applied to assess methodological quality of included trials. Overall survival was primary endpoint. Network calculation was based on random-effects model and the relative ranking of each node was numerically indicated by P-score. All procedures were conducted according to Cochrane Handbook 5.1 and PRISMA for Network Meta-analysis (CRD42018109147). As a result, a total of 11 studies were included into our systematic review, corresponding to 7235 patients. Regarding overall survival, "PeriCT (FLOT)" (perioperative 5-FU plus leucovorin plus oxaliplatin plus docetaxel chemotherapy) topped the hierarchy (HR 1.00, P-score = 0.918), followed by "PostCT (XP)" (postoperative capecitabine plus platinum chemotherapy; HR 1.14, P-score = 0.759) and "PostCT (S-1)" (postoperative S-1 monotherapy; HR 1.16, P-score = 0.732). In subgroup analyses, "PostCT (XP)" became the top regimen for eastern population while "PeriCT (FLOT)" was the optimal node for western population. In conclusion, perioperative FLOT chemotherapy could potentially be the best multimodal treatment against resectable gastric cancer than other recommended strategies. Therefore, a global D2-lymphadenectomy randomized controlled trial comparing perioperative FLOT chemotherapy with postoperative XELOX chemotherapy should be carried out.

Introduction

Gastric cancer is the fifth most common malignancy and third leading cause of cancer relevant mortality worldwide, with more than half of its cases occurring in East Asia [1,2]. During the past decade, although its overall survival rate has been greatly improved from 20% to 40% due to early detection techniques and progressed therapeutics, gastric cancer is still a heavy health burden which urges us to discover more effective therapeutic strategies [3–5].

Different stages of gastric cancer feature specific treatments [6]. Currently, surgical operation is the basic approach against resectable gastric cancer, which accounts for more than half of the patients at initial diagnosis [3,6]. Furthermore, numerous evidences have confirmed that multimodal treatments are able to greatly enhance the survival benefits among patients compared to surgery alone, which are therefore widely accepted as the standard strategies against resectable gastric cancer [7–10]. Nonetheless, owing to different regional evidences, there is lacking of a unified recommendation on specific multimodal treatments. Postoperative chemoradiotherapy is the preferred approach in USA, while perioperative chemotherapy and postoperative chemotherapy are respectively recommended in Europe and East Asia [3,6,11–13]. Meanwhile, even though within the same modality, such as postoperative chemotherapy, different guidelines could have different recommendations, such as XELOX (Capecitabine plus

* Corresponding author No.1277 Jiefang Avenue, Wuhan, 430022, China.
** Corresponding author No.1277 Jiefang Avenue, Wuhan, 430022, China.
E-mail addresses: jicheng1@hust.edu.cn (J. Cheng), kaixiongtaowhuh@126.com (K. Tao).

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oxaliplatin) by NCCN guideline [6] and S-1 monotherapy by Japanese guideline [12]. All these have hinted the necessity to perform a comprehensive comparison amid all available strategies in terms of efficacy and tolerability.

Network meta-analysis is a perfect tool to perform multi-arm comparisons, which could generate comparative outcomes even without specific pairwise evidences [14,15]. Therefore, we conducted a systematic review as well as the first network meta-analysis to compare all therapeutic combinations for resectable gastric cancer simultaneously and hierarchically, hoping to provide useful information for clinical application and future design of randomized controlled trials.

Methods

Registration and guidelines

The protocol of this systematic review and network meta-analysis had been published in PROSPERO (CRD42018109147). The design, conduct and writing of this systematic review and network meta-analysis was strictly in accordance with the requirements from PRISMA Checklist for Network Meta-analysis and Cochrane Handbook 5.1. Each step was conducted by two investigators of our research group. Any discrepancy was judged and solved by the third investigator.

Search strategy

Electronic databases including PubMed, Web of Science, Cochrane Central Register of Controlled Trials and Embase were comprehensively examined. Additionally, we also thoroughly searched major databases for meeting abstracts, including ASCO and ESMO libraries. The searching process started at July 15th until September 13th of 2018, covering the possible trials published from inception to September 2018. Both abstract and main text of the retrieved entries were rigorously assessed in order to guarantee the accuracy of selection. The full search strategies were presented in Supplementary Materials.

Selection criteria

Studies that simultaneously met the following criteria were eligibly included (PICOS framework):

1. Participant: trials featuring adult unselected patients with previously untreated resectable gastric cancer, not including specific pathological type, protein positivity or resectable superficial gastric cancer.
2. Intervention: trials containing multimodal treatments against resectable gastric cancer which were recommended as the preferred regimens by the latest guidelines, including NCCN (National Comprehensive Cancer Network) [6], ESMO (European Society for Medical Oncology) [13], JGCA (Japan Gastric Cancer Association) [12] and CSCO (Chinese Society of Clinical Oncology) [11]. Specifically, XELOX (Capecitabine plus oxaliplatin) [6,11], S-1 monotherapy [11,12] and XC (capecitabine plus cisplatin) [11] for postoperative chemotherapy, FLOT (5-FU plus leucovorin plus oxaliplatin plus docetaxel) [6] for perioperative chemotherapy, as well as FL-based (5-FU plus leucovorin) postoperative chemoradiotherapy [6]. Additionally, although FLOT had displayed significant superiority against EFP (epirubicin plus fluoropyrimidine plus platinum) as the preferred perioperative regimen [16], since EFP was the major control arm of most current trials, we still included studies with EFP to facilitate the proper formation of network quantitative calculation. Comparisons between auxiliary therapeutics, such as anti-inflammatory medications, supportive methods or immunomodulators were not qualified.
3. Comparator: FLOT-based perioperative chemotherapy was the common comparator node in the network meta-analysis.
4. Outcome: time-to-event survival analysis as well as safety analysis.
5. Study design: phase 2 and phase 3 randomized controlled trials reported from inception to September 2018 without language limitations.

Studies were excluded from systematic review due to the following reasons:

1. Interim or repetitive reports from the same registered study (we only included the one with the longest follow-up period).
2. Trials analyzing certain stage of resectable gastric cancer instead of a whole range of resectable patients.

Risk of bias assessment

The quality of each eligible study was evaluated by The Cochrane Risk of Bias Tool. The entire scale was constituted by seven domains, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias [17]. According to the criteria on Cochrane Handbook 5.1, each domain could be judged as any of the three levels, including low risk, unclear risk or high risk of bias. If the majority of items were judged as low risk of bias, then the entire methodological design of network meta-analysis was regarded as low risk of bias, and vice versa. Here, studies were defined to be low-quality if four or more items were scored as high risk of bias.

Data extraction

Pre-designed forms were utilized to collect and organize the original data. General information, survival and safety data were extracted from main text, tables, survival curves or supplementary materials, which had been cross-checked by two different investigators in our team before quantitative incorporations.

Baseline parameters and endpoints

All possible baseline parameters that could influence the clinical characteristics of each study were included and analyzed in our systematic review, including region, multimodal treatment, surgical type, systemic regimens, age, gender ratio, TNM stages, performance status, tumor location, 3 or 5-year overall survival rate and 3 or 5-year recurrence-free survival rate (Table 1).

The primary endpoint was overall survival, while secondary endpoints included recurrence-free survival, hematological adverse events and non-hematological adverse events. Consistent among all included trials, overall survival was defined as the time from randomization to death from any cause. Although there were some variations and differences among studies in terms of the definition of recurrence-free survival, it generally referred to the time from randomization until disease progression, locoregional or peritoneal tumor recurrence, distant metastases, or death from any cause, whichever occurred first (eTable 2). The hematological adverse events included leukopenia, neutropenia, anemia, thrombocytopenia and other relevant events such as febrile neutropenia and infection with neutropenia. The remaining adverse events were defined as non-hematological adverse events. We only

Table 1
Baseline features of included studies.

Study	Region	Registration	Phase	Enrollment	Treatment	Surgical type	Systemic regimens	Sample size	Age
Cats 2018 [24]	Western (Netherlands, Sweden and Denmark)	NCT00407186	3	2007.1–2015.4	Surgery plus preoperative chemotherapy plus postoperative chemoradiotherapy	Radical (D1+ and D2)	Pre: ECX/EOX: Capecitabine plus cisplatin/oxaliplatin plus epirubicin; Post: XC: Capecitabine plus cisplatin	395	63.0
					Surgery plus perioperative chemotherapy		ECX/EOX: Capecitabine plus cisplatin/ oxaliplatin plus epirubicin	393	62.0
Stahl 2018 [25]	Western (Germany)	NCT01234324	2	2010.11–2013.7	Surgery plus perioperative chemotherapy	Radical (D2)	ECXP: Capecitabine plus cisplatin plus epirubicin plus panitumumab	80	60.0
					Surgery plus perioperative chemotherapy		ECX: Capecitabine plus cisplatin plus epirubicin	80	61.0
Fuchs 2017 [26]	Western (USA)	NCT00052910	3	2002.4–2009.5	Surgery plus adjuvant chemoradiotherapy	Radical (D1 and D2)	ECF: 5-FU plus cisplatin plus epirubicin	266	58.0
					Surgery plus adjuvant chemoradiotherapy		FL: 5-FU plus leucovorin	280	59.0
Cunningham 2017 [27]	Western (UK)	NCT00450203	3	2007.10–2014.3	Surgery plus perioperative chemotherapy	Radical (D1 and D2)	ECXB: Capecitabine plus cisplatin plus epirubicin plus bevacizumab	530	64.0
					Surgery plus perioperative chemotherapy		ECX: Capecitabine plus cisplatin plus epirubicin	533	63.0
Al-Batran 2017 [16]	Western (Germany)	NCT01216644	3	2010.8–2015.2	Surgery plus perioperative chemotherapy	Radical (D2)	FLOT: 5-FU plus leucovorin plus oxaliplatin plus docetaxel	356	62.0
					Surgery plus perioperative chemotherapy		ECX/ECF: 5-FU/ Capecitabine plus cisplatin plus epirubicin	360	
Park 2015 [28]	Eastern (South Korea)	NCT00323830	3	2004.11–2008.4	Surgery plus adjuvant chemoradiotherapy	Radical (D2)	XC: Capecitabine and cisplatin	230	56.0
					Surgery plus adjuvant chemotherapy		XC: Capecitabine and cisplatin	228	56.0
Noh 2014 [7]	Eastern (China and South Korea)	NCT00411229	3	2006.6–2009.6	Surgery plus adjuvant chemotherapy	Radical (D2)	XELOX: Capecitabine plus oxaliplatin	520	56.1
					Surgery		None	515	55.8
Zhu 2012 [29]	Eastern (China)	NA	3	2003.9–2008.5	Surgery plus adjuvant chemotherapy	Radical (D2)	FL: 5-FU plus leucovorin	165	59.0
					Surgery plus adjuvant chemoradiotherapy		FL: 5-FU plus leucovorin	186	56.0
Smalley 2012 [8]	Western (USA)	NA	3	1991–1998	Surgery	Radical (D0, D1 and D2)	None	275	59.0
					Surgery plus adjuvant chemoradiotherapy		FL: 5-FU plus leucovorin	281	60.0
Sasako 2011 [9]	Eastern (Japan)	NCT00152217	3	2001.10–2004.12	Surgery plus adjuvant chemotherapy	Radical (D2)	S: S-1	529	63.0
					Surgery		None	530	63.0
Cunningham 2006 [10]	Western (UK)	ISRCTN93793971	3	1994.7–2002.4	Surgery plus perioperative chemotherapy	Radical (D1 and D2)	ECF: 5-FU plus cisplatin plus epirubicin	250	62.0
					Surgery		None	253	62.0

Notes: Underlined and bold-typed data in "PS (0/1/2)" indicated that the numbers should be interpreted as PS (0 and 1) vs PS (2). In "Location (G/J)", studies reporting both gastric and lower esophageal cases were underlined and bold-typed, with an asterisk "E" indicating esophageal cases. Underlined and bold-typed data in survival rates were estimated from Kaplan-Meier curves.
Abbreviations: NA: not available; D0/D1/D1+/D2: different extents of lymphadenectomy; M/F: male/female; G/J: gastric/junction; OS: overall survival; RFS: recurrence-free survival; 95% CI: 95% confidence interval.

counted grade 3 or higher (National Cancer Institute Common Terminology Criteria for Adverse Events) adverse events due to their clinical significances.

Statistical analysis

Our systematic review contained both narrative and quantitative analysis. Those trials with high homogeneity as well as adequate original data were incorporated into network meta-analysis. Hazard ratio (HR) and its 95% confidential interval (95% CI) were used as the effect size for overall survival (OS) and recurrence-free survival (RFS). Risk ratio (RR) and its 95% CI were applied as the effect size for hematological and non-hematological adverse events. In terms of adverse events, the total amount of

Gender (M/F)	TNM	PS (0/1/2)	Location (G/J)	3-year OS: Survival rate (95% CI)	5-year OS: Survival rate (95% CI)	3-year RFS: Survival rate (95% CI)	5-year RFS: Survival rate (95% CI)	Journal
265/130	cIB- cIVA(AJCC 6th)	274/106/NA	328/67	**51.6%**	40.0% (35.0%–46.0%)	**45.7%**	38.0% (33.0%–44.0%)	Lancet Oncol
264/129		260/103/NA	325/68	**53.4%**	42.0% (37.0%–48.0%)	**46.1%**	39.0% (34.0%–44.0%)	
53/27	cT3-4, cN0-3, cM0 (AJCC 7th)	0–1	47/33	49.0%	NA	NA	NA	Eur J Cancer
63/17			44/36	62.0%				
178/88	IB- IVA(AJCC 6th)	144/118/4	209/55	**53.5%**	44.0%	**45.6%**	37.0%	J Clin Oncol
193/87		132/139/9	208/65	**53.5%**	44.0%	**47.4%**	39.0%	
434/96	IB- IVA(AJCC 6th)	377/153/0	**189/271/70-E***	48.1% (43.2%–52.7%)	**35.6%**	NA	NA	Lancet Oncol
425/108		381/152/0	**194/265/74-E***	50.3% (45.5%–54.9%)	**40.1%**			
530/186	cT2-4, cN1-3, cM0	0–2	Gastric and junction	57.0%	NA	NA	NA	J Clin Oncol
				48.0%				
143/87	IB- IVA(AJCC 6th)	99/131	All gastric	**80.2%**	75.0%	78.2%	**73.6%**	J Clin Oncol
153/75		96/132		**83.5%**	73.0%	74.2%	**66.9%**	
373/147	IB- IVA(AJCC 6th)	0–1	505/15	**84.4%**	78.0% (74.0%–82.0%)	**76.5%**	68.0% (63.0%–73.0%)	Lancet Oncol
358/157			506/9	**79.4%**	69.0% (64.0%–73.0%)	**60.6%**	53.0% (47.0%–58.0%)	
126/39	IB- IVA(AJCC 7th)	0–1	150/15	**50.7%**	41.8%	**47.3%**	35.8%	Radiother Oncol
135/51			156/30	**60.1%**	48.4%	**58.2%**	45.2%	
195/80	IB- IVA(AJCC 3rd)	**259/16**	All gastric	41.0%	**27.1%**	31.0%	**21.6%**	J Clin Oncol
202/79		**264/17**		50.0%	**40.8%**	48.0%	**38.1%**	
367/162	IIA-IVA (AJCC 6th)	NA	All gastric	**81.8%**	71.7% (67.8%–75.7%)	**72.1%**	65.4% (61.2%–69.5%)	J Clin Oncol
369/161				**72.5%**	61.1% (56.8%–65.3%)	**70.0%**	53.1% (48.7%–57.4%)	
205/45	II-IV, M0 (AJCC 4th)	169/81/0	**185/28/37-E***	**44.4%**	**36.4%**	**38.1%**	**29.9%**	N Engl J Med
191/62		173/80/0	**187/30/36-E***	**30.9%**	**23.2%**	**25.4%**	**16.2%**	

grade 3 or higher adverse events were used for calculation, instead of the number of patients suffering grade 3 or higher adverse events.

Transitivity was the key hypothesis for network meta-analysis. When the head-to-head results of A versus C and B versus C were respectively gained, then the hypothesis of transitivity also permitted a statistical comparison between A and B. However, it required comparable general features within each node as the prerequisite condition to eliminate selection bias and justify statistical connections among indirect arms [18]. Both methodological designs (such as randomized controlled trials) and clinical features (such as region, surgical type and tumor location) were crucial for assessment of transitivity. Apart from clinical and methodological heterogeneity, since HR was a relative endpoint, the baseline

survival rate of studies among the same node is a critical indicator to determine the homogeneity as well as the rationality of quantitative incorporation. Statistical heterogeneity of the network meta-analysis was the overall degree of disparity within the same pairwise comparison [19]. I^2 static was the chief indicator of statistical heterogeneity, with its value < 25%, 25%–50% and >50% indicating low, moderate and high heterogeneity respectively. Besides, Q static of heterogeneity and its P value also facilitated the assessment of statistical heterogeneity. If the P value of Q static was less than 0.05, it suggested that there was a significant heterogeneity within.

On the other hand, the consistency, another crucial assumption for network meta-analysis, referred to the statistically consistent results between direct and indirect effect sizes regarding the same comparison. Significant differences between direct and network calculations might indicate inconsistency within the network meta-analysis while also suggest the unsuitability for transitivity [20]. Among closed loops of each network, we utilized a loop-specific method which assessed the mutual variance between direct and indirect results. Inconsistency factor (IF) was applied as the quantitative indicator which suggested the existence of inconsistency once its 95% confidence interval excluded zero [15]. Meanwhile, Q static of inconsistency was another statistical indicator to numerically estimate the consistency within the comparisons, whose P value (<0.05) could suggest a significant inconsistency of network meta-analysis. Both consistency and homogeneity were crucial basis to offer reliable outcomes by network meta-analysis. If inconsistency or significant heterogeneity occurred, we deleted the original data from the most inconsistent or heterogeneous pairwise comparisons to examine whether the results remained unchanged, otherwise it was not appropriate for pooled analysis [19,21].

A network plot and comparison-adjusted funnel plot were applied to display the network structure and examine the publication bias across the included trials respectively, where the more symmetrical it was, the less probability of publication bias the merged results would have. We conducted the random-effects network meta-analysis based on a frequentist model, with either HR or RR as the effect size. A network forest plot or league table were used for demonstrating the entire regimens with their relative confidential intervals. In addition, we also utilized P-score to rank all regimens based on their network estimates. The closer P-score approached 1, the best regimen it could be. Sensitivity analysis was performed to detect the stability of pooled outcomes by deleting potentially heterogenous studies. Quantitative network meta-analysis was conducted on R software 3.4.3, assisted by STATA 14.0 in terms of graphical functions.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Baseline characteristics

After screening through 9506 preliminary records (8960 from databases and 546 from abstract libraries), a total of 11 randomized controlled trials were eligibly included into our systematic review, corresponding to 7235 participants (Fig. 1 and Table 1). Reasons of ineligibility by full-text assessment were described in eTable 1. Overall, the median age was around 60 and the sex ratio was male dominant. 7 studies were based on western population while only 4 eligible trials originated from eastern countries. Predominantly, patients had a performance status of either 0 or 1. Among all included trials, 5 studies themed on perioperative treatments and 6 studies featured adjuvant chemotherapy or chemoradiotherapy. All surgical procedures were radically performed with either D2 or less lymphadenectomy. Therefore, the demographic characteristics of included trials were generally comparable (Table 1). Meanwhile, additional information including key definitions and evaluation criteria of eligible studies in our systematic review were listed in eTable 2.

Risk of bias

Overall, the included studies had low risk of bias since more half of the assessment parameters were scored as low risk of bias (51%), while unclear risk (30%) or high risk of bias (19%) took up relatively small proportions (Fig. 2). Individually, none of the eligible studies was in high risk of bias concerning methodological design (eTable 3).

Specifically, since the majority of trials were centrally allocated and adequately randomized, 55% and 55% of the studies were evaluated as low risk of bias concerning random sequence generation and allocation concealment respectively, while no high risk of bias was reported in these two key domains. Due to open-label design and impossibility for treatment masking with greatly differently administered arms, all of the include trials (100%) were scored as high risk of bias in terms of blinding or participants and personnel. Since there was lacking of enough descriptions on whether the independent reviewing had been made, 73% of the studies were assessed as unclear risk of bias in terms of blinding of outcome assessment. In addition, because most of the studies were analyzed based on the intention-to-treat population as well as had reported enough endpoints, 91% and 73% of the eligible trials had low risk of bias regarding incomplete outcome data and selective reporting respectively. Moreover, since the majority of studies were completely performed without early termination and also described adequate baseline details, more than half of the studies were appraised as low risk of bias with respect to other source of bias (73%) (Fig. 2).

Primary endpoint (overall survival)

(Network geometry) There were totally 11 randomized controlled trials merged into the quantitative analysis, corresponding to 12 network nodes (Fig. 3 and Table 2).

(Transitivity) We had re-organized and categorized studies with the same nodes into comparisons (eTable 4). Since all included trials were randomized controlled trials with relatively low risk of bias concerning study design, the overall methodological heterogeneity was considered in low level. Generally, all included trials were comparable concerning clinical features, however, in order to heighten the homogeneity inside the network, we performed further subgroup analyses based on different lymphadenectomy extents, sources of origin, TNM stages and invasion depths Besides, most importantly, the basic survival status of studies within the same node was key to maintain the transitivity when comparing hazard ratio of overall survival. No matter in “PeriCT (EFP)”, “PostCRT (FL)”, “PostCT (XP)” or “S”, the majority of the eligible trials shared similar baseline overall survival rates, which guaranteed the rationality to perform a network quantitation. Only Cats 2018 and Stahl 2018 in “PeriCT (EFP)” node, as well as Zhu 2012 in “PostCRT (FL)” had slightly different baseline survival status than others in the same node, which were then removed in sensitivity analysis to detect the outcome stability (eTable 4).

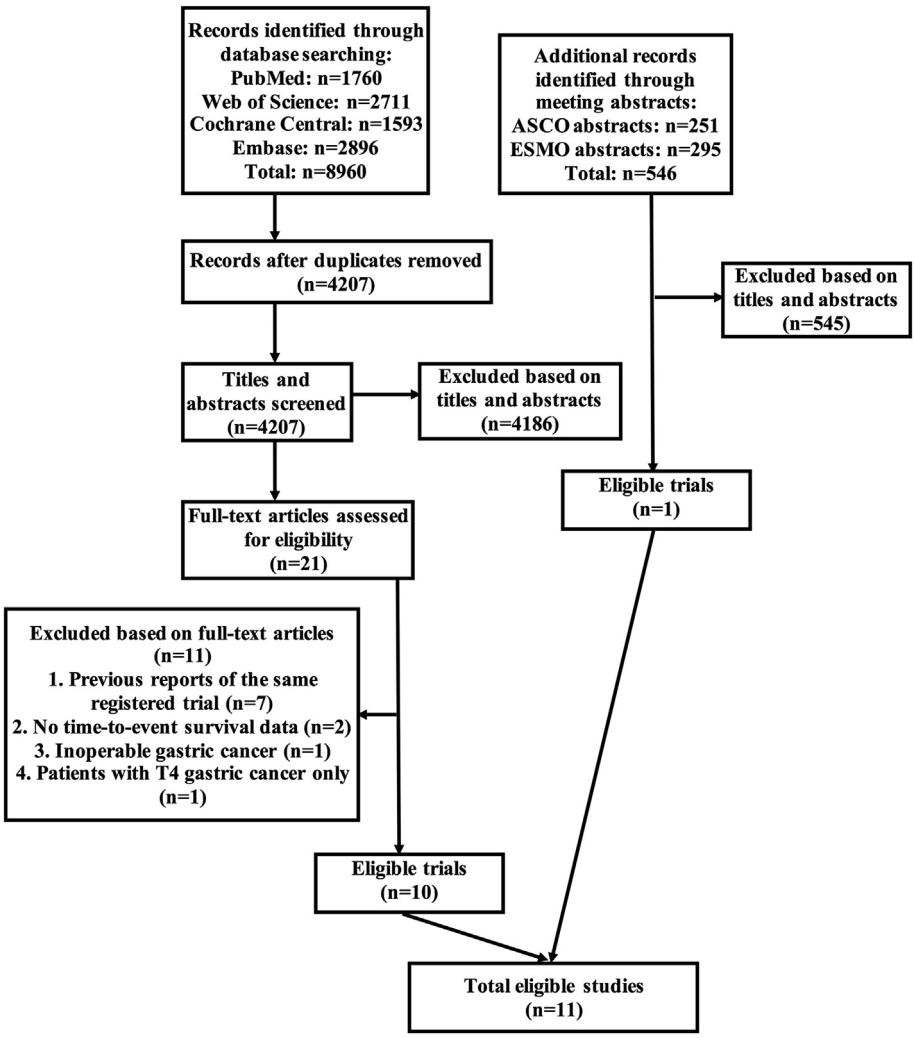

Fig. 1. Selection flow chart for systematic review.

(Consistency and heterogeneity) Since no closed loop had been found within the network, consistency of the network could not be analyzed. Meanwhile, since there were no two studies reporting identical two arms, thus the statistical heterogeneity inside the network also could not be met.

(Publication bias) There was no publication bias among the included studies due to symmetrical distribution of effect sizes inside the funnel plot (eFig. 1).

(Network calculation) Since FLOT-based perioperative chemotherapy had recently been recommended as the preferred regimen by NCCN guidelines, "PeriCT (FLOT)" was therefore selected as the common comparator. Based on P-score ranking of the network meta-analysis, "PeriCT (FLOT)" (network HR 1.00, P-score = 0.918) was the best ranking node, followed by "PostCT (XP)" (network HR 95%CI: 1.14 (0.77–1.68), P-score = 0.759) and "PostCT (S-1)" (network HR 95%CI: 1.16 (0.81–1.67), P-score = 0.732). The network forest plot and league table were demonstrated in Fig. 4 and eFig. 2 respectively.

(Sensitivity analysis) As aforementioned, Cats 2018, Stahl 2018 and Zhu 2012 were removed from the network due to possibly heterogeneous basic survival data. Meanwhile, since the baseline survival rates of 4 studies inside "S" node differed significantly due to possibly surgical technical differences, we separated "S" into "S1" and "S2", which corresponded to inadequate lymphadenectomy and D2 lymphadenectomy respectively. After making these changes, the original network also split into two sub-networks, where "PeriCT (FLOT)" and "PostCT (XP)" topped the hierarchies respectively, displaying dominant superiority against "S1" (network HR 95%CI: 1.73 (1.30–2.32), P-score = 0.023) or "S2" (network HR 95%CI: 1.52 (1.18–1.96), P-score = 0.032) (eFigs. 3 and 4). Therefore, the results of network meta-analysis were generally stable.

(Subgroup analysis) Although the entire network was in low heterogeneity, we still performed subgroup analyses to enhance the homogeneity in each subgroup network, which helped to examine the outcome stability as well as offer more specific clinical information (eTable 5). There were totally 8 subgroups, including gastric cases only (excluding data from junction cases), western population, eastern population, D2 lymphadenectomy, invasion depth (T1-2), invasion depth (T3-4), TNM stage (I/II) as well as TNM stage (III/IV). Without "PeriCT (FLOT)" being calculated, "PostCT (S-1)" and "PostCT (XP)" topped the rankings for gastric cases only and D2 lymphadenectomy subgroups respectively (data not shown). Moreover, "PeriCT (FLOT)" and "PostCT (XP)" were the optimal node for western and eastern population respectively (data not shown). Due to failure of obtaining the subgroup data, "PeriCT (FLOT)" was not included into the subgroup analyses of invasion depth and TNM stages. For less invasion (T1-2), "PostCT (XP)" was better than

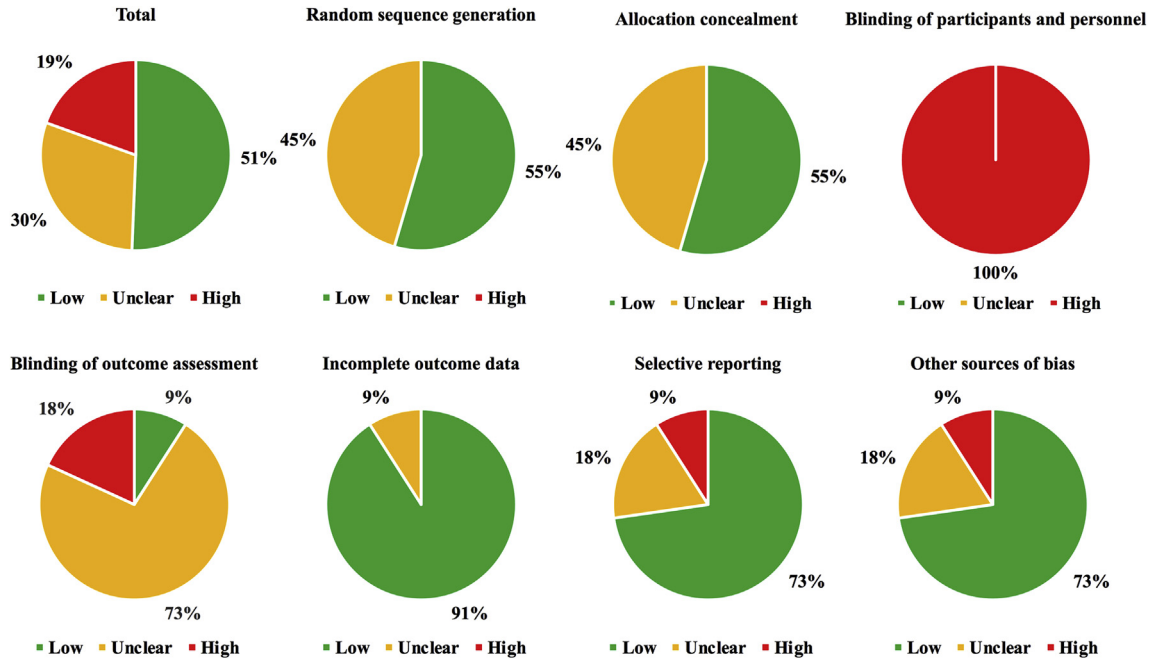

Fig. 2. Risk of bias assessment.

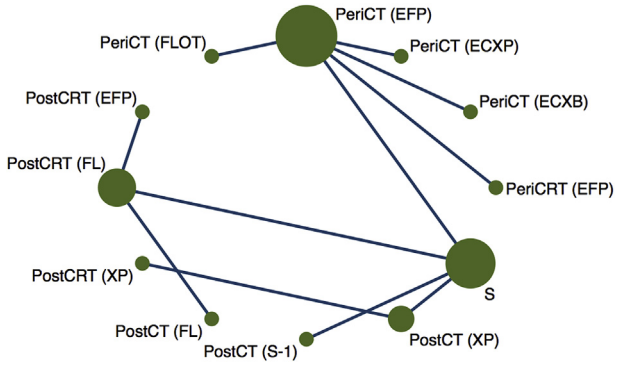

Fig. 3. Network structure plot of overall survival.
Node: Peri: perioperative**; Post:** postoperative**; CRT:** chemoradiotherapy**; CT:** chemotherapy**; EFP:** epirubicin plus fluoropyrimidine plus platinum; **ECXP:** epirubicin plus cisplatin plus capecitabine plus panitumumab; **FL:** 5-FU plus leucovorin; **ECXB:** epirubicin plus cisplatin plus capecitabine plus bevacizumab; **FLOT:** 5-FU plus leucovorin plus oxaliplatin plus docetaxel; **XP:** capecitabine plus platinum; **S:** surgery alone; **S-1:** S-1 monotherapy.

"PostCT (S-1)" to become the best node while "PostCT (S-1)" reigned in severer invasion depth (T3-4). For TNM stages, both "PostCT (XP)" and "PostCT (S-1)" closely ranked in the hierarchies, where "PostCT (XP)" was slightly better than "PostCT (S-1)" in later stages (TNM III-IV) while "PostCT (S-1)" was better in earlier stages (TNM I-II) (data not shown).

Secondary endpoint

(Recurrence-free survival) Data from 11 studies were included into the pooled analysis (Table 2). "PostCRT (XP)" became the optimal node in the entire hierarchy (network HR 95%CI: 0.88 (0.53–1.46), P-score = 0.940), closely followed by common comparator "PeriCT (FLOT)" (network HR 1.00, P-score = 0.895) and "PostCT (XP)" (network HR 95%CI: 1.19 (0.82–1.70), P-score = 0.696) (eFig. 5).

(Hematological and non-hematological adverse events) Since several studies failed to report adverse events, we made a narrative description instead of quantitative network meta-analysis. When compared to surgery alone, multimodal treatments certainly had greater incidence of adverse events, irrespective of "PostCT (XP)" or "PostCT (S-1)". However, the comparison between multimodal treatments, such as "PeriCRT (EFP)" with "PeriCT (EFP)", the adverse events seemed to be comparable (Table 2).

Discussion

Currently, clinical treatments for resectable gastric cancer are highly diverse across the globe [3,6]. Owing to limited and separately performed evidences, each region favors its own prevalent multimodal treatment, including postoperative chemotherapy in eastern countries, perioperative chemotherapy in Europe and postoperative chemoradiotherapy in the USA [3]. Therefore, to find a worldwide unified standard treatment is in urgent need, however which requires a globally performed randomized controlled trial. Based on that, we conducted a systematic review and the first network meta-analysis on this topic, in order to rank all potential treatments hierarchically and provide suggestive results for the design of future randomized controlled trial.

At present, FLOT has replaced EFP as the best perioperative chemotherapeutic regimen in NCCN guidelines [6], while XELOX and S-1 monotherapy are two main adjuvant regimens among eastern countries [11,12]. In terms of overall survival of our meta-analysis, "PeriCT (FLOT)" topped the hierarchy with insignificant superiority against other recommended treatments, such as "PostCT (XP)", "PostCT (S-1)" and "PostCRT (FL)". Since no pairwise trials between any two of these treatments had been reported, their comparative efficacies were interconnected by node "S" (surgery alone). However, as we mentioned in sensitivity analysis, potentially due to difference in investigation time, lymphadenectomy extent and ratio of tumor stages (patients from Japan and South Korea have higher proportion of earlier stages thanks to adequate screening process), the baseline survival rates of 4 studies comparing multimodal treatments with surgery alone were

Table 2
Survival and safety data of included studies.

Study	Node	Overall survival			Recurrence-free survival		hAE (E/T)	non-hAE (E/T)
		Hazard ratio	Network meta-analysis	Sensitivity analysis	Hazard ratio	Network meta-analysis		
Cats 2018	PeriCRT (EFP) PeriCT (EFP)	1.01 (95% CI 0.84–1.22)	Included	Removed	0.99 (95% CI 0.82–1.19)	Included	88/233-Post 27/245-Post	176/233-Post 200/245-Post
Stahl 2018	PeriCT (ECXP) PeriCT (EFP)	1.37 (95% CI 0.84–2.25)	Included	Removed	1.19 (95% CI 0.76–1.88)	Included	39/80-Pre 32/80-Pre	28/80-Pre 8/80-Pre
Fuchs 2017	PostCRT (EFP) PostCRT (FL)	0.98 (95% CI 0.78–1.24)	Included	Included into S1	0.96 (95% CI 0.77–1.20)	Included	121/251 145/272	184/251 248/272
Cunningham 2017	PeriCT (ECXB) PeriCT (EFP)	1.09 (95% CI 0.91–1.29)	Included	Included into S1	1.04 (95% CI 0.89–1.22)	Included	161/525-Pre; 87/254-Post 181/529-Pre; 103/292-Post	257/525-Pre; 97/254-Post 255/529-Pre; 106/292-Post
Al-Batran 2017	PeriCT (FLOT) PeriCT (EFP)	0.77 (95% CI 0.63–0.94)	Included	Included into S1	0.75 (95% CI 0.62–0.91)	Included	NA	NA
Park 2015	PostCRT (XP) PostCT (XP)	1.13 (95% CI 0.78–1.65)	Included	Included into S2	0.74 (95% CI 0.52–1.05)	Included	113/227 96/226	50/227 51/226
Noh 2014	PostCT (XP) S	0.66 (95% CI 0.51–0.85)	Included	Included into S2	0.58 (95% CI 0.47–0.72)	Included	147/496 1/478	177/496 6/478
Zhu 2012	PostCT (FL) PostCRT (FL)	1.24 (95% CI 0.94–1.65)	Included	Removed	1.35 (95% CI 1.03–1.78)	Included	12/165 14/186	0/165 11/186
Smalley 2012	S PostCRT (FL)	1.32 (95% CI 1.10–1.60)	Included	Included into S1	1.51 (95% CI 1.25–1.83)	Included	148/273 NA	174/273 NA
Sasako 2011	PostCT (S-1) S	0.67 (95% CI 0.54–0.83)	Included	Included into S2	0.65 (95% CI 0.54–0.79)	Included	13/517 8/526	104/517 76/526
Cunningham 2006	PeriCT (EFP) S	0.75 (95% CI 0.60–0.93)	Included	Included into S1	0.66 (95% CI 0.53–0.81)	Included	NA	NA

Node: **Peri:** perioperative**; Post:** postoperative**; CRT:** chemoradiotherapy**; CT:** chemotherapy**; EFP:** epirubicin plus fluoropyrimidine plus platinum; **ECXP:** epirubicin plus cisplatin plus capecitabine plus panitumumab; **FL:** 5-FU plus leucovorin; **ECXB:** epirubicin plus cisplatin plus capecitabine plus bevacizumab; **FLOT:** 5-FU plus leucovorin plus oxaliplatin plus docetaxel; **XP:** capecitabine plus platinum; **S:** surgery alone; **S-1:** S-1 monotherapy.
Note: In sensitivity analysis, since it could not form one network, all included trials were therefore separated into two networks, namely S1 and S2.
Abbreviations: NA: not available; hAE: hematological adverse event; non-hAE: non-hematological adverse event; E/T: event/total.

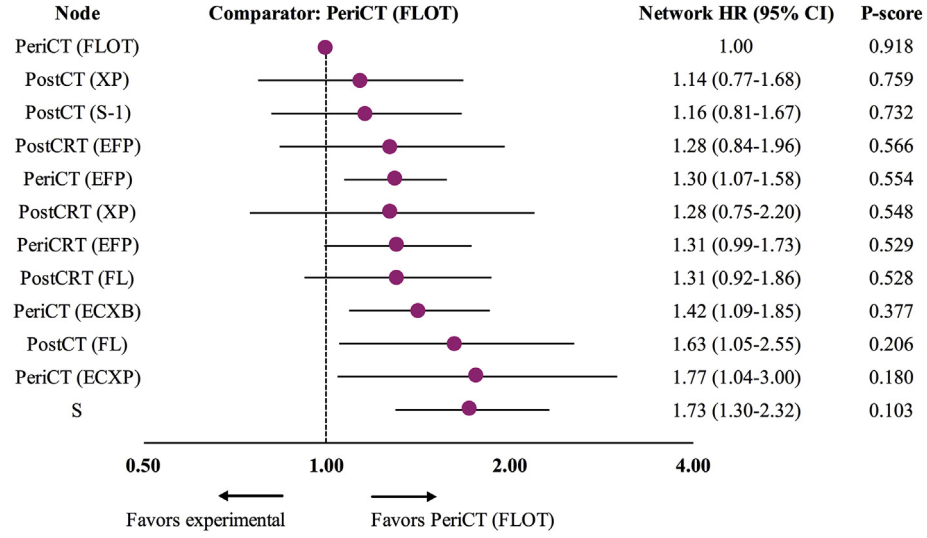

Fig. 4. Network forest plot of overall survival.

considerably different. That's why we performed a sensitivity analysis separating node "S" into "S1" and "S2". Both "PeriCT (FLOT)" and "PostCT (XP)" reigned two sub-hierarchies respectively, with "PeriCT (FLOT)" showing a slightly higher superiority against "S" than that of "PostCT (XP)", which to some extent proved the results to be stable despite of two separate networks. Moreover, among all subgroup analyses, "PostCT (XP)" became the top regimen for eastern population, D2 lymphadenectomy, less invasion depth and higher TNM stages, "PeriCT (FLOT)" was the optimal node for western population while "PostCT (S-1)" for gastric cases only, severer invasion depth and lower TNM stages. However, since all included trials were not global or comprehensive enough, only a few studies were included into each subgroup especially that we could not analyze "PeriCT (FLOT)", "PostCT (XP)" and "PostCT (S-1)" in a single subgroup network. All these made the subgroup results less credible and clinically applicable. But on the other side, this also hinted us that "PeriCT (FLOT)", "PostCT (XP)" and "PostCT (S-1)" were still the top three nodes and thus D2 lymphadenectomy-based global randomized controlled trials should be conducted, especially comparing "PeriCT (FLOT)" and "PostCT (XP)". Concerning recurrence-free survival, "PostCRT (XP)" topped the hierarchy with slight superiority against "PeriCT (FLOT)" on the second place,

indicating the potentially superior effect of suppressing tumor recurrence with the combination of chemotherapy and radiation. However, due to heterogeneous definitions among all studies regarding recurrence-free survival, whether there were some underlying biases inside the results could not be evaluated. With regard to adverse events, although no quantitative network meta-analysis had been performed, those top-ranking regimens in survival efficacies seemed to have acceptable tolerability compared to others.

Several randomized clinical trials are currently undergoing which compare perioperative chemotherapy with adjuvant chemotherapy as multimodal treatments. Ji et al. [22] have already launched a phase 3 trial (NCT01534546) comparing perioperative SOX (S-1 plus oxaliplatin) chemotherapy versus adjuvant SOX/XELOX chemotherapy among D2-resected Asian gastric adenocarcinoma patients. Meanwhile, Zhao et al. [23] also have started a similar phase 3 trial (NCT01516944) comparing perioperative XELOX chemotherapy versus adjuvant SOX chemotherapy after D2 lymphadenectomy. However, regimens in these trials are mainly used in eastern countries since S-1 has not yet been fully approved in USA, and only Asian patients were enrolled as well. Therefore, according to our quantitative results, a globally-involved randomized controlled trial comparing perioperative FLOT chemotherapy versus adjuvant XELOX chemotherapy should be designed instead.

Although our systematic review and network meta-analysis were rigorously designed and conducted, there were still some limitations within. Firstly, despite that all included trials were proven to be clinically comparable without significant heterogeneity and both sensitivity and subgroup analyses had also been conducted, underlying heterogeneity could not be fully eliminated. Therefore, an individual-patient-data (IPD) meta-analysis is needed in future updates, which could minimize the heterogeneity inside the quantitative network compared to study-level synthesis. Secondly, the amount of included trials was slightly inadequate, especially when subgroup analyses could be barely conducted and the evaluation of consistency and statistical heterogeneity could not be met.

Taken together, our network calculation suggests that perioperative FLOT chemotherapy could potentially be the best multimodal treatment against resectable gastric cancer than other recommended strategies, including postoperative XELOX chemotherapy, postoperative S-1 monotherapy or postoperative FL chemoradiotherapy. Therefore, a global D2-lymphadenectomy randomized controlled trial comparing perioperative FLOT chemotherapy with postoperative XELOX chemotherapy should be carried out.

Author contributions

Study design: Ji Cheng, Guobin Wang and Kaixiong Tao; Manuscript writing and revision: Ji Cheng and Kaixiong Tao; Literature retrieval: Ji Cheng and Ming Cai; Discretion of eligibility: Ji Cheng and Ming Cai; Quality assessment: Ji Cheng and Jinbo Gao; Data extraction: Ji Cheng and Xiaoming Shuai; Statistical analysis: Ji Cheng and Kaixiong Tao.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

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