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Original Article

Comparative effectiveness of perioperative strategies for resectable gastric and gastroesophageal junction cancer: a Bayesian network meta-analysis

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Abstract: Perioperative strategies for resectable gastric and gastroesophageal junction (GEJ) adenocarcinomas are continuously evolving, with recent regimens, particularly those incorporating immunotherapy, showing promising results, although their comparative efficacy remains uncertain. We conducted a Bayesian network meta-analysis of randomized controlled trials (RCTs) published between January 2004 and March 2025 that compared perioperative treatments involving chemotherapy, radiotherapy, immunotherapy, or targeted agents. Five outcomes were analyzed: overall survival (OS), progression-free survival (PFS), R0 resection, pathological complete response (pCR), and major pathological response (MPR). A Bayesian random-effects model was applied to estimate hazard ratios (HRs) and odds ratios (ORs), and surface under the cumulative ranking curve (SUCRA) values were used for treatment ranking. A total of 25 RCTs involving 11,317 patients were included. Neo/Peri DOS/DOX, comprising neoadjuvant or perioperative docetaxel-oxaliplatin-S-1 (DOS) or docetaxel-oxaliplatin-capecitabine (DOX), ranked highest for OS and PFS, showing significant survival benefits over both surgery alone and adjuvant chemotherapy. Regimens combining perioperative chemotherapy with PD-1/PD-L1 inhibitors (Neo/Peri CT+PD1/PDL1) achieved the greatest improvement in pCR and MPR, although their survival benefit was limited to comparisons with surgery alone. None of the regimens significantly improved R0 resection. The findings were robust across sensitivity analyses, with no major inconsistencies detected. In conclusion, DOS/DOX demonstrated superior survival outcomes and may represent a leading perioperative option, while PD-1/PD-L1-based combinations improved early pathological responses but require further validation with mature survival data.

Keywords: Gastric cancer, gastroesophageal junction cancer, neoadjuvant therapy, perioperative therapy, Bayesian network meta-analysis

Introduction

Gastric cancer remains a major global health burden, with 968,350 new cases and 659,853 deaths reported in 2022 [1]. While incidence has declined in some regions, prognosis remains poor due to late-stage diagnosis. In contrast, the incidence of gastroesophageal junction (GEJ) adenocarcinomas is increasing in Western countries [2, 3]. For resectable, locally advanced disease, perioperative therapy is now the standard of care according to the 2025 NCCN [4] and the 2024 CSCO [5] guidelines.

The MAGIC trial first demonstrated perioperative chemotherapy benefit using ECF (epirubicin, cisplatin, and fluorouracil), improving 5-year overall survival (OS) compared with surgery alone [6]. The FLOT4 trial showed improved survival with the FLOT regimen (fluorouracil, leucovorin, oxaliplatin, and docetaxel), achieving a median OS of 50.0 versus 35.0 months, establishing its preference in Western countries [7, 8]. The RESOLVE trial established SOX (S-1 plus oxaliplatin) as the standard regimen in East Asia, showing superior OS over CapOx/XELOX (capecitabine plus oxaliplatin) [9, 10].

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DOS (docetaxel, oxaliplatin, and S-1) and DOX (docetaxel, oxaliplatin, and capecitabine) regimens have shown promise in Asian trials [11-15]. PRODIGY demonstrated improved progression-free survival (PFS) and OS with perioperative DOS over surgery plus adjuvant S-1 [12, 13], whereas Tian et al. showed that neoadjuvant DOX improved 3-year OS versus XELOX [14, 15]. Earlier PF (cisplatin plus fluoropyrimidine) doublets showed modest benefits [16]. In JCOG0501, neoadjuvant SP (S-1 plus cisplatin) provided no benefit over postoperative S-1 in type 4/large type 3 gastric cancer [17]. Targeted therapy trials with anti-angiogenic or anti-EGFR agents failed to improve outcomes [18-20]. TOPGEAR showed improved pathological response with preoperative CRT (chemoradiotherapy) but no survival benefit [21]. Recent immune checkpoint inhibitor trials suggest PD-1/PD-L1-based regimens enhance pathological responses [22-24], although survival data remain limited.

Given the proliferation of treatment strategies and the lack of direct comparisons across key regimens, we conducted a Bayesian network meta-analysis (NMA) to evaluate the relative efficacy of chemotherapy, chemoimmunotherapy, radiotherapy, and targeted therapies in resectable gastric and GEJ adenocarcinoma. This study synthesized evidence from survival and pathological endpoints to inform evidence-based treatment selection.

Methods

Study design and registration

This systematic review and Bayesian NMA was conducted in accordance with the PRISMA extension for network meta-analyses (PRISMA-NMA) guidelines (Supplementary Table 1) [25]. The protocol was registered in PROSPERO (CRD420251006682) on March 7, 2025, and is available at https://www.crd.york.ac.uk/PROSPERO/view/CRD420251006682.

Eligibility criteria

We included randomized controlled trials (RCTs) published in English between January 2004 and March 2025 that enrolled adult patients with resectable, locally advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. Eligible studies assessed neoadjuvant or perioperative strategies involving chemotherapy, radiotherapy, immunotherapy, or targeted therapy and reported at least one of the following outcomes: OS, PFS, R0 resection, pathological complete response (pCR), or major pathological response (MPR). Trials were excluded if they (1) enrolled fewer than 100 patients, (2) focused exclusively on HER2-positive populations, (3) employed a factorial 2×2 design, or (4) lacked trial registration.

Search strategy and study selection

We conducted a comprehensive literature search using PubMed, Embase, and the Cochrane Central Register of Controlled Trials to identify relevant studies. In addition, manual searches were conducted to capture additional references. The search strategy combined Medical Subject Headings (MeSH) with free-text terms encompassing gastric and gastroesophageal junction (GEJ) cancer, resectable or locally advanced disease, and neoadjuvant, perioperative, or preoperative treatment approaches. A wide range of interventions - including chemotherapy, immunotherapy, radiotherapy, and targeted therapies - was considered. The full search strategy is presented in Supplementary Table 2.

After duplicates were removed using EndNote software, two reviewers independently screened all titles and abstracts. The full texts of potentially eligible articles were then reviewed in detail, and any discrepancies were resolved through discussion until consensus was reached.

Outcome definition and data extraction

The primary outcomes included OS, PFS, R0 resection, pCR, and MPR. OS was defined as the time from randomization to death from any cause, and PFS was defined as the time from randomization to recurrence, disease progression, or death. R0 resection was defined as a microscopically margin-negative resection. pCR was defined as the complete absence of viable tumor cells in both the primary tumor and regional lymph nodes (ypT0N0). MPR was defined as the presence of ≤ 10% residual viable tumor cells in the resected specimen. When not reported, comparable surrogates (e.g., Becker TRG 1a-1b, Mandard TRG 1-2, NCCN TRG 0-1, or author-defined near-complete res-

ponse) were considered acceptable, as detailed in Supplementary Table 3.

Two reviewers independently extracted data using a standardized template that focused on trial characteristics, study population, treatment arms, sample sizes, and reported outcomes. For time-to-event outcomes, hazard ratios (HRs) with 95% confidence intervals (CIs) were collected. Studies without HRs and CIs were excluded from survival analyses. The longest available follow-up was used when multiple follow-up periods were reported, to ensure consistency. For binary outcomes reported per protocol, intention-to-treat (ITT) denominators were reconstructed from all randomized participants whenever feasible (Supplementary Table 4A, 4B).

Risk of bias assessment

The risk of bias was assessed with the Cochrane Risk of Bias 2.0 tool [26]. Two reviewers independently conducted the assessments and discrepancies were resolved by discussion and consensus. Studies judged to be at high risk of bias were retained in the primary analysis to maintain network connectivity but were excluded from sensitivity analyses to assess their impact on treatment rankings and effect estimates.

Statistical analysis

Bayesian network meta-analyses were conducted using the gemtc package in R, interfacing with JAGS for Markov chain Monte Carlo (MCMC) simulation [27]. A random-effects model was applied with four parallel chains, each run for 5,000 burn-in iterations and 200,000 sampling iterations (thinning = 10). Treatment effects were reported as HRs with 95% credible intervals (CrI) for time-to-event outcomes and odds ratios (ORs) with 95% CrI for binary outcomes. Weakly informative priors (N (0, 1)) were used. Model convergence was assessed using trace plots and the Gelman-Rubin convergence statistic ($\hat{R} < 1.1$). To compare treatments, we estimated the surface under the cumulative ranking curve (SUCRA) and presented cumulative ranking probabilities as rankograms [28]. Sensitivity analyses included more informative priors (N (0, 0.5)), fixed-effect modeling, exclusion of weakly connected treatments, exclusion of high-risk-of-bias studies, and adjustment of denominators for binary outcomes with missing data. Network consistency was assessed globally using the deviance information criterion (DIC) and locally using node-splitting methods [29, 30]. Network geometry was visualized with plots in which the node size and edge width were weighted by sample size and the number of comparisons, respectively.

Results

Study selection and characteristics

A total of 1,495 records were identified through database searches (PubMed, 371; Embase, 333; Cochrane, 791), with three additional records identified through manual screening. After removing 449 duplicates, 1,049 records were screened by title and abstract, leaving 48 studies for full-text eligibility assessment. Ultimately, 25 RCTs met the inclusion criteria and were included in the NMA (**Figure 1**). Each study reported at least one of the predefined outcomes: R0 resection (23 trials), pCR (14 trials), MPR (13 trials), OS (15 trials), or PFS (15 trials). Detailed trial characteristics are summarized in Supplementary Table 3.

Risk of bias across included studies

The risk of bias was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. Most trials were judged to have a low risk of bias or some concerns. Three major sources of potential bias were identified. First, several studies lacked publicly available protocols or statistical analysis plans, limiting verification of prespecified analyses. Second, PFS was often assessed in open-label trials without independent review; for example, the MAGIC and AIO/CAO STO-0801 trials did not provide clear PFS definitions or assessment methods, leading to a potential of outcome measurement bias. Third, some trials reported binary outcomes using per-protocol populations; however, because the ITT populations were clearly defined with minimal missing data, these studies were rated as “some concerns” rather than “high risk”. Nevertheless, all studies were retained in the primary analysis to maintain the network structure. Sensitivity analyses excluding trials with a high risk of bias confirmed the robustness of the findings. The risk of bias assessment for individual studies is provided in Supplementary Figure 1A-D.

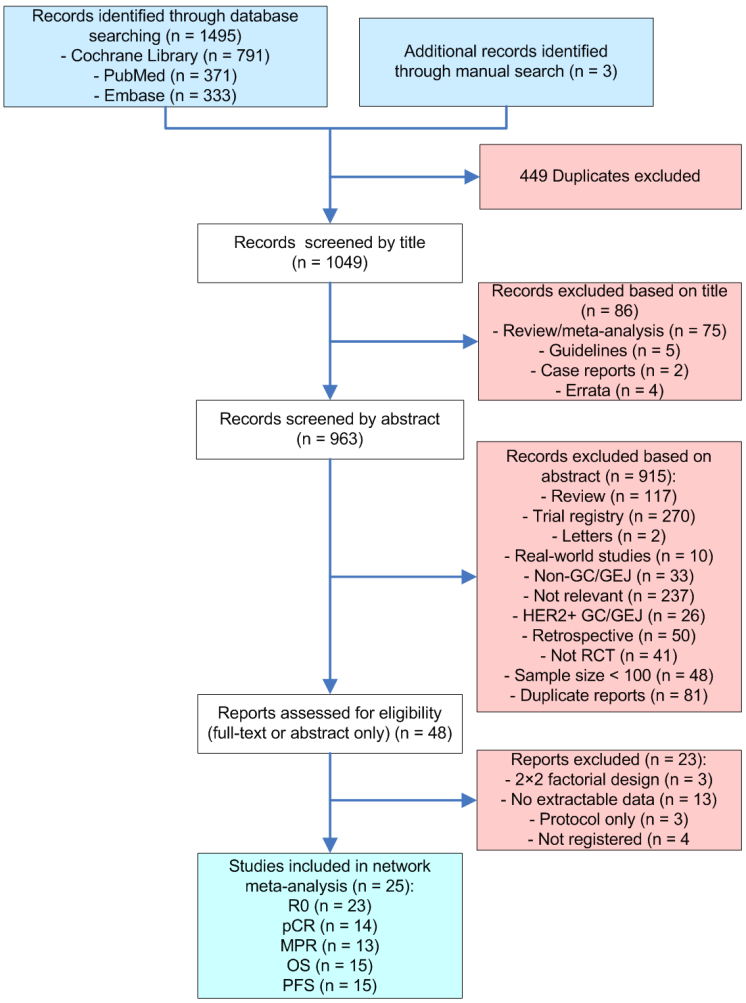

Figure 1. PRISMA flow diagram of study selection for the network meta-analysis.

Network geometry and evidence structure

Separate treatment networks were constructed for five predefined outcomes: OS, PFS, pCR, MPR, and R0 resection. Each network included 12-14 interventions, depending on availability. Most networks were well-connected, enabling both direct and indirect comparisons across perioperative strategies. For OS and PFS, surgery alone and adjuvant chemotherapy were included as comparators, but not for pCR and MPR. Most treatment strategies were supported by at least two head-to-head trials, enhancing network connectivity and supporting the assumption of transitivity. Frequently studied regimens, including Neo/Peri FLOT, DOS/DOX, SOX, CT+PD1/PDL1, XELOX, and ECF/ECX, were connected through multiple direct comparisons. In contrast, some interventions were evaluated in only single trials and thus weakly connected, such as preoperative CT+RT (chemoradiotherapy), Neo/Peri CT+anti-EGFR (chemotherapy plus anti-EGFR agents, e.g., panitumumab), SAP (cisplatin plus albumin-bound paclitaxel), and FOLFOX (folinic acid, fluorouracil, and oxaliplatin). Neo/Peri PF-based regimens (cisplatin plus fluoropyrimidine) were sparsely connected in the pCR network. These less connected interventions were retained in the primary analysis but were excluded from sensitivity analyses. No major structural issues, such as disconnection or closed loops, were observed (**Figures 2A**-**6A**).

Overall survival

Fifteen RCTs involving 7,062 patients and 13 perioperative strategies were included in the OS network meta-analysis (**Figure 2A**). Based on SUCRA values (**Figure 2B**), Neo/Peri DOS/DOX ranked the highest (SUCRA = 0.949), followed by Neo/Peri SOX, FLOT, and CT+PD1. Surgery alone and CT+antiEGFR ranked the lowest. The league table (**Figure 2C**) revealed multiple significant pairwise differences. Neo/Peri DOS/DOX consistently outperformed surgery alone, adjuvant chemotherapy, Neo/Peri CT+antiEGFR, and Neo/Peri PF-based regimens. Neo/Peri CT+PD1, SOX, and FLOT also showed significant benefits over surgery. According to the forest plot (**Figure 2D**), Neo/Peri DOS/DOX significantly improved OS compared with adjuvant chemotherapy (HR = 0.67, 95% CrI: 0.49-0.90). In contrast, CT+PD1, FLOT, and SOX did not reach significance, although favorable trends were observed. Notably, when compared with surgery alone, five regimens - Neo/Peri DOS/DOX, CT+PD1, FLOT, SOX, and PF-based regimens - showed significant OS advantages. Taken together, Neo/Peri DOS/DOX provided

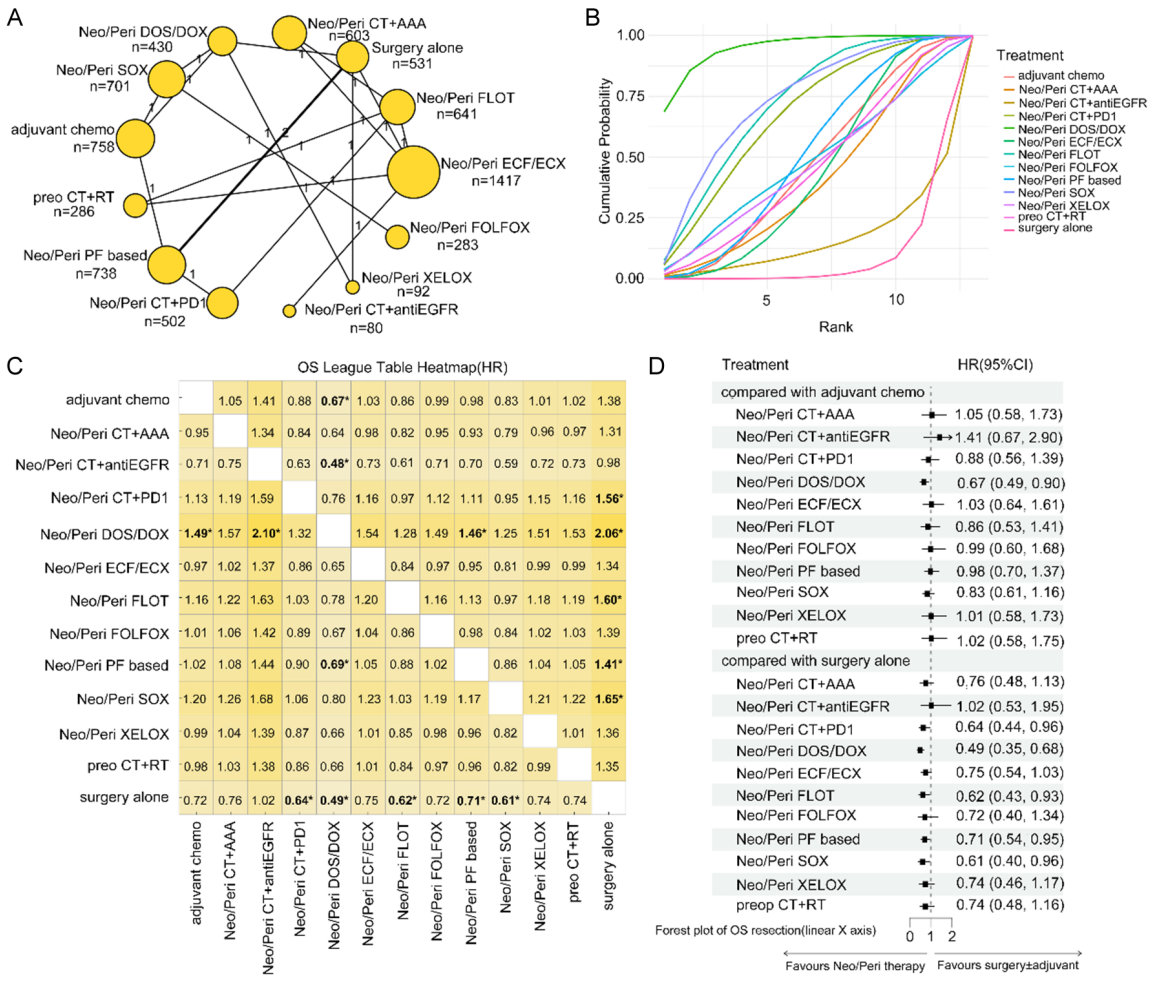

Figure 2. Network meta-analysis results for overall survival (OS). A. Network plot showing the comparative evidence structure for OS. Node size is proportional to the number of participants; edge thickness reflects the number of direct comparisons. B. Cumulative ranking curves of treatment strategies based on SUCRA values. C. Heatmap league table showing HRs for all pairwise comparisons. HRs with 95% CrI not crossing 1 are shown in bold with an asterisk (*), indicating statistical significance. D. Forest plot of HRs comparing each treatment with adjuvant chemotherapy and surgery alone.

the most consistent survival benefit, whereas Neo/Peri CT+PD1 ranked favorably but without statistically confirmed superiority.

Progression-free survival

Fifteen RCTs involving 7,585 patients and 13 perioperative strategies were included in the PFS network meta-analysis (**Figure 3A**). Based on SUCRA values (**Figure 3B**), Neo/Peri DOS/DOX ranked the highest (SUCRA = 0.874), followed by CT+PD1, FLOT, and SOX. Surgery alone and adjuvant chemotherapy ranked the lowest. The league table (**Figure 3C**) showed several significant pairwise differences. Neo/Peri DOS/DOX was superior to surgery and adjuvant chemotherapy. In contrast, Neo/Peri CT+PD1, FLOT, and SOX significantly outperformed surgery alone but did not demonstrate superiority over adjuvant chemotherapy. According to the forest plot (**Figure 3D**), only DOS/DOX significantly improved PFS compared with adjuvant chemotherapy (HR = 0.68, 95% CrI: 0.48-0.92), whereas Neo/Peri CT+PD1, FLOT, and SOX showed favorable but non-significant trends. When compared with surgery alone, however, all four regimens - DOS/DOX (HR = 0.51, 95% CrI: 0.35-0.71), CT+PD1 (HR = 0.54, 95% CrI: 0.34-0.86), FLOT (HR = 0.59, 95% CrI: 0.40-0.95), and SOX (HR = 0.61, 95% CrI: 0.39-0.98) - achieved statistically significant PFS improvements. These findings support perioperative

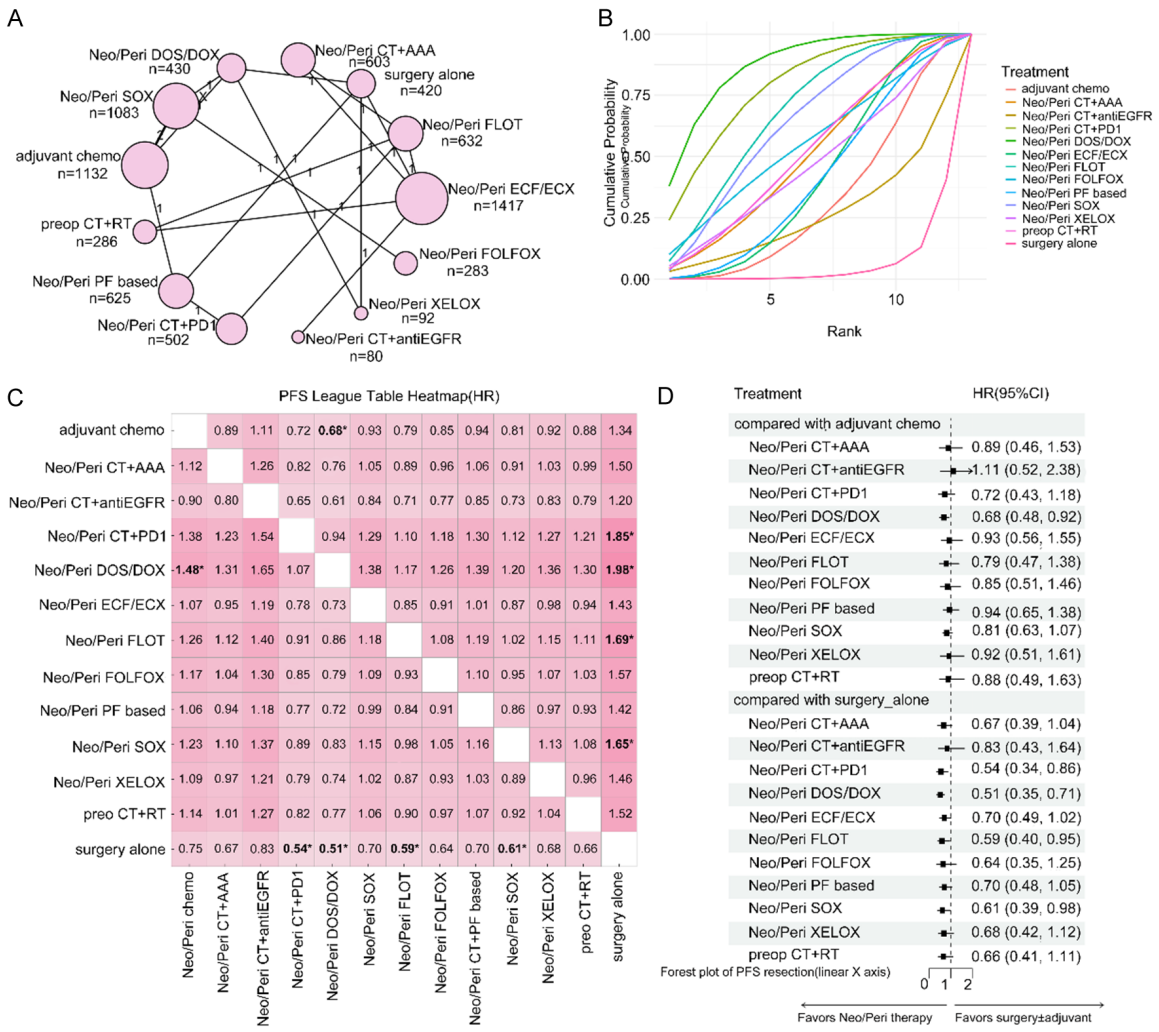

Figure 3. Network meta-analysis results for progression-free survival (PFS). A. Network plot of available comparisons for PFS. Node size and edge width reflect sample size and number of trials, respectively. B. SUCRA-based cumulative ranking curves of included treatments. C. Heatmap league table of pairwise HRs for PFS; statistically significant comparisons are indicated by bolded HRs with asterisks (*). D. Forest plot of HRs comparing each regimen with adjuvant chemotherapy and surgery alone.

strategies over surgery alone and highlight Neo/Peri DOS/DOX as the most promising regimen to improve PFS.

Pathological complete response (pCR)

Fourteen RCTs involving 5,565 patients and 12 perioperative strategies were included in the pCR network meta-analysis (**Figure 4A**). SUCRA rankings (**Figure 4B**) placed Neo/Peri CT+PD1/PDL1 as the top regimen (SUCRA = 0.865), followed by Neo/Peri CT+PD1+TKI, preoperative CT+RT, and Neo/Peri DOS/DOX. Neo/Peri FOLFOX and PF-based regimens ranked the lowest. The league table (**Figure 4C**) revealed multiple significant pairwise comparisons. Neo/Peri CT+PD1/PDL1 significantly outperformed six other comparators, including Neo/Peri FLOT, SOX, and XELOX. Neo/Peri CT+PD1+TKI and preoperative CT+RT also demonstrated superiority over several other regimens. According to the forest plot (**Figure 4D**), when compared with Neo/Peri FLOT, Neo/Peri CT+PD1/PDL1 was the only regimen with a significant advantage (OR = 2.58, 95% CrI: 1.22-5.31). Other regimens, including Neo/Peri CT+PD1+TKI and DOS/DOX, revealed favorable trends but did not reach statistical significance. When compared with Neo/Peri SOX, both Neo/Peri CT+PD1/PDL1 (OR = 4.35, 95% CrI: 1.20-

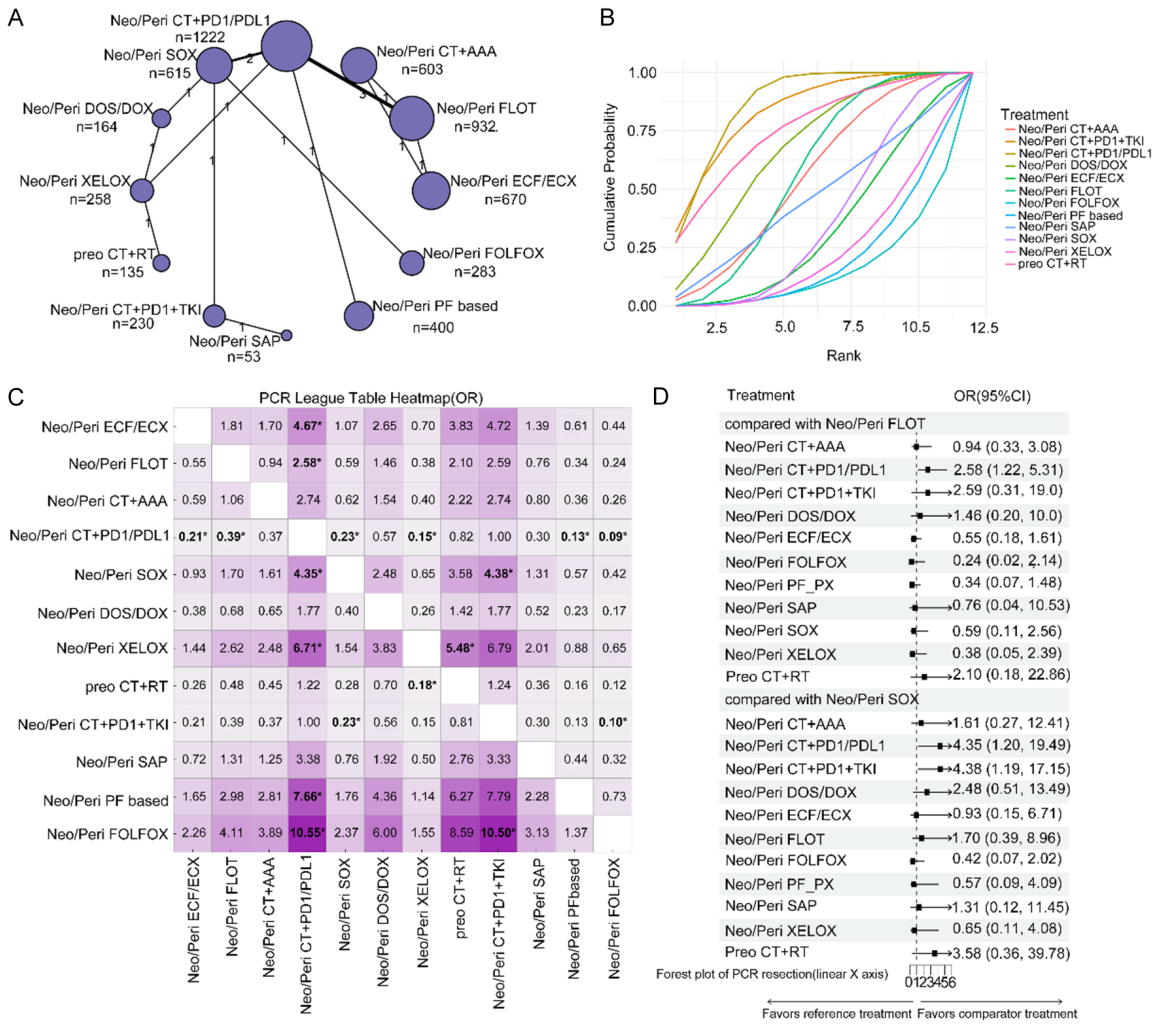

Figure 4. Network meta-analysis results for pathological complete response (pCR). A. Network diagram illustrating direct and indirect comparisons for pCR. B. SUCRA-based cumulative ranking curves of regimens according to probability of achieving higher pCR. C. League table heatmap showing ORs for all pairwise comparisons; statistically significant ORs are in bold with an asterisk (*). D. Forest plot comparing ORs for pCR, with each treatment compared against FLOT and SOX as comparators.

19.49) and Neo/Peri CT+PD1+TKI (OR = 4.38, 95% CrI: 1.19-17.15) showed significant improvements. Overall, Neo/Peri CT+PD1/PDL1 demonstrated the most consistent benefit in achieving pCR.

Major pathological response (MPR)

Thirteen RCTs involving 4,153 patients and 11 perioperative strategies were included in the MPR network meta-analysis (**Figure 5A**). SUCRA rankings (**Figure 5B**) placed Neo/Peri CT+PD1/PDL1 as the top regimen (SUCRA = 0.893), followed by preoperative CT+RT, Neo/Peri DOS/DOX, and Neo/Peri FLOT. Neo/Peri SAP and SOX ranked the lowest. The league table (**Figure 5C**) showed several significant pairwise differences in favor of Neo/Peri CT+PD1/PDL1, which outperformed Neo/Peri ECF/ECX, FLOT, SOX, XELOX, CT+AAA (chemotherapy plus an anti-angiogenic agent such as bevacizumab or ramucirumab), and SAP. In the forest plot (**Figure 5D**), Neo/Peri CT+PD1/PDL1 was the only regimen that significantly improved MPR when compared with Neo/Peri FLOT (OR = 1.91, 95% CrI: 1.04-3.38). Neo/Peri CT+PD1+TKI, CT+AAA, and DOS/DOX showed favorable trends but without statistical significance. When compared with SOX, Neo/Peri CT+PD1/PDL1 again demonstrated significant superiority (OR = 3.57, 95% CrI: 1.56-8.47), whereas Neo/Peri CT+PD1+TKI and DOS/DOX showed numerically higher responses without

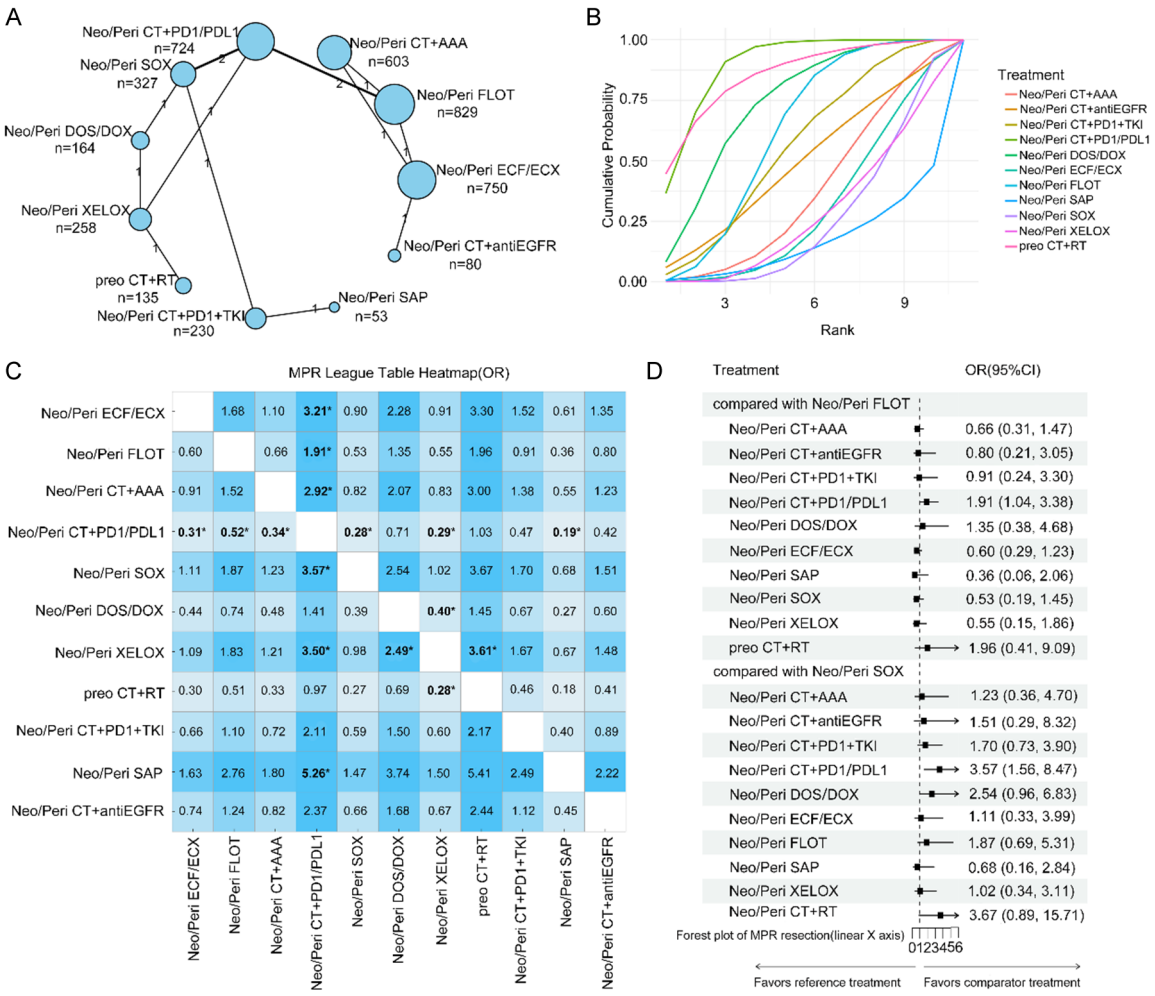

Figure 5. Network meta-analysis results for major pathological response (MPR). A. Network structure showing treatment comparisons contributing to MPR estimation. B. SUCRA-based cumulative probability ranking of each treatment for MPR. C. League table heatmap of pairwise ORs; statistically significant results (95% CrI not crossing 1) are marked in bold with an asterisk (*). D. Forest plot comparing ORs for MPR, with each treatment compared against FLOT and SOX as comparators.

statistical confirmation. Overall, Neo/Peri CT+PD1/PDL1 emerged as the most effective regimen for MPR.

R0 resection rate

Twenty-three RCTs involving 9,995 patients and 14 perioperative strategies were included in the R0 resection network meta-analysis (**Figure 6A**). Based on SUCRA rankings (**Figure 6B**), Neo/Peri CT+AAA ranked the highest (SUCRA = 0.805), followed by Neo/Peri PF-based regimens, Neo/Peri CT+PD1/PDL1, and Neo/Peri ECF/ECX. Neo/Peri SAP ranked lowest, suggesting a limited benefit for complete resection. However, the league table (**Figure 6C**) did not reveal any statistically significant pairwise differences between treatment strategies. The forest plot (**Figure 6D**) showed that most regimens, such as Neo/Peri CT+PD1/PDL1, DOS/DOX, and CT+AAA, had ORs > 1 compared with surgery ± adjuvant chemotherapy, indicating favorable but non-significant trends, as all 95% CrI crossed 1. In contrast, Neo/Peri SAP, XELOX, FOLFOX, and preoperative CT+RT had ORs < 1, suggesting potential disadvantage. Overall, no regimen demonstrated a statistically significant improvement in R0 resection rates.

Sensitivity analyses

SUCRA values and treatment rankings were largely consistent across sensitivity analyses,

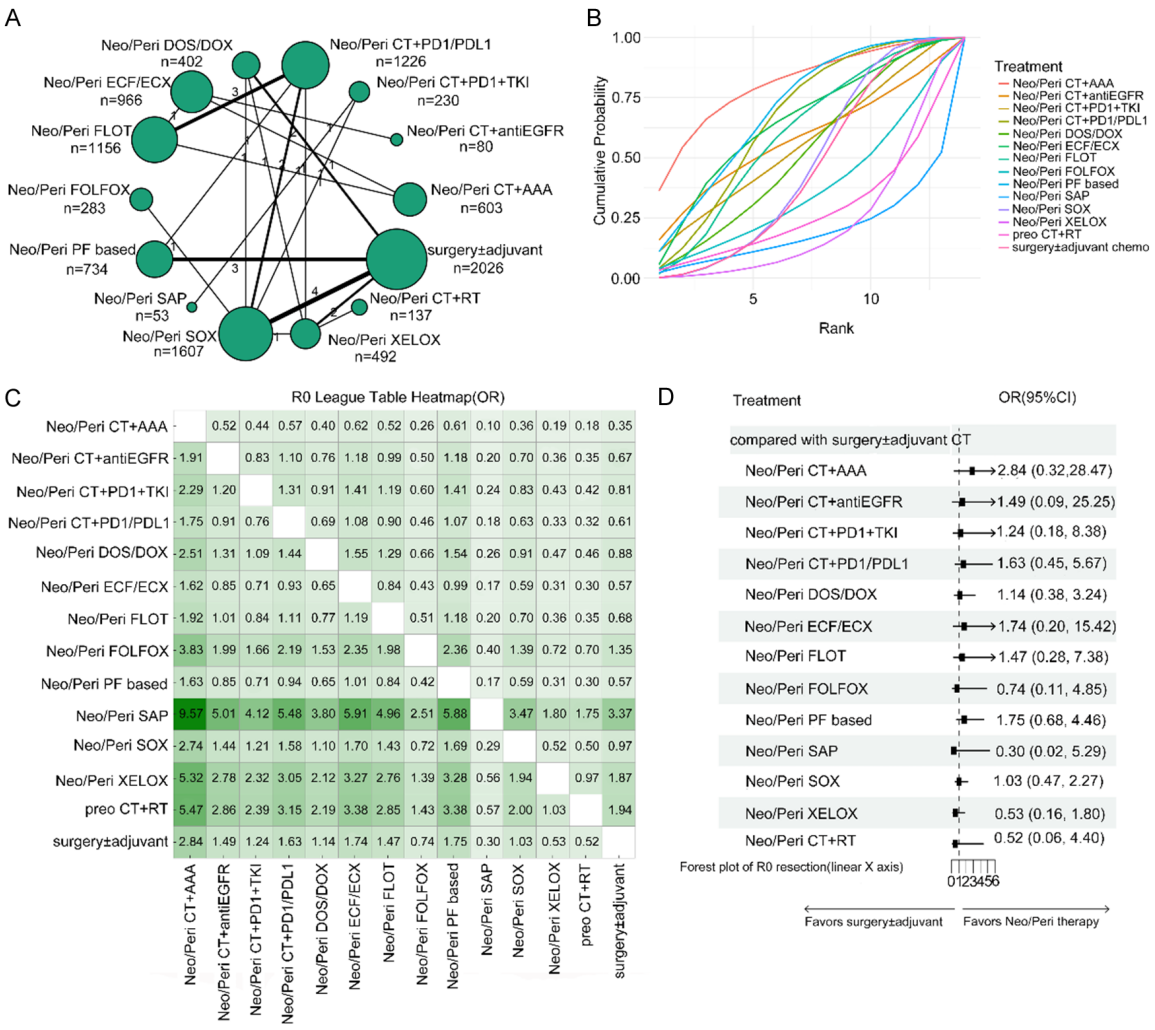

Figure 6. Network meta-analysis results for R0 resection rate. A. Evidence network showing direct comparisons across included trials. B. SUCRA ranking curves for R0 resection rate. C. Heatmap league table with ORs for each pairwise comparison; bolded ORs with asterisks (*) denote statistical significance. D. Forest plot comparing the odds of achieving R0 resection, with all treatments compared against surgery ± adjuvant chemotherapy.

including variations in model assumptions and trial inclusion. Minor ranking shifts occurred mainly among regimens lacking direct comparisons. Neo/Peri DOS/DOX consistently ranked among the top for OS and PFS, whereas Neo/Peri CT+PD1/PDL1 maintained its leading position for pCR and MPR, supporting the robustness of these effect estimates. In contrast, R0 resection showed greater variability, particularly under the fixed-effect model, reflecting sensitivity to the network structure and connectivity. Importantly, no reversal of the relative superiority of the key regimens was observed. Overall, these findings confirm the robustness of the main results across multiple analytical scenarios (Supplementary Figure 2A-E; Supplementary Table 5A-E).

Consistency and model fit

Model fit and consistency were assessed using both global and local methods. At the global level, small differences in DIC between the consistency and inconsistency models across all outcomes (ΔDIC ≤ 5.0) indicated good overall consistency (Supplementary Figure 3). At the local level, node-splitting analyses showed no significant inconsistencies between direct and indirect estimates for any outcome (all P > 0.05). Together, these results support

the assumption of consistency in the NMA and reinforce the validity of the pooled treatment effects (Supplementary Table 6A-E).

Discussion

This Bayesian NMA included 25 RCTs involving 11,317 patients with resectable, locally advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma. Neo/Peri DOS/DOX consistently ranked among the top regimens for OS and PFS based on SUCRA, exhibiting favorable trends but without statistically significant superiority over FLOT or SOX. Neo/Peri CT+PD1/PDL1 ranked highest for response-based outcomes (pCR and MPR), demonstrating significant advantages over Neo/Peri FLOT and SOX, although without corresponding OS or PFS benefits. For R0 resection, CT+AAA, PF-based regimens, CT+PD1/PDL1, and ECF/ECX achieved the highest SUCRA rankings, although none showed statistically significant pairwise differences.

This NMA confirmed the central role of perioperative or neoadjuvant chemotherapy in resectable gastric and GEJ adenocarcinomas. Neo/Peri DOS/DOX was the only regimen to demonstrate a significant survival advantage over adjuvant chemotherapy and ranked highest for OS and PFS, although it was not significantly superior to Neo/Peri SOX or XELOX. Given its high intensity and the predominantly Asian evidence base, it may be suitable for younger patients or those with a high disease burden. FLOT remains the preferred regimen in Western practice, supported by the FLOT4 trial [7], and is ranked highly and consistently across outcomes. Older regimens, such as ECF/ECX and PF-based doublets, ranked lower, supporting a shift to taxane-based triplets. SOX, endorsed regionally in East Asia, ranked favorably in SUCRA analyses and is supported by the RESOLVE [9, 10] and RESONANCE [31] trials in advanced-stage or high-risk patients. PD-1/PD-L1 combinations improved the pathological response but showed no statistically confirmed survival benefit, limiting their role in unselected patients. Chemoradiotherapy (CRT) provided modest pathological benefits without corresponding survival gains, while anti-angiogenic and anti-EGFR agents failed to improve outcomes, consistent with ST03 [18], RAMSES [20], and AIO/CAO STO-0801 [19]. Perioperative chemotherapy, particularly FLOT, SOX, and DOS/DOX, remains the treatment backbone. Regimen choice should be tailored according to the disease stage, resectability, geographic region, toxicity profile, and biomarker status.

Our findings are consistent with previous meta-analyses. Grizzi et al. [32] and Wang et al. [33] confirmed the superiority of perioperative chemotherapy, particularly taxane-based triplets such as FLOT and TPF, over surgery alone. Our results further suggest benefits of newer regimens like DOS and DOX in Asian populations. We also corroborate evidence questioning CRT, consistent with Ronellenfitsch et al. [34], and found that CRT-containing regimens provided modest pathological benefits but no statistically confirmed survival advantage. PD-1/PD-L1 combinations have been reported to improve pathological responses, as reported by Yu et al. [35] and de Moraes et al. [36], but our analysis additionally showed no benefit in OS or PFS. Our study incorporated a broader spectrum of treatment strategies, including recent trials of immunotherapy and Asian regimens, and uniquely assessed the survival impact of PD-1 combination therapy. Furthermore, we applied a robust Bayesian framework with sensitivity analyses to enhance methodological rigor.

This study has several limitations. First, most immunotherapy trials included are still ongoing, and long-term OS and PFS data remain insufficient, limiting firm conclusions regarding the survival benefit of PD-1/PD-L1-based regimens. Second, some treatment strategies (e.g., SAP, FOLFOX, and chemoradiotherapy) were evaluated in only one or two trials, leading to wide credible intervals and increased uncertainty in these comparisons. Third, clinical and methodological heterogeneity across trials - including differences in pathological response definitions, staging systems, tumor location, and patient selection - may have affected comparability. Fourth, several trials were reported only in abstract form and lacked detailed protocols or statistical analysis plans, reducing transparency and limiting the ability to adequately assess the risk of bias. Finally, as this study is a Bayesian network meta-analysis based exclusively on published RCTs, we were unable to perform external validation using an independent patient cohort, which may limit

generalizability. Nevertheless, we conducted extensive sensitivity analyses, including alternative prior distributions, fixed-effect modeling, and exclusion of high-risk or weakly connected studies, all of which yielded consistent results and confirmed the robustness of our main findings.

Future research should focus on confirming the long-term survival benefits of PD-1-based strategies, undertaking head-to-head comparisons of FLOT, SOX, and DOS/DOX, and investigating biomarker-driven approaches. Standardization of pathological response criteria and incorporating patient-centered outcomes are warranted to enhance clinical relevance.

Conclusions

Perioperative or neoadjuvant chemotherapy remains the treatment backbone for resectable gastric and GEJ cancers. Neo/Peri DOS and DOX regimens may provide superior survival outcomes compared with current standards, as suggested by observed trends. PD-1/PD-L1 regimens offer short-term pathological benefits but have not yet demonstrated a confirmed survival advantage.

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Disclosure of conflict of interest

None.

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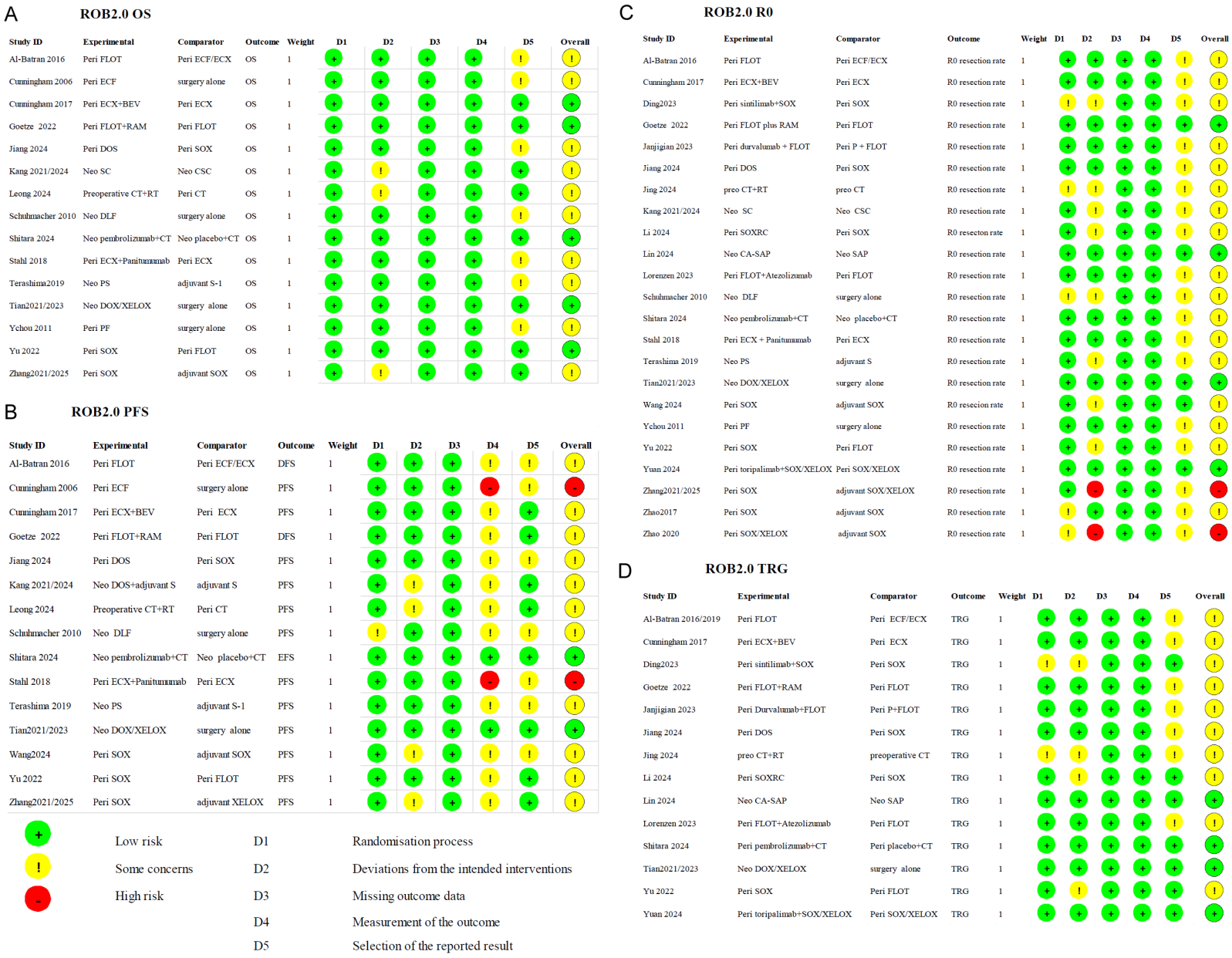
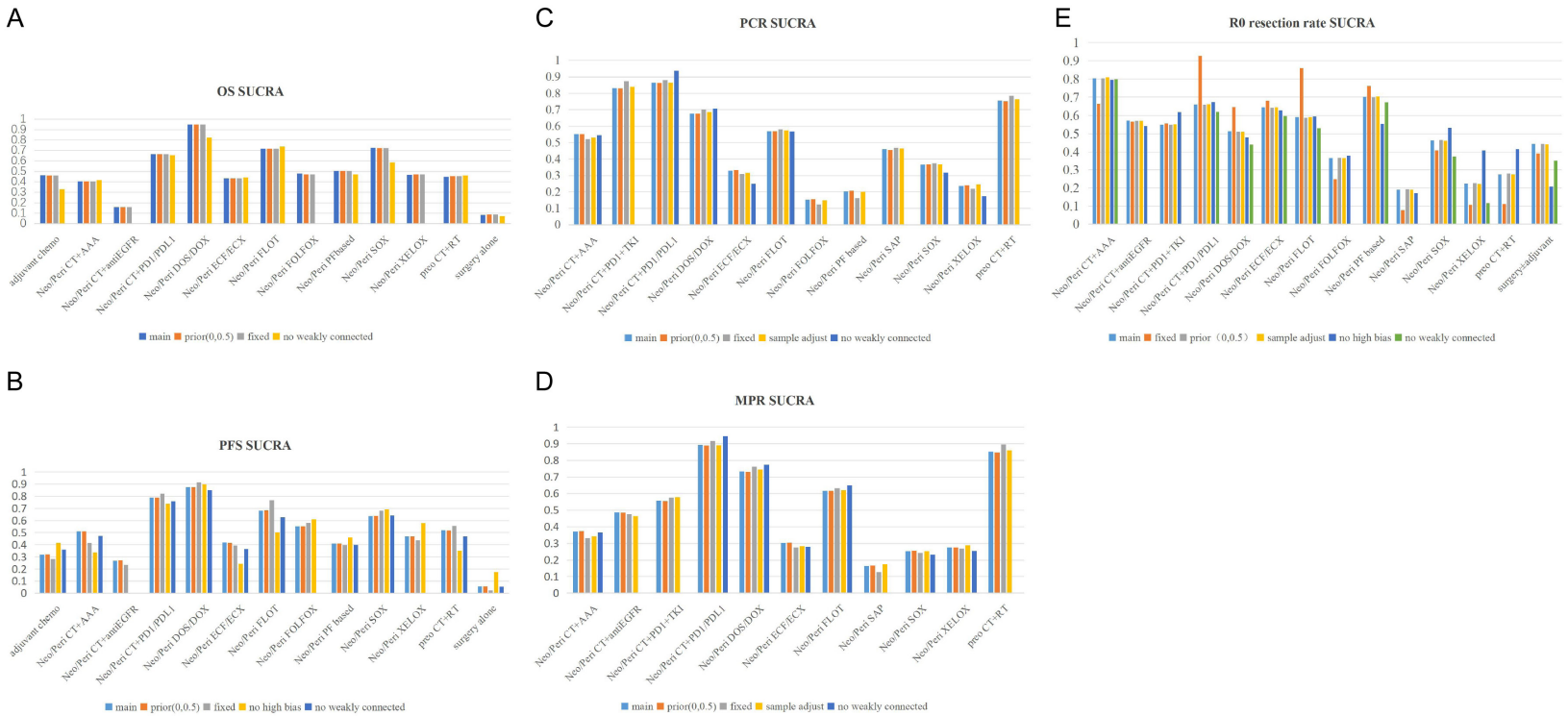
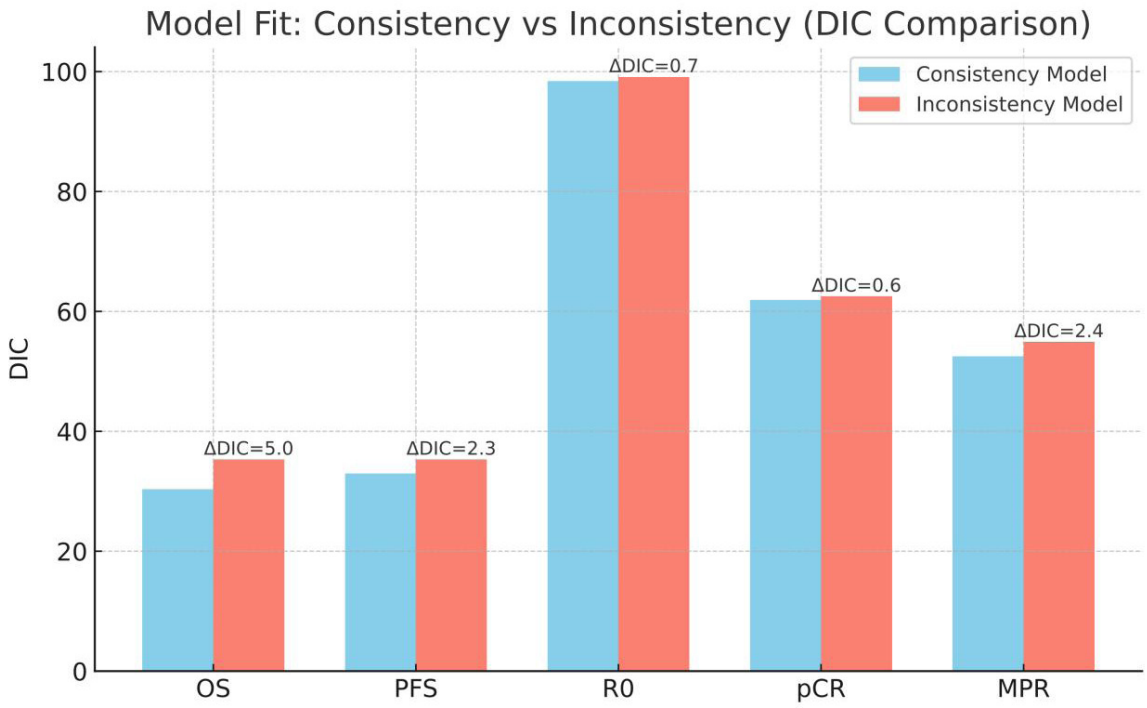


Supplementary Figure 1. Results of bias assessment.



Supplementary Figure 2. Sensitivity analyses figures.



Supplementary Figure 3. DIC comparison.