

SYSTEMATIC REVIEW

Open Access



Therapeutic efficacy of multiple neoadjuvant regimens involving targeted therapy, immunotherapy and chemotherapy in gastric cancer: a systematic review and meta-analysis

Chen Liang^{1†}, Zhiyuan Yu^{2†}, Siyu Hou¹, Chunzeng Jia¹, Yuxin Guan¹, Junfu Zheng¹, Yan Gao¹, Gailing Wu¹, Lei Niu^{2*}, Pengji Gao^{3*} and Lei Li^{1*}

Abstract

Background The utilization of neoadjuvant therapy, encompassing chemotherapy, molecular targeted therapy, and immunotherapy, has demonstrated a significant enhancement in the radical resection rate and an improved prognosis for patients with locally advanced gastric cancer (LAGC). The purpose of this meta-analysis was to evaluate the efficacy and safety of neoadjuvant chemotherapy (NCT) in combination with targeted therapy or (and) immunotherapy for LAGC patients.

Methods The PubMed, EmBase, and Cochrane Library databases were systematically searched to identify clinical studies comparing the efficacy of different neoadjuvant regimens in LAGC patients. Subsequently, paired and network meta-analyses were conducted using Stata software to evaluate the pooled results of different neoadjuvant regimens, including NCT, neoadjuvant immunotherapy plus chemotherapy (NICT), NCT plus targeted therapy (NCTT), and NICT plus targeted therapy (NICTT).

Results 21 studies [six randomized controlled trials (RCTs) and 15 non-RCTs] fulfilled the inclusion criteria were incorporated into the meta-analysis. Pairwise meta-analysis revealed that the NICTT, NICT, and NCTT groups exhibited a higher incidence of pathological complete response (pCR), major pathological response (MPR), and R0 resection compared to the NCT group. Compared to the NCT group, both the NICTT and NCTT groups demonstrated a tendency towards experiencing more severe treatment-related adverse events (TRAEs), while the NICT and NCTT groups exhibited a lower 2-year recurrence rate. Additionally, network meta-analysis revealed that the NICTT group exhibited superior efficacy in achieving pCR, albeit being associated with a higher incidence of severe TRAEs.

[†]Chen Liang and Zhiyuan Yu contributed equally to this work.

*Correspondence:

Lei Niu

lanyushinl@163.com

Pengji Gao

sunshinegao@pku.org.cn

Lei Li

m13699119545@mail.ccmu.edu.cn

Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Conclusion Compared to NCT alone, the combined application of targeted therapy and/or immunotherapy demonstrates greater efficacy in tumor downstaging and achieving pCR. However, it is crucial to remain vigilant regarding the occurrence of severe TRAEs. The future adoption of NICTT as a mainstream treatment is anticipated, however, further high-quality clinical studies are imperative to substantiate its efficacy.

Keywords Gastric cancer, Neoadjuvant therapy, PD-1 inhibitor, Targeted drugs, Meta-analysis

Introduction

According to the 2020 global cancer statistics released by the International Agency for Research on Cancer of the World Health Organization, gastric cancer (GC) ranks fifth in terms of prevalence worldwide, with the fourth highest mortality rate [1]. The surgical approach remains the cornerstone in the management of GC; however, a majority of patients are diagnosed at an advanced stage with low rates of achieving radical tumor resection, resulting in a dismal prognosis. The enhancement of radical resection rate and the optimization of prognosis have consistently constituted the focal point in the realm of GC treatment research [2, 3].

In recent years, significant advancements have been made in the treatment of locally advanced gastric cancer (LAGC) through the emergence and widespread adoption of neoadjuvant chemotherapy (NCT), molecular targeted therapy, and immunotherapy [3, 4]. The recent advancements in the field of LAGC have primarily been attributed to immunotherapy. Specifically, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) have demonstrated their efficacy across various solid tumors, including GC [5, 6]. Apatinib is a widely utilized anti-vascular targeted drug for the treatment of LAGC, which exerts an anti-angiogenic effect through highly selective binding to the vascular endothelial growth factor receptor 2 (VEGFR-2) and fundamentally obstructing tumor nutrient supply [3, 7]. With the continuous advancement of neoadjuvant therapy, a multitude of clinical trials and novel treatment concepts continue to emerge, leading to a transformation in its treatment approach from NCT alone to neoadjuvant immunotherapy plus chemotherapy (NICT), NCT plus targeted therapy (NCTT), as well as NICT plus targeted therapy (NICTT), and other innovative modalities [7–9].

The interim results of NCT03421288, KEYNOTE-585, and ChiCTR2000030610 trials demonstrated that the combination of NICT exhibits promising efficacy and acceptable toxicity compared to NCT alone in GC patients [10–12]. Additionally, the clinical trials NCT04208347 and NCT04661150 revealed that triple therapy with NICTT yielded superior treatment outcomes. The optimal combination of neoadjuvant therapy still remains a subject of ongoing controversy [13, 14]. Currently, there is a dearth of systematic reviews or

meta-analyses comparing the efficacy and safety of different neoadjuvant regimens in the treatment of LAGC.

Methods

Study design and literature search

This systematic review and meta-analysis was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [15] and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [16]. The protocol has been registered in PROSPERO database (CRD42024576132). We searched PubMed, EmBase, and Cochrane Library databases for published studies and registered clinical trials from database inception to July 2024 (Supplemental material 1). Besides, reference lists of included studies were checked for additional references. Two reviewers independently screened titles, abstracts, and, if potentially eligible, full texts for inclusion. Disagreement was resolved by a third reviewer. The inclusion of duplicate published trials was limited to the final or most comprehensive version, taking into account increasing patient numbers or extended follow-up durations.

Inclusion criteria and data extraction

The inclusion criteria for the study were as follows: (1) study types were randomized controlled trials (RCTs), well-designed prospective or retrospective comparative studies; (2) study population diagnosed with non-metastatic, untreated, and resectable LAGC (stage II–IV); (3) intervention and control groups treated with distinct regimens, which included NCT, NCTT, NICT, or NICTT; (4) there were no restrictions imposed on the study size, language, or follow-up duration. Exclusion criteria were as follows: (1) single-arm studies, review articles, case reports, or meta-analysis; (2) protocol, or repeated studies; (3) study population diagnosed with inoperable, recurrent, or metastatic GC; and (4) required outcome indicators were not reported.

For the coding and data extraction, 2 independent researchers evaluated each included study. All discrepancies in data extraction were resolved in discussion, and the required data for analyses could be obtained for all included studies. The baseline characteristics to be extracted and collated encompassed the author, publication year, study type, sample size, gender, age, cTNM tumor stage, intervention and control regimes. The

primary outcome measures were pathological complete response (pCR) and severe treatment-related adverse events (TRAEs). The term “severe TRAEs” was used to describe adverse events of grade 3 or higher. Secondary outcomes included major pathological response (MPR), R0 resection, and 2-year tumor recurrence.

Quality assessment

The quality assessment for RCTs and retrospective studies were conducted using criteria outlined in the Cochrane Collaboration’s tool and the Newcastle Ottawa scale (NOS), respectively. The tool developed by the Cochrane Collaboration evaluate bias in six aspects, including selection, implementation, evaluation, follow-up, reporting, and other [17]. Subsequently, the quality of RCTs was categorized into high (6 points), fair (4–5 points), and low (0–3 points) based on the number of positive answers to the aforementioned six questions. In NOS tool, three aspects were used to evaluate studies: selection (0–4 points), comparability (0–2 points), and exposure/outcome (0–3 points) [18]. The study was considered to be of satisfactory quality if it reaches or exceeds 6 points. Two authors independently evaluated the quality of included studies, and any discrepancies were resolved through discussion or by consulting a third reviewer when necessary.

Statistical analysis

All statistical analyses were conducted using Stata (version 15) software. In pairwise meta-analysis, pooled odds ratio (OR) with 95% confidence interval (CI) were estimated using the Mantel-Haenszel method. The I^2 and Q statistics were employed to evaluate the level of heterogeneity among the incorporated studies. $I^2 > 50\%$ or $P < 0.05$ was considered substantial heterogeneity, random effects model was adopted; otherwise, a fixed effects model was used. To minimize heterogeneity across studies and enhance the accuracy, subgroup analyses were conducted based on different intervention regimens. Additionally, a comprehensive evaluation of both direct and indirect comparisons was conducted through network meta-analysis. The network diagrams were created to illustrate the comparative relationship between each procedure, with nodes representing the available neoadjuvant regimens. The relative efficacy of each neoadjuvant regimen was estimated using ranking probabilities and the surface under the cumulative ranking curve (SUCRA) metrics. Besides, publication bias was evaluated using the Egger regression test and visualized through a funnel plot. A sensitivity analysis was performed by sequentially excluding individual studies to evaluate the robustness and stability of the pooled effect estimates. All statistical tests were two-sided, and p -values less than 0.05 were deemed to signify statistical significance.

Results

Study selection and study characteristics

Based on the search strategy, a total of 742 potential articles were identified. Upon exclusion of duplicates and irrelevant articles through title and abstract screening, 120 studies were selected for full-text evaluation. Of these, 21 studies (six RCTs and 15 non-RCTs) fulfilled the inclusion criteria were incorporated into the meta-analysis [10–14, 19–34] (Fig. 1). The study conducted by Shitara et al. consisted of two distinct intervention cohorts (main cohort and FLOT cohort), therefore, we provided separate descriptions and analyses for each of these cohorts [11]. The aggregated data encompassed 4,146 patients who were administered one of 4 distinct treatment regimens, as follows: NCT, NCTT, NICT, and NICTT. Baseline characteristics of the included clinical studies are delineated in Table 1. Besides, the outcome indicators utilized in the meta-analysis are provided in online Supplemental material 2. The risk of bias for RCTs and non-RCTs was assessed using the Cochrane and NOS bias risk tools, respectively. It is worth noting that all 21 incorporated studies demonstrated a low risk of bias (Table 1).

Pairwise meta-analysis

Primary outcomes

pCR The rates of pCR were reported in 19 incorporated studies, with the pCR rates in the NCT, NCTT, NICT, and NICTT groups being 5.7% (120/2,116), 16.3% (33/203), 16.4% (209/1,277), and 21.0% (73/347) respectively. The comparative analysis of each subgroup did not reveal any significant heterogeneity, thus a fixed effect model was employed. The comparative analysis of NICT vs. NCT (OR = 3.359, $P < 0.001$), NICTT vs. NCT (OR = 4.217, $P < 0.001$), NICTT vs. NCTT (OR = 2.130, $P = 0.027$), and NCTT vs. NCT (OR = 2.738, $P = 0.006$) all exhibited statistically significant differences (Fig. 2A). To summarize, NICTT, NICT, and NCTT demonstrated higher pCR rates compared to NCT, while NICTT exhibited a higher pCR rate than NCTT.

Severe TRAEs The rates of severe TRAEs were reported in 14 studies, with rates of 28.7% (458/1,597), 30.3% (66/218), 42.6% (355/834), and 34.2% (111/325) observed in the NCT, NCTT, NICT, and NICTT groups respectively. The comparative analysis of each subgroup did not reveal any significant heterogeneity. The subsequent meta-analysis employed a fixed effect model, revealing that patients in the NICTT (OR = 2.435, $P < 0.001$) and NCTT (OR = 1.970, $P = 0.003$) groups exhibited a higher incidence of severe TRAEs compared to those in the NCT group (Fig. 2B).

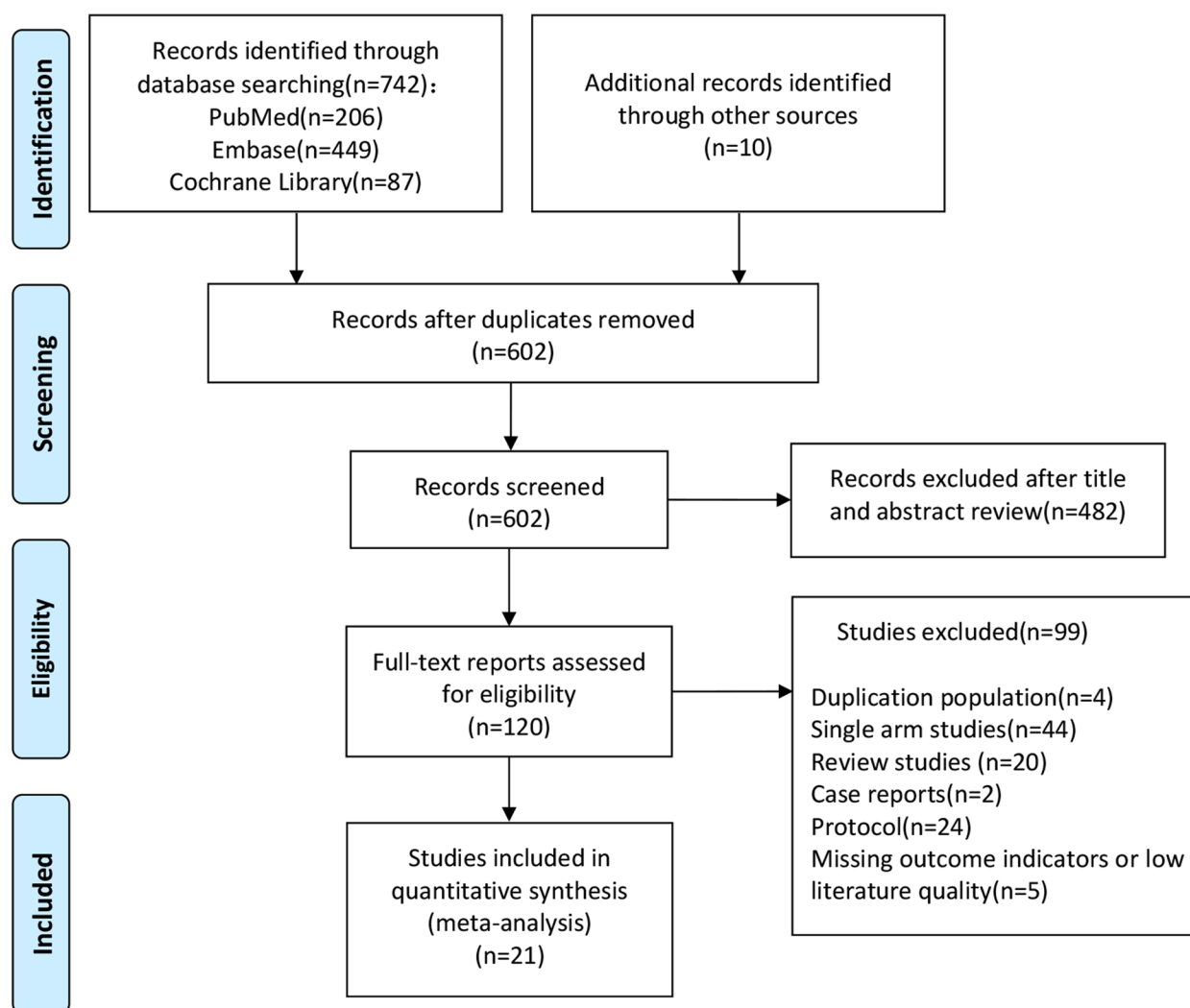


Fig. 1 Flow chart of the studies screening and selection

Secondary outcomes

MPR 13 studies reported the incidence of MPR. The rates of MPR in the NCT, NCTT, NICT, and NICTT groups were 26.3% (380/1,444), 40.5% (32/79), 40.1% (295/736), and 50.6% (117/231) respectively. Subsequently, fixed effect model was adopted in meta-analysis and analysis results revealed that NICTT (OR = 2.122, $P < 0.001$), NICT (OR = 1.928, $P < 0.001$), and NCTT (OR = 2.602, $P = 0.008$) exhibit a higher MPR rate than NCT (Fig. 3A).

R0 resection 20 studies reported the rates of R0 resection, and the rates of R0 resection in the NCT, NCTT, NICT, and NICTT groups were 88.8% (1,847/2,081), 89.2% (223/250), 90.7% (1,077/1,187), and 97.0% (292/301) respectively. The fixed-effect meta-analysis demonstrated that NICTT (OR = 4.017, $P = 0.001$), NICT (OR = 1.412, $P = 0.012$), and NCTT (OR = 1.744, $P = 0.050$) all exhibit a higher R0 resection rate compared to NCT (Fig. 3B).

2-year recurrence The incidence of 2-year recurrence after surgery was reported in 7 incorporated studies. The rates of 2-year recurrence in the NCT, NCTT, and NICT groups were 43.8% (534/1,218), 17.9% (12/67), and 34.3% (317/925) respectively. Subsequently, fixed effect model was adopted and meta-analysis results revealed that NICT (OR = 0.636, $P < 0.001$) and NCTT (OR = 0.363, $P = 0.011$) both exhibit a lower 2-year recurrence rate compared to NCT (Fig. 4).

Network meta-analysis

In order to comprehensively compare and evaluate the efficacy and safety of various neoadjuvant regimens, we conducted a network meta-analysis of the primary outcome measures. The network diagram and contribution diagram for pCR are illustrated in Fig. 5A and Supplementary material 3 A, respectively. One closed ring was formed by the four treatment measures, and the consistency test result was satisfactory ($P = 0.599$).

Table 1 Baseline characteristics of the clinical studies included in the meta-analysis

Study (Ref.) year	Study type	Sample size	Male/Female	Age/y	Tumor stage	Interventions arm	Controls arm	Qual- ity score
NICT vs. NCT								
Shitara [11] 2024	phase III RCT	402/402	575/229	64/63 ^a	cT ₁₋₄ N ₀₋₃ M ₀ (stage II-IVA)	pembrolizumab (3 cycles) +control regimens	cisplatin + capecitabine, or cisplatin + fluo- rouracil (3 cycles)	6
Shitara [11] 2024	phase III RCT	100/103	NA	NA	NA	pembrolizumab (3 cycles) +control regimens	FLOT (4 cycles)	6
Lorenzen [10] 2023	phase I/III RCT	146/149	217/78	61/62 ^a	cT ₁₋₄ N ₀₋₃ M ₀	atezolizumab (4 cycles) +control regimens	FLOT (4 cycles)	4
Min [12] 2022	RCT	31/23	42/12	63/63 ^a	NA	camrelizumab (4 cycles) +control regimens	FLOT (4 cycles)	4
Bao [19] 2024	retrospective	28/61	65/24	NA	cT ₁₋₄ N ₀₋₃ M ₀₋₁ (stage I-IV)	anti-PD1 ICIs +control regimens	SOX	6
Cui [20] 2024	retrospective	49/86	106/29	58.76/ 60.28 ^b	cT ₁₋₄ N ₊ M ₀ / cT _{3-4b} N ₀₋₃ M ₀ (stage II-IVA)	nivolumab/pembrolizumab/ toripalimab/camrelizumab/sin- tilimab + control regimens	SOX/XELOX/SAP/FLOT/FOLFOX (2–8 cycles)	7
Lin [21] 2024	retrospective	38/90	66/62	NA	cT ₄ N ₀₋₃ M ₀ (stage IIB-IVA)	camrelizumab + control regimens.	SAP	8
Sun [22] 2024	retrospective	195/390	446/ 139	62.13/ 62.27 ^b	cT _{3-4b} N ₀₋₃ M ₀ (stage II-IVA)	sintilimab/nivolumab/cameli- zumab + control regimens	SOX/XELOX/SAP/DS/FLOT/DOS/POF	8
Xu [23] 2024	retrospective	184/184	293/ 75	62.5/ 62.0 ^a	cT ₃ N ₀₋₃ M ₀ (stage IIA-IVA)	anti-PD1/PD-L1 ICIs + control regimens	SOX/XELOX/FLOT/DCF/DCX/DOS	8
Jiang [24] 2023	retrospective	50/119	142/27	NA	cT ₂₋₄ N ₀₋₃ M ₀ (stage II-III)	tislelizumab + control regimens	SOX/FOLFOX	7
Su [25] 2023	retrospective	30/50	60/20	54.9/ 55.5 ^b	cT _{1-4b} N ₀₋₃ M ₀₋₁ (stage II-IVB)	pembrolizumab/toripalimab/ camrelizumab/sintilimab + con- trol regimens	XELOX/FOLFOX/FLOT (2–8 cycles)	6
Zhang [26] 2023	retrospective	34/43	62/15	60.1/ 59.1 ^b	cT _{3-4b} N ₀₋₃ M ₀ (stage II-III)	camrelizumab/sintilimab/ toripalimab/nivolumab (2–4 cycles) + control regimens	SOX/FLOT (2–4 cycles)	7
NICTT vs. NCT								
Lin [27] 2024	phase II RCT	51/53	77/27	63/63 ^a	cT ₃₋₄ N ₊ M ₀	camrelizumab + apatinib (3 cycles) +control regimens	SAP (3 cycles)	4
Li [13] 2023	phase III RCT	180/180	NA	NA	cT _{3-4b} N ₊ M ₀	camrelizumab + rivoceranib (3 cycles) +control regimens	SOX (3 cycles)	4
NICTT vs. NCTT								
Peng [14] 2024	phase II RCT	21/21	39/3	61/65 ^a	NA	atezolizumab (3 cycles) + con- trol regimens	XELOX + trastuzumab (3 cycles)	4

Table 1 (continued)

Study (Ref.) year	Study type	Sample size	Male/Female	Age/y	Tumor stage	Interventions arm	Controls arm	Qual- ity score
Wang [28] 2023	prospective cohort	39/34	50/23	57.9/ 58.9 ^b	cT _{3-4a} N ₊ M ₀ (stage III)	sintilimab/carrelizumab/to- ripalimab (3 cycles) + control regimens	SOX/XELOX + apatinib (3 cycles)	7
NICTT vs. NCTT vs. NCT								
Xiong [29] 2023	retrospective	56/50/73	129/50	58.2/59.1/58.9 ^b	cT _{3-4a} N ₊ M ₀ (stage III)	sintilimab/camrelizumab + apa- tinib (4 cycles) + control regimens, or apatinib (4 cycles) + control regimens	SOX/XELOX (4 cycles)	6
NCTT vs. NCT								
Sun [30] 2023	prospective cohort	45/51	74/22	57.2/ 59.8 ^b	cT _{3-4a} N ₊ M ₀	apatinib (3 cycles) + control regimens	SOX/XELOX (3 cycles)	7
Wang [31] 2022	prospective cohort	25/35	45/15	55.2/ 58.2 ^b	cT _{3-4a} N ₊ M ₀ (stage III)	apatinib (5 cycles) + control regimens	SOX (3 cycles)	7
Zhang [32] 2021	retrospective	31/44	55/20	60.19/ 59.25 ^b	stage IIB-IV	apatinib + control regimens	FLOT (4 cycles)	6
Tang [33] 2020	prospective cohort	48/58	NA	NA	cT ₂₋₄ N ₊ M ₀	apatinib (2–4 cycles) + control regimens	SOX (2–5 cycles)	8
Zhang [34] 2020	phase III prospec- tive trial	33/31	NA	NA	stage III	apatinib (3 cycles) + control regimens	FLOT (4 cycles)	8

Abbreviations: NICT Neoadjuvant immunotherapy plus chemotherapy, NCT neoadjuvant chemotherapy, NICTT NICT plus targeted therapy, RCT randomized controlled trial, FLOT doc etaxel+oxaliplatin+tetrahydrofolic acid+fluorouracil, PD-1 programmed cell death 1, ICIs immune checkpoint inhibitors, SOX S-1+oxaliplatin, XELOX capecitabine+oxaliplatin, SAP S-1+nab-paclitaxel, DS docetaxel+S-1, DOS docetaxel+oxaliplatin+S-1, POF paclitaxel+oxaliplatin+fluorouracil, PD-L1 programmed cell death-ligand 1, DCF docetaxel+cisplatin+fluorouracil, DCX docetaxel+capecitabine, FOLFOLX oxaliplatin+calcium levofolinate+fluorouracil.

^aValues are presented as median.

^bValues are presented as mean.

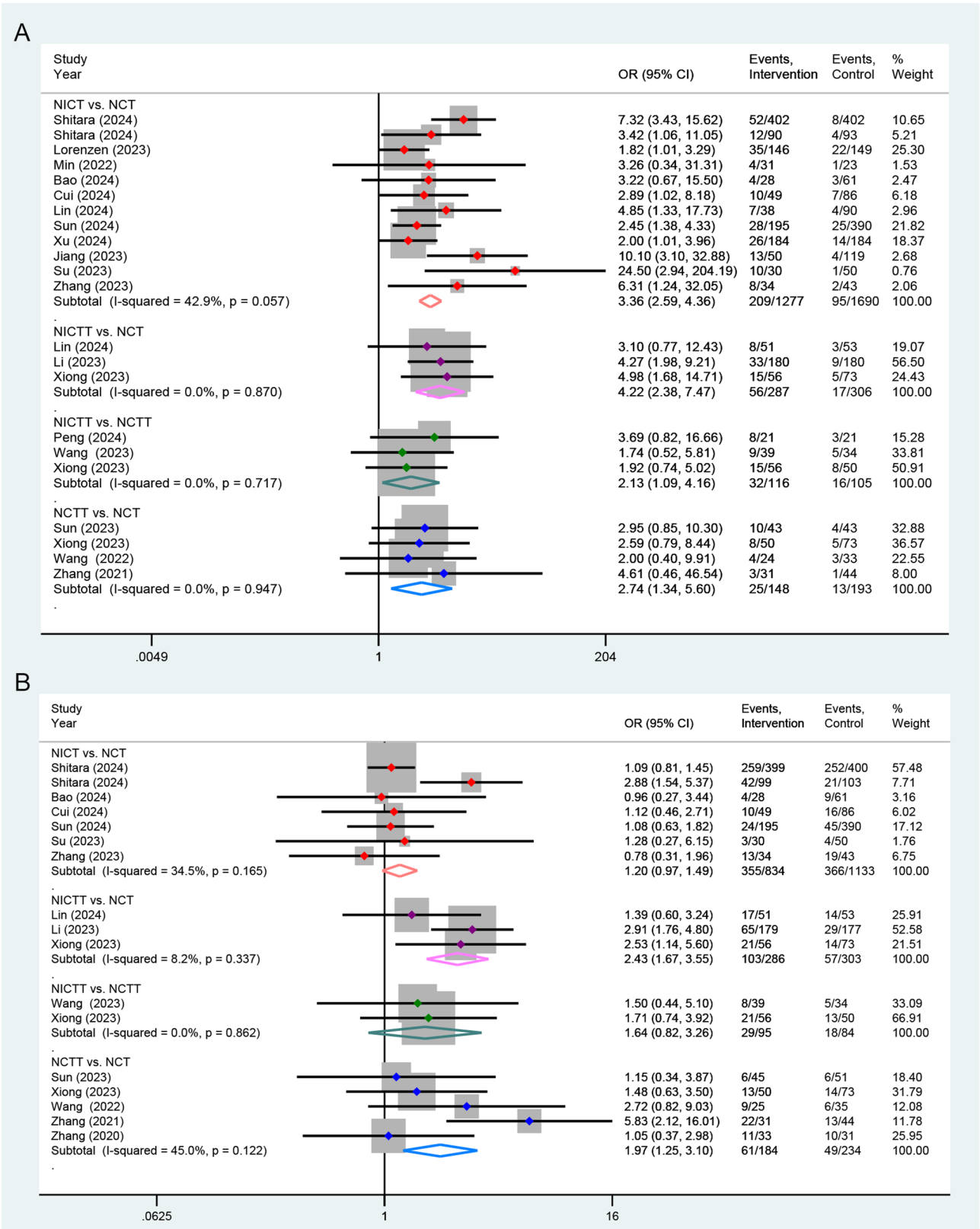


Fig. 2 Forest plots illustrating the pooled results of (A) pCR and (B) severe TRAEs outcomes. pCR, pathological complete response; TRAEs, treatment-related adverse events; OR, odds ratio; CI, confidence interval

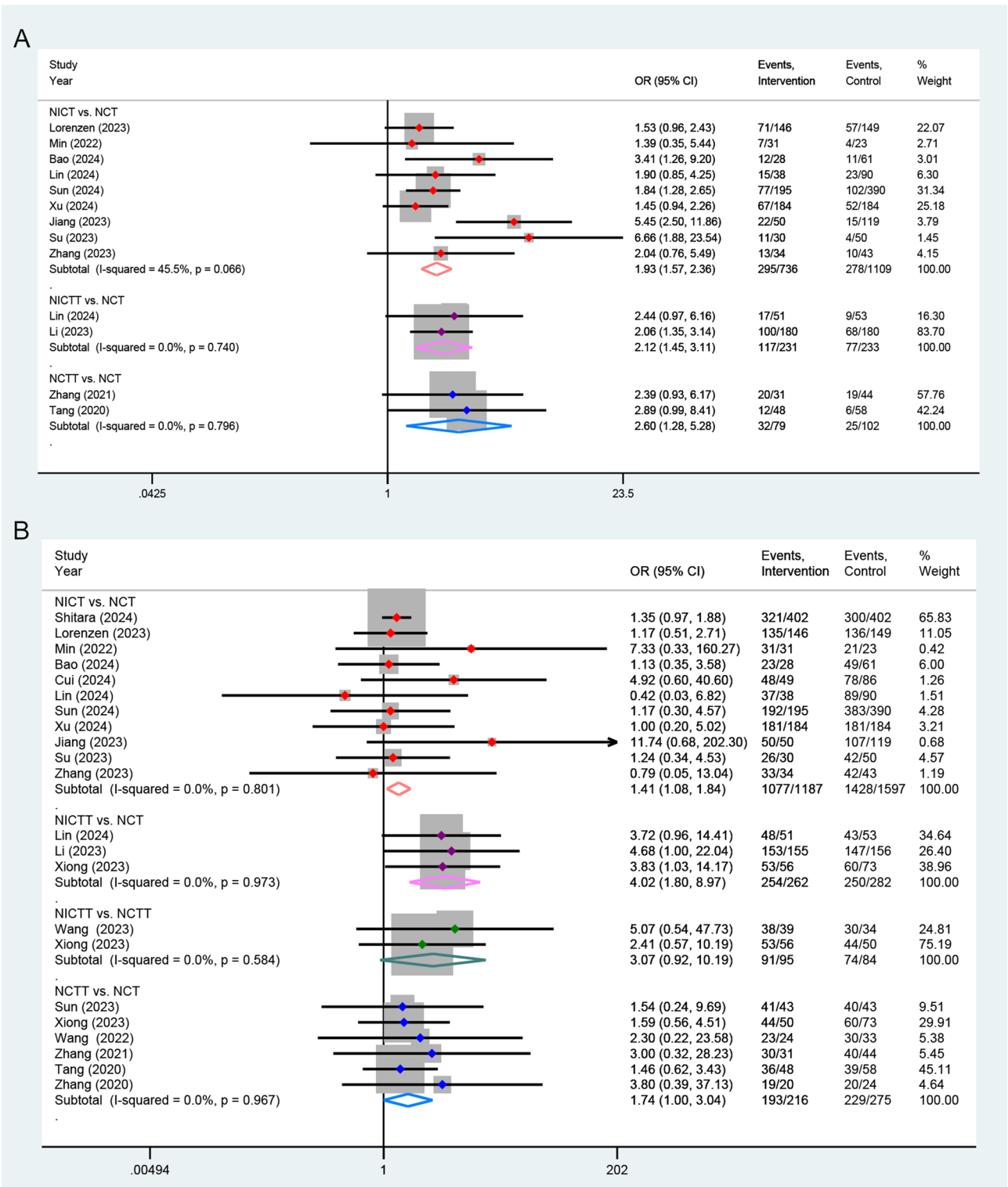


Fig. 3 Forest plots illustrating the pooled results of (A) MPR and (B) R0 resection outcomes. MPR, major pathological response; OR, odds ratio; CI, confidence interval

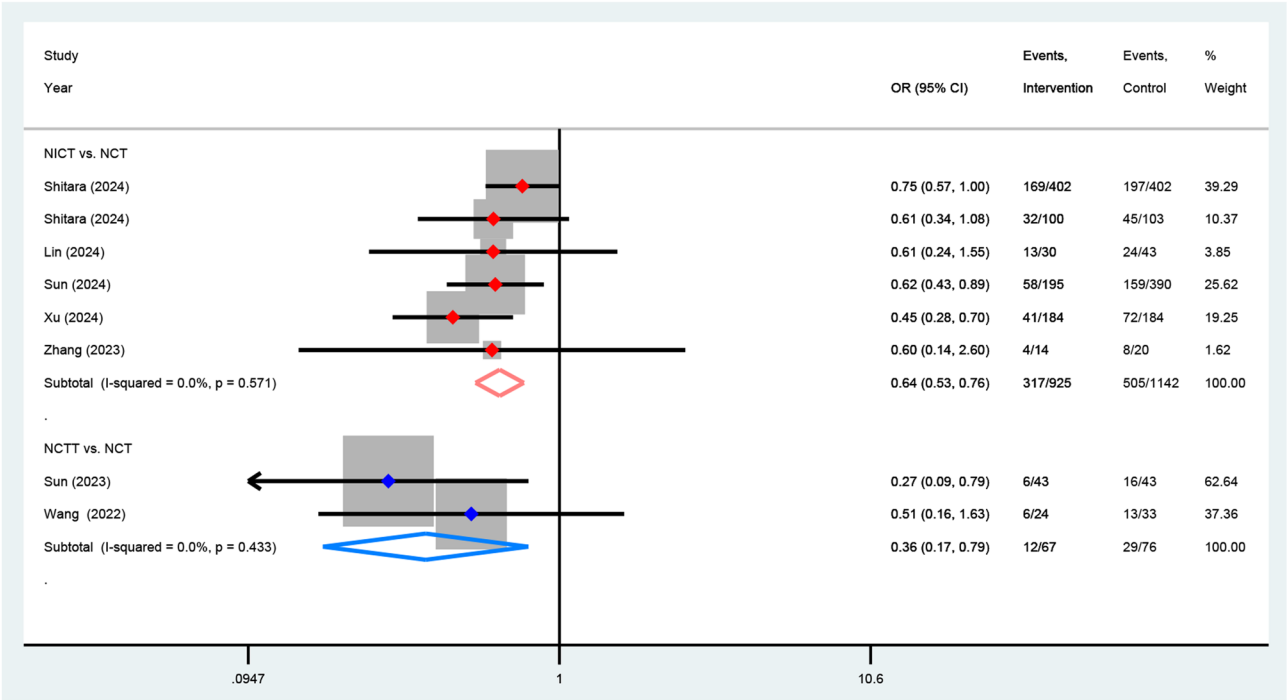


Fig. 4 Forest plots illustrating the pooled results of 2-year recurrence. OR, odds ratio; CI, confidence interval

(Supplementary material 4 A). The pCR rates were higher in the NICTT (OR 4.55, 95% CI 2.46–8.41), NICT (OR 3.44, 95% CI 2.38–4.95), and NCTT groups (OR 2.38, 95% CI 1.21–4.66) compared to NCT group. The NICTT group, in addition, exhibited a slightly superior performance compared to the NCTT group (OR 1.92, 95% CI 0.99–3.69) (Fig. 5B). The treatment with the highest SUCRA value was NICTT (SUCRA: 80.1), indicating its likelihood of being the most effective regimen for achieving pCR. NICT (SUCRA: 65.8) and NCTT (SUCRA: 53.2) followed suit in terms of effectiveness. Notably, NCT alone exhibited the lowest SUCRA value (0.9) (Fig. 5C).

The network diagram and contribution diagram for severe TRAEs are illustrated in Fig. 5D and Supplementary material 3B, respectively. One closed ring was formed and the consistency test result was satisfactory ($P=0.481$) (Supplementary material 4B). Severe TRAEs were more common in the NICTT (OR 2.52, 95% CI 1.65–3.85) and NCTT groups (OR 1.74, 95% CI 1.16–2.63) compared to the NCT group. Besides, the NICTT group exhibited a higher risk of severe TRAEs than NICT group (OR 2.03, 95% CI 1.20–3.45) (Fig. 5E). The treatment with the least toxicity was NCT alone (SUCRA: 94.3), followed by NICT (SUCRA: 65.5) and NCTT (SUCRA: 24.9). NICTT exhibited the highest likelihood of severe TRAEs (SUCRA: 15.2) (Fig. 5F).

Subgroup analysis

Three studies documented the PD-L1 expression levels or microsatellite instability-high (MSI-H) status of tumors in the NICT or NICTT groups. Subsequently, we categorized the cases according to the expression status of the aforementioned two biomarkers and conducted a systematic comparison and summary of the pCR and MPR outcomes between the groups. The analysis results demonstrated that the MSI-H tumors exhibited a higher likelihood of achieving pCR (OR=9.045, $P<0.001$) (Fig. 6A) and MPR (OR=4.529, $P=0.012$) (Fig. 6B) following immunotherapy-based neoadjuvant regimens, as compared to microsatellite stable (MSS) tumors. Additionally, PD-L1 positive expression [combined positive score (CPS)>1] group appeared to have a higher likelihood of achieving pCR (Fig. 7A) and MPR (Fig. 7B).

Publication bias and sensitivity analysis

The publication bias was evaluated through the construction of funnel plots based on primary outcomes. The funnel plot constructed for pCR outcomes exhibited an approximately symmetrical distribution, suggesting the absence of significant publication bias (Fig. 8A). However, the funnel plot constructed for severe TRAEs revealed that the majority of included studies were skewed towards the left side of the median line, which indicate the presence of potential publication bias (Fig. 8B).

Additionally, sensitivity analysis was conducted for pCR (Fig. 9A) and severe TRAEs outcomes (Fig. 9B),

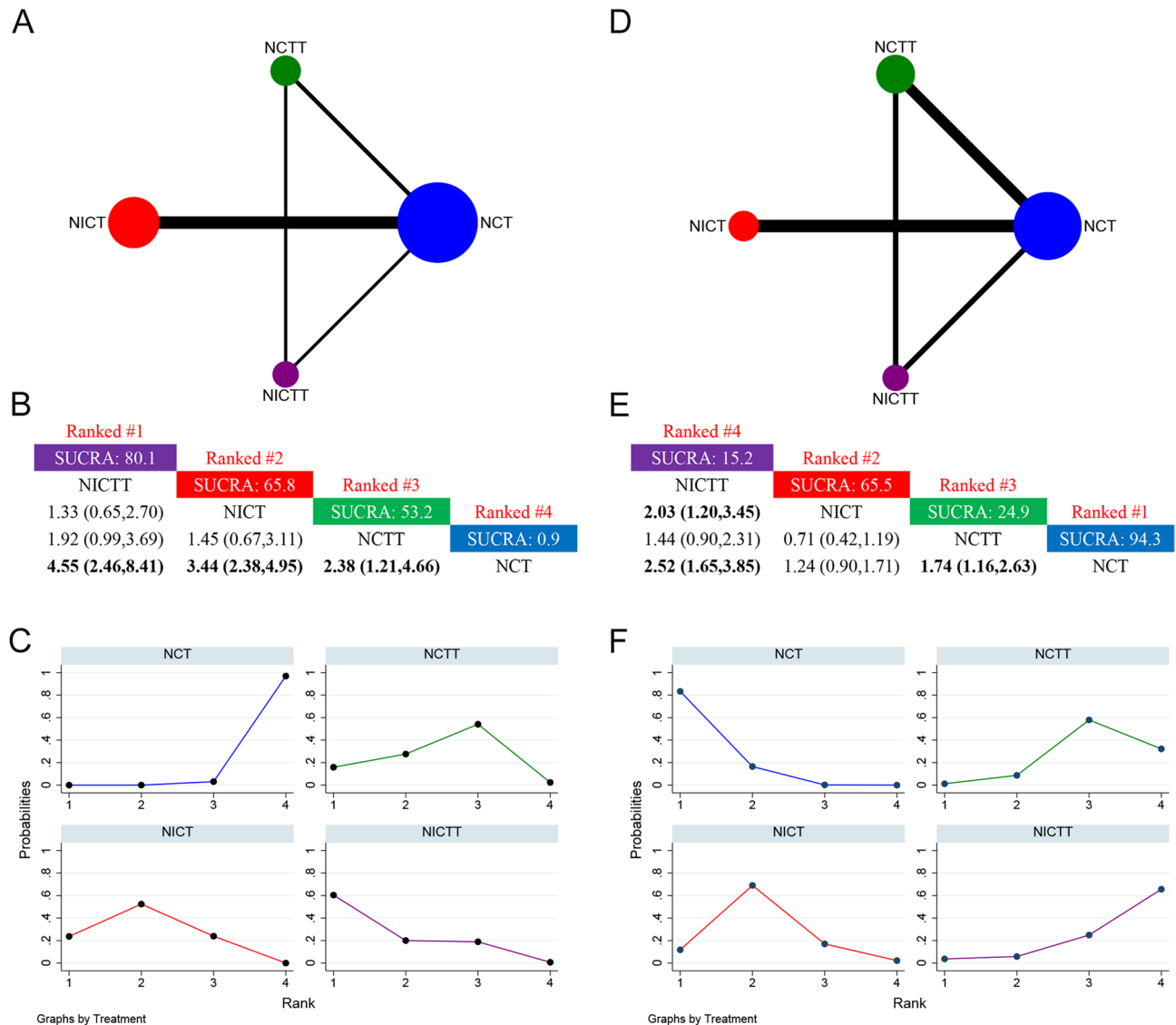


Fig. 5 Network meta-analysis results for primary outcomes. A network diagram was constructed for **(A)** pCR and **(D)** severe TRAEs outcomes, respectively. Each node in the network signifies a distinct treatment plan, and its size is proportional to the aggregate patient population subjected to that treatment. A ranking table that compares each treatment option was constructed based on the SUCRA values derived from the **(B)** pCR and **(E)** severe TRAEs outcomes, respectively. Text in bold indicates statistically significant variances. A cumulative ranking probability plot was constructed for **(C)** pCR and **(F)** severe TRAEs outcomes, respectively. The larger the area under the curve, the higher the likelihood of a treatment effect. pCR, pathological complete response; TRAEs, treatment-related adverse events; SUCRA, surface under the cumulative ranking curve

respectively, and no significant differences were observed after systematically excluding each study.

Discussion

In recent years, the deepening of exploration has led to the innovation of numerous treatment models and concepts, as well as the emergence of clinical trial results, thereby creating a novel landscape for the management of LAGC [3, 4]. The current management of LAGC has evolved from simple surgical resection to a novel approach involving neoadjuvant therapy followed by surgery and postoperative adjuvant therapy, significantly

enhancing the prognosis and survival outcomes for patients with LAGC. Therefore, the determination of an appropriate individualized neoadjuvant therapy program has gradually emerged as a prominent topic of discussion and research among academic experts [35, 36].

The previous studies have demonstrated that despite the introduction of preoperative NCT or postoperative adjuvant chemotherapy, which has shown some benefits for patients with LAGC, its efficacy remains limited. Furthermore, the median overall survival (OS) of advanced gastric cancer patients undergoing first-line chemotherapy still struggles to surpass 20 months [37, 38]. The

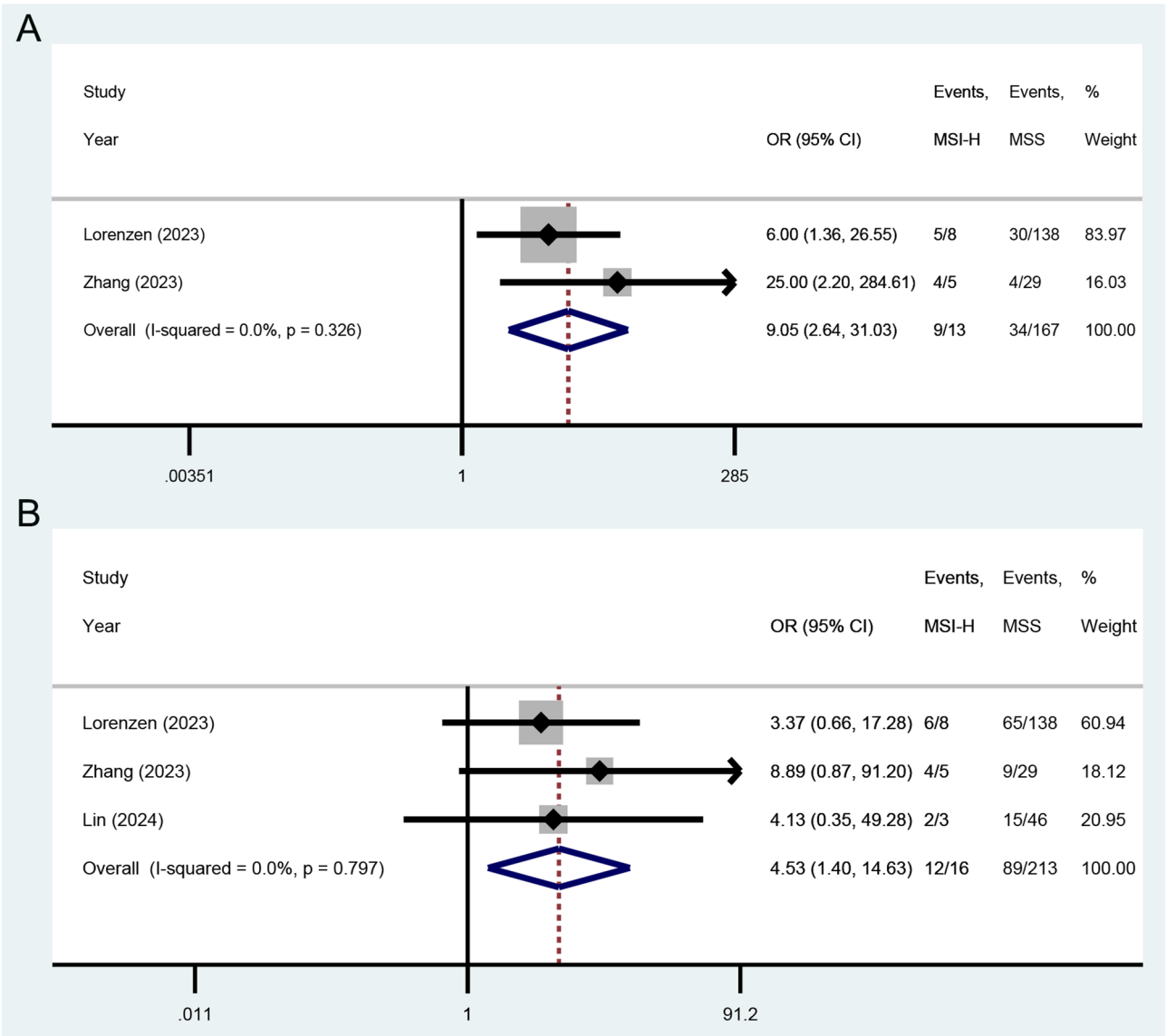


Fig. 6 Forest plots illustrating the impact of MSI-H on the (A) pCR and (B) MPR outcomes following the immunotherapy-based neoadjuvant regimens. pCR, pathological complete response; MPR, major pathological response; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OR, odds ratio; CI, confidence interval

efficacy of traditional chemotherapy is limited. With the advancement of personalized precision therapy, targeted therapy and immunotherapy have emerged as focal points in comprehensive treatment.

The human epidermal growth factor receptor 2 (HER-2) serves as a widely utilized therapeutic target in the field of LAGC, facilitating enhanced patient survival when combined with chemotherapy. However, the prevalence of HER2-positive in LAGC ranges from 6% to 30%, with only a limited proportion of patients deriving significant benefits [39]. VEGFR-2 regulates both lymphatic endothelial cells and vascular endothelial cells, thereby promoting the formation of lymphatic vessels and blood vessels. It also serves as a crucial therapeutic target for

LAGC treatment. The tyrosine kinase inhibitor apatinib exhibits high selectivity in competing for intracellular VEGFR-2 ATP-binding sites, thereby blocking downstream signal transduction and inhibiting the aberrant formation of tumor vessels [40, 41]. The results of the NCT02426034 trial have confirmed the acceptable and manageable safety profile as well as clinical benefits of apatinib in patients with advanced GC who have received it as a third- or later-line treatment [40]. Additionally, a nonrandomized controlled trial (NCT03192735) demonstrated the efficacy and acceptable safety profile of apatinib in combination with SOX as a neoadjuvant treatment for LAGC [41].

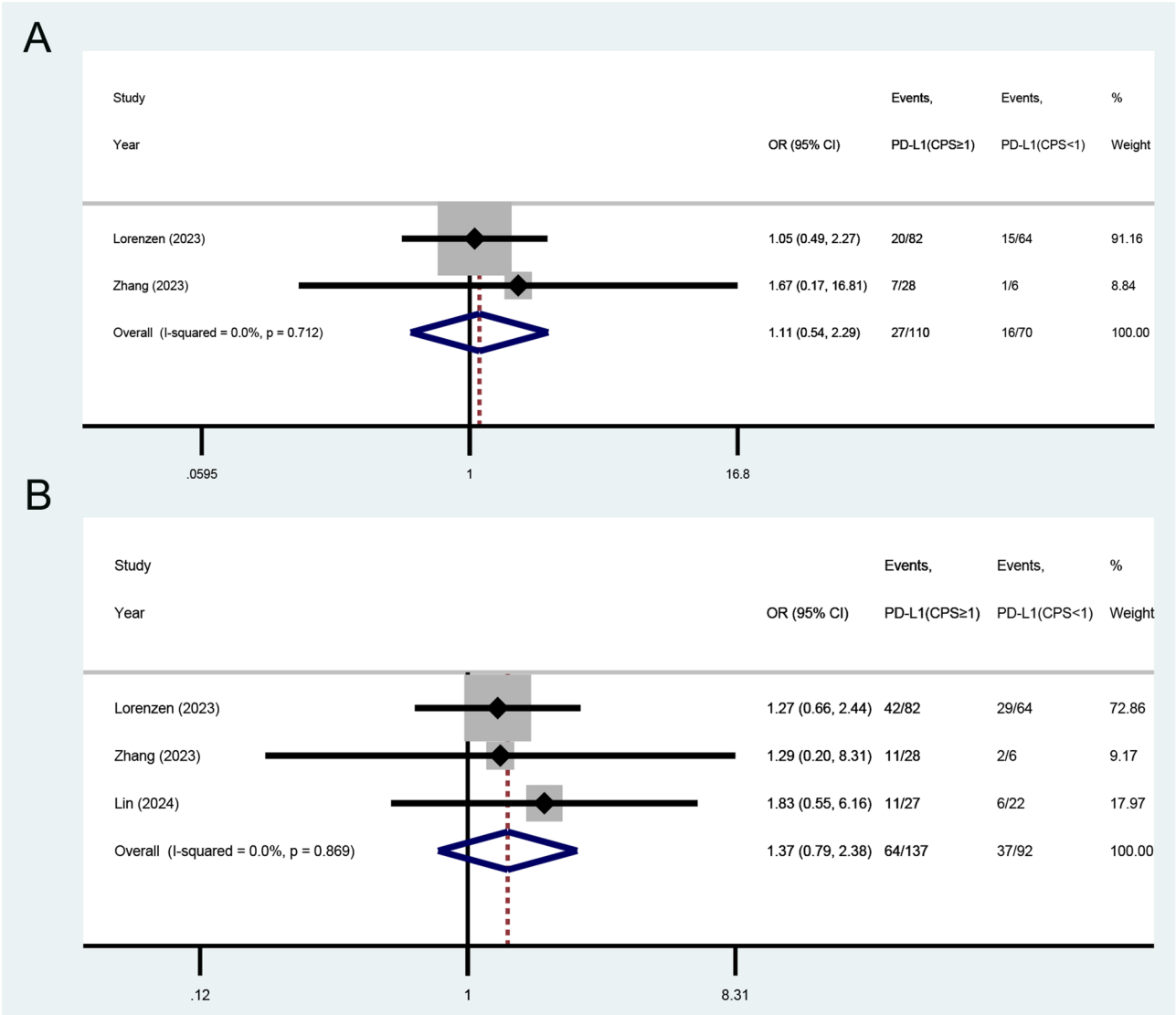


Fig. 7 Forest plots illustrating the impact of PD-L1 positive expression (CPS) > 1 on the (A) pCR and (B) MPR outcomes following the immunotherapy-based neoadjuvant regimens. CPS, combined positive score; pCR, pathological complete response; MPR, major pathological response; OR, odds ratio; CI, confidence interval

The ICIs therapy primarily utilizes monoclonal antibodies to specifically bind to the immune checkpoints located on the surface of tumor or immune cells, thereby impeding negative regulation and reactivating the immune system for efficient eradication of tumor cells. The advent of ICIs has revolutionized the conventional treatment paradigm for various malignant solid tumors, including GC. PD-1, which is expressed on the surface of T, B, and myeloid cells, functions as an inhibitory regulator in the immune system. Targeting this molecule with inhibitors can restore the immune system’s ability to effectively surveil, identify, and eliminate tumor cells [36, 42]. The CheckMate649, KEYNOTE-059, ATTRACTION-04, and ORIENT-16 studies all demonstrated significant efficacy of NICT as a first-line treatment for

advanced GC. Besides, the Chinese Society of Clinical Oncology, the European Society for Medical Oncology, and the National Comprehensive Cancer Network guidelines have all endorsed immunotherapy as a recommended treatment for advanced GC [43–45]. The favorable outcomes of immunotherapy in the adjuvant treatment of LAGC have prompted clinical trials to shift their focus towards neoadjuvant therapy. The interim findings from the KEYNOTE-585 trial demonstrated that perioperative administration of pembrolizumab led to a significant improvement in pCR, while exhibiting no statistically significant impact on disease-free survival (DFS) [11]. Additionally, ChiCTR2000030610 trial’s results suggested that NICT may improve the likelihood of achieving R0 resection, pCR, and postoperative node-negative

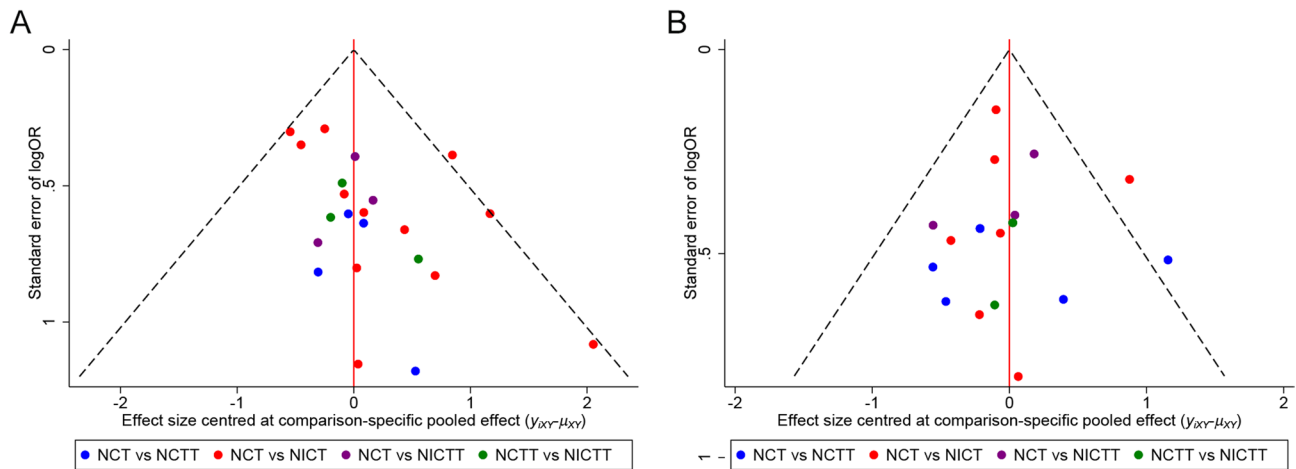


Fig. 8 Funnel plots were constructed based on (A) pCR and (B) severe TRAEs outcomes. pCR, pathological complete response; TRAEs, treatment-related adverse events

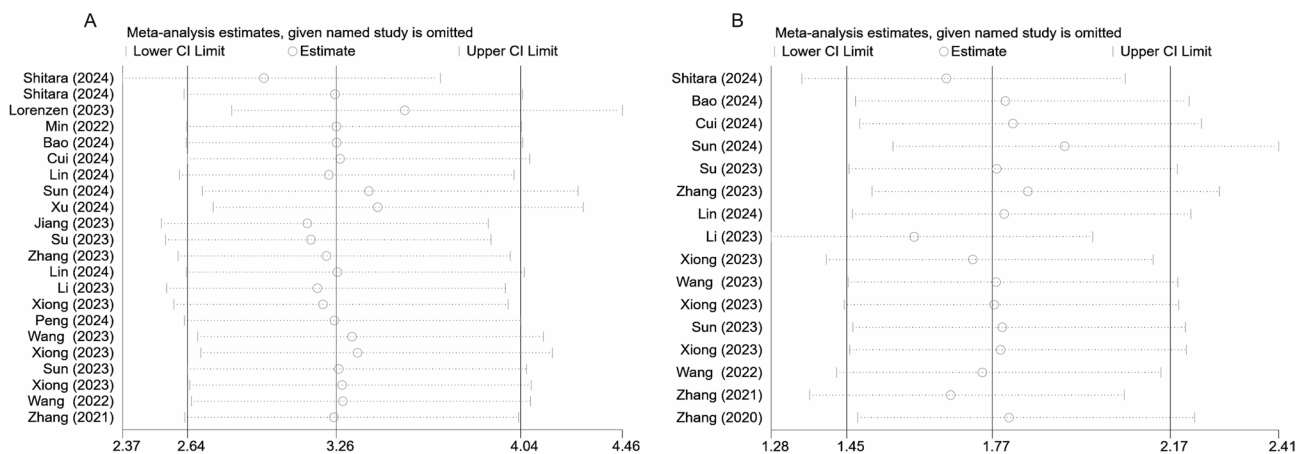


Fig. 9 Sensitivity analysis was conducted for (A) pCR and (B) severe TRAEs outcomes. pCR, pathological complete response; TRAEs, treatment-related adverse events

rate compared to treatment with NCT alone [12]. The application of PD-1 inhibitors in neoadjuvant therapy for LAGC has been sparsely reported; therefore, further exploration and analysis are required to determine its effects.

The anticancer effect of chemotherapy drugs is achieved by specifically targeting the genetic material (DNA and RNA), cellular proteins, enzymes, and other vital components to induce tumor cell death. The administration of apatinib can induce the normalization of tumor blood vessels, thereby enhancing tissue perfusion and facilitating improved penetration of chemotherapy drugs into the tumor tissue. Thus, the addition of apatinib to chemotherapy can enhance the efficacy of tumor treatment [7, 37]. Additionally, the combined effect of immunotherapy and chemotherapy can synergistically augment tumor eradication. When ICIs are combined with chemotherapy, on one hand, chemotherapy drugs can enhance the anti-tumor immune response of

patients; on the other hand, ICIs can augment chemotherapy sensitivity by boosting the anti-tumor immune response and further eliminate tumor cells that develop resistance after chemotherapy [46, 47]. Above all, compared to NCT alone, NCTT and NICT regimes both demonstrated superior efficacy in tumor cell eradication and enhances rates of pCR, MPR, and R0 resection while reducing the risk of postoperative recurrence.

The successful implementation of the NICT and NCTT regimes has prompted scholars to shift their research focus towards the NICTT triple regime. KEYNOTE-811 study has confirmed that the addition of immunotherapy to anti-HER-2 therapy + chemotherapy can significantly enhance the objective response rate, DFS, and OS [48]. Based on these findings, the China National Medical Products Administration granted approval for pembrolizumab in combination with trastuzumab, fluorouracil, and platinum on June 25, 2024. This approval was specifically for the first-line treatment of unresectable

or metastatic HER2-positive gastric adenocarcinoma (GA) and gastroesophageal junction adenocarcinoma (GEJA) expressing PD-L1 (composite positive score ≥ 1). DRAGON IV/AHEAD-G208 trial, the world's first phase III clinical trial assessing neoadjuvant PAC regime for resectable GA/GEJA, presented its interim analytical data through an oral presentation at ESMO Annual Meeting 2023. The findings demonstrated that in the perioperative management of resectable GA/GEJA, the addition of apatinib and carrelizumab to SOX regimen significantly augmented the pCR rate compared to SOX alone (18.3% vs. 5.0%). However, the follow-up of survival data from the DRAGON IV/AHEAD-G208 study is still ongoing and may require an additional 2–3 years of waiting [13]. In the future, more high-quality RCTs are needed to validate the efficacy and safety of NICTT triple therapy.

The combination of low-dose apatinib and carrelizumab has demonstrated a synergistic effect in suppressing tumor cell proliferation, as evidenced by various cellular and animal studies. The administration of apatinib concurrently enhances tumor hypoxia, acidosis, and hypoperfusion while facilitating immune cell infiltration to improve the tumor immune microenvironment. This transformation effectively converts tumor immunosuppression into immunoenhancement and aids in the recruitment and aggregation of T cells within the tumor microenvironment. Therefore, low-dose apatinib can enhance the efficacy of immunotherapy through multiple mechanisms, including facilitating antigen presentation, augmenting lymphocyte infiltration, inducing tumor vascular normalization, and improving the immune microenvironment. Simultaneously, it can also enhance the accumulation of chemotherapy drugs within tumor cells, thereby playing a multi-dimensional synergistic role [49, 50]. Drug safety is also a crucial area of research, particularly in relation to severe TRAEs, which require prompt attention to enable more patients to complete their course of treatment and achieve optimal outcomes. Our meta-analysis revealed no significant difference in the incidence of severe TRAEs between the NICT and NCT groups. However, both the NICTT and NCTT groups exhibited a higher incidence of severe TRAEs compared to the NCT group, indicating a more pronounced impact of apatinib on TRAEs. Therefore, it is imperative to closely monitor changes in vital signs during the application of NICTT regime, remain vigilant against severe TRAEs, and promptly formulate and adjust treatment plans based on patients' conditions [7, 51, 52]. With the emergence of more therapeutic targets and targeted drugs, NICTT regime is expected to achieve improved outcomes with reduced TRAEs.

Although this study systematically collected relevant literature evidence and employed diverse methodologies for meta-analysis, inherent limitations still persist.

Firstly, the majority of the published studies were retrospective cohort or case-control studies with limited levels of evidence. The potential publication bias, low research quality, and heterogeneity among patient populations inherent in retrospective studies may compromise the accuracy of analysis results. In addition, the outcome data of RCTs were preliminary and interim results obtained from the phase II/III clinical trials, with a limited duration of follow-up and an absence of survival outcomes. Last but not the least, almost all of the included studies were conducted exclusively on the Chinese population, thus necessitating further investigation into the generalizability of this analysis.

Conclusion

Compared to the exclusive use of NCT, the combined application of targeted therapy and/or immunotherapy demonstrates greater efficacy in tumor downstaging and achieving pCR, which in turn enhances the R0 resection rate and improves patient prognosis. However, it is crucial to remain vigilant regarding the occurrence of severe TRAEs. The present study conducted a comprehensive evaluation and comparison of the efficacy and safety of various neoadjuvant therapy regimens in GC, thereby providing practical and reliable high-level evidence-based support for perioperative NICTT strategies in LAGC. Owing to the relatively recent commencement of research on NICT, particularly NICTT, and the limited duration of follow-up, the actual impact of pCR on survival duration and long-term survival rates remains to be fully elucidated. It is anticipated that NICTT will emerge as a mainstream therapeutic approach in the future. Nevertheless, further high-quality clinical studies, tailored to specific tumor status, treatment protocols, and long-term follow-up, are required to substantiate its efficacy. We will also conduct a pooled analysis in the future, utilizing the most recent research data, with a particular emphasis on long-term survival outcomes, in order to complement the findings of this study.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-025-15136-2>.

Supplementary Material 1. The detailed strategies for literature retrieval

Supplementary Material 2. The outcome indicators utilized in the meta-analysis (events/total)

Supplementary Material 3. The contribution diagrams for (A) pathological complete response (pCR) and (B) severe treatment-related adverse events (TRAEs)

Supplementary Material 4. The consistency test results for (A) pathological complete response (pCR) and (B) severe treatment-related adverse events (TRAEs)

Acknowledgements

Not applicable.

Authors' contributions

L.L., P.G., and J.Z. contributed to protocol/project development and manuscript writing/editing. C.L., Z.Y., L.N., and S.H. contributed to statistical analyses, results interpretation, and manuscript writing/editing. C.J., Y.G., Y.G., and G.W. contributed to literature search and data collection. All authors have read and approved the final manuscript.

Funding

This work was supported by Beijing High-level Public Health Technical Talent Construction Project (Subject Backbone 02–19), Capital Health Development Research Special Project (2022-1-5082), and 2025 Beijing Jishuitan Hospital Youth Fund (QN202515).

Data availability

The article/Supplementary Material encompasses all the data generated or analyzed, as well as the software employed throughout this study. For further inquiries, please contact the corresponding author.

Declarations

Ethics approval and consent to participate

This study was conducted based on previously published studies, the necessity for informed consent and institutional review board approval was exempted.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Gastroenterology, Beijing Jishuitan Hospital, Capital Medical University, Xijiekou East Street 31, Xicheng District, Beijing 100035, China

²Department of General Surgery, Beijing Friendship Hospital, Capital Medical University, 95 Yong'an Road, Xi-Cheng District, Beijing 100050, China

³Department of General Surgery, Beijing Jishuitan Hospital, Capital Medical University, Xijiekou East Street 31, Xicheng District, Beijing 100035, China

Received: 14 July 2025 / Accepted: 1 October 2025

Published online: 03 November 2025

References

- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–49.
- Li GZ, Doherty GM, Wang J. Surgical management of gastric cancer: a review. *JAMA Surg*. 2022;157(5):446–54.
- Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. *J Hematol Oncol*. 2023;16(1):57.
- Ajani JA, D'Amico TA, Bentrem DJ, et al. Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022;20(2):167–92.
- Chen Y, Bai B, Ying K, Pan H, Xie B. Anti-PD-1 combined with targeted therapy: theory and practice in gastric and colorectal cancer. *Biochimica et Biophysica Acta (BBA)*. 2022;1877(5):188775.
- Hasegawa H, Shitara K, Takiguchi S, et al. A multicenter, open-label, single-arm phase I trial of neoadjuvant nivolumab monotherapy for resectable gastric cancer. *Gastric Cancer*. 2022;25(3):619–28.
- Scott LJ. Apatinib: a review in advanced gastric cancer and other advanced cancers. *Drugs*. 2018;78(7):747–58.
- Li S, Xu Q, Dai X, et al. Neoadjuvant therapy with immune checkpoint inhibitors in gastric cancer: a systematic review and meta-analysis. *Ann Surg Oncol*. 2023;30(6):3594–602.
- Chen X, Xu H, Chen X, et al. First-line camrelizumab (a PD-1 inhibitor) plus apatinib (an VEGFR-2 inhibitor) and chemotherapy for advanced gastric cancer (SPACE): a phase 1 study. *Signal Transduct Target Ther*. 2024;9(1):73.
- Lorenzen S, Gotze TO, Thuss-Patience P, et al. Perioperative atezolizumab plus fluorouracil, leucovorin, oxaliplatin, and docetaxel for resectable esophago-gastric cancer: interim results from the randomized, multicenter, phase II/III DANTE/IKF-s633 trial. *J Clin Oncol*. 2024;42(4):410–20.
- Shitara K, Rha SY, Wyrwicz LS, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. *Lancet Oncol*. 2024;25(2):212–24.
- Min LZ, Liu N, Zhou Y, Niu Z. Efficacy and safety of camrelizumab combined with FLOT versus FLOT alone as neoadjuvant therapy in patients with resectable locally advanced gastric and gastroesophageal junction adenocarcinoma who received D2 radical gastrectomy. *Ann Oncol*. 2022;33(7):S1106.
- Li C, Zheng Y, Shi Z, et al. Perioperative camrelizumab (C) combined with Rivo-ceranib (R) and chemotherapy (chemo) versus chemo for locally advanced resectable gastric or gastroesophageal junction (G/GJ) adenocarcinoma: the first interim analysis of a randomized, phase III trial (DRAGON IV). *Ann Oncol*. 2023;24(S2):S852.
- Peng Z, Zhang XT, Liang H, et al. Atezolizumab and trastuzumab plus chemotherapy in patients with HER2 + locally advanced resectable gastric cancer or adenocarcinoma of the gastroesophageal junction: a multicenter, randomized, open-label phase II study. *J Clin Oncol*. 2024;42(3):312.
- Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed)*. 2021;74(9):790–9.
- Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
- Higgins JP, Altman DG, Gotzsche PC, et al. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603–5.
- Bao ZH, Hu C, Zhang YQ, et al. Safety and efficacy of a programmed cell death 1 inhibitor combined with oxaliplatin plus S-1 in patients with Borrmann large type III and IV gastric cancers. *World J Gastrointest Oncol*. 2024;16(4):1281–95.
- Cui H, Liang W, Cui J, et al. Safety and feasibility of minimally invasive gastrectomy after neoadjuvant immunotherapy for locally advanced gastric cancer: a propensity score-matched analysis in China. *Gastroenterol Rep*. 2024;12:goae005.
- Lin JL, Lin M, Lin GT, et al. Oncological outcomes of sequential laparoscopic gastrectomy after treatment with camrelizumab combined with nab-paclitaxel plus S-1 for gastric cancer with serosal invasion. *Front Immunol*. 2024;15:1322152.
- Sun YQ, Zhong Q, Lv CB, et al. The safety and efficacy of neoadjuvant immunotherapy following laparoscopic gastrectomy for gastric cancer: a multicenter Real-world clinical study. *Int J Surg*. 2024;110(8):4830–8.
- Xu G, Liu T, Shen J, Guan Q. Neoadjuvant therapy with immune checkpoint inhibitors in combination with chemotherapy vs. chemotherapy alone in HER2(-) locally advanced gastric cancer: a propensity score-matched cohort study. *Chin Med J (Engl)*. 2024. <https://doi.org/10.1097/CM9.000000000000030>
- Jiang Q, Liu W, Zeng X, et al. Safety and efficacy of Tislelizumab plus chemotherapy versus chemotherapy alone as neoadjuvant treatment for patients with locally advanced gastric cancer: real-world experience with a consecutive patient cohort. *Front Immunol*. 2023;14:1122121.
- Su J, Guo W, Chen Z, et al. Safety and short-term outcomes of laparoscopic surgery for advanced gastric cancer after neoadjuvant immunotherapy: a retrospective cohort study. *Front Immunol*. 2022;13:1078196.
- Zhang X, Zhang C, Hou H, et al. Neoadjuvant PD-1 blockade plus chemotherapy versus chemotherapy alone in locally advanced stage II-III gastric cancer: a single-centre retrospective study. *Transl Oncol*. 2023;31:101657.
- Lin JX, Tang YH, Zheng HL, et al. Neoadjuvant camrelizumab and apatinib combined with chemotherapy versus chemotherapy alone for locally advanced gastric cancer: a multicenter randomized phase 2 trial. *Nat Commun*. 2024;15(1):41.

28. Wang C, Wang Z, Zhao Y, Wang F. Neoadjuvant. PD-1 inhibitor plus apatinib and chemotherapy versus apatinib plus chemotherapy in treating patients with locally advanced gastric cancer: A Prospective, cohort study. *J Gastric Cancer*. 2023;23(2):328–39.
29. Xiong H, Li Y. Neoadjuvant. PD-1 inhibitor plus apatinib and chemotherapy versus apatinib plus chemotherapy versus chemotherapy alone in patients with locally advanced gastric cancer. *Am J Cancer Res*. 2023;13(8):3559–70.
30. Sun Y, Fan Y, Ye Z, Dong J, Zhang L, Peng Y. Apatinib plus chemotherapy versus chemotherapy alone as neoadjuvant therapy in locally advanced gastric carcinoma patients: a prospective, cohort study. *Ir J Med Sci*. 2023;192(3):1033–40.
31. Wang Z, He T, Yu D, Qin X, Geng A, Yang H. Neoadjuvant apatinib plus tegafur/gimeracil/oteracil potassium (S–1)/oxaliplatin chemotherapy vs. chemotherapy alone in patients with locally advanced gastric carcinoma. *Exp Ther Med*. 2022;24(4):625.
32. Zhang Y, Zhang B, Yang J, Zhang J, Zhang W. Perioperative safety and effectiveness of neoadjuvant therapy with fluorouracil, leucovorin, oxaliplatin, and docetaxel plus apatinib in locally advanced gastric cancer. *Cancer Manag Res*. 2021;13:2279–86.
33. Tang YH, Wang FH, Lin GJ, et al. A multicenter, prospective study of apatinib plus chemotherapy as neoadjuvant treatment for locally advanced gastric cancer. *Ann Oncol*. 2020;31(S6):S1300.
34. Zhang J, Yang D, Zhao Q, Zhang HW, Zheng ZC. A prospective, multicenter, non-randomized, controlled trial of apatinib plus perioperative chemotherapy with FLOT protocol and surgery for the treatment of stage III gastric cancer. *Ann Oncol*. 2020;31(S4):S905.
35. Wang FH, Zhang XT, Li YF, et al. The Chinese society of clinical oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. *Cancer Commun*. 2021;41(8):747–95.
36. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science*. 2020. <https://doi.org/10.1126/science.aax0182>.
37. Zou K, Yang S, Zheng L, Yang C, Xiong B. Efficacy and safety of target combined chemotherapy in advanced gastric cancer: a meta-analysis and system review. *BMC Cancer*. 2016;16(1):737.
38. Kamran SC, Hong TS, Wo JY. Advances in the management of gastric and gastroesophageal cancers. *Curr Oncol Rep*. 2016;18(2):13.
39. Roviello G, Aprile G, D'Angelo A, et al. Human epidermal growth factor receptor 2 (HER2) in advanced gastric cancer: where do we stand? *Gastric Cancer*. 2021;24(4):765–79.
40. Li J, Qin S, Wen L, et al. Safety and efficacy of apatinib in patients with advanced gastric or gastroesophageal junction adenocarcinoma after the failure of two or more lines of chemotherapy (AHEAD): a prospective, single-arm, multicenter, phase IV study. *BMC Med*. 2023;21(1):173.
41. Lin JX, Xu YC, Lin W, et al. Effectiveness and safety of apatinib plus chemotherapy as neoadjuvant treatment for locally advanced gastric cancer: a nonrandomized controlled trial. *JAMA Netw Open*. 2021;4(7):e2116240.
42. Kim ST, Cristescu R, Bass AJ, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med*. 2018;24(9):1449–58.
43. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet*. 2021;398(10294):27–40.
44. Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastro-oesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. *JAMA Oncol*. 2018;4(5):e180013.
45. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2022;23(2):234–47.
46. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G. Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity*. 2013;39(1):74–88.
47. Ramakrishnan R, Huang C, Cho HI, et al. Autophagy induced by conventional chemotherapy mediates tumor cell sensitivity to immunotherapy. *Cancer Res*. 2012;72(21):5483–93.
48. Janjigian YY, Kawazoe A, Yanez P, et al. The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer. *Nature*. 2021;600(7890):727–30.
49. Liu Y, Li C, Lu Y, Liu C, Yang W. Tumor microenvironment-mediated immune tolerance in development and treatment of gastric cancer. *Front Immunol*. 2022;13:1016817.
50. Yang K, Halima A, Chan TA. Antigen presentation in cancer - mechanisms and clinical implications for immunotherapy. *Nat Rev Clin Oncol*. 2023;20(9):604–23.
51. Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70(2):86–104.
52. Naimi A, Mohammed RN, Raji A, et al. Tumor immunotherapies by immune checkpoint inhibitors (ICIs): the pros and cons. *Cell Commun Signal*. 2022;20(1):44.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.