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Efficacy and safety of XELOX combined with neoadjuvant radiotherapy versus neoadjuvant chemotherapy in locally advanced gastric cancer

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Abstract

Background The work aimed to compare the efficacy and safety of chemotherapy regimen (oxaliplatin + capecitabine, XELOX) combined with neoadjuvant radiotherapy (NART) and neoadjuvant chemotherapy (NACT) in locally advanced gastric cancer.

Methods We retrospectively analyzed clinical data from patients with locally advanced gastric cancer who underwent radical gastrectomy with D2 lymph node dissection at our center between January 2019 and December 2020. The study compared tumor markers, postoperative pathology, short-term efficacy, postoperative complications, and hospital stay between the chemoradiotherapy (CRT, XELOX + NART) group and the NACT-only group. Pearson correlation coefficients was used to analyze the correlations between clinical variables and tumor biomarkers. Inverse probability weighting (IPW) was used to adjust for confounding factors.

Results A total of 409 patients were included, with 369 (90.2%) in the NACT group and 40 (9.8%) in the CRT group. Significant correlations were found between clinical variables and tumor biomarkers, which may help identify potential prognostic factors for gastric cancer treatment. After IPW adjustment, baseline characteristics were similar between groups. The negative conversion rate of CEA-positive patients was significantly higher in the CRT group (38.1% vs. 11.8%, $P < 0.001$). The rate of pathological complete response was also higher in the CRT group (15.8% vs. 4.7%, $P = 0.017$). Postoperative pathological stages ypT0 and T1 were observed in 35.5% of the CRT group compared to 13.5% in the NACT group ($P = 0.031$). The CRT group had a lower average number of lymph nodes dissected (17 vs. 24,

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$P < 0.001$) but a higher ypN0 rate (60.3% vs. 39.8%, $P = 0.024$). The proportion of patients with tumor regression grade (TRG) 0–1 was higher in the CRT group (60.3% vs. 24.3%, $P = 0.003$). The R0 resection rate after IPW was 100% in the CRT group versus 96.5% in the NACT group ($P = 0.001$). No significant differences were found between the CRT and NACT groups in nerve invasion, vascular embolus, peritoneal invasion, bone marrow suppression, nausea, vomiting, esophagitis, diarrhea, other adverse reactions, postoperative complications, or average hospitalization time. The CRT group showed superior disease-free survival while no overall survival advantage ($P < 0.05$).

Conclusions The XELOX regimen combined with neoadjuvant chemoradiotherapy provided superior downstaging, short-term pathological response, and local control benifits compared to perioperative chemotherapy alone, with similar surgical safety profiles.

Keywords Locally advanced gastric cancer, Neoadjuvant chemoradiotherapy, Perioperative chemotherapy, Short-term efficacy

Background

Gastric cancer (GC) is one of the most common malignant tumors in China. 70.8% of the patients were at the locally advanced stage when first diagnosed [1–3]. The MAGIC [4] and FLOT4-AIO studies [5] confirm that preoperative neoadjuvant chemotherapy has significant downstaging effects for locally advanced gastric cancer. An R0 resection rate of 85% resulted in improved survival outcomes. The CROSS study [6] shows that preoperative chemoradiotherapy (CRT) for cancer of the esophagus and esophagogastric junction achieves a pathological complete response rate (PCR) of 29%. It is translated into survival benefits.

Several international phase-II clinical trials [7–9] have shown that the rate of PCR of GC patients is higher after receiving preoperative CRT. However, it is still controversial whether perioperative neoadjuvant chemotherapy (NACT) plus concurrent radiotherapy improves the curative effects of patients with locally advanced GC.

According to the 2019 NCCN Guidelines for Gastric Cancer, there are multiple perioperative chemotherapy options. The patients in this study were treated by several oncologist groups in hospital, resulting in a variety of treatment regimens, based on personal medication experience. XELOX was selected for all patients recepted radiochemotherapy in a single radiotherapy group, according to the proceeding clinical research NCT01815853. The reason comes from the result of CLASSIC study which demonstrated a significant improvement in 5-year overall survival (OS) and prolongs disease-free survival (DFS) for gastric cancer patients receiving adjuvant chemotherapy with capecitabine combined with oxaliplatin (XELOX) compared to surgery alone [10]. The work compared the efficacy and safety of XELOX regimen combined with concurrent radiotherapy and perioperative chemotherapy in patients with resectable GC. The evidence strength was low as retrospective studies were susceptible to factors of bias. We adopted propensity score matching and inverse probability weighting for analysis. Consequently, the bias was reduced between the two groups, and the statistical power was improved to provide a basis for clinical selection.

This study includes gastric cancer patients undergoing preoperative chemoradiotherapy, including those with gastroesophageal junction cancer. Through this retrospective study, we aim to explore the efficacy and safety of incorporating radiotherapy into neoadjuvant treatment for gastric cancer. The findings will provide evidence for optimizing treatment strategies and contribute to ongoing phase III randomized controlled trials of preoperative chemoradiotherapy for gastric cancer, such as POET, NeoCRAG, and PREACT.

Methods

Research objects and data collection

This retrospective study included 3,976 patients with histologically confirmed esophagogastric junction adenocarcinoma and gastric adenocarcinoma from 2019 to 2020. Patients who did not undergo surgical treatment (including those with distant metastasis, recurrence, or loss to follow-up) were excluded, totaling 2,765 cases. Among the remaining 1,211 patients who underwent surgery, 802 patients who received palliative gastrectomy (for bleeding or obstruction) or did not receive neoadjuvant therapy were further excluded. Ultimately, 409 patients who received neoadjuvant therapy followed by radical surgery were included in the analysis (Fig. 1). Inclusion criteria: (1) Patients with clinical stage II-III gastric adenocarcinoma confirmed by Multidisciplinary Team (MDT) consultation (the 8th edition of the American Joint Committee on Cancer (AJCC)). The same was for those with esophagogastric junction adenocarcinoma. (2) ECOG score ≤ 2. (3) All patients received radical gastrectomy with D2 lymph node dissection. (4) No history of other concurrent malignancies and chemoradiotherapy.

Exclusion criteria: (1) Patients receiving palliative surgery. (2) Patients with double primary malignant tumors. Grouping: Cases were screened according to inclusion and exclusion criteria and divided into the neoadjuvant

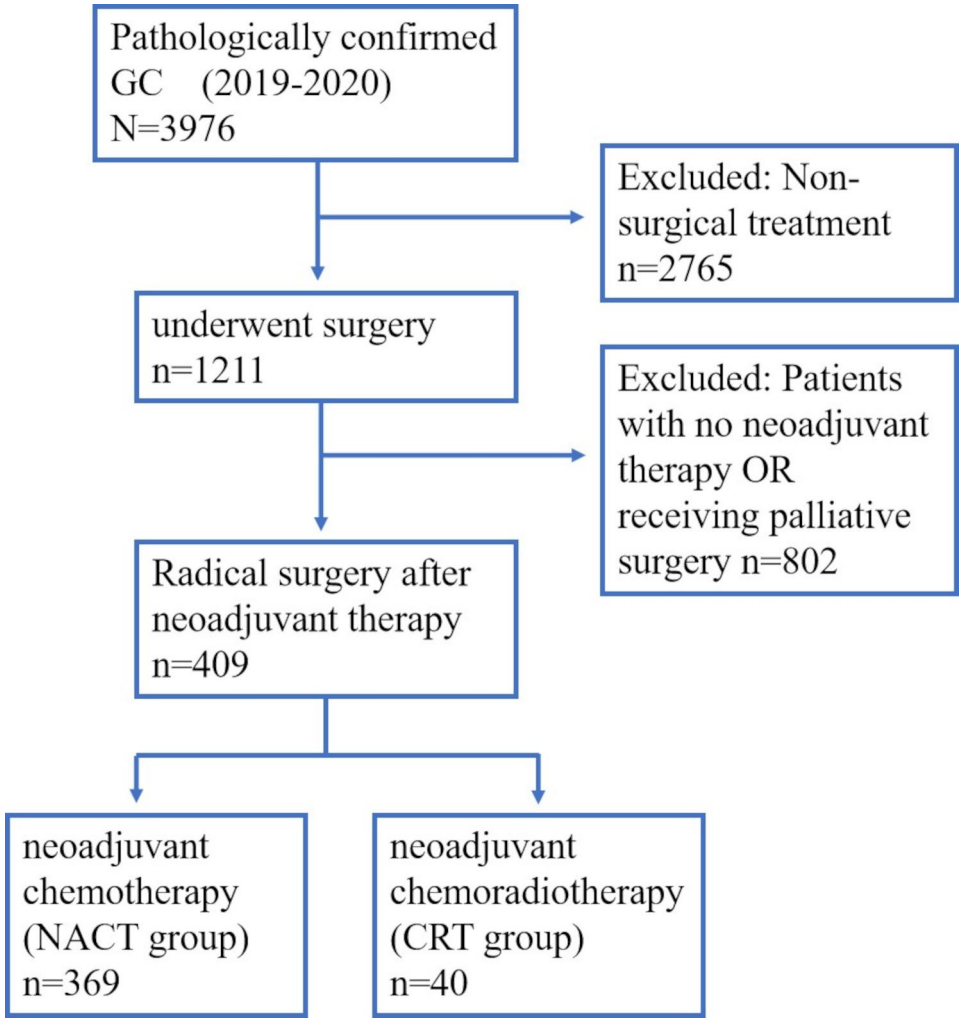

Fig. 1 The flowchart of patient selection

chemotherapy group (NACT group) and neoadjuvant chemoradiotherapy group (CRT group). The clinical and pathological characteristics of all patients were recorded in detail in the surgical and medical records (e.g., age, sex, stage, tumor location, CEA, CA199, CA724 before and after neoadjuvant therapy, postoperative pathology, and length of hospital stay).

Radiotherapy technology and target area delineation

The radiotherapy treatment was intensity-modulated radiation therapy (IMRT) or volume-modulated arc therapy (VMAT) implemented by a 6MV linear accelerator. All patients received radiation doses of 39.6–50.4 Gy/1.8–2.0 Gy/22–28 times/5–6 weeks. The clinical target volume (CTV) included tumor and regional lymph nodes /metastasis areas determined by enhanced CT, Positron Emission Tomography/Computed Tomography (PET/CT), or endoscopic ultrasonography. The delineation was from the expert consensus of American Society for Radiation Oncology (ASTRO) [11] and European Organisation for Research and Treatment of Cancer - Radiation Oncology Group (EORTC-ROG) [12].

CTV delineation of the primary tumor included at least 3 cm of mucosa proximal to the tumor. Regional lymph-node CTV selectively included perigastric, abdominal cavity, splenic hilum and artery, hepatic duodenum or hepatic hilar, and some retropancreatic and para-aortic lymph nodes according to the lesion location. The planning target volume (PTV) was 0.5 cm outside the CTV and optimized to ensure the PTV with the prescribed dose exceeded 95%. The average dose per kidney was < 18 Gy, and that to the liver was < 25 Gy. Small bowel volume ≤ 195 cm3 receiving > 45 Gy, and maximal spinal cord dose ≤ 45 Gy. The radiotherapy plan was decided by two clinicians with more than 10 years of experience in radiotherapy. The irradiation field, irradiation dose, and tumor imaging were reviewed before treatment. We had daily cone-beam CT (CBCT) position verification.

Chemotherapy regimen

All patients in the NACT group received 2–6 cycles of neoadjuvant chemotherapy and 4–12 cycles of postoperative adjuvant chemotherapy. Chemotherapy regimen included single-drug S-1; oxaliplatin + capecitabine (XELOX), oxaliplatin + S-1 (SOX), paclitaxel + cisplatin (TP), oxaliplatin + fluorouracil (FOLFOX); docetaxel + oxaliplatin + S-1 (DOS), docetaxel + oxaliplatin + fluorouracil (FLOT). 1–2 cycles of concurrent XELOX chemotherapy were given during radiotherapy, and 2–6 cycles of adjuvant chemotherapy were offered with the same program after surgery in the CRT group.

Follow-up and short-term efficacy evaluation

All patients were followed up from the date of diagnosis until death. Follow-up was performed every 3 months for the first 2 years, then every 6 months until 5 years, and annually thereafter. It was conducted through outpatient follow-up or telephone follow-up. Repeated examinations included a complete taking of medical history, physical examination, serum tumor biomarkers, CT scans from neck to pelvic, and intermittent endoscopy. Local recurrence was defined as recurrence in the anastomotic stoma, duodenal stump, tumor bed, residual stomach, and lymph nodes in the abdominal cavity. Distant metastasis was defined as metastasis of distant lymph nodes, distant organs, or sites outside the abdominal cavity. Peritoneal metastases were excluded [13].

OS was defined from the start of treatment to death from any cause. Short-term curative effect observation indicators included changes in tumor markers before and after surgery, tumor regression grade (TRG) grade, rate of pN0, nerve invasion, vascular tumor embolus, peritoneal invasion, and surgical margin. Long-term curative effect observation indicators included overall survival (OS) and disease-free survival (DFS). The safety evaluation included hematological toxicity of chemoradiotherapy, gastrointestinal reactions, postoperative complications, and length of hospital stay.

Statistical methods

All statistical analysis was performed using R language software (version 4.2.2). Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation. Continuous variables not normally distributed were represented by median and quartile M (P 25, P 75). Significant differences between groups were tested with Mann-Whitney U, and the $\chi 2$ test was used for categorical variables.

The work adopted propensity score matching (PSM) and inverse probability weighting (IPTW) to reduce the potential bias between the two groups. The influence of confounding factors was balanced to baseline data on the prognostic comparison. Propensity values were calculated by a multivariate logistic regression model. Included independent variables contained potential confounding factors affecting survival outcomes (e.g., "gender", "age", "T stage", "N stage", "primary tumor site", and "CEA, CA199, and CA724 before the treatment").

Standardized mean difference (SMD) was used to evaluate the balance of confounding variables weighted by the inverse probability of samples of the two groups. SMD ≤ 10 and 20% were considered to be ideally balanced and within an acceptable range, respectively. Statistical analysis was performed using the weighted chi-square test or weighted rank sum test for inter-group comparisons of surgical outcomes after inverse probability weighting. It was supported by the survey package of the R language. The Kaplan-Meier survival curve was drawn using the survminer package, and the test method was the log-rank test. Two-sided $P < 0.05$ was considered the difference was statistically significant.

Pearson correlation coefficients were chosen to measure the linear relationship between various clinical variables and tumor biomarkers. Pearson correlation coefficient is suitable for continuous data and can effectively reflect the linear correlation between variables, including the value of phase relation, *P*-value and their statistical significance. The larger the value of$|r|$, the higher the degree of linear correlation between the variables, and $p < 0.05$, was considered the significant correlation.

Results

Clinical features and treatment

We collected cases of 3,976 patients with esophagogastric junction adenocarcinoma and gastric adenocarcinoma diagnosed by MDT. Patients with distant metastases, recurrences, and those lost to follow-up were excluded. We made 1211 cases undergo radical or palliative (bleeding, obstruction) gastrectomy. Preoperative neoadjuvant therapy was used to treat 409 cases among them, and they were analyzed. NACT was applied in 369 (90.2%), and CRT was in 40 (9.8%) in the entire cohort. Four patients in the CRT group received radiotherapy doses of less than 40 Gy, and the rest received radiotherapy doses of more than 40 Gy. Six cases (15%) received one cycle of the XELOX regimen concurrently with chemotherapy, and the rest completed two cycles of the XELOX regimen concurrently.

We made 187 cases (50.7%) for the SOX scheme and 71 cases (19.2%) for the FLOT scheme in the NACT group. Fifty-two cases (14.1%) adopted the FOLFOX regimen, and 32 cases (8.7%) adopted the XELOX regimen. Nineteen cases (5.1%) adopted the DOS regimen, six cases (1.6%) adopted the TP regimen, and two cases (0.6%) adopted single drug S-1. The median follow-up time was 25.1 months. Baseline covariates (gender, age, T stage,

N stage, tumor location, and tumor markers) were controlled for confounding by PSM and IPTW, respectively. The SMD values decreased to less than 0.2, and the balance between groups was improved after IPTW compared with PSM. Therefore, the research results refer to the IPTW method (Fig. 2). Table 1 shows the comparison of the raw data of 409 patients with gastric cancer receiving neoadjuvant therapy and the baseline status after IPTW.

Correlation analysis and changes in tumor markers after neoadjuvant therapy

The correlation analysis between the clinical variables and tumor biomarkers yielded several statistically significant relationships in baseline. A moderate positive correlation was observed between Site and Age ($r = 0.16$, $p < 0.01$), suggesting that tumor location may have an age-related distribution. Additionally, a significant correlation was found between CEA and CA724 ($r = 0.19$, $p < 0.01$), indicating a potential interaction between these two biomarkers in this cohort. The correlation matrix reveals several statistically significant relationships among the clinical and pathological variables post-treatment. A moderate positive correlation was found between ΔCEA and CEA ($r = 0.59$, $p < 0.01$), suggesting a direct relationship between the change in CEA levels and the initial CEA measurements. Similarly, the correlation between Depth and TRG ($r = 0.55$, $p < 0.01$) indicates that deeper tumor invasion is associated with higher tumor regression grades. Significant correlations were also noted between NI and Depth ($r = 0.42$, $p < 0.01$) and between ΔCA199 and CA199 ($r = 0.22$, $p < 0.01$), highlighting potential interdependencies between nodal involvement, tumor depth, and biomarker changes (Fig. 3).

The negative rate of tumor marker CEA-positive patients was 38.1% in the CRT group after neoadjuvant chemoradiotherapy. It was higher than 11.8% of the NACT group, and the difference was statistically significant ($P < 0.001$). No significant difference existed in the changes of tumor markers CA199 and CA724 before and after neoadjuvant therapy between the two groups (Table 2 Comparison of the short-term efficacy of gastric cancer patients after neoadjuvant therapy before and after inverse probability weighting).

Short-term curative effects

R0 resection rate was processed by inverse probability weighting. The rate was 100% in the CRT group and 96.5% in the NACT group, and the difference was statistically significant ($P = 0.001$). The average number of lymph node dissection was 24 in the NACT group, which was significantly higher than that in the CRT group. The difference was statistically significant ($P < 0.001$). Both groups in the propensity score-matching cohort had

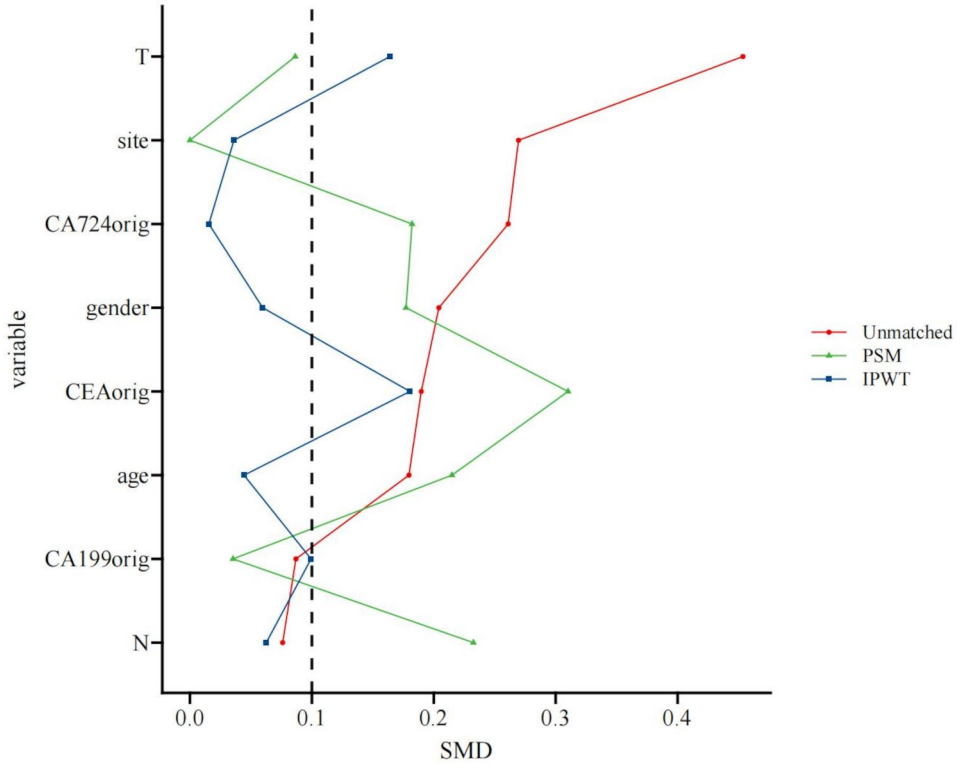

Fig. 2 Standardized mean difference: (SMD) diagram of equalization between propensity score matching (PSM) and inverse probability weighting (IPTW) groups

Table 1 Comparison of the Raw data of 409 patients with gastric cancer receiving neoadjuvant therapy and the baseline status after IPTW

	IPTW before			IPTW after		
	CRT (*n* = 40)	**NACT (*n* = 369)**	***P*-value**	**CRT (*n* = 388.2)**	**NACT (*n* = 408.6)**	***P*-value**
Gender, *n* (%)			0.199			0.721
Male	28 (70.0%)	291 (78.9%)		292.0 (75.2%)	317.7 (77.8%)	
Female	12 (30.0%)	78 (21.1%)		96.2 (24.8%)	90.9 (22.2%)	
Age (SD)	59.62(8.63)	61.20 (8.85)	0.286	61.44 (9.12)	61.04 (8.93)	0.818
Site, *n* (%)			0.115			0.849
EGJ	13 (32.5%)	168 (45.5%)		179.4(46.2%)	181.5 (44.4%)	
GA	27 (67.5%)	201 (54.5%)		208.8 (53.8%)	227.1 (55.6%)	
T Stage, *n* (%)			0.024			0.636
T2	0 (0.0%)	5 (1.4%)		0.0 (0.0%)	5.0 (1.2%)	
T3	17 (42.5%)	142 (38.5%)		162.0 (41.7%)	159.5 (39.0%)	
T4a	16 (40.0%)	201 (54.5%)		200.1 (51.6%)	216.9 (53.1%)	
T4b	7 (17.5%)	21 (5.7%)		26.0 (6.7%)	27.2 (6.7%)	
N Stage, *n* (%)			0.911			0.939
N0	1 (2.5%)	13 (3.5%)		10.3 (2.7%)	14.0(3.4%)	
N1	38 (95.0%)	344 (93.2%)		368.3 (94.9%)	381.6(93.4%)	
Nx	1 (2.5%)	12 (3.3%)		9.6 (2.5%)	13.0 (3.2%)	
CEA [IQR]	4.96 [2.24,7.07]	3.24 [1.85,6.66]	0.177	3.93 [2.20,6.59]	3.23 [1.82,6.52]	0.224
CA199 [IQR]	11.66 [2.99,32.68]	11.64 [5.74,32.67]	0.564	11.93 [2.99,30.13]	11.65 [5.72,32.76]	0.625
CA724 [IQR]	2.38 [1.28,7.95]	2.63 [1.30,7.01]	0.914	2.02 [1.11,5.11]	2.63 [1.29,7.05]	0.343

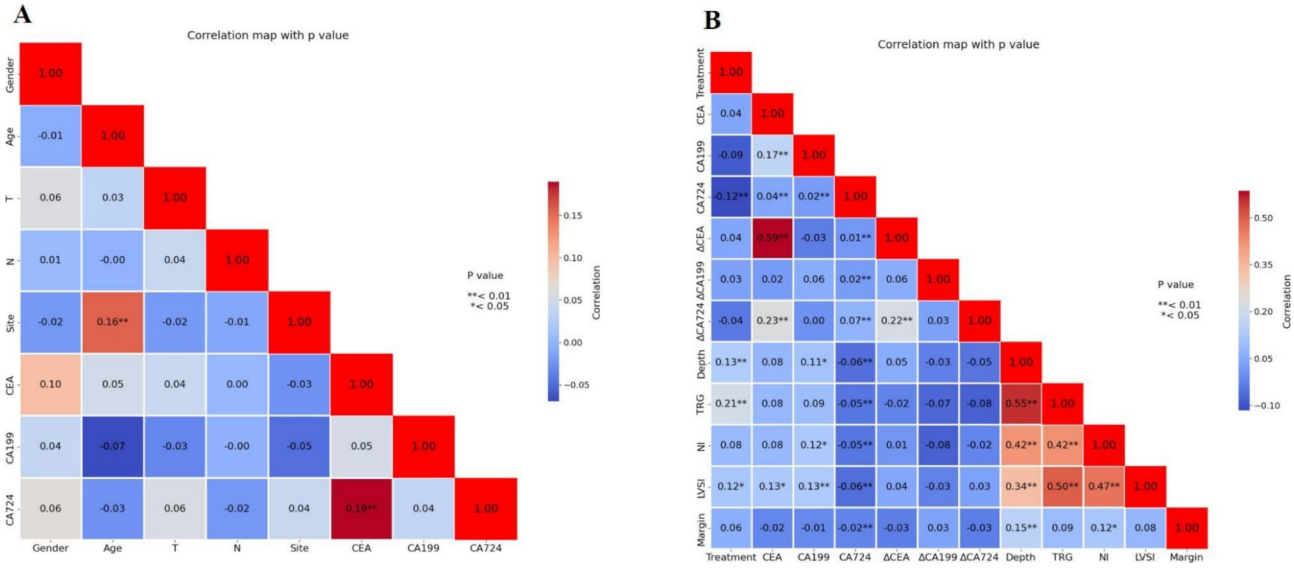

Fig. 3 Correlation heatmap with *p*-values for clinical, biomarker and pathological features variables pre and post-treatment. **A**, The correlation heatmap shows the Pearson correlation coefficients between gender, age, tumor size (T), lymph nodal involvement (N), site of tumor, and biomarker variables before treatment (CEA, CA199, CA724). **B**, The correlation heatmap displays the Pearson correlation coefficients between treatment, CEA, CA199, CA724, changes in their biomarkers (ΔCEA, ΔCA199, ΔCA724), tumor depth, tumor regression grade (TRG), nodal involvement (NI), lymphovascular space invasion (LVSI), and margin status post- treatment

similar preoperative clinical stages. However, patients receiving CRT had significantly lower final pathological stages. Additionally, patients accounted for 35.5% of the CRT group at the postoperative pathological stages of ypT0 and T1. It was significantly better than that in the NACT group (13.5%), and the difference was statistically significant ($P = 0.031$).

The ypN0 rate was 60.3% in the CRT group and 39.8% in the NACT group, and the difference was statistically significant ($P = 0.024$). The pathological response was better in the CRT group, and the patients with TRG 0 and 1 accounted for 60.3%. It was significantly higher than that in the NACT group (24.3%), and the difference was statistically significant ($P = 0.003$). The overall rate of PCR in

Table 2 Comparison of short-term efficacy in patients receiving neoadjuvant therapy for gastric cancer before and after IPTW

	IPTW before			IPTW after		
	NACT (*n* = 369)	**CRT (*n* = 40)**	***P*-Value**	**NACT (*n* = 408.6)**	**CRT (*n* = 388.2)**	***P*-Value**
ypT, *n*(%)			0.001			0.031
T0	17 (4.6%)	5 (12.5%)		19.4 (4.7%)	61.5 (15.8%)	
T1	32 (8.7%)	9 (22.5%)		35.8 (8.8%)	76.4 (19.7%)	
T2	116 (31.4%)	6 (15.0%)		127.7 (31.2%)	59.9 (15.4%)	
T3	125 (33.9%)	17 (42.5%)		137.4 (33.6%)	154.0 (39.7%)	
T4	79 (21.4%)	3 (7.5%)		88.4 (21.6%)	36.4 (9.4%)	
ypN, *n* (%)			0.079			0.06
N0	146 (39.6%)	23 (57.5%)		162.7 (39.8%)	234.2 (60.3%)	
N1	76 (20.6%)	5 (12.5%)		83.4 (20.4%)	41.0 (10.6%)	
N2	83 (22.5%)	4 (10.0%)		91.1 (22.3%)	36.5 (9.4%)	
N3	64 (17.3%)	8 (20.0%)		71.4 (17.5%)	76.6 (19.7%)	
TRG, *n* (%)			<0.001			0.003
N0	17 (4.6%)	5 (12.5%)		19.4 (4.7%)	61.5 (15.8%)	
N1	72 (19.5%)	18 (45.0%)		80.2 (19.6%)	172.6 (44.5%)	
N2	186 (50.4%)	13 (32.5%)		206.1 (50.4%)	109.5 (28.2%)	
N3	94 (25.5%)	4 (10.0%)		103.0 (25.2%)	44.6 (11.5%)	
Margin, *n* (%)			0.228			0.001
Negative	356 (96.5%)	40 (100.0%)		394.4 (96.5%)	388.2 (100.0%)	
Positive	13 (3.5%)	0 (0.0%)		14.2 (3.5%)	0.0 (0.0%)	
PNI, *n* (%)			0.089			0.234
Negative	197 (53.4%)	27 (67.5%)		219.2 (53.6%)	251.6 (64.8%)	
Positive	172 (46.6%)	13 (32.5%)		189.4 (46.4%)	136.5 (35.2%)	
LVI, *n* (%)			0.018			0.066
Negative	186 (50.4%)	28 (70.0%)		207.1 (50.7%)	264.8 (68.2%)	
Positive	183 (49.6%)	12 (30.0%)		201.5 (49.3%)	123.4 (31.8%)	
PTI, *n* (%)			0.101			0.103
Negative	359 (97.3%)	37 (92.5%)		397.6 (97.3%)	358.4 (92.3%)	
Positive	10 (2.7%)	3 (7.5%)		11.1 (2.7%)	29.7 (7.7%)	
Mean LN Removed, [IQR]	24.00 [19.00,31.00]	17.00 [16.00,19.25]	<0.001	24.00 [19.00, 31.00]	17.00 [16.00,20.00]	<0.001
CEA*, [*n*, %]	43 (11.7%)	17 (42.5%)	<0.001	48.1 (11.8)	148.0 (38.1)	<0.001
CA199*, [*n*, %]	46 (12.5%)	7 (17.5%)	0.368	52.1 (12.7)	51.0 (13.1)	0.95
CA724*, [*n*, %]	44 (11.9%)	5 (12.5%)	0.915	48.5 (11.9)	46.5 (12.0)	0.984

Perineural invasion (PNI); lymphovascular invasion (LVI); Peritoneal invasion (PTI); *Negative conversion rate of CEA、CA199 or CA724 seropositive patients

the CRT group was 15.8%, which was significantly higher than that in the NACT group (4.7%). The difference was statistically significant ($P = 0.017$). No significant differences existed in nerve invasion, vascular tumor embolus, and peritoneal invasion between the two groups. Table 2 shows the comparison of the short-term curative effects of gastric cancer patients in the two groups receiving neoadjuvant therapy before and after inverse probability weighting.

Survival analysis

The median follow-up time was 53.6 months in the whole group. We found that the DFS of patients in the CRT group was significantly higher ($P < 0.05$; Fig. 4A) after adopting the IPTW method, however, there was no statistical differences between two groups in the 5-y OS of patients ($P = 0.688$; Fig. 4B). Regardless of whether it was the NACT or the CRT group, the primary cause of death was tumor-related. Figure 4 shows a survival comparison of gastric cancer patients receiving neoadjuvant therapy after inverse probability weighting.

There were differences in recurrence patterns between gastric cancer patients receiving NACT and those receiving CRT after surgery (Fig. 5). In the chemotherapy group, recurrences were predominantly observed in the abdominal lymph nodes (23.7%), liver (12.5%), lungs (8.6%), and pelvis (9.9%). In contrast, in the radiotherapy group, the highest recurrence rate was in the lungs (25%), followed by the brain and other sites (both 16.7%). The radiotherapy group showed lower proportions of peritoneal and liver metastases (both 8.3%).

Adverse reactions and surgery-related complications

Adverse reactions were similar between the two groups after IPTW matching (e.g., myelosuppression, nausea, vomiting, esophagitis, and diarrhea), and no statistical

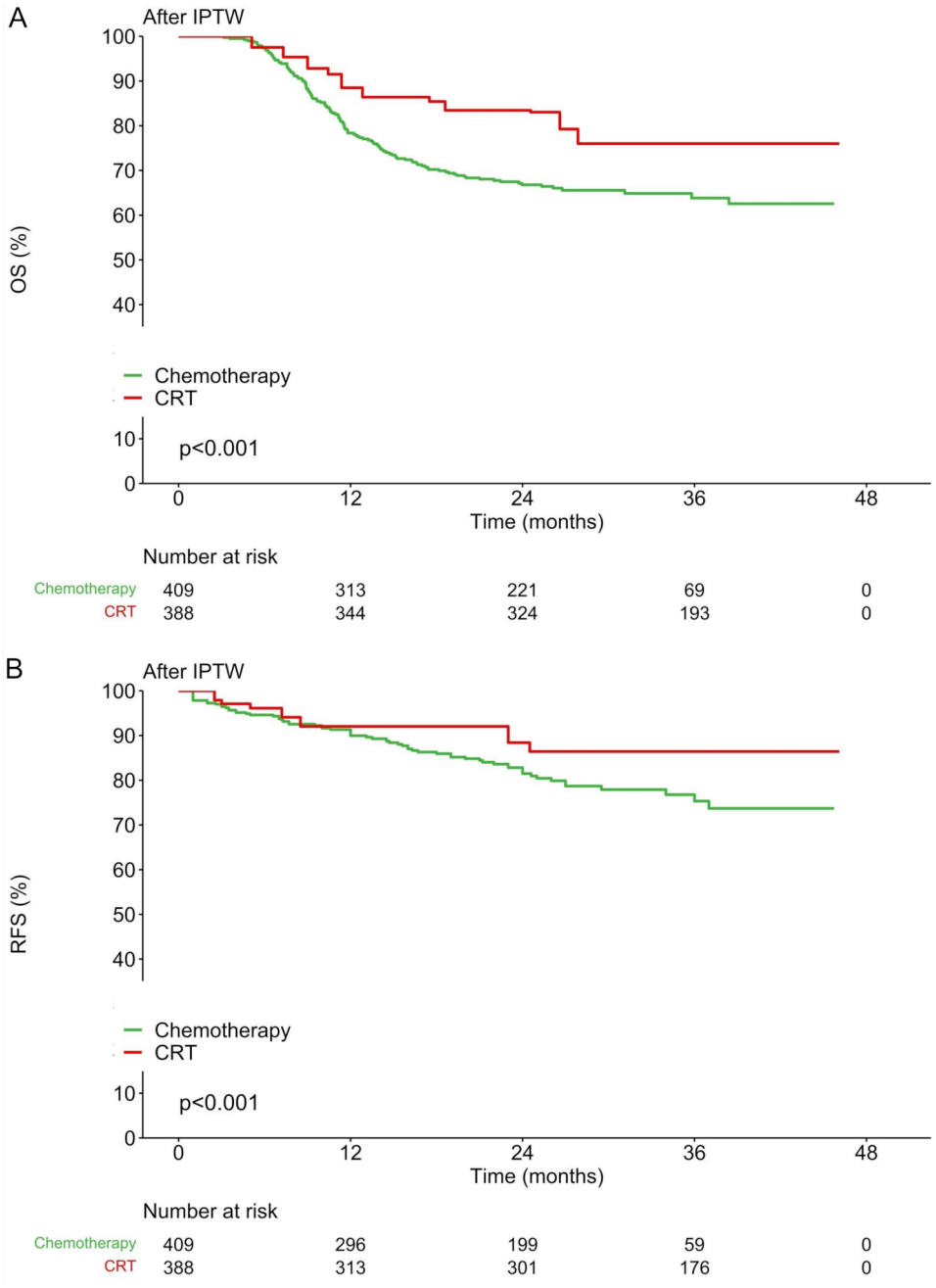

Fig. 4 Overall survival (**A**) and disease-free survival (**B**) in two group after IPTW method

difference existed. All patients in the group were followed up. One patient died in the NACT group and 0 in the CRT group. There were 9 cases of pneumonia, 3 cases of obstruction, 7 cases of fistula, 14 cases of pleural effusion, and 1 case of abdominal infection in the NACT group. Two cases of anastomotic leakage and 2 cases of pleural and peritoneal effusion existed in the CRT group.

The incidence of postoperative pneumonia was higher in the NACT group than that in the CRT group, and the difference was statistically significant ($P=0.004$). The average postoperative hospital stay was 13 days in the CRT group and 12 days in the NACT group. No statistical difference existed between the two groups ($P=0.274$). Table 3 shows the comparison of adverse reactions and postoperative complications in the two groups of gastric cancer patients receiving neoadjuvant therapy before and after inverse probability weighting.

Discussion

Surgery is currently the only possible cure for gastric cancer. The prognosis of patients undergoing surgical resection is better than that of unresectable patients even

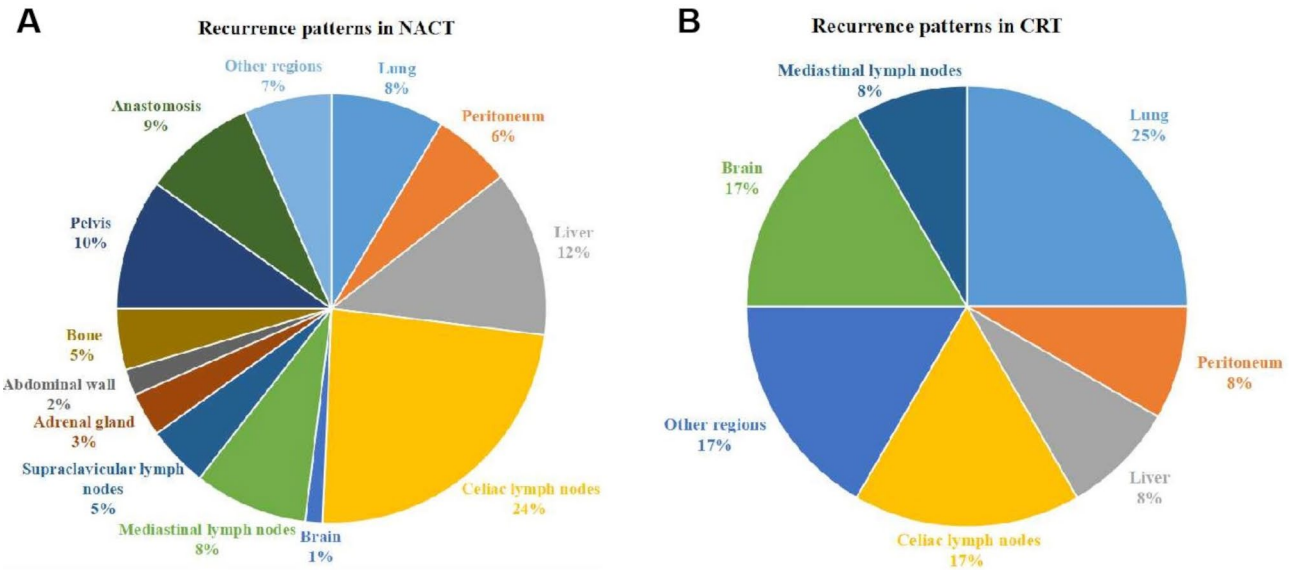

Fig. 5 Recurrence patterns in gastric cancer patients receiving adjuvant therapy after surgery. The figure illustrates the differences in recurrence proportions at various metastatic sites between the NACT and CRT

Table 3 Details of complications in the original samples before matching and after IPTW in the two groups

	IPTW before			IPTW after		
	NACT ($n=369$)	CRT ($n=40$)	*P*-Value	NACT ($n=40$)	CRT ($n=40$)	*P*-Value
Myelosuppression (*n*, %)			< 0.001			< 0.001
0	179 (48.5)	3 (7.5)		197.7 (48.4)	24.4 (6.3)	
1	101 (27.4)	22 (55.0)		111.2 (27.2)	201.5 (51.9)	
2	61 (16.5)	14 (35.0)		68.0 (16.6)	149.9 (38.6)	
3	24 (6.5)	1 (2.5)		27.3 (6.7)	12.4 (3.2)	
4	4 (1.1)	0 (0.0)		4.5 (1.1)	0.0 (0.0)	
Nausea (*n*, %)	36 (9.8)	5 (12.5)	0.583	40.0 (9.8)	39.0 (10.1)	0.957
Vomit (*n*, %)	30 (8.1)	4 (10.0)	0.684	33.2 (8.1)	33.5 (8.6)	0.918
Esophagitis (*n*, %)	7 (1.9)	3 (7.5)	0.029	8.3 (2.0)	26.6 (6.8)	0.072
Diarrhea (*n*, %)	48 (13.0)	6 (15.0)	0.724	53.7 (13.1)	74.0 (19.1)	0.401
Postoperative complications						
Pneumonia (*n*, %)	9 (2.4)	0 (0.0)	0.318	9.9 (2.4)	0.0 (0.0)	0.004
Obstruction (*n*, %)	3 (0.8)	0 (0.0)	0.567	3.3 (0.8)	0.0 (0.0)	0.095
Leak (*n*, %)	7 (1.9)	2 (5.0)	0.204	7.6 (1.8)	30.8 (7.9)	0.077
Effusion (*n*, %)	14 (3.8)	2 (5.0)	0.709	15.4 (3.8)	19.9 (5.1)	0.703
Celiac infection (*n*n, %)	2 (0.5)	0 (0.0)	0.641	2.2 (0.5)	0.0 (0.0)	0.171
Death (*n*, %)	1 (0.3)	0 (0.0)	0.742	1.0 (0.3)	0.0 (0.0)	0.332

in locally advanced gastric cancer. The resection rate of gastric cancer is significantly related to the survival of patients. Neoadjuvant therapy plays a key role in locally advanced gastric cancer, as it provides an opportunity to downstage tumors and increase resectability, leading to potentially better overall survival outcomes.

Some patients with esophagogastric junction adenocarcinoma were collected in the surgery study after chemoradiotherapy for esophageal cancer (CROSS trial [6]). The pCR rate is 23% and the R0 resection rate is 92%. It shows the benefit of preoperative CRT on overall survival in patients with esophagogastric junction adenocarcinoma. This finding reinforces the clinical value of preoperative CRT in improving the disease-free survival for patients with locally advanced gastric cancer, particularly in cases of esophagogastric junction cancers, while the addition of radiotherapy appears can not yield to significant survival benefits.

A phase-III clinical study conducted by Germany's Stahl [14] compared the efficacy and adverse reactions of preoperative chemoradiotherapy and preoperative chemotherapy. It is in patients with cT3-4NanyM0 esophagogastric junction adenocarcinoma. The study plans to enroll 354 cases, and 126 cases are finally included for the

slow enrolment. Patients recepted chemoradiotherapy had a significant higher probability of showing pathologic complete response (15.6% v 2.0%) or tumor-free lymph nodes (64.4% v 37.7%) at resection. Preoperative radiation therapy improved 3-year survival rate from 27.7 to 47.4% (log-rank $P = 0.07$, hazard ratio adjusted for randomization strata variables 0.67, 95% CI, 0.41 to 1.07). Although the study was closed early and statistical significance was not achieved, results point to a survival advantage for preoperative chemoradiotherapy compared with preoperative chemotherapy in adenocarcinomas of the esophagogastric junction.

Therefore, it is still inconclusive if perioperative chemoradiotherapy improves the curative effects of patients with locally advanced gastric cancer. No large randomized controlled study exists on preoperative CRT for GC. Consequently, we used inverse probability weighting to process the results of the retrospective work after CRT and NACT in patients with locally advanced GC.

The retrospective work in our center showed that patients with ypT0 and ypT1 receiving preoperative CRT accounted for 35.5% in the CRT group. It was significantly better than that in the NACT group (13.5%). The overall rate of PCR was 15.8% in the CRT group, which was significantly higher than 4.7% in the NACT group. This was consistent with the rate of PCR of 15.6% reported by Stahl et al. [14] for preoperative chemoradiotherapy for esophagogastric junction cancers. It was the same for the rate of PCR of 16% for gastric adenocarcinoma patients in a phase-II clinical study led by Maurel in Spain [15]. Nearly 60% of the cases included in the work were T4 patients. These findings provide further evidence that preoperative chemoradiotherapy (CRT) is associated with superior pathological response rates compared to neoadjuvant chemotherapy (NACT), especially in patients with advanced-stage disease (T4). This strengthens the case for incorporating CRT into treatment regimens for gastric cancer, particularly for patients with more advanced tumor stages. Retrospective studies by Martin et al. [16] showed that R0 resection was an independent prognostic factor for T4 patients.

Ikoma [17] found that both cN0 and ypN0 patients have better survival than N + patients. Therefore, the status of ypN0 obtained after neoadjuvant therapy is an important symbol reflecting the curative effects of preoperative treatment on gastric cancer. The R0 resection rate is 100% in the CRT group. Patients undergoing CRT have significantly less visible lymph node dissection intraoperatively than patients undergoing NACT. The pN0 rate (60.3%) in the CRT group is significantly higher than that in the NACT group (39.8%). Neoadjuvant CRT has better downstaging effects than NACT. These factors may play an important role in reducing the local recurrence rates and affecting survival [17–19]. The higher pN0 rate observed in the CRT group is particularly important, as it suggests a better overall prognosis for patients with gastric cancer undergoing preoperative CRT. This finding has significant clinical implications, as it provides support for incorporating CRT into treatment plans for gastric cancer patients, particularly in terms of improving nodal status and reducing recurrence.

The mechanisms underlying CEA and CA19-9 are comparable to the mechanisms underlying tumor invasion and metastasis [20–22]. Numerous previous studies assessed pre-operative serum tumor marker levels as risk factors for recurrence or metastasis [23, 24]; however, few studies investigated the association between post-operative positive tumor markers and recurrence or metastasis [25, 26]. Observing the changes of tumor markers before and after treatment is helpful for early detection and timely intervention, may improve the survival rate of patients with recurrence or metastasis of gastric cancer, following radical resection.The normalization rate of CEA after neoadjuvant therapy was significantly higher in the CRT group than that in the NACT group in the work. It further supported that the CRT group had a better prognosis. The follow-up time was insufficient, and the median survival time had not yet been reached in the two groups. However, the DFS and OS of the CRT group were significantly better than those of the NACT group after IPTW weighting. Statistical differences existed and had a certain correlation with the good pathological response of the CRT group.

Moreover, there are no statistically significant differences in surgical complications and surgery-related mortality between patients receiving CRT and those receiving NACT considering surgery-related adverse reactions. Postoperative hospital stay was not significantly longer in the CRT group than that in the NACT group. This was consistent with the results reported by Ikoma et al. that preoperative chemoradiotherapy for gastric cancer does not increase postoperative anastomotic leakage rates or peritoneal effusion [16]. Additionally, the safety of preoperative CRT was also confirmed in the TOPGEAR trial [27], a phase-III clinical study of gastric cancer.

This study is a retrospective analysis with the following limitations: Preoperative chemotherapy is an accepted standard in the treatment of localized esophagogastric adenocarcinoma. Adding radiation therapy to preoperative chemotherapy appears promising, but its definitive value remains unknown. Additionally, most surgeons are concerned that radiotherapy-induced edema may increase surgical difficulty and the risk of postoperative complications. As a result, far more patients received neoadjuvant chemotherapy (NACT) than CRT in routine clinical practice, leading to a significant imbalance in the number of cases between the two groups. Furthermore, data bias caused by treatment heterogeneity is another

limitation of this retrospective study. This study used varying treatment regimens based on oncologists' experience, with XELOX selected for all patients in the radiotherapy group, following clinical trial NCT01815853. The choice was supported by the CLASSIC study, which showed that XELOX significantly improved 5-year overall and disease-free survival in gastric cancer patients compared to surgery alone [10]. PSM and IPTW were used to exert confounding control on baseline covariates (gender, age, patients undergoing NACT far more than those of CRT, T stage, N stage, tumor location, and tumor markers) to admin confounding factors.The SMD values decreased to less than 0.2 after IPTW compared with PSM, and the balance between groups was improved. Therefore, the research results referred to the IPTW method. It was used to correct the imbalance of the baseline data. Some confounding factors remained to affect the results. Thirdly, the whole group of patients with gastric cancer did not undergo diagnostic laparoscopy at the initial diagnosis. However, the coincidence was only 60-70% between preoperative clinical staging and pathological staging [28–30]. We used the same MDT team combined with CT, PET-CT, and ultrasonography to conduct clinical staging on the baseline status in the two groups of patients. However, the bias of staging existed, which affected the selection of treatment decisions. Finally, we could not assess and grasp the physical and economic status of patients, the choice of chemotherapy regimens by doctors, and the completeness of the whole treatment in collecting retrospective data. All of these have affected the results. The work used single-center data, and IPTW could not replace prospective RCT.

Conclusions

In summary, neoadjuvant CRT for locally advanced GC had better disease control rate while seems no overall survival benefits than perioperative NACT. It was comparable to the NACT group concerning the safety of treatment. The work used single-center data, and IPTW could not replace prospective RCT. The ongoing multicenter phase-III randomized controlled TOPGEAR and CRITICS-II trials were used to observe the curative effects and long-term survival of perioperative NACT and CRT. The trials are expected to collectively provide valuable and high-quality data for determining optimal neoadjuvant therapy for gastric cancer.

Abbreviations

AJCC	American Joint Committee on Cancer
CBCT	Cone-Beam Computed Tomography
CEA	Carcinoembryonic Antigen
CRT	Chemoradiotherapy
CT	Computed Tomography
CTV	Clinical Target Volume
DFS	Disease-Free Survival
D2	A type of lymph node dissection (D2 lymph node dissection)
DOS	Docetaxel + Oxaliplatin + S-1
EORTC-ROG	European Organisation for Research and Treatment of Cancer - Radiation Oncology Group
FLOT	Docetaxel + Oxaliplatin + Fluorouracil
FOLFOX	Oxaliplatin + Fluorouracil
GC	Gastric Cancer
IMRT	Intensity-Modulated Radiation Therapy
IPW	Inverse Probability Weighting
MDT	Multidisciplinary Team
NACT	Neoadjuvant Chemotherapy
NART	Neoadjuvant Radiotherapy
OS	Overall Survival
PET/CT	Positron Emission Tomography/Computed Tomography
PCR	Pathological Complete Response
PSM	Propensity Score Matching
PTV	Planning Target Volume
SMD	Standardized Mean Difference
SOX	S-1 + Oxaliplatin
TRG	Tumor Regression Grade
TP	Paclitaxel + Cisplatin
VMAT	Volume-Modulated Arc Therapy
XELOX	Oxaliplatin + Capecitabine

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Author contributions

Study concept and design (YFL, XSW, XQD), acquisition of data (SSB, SYW, TW, HX, ZDZ, CS, XCT, YC), analysis and interpretation of data (SSB, SYW, TW, XQD), drafting of the manuscript (SSB, SYW), critical revision of the manuscript for important intellectual content (YFL, XSW, XQD), and study supervision (YFL, XSW, XQD). All authors read and approved the final manuscript.

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Data availability

Anonymized data can be available from the corresponding author upon reasonable request.

Declarations

Ethical recognition and consent to participate

This study was approved by the Ethics Committee of Henan Cancer Hospital (approval number: 2024 – 102), Patients were consented by an informed consent process that was reviewed by the Ethics Committee of Henan Cancer Hospital and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

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