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Evaluating the efficacy and safety of neoadjuvant immunochemotherapy versus chemotherapy in locally advanced gastric cancer undergoing radical gastrectomy: a retrospective study

Chaofeng Li[1,2†], Yu Duan[2,3†], Shengnan Zhou[2], Tao Tang[2], Yinmo Yang[1*] and Lei Zhou[2*]

Abstract

Background Locally advanced gastric cancer (LAGC) is challenging to treat, with neoadjuvant chemotherapy (NCT) improving survival. Recent advances suggest that neoadjuvant immunochemotherapy (NICT) may enhance treatment outcomes. This study compares the efficacy and safety of NICT with NCT in LAGC patients who received radical surgery.

Methods We retrospectively analyzed 67 LAGC patients treated at China-Japan Friendship Hospital from January 2023 to January 2024. Patients were divided into two groups: NICT (chemotherapy plus PD-1/PD-L1 inhibitors) and NCT (standard chemotherapy). We compared pathological complete response (pCR), postoperative recovery, complications, and laboratory markers.

Results The NICT group demonstrated a significantly higher pCR rate (25.7% vs. 6.2%, $P=0.032$) compared to the NCT group. Furthermore, the NICT group showed reduced rates of nerve and vascular invasion (28.6% vs. 31.4%, $P=0.041$). Tumor regression grades ($P=0.001$) were more favorable in the NICT group, with earlier ypN and ypTNM stages ($P=0.001$). Laboratory analysis revealed a greater reduction in tumor markers CEA and CA19-9 in the two groups, with decreased white blood cell counts and elevated liver enzymes. Surgical outcomes, including operative time, blood loss, and hospital stay, were similar between the two groups, with no significant increase in postoperative complications in the NICT group.

Conclusion NICT is more effective than traditional NCT in improving pathological responses and reducing tumor burden in LAGC patients. It also reduced nerve and vascular invasion without increasing surgical risks.

Introduction

Gastric cancer ranks as the fifth most common malignant tumor worldwide in both incidence and mortality, with approximately 970,000 new cases and 660,000 deaths reported annually [1].In China, the burden of gastric cancer is particularly significant, with an estimated 358,700 new cases and 260,400 deaths projected in 2022, accounting for 7.43% of all new cancer cases and 10.11% of cancer-related deaths [2]. This persistently high incidence

†Chaofeng Li and Yu Duan contributed equally to this work.

*Correspondence:
Yinmo Yang
yangyinmosci@bjmu.edu.cn
Lei Zhou
zhoulei1971@hotmail.com
[1] General Surgery, Peking University First Hospital, Bejing, China
[2] Gastrointestinal Surgery, China-Japan Friendship Hospital, Beijing, China
[3] Capital Medical University, Beijing, China

underscores the urgent need for effective treatment strategies, as gastric cancer is anticipated to remain one of the five most common cancers by 2032 [3].

Locally advanced gastric cancer constitutes the predominant clinical profile of the disease in China. Current management strategies emphasize a multidisciplinary approach with surgery as the cornerstone [4]. However, survival outcomes remain suboptimal in the patients with locally advanced gastric cancer [5]. Preoperative neoadjuvant chemotherapy has shown the potential to reduce tumor staging, enhance R0 resection rates, and improve overall survival, supporting its inclusion in treatment guidelines for locally advanced gastric cancer [6, 7].

Recent advancements in the molecular classification of gastric cancer and findings from clinical studies on immunotherapy have expanded therapeutic options. For patients with gastric cancer or gastroesophageal junction adenocarcinoma (GEJAC) exhibiting deficient mismatch repair (dMMR) or high microsatellite instability (MSI-H), perioperative immunotherapy is emerging as a promising alternative [4]. Notable strategies include immune checkpoint inhibitors (ICIs), adoptive cell therapy (ACT), chimeric antigen receptor T-cell (CAR-T) therapy, and cancer vaccines [8, 9]. Preliminary studies suggest that neoadjuvant immunotherapy may achieve a higher pathological complete response (pCR) rate before surgery by modulating the tumor microenvironment, inhibiting tumor progression, and reducing the risk of metastasis [10]. The pCR rate, a key marker of neoadjuvant therapy efficacy, is strongly associated with long-term survival and recurrence risk [11].

Given this context, the investigation of neoadjuvant immunochemotherapy (NICT) for locally advanced gastric cancer has garnered substantial research interest [12, 13]. This study aims to critically compare the efficacy of neoadjuvant immunochemotherapy (NICT) with that of neoadjuvant chemotherapy alone (NCT) in patients with locally advanced gastric cancer. Specifically, the study will examine the effects of these approaches on pathological response, neural and vascular infiltration and postoperative complications. The findings are expected to provide new insights and a stronger rationale for optimizing neoadjuvant treatment strategies for locally gastric cancer.

Patients and Methods

Patients

This retrospective clinical study included patients treated with surgery for gastric cancer following neoadjuvant therapy in the Department of Gastrointestinal Surgery at China-Japan Friendship Hospital from January 2023 to January 2024. The inclusion criteria were: (1) a pathological diagnosis of malignant tumor; (2) those who received neoadjuvant therapy; (3) with complete clinical data; (4) no concurrent malignant tumors; (5) without severe comorbidities, defined as American Society of Anesthesiologists (ASA) classification ≤ III; and (6) a preoperative Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Exclusion criteria included: (1) patients who did not undergo radical gastrectomy; (2) emergency surgery required due to gastric cancer complications (bleeding, perforation and obstruction) during treatment; and (3) patients with clinical staging other than cT2N + M0 or cT3-4bNanyM0 (as determined by CT scans and endoscopic ultrasonography) and not meeting the criteria for neoadjuvant therapy. This study received ethical approval from the China-Japan Friendship Hospital Ethics Committee (Approval No. 2024-KY-422), and all patients provided informed consent before perioperative treatment. The study flow is illustrated in Fig. 1.

Neoadjuvant therapy

All enrolled patients underwent 2–10 treatment cycles of neoadjuvant therapy that was indicated according to the Chinese Society of Clinical Oncology (CSCO) Gastric Cancer Guidelines. Due to regional disparities in health insurance coverage for immune-checkpoint inhibitors (ICIs) in China and patient concerns about immune-related adverse events (irAEs) during the informed consent process, some patients opted for neoadjuvant chemotherapy alone instead of immunochemotherapy. Chemotherapy regimens included the SOX regimen (S-1 combined with oxaliplatin), the XELOX regimen (capecitabine combined with oxaliplatin), and the FOLFOX regimen (oxaliplatin, leucovorin, and fluorouracil). Neoadjuvant immunotherapy regimens comprised programmed death-1 (PD-1) inhibitors, such as nivolumab, tirelizumab, and sintilimab, and programmed death-ligand 1 (PD-L1) inhibitors, such as envafolimab. All patients in the neoadjuvant immunochemotherapy (NICT) group received concurrent chemotherapy and immunotherapy.

Efficacy was assessed biweekly using enhanced abdominal CT based on the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Treatment-related adverse events (TRAEs) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). Furthermore, tumor regression grading (TRG) was defined from pathological results using the classical Mandard-TRG criteria, categorized as follows: TRG 1, absence of residual cancer cells with substantial fibrosis; TRG 2, scattered cancer cells within extensive fibrosis; TRG 3, more fibrosis than residual cancer cells; TRG 4, less fibrosis than residual cancer cells; and TRG 5, no tumor regression.

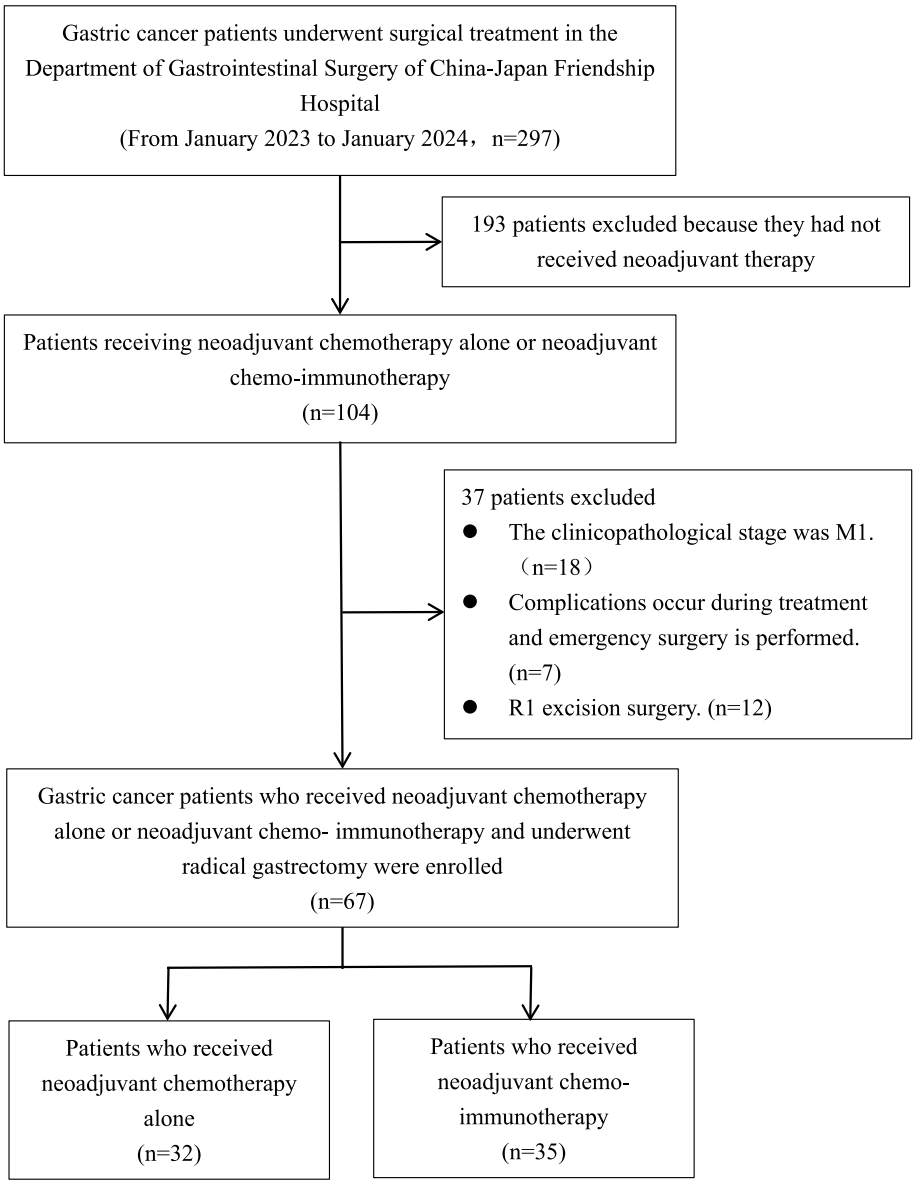

Fig. 1 Study flow chart

Laboratory parameters

Relevant laboratory parameters associated with gastric cancer were recorded, including the routine analysis of blood, tumor markers, and liver and kidney function indicators. The routine analysis of blood included peripheral white blood cell (WBC) count, neutrophil count, hemoglobin (Hb) concentration, and platelet count. Tumor markers included carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9). Liver and renal function assessments consisted of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bile acid (TBA), and creatinine (Cr) levels. Preoperative and postoperative laboratory parameters were compared between the two groups to evaluate potential differences in response to treatment.

Surgical approach

All enrolled patients underwent laparoscopic radical gastrectomy with D2 lymphadenectomy within 4–6 weeks following the completion of neoadjuvant therapy. Each procedure was performed by a chief surgeon with over ten years of extensive experience in laparoscopic gastric cancer surgery. The standardized surgical protocol followed the Japanese Gastric Cancer Treatment Guidelines

(6th Edition). Upon completion of the laparoscopic procedure, a specimen was retrieved through an upper abdominal midline incision less than 10 cm in length. Intracorporeal or extracorporeal anastomosis was then performed based on the surgeon's decision. Simple anastomosis techniques included: (1) distal gastrectomy with Billroth II with Braun or Roux-en-Y anastomosis; (2) esophagogastrostomy, tubular, or valvular anastomosis for proximal gastrectomy; and (3) Roux-en-Y anastomosis for total gastrectomy.

To assess surgical safety and postoperative recovery, key metrics were documented for each patient, including estimated blood loss, operative time, length of hospital stay, hospitalization costs, and overall postoperative complication rate, and complications were evaluated using the Clavien-Dindo classification system.

Statistical analysis

Statistical analyses were conducted using SPSS software (version 29.0; SPSS, Chicago, IL, USA). Categorical variables were analyzed using the Chi-square test, while continuous variables were assessed with the Student's t-test or Mann–Whitney U test. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD), whereas skewed continuous variables were reported as median (interquartile range). Univariate and multivariate logistic regression analyses were performed to evaluate factors associated with the pathological complete response (PCR) rate and risk factors for postoperative complications. A p-value of < 0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between the two groups

A total of 104 patients met the inclusion criteria, with 37 patients excluded from the study. The reasons for exclusion included 18 patients with clinicopathological stage M1, 7 patients who required emergency surgery due to complications during treatment, and 12 patients who underwent R1 resection (5 in the NICT group and 7 in the NCT group). Finally, 67 patients were included in the statistical analysis, with 35 patients in the NICT group and 32 patients in the NCT group. Baseline clinical parameters, including gender, age, BMI, cT stage, cN stage, and cTNM stage, demonstrated no statistically significant differences between the two groups, detailed data are presented in Table 1.

Table 1 Baseline characteristics of the NICT and NCT groups

Clinical characteristics	NICT(n = 35)	NCT(n = 32)	*P*-value
Sex,n(%)			0.290
Male	28(80)	22(68)	
Female	7(20)	10(32)	
Age,years,mean ± SD	61.22 ± 12.51	65.06 ± 11.42	0.196
BMI,kg/m2,mean ± SD	22.44 ± 3.49	22.45 ± 3.22	0.993
cT stage,n(%)			0.854
T2	1(2.9)	2(6.3)	
T3	19(54.3)	15(46.9)	
T4a	13(37.1)	14(43.7)	
T4b	2(5.7)	1(3.1)	
cN stage,n(%)			0.867
N0	6(17.1)	5(15.6)	
N +	29(82.9)	27(84.4)	
cTNM stage,n(%)			0.797
II	6(17.1)	7(21.9)	
III	27(77.2)	24(75.0)	
IVa	2(5.7)	1(3.1)	

Therapeutic efficacy and adverse events of neoadjuvant therapy

The details of neoadjuvant treatment for both the NICT and NCT groups are summarized in Table 2. There was no significant difference between the two groups regarding the number of treatment cycles or regimens. Pathological data demonstrated that the NICT group achieved significantly earlier ypN ($P = 0.001$) and ypTNM stages ($P = 0.001$) compared to the NCT group, along with reduced rates of neural and vascular invasion ($P = 0.041$, $P = 0.041$). Tumor diameter after neoadjuvant therapy did not differ significantly between the groups. Moreover, the pathological complete response (pCR) rate in the NICT group was significantly higher than in the NCT group (25.7% vs. 6.2%, $P = 0.032$). Regarding treatment-related adverse events, 7 cases were reported in the NICT group and 5 cases in the NCT group, with no statistically significant difference between the groups.

Comparison of laboratory parameters between the two groups

Prior to the initiation of neoadjuvant therapy, both the NICT and NCT groups exhibited elevated levels of CEA and CA19-9, with no statistically significant differences between the two groups ($P > 0.05$). Other laboratory parameters, including complete blood counts as well as liver and renal function tests, did not demonstrate statistically significant differences either, details are provided in Table 3 And Table 4 presents a comparison of laboratory parameters between the two groups following neoadjuvant treatment.

Following neoadjuvant therapy, the NICT group displayed a statistically significant reduction in both CEA and CA19-9 levels when compared to pre-neoadjuvant therapy ($P = 0.019$, $P = 0.045$), a similar trend was

Table 2 Pathological characteristics of the NICT and NCT groups

Items	NICT(n = 35)	NCT(n = 32)	P-value
Treatment cycles			0.378
≤ 4	24(68.6)	25(78.1)	
> 4	11(31.4)	7(21.9)	
Chemotherapy regimen, n (%)			0.393
SOX	28(80.0)	21(65.6)	
XELOX	5(14.3)	7(21.9)	
FOLFOX	2(5.7)	4(12.5)	
ypT stage, n (%)			0.304
T0	9(25.7)	4(12.5)	
T1	5(14.3)	2(6.3)	
T2	6(17.1)	4(12.5)	
T3	10(28.6)	14(43.7)	
T4	5(14.3)	8(25)	
ypN stage, n (%)			**0.001**
N0	14(40.0)	9(28.1)	
N1	7(20.0)	13(40.6)	
N2	6(17.1)	7(21.9)	
N3	8(22.9)	3(9.4)	
ypTNM stage, n (%)			**0.001**
0	9(25.7)	4(12.6)	
I	5(14.3)	3(9.4)	
II	9(25.7)	12(37.5)	
III	12(34.3)	13(37.5)	
Tumor diameters,cm	4.65 ± 2.98	5.02 ± 3.02	0.662
TRG			**0.001**
0	9(25.7)	2(6.2)	
1	4(11.4)	7(21.9)	
2	11(31.5)	7(21.9)	
3	7(20.0)	8(25)	
4	4(11.4)	8(25)	
Nerve invasion, n (%)			**0.041**
yes	10(28.6)	17(53.13)	
no	25(71.4)	15(46.87)	
Vascular invasion, n (%)			
yes	11(31.43)	18(56.25)	**0.041**
no	24(68.57)	14(43.75)	
pCR rate,n(%)	9(25.7)	2(6.2)	**0.032**
Treatment-related adverse reactions	7(20)	5(25.6)	0.641

observed in the NCT group ($P=0.024$, $P=0.032$). In the NICT group, WBC and neutrophil counts were significantly reduced following neoadjuvant treatment compared to baseline levels ($P=0.028$, $P=0.036$), whereas hemoglobin levels showed no statistically significant difference between pre- and post-neoadjuvant treatments ($P=0.136$). In the NCT group, although post-neoadjuvant treatments WBC levels and hemoglobin levels were lower than baseline, this reduction was not statistically significant ($P=0.217$, $P=0.247$). However, blood platelet levels in the NICT group and NCT group were significantly reduced after neoadjuvant treatment relative to baseline ($P=0.001$, $P=0.001$).

With regard to liver function tests, NICT group and NCT group exhibited significant elevations in ALT ($P=0.013$, $P=0.005$) and AST levels ($P=0.007$, $P=0.030$) post-neoadjuvant therapy compared with the pre-neoadjuvant therapy. Furthermore, in the NICT group, total bile acid levels significantly increased after neoadjuvant therapy ($P=0.018$), while creatinine levels demonstrated a significant reduction ($P=0.011$), details are provided in Table 5.

Surgical safety and postoperative recovery

The surgical duration for the NICT group was 3.39 ± 1.31 h, showing no statistically significant difference when compared to the NCT group (3.53 ± 0.84 h, $P=0.616$). The total length of hospital stay for the NICT group was 14.8 ± 7.25 days, which was not significantly different from the NCT group (14.8 ± 7.25 days, $P=0.940$). The estimated intraoperative blood loss in the NICT group was 139.11 ± 232.61 mL, with no significant difference compared to the NCT group's estimated blood loss of 133.43 ± 127.72 mL ($P=0.903$). The total number of lymph nodes dissected during surgery in the NICT group was 37.20 ± 18.57, which was similar to the NCT group (37.83 ± 17.97, $P=0.897$). In the NICT group, 3 patients experienced postoperative complications (postoperative bleeding, myocardial infarction, and arrhythmia), with a complication rate of 8.57%. In the NCT group, 5 patients experienced postoperative complications (pulmonary infection, pancreatitis, two cases of abdominal infection, and hydro-pneumothorax), with a complication rate of 15.6%. There was no statistically significant difference between the two groups ($P=0.374$). Additionally, there were no statistically significant differences in hospital stay and hospital costs between the two groups, as detailed in Table 6.

Correlation analysis of PCR rate

Univariate logistic regression analysis revealed that neoadjuvant immunochemotherapy was significantly associated with the pathologic complete response (PCR) rate compared to neoadjuvant chemotherapy, with an odds ratio (OR) of 5.192 (95% confidence interval [CI] 1.028–26.229, $P=0.046$), the results has been showed in Table 7. Additionally, the analysis showed a significant correlation between time of operation and the occurrence of postoperative complications, with an OR of 5.897 for surgical times of 4 h or more ($P=0.026$). Furthermore, the risk of developing postoperative complications increased with greater intraoperative blood loss, with an odds ratio (OR)

Table 3 Preoperative laboratory indexes between NICT and NCT groups

Items	NICT($n=35$)	NCT($n=32$)	*P*-value
Carcinoma Embryonic Antigen,CEA, ng/ml	46.15 ± 110.68	56.4 ± 131.24	0.796
Carbohydrate 19–9,CA19-9,U/ml	147.68 ± 389.65	135.01 ± 303.63	0.916
White blood cells,*10^9/L	6.52 ± 1.85	6.07 ± 1.55	0.432
Total neutrophil count,*10^9/L	4.29 ± 1.63	3.86 ± 1.24	0.385
Hemoglobin, g/L	119.04 ± 26.89	128.00 ± 22.13	0.278
Blood platelet,*10^9/L	301.29 ± 97.51	256.60 ± 102.48	0.170
Alanine aminotransferase,U/L	15.62 ± 8.92	15.53 ± 8.74	0.977
Glutamic oxalacetic transaminase,U/L	19.00 ± 6.75	17.80 ± 5.78	0.568
Total bile acids,umol/L	4.94 ± 3.90	5.53 ± 4.47	0.664
Creatinine,umol/L	71.43 ± 14.61	64.85 ± 10.92	0.138

Table 4 Post-operative laboratory indexes between NICT and NCT groups

Items	NICT($n=35$)	NCT($n=32$)	*P*-value
CEA,ng/ml	4.45 ± 4.43	5.15 ± 8.65	0.346
CA9-9,U/ml	24.61 ± 22.65	23.66 ± 30.22	0.893
White blood cells,*10^9/L	5.22 ± 2.99	5.43 ± 2.96	0.390
Total neutrophil count,*10^9/L	3.22 ± 2.62	3.38 ± 2.55	0.402
Hemoglobin,g/L	111.94 ± 23.10	115.40 ± 20.33	0.521
Blood platelet,*10^9/L	167.70 ± 69.93	174.84 ± 65.74	0.671
Alanine aminotransferase,U/L	24.88 ± 10.19	31.12 ± 23.47	0.081
Glutamic oxalacetic transaminase,U/L	19.00 ± 6.75	27.91 ± 18.22	0.568
Total bile acids,umol/L	7.96 ± 6.27	6.02 ± 6.39	0.109
Creatinine,umol/L	62.97 ± 13.14	60.46 ± 11.96	0.211

Table 5 Preoperative and Post-operative laboratory indexes between NICT and NCT groups

Items	NICT			NCT		
	Pre	Post	P	Pre	Post	P
CEA,ng/ml	46.15 ± 110.68	4.45 ± 4.43	**0.019**	56.4 ± 131.24	5.15 ± 8.65	**0.024**
CA9-9,U/ml	147.68 ± 389.65	24.61 ± 22.65	**0.045**	135.01 ± 303.63	23.66 ± 30.22	**0.032**
White blood cells,*10^9/L	6.52 ± 1.85	5.22 ± 2.99	**0.028**	6.07 ± 1.55	5.43 ± 2.96	0.219
Total neutrophil count,*10^9/L	4.29 ± 1.63	3.22 ± 2.62	**0.036**	3.86 ± 1.24	3.38 ± 2.55	0.247
Hemoglobin,g/L	119.04 ± 26.89	111.94 ± 23.10	0.136	128.00 ± 22.13	115.40 ± 20.33	**0.030**
Blood platelet,*10^9/L	301.29 ± 97.51	167.70 ± 69.93	**0.001**	256.60 ± 102.48	174.84 ± 65.74	**0.001**
ALT,U/L	15.62 ± 8.92	24.88 ± 10.19	**0.013**	15.53 ± 8.74	31.12 ± 23.47	**0.005**
AST,U/L	19.00 ± 6.75	24.88 ± 10.19	**0.007**	17.80 ± 5.78	27.91 ± 18.22	**0.030**
Total bile acids,umol/L	4.94 ± 3.90	7.96 ± 6.27	**0.018**	5.53 ± 4.47	6.02 ± 6.39	0.394
Creatinine,umol/L	71.43 ± 14.61	62.97 ± 13.14	**0.011**	64.85 ± 10.92	60.46 ± 11.96	0.118

of 3.917 (95% CI 0.853–17.980, $P=0.079$), although this finding did not reach statistical significance. Based on its previously demonstrated predictive value, a multivariate regression model was employed with a cutoff *P* value of < 0.1.

Discussion

Our study compared various clinical parameters and pathological outcomes between locally advanced gastric cancer patients treated with NICT therapy and NCT therapy alone. The findings demonstrate that NICT

Table 6 Preoperative treatment and radiological response between NICT and NCT groups

Items	NICT(n = 35)	NCT(n = 32)	*P*-value
Number of lymph node dissection	37.20 ± 18.57	37.83 ± 17.97	0.897
Length of stay, day	15.06 ± 11.96	14.8 ± 7.25	0.940
Hospitalization costs	11.46 ± 1.0	10.84 ± 0.50	0.802
Time of operation, h	3.39 ± 1.31	3.53 ± 0.84	0.616
Amount of bleeding,ml	139.11 ± 232.61	133.43 ± 127.72	0.903
Postoperative complications,n(%)	3(8.57)	5(15.6)	0.374

Table 7 Univariate logistic regression analysis for PCR after neoadjuvant therapy

Factor	Univariate analysis		P
	OR	95%CI	
Sex			0.552
Male	1.000		
Female	1.646	0.319–8.507	
Age,years			0.783
< 65	1.000		
≥ 65	1.200	0.328–4.391	
BMI			0.297
< 25	1.000		
≥ 25	0.444	0.097–2.039	
Neoadjuvant immunotherapy			**0.046**
No	1.000		
Yes	5.192	1.028–26.229	
cT stage			0.478
≤T3	1.000		
>T3	1.600	0.436–5.868	
cN stage			0.297
N0	1.000		
N +	0.444	0.097–2.039	
Tumor diameter(cm)			0.185
< 3	1.000		
≥ 3	0.375	0.088–1.600	

significantly improves postoperative pathological complete response (pCR) rates and tumor regression grade (TRG) compared to NCT. Additionally, NICT was associated with reduced neurological and vascular infiltration, highlighting its superior effectiveness in controlling local tumor progression and reducing metastatic potential.

Improved pCR rate, TRG and ypTNM stages

Our findings revealed a significantly higher pCR rate in the NICT group compared to the NCT group (25.7% vs. 6.2%, $P = 0.032$), along with more pronounced tumor regression scores and significantly earlier ypN and ypTNM stages. Additionally, the NICT group exhibited more pronounced TRG and significantly earlier ypN and ypTNM stages. These results align with previous studies emphasizing pCR as a critical prognostic marker linked to improved long-term survival [14]. For example, the MATTERHORN study reported enhanced pCR rates with durvalumab combined with FLOT compared to chemotherapy alone [15], while the INFINITY study achieved an impressive 60% pCR rates using trimetrezumab and durvalumab in MSI-H patient [16]. Similarly, phase II trials of combination therapies, such as triprozumab and sintilimab, demonstrated superior tumor regression, higher pCR rates, and improved downstaging compared to chemotherapy alone [17–19].

Collectively, these findings highlight the clinical promise of perioperative immunotherapy in enhancing cure rates and controlling tumor progression in gastric cancer. Evidence suggests that elevated pCR rates are frequently associated with heightened immune activation within the tumor microenvironment, particularly through immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis [20]. Thus, our study supports the role of neoadjuvant immunotherapy in gastric cancer as a strategy to strengthen local tumor control, inhibit metastasis, and potentially improve long-term survival outcomes.

Reduced rates of neurological and vascular infiltration

Pathological analysis revealed significantly lower rates of nerve and vascular infiltration in the NICT group compared to the NCT group (28.6% vs. 31.4%, respectively, with $P = 0.041$). Nerve and vascular infiltration are often associated with a higher risk of local recurrence and a poorer prognosis, underscoring the importance of controlling these factors for improved long-term outcomes [19, 20]. The observed reduction in infiltration rates in the NICT group may reflect the enhanced local control achieved by combining immunotherapy with chemotherapy. Neoadjuvant immunotherapy likely boosts systemic anti-tumor immunity and targets micrometastatic disease, thereby decreasing the risk of postoperative recurrence [21]. Immune checkpoint inhibitors (ICIs) are particularly effective in disrupting immunosuppressive signaling pathways, thereby amplifying immune

responses against tumor cells [22]. This suggests that NICT's effects extend beyond direct tumor cytotoxicity, possibly reshaping the tumor microenvironment in a way that suppresses metastatic progression [23, 24]. These findings provide compelling evidence for the incorporation of immunotherapy into comprehensive treatment strategies for high-risk, locally advanced gastric cancer, particularly in patients at risk for vascular and neurological infiltration.

Laboratory parameters

Following neoadjuvant therapy, both NICT and NCT groups demonstrated significant reductions in tumor marker levels, specifically CEA and CA19-9, reflecting the effectiveness of both treatments in reducing tumor burden. However, the NICT group showed more pronounced changes, with significant reductions in white blood cell (WBC) and neutrophil counts, suggesting a more substantial impact of immunochemotherapy on the immune and inflammatory responses [25, 26].

Additionally, the NICT group exhibited a significant increase in total bile acid levels, which may suggest an additional influence of immunochemotherapy on bile metabolism. This could be indicative of immune-mediated effects on hepatic function, potentially reflecting an alteration in liver enzyme activity or bile secretion pathways associated with the treatment [27]. Furthermore, renal function in the NICT group showed improvements, as evidenced by reduced creatinine levels, which may point to better renal perfusion or clearance. These findings are potentially linked to the systemic effects of immunochemotherapy, which might support overall organ function during treatment [28]. These laboratory changes highlight the need for vigilant monitoring of key parameters throughout the course of treatment to manage potential adverse effects effectively and optimize therapeutic outcomes. Future studies should investigate the long-term implications of these laboratory changes and their correlations with clinical outcomes, including survival and recurrence, to better understand the broader impacts of immunochemotherapy on patient health.

Risk assessment for perioperative and postoperative complications

In this study, the results of univariate logistic regression analysis revealed several significant associations between treatment and surgical factors and clinical outcomes, particularly focusing on pathologic complete response (PCR) rate and postoperative complications. Notably, neoadjuvant immunochemotherapy was significantly associated with an increased PCR rate compared to neoadjuvant chemotherapy, with an odds ratio (OR) of 5.192 (95% CI: 1.028–26.229, $P=0.046$). This suggests that the addition of immunotherapy to chemotherapy could potentially enhance the effectiveness of neoadjuvant treatment in achieving a complete response, offering important insights for treatment strategies in cancer care [26].

Perioperative assessments revealed no significant differences between the NICT and NCT groups regarding postoperative complications, hospital stay duration, or blood loss, suggesting that NICT does not increase postoperative risk. These findings support the safety and feasibility of incorporating neoadjuvant immunotherapy into treatment regimens for locally advanced gastric cancer [29].

Study limitations

The primary limitations of this study include a small sample size, which may limit the reliability and generalizability of the findings, as well as the detection of smaller, potentially clinically significant differences. The relatively short follow-up period also prevented a comprehensive evaluation of NICT's effects on long-term survival, recurrence, and overall prognosis. In addition, a portion of the enrolled patient population declined immunotherapy because of socioeconomic factors and concerns about irAEs, which may have led to selection bias and had some impact on the study results. Moreover, as a single-center study, the results may be subject to geographical and institutional biases, which could affect their broader applicability.

To address these limitations, future research should include large-scale, multicenter randomized controlled trials to enhance the reliability and generalizability of the results. Additionally, investigating molecular biomarkers associated with the immunotherapeutic response could help identify patients most likely to benefit from NICT. Optimizing neoadjuvant immunotherapy protocols and extending follow-up periods would be crucial for evaluating the long-term efficacy of NICT, supporting the development of more precise and individualized therapeutic strategies for gastric cancer treatment.

Conclusion

This study demonstrates that neoadjuvant immunotherapy (NICT) offers a promising anti-tumor effect while maintaining a favorable safety profile in the treatment of locally advanced gastric cancer. The significantly higher pCR rates, reduced rates of neurological and vascular infiltration, and the absence of increased postoperative risks suggest that NICT could be a viable neoadjuvant treatment strategy. These findings provide valuable insights into the potential of integrating immunotherapy into the comprehensive treatment of gastric cancer.

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Authors' contributions
Chaofeng Li and Yu Duan wrote the main manuscript text, Shengnan Zhou and Tao Tang prepared figures and Tables. Yinmo Yang and Lei Zhou designed and supervised the study. All authors reviewed the manuscript.

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Data Availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study has been performed in accordance with the Declaration of Helsinki and have received ethical approval from the China-Japan Friendship Hospital Ethics Committee (Approval No. 2024-KY-422).

Consent to publication
Informed consent was obtained from all subjects involved in the study. Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Competing interests
The authors declare no competing interests.

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