The safety and efficacy of neoadjuvant immunochemotherapy following laparoscopic gastrectomy for gastric cancer: a multicentre real-world clinical study

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Background: The safety and efficacy of neoadjuvant immunochemotherapy (nICT) for locally advanced gastric cancer (LAGC) remain controversial.

Methods: Patients with LAGC who received either nICT or neoadjuvant chemotherapy (nCT) at 3 tertiary referral teaching hospitals in China between January 2016 and October 2022 were analyzed. After propensity-score matching (PSM), comparing the radiological response, pathological response rate, perioperative outcomes, and early recurrence between the two groups.

Results: After PSM, 585 patients were included, with 195 and 390 patients comprising the nICT and nCT groups, respectively. The nICT group exhibited a higher objective response rate (79.5% vs. 59.0%; $P < 0.001$), pathological complete response rate (14.36% vs. 6.41%; $P = 0.002$) and major pathological response rate (39.49% vs. 26.15%; $P = 0.001$) compared with the nCT group. The incidence of surgical complications (17.44% vs. 16.15%, $P = 0.694$) and the proportion of perioperative textbook outcomes (80.0% vs. 81.0%; $P = 0.767$) were similar in both groups. The nICT group had a significantly lower proportion of early recurrence than the nCT group (29.7% vs. 40.8%; $P = 0.047$). Furthermore, the multivariable logistic analysis revealed that immunotherapy was an independent protective factor against early recurrence [odds ratio 0.62 (95% CI 0.41–0.92); $P = 0.018$]. No significant difference was found in neoadjuvant therapy drug toxicity between the two groups (51.79% vs. 45.38%; $P = 0.143$).

Conclusions: Compared with nCT, nICT is safe and effective, which significantly enhanced objective and pathological response rates and reduced the risk for early recurrence among patients with LAGC.

Trial registration: Clinical Trials.gov.

Keywords: efficacy, gastric cancer, laparoscopic gastrectomy, neoadjuvant immunochemotherapy, safety

Introduction

Gastric cancer (GC) is a significant global health issue, ranking fifth among the most common malignant tumour and the fourth leading cause of cancer-related deaths worldwide[1]. Surgery remains the primary treatment option for GC[2,3]. In China, the proportion of locally advanced GC (LAGC) is accounting for ~80%[4]. Unfortunately, some patients with LAGC cannot

undergo R0 resection at the time of initial diagnosis and are at a higher risk for postoperative recurrence, and have poor prognosis[5], thus posing significant challenges in the management of GC.

In recent years, perioperative treatment has been widely promoted, leading to an increase in the R0 resection rate and surgical efficacy for LAGC. Several large clinical studies, including MAGIC, PRODIGY and RESOLVE, have demonstrated the advantages of neoadjuvant chemotherapy (nCT)[6–9]. These advantages include reduced preoperative tumour stage, improved R0 resection rate, enhanced patient tolerance to treatment, and prolonged overall survival (OS)[10–12]. Despite the benefits of nCT, traditional approaches rely primarily on chemotherapeutic agents to achieve an objective response rate (ORR) of ~50%[13]. Therefore, there is an urgent need for new therapeutic options to improve ORR in the neoadjuvant treatment of LAGC.

Immunotherapy has emerged as a promising treatment option in recent years, and its effectiveness in advanced GC has been demonstrated in numerous studies[14–17]. The use of immunotherapy in the perioperative treatment of LAGC is being explored, such as Keynote-585 and MATTERHORN, are investigating the safety and efficacy of neoadjuvant immunochemotherapy (nICT) compared with nCT in patients with LAGC[18,19]. However, real-world studies are urgently needed to provide guidance for the clinical application of neoadjuvant immunotherapy in patients with LAGC.

Laparoscopic gastrectomy (LG) has become the standard procedure for patients with LAGC in many experienced centres. It has been shown to have short- and long-term outcomes comparable to open gastrectomy (OG) while offering advantages such as reduced intraoperative bleeding, smaller incisions, and faster postoperative recovery[20–23]. Several previous studies have reported that nCT followed by LG does not significantly increase postoperative complications and is considered to be safe and feasible compared with OG[24–28]. In fact, the mechanism of immunotherapy is complex, and the potential impact of nICT on LG complications is not well established. Although previous studies have demonstrated that nCT followed by LG does not significantly increase postoperative complications, it remains unclear whether the addition of immunotherapy to the treatment regimen has any effect on the perioperative safety and prognosis of LG. Further research is required to investigate the potential complications and outcomes associated with nICT followed by LG in patients with LAGC.

As such, this study aimed to compare the safety and efficacy of nICT and nCT for LAGC using a strict propensity-score matching (PSM) approach based on data from multiple high-volume centres in China to provide valuable information for healthcare professionals to design optimal treatment protocols in clinical practice in cases for which uncertainties exist.

Methods

Patients

Clinicopathological data of patients with LAGC who underwent neoadjuvant therapy were collected from multiple high-volume centres in China between January 2016 and October 2022. The eligibility criteria were as follows: pathologically confirmed adenocarcinoma; clinical staging at cT2N + M0 or cT3-4bNanyM0 based on the Union for International Cancer Control

HIGHLIGHTS

- The safety and efficacy of the perioperative use of immune checkpoint inhibitors (ICIs) in locally advanced gastric cancer (LAGC) remain controversial.
- This multicenter clinical study found that neoadjuvant immunochemotherapy (nICT) is safe and effective, which significantly enhanced objective and pathological response rates, and reduced the risk for early recurrence among patients with LAGC.
- These findings highlight the promising potential and wide-ranging application prospects for nICT.

(UICC)/American Joint Committee on Cancer (AJCC), 8th Edition guidelines; receiving nCT or nICT; undergoing LG after neoadjuvant therapy; and availability of complete clinicopathological data. Individuals with a history of other malignancies, an inability to undergo R0 resection, and those who underwent other anti-tumour treatments, such as preoperative radiotherapy or targeted therapy, were excluded. The study was approved by the Ethics Committees of the three participating research centres (2023KY160, 2023LWB046 and 2023YD079RS-01) and conformed to the Declaration of Helsinki guidelines. Informed consent was obtained from all enroled patients before perioperative treatment. This multicenter real-world clinical study has been reported in line with the Strengthening the reporting of cohort, cross-sectional and case-control studies in surgery (STROCSS) criteria[29]. The study was registered at Clinical Trials.gov.

PSM analysis

To minimize the effect of potential confounders in this retrospective study, PSM was used to remove potential preoperative influencing factors[30]. To enhance the comparability between the two groups, the research team held a consensus meeting to identify baseline characteristics that could affect surgical complications and outcomes. A total of 32 covariates (eTable 1, Supplemental Digital Content 1, http://links.lww.com/JS9/C421), including details of patient variables and tumour characteristics, were identified. Eleven factors [sex, age, BMI, history of laparotomy, age-corrected Charlson Comorbidity Index (aCCI), American Society of Anesthesiologists (ASA) class, tumour size, cT staging, cN staging, cTNM staging, and surgical type] were exactly matched using a logistic regression model by a biostatistician blinded to the outcomes. Greedy nearest neighbour matching (ratio 1:2 and matched without replacement) with a caliper width of 0.1 standard deviation of the estimated logit was performed. All data were compared between the nICT and nCT groups (n = 195 and n = 390, respectively) after PSM (Table 1 and eFigure 1, Supplemental Digital Content 8, http://links.lww.com/JS9/C422). In this study, an absolute standardized difference of < 0.10 was considered to indicate a relatively small imbalance.

Therapeutic regimens for nICT and nCT

Neoadjuvant chemotherapy regimens were primarily categorized into two- and three-agent regimens. The two-agent regimens included: SOX (S-1 + oxaliplatin), CapeOx (capecitabine + oxaliplatin), AS (S-1 + nab-paclitaxel), FOLFOX (oxaliplatin +

Sun et al. International Journal of Surgery (2024)

International Journal of Surgery

Table 1

Baseline characteristics before and after propensity-score matching.

Variable	Before PSM n (%)/mean (SD)			After PSM n (%)/mean (SD)			
	nICT group (n = 195)	nCT group (n = 537)	P	nICT group (n = 195)	nCT group (n = 390)	P	SMD
Age (year)	62.13 (9.95)	61.71 (10.10)	0.611	62.13 (9.95)	62.27 (9.73)	0.872	0.014
Sex			0.690			0.810	0.030
Male	147 (75.39)	397 (73.93)		147 (75.39)	299 (76.67)		
Female	48 (24.61)	140 (26.07)		48 (24.61)	91 (23.33)		
BMI (kg/m^2)	22.01 (3.18)	21.61 (3.04)	0.127	22.01 (3.18)	21.93 (3.08)	0.756	0.027
History of abdominal surgery			0.983			0.969	0.014
Yes	34 (17.44)	94 (17.50)		34 (17.44)	66 (16.92)		
No	161 (82.56)	443 (82.50)		161 (82.56)	324 (83.08)		
aCCI score			0.345			0.608	0.053
< 5	77 (39.49)	192 (35.75)		77 (39.49)	144 (36.92)		
≥ 5	118 (60.51)	345 (64.25)		118 (60.51)	246 (63.08)		
ASA Grade			0.954			0.876	0.045
I	14 (7.18)	36 (6.70)		14 (7.18)	25 (6.41)		
II	152 (77.45)	424 (78.96)		152 (77.45)	311 (79.74)		
III	29 (14.87)	77 (14.34)		29 (14.87)	54 (13.85)		
Tumour size (cm)			0.037			0.578	0.056
< 5	96 (49.23)	218 (40.60)		96 (49.23)	181 (46.41)		
≥ 5	99 (50.77)	319 (59.40)		99 (50.77)	209 (53.59)		
cT			0.468			0.938	0.032
T3	28 (14.36)	67 (12.48)		28 (14.36)	56 (14.36)		
T4a	144 (78.85)	389 (72.44)		144 (78.85)	284 (72.82)		
T4b	23 (11.79)	81 (15.08)		23 (11.79)	50 (12.82)		
cN			0.271			1.000	0.012
N0	10 (5.13)	40 (7.45)		10 (5.13)	19 (4.87)		
N+	185 (94.87)	497 (92.55)		185 (94.87)	371 (95.13)		
Clinical stage TNM			0.509			0.931	0.033
II	23 (11.79)	65 (12.11)		23 (11.79)	44 (11.28)		
III	149 (76.42)	391 (72.81)		149 (76.42)	296 (75.90)		
IVA	23 (11.79)	81 (15.08)		23 (11.79)	50 (12.82)		
Surgical type			0.068			0.793	0.033
Distal	38 (19.49)	75 (13.97)		38 (19.49)	71 (18.21)		
Total	157 (80.51)	462 (86.03)		157 (80.51)	319 (81.79)		

aCCI, age-adjusted Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; nCT, neoadjuvant chemotherapy; nICT, neoadjuvant chemotherapy combined with immunotherapy; PSM, propensity-score matching; SMD, standardized mean difference.

fluorouracil) and DS (S-1 + docetaxel). The three-agent regimens included: FLOT (docetaxel + oxaliplatin + fluorouracil), DOS (docetaxel + oxaliplatin + S-1) and POF (paclitaxel + oxaliplatin + fluorouracil). The immune checkpoint inhibitors (ICIs) used for neoadjuvant immunotherapy in this study included sintilimab, nivolumab, and camrelizumab. Dosages were calculated based on drug monographs, guidelines, and patient body surface area. The number of patients treated with each regimen is shown in eTable 2, Supplemental Digital Content 2, http://links.lww.com/JS9/C421. The patients underwent LG within 4–6 weeks after completing neoadjuvant therapy.

Laparoscopic surgery

All patients included in the present study underwent LG after the completion of neoadjuvant therapy, with experienced surgeons performing all procedures. For tumours located in the gastric antrum or the lower part of the gastric body, laparoscopic distal gastrectomy (LDG) and Billroth II gastrojejunostomy were performed; for tumours located in the upper part of the gastric body, gastric fundus, and cardia, laparoscopic total gastrectomy (LTG)

and Roux-en-Y esophagojejunostomy were performed. Combined resection was performed in patients with local invasion of adjacent structures to achieve intraoperative R0 resection.

Definitions

The study's median follow-up duration was 38 months. The primary end point was pathological complete response (pCR), and the secondary end points were major pathological remission (MPR) and safety. Preoperative treatment response was assessed according to RECIST version 1.1 criteria[31]. The ORR was defined as the sum of the percentages of patients achieving complete response (CR) and partial response (PR). The disease control rate (DCR) was calculated by adding the rate of stable disease (SD) to ORR. Postoperative complications were defined as those occurring during hospitalization after surgery and graded using the Clavien–Dindo classification system[32,33]. Severe complications were defined as Clavien–Dindo greater than or equal to II grade. Tumour regression grading (TRG) was evaluated according to the Becker criteria[34]. The pCR was defined as the absence of residual cancer cells in both the primary site of the

surgical specimen and the resected lymph nodes. Textbook outcome (TO) encompasses a comprehensive set of 8 quality metrics that evaluate various aspects of the surgical management of patients with GC undergoing gastrectomy[35,36]. These metrics included negative tumour margins, greater than 15 cleared lymph nodes, no severe complications, no unplanned reoperations, no unplanned ICU admissions, length of hospital stay no more than 21 days, no readmission within 30 days of discharge, and no mortality within 30 days of surgery. Early recurrence was defined as the patient experiencing recurrence within 2 years after surgery[37]. The recurrence-free survival (RFS) was defined as the period from the date of surgery to the first documented recurrence or metastasis. Overall survival (OS) was defined as the period from the date of surgery to the date of death or final follow-up.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corporation) and R version 4.3.1. To address baseline bias, PSM was performed at a 1:2 ratio. Categorical variables were assessed using the chi-squared test or Fisher's exact test, whereas continuous variables were analyzed using the Student's t-test or Mann–Whitney U test. Differences in the perioperative TO between the two groups were visualized using histograms and line graphs created using GraphPad Prism version 8.0 (GraphPad Inc.). The cumulative risk for tumour recurrence was analyzed using the log-rank test. Univariable and multivariable logistic regression analyses were performed to identify factors influencing recurrence. Variables with a value of P less than 0.05 in the univariate analysis were subsequently included in a multivariate logistic regression. Stepwise backward variable removal was applied to the multivariate model. Differences with P less than 0.05 were considered to be statistically significant.

Results

Baseline characteristics

Based on the inclusion and exclusion criteria, 732 patients from three high-volume centres were enroled, with 195 and 537 patients comprising the nICT and nCT groups, respectively. Before PSM, there was a significant difference in the distribution of patients between the two groups in terms of tumour size ($P = 0.036$), and after 1:2 PSM, a total of 585 patients were incorporated into the analysis, including 195 patients in nICT group and 390 patients in nCT group (Fig. 1). There were no statistically significant differences in clinical baseline characteristics, including sex, age, BMI, history of laparotomy, aCCI, ASA class, tumour size, cT, cN, cTNM staging, and surgical type, between the two groups [standardized mean difference (SMD) <0.1 (all $P > 0.05$)] (Table 1).

Neoadjuvant therapy and radiological response

After PSM, there were no significant differences in neoadjuvant treatment cycles and chemotherapy regimens between the two groups (eTable 3, Supplemental Digital Content 3, http://links. lww.com/JS9/C421). According to the RECIST v1.1 criteria, patients in the nICT group exhibited had a higher CR rate (11.8% vs. 6.2%; $P < 0.001$), PR rate (67.7% vs. 52.8%; $P < 0.001$), ORR (79.5% vs. 59.0%; $P < 0.001$), and DCR (99.5% vs. 98.5%; $P = 0.434$) compared to the nCT group (eFigure 2,
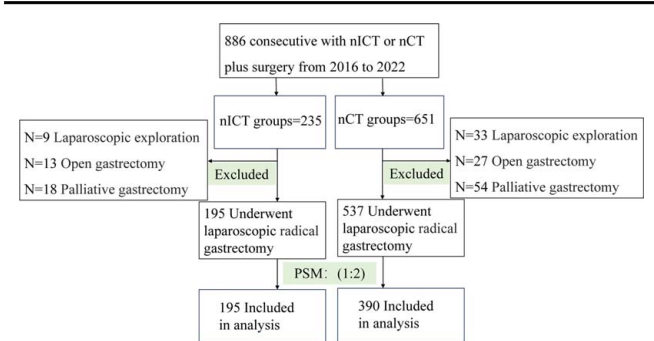
Figure 1. Flow-diagram illustrating the patient selection process. nCT, neoadjuvant chemotherapy; nICT, neoadjuvant chemotherapy combined with immunotherapy; PSM, propensity-score matching.

Supplemental Digital Content 9, http://links.lww.com/JS9/ C424). Subgroup analysis indicated that the nICT group exhibited a higher ORR compared to the nCT group (Double-drug: 79.1% vs. 58.9%, $P < 0.05$; Triple-drug: 87.5% vs. 60.0%, $P < 0.05$; eFigure 3A, Supplemental Digital Content 10, http:// links.lww.com/JS9/C423), regardless of the number of drugs used.

Surgical and pathology findings

The surgical and pathological characteristics of the two groups are summarized in Table 2. All patients underwent LG with D2 or D2 + lymph node dissection, and none required conversion to open surgery. Combined organ resection was performed in 17 (8.72%) and 25 patients (6.41%) in the nICT and nCT groups, respectively. A detailed list of the combined organs is presented in eTable 4, Supplemental Digital Content 4, http://links.lww.com/ JS9/C421. LTG with Roux-en-Y gastrointestinal reconstruction was performed in 476 patients [nICT group, 157 patients (80.51%); nCT group, 319 patients (81.79%)], and LDG with Billroth II anastomosis was performed in 109 patients [nICT group, 38 patients (19.49%); nCT group, 71 patients (18.21%)]. Postoperative pathology indicated positive margins in 3 cases (1.54%) in the nICT group and 7 (1.79%) in the nCT group, and there was no significant difference between the 2 groups in terms of tumour site, degree of lymph node eradication, and length of the surgical incision (8.89 ± 2.10 vs. 8.95 ± 2.11; $P = 0.729$).

Pathological results revealed that tumours in the nICT group had earlier ypT and ypTNM staging, and more lymph nodes were dissected than those in the nCT group (43.97 ± 17.89 vs. 39.54 ± 15.01; $P = 0.003$). Furthermore, the tumours in the nICT group exhibited a greater extent of regression, with higher pCR rate (14.36% vs. 6.41%; $P = 0.002$) and MPR rate (39.49% vs. 26.15%; $P = 0.001$), while there was no significant difference in the distribution of patients between the two groups in terms of the differentiation, Lauren type, choroidal embolus, nerve invasion, pN staging and number of positive lymph nodes. Subgroup analysis showed that the nICT group exhibited a higher pCR rate compared to the nCT group (Double-drug: 13.9% vs 6.5%, $P < 0.05$; Triple-drug: 25.0% vs 5.0%, $P < 0.05$; eFigure 3B, Supplemental Digital Content 10, http://links.lww.com/JS9/ C423).

Sun et al. International Journal of Surgery (2024)

International Journal of Surgery

Table 2

Operative findings and pathological characteristics.

Variable	nICT group (n = 195)	nCT Group (n = 390)	
	n (%)/mean (SD)	n (%)/mean (SD)	P
Reconstruction approach			0.793
Billroth II	38 (19.49)	71 (18.21)	
Roux-en-Y	157 (80.51)	319 (81.79)	
Lymph nodes dissection range			0.777
D2	187 (95.90)	372 (95.38)	
D2 +	8 (4.10)	18 (4.62)	
Surgical radicalness			
R0	192 (98.46)	383 (98.21)	0.822
R1	3 (1.54)	7 (1.79)	
Combined resection			0.308
Yes	17 (8.72)	25 (6.41)	
No	17 8 (91.28)	365 (93.59)	
Incision length (cm)	8.89 (2.10)	8.95 (2.11)	0.729
Tumour location			0.217
Upper	91 (46.67)	187 (47.95)	
Middle	59 (30.26)	90 (23.08)	
Lower	42 (51.24)	107 (27.44)	
Mix	3 (1.53)	6 (1.53)	
Lauren type			0.378
Intestinal	93 (47.69)	201 (51.54)	
Diffused	73 (37.44)	146 (37.43)	
Mixed	29 (14.87)	43 (11.03)	
Differentiation			0.237
Well/moderate	76 (38.97)	172 (44.11)	
Poor/undifferentiated	119 (61.03)	218 (55.89)	
Nerve invasion			0.726
Yes	99 (50.77)	204 (52.31)	
No	96 (49.23)	186 (47.69)	
Vascular invasion			0.262
Yes	91 (46.67)	163 (41.79)	
No	104 (53.33)	227 (58.21)	
No. lymph nodes dissected	43.97 (17.89)	39.54 (15.01)	0.003
Positive lymph nodes	4.45 (7.63)	4.71 (7.45)	0.686
ypT stage			0.013
ypT0	30 (15.38)	28 (7.18)	
ypT1	25 (12.82)	37 (9/49)	
ypT2	21 (10.77)	46 (11.79)	
ypT3	56 (28.72)	139 (35.64)	
ypT4	63 (32.31)	140 (35.90)	
ypN stage			0.161
ypN0	85 (43.59)	140 (35.90)	
ypN1	38 (19.49)	87 (22.31)	
ypN2	34 (17.43)	61 (15.64)	
ypN3	38 (19.49)	102 (26.15)	
ypTNM stage			0.008
ypT0N0M0	28 (14.36)	25 (6.41)	
I	33 (16.92)	56 (14.36)	
II	52 (26.67)	127 (32.56)	
III	82 (42.05)	182 (46.67)	
Tumour regression grade			0.002
1a	30 (15.38)	27 (6.92)	
1b	47 (24.10)	75 (19.23)	
2	63 (32.31)	142 (36.41)	
3	55 (28.21)	146 (37.44)	
pCR	28 (14.36)	25 (6.41)	0.002
MPR	77 (39.49)	102 (26.15)	0.001

MPR, major pathological response; nCT, neoadjuvant chemotherapy; nICT, neoadjuvant chemotherapy combined with immunotherapy; pCR, pathological complete response.

Postoperative complications and 30-day perioperative outcomes

Thirty-four (17.44%) patients in the nICT group and 63 (16.15%) in the nCT group experienced postoperative complications, and there was no statistically significant difference in the incidence of total postoperative complications between the two groups ($P = 0.694$). The most common postoperative complications included pulmonary infections (20 vs. 46 patients), abdominal infections (8 vs. 14 patients), and anastomotic fistulas (3 vs. 5 patients). According to the Clavien–Dindo grading of surgical complications, the severity of complications was similar between the two groups (16.41% vs. 14.87%; $P = 0.627$). The detailed distribution of complications is shown in eTable 5, Supplemental Digital Content 5, http://links.lww.com/JS9/C421.

The percentage of 30-day perioperative TO was similar in both groups (80.0% vs. 81.0%; $P = 0.767$) (eFigure 4, Supplemental Digital Content 11, http://links.lww.com/JS9/C425). There was no significant difference in the mean duration of surgery (214.75 ± 49.03 vs. 211.65 ± 44.71 min; $P = 0.554$), intraoperative bleeding (68.59 ± 106.78 vs 66.03 ± 68.04 ml; $P = 0.831$), perioperative transfusion (9.23% vs 6.15%; $P = 0.174$), and use of antibiotics (25.64% vs 21.79%; $P = 0.298$), between the two groups, in which it should be noted that the percentage of intraoperative haemorrhage (> 200 ml) in the nICT group was less than that in the nCT group (4.10% vs. 9.23%; $P = 0.027$). Postoperative recovery was comparable between the two groups, with time to first aerofluxus (2.61 ± 0.81 vs. 2.64 ± 0.71; $P = 0.695$), time to first defecation (3.60 ± 0.61 vs. 3.64 ± 0.54; $P = 0.409$), time to first fluid intake (4.43 ± 2.18 vs. 4.41 ± 2.56; $P = 0.927$), and time to first semifluid intake (6.68 ± 2.76 vs. 6.41 ± 2.98; $P = 0.124$) were not significantly different. None of the patients in either group died within 30 days, and the proportion of postoperative ICU admissions was similar (7.18% vs. 5.90%; $P = 0.548$). The postoperative hospitalization time (9.11 ± 5.07 vs. 9.00 ± 7.43 days; $P = .849$), total cost (8456.74 ± 3024.46 vs. 8523.71 ± 4763.70 USD; $P = 0.877$) neoadjuvant therapy to surgery time (107.48 ± 58.64 vs. 101.96 ± 41.68 days; $P = 0.190$), the proportion of postoperative adjuvant therapy (90.26% vs. 90.26%; $P = 1.000$), and the duration of postoperative adjuvant therapy (32.63 ± 10.27 vs. 33.06 ± 24.77 days; $P = 0.827$) were comparable, and the differences were not statistically significant (eTable 6, Supplemental Digital Content 6, http://links.lww.com/JS9/C421).

Survival

Regarding follow-up data, 58 patients in the nICT group and 159 in the nCT group experienced recurrence within 2 years, and the proportion of early recurrence in the nICT group was significantly lower than that in the nCT group (29.7% vs. 40.8%; $P = 0.047$) (Fig. 2A). The pattern of distant metastasis, peritoneal metastasis, and local recurrence were similar between the two groups, as shown in Figs. 2B and C. Univariable and multivariable logistic regression analysis identified immunotherapy as an independent protective factor for early recurrence [OR 0.62 (95% CI 0.41–0.92)]; $P = 0.018$] (eTable 7, Supplemental Digital Content 7, http://links.lww.com/JS9/C421). The RFS and OS curves obtained using the Kaplan–Meier method are shown in eFigure 5, Supplemental Digital Content 12, http://links.lww.
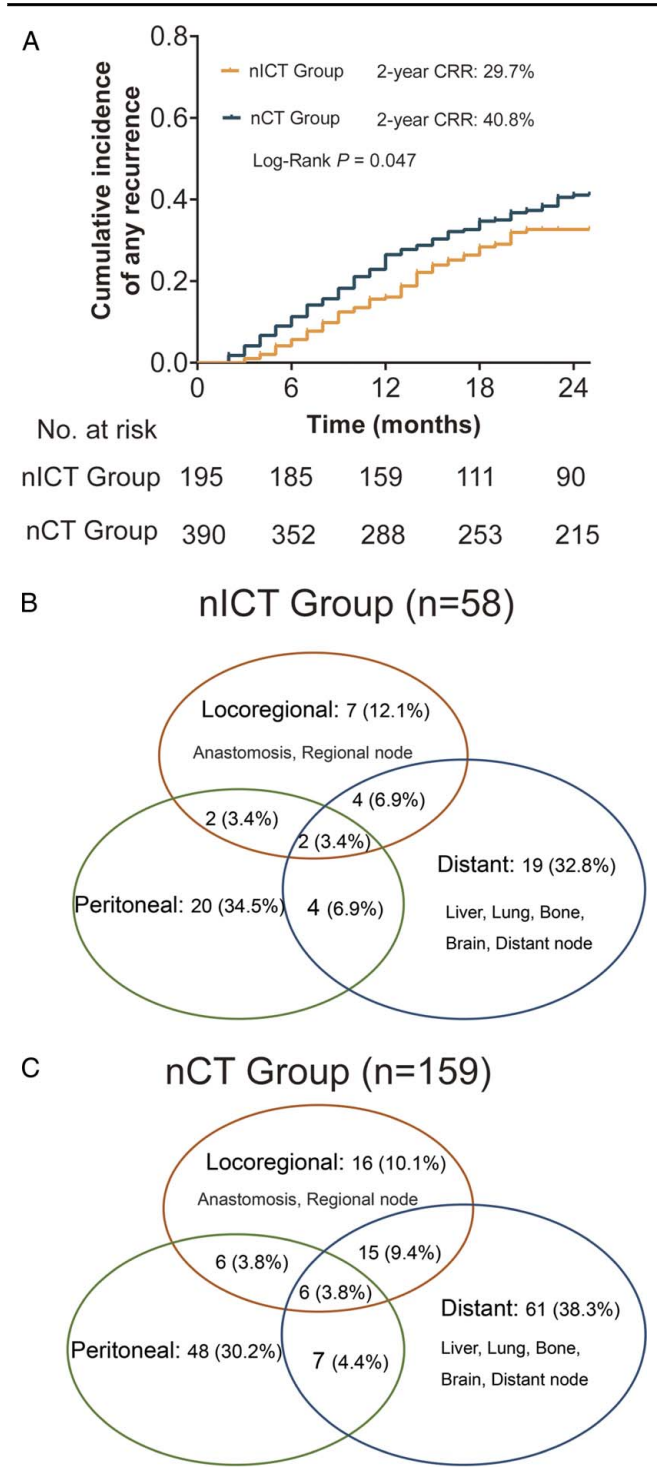
Figure 2. Kaplan–Meier curves for cumulative incidence of any recurrence for the neoadjuvant chemotherapy combined with immunotherapy (nICT) group versus the neoadjuvant chemotherapy (nCT) group (A). Venn diagram of recurrence patterns in the nICT (B), and nCT (C) groups.

com/JS9/C426. Compared to the nCT group, nICT group had a higher 2-year RFS (67.1% vs. 58.1%, $P = 0.027$) and 2-year OS (67.0% vs. 64.3%, $P = 0.223$).

Safety

In this study, the incidence of neoadjuvant therapy-related adverse events (nTRAEs) was slightly higher in the nICT group than in the nCT group (51.79% vs. 45.38%; $P = 0.143$). However, the rate of grade 3/4 nTRAEs was comparable between the two groups (12.03% vs. 11.53%; $P = 0.786$), and the difference was not statistically significant. The most common nTRAEs in both groups were hematopoietic events, such as leukopenia, neutropenia, and thrombocytopenia. In the immunotherapy group, hyper- or hypothyroidism was common (Table 3). None of the patients in either group died of nTRAEs during neoadjuvant therapy.

Discussion

In the past decade, there have been significant changes in treatment approaches to GCs, particularly with the emergence of ICIs for the treatment of unresectable, recurrent, and metastatic GC[14,38]. As a result, immunotherapy has also been considered for the perioperative treatment of LAGC. Nevertheless, the safety and effectiveness of LG in the treatment of GC after nICT remains unclear.

Neoadjuvant therapy has the potential to reduce the tumour burden, downgrade the preoperative tumour stage, and even achieve pCR[6,7]. However, it is important to note that the proportion of patients who benefit from nCT alone is limited. Recent studies have confirmed that nICT can significantly improve pCR rates and short-term outcomes in colorectal, lung, oesophageal, and triple-negative breast cancers[39–42]. nICT has the same effect in GC, and a prospective phase II clinical study reported that

Table 3

Neoadjuvant therapy-related adverse events.

Neoadjuvant therapy-related adverse events (nTRAEs)	nICT group (n = 195)		nCT group (n = 390)		
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3	P
Tumour perforation	2	2	3	3	
Tumour haemorrhage	2	2	4	4	
Bone marrow suppression	70	21	145	40	
White blood cell count decrease	60	18	121	35	
Neutrophil decrease	55	18	120	35	
Platelet decrease	26	9	39	15	
Transaminase elevation	9	0	21	0	
Rash	4	0	7	0	
Nausea or vomiting or diarrhoea	25	0	44	0	
Immune-related adverse events					
Hyperthyroidism	7	0	0	0	
Hypothyroidism	8	0	0	0	
Hypoadrenocorticism	2	0	0	0	
Reactive capillary endothelial proliferation	4	0	0	0	
Pneumonitis	1	0	0	0	
Myocarditis	1	0	0	0	
Overall nTRAEs rate [n (%)]	101 (51.79)		177 (45.38)		0.143
Severe nTRAEs rate[a] [n (%)]	24 (12.03)		45 (11.53)		0.786

nCT, Neoadjuvant chemotherapy; nICT, Neoadjuvant chemotherapy combined with immunotherapy.
[a]nTRAEs Grade ≥ 3 was regarded as severe adverse events.

Sun et al. International Journal of Surgery (2024)

International Journal of Surgery

patients who received nICT (CapeOx combined with sintilimab) had higher pCR (19.4%) and MRP rates (47.2%)[43]. In the present study, the radiological evaluation revealed that patients in the nICT group exhibited a higher ORR than those in the nCT group (79.5% vs. 59.0%; $P < 0.001$). Furthermore, post-operative pathology revealed that the nICT group, compared with the nCT group, had significantly pCR (14.36% vs. 6.41%; $P = 0.002$) and MPR (39.49% vs. 26.15%; $P = 0.001$) improved, which could potentially result in a survival benefit for patients with GC.

Many large randomized controlled clinical trials have demonstrated the safety and efficacy of LG compared with OG; as a result, the procedure has gained widespread acceptance and is now available in experienced centres worldwide[20,22,38]. Despite the potential risks of neoadjuvant therapy, such as myelosuppression, malnutrition, impaired immune function, and tissue oedema, which may contribute to increased postoperative complications, several previous studies have successfully demonstrated the safety and feasibility of LG following nCT compared to OG[24,25,27]. However, it remains unclear whether the benefits of laparoscopic surgery persist after immunochemotherapy. Sihag et al.[44] reported the safety and feasibility of esophagectomy after nICT for locally advanced oesophageal cancer. Similarly, the Checkmate-816 study demonstrated that nICT did not compromise the safety of surgery for resectable lung cancer[40]. Several small-sample retrospective studies have investigated the safety of gastrectomy after nICT. Su et al.[45] observed that the nICT and nCT groups exhibited comparable operative times, postoperative recoveries, and complication rates. Similarly, Wang et al.[46] reported that the complication rates for laparoscopic and open surgery after nICT were 33.3% and 31.2%, respectively ($P = 1.000$). In our study, we found that the overall rates of surgical complications in the nICT and nCT groups were 17.44% and 16.15%, respectively ($P = 0.694$). These findings are consistent with previous studies investigating nCT combined with LG, and there was no significant difference compared with LG alone[20,24]. Notably, the most common postoperative complication in both groups was pulmonary infection, which may be attributed to the higher proportion of total gastrectomy performed in this study (80.51% in the nICT group and 81.79% in the nCT group). Collectively, our study supports the hypothesis that LG is safe and feasible for LAGC after nICT.

In this study, the 30-day perioperative TO were similar in the two groups (80.0% vs. 81.0%; $P = 0.767$). We observed a significant increase in the number of lymph node dissections in the nICT group compared to the nCT group. However, there was no significant prolongation of the operative duration or increase in intraoperative bleeding, and the two groups were comparable in terms of perioperative transfusion and antibiotic use. Interestingly, the proportion of patients with intraoperative haemorrhage (blood loss > 200 ml) was lower in the nICT group than in the nCT group (4.10% vs. 9.23%; $P = 0.027$). This may be attributed to the fact that some of the patients in the nCT group had minimal tumour regression, which increased the difficulty of lymph node dissection and the risk of perigastric vascular injuries during the operation, thereby increasing the likelihood of haemorrhage. In the present study, no significant differences were observed between the nICT and nCT groups in terms of postoperative recovery, postoperative hospitalization days, postoperative ICU admission, readmission within 30 days,

unplanned reoperation, or total cost. Previous studies have indicated that postoperative complications in GC can affect the completion of subsequent comprehensive anti-tumour therapy, and higher complication rates can lead to shorter long-term survival in patients[47,48]. However, in our study, we found that nICT did not result in delayed surgery, and the rate and duration of postoperative adjuvant chemotherapy were comparable to those in the nCT group.

In this multicenter study, we also observed that the early recurrence rate in the nICT group was significantly lower than that in the nCT group (29.7% vs. 40.8%; $P = 0.047$). Furthermore, both univariable and multivariable logistic regression analyses identified immunotherapy as an independent protective factor for early recurrence (≤ 24 months) [OR 0.62 (95% CI 0.41–0.92); $P = 0.018$]. Survival analysis indicates a higher 2-year RFS (67.1% vs. 58.1%, $P = 0.027$) and 2-year OS (67.0% vs. 64.3%, $P = 0.223$) in the nICT group compared to the nCT group, although the difference of OS did not achieve statistical significance. These findings suggest that LG for LAGC after nICT may afford favourable survival benefits. However, the long-term prognosis needs to be confirmed through long-term follow-up.

However, whether neoadjuvant immunotherapy yields effectiveness with an increase in nTRAEs is noteworthy. The Checkmate-649 and Keynote-859 studies demonstrated that the occurrence of TRAEs in chemotherapy combined with immunotherapy for advanced GC is comparable to that of chemotherapy alone[49,50]. In this study, there was no statistically significant difference in the incidence of total nTRAEs (51.79% vs. 45.38%; $P = 0.143$) or grade 3/4 nTRAEs (12.03% vs. 11.53%; $P = 0.786$) between the two groups. Some patients in the nICT group experienced immune-related adverse events, specifically related to thyroid and adrenocorticotropic hormones, which is consistent with findings reported in previous studies[43]. However, all of these adverse events were successfully managed according to safety guidelines, and no patient had to discontinue immunotherapy or delay surgery because of these immune-related adverse events. Although neoadjuvant immunotherapy has demonstrated promising results in the treatment of GC, it is important to acknowledge the complex mechanism of immunotherapy that poses challenges in terms of potentially serious immunotherapy-related toxicity in clinical practice.

This study, however, did have limitations that should be acknowledged, the first of which was its retrospective design, although it is noteworthy that the clinical data used were obtained from three independent, high-volume centres. Additionally, rigorous PSM was conducted to minimize disparities between the two groups to ensure reliable and generalizable results. Second, patients were not screened based on programmed death-ligand-1 expression and microsatellite instability status before immunotherapy, which is consistent with the fact that most clinical studies investigating ICIs are still conducted in the overall population, suggesting that there is still a need to explore biomarkers related to ICIs and their efficacy. Finally, although nICT can significantly reduce the risk for early recurrence, long-term follow-up is necessary to confirm the outcomes of nICT. We also anticipate that the results of subsequent phase III clinical studies will confirm the real effect of ICIs in neoadjuvant therapy for GC, which will represent a significant breakthrough in the field of immunotherapy and have the potential to further improve the prognosis of patients with GC.

Conclusions

In conclusion, this observational study, which was rigorously adjusted for confounding factors, provides evidence suggesting that nICT is safe and effective, which significantly enhanced objective and pathological response rates and reduced the risk for early recurrence without increasing surgical complications and drug toxicity among patients with LAGC. These findings highlight the promising potential and wide-ranging application prospects for nICT.

Ethical approval

This study passed the Institutional Review Board (IRB) of the FJMUUH (IRB number: 2023KY160).

Consent for publication

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal.

Author contribution

Study concept or design: S.Y.Q. Z.Q., L.J. C.L.S. and H.C.M. Data collection, data analysis or interpretation: L.C.B., C.Q.X., L.M.Q., Z.W.M., Z.Y.B., W.C.M., L.G.T., and Z.Z.Q. writing the paper: S.Y.Q., Z.Q., L.C.B., L.J., C.L.S. and H.C.M. Statistical analysis: S.Y.Q., Z.Q., W.D., L.G.T., and L.J. Administrative, technical, or material support: S.Y.Q., Z.Q., C.Q.Y., L.G.T., W.D., L.J.X., X.J.W., L.P. and Z.C.H. Supervision: S.Y.Q., Z.Q., L.C.B. and H.C.M.

Conflicts of interest disclosure

All authors have no conflict of interest and no potential benefits.

Research registration unique identifying number (UIN)

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Guarantor

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Provenance and peer review

Not applicable.

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Sun et al. International Journal of Surgery (2024)

International Journal of Surgery

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