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Original Article

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Safety and feasibility of minimally invasive gastrectomy after neoadjuvant immunotherapy for locally advanced gastric cancer: a propensity score-matched analysis in China

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Abstract

Background: The effect of neoadjuvant immunotherapy on minimally invasive gastrectomy (MIG) for locally advanced gastric cancer (LAGC) remains controversial. This study aimed to compare short-term outcomes between MIG after neoadjuvant chemo-immunotherapy (NICT-MIG) and MIG after neoadjuvant chemotherapy alone (NCT-MIG), and determine risk factors for post-operative complications (POCs).

Methods: This retrospective study included clinicopathologic data from 193 patients who underwent NCT-MIG or NICT-MIG between January 2020 and February 2023 in the Department of General Surgery, Chinese People's Liberation Army General Hospital First Medical Center (Beijing, China). Propensity score-matched analysis at a ratio of 1:2 was performed to reduce bias from confounding patient-related variables and short-term outcomes were compared between the two groups.

Results: The baseline characteristics were comparable between 49 patients in the NICT-MIG group and 86 patients in the NCT-MIG group after propensity score matching. Objective and pathologic complete response rates were significantly higher in the NICT-MIG group than in the NCT-MIG group ($P < 0.05$). The overall incidence of treat-related adverse events, intraoperative bleeding, operation time, number of retrieved lymph nodes, time to the first flatus, post-operative duration of hospitalization, overall morbidity, and severe morbidity were comparable between the NCT-MIG and NICT-MIG groups ($P > 0.05$). By multivariate logistic analysis, estimated blood loss of >200 mL ($P = 0.010$) and prognostic nutritional index (PNI) score of <45 ($P = 0.003$) were independent risk factors for POCs after MIG following neoadjuvant therapy.

Conclusions: Safety and feasibility of NICT were comparable to those of NCT in patients undergoing MIG for LAGC. Patients with an estimated blood loss of >200 mL or a PNI score of <45 should be carefully evaluated for increased POCs risk.

Keywords: gastric neoplasm; neoadjuvant immunotherapy; post-operative complications; risk factor

Introduction

In China, gastric cancer (GC) has the third-highest incidence and mortality rates among all malignancies [1]. Approximately 80% of patients with GC in China are in the advanced stages of the disease, which, given the high incidence and poor prognosis, is associated with a severe health burden [2, 3]. In patients with resectable locally advanced GC (LAGC), perioperative comprehensive treatment regimens, including chemotherapy and immunotherapy, combined with radical gastrectomy may improve the therapeutic effect of tumor resection, thereby increasing the likelihood of survival [4].

The MAGIC trial was the first to find neoadjuvant chemotherapy (NCT) to be associated with a higher R0 resection rate and superior 5-year overall and progression-free survival rates than surgery alone in patients with LAGC [5]. The therapeutic advantages of NCT, including tumor downstaging, improved tolerability of total therapy, and superior long-term outcomes, have been confirmed in several authoritative randomized control trials (RCTs) in East Asia, such as PRODIGY [6] and RESOLVE [7], leading to the gradual emergence of NCT as a promising perioperative approach to treating LAGC [8].

Minimally invasive gastrectomy (MIG) has several advantages such as smaller surgical incision and faster post-operative recovery [9]. Most studies also demonstrated the comparable short-term and long-term outcomes between MIG and open gastrectomy (OG) [10, 11]. Therefore, MIG is commonly recommended as the standard surgical approach for GC cases. With the popularization of NCT, scholars have begun to evaluate its impact on surgical safety and perioperative complications. Several studies have shown that MIG after NCT does not significantly increase

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the rate of post-operative complications (POCs) when compared with open gastrectomy after NCT [12], which supports the surgical safety and feasibility of MIG.

Immunotherapy is an emerging approach for the treatment of GC. Several studies have demonstrated that NCT combined with immunotherapy (NICT) improves pathologic response and induces the production of antitumor immune subsets, among other benefits, in patients with LAGC [13–15]. At the same time, Phase III RCTs, such as Keynote-585 [16] and MATTERHORN [17], have explored the potential advantages of using NICT over NCT alone in patients with LAGC. However, few studies have focused on the perioperative safety of MIG following NICT in these patients. In the present study, we evaluated the surgical safety and short-term efficacy of MIG after NICT and NCT to provide a clinical reference for the selection of optimal treatment regimens for patients with LAGC.

Patients and methods

Patients

This study was conducted at the Department of General Surgery, Chinese People's Liberation Army (PLA) General Hospital First Medical Center (Beijing, China) and included retrospectively collected clinicopathologic data of patients with LAGC meeting the following criteria: (i) histologically proven gastric adenocarcinoma based on preoperative gastroscopy, (ii) suitable for laparoscopic or robotic gastrectomy, (iii) clinical tumor stage of $cT_2N_+M_0$ or $cT_{3-4b}N_{any}M_0$ based on the guidelines of the International Union Against Cancer/American Joint Committee on Cancer (8th edition), (iv) treatment with NCT or NICT, and (v) available integrated clinical and pathological data. Patients with severe comorbidities, defined as having an American Society of Anesthesiologists (ASA) grade of >III, and those who had received other preoperative regimens, such as radiotherapy and targeted therapy, were excluded from the study. Data from a total of 193 patients who underwent neoadjuvant therapy and MIG between January 2020 and February 2023, consisting of 53 patients who had received NICT (NICT-MIG group) and 140 patients who had received NCT alone (NCT-MIG group), were included. This study was approved by the Ethics Committee of the Chinese PLA General Hospital (approval No. S2023-190–01) and informed consent before perioperative treatment was obtained from all patients.

Propensity score-matched analysis

Confounding factors can affect the outcomes of retrospective studies. Therefore, propensity score-matched analysis was conducted using R statistical software (version 4.2.2; R Foundation, Vienna, Austria). The propensity score of each patient was determined by using a logistic regression model that considered the following clinical indices: sex, age, body mass index (BMI), age-adjusted Charlson comorbidity index (aCCI) score, ASA grade, nutritional risk screening-2002 (NRS-2002) score, history of abdominal surgery, surgical approach, tumor resection, and cT, cN, and cTNM stages. Patients in the NICT-MIG and NCT-MIG groups were matched at a 1:2 ratio using nearest neighbor matching with an optimal caliper width of 0.20 without replacement. After matching, the NCT-MIG group included 49 patients and the NICT-MIG group included 86 patients (Table 1 and Supplementary Figure 1).

Neoadjuvant therapy

Each study participant received either a dual-drug NCT regimen, such as S-1 combined with oxaliplatin (SOX), capecitabine combined with oxaliplatin (XELOX), and S-1 combined with nab-paclitaxel (TS), or triple-drug NCT regimens, such as docetaxel + oxaliplatin + fluorouracil (FLOT) and oxaliplatin + calcium levofolinate + fluorouracil (FOLFOX). Neoadjuvant immunotherapy regimens included programmed death-1 inhibitors such as nivolumab, pembrolizumab, toripalimab, camrelizumab, and sintilimab. The duration of NCT and NICT ranged from two to eight cycles. All patients in the NICT-MIG group received synchronous cycles of chemotherapy and immunotherapy, and none of the patients in the study received dual immunotherapy before surgery. MIG was performed 4–6 weeks after the completion of neoadjuvant therapy. The present study also considered the number of treatment cycles, radiologic response based on the Response Evaluation Criteria in Solid Tumors (version 1.1), and treatment-related adverse events (TRAEs) according to the Common Terminology Criteria for Adverse Events (version 5.0).

Preoperative laboratory indices

Several crucial preoperative indices, including hemoglobin level; leukocyte, neutrophil, lymphocyte, and platelet counts in peripheral blood; and serum albumin level before surgery, were included in the comparison of the two groups. Several combined indicators, such as neutrophil/lymphocyte ratio (NLR; neutrophil count/lymphocyte count), platelet/lymphocyte ratio (PLR; platelet count/lymphocyte count), Onodera's prognostic nutritional index (PNI) score ($10 \times$ albumin [g/dL] + $0.005 \times$ lymphocyte count/mm^3) [18], and systemic immune-inflammation (SII) index score (platelet count × neutrophil count/lymphocyte count) [19], were also included.

Surgical approach

The study participants underwent laparoscopic or robotic radical gastrectomy plus D2 lymphadenectomy. All surgeries were performed by chief surgeons with significant experience in laparoscopic and robotic gastrectomy. The surgical details of each gastrectomy were in accordance with the Japanese Gastric Cancer Treatment Guidelines (version 5) [20]. Briefly, the process was as follows: after the intracorporeal procedure, an incision of <10 cm was made in the middle of the epigastrium to remove the specimen, and gastrointestinal anastomosis was completed using a circular stapler for esophagojejunostomy and esophagogastrostomy and a linear stapler for jejunojejunostomy.

Perioperative indicators

Data on estimated intraoperative blood loss and operation time were collected to evaluate surgical difficulty. Data on time to the first flatus and post-operative duration of hospitalization were collected to assess post-operative recovery. The Clavien–Dindo classification [21] was used to evaluate complications within 30 days after surgery. Due to the limitations of retrospective studies, Clavien–Dindo grade I complications, i.e. those not requiring medical intervention, were not included in the analyses of overall morbidity. Clavien–Dindo grade ≥IIIa complications were considered as severe. Data on the rate of R0 resection and the number of retrieved lymph nodes were obtained from pathologic evaluations.

Variables for risk analysis

The following clinical and operative variables were investigated as potential risk factors for POCs after neoadjuvant therapy: sex (male vs female), age (<70 vs ≥70 years), BMI (<25 vs ≥25 kg/m^2), abdominal surgery (yes vs no), cT stage (T_{2-3} vs T_{4a-4b}), cN stage (N_0 vs N_+), combination of neoadjuvant immunotherapy (yes vs no), severe TRAEs (yes vs no), aCCI score (<5 vs ≥5), NRS-2002 score (<3 vs ≥3), surgical approach (laparoscopic vs robotic), tumor diameter (<5 vs

Table 1. Baseline characteristics of the NICT-MIG and NCT-MIG groups before and after PSM

Clinical characteristic	Before PSM			After PSM		
	NCT-MIG group ($n = 140$)	NICT-MIG group ($n = 53$)	P-value	NCT-MIG group ($n = 86$)	NICT-MIG group ($n = 49$)	P-value
Sex, *n* (%)			0.644			0.521
Male	110 (78.6)	40 (75.5)		69 (80.2)	37 (75.5)	
Female	30 (21.4)	13 (24.5)		17 (19.8)	12 (24.5)	
Age, years, mean ± SD	60.61 ± 9.95	58.83 ± 10.53	0.277	60.28 ± 10.16	58.76 ± 10.87	0.415
BMI, kg/m^2, mean ± SD	23.44 ± 3.24	23.61 ± 3.39	0.744	23.56 ± 3.37	23.43 ± 3.36	0.825
NRS-2002 score, *n* (%)						0.960
<3	82 (58.6)	29 (54.7)		47 (54.7)	27 (55.1)	
≥3	58 (41.4)	24 (45.3)		39 (45.3)	22 (44.9)	
aCCI score, *n* (%)			0.939			0.691
<5	93 (66.4)	35 (66.0)		55 (64.0)	33 (67.3)	
≥5	47 (33.6)	18 (34.0)		31 (36.0)	16 (32.7)	
History of abdominal surgery, *n* (%)			0.664			0.759
Yes	22 (15.7)	7 (13.2)		72 (83.7)	42 (85.7)	
No	118 (84.3)	46 (86.8)		14 (16.3)	7 (14.3)	
ASA grade, *n* (%)			0.446			0.800
I	1 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
II	119 (85.0)	48 (90.6)		76 (88.4)	44 (89.8)	
III	20 (14.3)	5 (9.4)		10 (11.6)	5 (10.2)	
Minimally invasive surgery, *n* (%)			0.034			0.973
Laparoscopic	123 (87.9)	40 (75.5)		70 (81.4)	40 (81.6)	
Robotic	17 (12.1)	13 (24.5)		16 (18.6)	9 (18.4)	
Tumor resection, *n* (%)			0.416			0.939
Proximal	28 (20.0)	13 (24.5)		20 (23.3)	12 (24.5)	
Distal	43 (30.7)	17 (32.1)		29 (33.7)	15 (30.6)	
Total	69 (49.2)	23 (43.4)		37 (43.0)	22 (44.9)	
cT stage, *n* (%)			0.387			0.975
T2	9 (6.4)	2 (3.8)		5 (5.8)	2 (4.1)	
T3	81 (57.9)	29 (54.7)		46 (53.5)	28 (57.1)	
T4a	41 (29.3)	18 (34.0)		30 (34.9)	15 (30.6)	
T4b	9 (6.4)	4 (7.5)		5 (5.8)	4 (8.2)	
cN stage, *n* (%)			0.216			0.819
N0	28 (20.0)	15 (28.3)		23 (26.7)	14 (28.6)	
N+	112 (80.0)	38 (71.7)		63 (73.3)	35 (71.4)	
cTNM stage, *n* (%)			0.510			0.867
II	36 (25.7)	17 (32.1)		28 (32.6)	16 (32.7)	
III	97 (67.9)	32 (60.4)		53 (61.6)	29 (59.2)	
IVa	9 (6.4)	4 (7.5)		5 (5.8)	4 (8.2)	

NCT = neoadjuvant chemotherapy, NICT = neoadjuvant immunotherapy plus chemotherapy, MIG = minimally invasive gastrectomy, PSM = proportion-score matching, SD = standard deviation, BMI = body mass index, NRS = nutritional risk screening, aCCI = age-adjusted Charlson comorbidity index, ASA = American Association of Anesthesiologists.

≥5 cm), operation time (<240 vs ≥240 min), estimated blood loss (<200 vs ≥200 mL), PNI score (<45 vs ≥45), SII index (<550 vs ≥550), NLR (<2.7 vs ≥2.7), and PLR (<145 vs ≥145).

Statistical analysis

SPSS (version 26.0; SPSS, Chicago, IL, USA) and R (version 4.2.2; R Foundation, Vienna, Austria) were used for statistical analyses. Propensity score matching with a 1:2 ratio was used to eliminate bias introduced by baseline characteristics. Categorical data were analysed using the chi-square or Fisher's exact test, whereas continuous data were analysed by using the Student's *t*-test or the Mann–Whitney *U* test. Mean ± standard deviation (SD) was used to represent continuous variables with normal distribution while median (interquartile range) was used to represent continuous variables skew distribution. Uni- and multivariate logistic regression analyses were used to evaluate risk factors for Clavien–Dindo grade ≥II POCs. GraphPad Prism (version 8.0) was used to present differences in perioperative laboratorial indices, including hemoglobin level, serum albumin level, NLR, PLR, SII index, and PNI score, between the two groups using violin plots and histograms. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between the NICT-MIG and NCT-MIG groups

After propensity score-matched analysis, a total of 135 patients, including 86 and 49 patients in the NCT-MIG and NICT-MIG groups, respectively, comprised the final study population. Baseline clinical parameters, including sex, age, BMI, aCCI score, NRS-2002 score, history of abdominal surgery, ASA grade, surgical approach, tumor resection, cT stage, cN stage, and cTNM stage, were not significantly different between the two groups. Comparison of the pathologic data revealed that the tumor ypT and ypTNM stages were earlier and the rates of nerve and vascular invasion were lower in the NICT-MIG group than in the NCT-MIG group ($P < 0.05$). No significant differences in tumor diameter and differentiation were noted between the two groups (Table 2).

The therapeutic effect and adverse events of neoadjuvant therapy

Table 3 presents the details of neoadjuvant therapy. The results indicated that the NICT-MIG and NCT-MIG groups did not exhibit significant differences in the number of treatment cycles and the NCT regimens. The objective response rate was significantly higher in the NICT-MIG group than in the NCT-MIG group (77.6%

Table 2. Pathological characteristics of the NICT-MIG and NCT-MIG groups after PSM

Pathological characteristic	NCT-MIG group ($n=86$)	NICT-MIG group ($n=49$)	P-value
ypT stage, *n* (%)			0.012
T0	7 (8.1)	10 (20.4)	
T1	9 (10.5)	10 (20.4)	
T2	14 (16.3)	8 (16.3)	
T3	40 (46.5)	14 (28.6)	
T4a	16 (18.6)	7 (14.3)	
ypN stage, *n* (%)			0.171
N0	37 (43.0)	27 (55.1)	
N1	14 (16.3)	8 (16.3)	
N2	10 (11.6)	3 (6.1)	
N3	25 (29.1)	11 (22.4)	
ypTNM stage, *n* (%)			0.012
0	7 (8.1)	10 (20.4)	
I	17 (19.8)	15 (30.6)	
II	28 (32.6)	11 (22.4)	
III	34 (39.5)	13 (26.5)	
Tumor diameters, cm, median (IQR)	3.5 (2.0–6.0)	3.0 (1.5–5.0)	0.113
Differentiation, *n* (%)			0.934
Well/moderate	45 (52.3)	26 (53.1)	
Poor/undifferentiated	41 (47.7)	23 (46.9)	
Nerve invasion, *n* (%)			0.025
Yes	25 (29.1)	6 (12.2)	
No	61 (70.9)	43 (87.8)	
Vascular invasion, *n* (%)			0.010
Yes	30 (34.9)	7 (14.3)	
No	56 (65.1)	42 (85.7)	
MMR status, *n* (%)			1.000
pMMR	83 (96.5)	47 (95.9)	
dMMR	3 (3.5)	2 (4.1)	
pCR rate, *n* (%)	7 (8.1)	10 (20.4)	0.039

NCT = neoadjuvant chemotherapy, NICT = neoadjuvant immunotherapy plus chemotherapy, MIG = minimally invasive gastrectomy, IQR = interquartile range, pMMR = proficient mismatch repair, dMMR = deficient mismatch repair, pCR = Pathological complete response.

Table 3. Preoperative treatment and radiological response between NCT-MIG and NICT-MIG groups

Treatment characteristic	NCT-MIG group ($n=86$)	NICT-MIG group ($n=49$)	P-value
Treatment cycle, *n* (%)			0.067
≤4	67 (77.9)	31 (63.3)	
>4	19 (22.1)	18 (36.7)	
Chemotherapy regimen, *n* (%)			0.845
SOX	53 (61.6)	35 (71.4)	
XELOX	17 (19.8)	7 (14.3)	
FOLFOX	3 (3.5)	1 (2.0)	
TS	11 (12.8)	5 (10.2)	
FLOT	2 (2.3)	1 (2.0)	
Radiological response, *n* (%)			0.021
CR	7 (8.1)	6 (12.2)	
PR	42 (48.8)	32 (65.3)	
SD	33 (38.4)	10 (20.4)	
PD	4 (4.7)	1 (2.0)	
ORR, *n* (%)	49 (57.0)	38 (77.6)	0.016
DCR, *n* (%)	82 (95.3)	48 (98.0)	1.000

NCT = neoadjuvant chemotherapy, NICT = neoadjuvant immunotherapy plus chemotherapy, MIG = minimally invasive gastrectomy, SOX = S-1 combined with oxaliplatin, XELOX = capecitabine combined with oxaliplatin, FOLFOX = oxaliplatin + calcium levofolinate + fluorouracil, TS = S-1 combined with nab-paclitaxel, FLOT = docetaxel + oxaliplatin + fluorouracil, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ORR = objective response rate, DCR = disease-control rate.

vs 57.0%, $P=0.016$), although the disease-control rate was comparable between the two groups (98.0% vs 95.3%, $P=1.000$). Similarly, the pathologic complete response (pCR) rate was significantly higher in the NICT-MIG group than in the NCT-MIG group (20.4% vs 8.1%, $P=0.039$).

The evaluation of TRAEs to compare the treatment safety between the two groups indicated that the rates of any-grade TRAEs and severe TRAEs were comparable between the NICT-MIG and NCT-MIG groups (77.6% vs 73.3%, $P=0.580$; 20.4% vs 18.6%, $P=0.798$) (Table 4). The most common TRAEs in both groups were hematopoietic events, such as leukopenia, thrombocytopenia, neutropenia, and anemia. No patient deaths due to TRAEs were observed during neoadjuvant therapy.

Preoperative laboratory indices

In the present study, preoperative laboratory indices, including hemoglobin level, albumin, total white blood count, neutrophil count, lymphocyte count, and platelet count, were used to calculate NLR, PLR, PNI score, and SII index. As shown in Table 5 and Supplementary Figure 2, compared with the patients in the NICT-MIG group, those in the NCT-MIG group had higher white blood count (5.42 [4.41–7.73] vs 4.43 [3.75–5.40] $\times 10^9$/L, $P=0.002$), neutrophil counts (3.36 [2.38–5.70] vs 2.69 [1.97–3.17] $\times 10^9$/L, $P=0.006$), and SII index (408.47 [245.27–958.85] vs 296.83 [189.11–444.56], $P=0.015$). Conversely, no significant between-group differences were observed in hemoglobin ($P=0.485$) and serum albumin ($P=0.478$) levels, NLR ($P=0.052$), PLR ($P=0.240$), or PNI score ($P=0.235$).

Surgical safety and post-operative recovery

Table 6 shows the comparison of variables related to surgical safety and post-operative recovery between the two groups. No significant differences were observed between the NCT-MIG and NICT-MIG groups in terms of intraoperative bleeding (100 [50–200] vs 100 [50–175] mL, $P=0.255$), operation time (234.58 ± 65.01 vs 234.51 ± 63.20 min, $P=0.995$), number of retrieved lymph nodes (27.59 ± 11.93 vs 26.80 ± 10.29, $P=0.696$), time to the first flatus (3.0 [3.0–5.0] vs 4.0 [3.0–5.0] days, $P=0.303$), R0 resection rate (90.7% vs 98.0%, $P=0.205$), surgical costs (7,281.75 ± 2,076.59 vs 7,501.88 ± 1,955.65 dollar, $P=0.546$), hospitalized costs (15,923.29 ± 5,894.49 vs 15,443.14 ± 3,036.78 dollar, $P=0.596$), and post-operative duration of hospitalization (8.0 [7.0–10.0] vs 9.0 [7.0–10.0] days, $P=0.623$).

Clavien–Dindo grade ≥II POCs were noted in 22 of the 86 patients (25.6%) in the NCT-MIG group and 15 of the 49 patients (30.6%) in the NICT-MIG group, with no significant difference between the two groups ($P=0.529$). The most common POCs were anemia and hypoproteinemia in both groups. The rate of severe morbidity was not significantly different between the NICT-MIG and NCT-MIG groups (6.1% vs 4.7%, $P=0.704$). One patient in the NICT-MIG group died because of acute pulmonary embolism, which was deemed not to be directly associated with neoadjuvant therapy by the multidisciplinary team.

Risk factors for POCs after NICT-MIG and NCT-MIG

By univariable binary logistic analysis, age, BMI, aCCI score, NRS-2002 score, estimated blood loss, and PNI score were associated with POCs (all $P<0.05$). Although not significantly associated with increased POCs risk, tumor diameter of ≥5 cm (odds ratio [OR] 2.004, 95% confidence interval [CI] 0.912–4.401, $P=0.084$) and PLR of ≥145 (OR 1.954, 95% CI 0.904–4.223, $P=0.088$) were included in a multivariate regression model using a cut-off P-value of <0.1 based on their previously demonstrated predictive value. By multivariate regression analysis, intracorporal blood loss of >200 mL (OR 4.092, 95% CI 1.397–11.991, $P=0.010$) and PNI score of <45 (OR 4.971, 95% CI 1.733–14.260, $P=0.003$) were

Table 4. Treatment-related adverse events between NCT-MIG and NICT-MIG groups

TRAE	NCT-MIG group ($n = 86$)			NICT-MIG group ($n = 49$)			*P*-value
	Total	Grade 1–2	Grade 3–4	Total	Grade 1–2	Grade 3–4	
Leukopenia	18	12	6	11	7	4	
Thrombocytopenia	14	12	2	6	4	2	
Neutropenia	11	9	2	6	3	3	
Nausea and vomiting	9	8	1	7	5	2	
Dysphagia	2	2	0	1	1	0	
Anemia	11	8	3	6	6	0	
Fatigue	7	7	0	4	4	0	
Aminotransferase increased	3	3	0	1	1	0	
Cholangitis	1	0	1	1	1	0	
Medicamentosa	2	1	1	1	1	0	
Peripheral neuropathy	1	1	0	1	1	0	
Gastric perforation	1	0	1	0	0	0	
Gastrorrhagia	1	0	1	1	1	0	
Acute kidney injury	1	0	1	0	0	0	
Hypothyroidism	1	1	0	0	0	0	
Diarrhea	0	0	0	2	2	0	
Overall TRAEs rate, *n* (%)	63 (73.3)			38 (77.6)			0.580
Severe TRAEs rate, *n* (%)	16 (18.6)			10 (20.4)			0.798

NCT = neoadjuvant chemo therapy, NICT = neoadjuvant immunotherapy plus chemotherapy, MIG = minimally invasive gastrectomy, TRAEs = treatment-related adverse event.

Table 5. Preoperative laboratory indexes between NCT-MIG and NICT-MIG groups

Variable	NCT-MIG group ($n = 86$)	NICT-MIG group ($n = 49$)	*P*-value
Hemoglobin level, g/L, mean ± SD	116.00 ± 21.54	113.43 ± 18.61	0.485
White blood count, $\times 10^9$/L, median, (IQR)	5.42 (4.41–7.73)	4.43 (3.75–5.40)	0.002
Total neutrophil count, $\times 10^9$/L, median, (IQR)	3.36 (2.38–5.70)	2.69 (1.97–3.17)	0.006
Total lymphocytes count, $\times 10^9$/L, mean ± SD	1.42 ± 0.80	1.32 ± 0.51	0.398
Platelet count, $\times 10^9$/L, mean±SD	170.15 ± 58.57	159.20 ± 69.36	0.331
Serum albumin level, g/L, mean±SD	37.55 ± 5.60	38.20 ± 4.25	0.478
NLR, median (IQR)	2.34 (1.53–5.29)	1.97 (1.44–2.87)	0.052
PLR, median (IQR)	127.06 (90.57–191.73)	116.72 (80.51–160.61)	0.240
PNI, mean ± SD	44.17 ± 6.38	45.63 ± 7.52	0.235
SII, $\times 10^9$/L, median (IQR)	408.47 (245.27–958.85)	296.83 (189.11–444.56)	0.015

NCT = neoadjuvant chemo therapy, NICT = neoadjuvant immunotherapy plus chemotherapy, MIG = minimally invasive gastrectomy, SD = standard deviation, IQR = interquartile range, NLR = neutrophil–lymphocyte ratio, PLR = platelet-lymphocyte ratio, PNI = Onodera's prognostic nutritional index, SII = systemic immune-inflammation index.

independent risk factors for POCs in patients undergoing MIG after neoadjuvant therapy (Table 7 and Supplementary Figure 3).

Discussion

In current clinical practice, neoadjuvant immunotherapy has demonstrated considerable promise in solid tumors due to several reasons, including the reduction in tumor burden, the elimination of tumor micrometastases, and the improvement of long-term survival rates [22, 23]. Liu *et al.* [24] suggested that these clinical benefits could be attributed to the activation of tumor-specific $CD8^+$ T cells in response to endogenous retroviral antigens, leading to the development of systemic antitumor immunity. The first clinical application of neoadjuvant anti-PD-1 therapy was reported by Forde *et al.* [25] in a study of 21 patients diagnosed with non-small cell lung cancer, showing that the treatment regimen was well tolerated with no surgical delays and unanticipated toxicities. In the past several years, NICT has been increasingly used together with other treatment modalities for the management of most solid tumors, garnering interest regarding the safety of administering NICT prior to surgery. To address these concerns, we sought to evaluate the surgical safety and perioperative outcomes of NICT vs NCT in patients with LAGC undergoing MIG.

TRAEs are representative indicators of medication safety. The Checkmate-649, Keynote-859, and ORIENT-16 trials demonstrated that the incidence of TRAEs in patients receiving chemo-immunotherapy was comparable with that in patients receiving chemotherapy alone for advanced GC [26–28]. In the present study, the incidence rates of any-grade and severe TRAEs were not significantly higher in the NICT-MIG group than in the NCT-MIG group. Furthermore, the univariate analysis did not reveal a significant association between severe TRAEs and POCs (OR 1.226, 95% CI 0.481–3.123, $P = 0.669$). Nonetheless, vigilance is advised regarding the potential adverse impact of preoperative therapy on surgical safety and post-operative recovery, such as immune, nutritional, and physical decline [29].

Tumor regression and pathologic downstaging are the most prominent advantages of neoadjuvant therapy. Some susceptible patients might acquire major pathologic response and even pCR after preoperative treatment, which might lead to better survival benefit [30]. In recent studies, NICT was associated with significantly higher pCR rates in triple-negative breast cancer [31], muscle-invasive bladder cancer [32], and colon cancer [33], among others. The superior effect of NICT is still presented in GC. A meta-analysis demonstrated that patients who received immune checkpoint inhibitor (ICI)-based neoadjuvant therapy achieved a pCR rate of 21% and a major pathologic response rate of 41% and that neoadjuvant therapy with ICIs plus

Table 6. Comparison of surgical characteristics and post-operative recovery between NCT-MIG and NICT-MIG groups

Variable	NCT-MIG group ($n = 86$)	NICT-MIG group ($n = 49$)	*P*-value
Surgical time, min, mean ± SD	234.58 ± 65.01	234.51 ± 63.20	0.995
Estimated blood loss, mL, median (IQR)	100 (50–200)	100 (50–175)	0.255
Number of retrieved lymph nodes, mean ± SD	27.59 ± 11.93	26.80 ± 10.29	0.696
Time to the first flatus, days, median (IQR)	3.0 (3.0–5.0)	4.0 (3.0–5.0)	0.303
Radical resection, *n* (%)			0.205
R0	78 (90.7)	48 (98.0)	
R1	8 (9.3)	1 (2.0)	
Combined resection, *n* (%)			1.000
Yes	5 (5.8)	3 (6.1)	
No	81 (94.2)	46 (93.9)	
Post-operative duration of hospitalization, days, median (IQR)	8.0 (7.0–10.0)	9.0 (7.0–10.0)	0.623
Surgical cost, dollars, mean ± SD	7,281.75 ± 2,076.59	7,501.88 ± 1,955.65	0.546
Hospitalized cost, dollars, mean ± SD	15,923.29 ± 5,894.49	15,443.14 ± 3,036.78	0.596
Total complication rate, *n* (%)	22 (25.6)	15 (30.6)	0.529
Clavien–Dindo classification			
Grade II			
Anastomosis hemorrhage	1	1	
Lymphatic leakage	1	0	
Anastomosis leakage	1	1	
Duodenal stump fistula	1	0	
Acute kidney injury	1	0	
Aminotransferase increased	1	0	
Anemia	6	4	
Pneumonia	2	0	
Hypoproteinemia	4	6	
Grade III			
Pancreatic fistula	1	0	
Anastomosis leakage	1	0	
Intestinal leakage	1	0	
Perianal abscess	0	1	
Pleural effusion	0	1	
Grade IV			
Intra-abdominal hemorrhage	1	0	
Grade V			
Acute pulmonary embolism	0	1	
Severe complication rate, *n* (%)	4 (4.7)	3 (6.1)	0.704

NCT = neoadjuvant chemo therapy, NICT = neoadjuvant immunotherapy plus chemotherapy, MIG = minimally invasive gastrectomy, SD = standard deviation, IQR = interquartile range.

radiochemotherapy exhibited the highest efficacy [34]. A prospective phase IIb trial reported that patients who received NICT (SOX combined with sintilimab) had better pCR rates (26.9%, 95% CI 11.6%–47.8%) than those who received NCT (4.8%, 95% CI 0.1%–23.8%) [15]. In the present study, the pCR rate was significantly different between the NICT-MIG and NCT-MIG groups (20.4% vs 8.0%, $P = 0.039$), similarly to that reported in previous studies. Further studies are warranted to determine whether a higher pCR rate achieved with NICT might provide potential survival benefit in patients with LAGC.

Post-operative recovery and complications are crucial indices of short-term safety and efficacy. Neoadjuvant therapy can increase the incidence of myelosuppression and malnutrition, decrease immune function, and aggravate tissue edema, fibrosis, and chronic inflammation, further increasing structural complexity, all of which can increase the risk of poor surgical safety and POCs [35]. Hong *et al.* [36] reported that esophagectomy was safe and feasible following NICT for locally advanced esophageal cancer. The Checkmate-816 study demonstrated that neoadjuvant nivolumab plus chemotherapy did not interfere with the feasibility of surgery for resectable non-small cell lung cancer [37]. These findings provide further evidence for the safety of surgery after NICT.

Due to its advantages, MIG is the predominantly utilized approach for radical gastrectomy in China. The safety of MIG as an approach after NCT has been extensively demonstrated [38–40]. However, the safety and feasibility of MIG after NICT remain controversial. In the present study, the operation time was not significantly longer, the estimated blood loss was not significantly higher, and the number of retrieved lymph nodes was not significantly lower in the NICT-MIG group than in the NCT-MIG group. Furthermore, the time to the first flatus, the length of post-operative hospital stay, surgical costs, and hospitalization costs were not significantly different between the two groups, which demonstrated the acceptable surgical safety and post-operative recovery achieved with NICT-MIG. Based on our initial clinical experience, tissue edema and fibrosis caused by neoadjuvant therapy indeed increase surgical difficulty, especially for lymph node dissection and exposure of perigastric vessels. However, we did not identify other risks associated with NICT-MIG compared to NCT-MIG in this study. We attribute this phenomenon to the advantages of MIG, which could improve visualization of the surgical field and delicate manipulation, counteracting the negative impact of combined neoadjuvant immunotherapy.

Many recent prospective studies have focused on the POCs of gastrectomy after NICT. In 2022, the American Society of Clinical Oncology reported the interim results of DANTE, an international multicenter phase IIb trial, showing that the rate of POCs was similar between the NICT and NCT groups (45% and 42%, respectively) [41]. Wang *et al.* [42] found no significant difference in the rate of POCs between MIG and open gastrectomy (33.3% vs 31.2%, $P = 1.000$) following NICT. In a study comparing short-term outcomes, Su *et al.* [13] reported comparable overall morbidity after

Table 7. Uni- and multivariate logistic regression analysis for Clavien–Dindo ≥ grade II post-operative complications after MIG following neoadjuvant therapy

Factor	Univariate analysis		P-value	Multivariate analysis		P-value
	OR	95% CI		OR	95% CI	
Sex			0.981			
Male	1.000					
Female	1.011	0.403–2.537				
Age, years			0.002			0.117
<70	1.000			1.000		
≥70	3.980	1.644–9.637		3.577	0.728–17.589	
BMI, kg/m^2			0.040			0.156
<25	1.000			1.000		
≥25	0.338	0.120–0.950		0.421	0.128–1.390	
Abdominal surgery			0.896			
No	1.000					
Yes	1.071	0.381–3.008				
cT stage			0.272			
$T_{2–3}$	1.000					
$T_{4a–4b}$	0.640	0.289–1.419				
cN stage			0.951			
N_0	1.000					
N_+	1.027	0.439–2.403				
Neoadjuvant immunotherapy			0.529			
No	1.000					
Yes	1.283	0.590–2.791				
Severe TRAEs			0.669			
No	1.000					
Yes	1.226	0.481–3.123				
aCCI score			0.015			0.460
<5	1.000			1.000		
≥5	2.639	1.210–5.754		1.630	0.446–5.948	
NRS-2002 score			0.043			0.476
<3	1.000			1.000		
≥3	2.219	1.026–4.797		0.672	0.226–2.005	
Surgical approach			0.361			
Laparoscopic	1.000					
Robotic	0.609	0.211–1.764				
Tumor diameter, cm			0.084			0.269
<5	1.000			1.000		
≥5	2.004	0.912–4.401		1.727	0.656–4.546	
Operation time, min			0.716			
<240	1.000					
≥240	1.153	0.536–2.479				
Estimated blood loss, mL			0.004			0.010
≥200	1.000			1.000		
>200	3.652	1.526–8.741		4.092	1.397–11.991	
PNI score			0.000			0.003
≥45	1.000			1.000		
<45	6.889	2.634–18.016		4.971	1.733–14.260	
SII index			0.391			
<550	1.000					
≥550	1.424	0.635–3.194				
NLR			0.993			
<2.7	1.000					
≥2.7	1.004	0.460–2.189				
PLR			0.088			0.292
<145	1.000			1.000		
≥145	1.954	0.904–4.223		1.714	0.629–4.668	

MIG = minimally invasive gastrectomy, OR = odd ratio, CI = confidence interval, BMI = body mass index, TRAEs = treatment-related adverse events, aCCI = age-adjusted Charlson comorbidity index, NRS-2002 = nutritional risk screening-2002, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, PNI = Onodera's prognostic nutritional index, SII = systemic immune-inflammation index, NLR = neutrophil–lymphocyte ratio, PLR = platelet-lymphocyte ratio.

laparoscopic gastrectomy between patients receiving NICT and those receiving NCT (30% and 30%, respectively; $P = 1.000$). In the present study, we observed no significant differences in overall or severe morbidity between the NICT-MIG and NCT-MIG groups. The combination of neoadjuvant immunotherapy was not significantly associated with POCs by univariate analysis (OR 1.283, 95% CI 0.590–2.791, $P = 0.529$). These results, which were similar to those of other studies, indicated MIG as a safe and efficient approach that could be performed after NICT. Moreover, our analyses indicated that an estimated blood loss of >200 mL was an independent risk factor for POCs after MIG in patients who received neoadjuvant therapy. Previous studies also demonstrated that more blood loss was a prognostic factor of POCs after gastrectomy [43, 44]. Therefore, the control of blood loss through appropriate intracorporal manipulation and enhanced perioperative management is necessary to prevent POCs.

The PNI score, which is calculated based on serum albumin level and total lymphocyte count, is a representative immune-nutritional marker. Previous studies reported that a lower PNI score was associated with POCs in patients undergoing surgery for gastrointestinal or lung cancer [18, 45]. Zhang *et al.* [46] suggested that remnant GC patients with a PNI score of <45 should be considered at high risk of weakened immune response and nutritional status. A multi-institutional data-set analysis revealed that clinically relevant POCs were more commonly observed in patients with low PNI scores [47]. In patients with LAGC, neoadjuvant therapy might increase the incidence of gastrointestinal toxicities, worsening the nutritional status. In the present study, we found that a lower preoperative PNI score was an independent risk factor for POCs in patients who underwent MIG after neoadjuvant therapy, which seemed to be a better pattern for post-operative risk prediction in NICT-MIG and NCT-MIG. Meanwhile, we should also attach importance to the potential value of PNI on tumor response and survival benefit [48, 49], so that it may provide surgeons with reliable references to make individualized therapeutic strategies.

We acknowledge the inherent limitations of the present study. First, due to the restriction of this exploratory retrospective study with small sample size, some bias might still exist despite the propensity score-matched analysis applied to balance baseline characteristics between the NICT-MIG and NCT-MIG groups. Second, because recent RCTs such as Checkmate-649 and ORIENT-16 demonstrated the survival benefit regardless of programmed death-ligand 1 expression in advanced GC, some patients in this retrospective study did not receive this test. Thus, we did not include this index in the present study. Third, NICT has been increasingly administered to patients with LAGC in recent years and its potential advantages are still at the initial stage. Thus, the neoadjuvant regimens and cycles were not combined in the present study, which might have affected the analyses of tumor response and survival benefit due to the small sample size. For further implementation of NICT for LAGC, more attention should be paid to individual lymph node dissection, a different approach to MIG [50], quality of life, potential advantages of total NICT, and exploration of biomarkers for predicting response to NICT. Meanwhile, multi-institutional prospective studies are necessary to provide high-level evidence on short- and long-term outcomes of MIG after NICT.

Conclusions

The present study revealed that NICT was associated with better radiologic and pathologic tumor response and acceptable TRAE incidence after MIG than NCT in patients with LAGC. MIG after NICT was safe and feasible to conduct in these patients. For patients with an estimated blood loss of >200 mL and those with a PNI score of <45, attention is warranted regarding increased risk of POCs after MIG following NICT or NCT.

Supplementary Data

Supplementary data is available at *Gastroenterology Report* online.

Authors' Contributions

H.C., L.C., and B.W. designed the study. H.C. and Z.Y. collected the data. H.C., J.X.C., W.Q.L., and L.Q.S. analysed and interpreted the data. H.C. prepared the manuscript. L.C. and B.W. provided whole guidance for the paper. All the authors read and approved the final manuscript.

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Conflicts of Interest

None declared.

References

1. Xia C, Dong X, Li H *et al.* Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl)* 2022;**135**:584–90.
2. Tan YE, Wang PL, Yin SC *et al.* Thirty-year trends in clinicopathologic characteristics and prognosis after gastrectomy for gastric cancer: a single institution in Northern China. *J Cancer* 2020; **11**:1056–62.
3. Wang FH, Zhang XT, Li YF *et al.* The Chinese Society of Clinical Oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. *Cancer Commun (Lond)* 2021; **41**:747–95.
4. Cann C, Ciombor KK. Systemic therapy for gastric cancer: perioperative strategies and beyond. *J Surg Oncol* 2022;**125**:1151–60.
5. Cunningham D, Allum WH, Stenning SP *et al.* Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;**355**:11–20.
6. Kang YK, Yook JH, Park YK *et al.* PRODIGY: a phase III study of neoadjuvant docetaxel, oxaliplatin, and S-1 plus surgery and adjuvant S-1 versus surgery and adjuvant S-1 for resectable advanced gastric cancer. *J Clin Oncol* 2021;**39**:2903–13.
7. Zhang X, Liang H, Li Z, RESOLVE study group *et al.* Perioperative or postoperative adjuvant oxaliplatin with S-1 versus adjuvant oxaliplatin with capecitabine in patients with locally advanced gastric or gastro-oesophageal junction adenocarcinoma undergoing D2 gastrectomy (RESOLVE): an open-label, superiority and non-inferiority, phase 3 randomised controlled trial. *Lancet Oncol* 2021;**22**:1081–92.
8. Tokunaga M, Sato Y, Nakagawa M *et al.* Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. *Surg Today* 2020;**50**:30–7.
9. Cui H, Cui JX, Zhang KC *et al.* Can a single-port robot be safely used for robotic total gastrectomy for advanced gastric cancer? First experience using the da Vinci SP platform. *Gastroenterol Rep (Oxf)* 2022;**10**:goac023.
10. Yu J, Huang C, Sun Y *et al.*; Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. *JAMA* 2019;**321**:1983–92.

11. Lombardi PM, Bernasconi D, Baiocchi GL *et al.*; Italian Research Group for Gastric Cancer (GIRCG). Open versus laparoscopic gastrectomy for advanced gastric cancer: a propensity score matching analysis of survival in a western population-on behalf of the Italian Research Group for Gastric Cancer. *Gastric Cancer* 2022;**25**:1105–16.
12. van der Wielen N, Straatman J, Daams F *et al.* Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer* 2021; **24**:258–71.
13. Su J, Guo W, Chen Z *et al.* Safety and short-term outcomes of laparoscopic surgery for advanced gastric cancer after neoadjuvant immunotherapy: a retrospective cohort study. *Front Immunol* 2022;**13**:1078196.
14. Tang X, Li M, Wu X *et al.* Neoadjuvant PD-1 blockade plus chemotherapy induces a high pathological complete response rate and anti-tumor immune subsets in clinical stage III gastric cancer. *Oncoimmunology* 2022;**11**:2135819.
15. Ding X, Wang X, Li B *et al.* PERSIST: a multicenter, randomized phase II trial of perioperative oxaliplatin and S-1 (SOX) with or without sintilimab in resectable locally advanced gastric/gastroesophageal junction cancer (GC/GEJC). *JCO* 2023;**41**:364.
16. Bang YJ, Van Cutsem E, Fuchs CS *et al.* KEYNOTE-585: phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. *Future Oncol* 2019;**15**:943–52.
17. Janjigian YY, Van Cutsem E, Muro K *et al.* MATTERHORN: phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. *Future Oncol* 2022; **18**:2465–73.
18. Onodera T, Goseki N, Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. *Nihon Geka Gakkai Zasshi* 1984;**85**:1001–5.
19. Hirahara N, Tajima Y, Matsubara T *et al.* Systemic immune-inflammation index predicts overall survival in patients with gastric cancer: a propensity score-matched analysis. *J Gastrointest Surg* 2021;**25**:1124–33.
20. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021;**24**:1–21. https://doi.org/10.1007/s10120-020-01042-y.
21. Katayama H, Kurokawa Y, Nakamura K *et al.* Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today* 2016;**46**:668–85.
22. Petricevic B, Kabiljo J, Zirnbauer R *et al.* Neoadjuvant immunotherapy in gastrointestinal cancers—the new standard of care? *Semin Cancer Biol* 2022;**86**:834–50.
23. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. *Science* 2020;**367**(6477): eaax0182. https://doi.org/10.1126/science.aax0182.
24. Liu J, Blake SJ, Yong MC *et al.* Improved efficacy of neoadjuvant compared to adjuvant immunotherapy to eradicate metastatic disease. *Cancer Discov* 2016;**6**:1382–99.
25. Forde PM, Chaft JE, Smith KN *et al.* Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med* 2018;**378**:1976–86.
26. Janjigian YY, Shitara K, Moehler M *et al.* First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;**398**:27–40.
27. Xu J, Jiang H, Pan Y *et al.* LBA53 Sintilimab plus chemotherapy (chemo) versus chemo as first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16): first results of a randomized, double-blind, phase III study. *Ann Oncol* 2021;**32**:S1331.
28. Rha SY, Wyrwicz LS, Weber PEY *et al.* VP1-2023: pembrolizumab (pembro) plus chemotherapy (chemo) as first-line therapy for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: phase III KEYNOTE-859 study. *Ann Oncol* 2023; **34**:319–20.
29. Tang Q, Zhao S, Zhou N *et al.* PD-1/PD-L1 immune checkpoint inhibitors in neoadjuvant therapy for solid tumors (Review). *Int J Oncol* 2023;**62**(4):49. https://doi.org/10.3892/ijo.2023.5497.
30. Li Z, Shan F, Wang Y *et al.* Correlation of pathological complete response with survival after neoadjuvant chemotherapy in gastric or gastroesophageal junction cancer treated with radical surgery: a meta-analysis. *PLoS One* 2018;**13**:e0189294.
31. Tarantino P, Gandini S, Trapani D *et al.* Immunotherapy addition to neoadjuvant chemotherapy for early triple negative breast cancer: a systematic review and meta-analysis of randomized clinical trials. *Crit Rev Oncol Hematol* 2021;**159**:103223.
32. Hu J, Chen J, Ou Z *et al.* Neoadjuvant immunotherapy, chemotherapy, and combination therapy in muscle-invasive bladder cancer: a multi-center real-world retrospective study. *Cell Rep Med* 2022;**3**:100785.
33. Zhou L, Yang XQ, Zhao GY *et al.* Meta-analysis of neoadjuvant immunotherapy for non-metastatic colorectal cancer. *Front Immunol* 2023;**14**:1044353.
34. Li S, Xu Q, Dai X *et al.* Neoadjuvant therapy with immune checkpoint inhibitors in gastric cancer: a systematic review and meta-analysis. *Ann Surg Oncol* 2023;**30**:3594–602.
35. Yu H, Xu L, Yin S *et al.* Risk factors and prognostic impact of postoperative complications in patients with advanced gastric cancer receiving neoadjuvant chemotherapy. *Curr Oncol* 2022; **29**:6496–507.
36. Hong ZN, Zhang Z, Chen Z *et al.* Safety and feasibility of esophagectomy following combined neoadjuvant immunotherapy and chemotherapy for locally advanced esophageal cancer: a propensity score matching. *Esophagus* 2022;**19**:224–32.
37. Forde PM, Spicer J, Lu S *et al.*; CheckMate 816 Investigators. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 2022;**386**:1973–85.
38. Li Z, Shan F, Ying X *et al.* Assessment of laparoscopic distal gastrectomy after neoadjuvant chemotherapy for locally advanced gastric cancer: a randomized clinical trial. *JAMA Surg* 2019;**154**:1093–101.
39. Ge R, Liu K, Zhang W *et al.* The safety and feasibility of laparoscopic gastrectomy after neoadjuvant chemotherapy for locally advanced gastric cancer. *J Oncol* 2022;**2022**:9511066.
40. Cui H, Zhang KC, Cao B *et al.* Short and long-term outcomes between laparoscopic and open total gastrectomy for advanced gastric cancer after neoadjuvant chemotherapy. *World J Gastrointest Surg* 2022;**14**:452–69.
41. Al-Batran S-E, Lorenzen S, Thuss-Patience PC *et al.* Surgical and pathological outcome, and pathological regression, in patients receiving perioperative atezolizumab in combination with FLOT chemotherapy versus FLOT alone for resectable esophagogastric adenocarcinoma: interim results from DANTE, a randomized, multicenter, phase IIb trial of the FLOT-AIO German Gastric Cancer Group and Swiss SAKK. *JCO* 2022;**40**:4003.
42. Wang Y, Lei X, Shan F *et al.* Safety and short-term outcomes of gastrectomy after preoperative chemotherapy plus immunotherapy versus preoperative chemotherapy: a retrospective cohort study. *BMC Cancer* 2022;**22**:1306.
43. Lin JX, Lin JP, Desiderio J *et al.* Difference in the short-term outcomes of laparoscopic gastrectomy for gastric carcinoma

between the east and west: a retrospective study from the IMIGASTRIC trial. *J Cancer* 2019;**10**:4106–13.
44. Lian B, Chen J, Li Z *et al.* Risk factors and Clavien-Dindo classification of postoperative complications after laparoscopic and open gastrectomies for gastric cancer: a single-center, large sample, retrospective cohort study. *Cancer Manag Res* 2020;**12**:12029–39.
45. Okada S, Shimada J, Teramukai S *et al.* Risk stratification according to the prognostic nutritional index for predicting postoperative complications after lung cancer surgery. *Ann Surg Oncol* 2018;**25**:1254–61.
46. Zhang Y, Wang LJ, Li QY *et al.* Prognostic value of preoperative immune-nutritional scoring systems in remnant gastric cancer patients undergoing surgery. *World J Gastrointest Surg* 2023;**15**:211–21.
47. Sasahara M, Kanda M, Ito S *et al.* The preoperative prognostic nutritional index predicts short-term and long-term outcomes of patients with stage II/III gastric cancer: analysis of a multi-institution dataset. *Dig Surg* 2020;**37**:135–44.
48. Ding P, Guo H, Sun C *et al.* Combined systemic immune-inflammatory index (SII) and prognostic nutritional index (PNI) predicts chemotherapy response and prognosis in locally advanced gastric cancer patients receiving neoadjuvant chemotherapy with PD-1 antibody sintilimab and XELOX: a prospective study. *BMC Gastroenterol* 2022;**22**:121.
49. Migita K, Matsumoto S, Wakatsuki K *et al.* A decrease in the prognostic nutritional index is associated with a worse long-term outcome in gastric cancer patients undergoing neoadjuvant chemotherapy. *Surg Today* 2017;**47**:1018–26.
50. Li ZY, Liu JJ, Yu PW *et al.* Robotic total gastrectomy for carcinoma in the remnant stomach: a comparison with laparoscopic total gastrectomy. *Gastroenterol Rep (Oxf)* 2021;**9**:583–8.