World Journal of Surgical Oncology

RESEARCH

Open Access

Identifying beneficial gastric cancer patient on prognosis after treating with perioperative or postoperative-only chemotherapy: a single-center real-world study

Weiwei Zhu[1,2†], Jiaqing Zhang[1,2†], Siwei Pan[2,3,4], Ruolan Zhang[1,2], Yanqiang Zhang[2,3,4], Qing Yang[2,3,4], Can Hu[2,3,4*] and Zhiyuan Xu[2,3,4*]

Abstract

Background This study evaluates the impact of perioperative S-1 and oxaliplatin (SOX) versus postoperative SOX or capecitabine and oxaliplatin (XELOX) on patient prognosis to identify suitable candidates for each therapy.

Method A retrospective real-world cohort study was conducted using data from Zhejiang Cancer Hospital on gastric cancer patients treated between 2010 and 2019. Patients were divided into perioperative SOX and postoperative SOX or XELOX groups. Propensity score matching (PSM) was used to control for selection bias. Overall survival (OS) was the primary outcome, analyzed using the Kaplan-Meier method and Cox regression.

Result A total of 816 patients were included: 293 in the perioperative SOX group and 523 in the postoperative chemotherapy group (408 SOX and 115 XELOX). In the perioperative SOX group, the tumor regression grade (TRG) 2–3 subgroup demonstrated a significantly worse overall survival (OS) compared to the postoperative XELOX group (95% CI = 1.064–3.444, $P = 0.027$). Subgroup analysis revealed that older patients (95% CI = 0.210–0.950, $P = 0.036$), and those at the cT3 (95% CI = 0.05–1.19, $P = 0.008$) stage experienced greater benefits from postoperative chemotherapy. When comparing the benefited populations, it was found that patients with CA125 positivity had an advantage trend with adjuvant chemotherapy compared to perioperative SOX chemotherapy.

Conclusion Real-world data suggest that perioperative SOX chemotherapy does not benefit all patients with advanced gastric cancer. Patients with TRG 2–3, older age, or cT3 stage may achieve better outcomes with postoperative chemotherapy. Additionally, an exploratory analysis indicated that CA125 positivity may be associated with improved survival following adjuvant treatment.

Keywords Gastric cancer, Real-world study, Propensity score matching, Neoadjuvant therapy

[†]Weiwei Zhu and Jiaqing Zhang contributed equally to this work.

*Correspondence:
Can Hu
hucanchina@163.com
Zhiyuan Xu
xuzy@zjcc.org.cn
[1]Second clinical medical College, Zhejiang Chinese Medical University, Hangzhou 310053, China
[2]Department of Gastric surgery, The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institutes of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou 310022, China
[3]Key Laboratory of Prevention, Diagnosis and Therapy of Upper Gastrointestinal Cancer of Zhejiang Province, Hangzhou 310022, China
[4]Zhejiang Provincial Research Center for Upper Gastrointestinal Tract Cancer, Zhejiang Cancer Hospital, Hangzhou 310022, China

Introduction

Gastric cancer is one of the most prevalent malignancies globally, ranking fifth in incidence and third in cancer-related mortality rates [1]. In China, gastric cancer has notably high incidence and mortality rates [2, 3].

Neoadjuvant chemotherapy has shown to eliminate micrometastatic cancer cells beyond the surgical margin, reduce the primary tumor size, and potentially achieve pathological complete response, thereby improving the R0 resection rate and patient survival [4–6]. The MAGIC trial established the treatment model of neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy [7]. In Asia, the ACTS-GC study [8] and the Korean CLASSIC study [9] confirmed the efficacy of D2 gastrectomy followed by postoperative chemotherapy—S-1 monotherapy or the XELOX regimen—as the standard approach for stage II–III gastric cancer. The latest RESOLVE study [10], which compared perioperative SOX to adjuvant XELOX and adjuvant SOX to adjuvant XELOX in patients with locally advanced cT4aN + M0 and cT4b-NxM0 gastric cancer undergoing D2 gastrectomy, demonstrated a significant survival benefit for perioperative SOX over adjuvant XELOX alone. However, the Japanese JCOG0501 study, involving 300 patients with stage III (lesions > 8 cm^3) to stage IV gastric cancer, found no significant survival difference between the neoadjuvant S-1/cisplatin group and the adjuvant chemotherapy group, indicating that neoadjuvant chemotherapy may not universally enhance survival [11]. Based on multiple study results, neoadjuvant therapy is not universally applicable and should be personalized for different patient populations.

Given these mixed results, the personalization of neoadjuvant therapy is essential. However, real-world data comparing perioperative and adjuvant chemotherapy regimens—particularly perioperative SOX versus adjuvant SOX or XELOX—remain limited, particularly under the RESOLVE study framework. To address this gap, we conducted a retrospective analysis using data from Zhejiang Cancer Hospital, applying the grouping strategy of the RESOLVE study. We evaluated the survival impact of perioperative SOX compared to adjuvant SOX and XELOX in patients with locally advanced gastric cancer. This study aims to provide practical evidence for the effectiveness of perioperative SOX and to identify subpopulations who may derive the greatest benefit, thereby informing more personalized treatment strategies in clinical practice.

Method

Patient population

We retrospectively collected real-world data from Zhejiang Cancer Hospital on gastric cancer patients who received perioperative SOX chemotherapy and surgery followed by adjuvant chemotherapy (SOX [S-1 + oxaliplatin] or XELOX [capecitabine + oxaliplatin]) between January 1, 2010, and December 31, 2019. Treatment decisions regarding neoadjuvant chemotherapy were made based on physician discretion, patient comorbidities, treatment tolerance, and clinical assessment at the time. These real-world factors contributed to the variation in treatment patterns. The inclusion criteria were: (1) pathologically confirmed gastric adenocarcinoma, clinical stage cT2-4aN1-3M0 (AJCC 8th edition); (2) undergoing D2 gastrectomy; (3) completion of 2–4 cycles of preoperative SOX neoadjuvant chemotherapy; and (4) completion of at least 3–4 cycles of adjuvant chemotherapy (SOX or XELOX). The exclusion criteria were: (1) concurrent other malignancies; (2) prior immunotherapy, radiotherapy, or other treatments; and (3) incomplete data. Based on these criteria, we included clinical and pathological data from 816 patients with locally advanced gastric cancer who received either perioperative or adjuvant chemotherapy. Among them, 523 patients received only adjuvant chemotherapy (surgery + adjuvant chemotherapy group), while 293 patients received perioperative SOX chemotherapy (perioperative SOX group). Following the classification method of the RESOLVE study, we divided patients into the perioperative SOX group, adjuvant XELOX group, and adjuvant SOX group, and further studied the perioperative SOX group versus the adjuvant XELOX group and the perioperative SOX group versus the adjuvant SOX group.

Outcome

The primary outcome measure was overall survival (OS), defined as the time from the first neoadjuvant chemotherapy session (or from the date of surgery for the surgery + adjuvant chemotherapy group) to the last effective follow-up or the time of death. Subgroup analyses of OS were also performed. We considered CEA > 5 ng/ml, CA199 > 37 U/ml, CA125 > 35 U/ml, AFP > 8.1 ng/ml, CA242 > 20 IU/ml, CA72-4 > 6.9 U/ml, and CA50 > 25 IU/ml as positive markers; otherwise, they were considered negative. Follow-up was conducted through outpatient visits, telephone calls, and social media platforms to determine the postoperative survival status of patients, with follow-up ending in September 2024. This retrospective study was approved by the Ethics Committee of Zhejiang Cancer Hospital (Ethics Approval No.: IRB-2023-960[IIT]), and informed consent was obtained from all patients.

Statistical analysis

To make the baseline characteristics of the two groups more comparable before the intervention and to eliminate selection bias and control for potential confounders, we used propensity score matching (PSM) to compare OS and preoperative tumor markers between the perioperative SOX group and the adjuvant XELOX group, as well as between the perioperative SOX group and the adjuvant SOX group. This method increases the likelihood that the study results reflect true effects. Balancing factors included cT stage, cN stage, sex, age, BMI, tumor location, Borrmann classification, and degree of tumor differentiation. PSM was performed at a 1:1 ratio (caliper value = 0.03). The matched groups showed good balance, with no statistically significant differences in cT stage, cN stage, sex, age, BMI, tumor location, Borrmann classification, or degree of tumor differentiation between the groups (all $P > 0.05$).

Categorical data were expressed as [n (%)], and comparisons between groups were made using the $\chi 2$ test or Fisher's exact test. Normally distributed continuous data were expressed as mean ± standard deviation ($x \pm s$), and comparisons between groups were made using the independent samples t-test. For non-normally distributed continuous data, median (range) was used, and comparisons were made using the Mann-Whitney U rank-sum test. Survival rates were estimated using the Kaplan-Meier method, and hazard ratios (HR) with 95% confidence intervals (CI) were reported. Subgroup analyses of balancing factors were performed and presented as forest plots. All tests were two-sided, with a significance level set at $\alpha = 0.05$, indicating that $P < 0.05$ was considered statistically

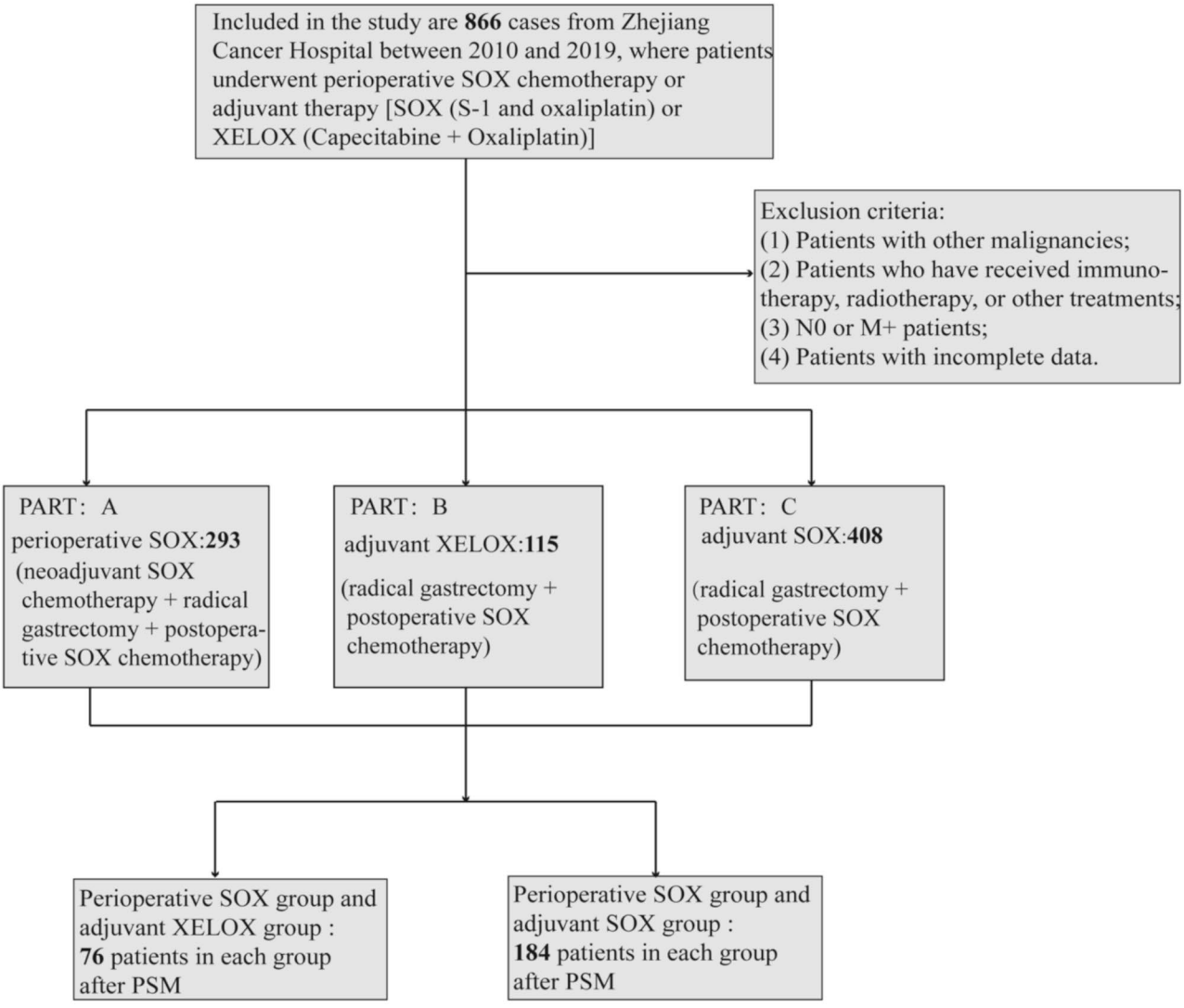

Fig. 1 A flowchart illustrating the patient enrollment process and the grouping into perioperative SOX and adjuvant XELOX/SOX groups

significant. Statistical analyses were performed using SPSS 26 and R 4.03 software packages.

Results

Propensity score matching results

Before PSM, patients in the adjuvant XELOX group were more likely to have a cT stage of T4, a cN stage of N3, and were younger compared to those in the perioperative SOX chemotherapy group, suggesting a selection bias between the groups. To eliminate the impact of this bias, PSM was conducted. After matching, 76 patients were included in each of the perioperative SOX and adjuvant XELOX groups, totaling 154 patients for survival analysis. The enrollment flow is detailed in Fig. 1. Post-matching comparisons between the two groups showed $P > 0.05$, indicating good balance and comparability of the controlled factors between the groups. A comparison of baseline characteristics before and after matching is shown in Table 1.

Prior to matching, patients in the adjuvant SOX group were more likely to present with a cT stage of T4, a cN stage of N3, were younger, had a higher body mass index, and were more frequently diagnosed with Borrmann type III, compared to those in the perioperative SOX chemotherapy group. These disparities indicate a potential selection bias. After PSM, 184 patients were included in each of the perioperative SOX group and the adjuvant SOX group, totaling 368 patients for analysis. Post-matching comparisons also showed $P > 0.05$, indicating good balance and high comparability of the controlled factors between the groups. A comparison of baseline characteristics before and after matching is shown in Table 2.

Comparison of tumor markers and treatment after propensity score matching

Compared to the adjuvant XELOX group, the perioperative SOX group had a higher preoperative CA125 positivity rate ($\chi^2 = 6.851$, $P = 0.022$) and lower rates of Lymphovascular and Blood Vessel Invasion (LBVI) ($\chi^2 = 23.750$, $P < 0.001$) and nerve invasion ($\chi^2 = 23.950$, $P < 0.001$). However, there were no significant differences between the groups in the levels of CEA, CA199, AFP, CA242, and CA72-4 ($P > 0.05$) (Table 3).

Similarly, when comparing the perioperative SOX group to the adjuvant SOX group, the perioperative SOX group had higher positivity rates for preoperative CEA ($\chi^2 = 10.265$, $P = 0.002$), CA19-9 ($\chi^2 = 0.738$, $P = 0.008$), CA125 ($\chi^2 = 8.993$, $P = 0.005$), and AFP ($\chi^2 = 7.113$, $P = 0.013$). The perioperative SOX group also had lower rates of LBVI ($\chi^2 = 63.121$, $P < 0.001$) and nerve invasion ($\chi^2 = 72.070$, $P < 0.001$) (Table 3).

Comparison of survival after propensity score matching and neoadjuvant chemotherapy prognostic factors

The adjuvant XELOX group showed a trend toward better survival compared to the perioperative SOX group (95% CI = 0.388–1.205, $P = 0.18$). The comparison of OS between the perioperative SOX group and the adjuvant SOX group showed similar survival rates (95% CI = 0.613–1.253, $P = 0.47$) (Fig. 2).

The efficacy of neoadjuvant chemotherapy significantly affects patient prognosis. A commonly used method to evaluate the efficacy of neoadjuvant chemotherapy is the Tumor Regression Grade (TRG) [12]. Therefore, we further divided the perioperative SOX chemotherapy group into TRG 0–1 (benefit from neoadjuvant chemotherapy) and TRG 2–3 (no significant benefit from neoadjuvant chemotherapy) [13] to explore the prognostic differences between patients who benefited or did not benefit from neoadjuvant chemotherapy and those who received adjuvant chemotherapy. Results showed no significant difference in OS between TRG0-1 patients in the perioperative SOX group and the adjuvant XELOX group (95% CI = 0.208–1.770, $P = 0.35$), although there was a trend toward better survival in the TRG0-1 group compared to the adjuvant XELOX group (Fig. 2e). The adjuvant XELOX group had significantly better OS than the TRG2-3 group (95% CI = 1.064–3.444, $P = 0.027$) (Fig. 2g). Additionally, TRG 0–1 patients in the perioperative SOX group had significantly better survival than TRG 2–3 patients (95% CI = 1.086–9.048, $P = 0.025$) (Fig. 2c).

Similarly, in the comparison between the perioperative SOX group and the adjuvant SOX group, long-term survival advantage was observed for TRG 0–1 patients (Fig. 2f). However, there was no observed advantage of adjuvant SOX chemotherapy over perioperative SOX in TRG 2–3 patients (95% CI = 0.545–1.162, $P = 0.23$) (Fig. 2h).

Subgroup analysis and characteristics of neoadjuvant chemotherapy benefit people

In the comparison of OS between the perioperative SOX group and the adjuvant XELOX group across various subgroups, factors such as cT stage, cN stage, gender, BMI, tumor location, Borrmann type, and histological differentiation did not significantly influence survival ($P > 0.05$). However, for patients older than 60 years (95% CI = 0.210–0.950, $P = 0.036$) and those with poorly differentiated histology (95% CI = 0.270–0.920, $P = 0.025$), adjuvant XELOX provided greater benefit (Fig. 3). Similarly, in the comparison between the perioperative SOX group and the adjuvant SOX group, there were no significant survival differences related to cN stage, gender, BMI, tumor location, Borrmann

Table 1 The basic data of perioperative gastric cancer patients in SOX group and adjuvant XELOX group were compared before and after propensity score matching

	Before PSM				After PSM		
	Perioperative SOX (*n* = 293)	**Adjuvant XELOX (*n* = 115)**	***P* value**		**Perioperative SOX (*n* = 76)**	**Adjuvant XELOX (*n* = 76)**	***P* value**
cT stage (%)			**< 0.001**	cT stage (%)			0.97
cT2	25 (8.5)	10 (8.7)		cT2	6 (7.9)	6 (7.9)	
cT3	124 (42.3)	10 (8.7)		cT3	10 (13.2)	9 (11.8)	
cT4	144 (49.1)	95 (82.6)		cT4	60 (78.9)	61 (80.3)	
cN stage (%)			**< 0.001**	cN stage (%)			0.92
cN1	78 (26.6)	31 (27.0)		cN1	21 (27.6)	23 (30.3)	
cN2	166 (56.7)	39 (33.9)		cN2	28 (36.8)	28 (36.8)	
cN3	49 (16.7)	45 (39.1)		cN3	27 (35.5)	25 (32.9)	
Gender (%)			1.000	Gender (%)			0.34
male	218 (74.4)	86 (74.8)		male	61 (80.3)	55 (72.4)	
female	75 (25.6)	29 (25.2)		female	15 (19.7)	21 (27.6)	
Age (%)			**0.013**	Age (%)			0.625
< 60	119 (40.6)	63 (54.8)		< 60	33 (43.4)	37 (48.7)	
≥ 60	174 (59.4)	52 (45.2)		≥ 60	43 (56.6)	39 (51.3)	
BMI (%)			0.188	BMI (%)			1.000
< 18.5	27 (9.2)	7 (6.1)		< 18.5	6 (7.9)	6 (7.9)	
18.5–24	200 (68.3)	73 (63.5)		18.5–24	53 (69.7)	53 (69.7)	
> 24	66 (22.5)	35 (30.4)		> 24	17 (22.4)	17 (22.4)	
Borrmann (%)			0.191	Borrmann (%)			0.958
I	20 (6.8)	3 (2.6)		I	2 (2.6)	3 (3.9)	
II	174 (59.4)	65 (56.5)		II	47 (61.8)	48 (63.2)	
III	62 (21.2)	33 (28.7)		III	21 (27.6)	19 (25.0)	
IV	37 (12.6)	14 (12.2)		IV	6 (7.9)	6 (7.9)	
Tumor site (%)			0.546	Tumor site (%)			0.967
Proximal 1/3	84 (28.7)	26 (22.6)		Proximal 1/3	22 (28.9)	23 (30.3)	
Middle 1/3	70 (23.9)	29 (25.2)		Middle 1/3	17 (22.4)	19 (25.0)	
Distal 1/3	128 (43.7)	57 (49.6)		Distal 1/3	36 (47.4)	33 (43.4)	
Whole	11 (3.8)	3 (2.6)		Whole	1 (1.3)	1 (1.3)	
Degree of differentiation (%)			1.000	Degree of differentiation (%)			0.505
Poorly	255 (87.0)	100 (87.0)		Poorly	62 (81.6)	66 (86.8)	
Medium to high	38 (13.0)	15 (13.0)		Medium to high	14 (18.4)	10 (13.2)	

Bold represent significant difference (*P* < 0.05)

Table 2 The basic data of perioperative gastric cancer patients in SOX group and adjuvant SOX group were compared before and after propensity score matching

	Before PSM			After PSM		
	Perioperative SOX (*n* = 293)	**Adjuvant SOX (*n* = 408)**	***P* value**	**Perioperative SOX (*n* = 184)**	**Adjuvant SOX (*n* = 184)**	***P* value**
cT stage (%)			**< 0.001**	cT stage (%)		0.815
cT2	25 (8.5)	54 (13.2)		cT2	21 (11.4)	24 (13.0)
cT3	124 (42.3)	42 (10.3)		cT3	41 (22.3)	37 (20.1)
cT4	144 (49.1)	312 (76.5)		cT4	122 (66.3)	123 (66.8)
cN stage (%)			**< 0.001**	cN stage (%)		0.653
cN1	78 (26.6)	118 (28.9)		cN1	54 (29.3)	62 (33.7)
cN2	166 (56.7)	135 (33.1)		cN2	90 (48.9)	86 (46.7)
cN3	49 (16.7)	155 (38.0)		cN3	40 (21.7)	36 (19.6)
Gender (%)			0.190	Gender (%)		0.808
male	218 (74.4)	322 (78.9)		male	141 (76.6)	138 (75.0)
female	75 (25.6)	86 (21.1)		female	43 (23.4)	46 (25.0)
Age (%)			**0.006**	Age (%)		0.207
< 60	119 (40.6)	210 (51.5)		< 60	87 (47.3)	74 (40.2)
≥ 60	174 (59.4)	198 (48.5)		≥ 60	97 (52.7)	110 (59.8)
BMI (%)			**0.002**	BMI (%)		0.522
< 18.5	27 (9.2)	25 (6.1)		< 18.5	14 (7.6)	18 (9.8)
18.5–24	200 (68.3)	255 (62.5)		18.5–24	127 (69.0)	117 (63.6)
> 24	66 (22.5)	115 (28.2)		> 24	14 (7.6)	18 (9.8)
Borrmann (%)			**< 0.001**	Borrmann (%)		0.351
I	20 (6.8)	17 (4.2)		I	14 (7.6)	10 (5.4)
II	174 (59.4)	260 (63.7)		II	122 (66.3)	111 (60.3)
III	62 (21.2)	113 (27.7)		III	39 (21.2)	50 (27.2)
IV	37 (12.6)	18 (4.4)		IV	9 (4.9)	13 (7.1)
Tumor site (%)			**0.001**	Tumor site (%)		0.743
Proximal 1/3	84 (28.7)	98 (24.0)		Proximal 1/3	51 (27.7)	60 (32.6)
Middle 1/3	70 (23.9)	74 (18.1)		Middle 1/3	42 (22.8)	36 (19.6)
Distal 1/3	128 (43.7)	232 (56.9)		Distal 1/3	88 (47.8)	85 (46.2)
Whole	11 (3.8)	4 (1.0)		Whole	3 (1.6)	3 (1.6)
Degree of differentiation (%)			0.284	Degree of differentiation (%)		1.000
Poorly	255 (87.0)	342 (83.8)		Poorly	154 (83.7)	153 (83.2)
Medium to high	38 (13.0)	66 (16.2)		Medium to high	30 (16.3)	31 (16.8)

Bold represent significant difference (*P* < 0.05)

type, or histological differentiation ($P > 0.05$). However, patients older than 60 years (95% CI = 0.610–0.970, $P = 0.028$) and those with cT3 stage (95% CI = 0.400–0.980, $P = 0.038$) might benefit more from adjuvant SOX (Fig. 3).

To further investigate the characteristic differences among patients with varying therapeutic responses, we distinguished between those who benefited from neoadjuvant therapy and those who did not, and performed a subgroup analysis including the XELOX group: there were no significant differences in cT stage, cN stage, gender, age, BMI, tumor location, Borrmann type, or histological differentiation between the TRG0-1 group and the adjuvant XELOX group, between the TRG 0–1 and TRG 2–3 groups, and between the TRG 2–3 and adjuvant XELOX groups (all $P > 0.05$). However, in the TRG 2–3 group, the proportion of preoperative CA125 positive patients (14.8%) was significantly higher compared to the adjuvant XELOX group (1.3%), with statistical significance ($P = 0.008$). This suggests that CA125 positive patients may not benefit from the perioperative SOX chemotherapy regimen (Table 4).

CA125 in patients with negative and positive contrast different treatments

In the analysis above, we identified CA125 as a characteristic marker. Therefore, we conducted further analysis of the survival status of patients with negative and positive CA125 expression under different treatments.

Perioperative SOX group vs. adjuvant XELOX group: For CA125 negative patients, the 5-year OS was 67.16% after perioperative SOX treatment, compared to 74.67% after adjuvant XELOX treatment ($P = 0.36$). For CA125 positive patients, the 5-year OS was 44.44% after perioperative SOX treatment, compared to 100% after adjuvant XELOX treatment ($P = 0.35$), indicating a trend of inferiority for perioperative SOX chemotherapy.

Perioperative SOX group vs. adjuvant SOX group: For CA125 negative patients, the 5-year OS was 71.15% after perioperative SOX treatment, compared to 71.37% after adjuvant SOX chemotherapy, with similar OS trends ($P = 0.74$). For CA125 positive patients, the 5-year OS was 61.90% after perioperative SOX treatment, compared to 83.33% after adjuvant SOX treatment ($P = 0.28$), again showing a trend of inferiority for perioperative SOX chemotherapy (Fig. 4).

Table 3 After propensity score matching perioperative SOX and auxiliary XELOX group, **perioperative SOX group and auxiliary SOX tumor markers in patients with gastric cancer and its treatment**

	Perioperative SOX ($n = 76$)	Adjuvant XELOX ($n = 76$)	*P* value		Perioperative SOX ($n = 184$)	Adjuvant SOX ($n = 184$)	*P* value
CEA (%)			0.155	CEA (%)			**0.002**
Negative	49 (64.5)	58 (76.3)		Negative	133 (72.3)	158 (89.0)	
Positive	27 (35.5)	18 (23.7)		Positive	51 (27.7)	26 (14.1)	
CA199 (%)			0.842	CA199 (%)			**0.008**
Negative	59 (77.6)	61 (80.3)		Negative	137 (74.5)	144 (78.3)	
Positive	17 (22.4)	15 (19.7)		Positive	47 (25.5)	40 (21.7)	
CA125 (%)			**0.022**	CA125 (%)			**0.005**
Negative	67 (88.2)	75 (98.7)		Negative	163 (88.6)	178 (96.7)	
Positive	9 (11.8)	1 (1.3)		Positive	21 (11.4)	6 (3.3)	
AFP (%)			0.123	AFP (%)			**0.013**
Negative	64 (84.2)	71 (93.4)		Negative	162 (88.0)	176 (95.7)	
Positive	12 (15.8)	5 (6.6)		Positive	22 (12.0)	8 (4.3)	
CA242 (%)			0.472	CA242 (%)			0.881
Negative	64 (84.2)	68 (89.5)		Negative	157 (85.3)	159 (86.4)	
Positive	12 (15.8)	8 (10.5)		Positive	27 (14.7)	25 (13.6)	
CA724(%)			0.458	CA724(%)			0.208
Negative	54 (71.1)	59 (77.6)		Negative	138 (75.0)	149 (81.0)	
Positive	22 (28.9)	17 (22.4)		Positive	46 (25.0)	35 (19.0)	
LBVI (%)			**< 0.001**	LBVI (%)			**< 0.001**
No	55 (72.4)	25 (32.9)		No	140 (76.9)	67 (36.4)	
Yes	21 (27.6)	51 (67.1)		Yes	42 (23.1)	117 (63.6)	
Neural invasion (%)			**< 0.001**	Neural invasion (%)			**< 0.001**
No	57 (75.0)	27 (35.5)		No	126 (69.2)	47 (25.5)	
Yes	19 (25.0)	49 (64.5)		Yes	56 (30.8)	137 (74.5)	

Bold represent significant difference ($P < 0.05$)

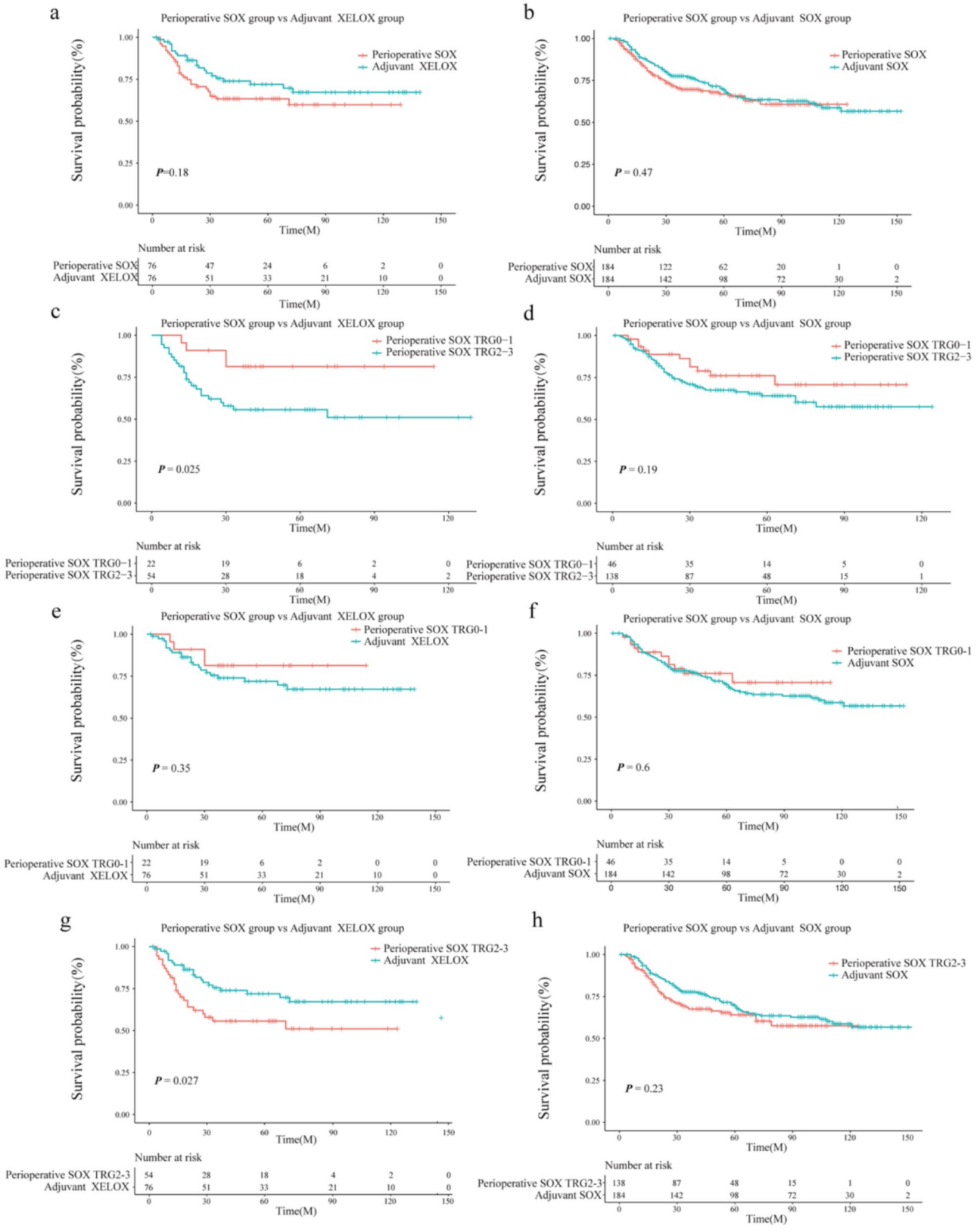

Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Perioperative SOX group and adjuvant XELOX group, perioperative SOX group and adjuvant SOX group overall and different TRG subgroups survival curves. (**a**) perioperative SOX group vs. adjuvant XELOX group (**b**) perioperative SOX group vs. adjuvant SOX group (**c**) In the adjuvant XELOX group and perioperative SOX group: TRG0-1 group vs. TRG2-3 group (**d**) In the adjuvant SOX group and perioperative SOX group: TRG0-1 group vs. TRG2-3 group (**e**) perioperative SOX TRG0-1 group vs. adjuvant XELOX group (**f**) perioperative SOX TRG0-1 group vs. adjuvant SOX group (**g**) perioperative SOX TRG2-3 group vs. adjuvant XELOX group (**h**) perioperative SOX TRG2-3 group vs. adjuvant SOX group

Discussion

In recent years, the application of neoadjuvant chemotherapy has increased the 5-year overall survival rate of gastric cancer patients [14, 15]. The RESOLVE study [10] which included 1094 patients with cT4aN + M0 or cT4bNxM0, divided participants into adjuvant XELOX group, adjuvant SOX group, and perioperative SOX group to compare the efficacy of perioperative SOX versus adjuvant XELOX treatment. The results demonstrated that perioperative SOX increased 3-year disease-free survival (DFS) by 8.3% compared to adjuvant XELOX, significantly improving survival rates. However, relying solely on clinical staging to decide perioperative chemotherapy plans lacks sufficient accuracy. For instance, Rossella et al. [16] summarized clinical studies on neoadjuvant chemotherapy for gastric cancer from 1993 to 2017, finding that two-thirds of neoadjuvant chemotherapy groups did not show a survival advantage. Although numerous studies on neoadjuvant chemotherapy for locally advanced gastric cancer have been conducted both domestically and internationally, there are contradictions regarding the suitable population for neoadjuvant SOX chemotherapy [17]. Based on these contradictory findings, this study aims to analyze the effects of perioperative SOX and adjuvant SOX and XELOX regimens using real-world data. We aim to explore the suitable populations for perioperative SOX and adjuvant chemotherapy, thereby providing clinical evidence for individualized treatment of patients.

This study found that patients in the perioperative SOX group had lower rates of LBVI and nerve invasion compared to the adjuvant XELOX/SOX groups, consistent with other studies [18]. Although this did not affect the final survival differences in this study, it suggests that perioperative SOX chemotherapy may reduce the likelihood of LBVI and nerve invasion in patients [15, 19].

The response to neoadjuvant treatment is significantly related to the prognosis of patients with advanced gastric cancer [20]. Studies have shown that patients with effective pathological responses have significantly better OS than those without effective pathological responses [12]. After PSM, survival did not differ significantly between perioperative SOX and adjuvant XELOX ($P = 0.18$) or SOX ($P = 0.47$). To account for varied neoadjuvant responses, the perioperative SOX group was stratified into TRG0-1 (responders) and TRG2-3 (non-responders) [13]. While OS did not differ between the TRG0-1 and adjuvant XELOX groups ($P = 0.35$), TRG2-3 patients had significantly worse OS compared to adjuvant XELOX ($P = 0.027$), suggesting limited benefit from neoadjuvant SOX in non-responders. No such difference was seen with adjuvant SOX, possibly due to limited sample size. Patients with TRG2-3 tend to have a poor response to neoadjuvant chemotherapy, often due to unfavorable tumor environments—such as poor blood supply or low oxygen levels—that limit drug delivery. In addition, some tumors may have built-in resistance mechanisms, like enhanced drug expulsion or resistance to cell death [21, 22]. As a result, these patients may benefit more from adjuvant chemotherapy after surgery, which targets any remaining tumor cells that were not affected by the initial treatment.

Age is an important factor affecting patient prognosis. Elderly patients undergoing neoadjuvant chemotherapy have more complications than younger patients [23], raising questions about the suitability of neoadjuvant chemotherapy for elderly patients with locally advanced gastric cancer. Kammy et al. [24] found that the median OS for patients aged ≥ 75 undergoing neoadjuvant chemotherapy was 34.9 months, compared to 32.3 months for those directly undergoing surgery ($P = 0.506$), with no significant difference. Caroline et al. [25] also pointed out that neoadjuvant chemotherapy does not increase surgical benefits for elderly patients but rather results in more adverse reactions. In a study of 1510 NSCLC patients receiving preoperative chemotherapy, they found that patients aged ≥ 75 had significantly higher complication rates ($P = 0.04$). Among elderly patients undergoing lung resection after neoadjuvant chemotherapy, 50.6% ($n = 41$) experienced one or more complications compared to 30.9% ($n = 25$) of younger controls, and these complications were more severe ($P = 0.03$). In this study, our subgroup analysis showed that patients aged > 60 could achieve better survival benefits with adjuvant XELOX ($P = 0.036$) or SOX ($P = 0.028$) compared to neoadjuvant SOX. This suggests that elderly patients may need to be more cautious in selecting neoadjuvant SOX chemotherapy.

The prognosis of gastric cancer is often closely related to certain serological markers. In this study, CA125 emerged as a significant differential factor ($P = 0.008$). Although survival differences by CA125

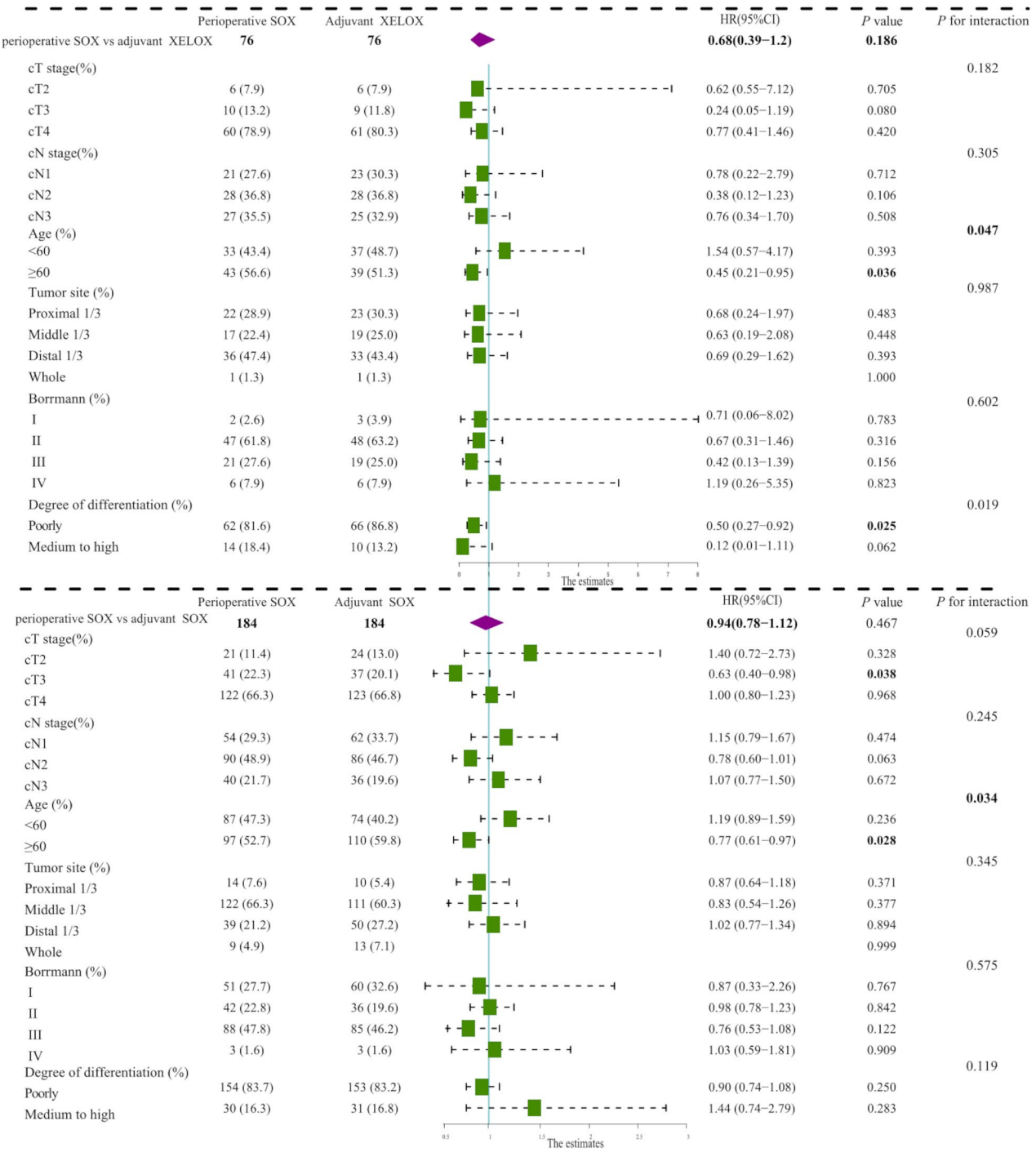

Fig. 3 Perioperative SOX and adjuvant XELOX group, perioperative SOX and adjuvant SOX subgroup analysis
Bold represent significant difference ($P < 0.05$)

status were not statistically significant ($P > 0.05$), likely due to small sample size, survival curves suggested that CA125-positive patients may have worse outcomes and might be less suited for neoadjuvant SOX chemotherapy. Studies suggest that CA125-positive patients may not be sensitive to chemotherapy, and preoperative neoadjuvant chemotherapy may cause the tumor to miss the optimal timing for R0 resection, leading to poorer survival [26]. Dae et al. [27] observed that CA125 positivity was an independent risk factor for non-therapeutic resection and recurrence in 679 gastric cancer patients, which also indicates the poor

Table 4 Characteristics of tumor markers in TRG0-1 group, TRG2-3 group and adjuvant XELOX group in perioperative SOX group were analyzed

	Perioperative SOX TRG2-3 ($n=54$)	Adjuvant XELOX ($n=76$)	*P* value	Perioperative SOX TRG0-1 ($n=22$)	Adjuvant XELOX ($n=76$)	*P* value	Perioperative SOX TRG0-1 ($n=22$)	Perioperative SOX TRG2-3 ($n=54$)	*P* value
CEA (%)			0.060			1			0.221
Negative	32 (59.3)	58 (76.3)		17 (77.3)	58 (76.3)		17 (77.3)	32 (59.3)	
Positive	22 (40.7)	18 (23.7)		5 (22.7)	18 (23.7)		5 (22.7)	22 (40.7)	
CA199 (%)			0.534			0.735			0.388
Negative	40 (74.1)	61 (80.3)		19 (86.4)	61 (80.3)		19 (86.4)	40 (74.1)	
Positive	14 (25.9)	15 (19.7)		3 (13.6)	15 (19.7)		3 (13.6)	14 (25.9)	
CA125 (%)			**0.008**			0.93			0.387
Negative	46 (85.2)	75 (98.7)		21 (95.5)	75 (98.7)		21 (95.5)	46 (85.2)	
Positive	8 (14.8)	1 (1.3)		1 (4.5)	1 (1.3)		1 (4.5)	8 (14.8)	
AFP (%)			0.069			1			0.499
Negative	44 (81.5)	71 (93.4)		20 (90.9)	71 (93.4)		20 (90.9)	44 (81.5)	
Positive	10 (18.5)	5 (6.6)		2 (9.1)	5 (6.6)		2 (9.1)	10 (18.5)	
CA242 (%)			0.297			1			0.499
Negative	44 (81.5)	68 (89.5)		20 (90.9)	68 (89.5)		20 (90.9)	44 (81.5)	
Positive	10 (18.5)	8 (10.5)		2 (9.1)	8 (10.5)		2 (9.1)	10 (18.5)	
CA724(%)			0.235			0.899			0.297
Negative	36 (66.7)	59 (77.6)		18 (81.8)	59 (77.6)		18 (81.8)	36 (66.7)	
Positive	18 (33.3)	17 (22.4)		4 (18.2)	17 (22.4)		4 (18.2)	18 (33.3)	

Bold represent significant difference ($P<0.05$)

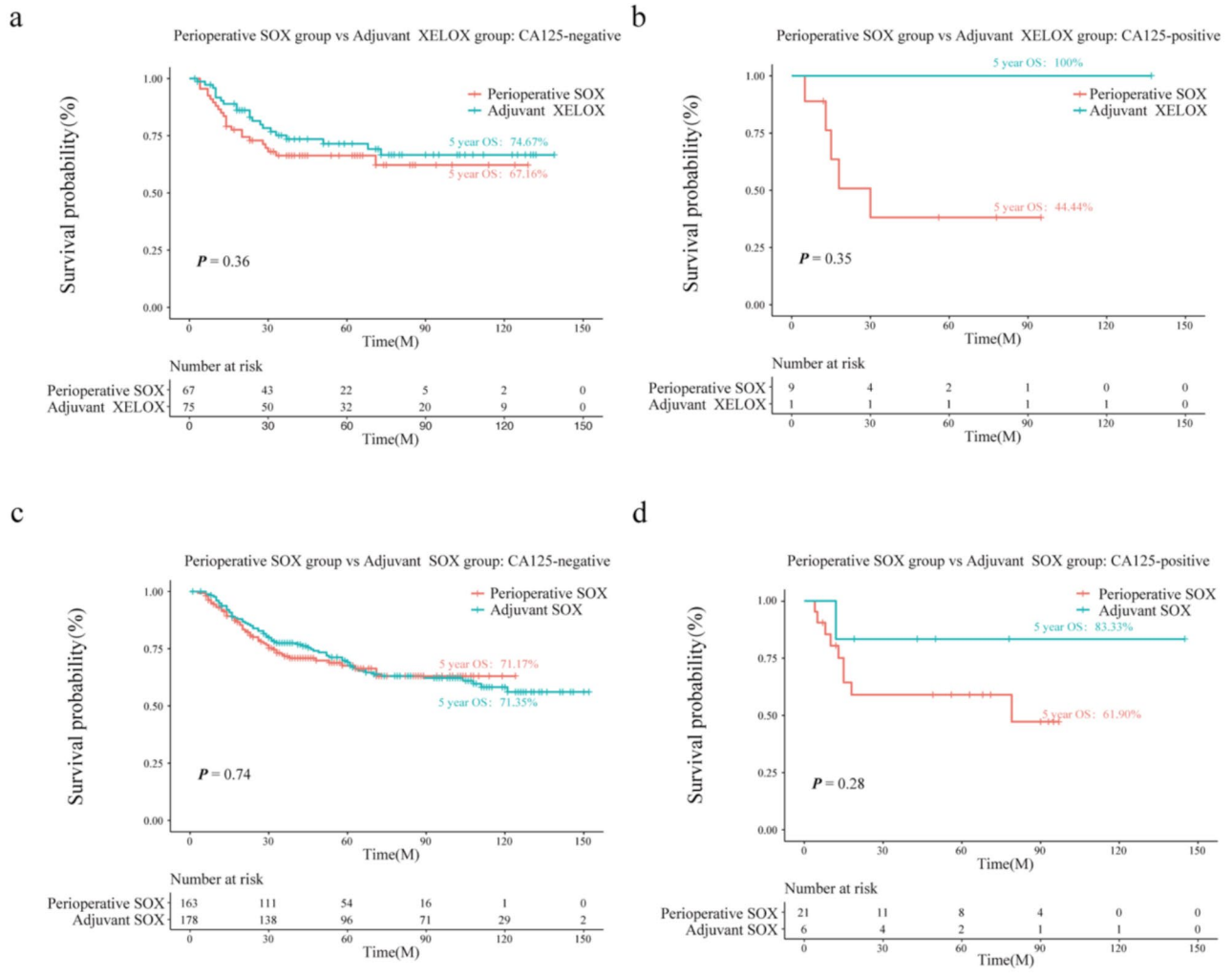

Fig. 4 Survival outcomes of CA125-negative and CA125-positive patients under different treatments. (**a**) Survival status of CA125-negative patients in the perioperative SOX group versus the adjuvant XELOX group. (**b**) Survival status of CA125-positive patients in the perioperative SOX group versus the adjuvant XELOX group. (**c**) Survival status of CA125-negative patients in the perioperative SOX group versus the adjuvant SOX group. (**d**) Survival status of CA125-positive patients in the perioperative SOX group versus the adjuvant SOX group

prognosis of CA125-positive patients. This suggests that while CA125 is not a universal marker for gastric cancer, it may have prognostic or predictive value for a specific group of patients. Further large-scale studies are necessary to explore the broader applicability of this marker in the management of gastric cancer.

This study has certain limitations. Unlike prospective studies such as FLOT and RESOLVE, this study is a retrospective analysis, and the results need further validation and refinement in prospective multicenter studies. Additionally, as a single-center study, the small number of patients collected may not represent patients from other hospitals. Moreover, although PSM balanced observable variables, retrospective comparisons may still be affected by unmeasured confounders. In some advanced-stage cases, neoadjuvant therapy may withhold due to factors like age, comorbidities, or surgical urgency—details not fully captured in our dataset. Therefore, more comprehensive data is needed in the future to further verify these ideas.

In summary, based on single-center real-world data, neoadjuvant SOX chemotherapy does not benefit all patients with advanced gastric cancer. Specifically, those with TRG 2–3, preoperative CA125 positivity, cT3 stage and older age is more appropriate for adjuvant chemotherapy. In future studies, we will continue to screen other influencing factors for continuous improvement and conduct external validation. We look forward to future studies with higher-level evidence to derive more reliable conclusions.

Acknowledgements
We thank the current and former members of our laboratories and collaborators for their contributions to the publications cited in this review article.

Author contributions
W.Z., Z.X. and C.H.conceived and designed the study.W.Z., S.P., Q.Y., R.Z. Y.Z. and J.Z. carried out data acquisition. W.Z., S.P.carried out the data preprocessing. W.Z., S.P. and J.Z. analyzed and interpreted the data. carried out the clinical deployment. W.Z., S.P. carried out the statistical analysis. W.Z., S.P. and C.H.wrote and revised the paper.

Funding
Medical Science and Technology Project of Zhejiang Province (WKJ-ZJ-2202, WKJ-ZJ-2104), National Natural Science Foundation of China (82304946, 82074245, 81973634, 81903842).

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

Declarations

Ethics approval and consent to participate
This retrospective study was approved by the Ethics Committee of Zhejiang Cancer Hospital (Ethics Approval No.: IRB-2023-960[IIT]), and informed consent was obtained from all patients.

Consent for publication
The content of this manuscript has not been previously published and is not under consideration for publication elsewhere. All of the authors agree to the content of the paper and their being listed as a co-author of the paper.

Competing interests
The authors declare no competing interests.

Received: 6 February 2025 / Accepted: 25 April 2025
Published online: 04 May 2025

References

1. KELLY R J, AJANI J A, KUZDZAL J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction Cancer [J]. N Engl J Med. 2021;384(13):1191–203.
2. YU J, HUANG C, SUN Y, et al. 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 [J]. JAMA. 2019;321(20):1983–92.
3. BRAY F, FERLAY J, SOERJOMATARAM I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. CA Cancer J Clin. 2018;68(6):394–424.
4. XU H, LI T, SHAO G, et al. Evaluation of neoadjuvant immunotherapy plus chemotherapy in Chinese surgically resectable gastric cancer: a pilot study by meta-analysis [J]. Front Immunol. 2023;14:1193614.
5. WANG F-H, ZHANG X-T TANGL, et al. The Chinese society of clinical oncology (CSCO): clinical guidelines for the diagnosis and treatment of gastric cancer, 2023 [J]. Cancer Commun (Lond). 2024;44(1):127–72.
6. WU A W, XU G W, WANG H, Y et al. Neoadjuvant chemotherapy versus none for resectable gastric cancer [J]. Cochrane Database Syst Rev, 2007, (2): CD005047.
7. CHOI A H, KIM J, CHAO J. Perioperative chemotherapy for resectable gastric cancer: MAGIC and beyond [J]. World J Gastroenterol. 2015;21(24):7343–8.
8. SASAKO M, SAKURAMOTO S, KATAI H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer [J]. J Clin Oncol. 2011;29(33):4387–93.
9. BANG Y-J, KIM Y-W, YANG H-K, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial [J]. Lancet. 2012;379(9813):315–21.
10. ZHANG X, LIANG H, LI Z, 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 [J]. Lancet Oncol. 2021;22(8):1081–92.
11. IWASAKI Y, TERASHIMA M, MIZUSAWA J, et al. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0501): an open-label, phase 3, randomized controlled trial [J]. Gastric Cancer. 2021;24(2):492–502.
12. TOMASELLO G, PETRELLI F. Tumor regression grade and survival after neoadjuvant treatment in gastro-esophageal cancer: A meta-analysis of 17 published studies [J]. Eur J Surg Oncology: J Eur Soc Surg Oncol Br Association Surg Oncol. 2017;43(9):1607–16.
13. YUAN S-Q, NIE R-C, JIN Y, et al. Perioperative Toripalimab and chemotherapy in locally advanced gastric or gastro-esophageal junction cancer: a randomized phase 2 trial [J]. Nat Med. 2024;30(2):552–9.
14. SHEN L-L, ZHENG H-L, DING F-H, et al. Delta computed tomography radiomics features-based nomogram predicts long-term efficacy after neoadjuvant chemotherapy in advanced gastric cancer [J]. Radiol Med. 2023;128(4):402–14.
15. AL-BATRAN S-E HOMANNN, PAULIGK C, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial [J]. JAMA Oncol. 2017;3(9):1237–44.
16. REDDAVID R, SOFIA S, CHIARO P, et al. Neoadjuvant chemotherapy for gastric cancer. Is it a must or a fake? [J]. World J Gastroenterol. 2018;24(2):274–89.
17. WANG X, LU C, WEI B, et al. Perioperative versus adjuvant S-1 plus oxaliplatin chemotherapy for stage II/III resectable gastric cancer (RESONANCE): a randomized, open-label, phase 3 trial [J]. J Hematol Oncol. 2024;17(1):17.
18. ZHOU Y, HE W, GUO P, et al. Development and validation of a Recurrence-Free survival prediction model for locally advanced esophageal squamous cell carcinoma with neoadjuvant chemoradiotherapy [J]. Ann Surg Oncol. 2024;31(1):178–91.
19. YILMAZ A, DUYAR S S CAKIRE, et al. Clinical impact of visceral pleural, lymphovascular and perineural invasion in completely resected non-small cell lung cancer [J]. Eur J Cardiothorac Surg. 2011;40(3):664–70.
20. LIU C, LI L, CHEN X, et al. Intratumoral and peritumoral radiomics predict pathological response after neoadjuvant chemotherapy against advanced gastric cancer [J]. Insights Imaging. 2024;15(1):23.
21. HOLOHAN C, VAN SCHAEYBROECK S, LONGLEY D B, et al. Cancer drug resistance: an evolving paradigm [J]. Nat Rev Cancer. 2013;13(10):714–26.
22. GOTTESMAN MM. Mechanisms of cancer drug resistance [J]. Annu Rev Med. 2002;53:615–27.
23. SYLVIE L, SILVIA S, SALAH-EDDIN A-B, et al. Impact of age on the feasibility and efficacy of neoadjuvant chemotherapy in patients with locally advanced oesophagogastric cancer [J]. Eur J Cancer. 2015;51(14):1918–26.
24. KEYWANI K, BORGSTEIN A B J, ESHUIS W J, et al. Neoadjuvant chemotherapy in older patients with gastric cancer undergoing surgery: a population-based cohort study [J]. Gastric Cancer. 2023;26(5):763–74.
25. RIVERA C, JOUGON J, DAHAN M, et al. Are postoperative consequences of neoadjuvant chemotherapy for non-small cell lung cancer more severe in elderly patients? [J]. Lung Cancer. 2012;76(2):216–21.
26. KAWAI J, YASUFUKU I, FUKADA M, et al. Successful R0 resection after chemotherapy, including nivolumab, for gastric cancer with liver metastases: three case reports [J]. Surg Case Rep. 2024;10(1):138.
27. KIM D H, YUN H Y, RYU D H, et al. Preoperative CA 125 is significant indicator of curative resection in gastric cancer patients [J]. World J Gastroenterol. 2015;21(4):1216–21.

Publisher's note