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Comparison of PSOX (paclitaxel, oxaliplatin, S-1) and SOX (oxaliplatin, S-1) as postoperative adjuvant chemotherapy for stage II-III gastric cancer

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Abstract

Background Adjuvant chemotherapy is the conventional treatment for stage II and III gastric cancer(GC). Postoperative doublet chemotherapy has consistently shown improved survival outcomes in advanced-stage GC patients compared to single-agent regimens. Triplet regimens have shown significant survival benefits in the perioperative settings. This retrospective study evaluated the efficacy and safety of paclitaxel/S-1/oxaliplatin (PSOX) compared to S-1/oxaliplatin (SOX) as postoperative adjuvant chemotherapy in stage II-III GC patients following D2 gastrectomy.

Methods A retrospective review was conducted on patients with histologically confirmed stage II-III gastric cancer who underwent D2 gastrectomy at Jiangsu Cancer Hospital, categorizing them into two groups. A total of 75 patients were included in PSOX group and 81 patients in the SOX group between April 2018 and August 2021. Patients in PSOX group received paclitaxel (120 mg/m^2), oxaliplatin (100 mg/m^2) and S-1 (80 – 60 mg/d) per cycle, while those patients in SOX group were administrated oxaliplatin (130 mg/m^2) and S-1 (80–120 mg/d) per cycle. Patients from both groups were matched in a 1:1 ratio using propensity scores to assess differences in disease-free survival (DFS) and safety.

Results The 3-year DFS rate was 78.2% for the PSOX group and 74.0% for the SOX group ($P=0.355$), with a hazard ratio for peritoneal relapse of 0.287 (95% CI, 0.090–0.915; $P=0.035$). Subgroup analysis indicated that stage IIIC GC patients in the PSOX group had a higher DFS rate than those in the SOX group($P=0.032$). Grade 3 or 4 adverse events, as per the National Cancer Institute Common Toxicity Criteria, such as leucopenia (10.6% vs. 4.5%), neutropenia (10.6% vs. 9.1%), nausea/vomiting (4.5% vs. 3.0%), and diarrhea (4.5% vs. 3.0%) were relatively common in the PSOX group compared to the SOX group, with no statistically significant differences between the two groups.

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Conclusion Our findings suggested that adjuvant PSOX chemotherapy offers superior survival benefits compared to the SOX regimen in patients with staged IIIC GC after D2 gastrectomy. The incidence of adverse events with PSOX chemotherapy was comparable to that of SOX chemotherapy.

Keywords Gastric cancer, Gastrectomy, Adjuvant chemotherapy, Paclitaxel, Oxaliplatin, S-1

Introduction

Globally, gastric cancer (GC) is a leading malignant tumor, noted for its high morbidity and mortality [1]. Surgical resection is the preferred treatment for early-stage GC patients. In East Asia, gastrectomy with D2 lymph node dissection is the standard surgical method [2, 3]. In Western countries, D2 dissection is advised for radical gastrectomy due to a Dutch trial showing it lowers local recurrence and GC mortality [4]. Despite potentially curative surgery, about 50% of patients face recurrence within 5 years, with 50–90% succumbing to tumor recurrence [5, 6]. Studies indicate that patients completing postoperative adjuvant treatment experience notably improved disease-free survival (DFS) and overall survival (OS) [7], highlighting the need for more effective adjuvant chemotherapy (AC) development.

An early clinical trial in Japan indicated that S-1 enhances survival following D2 gastrectomy [8]. S-1 is considered a convenient alternative to continuous 5-FU infusion due to its lower risk profile [9]. The Japanese ACT-GC trial found that adjuvant S-1 monotherapy improved relapse-free survival (RFS) and overall survival (OS) compared to surgery alone. Furthermore, the combination of adjuvant oxaliplatin and S-1 (SOX) has demonstrated survival benefits and is now an established therapeutic option for gastric cancer [10, 11]. The ARTIST 2 trial reported that 3-year DFS rates of 64.8% and 74.3% in the S-1 and SOX groups, respectively. In patients with stage II/III, node-positive GC who underwent D2 resection, SOX regimen was more effective in extending DFS than S-1 monotherapy [12]. Nonetheless, even with dual adjuvant chemotherapy, some stage III GC patients continue to experience a poor prognosis. This underscores the necessity for improved adjuvant chemotherapy protocols. The PSOX regimen, combining paclitaxel, oxaliplatin and S-1, has demonstrated a notable survival advantage in the perioperative treatment of advanced gastric cancer(AGC) [13]. Additionally, a study looked into the safety and efficacy of PSOX in comparison to the DOF (docetaxel/oxaliplatin/fluorouracil) and SOX regimens as neoadjuvant chemotherapy for AGC. The PSOX group demonstrated the highest total effective and disease control rates with no significant severe adverse events(AEs) [14]. However, there is a lack of direct comparative studies on the effectiveness of adjuvant PSOX versus SOX in GC patients post-D2 gastrectomy. This retrospective study was conducted to assess the efficacy and safety of adjuvant PSOX compared to SOX in patients with stage II-III GC. This study aimed to compare 3-year DFS between PSOX and SOX regimens as postoperative adjuvant treatments. The secondary objective was to assess and compare the adverse events associated with each regimen.

Methods and materials

Patients

This study retrospectively included consecutive gastric cancer patients diagnosed at Jiangsu Cancer Hospital from April 2018 to August 2021. All diagnostic and therapeutic procedures were conducted in accordance with established guidelines. Eligibility criteria included: (1) Individuals aged 18–80 years; (2) Histologically confirmed stage II or III gastric carcinoma, including gastroesophageal junction carcinoma(Siewart type III), post-R0 resection with D2 lymph node dissection and no metastatic disease; (3) Karnofsky Performance Status (KPS) score of ≥ 70; (4) No prior systemic antitumor treatments such as chemotherapy, immunotherapy or radiotherapy; (5) No other malignancies in the past few years; (6) Adequate organ function; (7) All patients provided written informed consent prior to treatment. Exclusion criteria encompassed: (1) Other primary malignancies, gastrointestinal bleeding or contraindications to corticosteroids; (2) Allergy or intolerance to study drugs; (3) Inability to proceed with adjuvant chemotherapy, even with one regimen; (4) Severe consciousness disorders, significant organ insufficiencies, hematologic disorders, or autoimmune diseases; (5) Serious injuries or infections occurring during therapy.

Treatment method

Patients meeting the eligibility criteria were allocated to either the PSOX or SOX group. In the PSOX group, patients received paclitaxel at a dose of 120mg/m^2 administered intravenously (iv.) on day 1 and 8, along with oxaliplatin (Jiangsu Hengrui Pharmaceutical Co., Ltd) at 100 mg/m^2 iv. on day 1, oral S-1 (Jiangsu Hengrui Pharmaceutical Co., Ltd) is administered at a dose of 40–60 mg, based on body surface area (BSA): 40 mg for BSA < 1.25 m^2, 50 mg for BSA between 1.25 and 1.5 m^2, and 60 mg for BSA > 1.5 m^2. S-1 was given twice daily on days 1–14 in each 3-week cycle, over six cycles. In the SOX group, patients were administered oral S-1 at 40–60 mg per dose twice daily from days 1 to 14, in combination with 130 mg/m^2 of intravenous oxaliplatin

on the first day of each three-week cycle, for a total of six cycles.

Follow-up

All patients underwent at least three follow-up visits, which included both in-person hospital visits and telephone follow-ups. The follow-up period commenced on the surgery date and extended until February 2, 2024, or loss of follow-up. DFS is the period from the first day after surgery until recurrence, metastasis, or death occurs. Tumor recurrence was identified through imaging or pathology confirmation of local recurrence or metastasis.

Statistical methods

Statistical analysis of all data was performed with SPSS 27.0 and Stata MP18 software. Categorical variables were analyzed with Chi-square or Fisher's exact tests, and continuous variables with the Mann-Whitney U test. A P-value under 0.05 was deemed statistically significant. Survival analysis utilized the Kaplan-Meier method to plot the survival curve. The log-rank test was used to compare time-to-event curves for DFS. The Cox proportional-hazards model was employed to compute hazard ratios (HRs) and 95% confidence intervals (CIs). Propensity score matching (PSM) was employed to minimize baseline characteristic disparities between the PSOX and SOX groups. Patients were matched using PSM with a 1:1 nearest neighbor method and a caliper size of 0.02. PSM includes gender, age, KPS score, gastrectomy and tumor T stage.

Results

Baseline characteristics

The analysis included 156 patients with stage II-III GC who underwent postoperative adjuvant chemotherapy and were monitored at Jiangsu Cancer Hospital and Research Institute from April 2018 to August 2021. Among them, 75 patients were in the PSOX and 81 in the SOX group. The two groups were matched using PSM at a 1:1 ratio, based on age, gender, KPS, gastrectomy and tumor T stage to ensure comparability. There were 132 patients in total, with 66 assigned to the PSOX group and 66 to the SOX group. Figure 1 illustrates the trial profile. In the initial dataset, there was an uneven distribution of gastrectomy and tumor T stage across the two groups. After 1:1 PSM, the covariates were balanced between the two groups, with no statistically significant differences observed (Table 1).

Survival analysis

The follow-up period was extended to February 2024, with the PSOX group having a median follow-up of 45 months (15.3–72.8) and the SOX group having 48 months

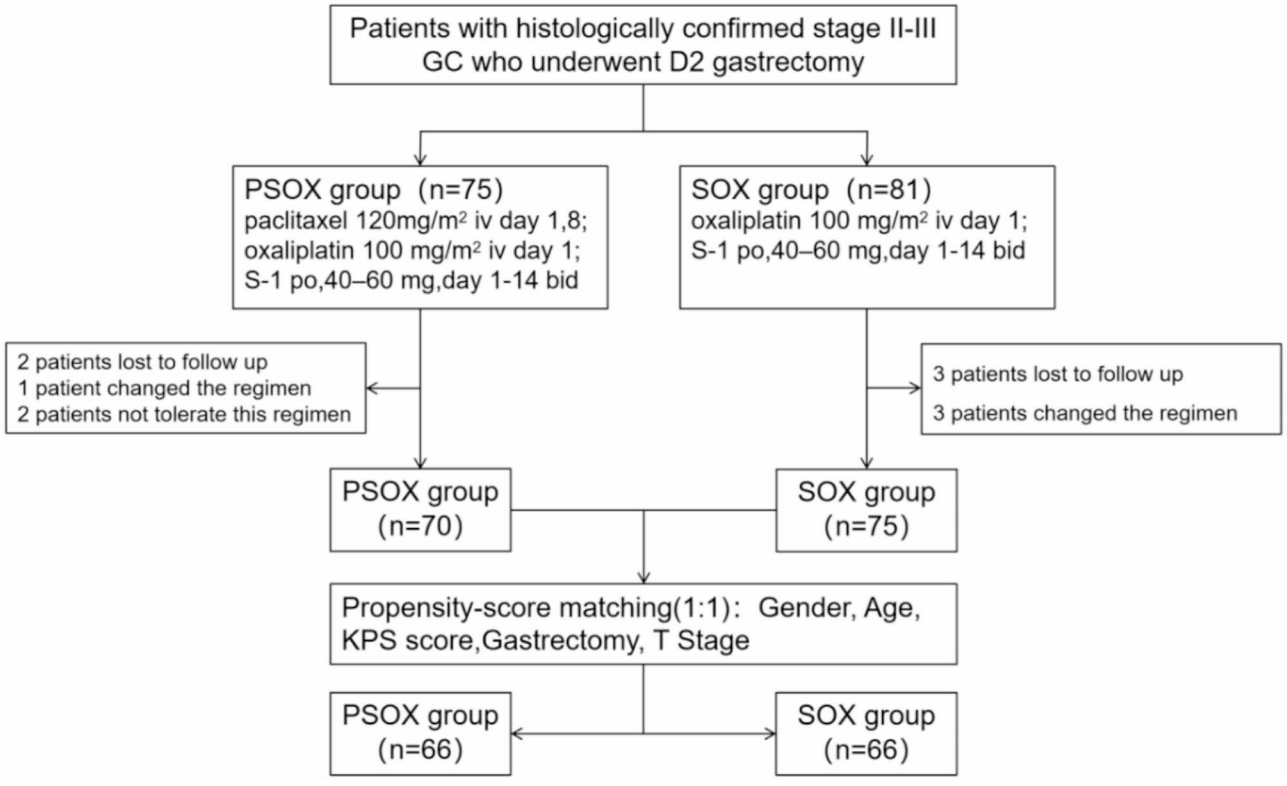

Fig. 1 Trial flowchart

Table 1 Patients baseline characteristics between two groups before and after matching

Parameter	Before matching			After matching		
	PSOX *n* = 70(100%)	SOX *n* = 75(100%)	*P* value	PSOX *n* = 66(100%)	SOX *n* = 66(100%)	*P* value
Gender			0.443*			1.000*
Male	49(70%)	48(64%)		45(68%)	45(68%)	
Female	21(30%)	27(36%)		21(32%)	21(32%)	
Age(years)			0.827*			0.861*
Median	60(31–76)	60(26–80)		60(31 ~ 76)	61(26 ~ 80)	
<60	33(47%)	34(45%)		29(44%)	28(42%)	
≥ 60	37(53%)	41(55%)		37(56%)	38(58%)	
KPS score			0.536*			0.359*
90–100	50(71%)	50(67%)		46(70%)	41(62%)	
70–80	20(29%)	25(33%)		20(30%)	25(38%)	
Gastrectomy			0.009*			0.721*
total	34(49%)	34(45%)		34(52%)	32(49%)	
distal	24(34%)	35(47%)		24(36%)	28(42%)	
proximal	12(17%)	6(8%)		8(12%)	6(9%)	
Lauren's classification			0.686*			0.397*
Diffuse	31(44%)	29(39%)		30(45%)	23(35%)	
Intestinal	14(20%)	14(19%)		13(20%)	13(20%)	
Mixed	25(36%)	32(42%)		23(35%)	30(45%)	
Grade			0.418*			0.449*
Low differentiation	51(73%)	50(67%)		48(73%)	44(67%)	
Medium differentiation	19(27%)	25(33%)		18(27%)	22(33%)	
Histological type			0.453*			1.000*
Signet cell carcinoma	9(13%)	13(17%)		9(14%)	9(14%)	
Adenocarcinoma	61(87%)	62(83%)		57(86%)	57(86%)	
Tumor T Stage			0.001[a]			0.382[a]
T1	1(1%)	5(7%)		1(2%)	5(7%)	
T2	13(19%)	10(13%)		12(18%)	9(14%)	
T3	16(23%)	16(21%)		16(24%)	14(21%)	
T4	40(57%)	44(59%)		37(56%)	38(58%)	
Nodal stage			0.974*			0.906*
N0	8(11%)	7(9%)		8(12%)	7(11%)	
N1	20(59%)	21(28%)		18(27%)	15(23%)	
N2	23(33%)	25(33%)		22(34%)	25(38%)	
N3	19(27%)	22(29%)		18(27%)	19(29%)	
TNM stage(UICC 8th)			0.913*			0.959*
II	24(34%)	28(37%)		23(35%)	25(38%)	
IIIA	14(20%)	14(19%)		14(21%)	12(18%)	
IIIB	16(23%)	14(19%)		14(21%)	13(20%)	
IIIC	16(23%)	19(25%)		15(23%)	16(24%)	
Harvested lymph nodes						
Median	32(20–51)	34(17–49)	0.663[b]	32(20–49)	33(17–49)	0.471[b]

*, Chi-square test; [a], Fisher's exact test; [b],Mann-Whitney U test; PSOX, paclitaxel/oxaliplatin/S-1; SOX, oxaliplatin/S-1;UICC, International Union Against Cancer (UICC) TNM Classification of Malignant Tumours

(25.3–75.3). Before conducting PSM, 3-year disease-free survival rate for the SOX group were comparable to that of the PSOX group (72.8% vs. 74.7%, $P = 0.642$) (Fig. 2a). Within the PSOX group, patients with stage IIIC demonstrated a higher disease-free survival rate compared to those in the SOX group, though not statistically significant ($P = 0.053$, Fig. 2b).

After matching, the 3-year DFS rate was 78.2% for the PSOX group and 74.0% for the SOX group, with no statistically significant difference ($P = 0.355$) (Fig. 3). 25 patients (37.8%) in the PSOX group had recurred, 13 of the cases were diffuse type GC and 20 were low differentiation GC. In contrast, the SOX group had 31 patients (46.9%) with recurrence, including 13 diffuse type GC and 25 low differentiation GC. Subgroup analysis

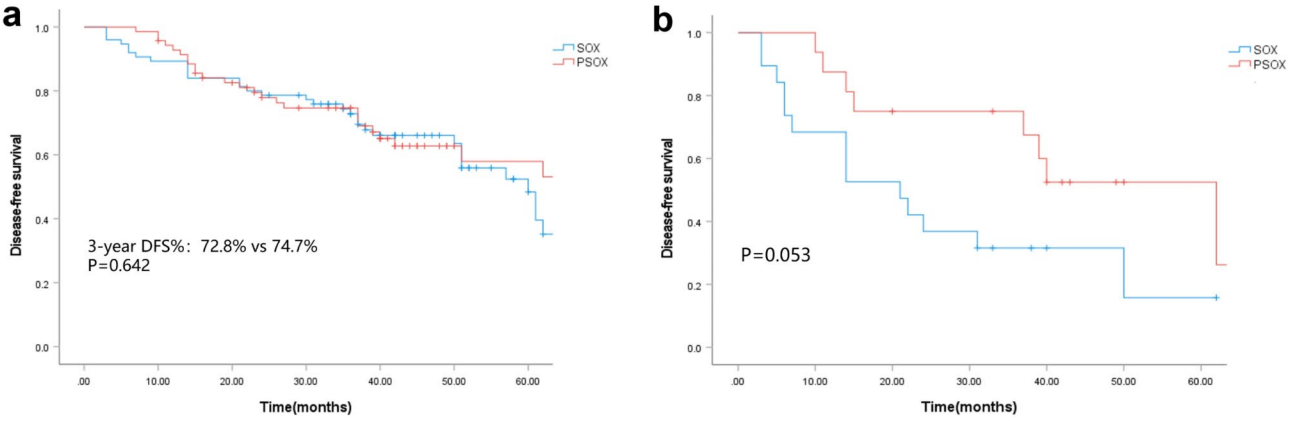

Fig. 2 Comparison of the disease-free survival of patients in the SOX and PSOX groups before matching: (**a**) disease-free survival outcomes of all patients, (**b**) disease-free survival outcomes of stage IIIC patients

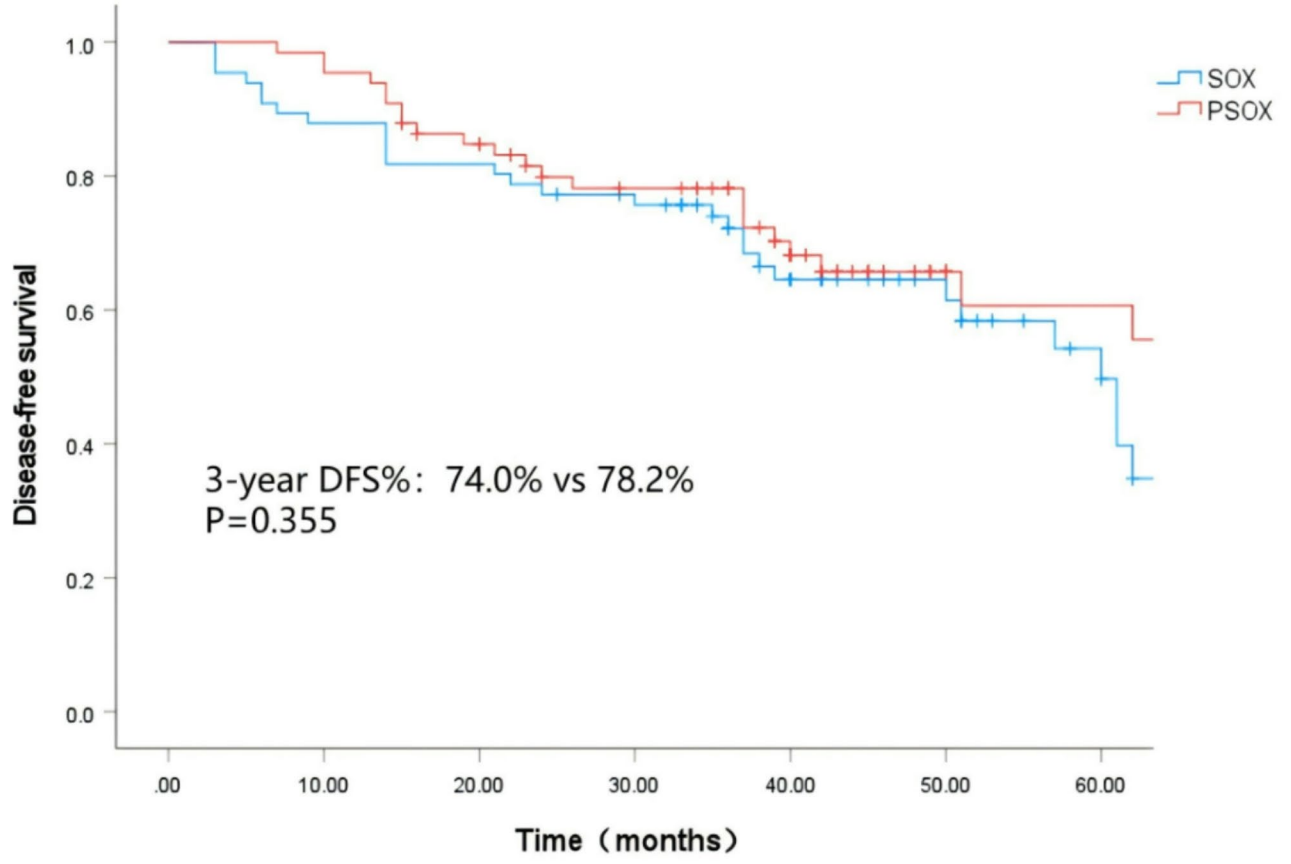

Fig. 3 Kaplan–Meier curves for disease-free survival in patients treated with PSOX and SOX after matching

indicated that among the 48 patients with low differentiation gastric cancer in the PSOX group, the median DFS was 67 months, with a 3-year DFS rate of 78.8% (Fig. 4a). In the PSOX group, 21 patients were classified as diffuse type, exhibiting a median DFS of 62 months and a 3-year DFS rate of 76.6% (Fig. 4c). Patients with low differentiation or diffuse GC in the PSOX group experienced longer DFS than those in the SOX group. The difference was not statistically significant, with p-values of 0.170 and 0.305, respectively. For patients with medium differentiation, non-diffuse GC, and stage II-IIIB, DFS did not show any statistically significant differences between the two groups. (Figure 4b, d and e-f). In the PSOX group, there were 15 patients with stage IIIC, and they exhibited a higher DFS rate than those in the SOX group, as shown by the distinct separation in the Kaplan-Meier curves for

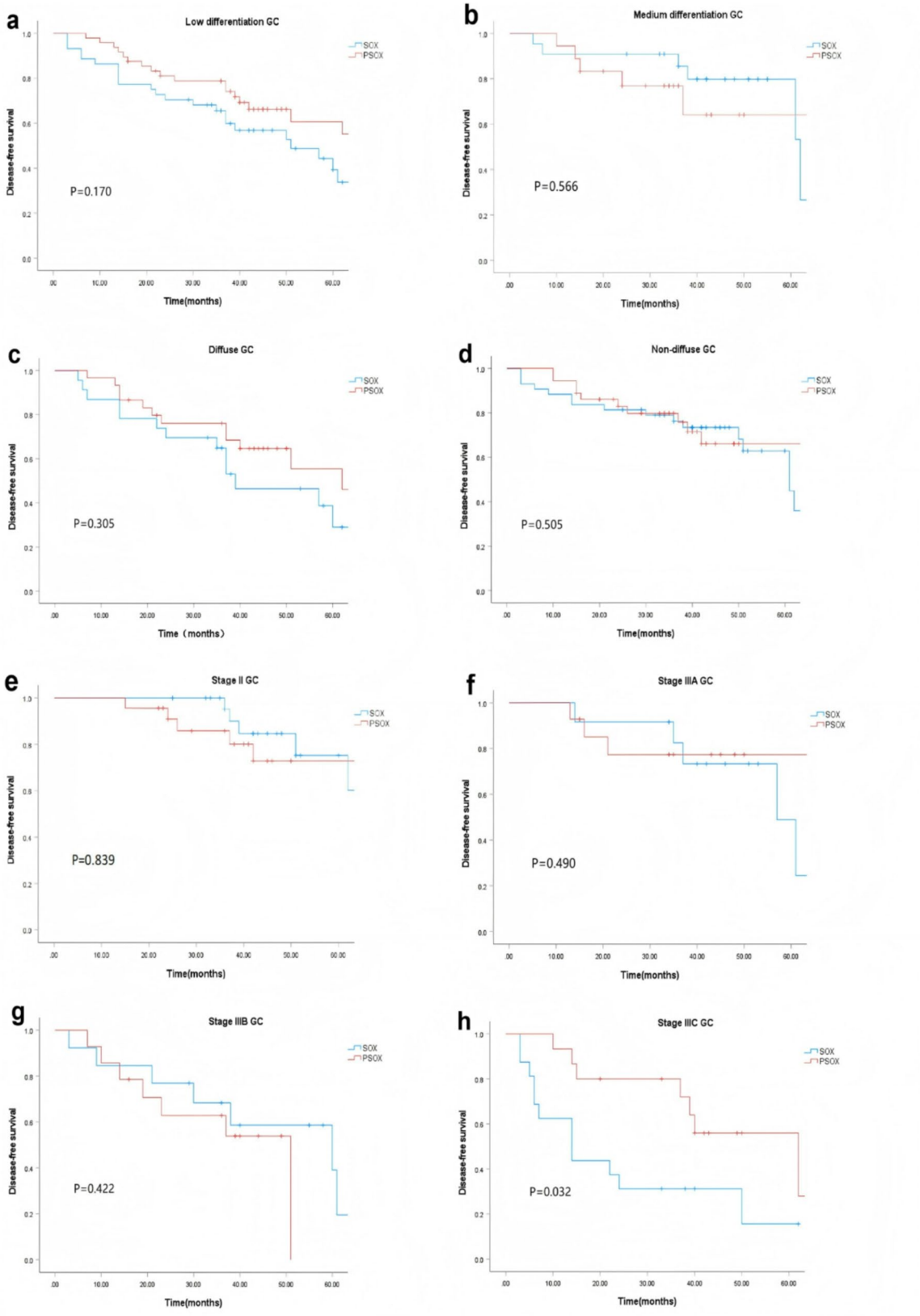

Fig. 4 Disease-free survival for the subgroups of the SOX and PSOX group after matching. (**a**) Low differentiation GC, (**b**) Middle differentiation GC, (**c**) Diffuse GC, (**d**) Non-Diffuse GC, (**e**) Stage II GC, (**f**) Stage IIIA GC, (**g**) Stage IIIB GC, (**h**) Stage IIIC GC

DFS ($P = 0.032$, Fig. 4h). And, the baseline characteristics of this subgroup between the SOX group and the PSOX group are comparable ($P > 0.05$, Table 2).

Toxicity assessment

In the PSOX group, the most frequent adverse effects (AEs) were anemia (78.8%), leucopenia (50.0%), and neutropenia (42.4%), whereas in the SOX group, anemia (80.3%), thrombocytopenia (50.0%), and leucopenia (43.9%) were most common. Leucopenia and neutropenia, both at 10.6%, were the most common grade 3 or 4 AEs in the PSOX group, while in the SOX group, neutropenia was the most frequent at 9.1%. (Table 3). These side effects were generally manageable with preventive and symptomatic treatments.

Site of first recurrence

Lymph nodes and peritoneum were the primary sites for initial recurrence. Local recurrence was observed in 2 patients (3.0%) in the PSOX group and 7 patients (10.6%) in the SOX group. In the SOX group, 11 patients (16.7%) experienced peritoneal recurrence, and 14 patients (21.2%) had lymph-node recurrence. In the PSOX group, 7 patients (10.6%) had peritoneal recurrence, while 12 patients (18.2%) had lymph-node recurrence. Post-surgical administration of PSOX was linked to a lower incidence of lymph node and peritoneal recurrences compared to the SOX group. The hazard ratio for peritoneal relapse in the PSOX group compared to the SOX group was 0.287 (95% confidence interval, 0.090–0.915; $P = 0.035$) (Table 4).

Discussion

In this single-center retrospective study, the 3-year DFS rate for stage II-III GC patients post-D2 gastrectomy improved modestly to 78.2% with PSOX treatment, in contrast to 74.0% with SOX treatment. The 3-year DFS rate for the SOX group matched the 74.2% reported in

Table 2 Baseline characteristics of patients with IIIC GC between two groups after matching

Parameter	PSOX($n = 15$)	SOX($n = 16$)	*P* value
Gender			0.220[a]
Male	13	10	
Female	2	6	
Age(years)			0.828[b]
Median	60(46–76)	60(40–71)	
KPS score			1.000[a]
90–100	9	10	
70–80	6	6	
Gastrectomy			1.000[a]
total	8	9	
distal	5	6	
proximal	2	1	
Lauren's classification			0.613[a]
Diffuse	8	9	
Intestinal	3	1	
Mixed	4	6	
Grade			1.000[a]
Low differentiation	12	13	
Medium differentiation	3	3	
Histological type			0.654[a]
Signet cell carcinoma	3	2	
Adenocarcinoma	12	14	
Harvested lymph nodes			
Median	33(24–44)	35.5(27–49)	0.281[b]
Surgical margin			
negative	15	16	1.000[a]
positive	0	0	
Postoperative complication follow-up			1.000[a]
Anastomotic fistula	1	0	
Anastomotic bleeding	0	1	
Intestinal obstruction	1	0	
Anaemia	1	2	

[a], Fisher's exact test; [b],Mann-Whitney U test; PSOX, paclitaxel/oxaliplatin/S-1; SOX, oxaliplatin/S-1

Table 3 Toxicity evaluation in patients with stage II - III gastric cancer in two groups*

Type of toxicity	PSOX (*n* = 66)					SOX (*n* = 66)					*P* value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4(%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 or 4(%)	
Leucopenia	7	19	5	2	10.6	15	11	2	1	4.5	0.152
Neutropenia	8	13	3	4	10.6	7	12	5	1	9.1	0.575
Anemia	43	8	1	0	1.5	38	13	2	0	3.0	0.330
Thrombocytopenia	12	9	2	0	3.0	27	4	2	0	3.0	0.252
Elevated AST level	2	0	1	0	1.5	1	0	2	0	3.0	0.985
Elevated ALT level	2	0	1	0	1.5	1	0	1	0	1.5	0.655
Elevated total serum bilirubin level	2	1	0	1	1.5	2	3	1	0	1.5	0.286
Nausea/vomiting	10	4	2	1	4.5	9	3	2	0	3.0	0.511
Diarrhea	4	3	3	0	4.5	4	2	2	0	3.0	0.160
Fatigue	23	4	1	0	1.5	19	3	2	0	3.0	0.529
Peripheral neuropathy	18	5	3	0	4.5	16	4	2	0	3.0	0.445

*Grades of adverse effects were defined according to the Common Toxicity Criteria of the National Cancer Institute (version 5.0).AST, aspartate aminotransferase; ALT, alanine aminotransferase; PSOX, paclitaxel/oxaliplatin/S-1; SOX, oxaliplatin/S-1

Table 4 Site of first recurrence in two groups*

Site	PSOX(*n* = 66)	SOX(*n* = 66)	HR for Recurrence in the PSOX Group (95% CI)	*P* Value
	No. of patients(%)			
Total no. of relapse	25(37.9)	31(47.0)		
Local	2(3.0)	7(10.6)	0.955(0.184 to 4.971)	0.957
Lymph nodes	12(18.2)	14(21.2)	1.346(0.602 to 3.008)	0.469
Hematogenous	9(13.6)	8(12.1)	1.328(0.477 to 3.697)	0.587
Peritoneum	7(10.6)	11(16.7)	0.287(0.090 to 0.915)	0.035

Abbreviations: HR, hazard ratio; CI, confidence interval

*Some patients recurred at more than one site

the ARTIST 2 trial [12]. Diffuse gastric cancer (DGC) is poorly differentiated cancer with poor prognosis. An analysis of 580 participants receiving oxaliplatin as adjuvant therapy post-D2 gastrectomy indicated varying chemotherapeutic sensitivity between intestinal gastric cancer (iGC) and DGC. The median DFS was 21.2 months for DGC and 32.2 months for IGC, with a hazard ratio of 1.56 ($P < 0.001$) [15]. The study revealed that the PSOX group exhibited a higher incidence of DGC cases (45% versus 35%) and a greater rate of low differentiation (73% versus 67%) than the SOX group. The Kaplan-Meier curve indicated a trend towards divergence between the two groups. In the PSOX group, patients with DGC or low differentiation exhibited longer DFS compared to the SOX group, although this difference lacked statistical significance. ($P = 0.305$ and $P = 0.170$ respectively). More definitive and reliable results may require prospective randomised controlled trials with larger sample sizes to demonstrate that PSOX provides a better survival benefit in poorly differentiated GC.

According to the ACTS-GC study, the 5-year relapse-free survival (RFS) rates for patients treated with S-1 were 79.2% for stage II, 61.4% for stage IIIA, and 37.6% for stage IIIB. The CLASSIC study indicated that patients with stage IIIA or IIIB GC may benefit less from oxaliplatin and capecitabine treatment than those with stage II GC. The study reported 3-year DFS rates of 85% for stage II, 66% for stage IIIA, and 61% for stage IIIB patients [16]. Subgroup IIIC was not analyzed as the TNM staging system used was based on the UICC's 6th edition classification of malignant tumors. However, it has been shown that the later the TNM stage of GC, the less likely it is that patients will benefit from adjuvant therapy. Our subgroup analysis showed that the PSOX group had a higher 3-year DFS rate for stage IIIC than the SOX group (64.0% vs. 31.3%, $P = 0.032$), suggesting that the PSOX regimen may be an option for some people with later-stage disease who are less likely to benefit from a single or doublet agent. Paclitaxel plus oral fluoropyrimidine is a potential therapeutic option for postoperative GC patients at high risk of peritoneal recurrence [17]. In our research, 7 patients (10.6%) experienced peritoneal recurrence in the PSOX group, whereas 11 patients (16.7%) experienced it in the SOX group. The PSOX group demonstrated a reduced incidence and risk of peritoneal recurrence compared to the SOX group, with a hazard ratio of 0.287 (95% CI, 0.090–0.915; $P = 0.035$).

Anaemia was the most common adverse event of any grade in both the PSOX (78.8%) and SOX (80.3%) groups. The most prevalent grade 3 or 4 AEs in the PSOX group were leucopenia and neutropenia (both 10.6%), whereas neutropenia (9.1%) was more common in the SOX group. The incidence of nausea/vomiting, diarrhoea and peripheral neuropathy was higher in the PSOX group than in the SOX group for grade 3 or 4 AEs. Although the PSOX group demonstrated a slightly elevated incidence of certain adverse reactions in comparison to the SOX group. The development of new paclitaxel formulations, like polymeric micellar and albumin-bound paclitaxel, may improve the safety and effectiveness of triplet regimens such as PSOX. These new formulations allow for the administration of higher doses of paclitaxel directly to the tumour, while reducing the incidence of serious AEs [18, 19].

Recent advancements in early cancer screening and medical technology have enabled the diagnosis of early-stage cancers [20, 21]. Surgical resection is essential for treating localized GC, with adjuvant chemotherapy recommended for stage II-III GC patients post-radical resection [22, 23]. The ACTS-GC study confirmed the effectiveness of 1-year oral S-1 as adjuvant chemotherapy [8]. The combination of surgical resection and adjuvant monotherapy with S-1 proved to be superior to the surgery alone, leading to a 12% improvement in the 3-year OS rate and a 10% increase in the 3-year RFS rate [8]. Therefore, adjuvant S-1 has been established as the standard treatment for patients with stage II or stage III GC after curative resection. The effectiveness of S-1 is restricted, showing a 5-year OS rate of 67.1% for stage IIIA patients and 50.2% for stage IIIB patients [24]. According to the ACTS-GC study, patients with stage IIIA or IIIB GC benefit less from S-1 treatment than those with stage II [24]. Therefore, there is a pressing need to optimize treatment strategies for this subgroup of patients.

Several studies have investigated combined regimens as adjuvant chemotherapy for GC [16, 25, 26]. The CLASSIC study assessed the effectiveness of adjuvant capecitabine and oxaliplatin versus surgery alone in patients who underwent D2 gastrectomy of stage II-IIIB GC. The study demonstrated a significant improvement in the 3-year DFS, the primary endpoint, with the addition of capecitabine and oxaliplatin [16]. A Japanese study evaluated the tolerability of S-1 plus cisplatin (SP) regimen for gastric cancer [25]. The study showed that starting treatment with S-1 monotherapy for the first cycle, followed by three cycles of S-1 combined with cisplatin, is feasible and well-tolerated [26]. A randomized phase III trial indicated that the SOX regimen was almost as effective as SP for AGC, with a better safety profile [27].

The POF regimen, comprising paclitaxel, 5-Fu and oxaliplatin, demonstrates superior efficacy and tolerability compared to two-drug regimens in the perioperative context [28, 29]. A recent retrospective analysis evaluated the efficacy and safety of PSOX, DOF and SOX as neoadjuvant chemotherapy for GC [14]. The PSOX regimen demonstrated superior effectiveness and disease control, with total effective rates of 31.4% and disease control rates of 96.1%, compared to the DOF regimen's 18% and 94%, and the SOX regimen's 16.3% and 92.3%, respectively. This indicates that triple-drug neoadjuvant therapy might be more effective than dual-drug regimens for gastric cancer patients. Thus, we hypothesized that adjuvant PSOX could offer enhanced benefits over SOX for patients with stage II-III post-D2 gastrectomy.

In conclusion, our study demonstrates the long-term efficacy of PSOX (paclitaxel/oxaliplatin/S-1) compared to SOX (oxaliplatin/S-1) as adjuvant therapy following D2 gastrectomy for stage II-III gastric cancer. The findings indicated an extended DFS trend in the PSOX group, especially in stage IIIC GC. PSOX reduces the risk of peritoneal metastasis compared to the SOX group. PSOX chemotherapy has similar AEs as compared with SOX chemotherapy ($P < 0.05$). However, we acknowledge several limitations of this study. The retrospective study's findings could be affected by sample size and selection bias. The sample size in our study was marginally smaller than that of previous related research. Besides, the study was conducted at a single center within a provincial hospital, which may affect the generalizability of the results. Conducting large multicenter, prospective and randomized controlled trials is crucial to validate these findings and further assess the PSOX regimen's efficacy and safety.

Abbreviations

GC	Gastric Cancer
PSOX	Paclitaxel/S-1/Oxaliplatin
SOX	S-1/Oxaliplatin
AC	Adjuvant Chemotherapy
RFS	Relapse Free Survival
OS	Overall Survival
DOF	Docetaxel/Oxaliplatin/Fluorouracil
DFS	Disease Free Survival
KPS	Karnofsky Performance Status
SP	S-1/Cisplatin
POF	Paclitaxel/Oxaliplatin/5-Fu
HR	Hazard ratio
CI	Confidence interval
PSM	Propensity Score Matching
AE	Adverse Effect

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Author contributions
(I) Conception and design: Fei-Yu Wang, Xin-En Huang; (II) Administrative support: Zhi-Jun Fang, Xin-En Huang; (III) Provision of study materials or patients: Jie Cao, Meng Song; (IV) Data collection and assembly: Fei-Yu Wang, Xiang-Ming Huang, Yu-Qing Cao; (V) Data analysis and interpretation: Fei-Yu Wang, Yu-Qing Cao, Xiang-Ming Huang; (VI) Manuscript writing: All authors; (VII) Final manuscript approval: All authors.

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Data availability
The dataset was obtained from the big data center of Jiangsu Cancer Hospital (Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University). For access to the shared data, please contact huangxinen06@163.com.

Declarations

Ethics approval and consent to participate
The Medical Ethical Committee of Jiangsu Cancer Hospital approved the study, which adhered to the 1964 Declaration of Helsinki and its amendments.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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