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ORIGINAL ARTICLE

# A two centers study of postoperative adjuvant chemotherapy with S-1 versus SOX/XELOX regimens for gastric cancer after D2 resection: a cohort study

Song Zheng[1] · Yao Zhou[1] · Yangcheng Sun[1] · Zhen Wang[1] · Yidan Lu[1]

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## Abstract

**Objective** Currently, radical surgery with D2 lymphadenectomy has become the standard operation mode of patients in East Asian countries who suffer from resectable gastric cancer. Our target is to compare the efficacy of postoperative adjuvant chemotherapy with S-1 versus SOX/XELOX regimens for gastric cancer after D2 resection.

**Methods** We selected 186 patients with gastric cancer who underwent D2 resection in Hangzhou First People's Hospital and Hangzhou Cancer Hospital from June 2014 to June 2017. All patients were followed up for more than 3 years. The primary endpoint was disease-free survival (DFS), and the secondary endpoints were overall survival (OS) and toxicity.

**Results** The 3-year DFS of monotherapy group and combined group were, respectively, 50.7% and 64.0%, while the 3-year OS were, respectively, 62.7% and 71.2%. The 3-year DFS and OS of the combined group were higher than the monotherapy group, but the differences had no statistical significance (3-year DFS: $P=0.071$; 3-year OS: $P=0.224$). Subgroup analysis showed that the DFS of patients with stage III gastric cancer in monotherapy group was significantly lower than the combined group, with the difference that had statistical significance ($P=0.030$), while there was no significant difference in OS ($P=0.186$). Most toxic and side effects seen in both groups had no significant differences, while the incidence of hand-foot syndrome and peripheral neurotoxicity in combined group was significantly higher than that in the monotherapy group ($P<0.001$).

**Conclusion** For patients with advanced gastric cancer who underwent D2 resection, compared with S-1 regimen, there is prolonged disease-free survival trend with SOX/XELOX regimen, while there is no significant overall survival benefit.

**Keywords** Gastric cancer · D2 resection · Adjuvant chemotherapy · Monotherapy · Combined therapy

## Introduction

Gastric cancer is one of the most common malignant cancers worldwide, with the fourth-highest incidence and the second-highest mortality. Epidemiological research identified an estimated 951,000 new cases of gastric cancer worldwide and around 723,000 deaths resulting from gastric cancer in 2012, making gastric cancer the fifth most common and the third most fatal malignancy. The numbers of new cases and deaths in China accounted for 42.6% and 45.0% of the global incidence and mortality, respectively, in the same year [1]. In 2015, gastric cancer accounted for approximately 679,000 new cases and 498,000 deaths in China, which made it the second leading cancer in terms of incidence and mortality, only after lung cancer [2]. Proximal gastric cancer is the most common type of gastric cancer in developed countries, where the incidence of carcinoma of the gastric cardia comes is only next to that of esophageal cancer [3, 4]. Meanwhile, in East Asian countries like China, Japan, and Korea, most cases of gastric cancer are non-proximal [5, 6].

The 5-year survival rate of patients with early gastric cancer is more than 90%, but that of patients with advanced gastric cancer with extensive nodal involvement is less than 30%. Currently, surgical resection is not only the main treatment modality for gastric cancer but also the only cure.

✉ Song Zheng
tztree@126.com

[1] Department of Oncology, Hangzhou First People's Hospital, Hangzhou Cancer Hospital, Zhejiang University School of Medicine Affiliated Hangzhou First People's Hospital, Nanjing Medical University Affiliated Hangzhou Hospital, Zhejiang Chinese Medical University Affiliated Hangzhou First Hospital, Hangzhou 310006, China

Nevertheless, there remain differences between East Asian and Western countries in terms of their choice of operation and lymphadenectomy. Radical surgery for advanced gastric cancer yields a low postoperative survival rate and relatively high rates of local recurrence and distant metastasis. Therefore, to reduce local recurrence and distant metastasis and prolong patient survival, adjuvant therapy is used for resectable advanced gastric cancer. In East Asian countries, radical D2 lymphadenectomy has become the standard operation for patients with stage II–III advanced gastric cancer, and consensus on the necessity of postoperative adjuvant chemotherapy for D2 dissection has been achieved [7, 8].

There are several ongoing large-scale clinical trials on postoperative adjuvant chemotherapy for gastric cancer, with each trial using a different chemotherapy regimen. However, guiding principles for choosing the appropriate postoperative adjuvant chemotherapy regimen for gastric cancer patients undergoing D2 dissection are yet to be developed. As such, this study performed a retrospective analysis and comparison of the long-term therapeutic outcomes and toxic and side effects of single-drug and two-drug postoperative adjuvant chemotherapy for gastric cancer in Nanjing Medical University affiliated Hangzhou hospital and Hangzhou Cancer Hospital, between June 2014 and June 2017. The purpose of this study was to determine the advantages and disadvantages of these two regimens in patients with stage II/III gastric cancer undergoing radical D2 surgery to provide scientific evidence for the clinical management of such patients, including the selection of optimal individualized treatment regimens.

## Data and methods

### Research targets

Follow-up targets were selected among the patients with gastric cancer treated in Hangzhou First People's Hospital between June 2014 and June 2017.

Inclusion criteria were as follows: (1) patients with stage IB/II/III gastric cancer (AJCC TNM classification, 7th edition) who underwent radical D2 dissection (i.e., the removal of the proximal, distant, or entire stomach involved) and lymphadenectomy of lymph nodes at the greater and lesser omenta (including lymph nodes at the left and right sides of the cardia and the lesser and greater curvatures of the stomach as well as the suprapyloric and subpyloric lymph nodes), those next to the left gastric artery and common hepatic artery, those at the celiac axis and the hilum of the spleen, and those next to the spleen artery; (2) postoperative pathological diagnosis of gastric adenocarcinoma (including tubular and villoglandular adenocarcinoma), mucinous adenocarcinoma, or signet ring cell carcinoma (excluding squamous cell carcinoma and adenosquamous carcinoma); (3) Karnofsky Performance Scale (KPS) score of $\geq 70$; (4) no patients showed any evident abnormalities in routine urinalysis and blood test as well as liver and kidney functioning; there was also no severe disease of the heart, brain, lungs, or other organs; (5) first-time patients who had not received any related chemotherapy and had only undergone simple post-operative adjuvant therapy excluding post-operative combined adjuvant therapy, thermal therapy, and intraperitoneal chemohyperthermic perfusion.

The exclusion criteria were as follows: (1) received chemotherapy regimens other than S-1, SOX, or XELOX after radical D2 surgery for gastric cancer; (2) unable to complete the designated adjuvant chemotherapy cycle as required, for any reason; (3) a reduction of over 30% in the standard chemotherapy dosage for any reason.

### Treatment

All patients in both groups underwent radical D2 surgery for gastric cancer prior to chemotherapy. The monotherapy group received an S-1 single-drug chemotherapy regimen as follows: tegafur, gimeracil, and oteracil potassium capsules (S-1) 40 mg/m$^2$ twice daily on days 1–14 every 3 weeks (oral administration). Meanwhile, the combination therapy group received a combined SOX and XELOX regimen as follows: (1) SOX regimen: oxaliplatin 130 mg/m$^2$ on day 1 every 3 weeks (intravenous drip) + tegafur, gimeracil, and oteracil potassium capsules (S-1) 40 mg/m$^2$ twice daily on days 1–14 every 3 weeks (oral administration); (2) XELOX regimen: oxaliplatin 130 mg/m$^2$ on day 1 every 3 weeks (intravenous drip) + capecitabine (Xeloda) 1000 mg/m$^2$ twice daily on days 1–14 every 3 weeks (oral administration).

The monotherapy group received chemotherapy for 1 year, whereas the combination therapy group received chemotherapy for cycles of 6–8 weeks. During the chemotherapy, symptomatic treatments were given by administering antiemetics, antacids, and stomach- and liver-protecting drugs. Any toxic and side effects were also treated immediately. Only in extremely rare cases was the chemotherapy dosage moderately reduced in patients demonstrating grade III–IV myelosuppression after the chemotherapy. During each 6- to 8-week cycle of chemotherapy, imaging modalities such as pulmonary and abdominal CT scans and B-scan ultrasonography of the superficial lymph nodes were used to evaluate therapeutic efficacy. After the chemotherapy, a follow-up was conducted via telephone every 3–6 months.

### Assessment criteria

All patients were followed up for over 3 years to observe disease-free survival (DFS), overall survival (OS), and toxic and side effects, which were classified from grade 0

to IV according to the criteria recommended by the World Health Organization for common toxic and side effects of anti-cancer drugs.

### Statistical methods

The SPSS 20.0 software package was employed for data analysis. The enumeration data were analyzed via $\chi^2$ test, whereas the survival data were analyzed via the Kaplan–Meier method, and treatment groups were compared with the log-rank test. Statistical significance was set at $P < 0.05$.

## Results

### Patients' baseline characteristics

A total of 211 follow-up targets were enrolled in strict compliance with the inclusion criteria, after which 25 were excluded based on the exclusion criteria. Eventually, there were 186 enrolled patients (Hangzhou Cancer Hospital: 110 patients, Nanjing Medical University affiliated Hangzhou hospital: 76 patients), among which 104 were men and 82 were women. The median age was 65 years (range 38–82 years). These patients were randomly assigned to receive monotherapy or combination therapy. Finally, the monotherapy group comprised 75 cases, while the combination therapy group comprised 111 cases. The two groups had similar basic conditions and showed no statistical differences in sex, KPS score, tumor location, WHO grade, and histological classification ($P > 0.05$).

However, they were significantly different in terms of age and tumor stage. In the monotherapy group, there were 46 patients aged ≥ 65, accounting for 61.3% of the entire group. In the combination therapy group, there were 51 patients aged ≥ 65, accounting for 45.9% of the group population. Apparently, the number of elderly patients was higher in the monotherapy group than in the combination therapy group ($P = 0.039$). Moreover, the percentage of stage IB and II patients in the monotherapy group was also significantly higher than that in the combination therapy group ($P = 0.040$) (Table 1).

### Survival analysis

The last follow-up was conducted in June 2017. All patients were followed up for at least 3 years. Among them, five in the monotherapy group and nine in the combination therapy group were lost to follow-up, yielding a follow-up rate of 92.5%. The 3-year DFS rates in the monotherapy and combination therapy groups were 50.7% and 64.0%, respectively, while the 3-year OS rates were 62.7% and 71.2%, respectively. Although the 3-year DFS and OS were substantially higher in the combination therapy group than the monotherapy group, the difference was not statistically significant (3-year DFS: $P = 0.071$, log-rank $P = 0.052$; 3-year OS: $P = 0.224$, log-rank $P = 0.200$) (Table 2). The Kaplan–Meier method was used for performing survival analysis and drawing the DFS and OS survival curves (Fig. 1).

### Subgroup analysis

Subgroup analysis showed no significant differences in DFS and OS between the two groups ($P > 0.05$) according to sex, age, KPS score, tumor location, WHO grade, and histological classification. The inter-group differences in the DFS and OS of patients with stage IB and II gastric cancer were not statistically significant either ($P > 0.05$). However, in stage III patients, the DFS of the monotherapy group was evidently lower than that of the combination therapy group, and the difference was statistically significant ($\chi^2 = 4.833$, $P = 0.028$). Meanwhile, there was no significant difference in their OS rates ($\chi^2 = 1.677$, $P = 0.195$) (Tables 3 and 4).

### Cox multivariate analysis

Due to the evident differences in age and tumor stage between the two groups, Cox multivariate analysis of these two factors was conducted. The results showed that age ($P = 0.665$) and stage ($P = 0.227$) had no significant impacts on DFS, but the choice of chemotherapy regimen, or the combination, influenced the final DFS ($P = 0.029$). Moreover, age ($P = 0.505$), stage ($P = 0.069$), and choice of chemotherapy regimen ($P = 0.052$) had no significant effects on the final OS rates (Table 5).

### Toxic and side effects

The main toxic and side effects that developed in the two groups were myelosuppression [liver and kidney function damage, gastrointestinal reaction (including nausea, vomiting, and loss of appetite)], fatigue, oral mucositis, hand-foot syndrome, and peripheral nerve toxicity. Despite that, most side effects were only grade I or II, and grade III and IV reactions were few and were relieved by symptomatic treatments. Only an extremely small number of patients had their dosage reduced moderately due to the occurrence of grade III myelosuppression. The rate of hand-foot syndrome and peripheral nerve toxicity was significantly higher in the combination therapy group than that in the monotherapy group ($P < 0.001$) (Table 6).

**Table 1** Comparison of the general characteristics between the monotherapy group and the combination therapy group

| General characteristics | Monotherapy group ($n=75$) | Combination therapy group ($n=111$) | $\chi^2$ | $P$ value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 41 | 63 | 0.079 | 0.778 |
| Female | 34 | 48 | | |
| Age | | | | |
| < 65 years | 29 | 60 | 4.247 | 0.039 |
| ≥ 65 years | 46 | 51 | | |
| KPS score | | | | |
| ≥ 90 | 23 | 53 | 5.493 | 0.064 |
| 80 | 40 | 45 | | |
| 70 | 12 | 13 | | |
| Tumor location | | | | |
| Cardia | 28 | 42 | 0.011 | 0.994 |
| Gastric body, the whole stomach | 16 | 23 | | |
| Gastric antrum | 31 | 46 | | |
| WHO grade | | | | |
| Tubular adenocarcinoma | 44 | 60 | 0.517 | 0.915 |
| Villoglandular adenocarcinoma | 17 | 29 | | |
| Mucinous adenocarcinoma | 5 | 9 | | |
| Signet ring cell carcinoma | 9 | 13 | | |
| Histological classification | | | | |
| Poorly differentiated | 31 | 53 | 1.239 | 0.538 |
| Moderately differentiated | 22 | 25 | | |
| Well differentiated | 8 | 11 | | |
| Undifferentiated | 0 | 0 | | |
| Staging | | | | |
| Stage IB | 4 | 2 | 6.435 | 0.040 |
| Stage II | 41 | 45 | | |
| Stage III | 30 | 64 | | |

**Table 2** Comparisons of DFS and OS between the monotherapy group and combination therapy group [$n$ (%)]

| Group | 3-year DFS | 3-year OS |
|---|---|---|
| Monotherapy | 38/75 (50.7) | 47/75 (62.7) |
| Combination therapy | 71/111 (64.0) | 79/111 (71.2) |
| $\chi^2$ | 3.262 | 1.481 |
| $P$ value | 0.071 | 0.224 |

## Discussion

Surgical resection remains the main treatment modality as well as the only cure for gastric cancer. Due to the bio-behavioral features of advanced gastric cancer, the rate of local recurrence and lymph node metastasis remains high at 50% and 50–60%, respectively, even after radical surgery. Such high rates of postoperative recurrence and metastasis are the primary cause of the low postoperative survival rates of patients with gastric cancer. To decrease the rate of postoperative local recurrence and metastasis and prolong patient survival, adjuvant therapy can be administered for patients with resectable gastric cancer.

Although initial clinical trials revealed no evident benefits of postoperative adjuvant chemotherapy to the survival of patients with gastric cancer, positive results were recently obtained in several critical phase III randomized controlled trials; thus, the appropriateness of postoperative adjuvant chemotherapy for gastric cancer was finally recognized. The most influential of these trials were the ACTS-GC and the CLASSIC studies.

The ACTS-GC study, a large-scale phase III randomized clinical trial in Japan [9], enrolled 1059 patients with stage II or III gastric cancer who underwent standard radical D2 surgery and randomized them into two groups: the group with post-operative single-drug administration of Tegafur, gimeracil, and oteracil potassium (S-1) ($n=529$ cases) and the surgery-only group ($n=530$ cases). The results showed that the S-1 group had significantly higher 5-year OS and

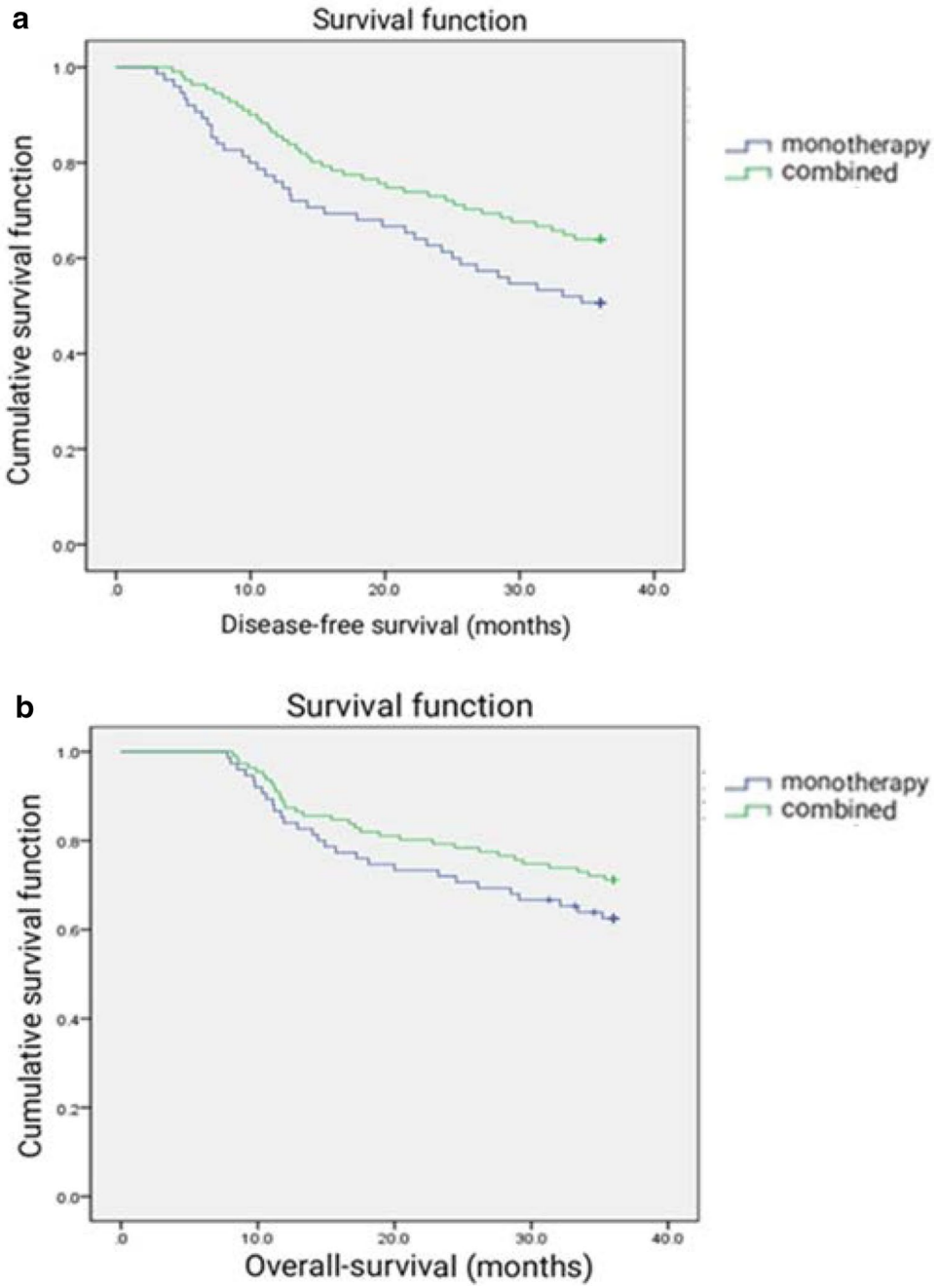


**Fig. 1** Comparison of DFS and OS between monotherapy group and combined group. **a** Comparison of DFS between monotherapy group and combined group. **b** Comparison of OS between monotherapy group and combined group

relapse-free survival than the surgery-only group at 71.7% vs 61.1% (HR = 0.67) and 65.4% vs 53.1% (HR = 0.65), respectively. The HR for death was also lower in the S-1 group. This was the first large-scale clinical trial that proved the survival advantages of postoperative adjuvant chemotherapy for patients with gastric cancer after D2 dissection. However, as it only targeted patients in Japan, the results of this study cannot be generalized to other countries or regions.

The CLASSIC study in 2012 [10] was a multi-center, phase III clinical randomized controlled trial conducted in 37 centers in South Korea, mainland China, and Taiwan. It enrolled 1035 patients with stage II-III gastric cancer who underwent D2 surgery and randomized them into the capecitabine plus oxaliplatin (XELOX regimen) group ($n = 520$ cases) and the surgery-only group ($n = 515$ cases). The results showed that postoperative adjuvant chemotherapy could significantly improve the patients' 3-year DFS (74% vs 59%, $P < 0.0001$) and OS (83% vs 78%, $P = 0.0493$), compared with surgery alone. A follow-up study reported a 5-year DFS of 68% and 53% and the 5-year OS of 78% and 69% in the XELOX group and the control group, respectively [11]. The results of a subgroup

**Table 3** Subgroup analysis of DFS between monotherapy group and combination therapy group

| General characteristics | Monotherapy group ($n=38$) | Combination therapy group ($n=71$) | $\chi^2$ | $P$-value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 23/41 | 40/63 | 0.569 | 0.451 |
| Female | 15/34 | 31/48 | 3.385 | 0.066 |
| Age | | | | |
| < 65 years | 18/29 | 39/60 | 0.073 | 0.787 |
| ≥ 65 years | 20/46 | 32/51 | 3.610 | 0.057 |
| KPS score | | | | |
| ≥ 90 | 11/23 | 35/53 | 2.227 | 0.136 |
| 80 | 24/40 | 30/45 | 0.406 | 0.524 |
| 70 | 3/12 | 6/13 | 1.212 | 0.271 |
| Tumor location | | | | |
| Cardia | 13/28 | 28/42 | 2.836 | 0.092 |
| Gastric body | 7/16 | 12/23 | 0.268 | 0.605 |
| Pylorus | 18/31 | 31/46 | 0.696 | 0.404 |
| Pathological type | | | | |
| Tubular adenocarcinoma | 23/44 | 41/60 | 2.766 | 0.096 |
| Villoglandular adenocarcinoma | 9/17 | 18/29 | 0.368 | 0.544 |
| Mucinous adenocarcinoma | 2/5 | 5/9 | 0.311 | 0.577 |
| Signet ring cell carcinoma | 4/9 | 7/13 | 0.188 | 0.665 |
| Histological classification | | | | |
| Poorly differentiated | 13/31 | 31/53 | 2.149 | 0.143 |
| Moderately differentiated | 13/22 | 18/25 | 0.869 | 0.351 |
| Well differentiated | 6/8 | 10/11 | 0.882 | 0.348 |
| Undifferentiated | 0/0 | 0/0 | – | – |
| Staging | | | | |
| Stage IB | 3/4 | 2/2 | 0.600 | 0.439 |
| Stage II | 24/41 | 30/45 | 0.607 | 0.436 |
| Stage III | 11/30 | 39/64 | 4.833 | 0.028 |

analysis of the patients from China were also in line with the overall results of the CLASSIC study [12]. The results of the CLASSIC study provided additional solid evidence to support the significance of postoperative adjuvant chemotherapy for gastric cancer.

In addition to the above randomized controlled studies, a number of meta-analyses published in recent years further recognized the efficacy of postoperative adjuvant chemotherapy for gastric cancer. In 2009, Sun et al. conducted a meta-analysis [13] that enrolled 3809 patients from 12 randomized controlled trials and found that compared with surgery alone, postoperative adjuvant chemotherapy could reduce the risk of death by 22% and prolong the OS (HR = 0.78, 95% CI 0.71–0.85) among patients with gastric cancer patients who underwent radical D1 or D2 lymphadenectomy. The GASTRIC meta-analysis published in 2010 [14] enrolled 3838 patients with gastric cancer from 17 clinical randomized controlled trials and reported that postoperative adjuvant chemotherapy could increase the 5- and 10-year survival rates of patients with advanced gastric cancer by 5.7% and 7.4%, respectively.

In East Asian countries, radical D2 lymphadenectomy has become the standard operation for patients with stage II–III advanced gastric cancer. A consensus has also been formed on using postoperative adjuvant chemotherapy after D2 dissection. However, the optimal adjuvant chemotherapy regimen is yet to be determined. Traditionally, 5-FU-based or platinum-based regimens were the most commonly used. S-1 is an oral anticancer fluoropyrimidine derivative that can maintain a higher level of plasma concentration and has similar effects with the continuous intravenous infusion of 5-FU.

As it can enhance anticancer activity while reducing the toxicity, it has been widely used to treat gastrointestinal tumors. Capecitabine is also a prodrug of 5-FU. It does not have an anti-cancer effect in itself but becomes cytotoxic at the liver and the locations of the solid tumors, thereby increasing the drug concentration in tumor cells

**Table 4** Subgroup analysis of OS between the monotherapy group and the combination therapy group

| General data | Monotherapy group ($n=47$) | Combination therapy group ($n=79$) | $\chi^2$ | $P$ value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 27/41 | 43/63 | 0.065 | 0.799 |
| Female | 20/34 | 36/48 | 0.462 | 0.497 |
| Age | | | | |
| < 65 | 19/29 | 45/60 | 0.870 | 0.351 |
| ≥ 65 | 28/46 | 34/51 | 0.352 | 0.553 |
| KPS score | | | | |
| ≥ 90 | 16/23 | 41/53 | 0.520 | 0.471 |
| 80 | 26/40 | 31/45 | 0.145 | 0.703 |
| 70 | 5/12 | 7/13 | 0.371 | 0.543 |
| Tumor location | | | | |
| Cardia | 15/28 | 29/42 | 1.723 | 0.189 |
| Gastric body | 9/16 | 14/23 | 0.083 | 0.773 |
| Pylorus | 23/31 | 36/46 | 0.171 | 0.679 |
| Pathological type | | | | |
| Tubular adenocarcinoma | 27/44 | 44/60 | 1.679 | 0.195 |
| Villoglandular adenocarcinoma | 12/17 | 21/29 | 0.018 | 0.894 |
| Mucinous adenocarcinoma | 3/5 | 6/9 | 0.062 | 0.803 |
| Signet ring cell carcinoma | 5/9 | 8/13 | 0.079 | 0.779 |
| Histological classification | ($n=39$) | ($n=65$) | | |
| Poorly differentiated | 17/31 | 34/53 | 0.711 | 0.399 |
| Moderately differentiated | 15/22 | 20/25 | 0.860 | 0.354 |
| Well-differentiated | 7/8 | 11/11 | 1.451 | 0.228 |
| Undifferentiated | 0/0 | 0/0 | – | – |
| Staging | | | | |
| Stage IB | 4/4 | 2/2 | – | – |
| Stage II | 28/41 | 36/45 | 1.545 | 0.214 |
| Stage III | 15/30 | 41/64 | 1.677 | 0.195 |

**Table 5** Cox multivariate regression analysis of related factors

| Factor | DFS ($P$-value) | OS ($P$-value) |
|---|---|---|
| Age | 0.665 | 0.505 |
| Stage | 0.227 | 0.069 |
| Chemotherapy regimen (grouping) | 0.029 | 0.052 |

and minimizing the systemic toxicity of chemotherapeutics. Oxaliplatin is a third-generation platinum complex that produces aquated derivatives to act on DNA and form intra- and interstrand crosslinks, in turn inhibiting DNA synthesis and producing cytotoxicity and anti-tumor activity. It also leads to fewer toxic and side effects.

Zhang et al. [15] compared the efficacy of the SOX regimen and the XELOX regimen used in the postoperative adjuvant chemotherapy for gastric cancer. The results showed that the OS and PFS was note significantly different between the SOX and XELOX groups, indicating that both regimens had similar effectiveness in postoperative adjuvant chemotherapy for gastric cancer. Jiang et al. [16] conducted a meta-analysis of the ACTS-GC and CLASSIC studies and indirectly compared the efficacy of S-1 and XELOX used in postoperative adjuvant chemotherapy for patients with gastric cancer who underwent D2 surgery. They found that the impacts of the regimens on OS was not significantly different (HR = 0.94, 95% CI 0.62–1.44, $P=0.79$). Meanwhile, S-1 increased the risk of postoperative recurrence by 11% compared with the XELOX regimen, but the difference was not statistically significant (HR = 1.11, 95% CI 0.80–1.53, $P=0.54$). These findings indicate that although the XELOX regimen is not superior to the S-1 regimen, the former may be able to reduce recurrence.

The current study directly compared the clinical efficacy of S-1 monotherapy regimen and SOX/XELOX combined regimen in the postoperative adjuvant chemotherapy for patients with gastric cancer who underwent D2 surgery. The results showed that the SOX/XELOX combination therapy group had evidently higher OFS and OS than the

**Table 6** Comparison of the toxic and side effects between the monotherapy group and combination therapy group

| Adverse reaction | Monotherapy group ($n=75$) | | | | Combination therapy group ($n=111$) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | I | II | III/IV | *N* (%) | I | II | III/IV | *N* (%) | *P*-value |
| Decreased leukocyte | 20 | 11 | 5 | 36 (48.0) | 29 | 24 | 8 | 61 (54.9) | > 0.05 |
| Decreased neutrophil | 15 | 9 | 5 | 29 (38.7) | 23 | 17 | 5 | 45 (40.5) | > 0.05 |
| Decreased hemoglobin | 31 | 13 | 6 | 50 (66.7) | 42 | 35 | 8 | 85 (76.6) | > 0.05 |
| Decreased platelet | 13 | 8 | 4 | 25 (33.3) | 25 | 9 | 5 | 39 (35.1) | > 0.05 |
| Nausea and vomiting | 33 | 18 | 4 | 55 (73.3) | 43 | 27 | 10 | 80 (72.1) | > 0.05 |
| Loss of appetite and fatigue | 29 | 8 | 0 | 37 (49.3) | 37 | 17 | 0 | 54 (48.6) | > 0.05 |
| Oral mucositis | 15 | 4 | 1 | 20 (26.7) | 16 | 4 | 0 | 20 (18.0) | > 0.05 |
| Hand–foot syndrome | 7 | 2 | 0 | 9 (12.0) | 36 | 22 | 3 | 61 (54.9) | < 0.001 |
| Liver function damage | 16 | 7 | 0 | 23 (30.7) | 22 | 10 | 0 | 32 (28.8) | > 0.05 |
| Kidney function damage | 6 | 1 | 0 | 7 (9.3) | 7 | 3 | 0 | 10 (9.0) | > 0.05 |
| Peripheral nerve toxicity | 5 | 0 | 0 | 5 (6.7) | 39 | 29 | 5 | 73 (65.8) | < 0.001 |

S-1 monotherapy group, but the difference was not statistically significant. In particular, compared with the monotherapy regimen, the combined regimen tended to prolong the patients' DFS; however, it lacked substantial survival benefits.

This might be related to the differences in age and tumor stage between the two groups, as the high percentage of elderly patients in the monotherapy group might have lowered the DFS and OS to a certain extent. Concurrently, the higher percentage of patients with stage II disease in the monotherapy group than that in the combination therapy group might also have improved the DFS and OS to a certain extent. To solve this issue, Cox multivariate analysis was conducted. The results showed that age and tumor stage did not exert evident impacts on both the patients' DFS and OS. However, the lack of statistical significance might be caused by the small number of follow-up cases and the short follow-up duration.

The primary toxic and side effects that occurred in both groups were myelosuppression, liver and kidney function damage, gastrointestinal reaction, fatigue, oral mucositis, hand-foot syndrome, and peripheral nerve toxicity. They were mainly grade I and II, and rarely grade III or IV. Except for hand-foot syndrome and peripheral nerve toxicity, which was higher in the dual therapy group than in the monotherapy group, the incidence of side effects were not significantly different between the two groups.

Subgroup analysis by sex, age, KPS score, tumor location, WHO grade, and histological classification showed no significant difference in the DFS and OS of the two groups. Meanwhile, the two groups demonstrated significant differences in OS and DFS according to tumor stage. The DFS and OS were not significantly different between the patients with stage IB and II gastric cancer. Meanwhile, for patients with stage III disease, the monotherapy group clearly had a significantly lower DFS than the combination therapy group, and the difference was statistically significant. There was no evident difference in the patients' OS.

This result indicated that either regimens can be used in patients with stage IB and II gastric cancer, whereas S-1 monotherapy is recommended for elderly patients with stage II disease and have poorer KPS scores because of its slightly fewer toxic and side effects compared with the combined chemotherapy. By contrast, SOX/XELOX combination chemotherapy is recommended for patients with stage III disease to reduce the risks of local recurrence and distant metastasis. Such findings were consistent with the results of the ACTS-GC study [9], the CLASSIC study [10], and the meta-analysis by Jiang et al. [16].

The subgroup analysis of the ACTS-GC study indicated that patients with stage IIIB disease do not benefit from S-1 adjuvant monotherapy, whereas the CLASSIC study suggested that the XELOX regimen yielded survival benefits to patients with gastric cancer at all stages, including stage IIIB. Further, the XELOX regimen was also proven to significantly reduce the rate of distant metastasis, which could not be achieved using S-1 alone. This might be one of the reasons why patients with stage IIIB disease significantly benefitted from the XELOX regiment instead of the S-1 monotherapy.

This study conducted a retrospective analysis of the clinical efficacy of S-1 monotherapy and SOX/XELOX combination regimen as adjuvant treatment for patients with gastric cancer who underwent radical D2 surgery. Despite having no superior survival benefits to S-1 monotherapy, the SOX/XELOX combination chemotherapy demonstrated tended to prolong the patients' DFS and was effective in improving their quality of life to some extent. This finding can serve as a useful reference for selecting the appropriate postoperative adjuvant chemotherapy regimen in clinical practice.

This study has some limitations that should be considered when interpreting the results. First, as this was a

retrospective study, the collected data were inevitably biased. The second limitation was the small number of cases collected, which meant a relatively small sample size. In addition, because this study was not a prospective randomized controlled trial, it might not have strict control on factors like the chemotherapy dosage and the follow-up check-ups. This might have affected the final research results to a certain extent. Hence, to further verify the results, a prospective randomized controlled trial with large sample size is necessary.

## Conclusion

For patients with advanced gastric cancer who underwent radical D2 surgery, the SOX/XELOX combination regimen tended to prolong the DFS but did not have significant benefits to their OS compared with S-1 monotherapy in the adjuvant setting.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Human rights statement** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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