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Original Article

Efficacy of Different Number of XELOX or SOX Chemotherapy Cycles After D2 Resection for Stage III Gastric Cancer

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ABSTRACT

Purpose: We aimed to explore whether the prognosis of patients treated with capecitabine and oxaliplatin (XELOX) or S-1 and oxaliplatin (SOX) regimens who received fewer cycles of chemotherapy after D2 radical resection for gastric cancer (GC) would be non-inferior to that of patients who received the standard number of cycles of chemotherapy.
Materials and Methods: Data on patients who received XELOX or SOX chemotherapy after undergoing D2 radical resection at Harbin Medical University Cancer Hospital between January 2011 and May 2016 were collected.
Results: In patients who received 4, 6, and 8 cycles of chemotherapy, the 5-year overall survival (OS) rates were 59.4%, 64.8%, and 62.7%, respectively. Compared to patients who received 4 cycles of chemotherapy, those who received 6 cycles (hazard ratio [HR], 0.882; 95% confidence interval [CI], 0.599–1.299; P=0.52) or 8 cycles (HR, 0.882; 95% CI, 0.533–1.458; P=0.62) of chemotherapy did not exhibit significantly prolonged OS. The 3-year disease-free survival (DFS) rate of patients who received 4, 6, and 8 cycles of chemotherapy was 62.1%, 67.2%, and 60.8%, respectively. Compared to patients who received 4 cycles of chemotherapy, those who received 6 cycles (HR, 0.835; 95% CI, 0.572–1.221; P=0.35) or 8 cycles (HR, 0.972; 95% CI, 0.606–1.558; P=0.91) of chemotherapy did not show significantly prolonged DFS. However, the 3-year DFS and 5-year OS rates of patients who received 6 cycles of chemotherapy appeared to be superior to those of patients who received 4 and 8 cycles of chemotherapy.
Conclusions: For patients with stage III GC, 4 to 6 cycles of XELOX or SOX chemotherapy may be a favorable option. This study provides a rationale for further randomized clinical trials.

Keywords: Chemotherapy cycles; Adjuvant chemotherapy; Gastric cancer; Capecitabine; Oxaliplatin; S-1

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies and the second most common cancer of the digestive system after colorectal cancer [1]. GC is a multifactorial disease, and many factors, mainly genetic and environmental factors, can influence its occurrence and development [2]. An estimated 1,090,000 new cases of GC and approximately 769,000 deaths due to GC are reported each year globally, making it the 5th most common cancer and

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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the 4th leading cause of cancer-related deaths worldwide [3]. According to a previous study, the incidence of GC is nearly 2 times higher in men than in women[3-7]. Such differences can be attributed to lifestyle, occupational exposure, and physiological differences [3-7]. Although there have been continuous improvements in treatment strategies, 80% patients are diagnosed with GC at an advanced stage owing to the highly aggressive and heterogeneous nature of GC [8]. Therefore, precision medicine is imperative for improving the quality of life of patients with GC.

D2 radical resection has been accepted as the only effective treatment for resectable GC [9-11]. However, a large proportion of patients experience recurrence and metastasis within 2 years of D2 radical resection, resulting in poor prognosis, with a 5-year survival rate of <50% [12-15]. The emergence of adjuvant chemotherapy has brought revolutionary changes to the outlook of GC treatment [16-18], and its effectiveness has been confirmed in several large clinical trials [19-23]. However, standard adjuvant treatment varies from region to region. In North America, the standard treatment is postoperative adjuvant chemoradiotherapy, based on the findings of the INT-0116 study [24]. In South Korea, the ARTIST and ARTIST 2 studies aimed to explore the efficacy of adjuvant chemoradiotherapy after gastric D2 radical resection [25-27]. However, the overall population failed to obtain a survival advantage, which is consistent with the findings of previous randomized clinical trials, showing that adjuvant chemoradiotherapy should not be considered the standard treatment for patients with lymph node-positive GC after D2 radical resection [28,29]. In Europe, the standard treatment is perioperative chemotherapy, based on the findings of the MAGIC, FNCLCC/FFCD9703, and FLOT4 studies [30-32]. In addition, the South Korean PRODIGY study and the Chinese RESOLVE study published by the European Society for Medical Oncology in 2019 have proposed that preoperative chemotherapy may provide new treatment options for locally advanced GC and have contributed to revision of the clinical practice guidelines [33-35]. Similarly, the preliminary results of the Chinese RESONANCE study on the perioperative period of GC show that neoadjuvant chemotherapy can improve the R0 resection rate of patients with GC(NCT01583361) [36]. In Asia, the standard treatment is postoperative adjuvant chemotherapy, based on the findings of the ACTS-GC, CLASSIC, and JACCRO GC-07 studies [19,21,23].

Research on adjuvant chemotherapy for GC is ongoing and is expected to further improve the survival rates of patients with GC [37-40]. Although these findings support the importance of adjuvant chemotherapy, there is no consensus regarding the duration of adjuvant chemotherapy. According to Chinese Society of Clinical Oncology guidelines [35], patients with postoperative pathological stage III GC should receive 8 cycles of capecitabine and oxaliplatin (XELOX) or S-1 and oxaliplatin (SOX) adjuvant chemotherapy every 3 weeks. However, in clinical practice, different individuals have varying tolerance to chemotherapy drugs. Therefore, some patients cannot complete the standard chemotherapy cycle due to the toxicity of chemotherapy drugs or family and social burdens, leading to early termination of chemotherapy. Therefore, we enrolled patients who received 4, 6, and 8 cycles of chemotherapy after D2 radical resection for GC. Moreover, increasing the duration of chemotherapy increases the risk of chemotherapy-related adverse reactions, while shortening the duration of chemotherapy increases the risk of recurrence and metastasis. Therefore, we aimed to explore the influence of different XELOX or SOX chemotherapy cycles on the survival of patients with GC. We only included patients with pathological tumor-node-metastasis (TNM) stage III GC after D2 radical resection.

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MATERIALS AND METHODS

Study design and participants

In this retrospective study, we collected survival data of patients with GC who underwent D2 radical resection and received postoperative XELOX or SOX adjuvant chemotherapy at Harbin Medical University Cancer Hospital between January 2011 and May 2016. Clinical data (age, sex, chemotherapy regimen, Lauren classification, tumor location, World Health Organization [WHO] grade, histological classification, and TNM stage) and follow-up information (clinical outcome and survival time) were collected from electronic medical records. This study was approved by the Ethics Committee of Harbin Medical University Cancer Hospital and complied with the principles outlined in the Declaration of Helsinki. All patients provided written informed consent before undergoing chemotherapy. All patient data were kept confidential.

Inclusion criteria

The inclusion criteria were as follows: 1) preoperative endoscopic biopsy or postoperative pathological diagnosis of GC/gastroesophageal junction cancer, 2) D2 radical resection or R0/R1 resection, 3) postoperative pathological stage III disease based on the American Joint Committee on Cancer TNM staging (8th edition), 4) postoperative adjuvant chemotherapy regimen of either XELOX or SOX, and 5) administration of 4, 6, or 8 cycles of chemotherapy.

Exclusion criteria

The exclusion criteria were as follows: 1) neoadjuvant treatment before surgery, 2) intraoperative metastasis or recurrence within 8 weeks of surgery, 3) history of other malignant tumors, 4) patients who received chemotherapy regimens other than XELOX or SOX after D2 radical resection, and 5) changes in the chemotherapy regimen for any reason during adjuvant treatment.

Treatment regimen

The XELOX treatment regimen included oxaliplatin administration via an intravenous drip (130 mg/m^2) on day 1 and twice-daily oral administration of capecitabine (1,000 mg/m^2) on days 1–14; the regimen was repeated every 3 weeks. The SOX treatment regimen included oxaliplatin (130 mg/m^2) treatment via an intravenous drip on day 1 and twice-daily oral administration of S-1 treatment (60 mg/m^2) on days 1–14; the regimen was repeated every 3 weeks. All patients received 4, 6, or 8 cycles of chemotherapy. B-ultrasound, computed tomography, and other imaging examinations were performed after every 3 cycles to evaluate the treatment effect.

Study endpoints

Disease-free survival (DFS) was defined as the time from the date of D2 resection to the date of diagnosis of recurrence or metastasis or death due to any cause. Overall survival (OS) was defined as the time from the date of D2 resection to the date of death due to any cause. The primary endpoint was 5-year OS, whereas the secondary endpoint was 3-year DFS.

Statistical analysis

The χ^2 test was used to compare the clinicopathological characteristics, 3-year DFS rates, and 5-year OS rates between patients who received 4, 6, and 8 cycles of chemotherapy. DFS and OS curves were drawn using the Kaplan–Meier method, and the log-rank test was used for comparisons. The Cox proportional hazard regression model was used to assess the relationship between the number of chemotherapy cycles and survival prognosis, and the hazard ratio (HR)

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of DFS and OS and the corresponding 95% confidence interval (CI) were estimated. In addition, confounding factors, such as sex and age, which may affect DFS and OS, were analyzed. P<0.05 was considered to indicate statistical significance. All statistical analyses were performed using R Statistical Software (version 4.0.3). This study was performed in July 2021.

RESULTS

Between January 2011 and May 2016, 356 patients with TNM stage III GC who underwent D2 radical resection, followed by XELOX or SOX adjuvant chemotherapy at Harbin Medical University Cancer Hospital were included. In total, 75 patients were excluded owing to follow-up loss, incomplete follow-up data, or refusal to cooperate during follow-up. In addition, one patient was excluded because of metastasis within 8 weeks of surgery. Among the 280 patients who met the inclusion criteria, 80 patients received SOX chemotherapy, while 200 received XELOX chemotherapy. Regardless of the chemotherapy regimen, 101, 128, and 51 patients received 4, 6, and 8 cycles of chemotherapy, respectively.

The baseline characteristics of patients who received different numbers of chemotherapy cycles were similar (**Table 1**). The median patient age (range) was 51 (30–73) years, and 208 (74%) patients were men. There were no significant differences in age, sex, Lauren classification [41], tumor location, WHO grade, histological classification, or TNM stage between the groups (P>0.05; **Table 1**).

Table 1. Clinical characteristics of patients with gastric cancer after D2 resection enrolled

Clinical characteristics	Cycle 4 (n=101)	Cycle 6 (n=128)	Cycle 8 (n=51)	χ^2	P-value
Age (year)				2.928	0.231
≤65	83	115	43		
>65	18	13	8		
Regimen				16.578	<0.001
XELOX	75	86	39		
SOX	26	42	12		
Sex				2.791	0.248
Male	79	89	40		
Female	22	39	11		
Lauren classification				3.045	0.550
Intestinal type	22	29	6		
Diffuse type	43	57	25		
Mixed type	36	42	20		
Tumor site				2.825	0.244
Gastric body and the whole stomach	44	43	22		
Gastric antrum	57	85	29		
World Health Organization grade				10.864	0.093
Adenocarcinoma	54	62	25		
Signet ring cell carcinoma	11	4	5		
Low adhesion carcinoma	7	6	1		
Mixed cancer	29	56	20		
Histological classification				1.523	0.823
Poorly differentiated	57	72	27		
Moderately differentiated	43	53	22		
Well differentiated	1	3	2		
Tumor-node-metastasis stage				3.759	0.440
IIIA	45	72	26		
IIIB	39	35	17		
IIIC	17	21	8		

XELOX = capecitabine and oxaliplatin; SOX = S-1 and oxaliplatin.

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The median (range) follow-up time was 66.5 (8.5–124.5) months. At the last follow-up (May 2021), 133 patients experienced recurrence or metastasis or succumbed to the disease. For patients who did not reach the primary or secondary endpoints, the last follow-up time was recorded as the time at which either endpoint occurred.

Survival was compared between patients who received 4 cycles of chemotherapy and those who received 6 cycles of chemotherapy and between patients who received 4 cycles of chemotherapy and those who received 8 cycles of chemotherapy. The median OS for the primary endpoint was 8.29, 8.80, and 6 years in the 4-, 6-, and 8-cycle chemotherapy groups, respectively. The 5-year OS rates were 59.4%, 64.8%, and 62.7% in the 4-, 6-, 8-cycle chemotherapy groups, respectively. Compared to patients who received 4 cycles of chemotherapy, those who received 6 (HR, 0.882; 95% CI, 0.599–1.299; P=0.52) and 8 (HR, 0.882; 95% CI, 0.533–1.458; P=0.62) cycles of chemotherapy did not exhibit significantly prolonged OS (**Fig. 1A and D**).

The median DFS for the secondary endpoint was 6.06, 8.48, and 5.79 years in the 4-, 6-, and 8-cycle chemotherapy groups, respectively. The 3-year DFS rates were 62.1%, 67.2%, and 60.8% in the 4-, 6-, and 8-cycle chemotherapy group, respectively. Compared to patients who received 4 cycles of chemotherapy, those who received 6 (HR, 0.835; 95% CI, 0.572–1.221; P=0.35) and 8 (HR, 0.972; 95% CI, 0.606–1.558; P=0.91) cycles of chemotherapy did not exhibit significantly prolonged DFS (**Fig. 1B and C**).

A single-factor Cox proportional hazard regression model was used to analyze factors, such as sex and age, which may affect DFS and OS. There was no significant difference between the different chemotherapy cycle groups within each subgroup, although the HR for OS (HR, 0.421; 95% CI, 0.226–0.786; P=0.007) and DFS (HR, 0.39; 95% CI, 0.209–0.727; P=0.003) favored 6 cycles of chemotherapy over 4 cycles of chemotherapy in the moderately differentiated histological subgroup. The HR for DFS (HR, 0.492; 95% CI, 0.262–0.924; P=0.027) favored 6 cycles of chemotherapy over 4 cycles of chemotherapy in the TNM stage IIIA subgroup. There was no significant difference in OS or DFS between patients who received 4 and 8 cycles of chemotherapy in the moderately differentiated histological and TNM stage IIIA subgroups (**Fig. 2**).

DISCUSSION

Advances in surgical techniques and comprehensive treatment techniques have improved the local control rate and quality of life of patients with GC. Fluoruracil (FU)-based chemotherapy combined with platinum is the standard treatment for patients with resectable GC. In China, 6 months of XELOX and SOX treatment is recommended for patients with postoperative pathological stage III GC after D2 radical resection [19,20,34,35]. The CLASSIC study showed that the DFS and OS of patients with GC who received 8 cycles XELOX adjuvant chemotherapy were significantly higher than those of patients who received surgery alone [19,20]. However, in the CLASSIC trial, only 346 (67%) patients completed 8 cycles of chemotherapy, as planned. Moreover, 48% and 47% patients required XELOX dose reductions, respectively. The most common adverse events in the chemotherapy group were nausea, vomiting, neutropenia, decreased appetite, diarrhea, and peripheral neuropathy. The Chinese RESOLVE study confirmed for the first time that the SOX adjuvant chemotherapy regimen (8 cycles) after D2 radical resection of GC was not inferior to the XELOX regimen

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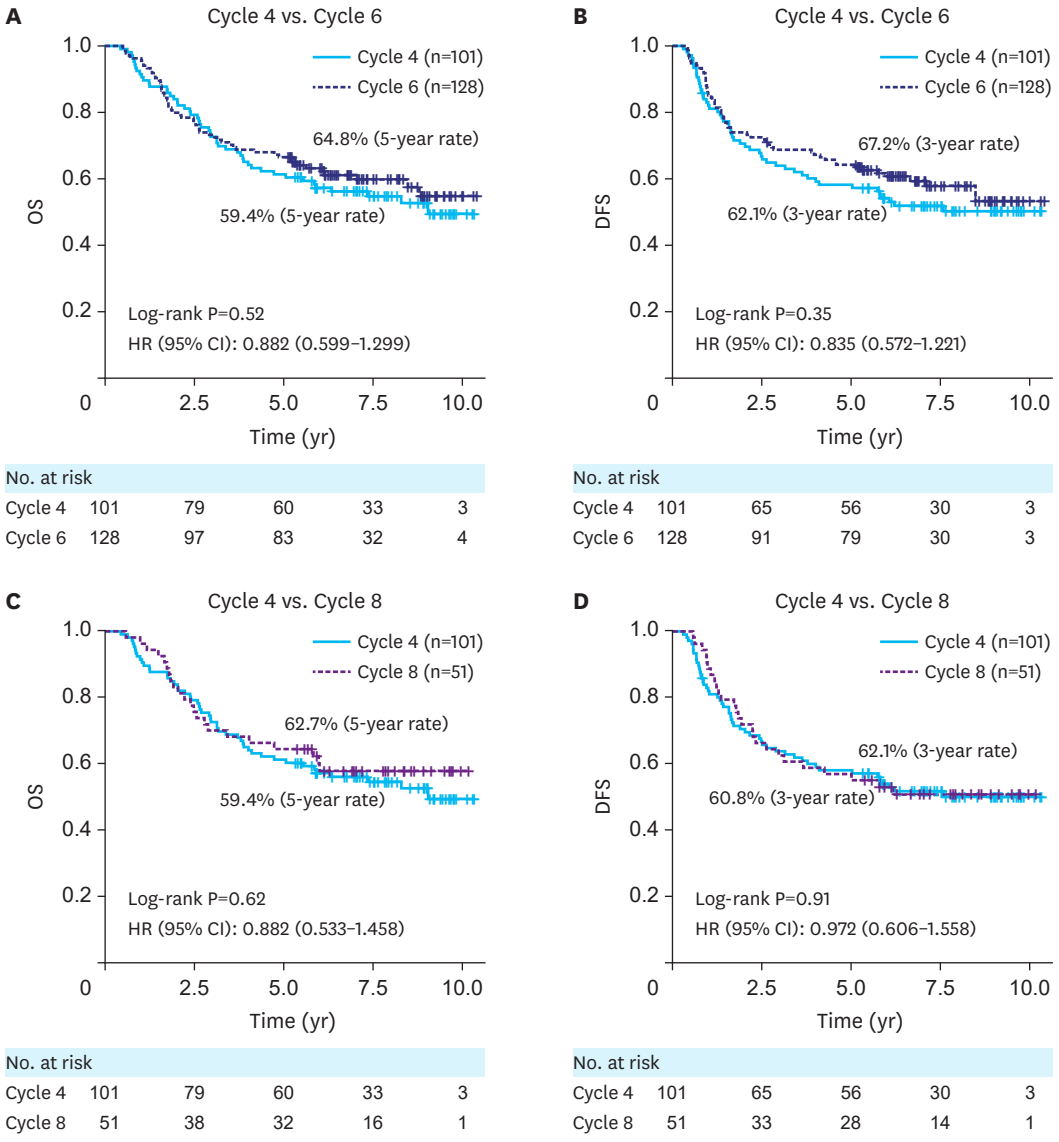

Fig. 1. Kaplan–Meier survival analysis for OS and DFS. (A) OS and (B) DFS analyses of patients with stage III gastric cancer who received four and 6 cycles of chemotherapy, irrespective of whether they underwent SOX or XELOX regimens. (C) OS and (D) DFS analyses of patients with stage III gastric cancer who received four and 8 cycles of chemotherapy, irrespective of whether they underwent SOX or XELOX regimens.
SOX = S-1 plus oxaliplatin; XELOX = capecitabine plus oxaliplatin; OS = overall survival; DFS = disease-free survival; HR = hazard ratio; CI = confidence interval.

[34]. Among the 249 patients who received SOX chemotherapy, 70% completed 8 cycles, as planned. Among them, 17% patients required dose reductions, while 19% patients discontinued treatment due to drug-related toxicity. The most common grade 3–4 adverse event is neutropenia. Owing to the occurrence of chemotherapy-related adverse events, many patients cannot complete the full course of treatment. The post-analysis of the MAGIC and CLASSIC studies [42,43] reported that patients with GC and high microsatellite instability (MSI) could not benefit from adjuvant chemotherapy. Compared to postoperative adjuvant chemotherapy, surgery alone is positively correlated with better prognosis. A multicenter meta-analysis aimed to explore the relationship between MSI-high status and prognosis after surgery and efficacy of perioperative chemotherapy [44]. The results showed that for patients with resectable GC and high MSI, surgery alone had a better prognosis than postoperative adjuvant chemotherapy. The results of multiple small-sample retrospective

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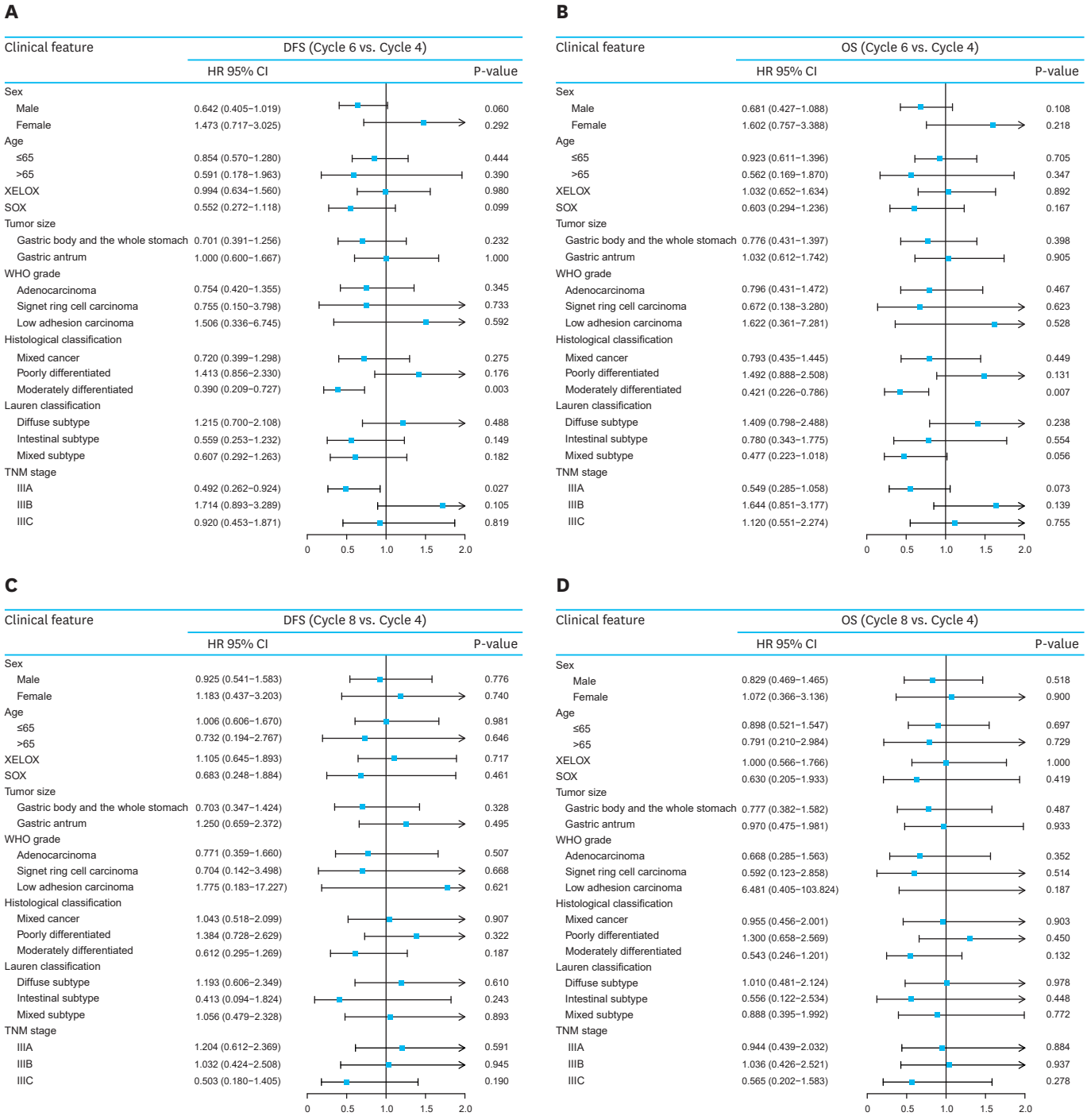

Fig. 2. Subgroup analyses of DFS and OS.
DFS = disease-free survival; OS = overall survival; XELOX = capecitabine plus oxaliplatin; SOX = S-1 plus oxaliplatin; HR = hazard ratio; CI = confidence interval; WHO = World Health Organization; TNM = tumor-node-metastasis.

studies have shown that patients with GC and high MSI have a better prognosis, but the benefits of adjuvant chemotherapy are inconsistent [45-47]. Therefore, it is crucial to further explore the optimal duration of chemotherapy. However, most of the current prospective studies have focused on therapeutic efficacy rather than treatment strategies. Therefore, we sought to explore the influence of different XELOX or SOX chemotherapy cycles on

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the survival of patients with GC. We used stringent inclusion/exclusion criteria to extract data from electronic medical records at our center. The primary endpoint was 5-year OS, whereas the secondary endpoint was 3-year DFS. The present study was performed without considering the chemotherapy regimen, and the results of previous studies, including those of the RESOLVE trial [34,48,49], support those of the present study. Our results showed that compared to patients who received 4 cycles of chemotherapy, those who received 6 and 8 cycles of chemotherapy could confer significant additional survival benefits. However, although not statistically significant, the 3-year DFS and 5-year OS rates of patients who received 6 cycles of chemotherapy appeared to be superior to those of patients who received 4 and 8 cycles of chemotherapy. Therefore, for patients with stage III GC, 4 to 6 cycles of XELOX or SOX chemotherapy may be a favorable option. Although this study was limited by its inability to describe the isodose cumulative toxicity of oxaliplatin-induced peripheral neuropathy, any interpretation of the present results should consider the effects of the treatment regimen. We speculate that significant reduction in adverse events may be reason why 4 to 6 cycles of adjuvant chemotherapy can prolong prognosis.

The optimal duration of adjuvant chemotherapy for colorectal cancer has been established. The IDEA study [50,51] showed that in low-risk patients (T1, T2, T3, and N1 cancers), adjuvant chemotherapy with XELOX for 3 months was not inferior to that for 6 months. In high-risk patients (T4, N2, or both), adjuvant chemotherapy with XELOX for 3 months did not achieve statistically significant non-inferiority compared to that for 6 months. Two phase III studies have compared the duration of chemotherapy in patients with resectable GC. JCOG1104 (OPAS-1), an open-label, phase III, non-inferiority, randomized trial, showed that for patients with stage II GC, 4 cycles of S-1 were inferior to 8 cycles of S-1 [52]. Therefore, S-1 should remain the standard adjuvant chemotherapy for stage II GC for 1 year. However, prolonging the duration of postoperative chemotherapy did not improve the survival time of patients. Another prospective study showed that adding 8 cycles of oral capecitabine to 8 cycles of XELOX regimen did not significantly improve the OS of patients with stage II–III GC [53]. However, there are no relevant prospective clinical studies to successfully guide clinical practice regarding the duration of adjuvant chemotherapy after GC surgery. The LOMAC study (NCT03399110), an ongoing multicenter, randomized, parallel-assignment clinical trial initiated by Fudan University in China, aims to confirm that 4 months XELOX is not inferior to 6 months XELOX in terms of DFS and safety. The ongoing SMAC study (NCT03941561), also initiated by Fudan University in China, aims to compare the efficacy and safety of S-1 for 9 months and S-1 for 1 year as adjuvant chemotherapy after D2 radical resection. The ongoing EXODOX study (NCT04787354), initiated by Hallym University Medical Center, aims to compare the efficacy and safety of reduced-dose adjuvant XELOX therapy (4 cycles of XELOX, followed by 4 cycles of capecitabine alone) and standard adjuvant XELOX therapy (8 cycles of XELOX). These ongoing prospective clinical studies will provide a theoretical basis for guiding clinical practice.

A retrospective study aimed to explore the influence of time to adjuvant chemotherapy and number of chemotherapy cycles on patient survival [54]. The results suggested that 6 cycles of chemotherapy tended to achieve the maximum survival benefit. Since the number of chemotherapy cycles was associated with survival outcomes of both perioperative chemotherapy and postoperative chemotherapy, the analysis of number of chemotherapy cycles was based on the whole sample of patients. In this study, 7 dual chemotherapy regimens based on 5-FU were used—SOX, XELOX, FOLFOX, S-1 plus cisplatin, capecitabine plus paclitaxel, S-1 plus paclitaxel, and capecitabine plus irinotecan. Qu et al. [55] retrospectively identified 237 patients with stage IB–IIIC GC who received 4, 6, and 8 cycles of FU-based

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adjuvant chemotherapy every 3 weeks after radical gastrectomy [55]. The estimated 5-year OS rates of patients who received 4, 6, and 8 cycles of chemotherapy were 41.2%, 74.0%, and 65.8%, respectively. The study showed that patients who received 6 cycles of chemotherapy were more likely to have a better OS. In our study, the 5-year OS rates of patients who received 4, 6, and 8 cycles of SOX or XELOX chemotherapy were 59.4%, 64.8%, and 62.7%, respectively. Patients who received 6 cycles of chemotherapy had a better OS than those who received 4 and 8 cycles of chemotherapy, which is consistent with the findings reported by Qu et al. [55]. A recent study retrospectively identified 428 patients with stage II–III GC who underwent D2 gastrectomy between 2009 and 2016 [56]. Patients were divided into 4 groups according to the duration of adjuvant chemotherapy—0 weeks (no adjuvant, group A), 20–24 weeks (completed 7 to 8 cycles every 3 weeks or 10–12 cycles every 2 weeks, group B), and 12–18 weeks (completed 4 to 6 cycles every 3 weeks or 6 to 9 cycles every 2 weeks, group C), and <12 weeks (received up to 3 cycles every 3 weeks or 5 cycles every 2 weeks, group D). The chemotherapy regimens included XELOX, SOX, and FOLFOX. The study showed that 4 to 6 cycles of XELOX or SOX chemotherapy administered every 3 weeks or 6 to 9 cycles of FOLFOX administered every 2 weeks (group C) might be a favorable option for patients with stage II–III GC after D2 radical gastrectomy. This finding is consistent with the results of our study.

The limitations our study should be considered when analyzing the results. The present study was a single-center, retrospective study in which the data collected inevitably exhibited some deviations. In addition, the number of included patients was relatively small; therefore, the sample distribution was uneven. Treatment after recurrence was not specified in our study, which might have confounded patients' OS. Moreover, detailed data on short- and long-term chemotherapy-related adverse reactions and postoperative recurrence patterns were not statistically analyzed. These factors might have affected the experimental results. Therefore, to verify the accuracy of these results, it is necessary to conduct large-scale retrospective or prospective randomized controlled clinical trials.

Our study results suggest that 4 to 6 cycles of chemotherapy might be a favorable option for patients with postoperative TNM stage III GC, depending on the willingness of the patient to undergo treatment, financial situation of the family, and tolerance to chemotherapy drugs. However, this result should be further confirmed in future prospective or retrospective studies with larger sample sizes.

In conclusion, for patients with stage III GC, 4 to 6 cycles of XELOX or SOX chemotherapy may be a favorable option. This study provides a rationale for further randomized clinical trials.

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