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Original Article

Long-term Efficacy of S-1 Monotherapy or Capecitabine Plus Oxaliplatin as Adjuvant Chemotherapy for Patients with Stage II or III Gastric Cancer after Curative Gastrectomy: a Propensity Score-Matched Multicenter Cohort Study

Chang Min Lee [1], Moon-Won Yoo[2], Young-Gil Son[3], Sung Jin Oh[4], Jong-Han Kim[1], Hyoung-Il Kim[5], Joong-Min Park[6], Hoon Hur[7], Ye Seob Jee[8], Sun-Hwi Hwang[9], Sung-Ho Jin[10], Sang Eok Lee[11], Ji-Ho Park[12], Kyung Won Seo[13], Sungsoo Park[1], Chang Hyun Kim[14], In Ho Jeong[15], Han Hong Lee[16], Sung Il Choi[17], Sang-Il Lee[18], Chan Young Kim[19], In-Hwan Kim[20], Myoung-Won Son[21], Kyung Ho Pak[22], Sungsoo Kim[15], Moon-Soo Lee[23], Jae-Seok Min [24]

[1]Department of Surgery, Korea University College of Medicine, Seoul, Korea
[2]Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Department of Surgery, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea
[4]Department of Surgery, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea
[5]Department of Surgery, Yonsei University College of Medicine, Seoul, Korea
[6]Department of Surgery, Chung-Ang University College of Medicine, Seoul, Korea
[7]Department of Surgery, Ajou University School of Medicine, Suwon, Korea
[8]Department of Surgery, Dankook University Hospital, Cheonan, Korea
[9]Department of Surgery, Pusan National University Yangsan Hospital, Yangsan, Korea
[10]Department of Surgery, Korea Cancer Center Hospital, Seoul, Korea
[11]Department of Surgery, Konyang University Hospital, Daejeon, Korea
[12]Department of Surgery, Gyeongsang National University Hospital, Jinju, Korea
[13]Department of Surgery, Kosin University College of Medicine, Busan, Korea
[14]Department of Surgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea
[15]Department of Surgery, Jeju National University Hospital, Jeju, Korea
[16]Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[17]Department of Surgery, Kyung Hee University Hospital at Gangdong, Seoul, Korea
[18]Department of Surgery, Chungnam National University College of Medicine, Daejeon, Korea
[19]Department of Surgery, Chonbuk National University College of Medicine, Jeonju, Korea
[20]Department of Surgery, Daegu Catholic University College of Medicine, Daegu, Korea
[21]Department of Surgery, Soonchunhyang University Cheonan Hospital, Cheonan, Korea
[22]Department of Surgery, Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Korea
[23]Department of Surgery, Eulji University Hospital, Daejeon, Korea
[24]Department of Surgery, Dongnam Institute of Radiological and Medical Sciences, Cancer Center, Busan, Korea

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Correspondence to
Jae-Seok Min
Department of Surgery, Dongnam Institute of Radiological and Medical Sciences, Cancer Center, 40 Jwadong-gil, Busan 46033, Korea.
E-mail: mdoogy@naver.com

ORCID iDs
Chang Min Lee
https://orcid.org/0000-0003-2567-5533
Jae-Seok Min
https://orcid.org/0000-0002-5798-4595

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Author Contributions
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ABSTRACT

Purpose: To compare long-term disease-free survival (DFS) between patients receiving tegafur/gimeracil/oteracil (S-1) or capecitabine plus oxaliplatin (CAPOX) adjuvant chemotherapy (AC) for gastric cancer (GC).

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

Materials and Methods: This retrospective multicenter observational study enrolled 983 patients who underwent curative gastrectomy with consecutive AC with S-1 or CAPOX for stage II or III GC at 27 hospitals in Korea between February 2012 and December 2013. We conducted propensity score matching to reduce selection bias. Long-term oncologic outcomes, including DFS rate over 5 years (over-5yr DFS), were analyzed postoperatively.
Results: The median and longest follow-up period were 59.0 and 87.6 months, respectively. DFS rate did not differ between patients who received S-1 and CAPOX for pathologic stage II (P=0.677) and stage III (P=0.899) GC. Moreover, hazard ratio (HR) for recurrence did not differ significantly between S-1 and CAPOX (reference) in stage II (HR, 1.846; 95% confidence interval [CI], 0.693–4.919; P=0.220) and stage III (HR, 0.942; 95% CI, 0.664–1.337; P=0.738) GC. After adjustment for significance in multivariate analysis, pT (4 vs. 1) (HR, 11.667; 95% CI, 1.595–85.351; P=0.016), pN stage (0 vs. 3) (HR, 2.788; 95% CI, 1.502–5.174; P=0.001), and completion of planned chemotherapy (HR, 2.213; 95% CI, 1.618–3.028; P<0.001) were determined as independent prognostic factors for DFS.
Conclusions: S-1 and CAPOX AC regimens did not show significant difference in over-5yr DFS after curative gastrectomy in patients with stage II or III GC. The pT, pN stage, and completion of planned chemotherapy were prognostic factors for GC recurrence.

Keywords: Gastric cancer; Adjuvant chemotherapy; Disease-free survival

INTRODUCTION

Among various agents for adjuvant chemotherapy (AC) after curative radical gastrectomy in patients with stage II and III gastric cancer (GC), tegafur/gimeracil/oteracil (S-1) and capecitabine plus oxaliplatin (CAPOX) predominate owing to their remarkable oncologic outcomes in 2 multicenter randomized controlled trials (RCTs) proving the efficacy of ACs [1,2]. Most physicians or surgical oncologists, especially in Asia, follow similar strategies to select AC regimen for GC; in general, the selection is based on the clinicopathologic status of a patient. Although the efficacies of S-1 and CAPOX regimens could not be compared directly by the 2 previous RCTs, a subgroup analysis of these trials proposed the indications of AC regimens. The CAPOX regimen tended to be administered to patients with relatively higher stages of GC, whereas S-1 monotherapy was administered to less advanced cases. These strategies come from the assumption that CAPOX, a doublet regimen, might be superior over S-1 monotherapy in terms of oncologic outcomes.

However, these strategies are not based on reliable studies that directly compare both regimens. This issue has remained controversial because the therapeutic effects of the 2 AC regimens have not been verified by a high-quality evidence extracted from multicenter RCTs involving both regimens. In addition, we have no scientific basis to determine whether either of the 2 regimens is more effective than the other in terms of long-term oncologic outcomes. This issue remains unresolved owing to difficulties in performing prospective comparative trials due to commercial and other challenges.

For these reasons, the Surgical Oncology Forum study group launched a multicenter retrospective study to compare disease-free survival (DFS) rates at 3 years after surgery between patients receiving S-1 monotherapy and those receiving CAPOX doublet chemotherapy [3]. The results showed that in patients with relatively higher-stage disease, CAPOX was associated with higher DFS than S-1 monotherapy. Although CAPOX regimen

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may be superior to S-1 monotherapy in terms of 3-year DFS rates in patients with high-stage disease, there is still no evidence that CAPOX is superior to S-1 monotherapy in terms of outcomes after long-term follow-up in these patients. The results of the previous studies investigated the relatively short-term oncologic outcomes rather than the long-term efficacy of these 2 AC regimens.

Therefore, the present propensity score-matched multicenter cohort study compared the long-term oncologic results over 5 years (over-5yr DFS) after curative resection between patients who received AC with S-1 or CAPOX. To the best of our knowledge, this was the first multicenter cohort study to evaluate the long-term recurrence outcomes (over-5yr DFS) of 2 AC regimens in patients with GC after curative gastrectomy.

MATERIALS AND METHODS

Patients

This study included data from 983 patients who underwent curative resection and received AC for GC between January 2012 and December 2013 at 27 hospitals in the Republic of Korea. The enrolled patients underwent R0 resection by radical gastrectomy with D2 or more lymph node dissection according to guidelines [4,5].

Eligible patients 1) were 20 years of age or older; 2) had histologically proven stage II or III GC after radical gastrectomy based on the 8th edition of American Joint Committee on Cancer (AJCC) cancer staging system; 3) had received S-1 monotherapy or CAPOX regimen as an AC within 8 weeks after surgery; 4) had not received preoperative chemotherapy, radiotherapy, or immunotherapy; 5) did not have synchronous or metachronous cancer; 6) did not have distant metastasis; and 7) did not have tumor cells according to peritoneal washing cytologic examination [6].

Study design and data collection

We reviewed the clinical status data and medical records of all participating institutions in May 2019. The primary endpoint was over-5yr DFS after curative gastrectomy. DFS was defined as the time elapsed from the operation date to the recurrence date or the time of the last follow-up. The study protocol was approved by the Institutional Review Board of the Institute of Radiological and Medical Sciences, Busan, Republic of Korea (No. D-1902-031-002), which waived the requirement for written informed consent from the patients owing to the retrospective study design.

AC regimens

The AC treatments were initiated within 4–8 weeks after curative resection. The chemotherapeutic regimens were administered as described by the ACTS-GC and the CLASSIC trial [1,2]. Patients in the S-1 group received the treatment at a dose of 40, 50, or 60 mg twice daily. The dose was determined based on the body surface area of each individual patient. Each S-1 cycle included drug administration for 4 weeks, followed by 2 weeks of rest; the 6-week cycle was repeated for a total of 8 cycles. Patients in the CAPOX group received 3-week cycles of oral capecitabine (1,000 mg/m^2 twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle) for a total of 8 cycles. Reductions of doses, modifications of schedules, or interruptions of AC were conducted based on a clinician's decision considering the events that occurred during AC.

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Follow-up

The patients underwent follow-up examinations including abdominal computed tomography (CT) scan and/or endoscopy to detect GC recurrence. After AC completion, follow-up medical consultations, history-taking, physical examinations, and clinical evaluations were recommended every 3–4 months for 2 years and then every half-year for the subsequent 2 years. After approximately 5 years following surgery, assessments were performed annually or once every 2 years. The follow-up evaluations included measurement of gastrointestinal tumor markers, simple chest X-ray, abdominal and pelvic enhanced CT scan (AP-CT), and upper gastrointestinal endoscopy. Abdominal ultrasonography, chest CT scan, abdominal magnetic resonance imaging, positron emission tomography scan, and bone scan were additionally performed when AP-CT revealed equivocal abnormalities.

Statistical analysis

Propensity score matching (PSM) based on binary logistic regression was used to minimize selection bias caused by imbalanced variables in the historical cohort study (**Fig. 1**). The propensity score model considered clinicopathological characteristics including patients' age, sex, American Society of Anesthesiologists (ASA) score, extent of gastrectomy, operation method, T stage, N stage, stage according to the 8th AJCC staging system, retrieved lymph nodes, tumor size and differentiation, Lauren's classification, and lymphatic and vascular invasion. We performed 1:3 matching between the S-1 and CAPOX groups using the nearest-neighbor matching method without replacement.

IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. The chi-square test was used to compare baseline characteristics between the 2 groups. The Kaplan–Meier method was used to estimate cumulative DFS with 95% confidence intervals (CIs). Breslow or 2-sided log-rank test was used to compare DFS rate between the treatment groups. Significant factors in the univariate analysis were included in

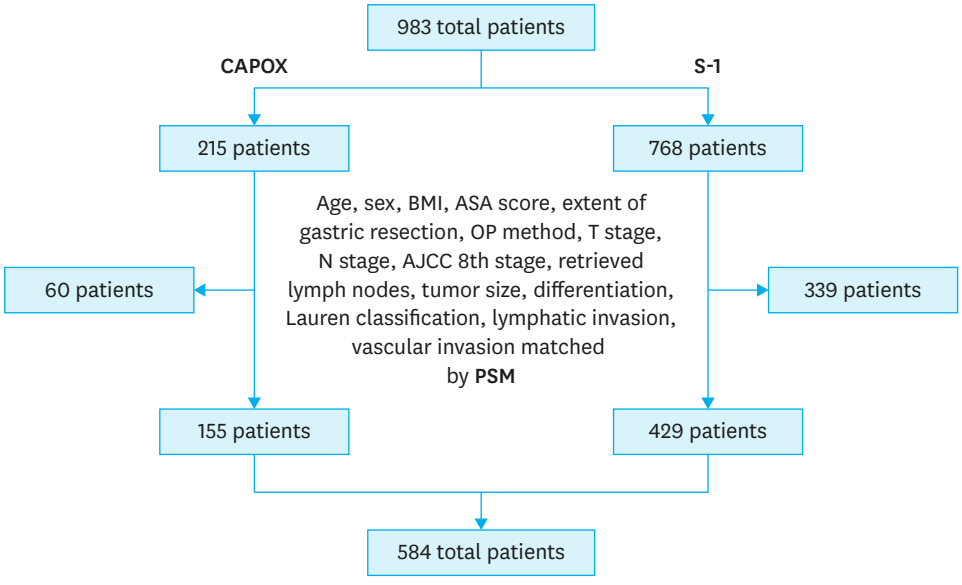

Fig. 1. Flowchart of PSM.
CAPOX = capecitabine and oxaliplatin; S-1 = tegafur/gimeracil/oteracil; BMI = body mass index; ASA = American Society of Anesthesiologists; OP = operation; AJCC = American Joint Committee on Cancer; PSM = propensity score matching.

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the multivariate analysis, and the hazard ratios (HRs) for recurrence in the S-1 group, with the CAPOX group as a reference, were analyzed using the Cox proportional hazards model. P-values less than 0.05 were considered statistically significant.

RESULTS

Patient baseline characteristics

The median and longest follow-up periods were determined to be 59.2 and 87.6 months, respectively, before PSM and 59.0 and 87.6 months, respectively, after PSM until the cutoff date of April 31, 2019. **Table 1** presents the baseline characteristics of patients in the S-1 and CAPOX groups. Before PSM (n=983), some clinicopathologic variables differed significantly between the 2 groups. Patients in the S-1 group were older (P<0.001); more commonly underwent a minimally invasive approach (P<0.001); had less advanced pathologic T, N, and AJCC 8th stages (P=0.016, P<0.001, P<0.001); had smaller tumor size (P<0.001); more commonly had intestinal-type Lauren classification (P=0.007); less often had lymphatic or vascular invasion (P=0.007, P=0.002); and less often completed the planned chemotherapy (P=0.027) compared with those in the CAPOX group. After PSM (n=584, **Fig. 1**), to reduce the bias caused by the historical nature of the cohort study, no significant differences in baseline characteristics were observed between the S-1 and CAPOX groups.

Table 1. Baseline characteristics of patients in S-1 and CAPOX groups

Variables	Before PSM (n=983)				After PSM (n=584)			
	S-1 (n=768)	CAPOX (n=215)	P-value	Standardized difference	S-1 (n=429)	CAPOX (n=155)	P-value	Standardized difference
Age (yr)			<0.001*	0.343			0.907	0.011
<60	313 (40.76)	124 (57.67)			208 (48.48)	76 (49.03)		
≥60	455 (59.24)	91 (42.33)			221 (51.52)	79 (50.97)		
Sex			0.091	0.133			0.237	0.112
Male	518 (67.45)	158 (73.49)			285 (66.43)	111 (71.61)		
Female	250 (32.55)	57 (26.51)			144 (33.57)	44 (28.39)		
BMI (kg/m^2)			0.982	0.002			0.394	0.081
≤23	371 (48.5)	103 (48.58)			211 (49.41)	69 (45.39)		
>23	394 (51.5)	109 (51.42)			216 (50.59)	83 (54.61)		
ASA score			0.440	0.137			0.499	0.152
1	267 (34.86)	86 (40)			168 (39.25)	60 (38.71)		
2	407 (53.13)	105 (48.84)			216 (50.47)	74 (47.74)		
3	89 (11.62)	24 (11.16)			42 (9.81)	21 (13.55)		
4	3 (0.39)	0 (0)			2 (0.47)	0 (0)		
Extent of gastric resection			0.946	0.005			0.530	0.059
Subtotal gastrectomy	502 (65.36)	140 (65.12)			273 (63.64)	103 (66.45)		
Total gastrectomy	266 (34.64)	75 (34.88)			156 (36.36)	52 (33.55)		
Operation approach method			<0.001*	0.305			0.530	0.018
Open	605 (78.78)	193 (89.77)			273 (63.64)	103 (66.45)		
Laparoscopy or robot	163 (21.22)	22 (10.23)			156 (36.36)	52 (33.55)		
pT stage			0.016*	0.254			0.978	0.042
T1	42 (5.47)	6 (2.79)			18 (4.2)	6 (3.87)		
T2	120 (15.63)	24 (11.16)			61 (14.22)	23 (14.84)		
T3	370 (48.18)	97 (45.12)			185 (43.12)	69 (44.52)		
T4	236 (30.73)	88 (40.93)			165 (38.46)	57 (36.77)		
pN stage			<0.001*	0.661			0.811	0.093
N0	186 (24.22)	17 (7.91)			57 (13.29)	17 (10.97)		
N1	184 (23.96)	25 (11.63)			64 (14.92)	25 (16.13)		
N2	172 (22.4)	60 (27.91)			113 (26.34)	45 (29.03)		
N3	226 (29.43)	113 (52.56)			195 (45.45)	68 (43.87)		

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Table 1. (Continued) Baseline characteristics of patients in S-1 and CAPOX groups

Variables	Before PSM (n=983)				After PSM (n=584)			
	S-1 (n=768)	CAPOX (n=215)	P-value	Standardized difference	S-1 (n=429)	CAPOX (n=155)	P-value	Standardized difference
AJCC 8th stage			<0.001*	0.666			0.807	0.023
Stage II	415 (54.04)	50 (23.26)			143 (33.33)	50 (32.26)		
Stage III	353 (45.96)	165 (76.74)			286 (66.67)	105 (67.74)		
Retrieved lymph nodes			0.229	−0.059			0.380	−0.101
≤45	439 (57.16)	113 (52.56)			239 (55.71)	80 (51.61)		
>45	329 (42.84)	102 (47.44)			190 (44.29)	75 (48.39)		
Tumor size (cm)			<0.001*	0.260			0.384	0.082
≤5	430 (56.14)	93 (43.26)			214 (49.88)	71 (45.81)		
>5	336 (43.86)	122 (56.74)			215 (50.12)	84 (54.19)		
Differentiation			0.341	0.109			0.818	0.059
W or M	263 (34.24)	67 (31.16)			124 (28.9)	49 (31.61)		
P or S	463 (60.29)	131 (60.93)			276 (64.34)	96 (61.94)		
Others	42 (5.47)	17 (7.91)			29 (6.76)	10 (6.45)		
Lauren classification			0.007*	0.276			0.076	0.251
Intestinal	284 (40.34)	62 (34.44)			142 (35.86)	46 (35.94)		
Diffuse	335 (47.59)	107 (59.44)			205 (51.77)	75 (58.59)		
Mixed	85 (12.07)	11 (6.11)			49 (12.37)	7 (5.47)		
Lymphatic invasion			0.007*	0.220			0.781	0.027
No	263 (36.23)	54 (26.09)			113 (28.32)	44 (29.53)		
Yes	463 (63.77)	153 (73.91)			286 (71.68)	105 (70.47)		
Vascular invasion			0.002*	0.236			0.511	0.063
No	507 (69.26)	120 (57.97)			267 (66.09)	94 (63.09)		
Yes	225 (30.74)	87 (42.03)			137 (33.91)	55 (36.91)		
Completion of planned chemotherapy			0.027*	0.174			0.908	0.011
Yes	503 (65.49)	158 (73.49)			294 (68.53)	107 (69.03)		
No	265 (34.51)	57 (26.51)			135 (31.47)	48 (30.97)		

Values are presented as number (%).
PSM = propensity score matching; S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin; BMI = body mass index; ASA = American society of anesthesiologist; AJCC 8th = 8th edition of American Joint Committee on Cancer; W = well-differentiated; M = moderately-differentiated; P = poorly-differentiated; S = signet ring cell carcinoma.
*Statistically significant with P<0.05.

DFS and HRs for recurrence after PSM

After PSM, no differences in DFS rate for pathologic stage II (P=0.677) and III (P=0.899) GC were observed between the S-1 and CAPOX groups (**Fig. 2**). In patients with stage II GC, the DFS rates were 85.4% (95% CI, 82.3%–88.5%) in the S-1 group and 89.3% (95% CI, 82.6%–96.0%) in the CAPOX group. In patients with stage III GC, the DFS rates were 56.0% (95% CI, 53.2%–58.8%) in the S-1 group and 56.2% (95% CI, 50.5%–61.9%) in the CAPOX group (**Table 2**). Subgroup analysis of stage III GC did not reveal significant differences in DFS rate for stage IIIA (P=0.784), IIIB (P=0.834), and IIIC (P=0.435) GC between the 2 groups.

No significant differences in recurrence according to the HR of S-1 compared with that of CAPOX as a reference for stage II (HR, 1.846; 95% CI, 0.693–4.919; P=0.220) and stage III (HR, 0.942; 95% CI, 0.664–1.337; P=0.738) GC were observed between groups (**Table 3**). Subgroup analysis of patients with stage III GC showed HRs of S-1 for recurrence of 0.873 (95% CI, 0.466–1.635; P=0.671) for stage IIIA, 1.220 (95% CI, 0.571–2.610; P=0.608) for stage IIIB, and 0.813 (95% CI, 0.482–1.371; P=0.437) for stage IIIC. **Fig. 3** shows forest plots from subgroup analysis of DFS for the 2 groups. The subgroup analysis did not reveal any significant differences in recurrence between the S-1 and CAPOX groups.

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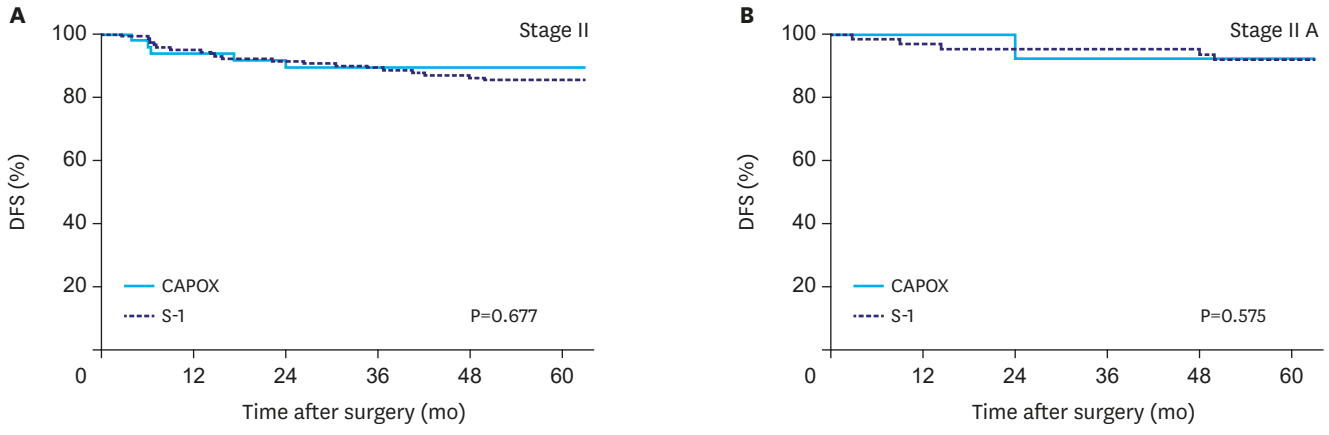
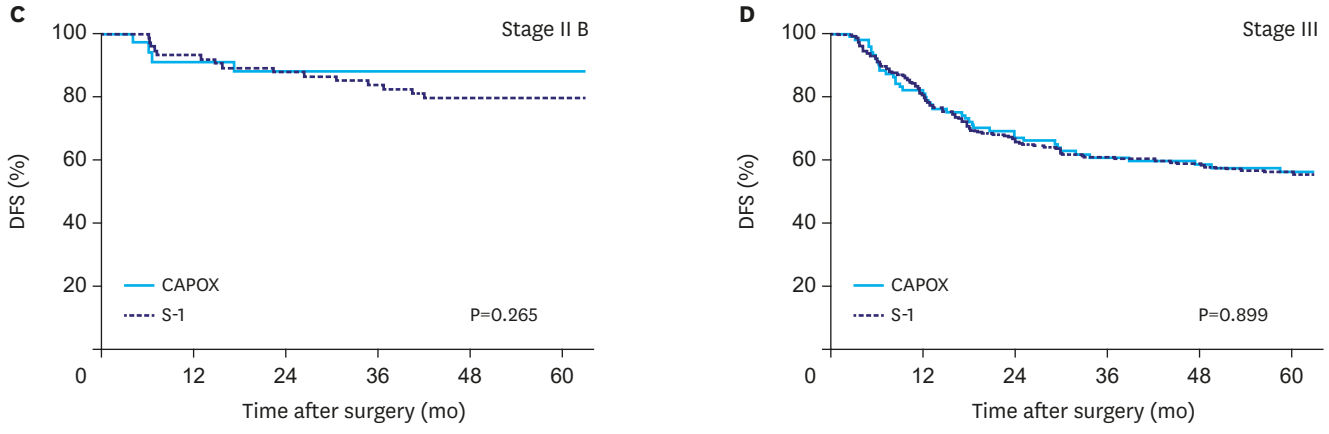


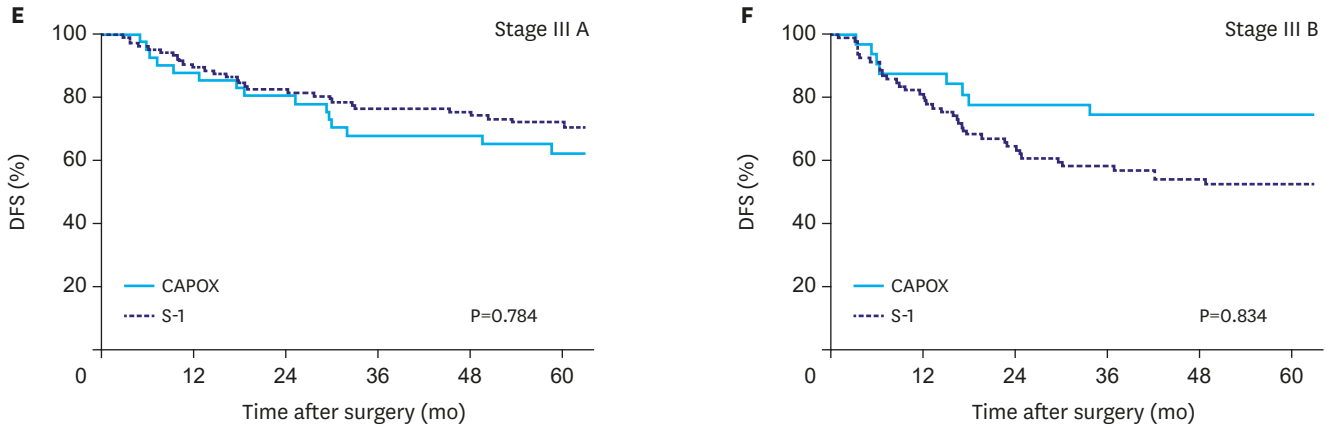
No. at risk						
CAPOX	50	44	40	37	35	16
S-1	141	130	124	119	114	72

No. at risk						
CAPOX	17	17	12	12	12	4
S-1	66	61	59	58	57	34



No. at risk						
CAPOX	33	30	28	25	23	12
S-1	75	69	65	61	57	38

No. at risk						
CAPOX	103	81	66	57	53	36
S-1	285	218	170	149	136	88



No. at risk						
CAPOX	43	36	33	26	26	16
S-1	106	92	82	74	69	50

No. at risk						
CAPOX	32	27	24	23	21	16
S-1	94	70	53	43	37	21

Fig. 2. DFS of patients with stage II and III gastric cancer according to adjuvant chemotherapy regimen; (A) stage II, (B) stage IIA, (C) stage IIB, (D) stage III, (E) stage IIIA, (F) stage IIIB, and (G) stage IIIC.
CAPOX = capecitabine and oxaliplatin; S-1 = tegafur/gimeracil/oteracil; DFS = disease-free survival.

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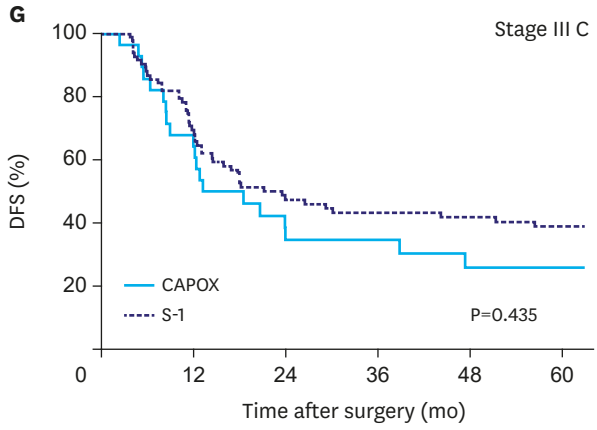

Fig. 2. (Continued) DFS of patients with stage II and III gastric cancer according to adjuvant chemotherapy regimen; (A) stage II, (B) stage IIA, (C) stage IIB, (D) stage III, (E) stage IIIA, (F) stage IIIB, and (G) stage IIIC.
CAPOX = capecitabine and oxaliplatin; S-1 = tegafur/gimeracil/oteracil; DFS = disease-free survival.

Table 2. Disease free survival rates of S-1 and CAPOX groups according to stages (AJCC 8th) using log-rank test

Stages	S-1 (n=429)	CAPOX (n=155)	P-value
All	66.1 (64.3–67.9)	66.5 (62.5–70.5)	0.961
Stage II			
All of stage II	85.4 (82.3–88.5)	89.3 (82.6–96.0)	0.677
Stage IIA	92.1 (87.4–96.8)	92.3 (77.5–107.1)	0.575
Stage IIB	79.6 (74.3–84.9)	87.9 (78.8–97.0)	0.265
Stage III			
All of stage III	56.0 (53.2–58.8)	56.2 (50.5–61.9)	0.899
Stage IIIA	72.1 (67.4–76.8)	62.2 (51.9–72.5)	0.784
Stage IIIB	52.5 (45.7–59.3)	74.5 (63.5–85.5)	0.834
Stage IIIC	38.9 (30.9–46.9)	26.0 (6.5–45.5)	0.435

Values are presented as disease free survival rates (95% confidence interval).
S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin; AJCC 8th = 8th edition of American Joint Committee on Cancer.

Table 3. HR of S-1 compared with CAPOX as reference for recurrence of gastric cancer

Stages	HR	95% CI	P-value
All	1.008	0.728–1.395	0.963
Stage II	1.846	0.693–4.919	0.220
Stage IIA	1.727	0.202–14.787	0.618
Stage IIB	2.140	0.710–6.450	0.176
Stage III	0.942	0.664–1.337	0.738
Stage IIIA	0.873	0.466–1.635	0.671
Stage IIIB	1.220	0.571–2.610	0.608
Stage IIIC	0.813	0.482–1.371	0.437

S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin; HR = hazard ratio; CI = confidence interval.

Sites of recurrence after AC

Table 4 lists the major sites of GC recurrence after AC. The total incidences of recurrence were similar between the S-1 (32.9%) and CAPOX (31.6%) groups. Among the major sites of recurrence, there were no differences between the peritoneum (HR, 1.040; 95% CI, 0.633–1.708; P=0.878), hematogenous sites (HR, 0.813; 95% CI, 0.398–1.659; P=0.568), lymph nodes (HR, 1.442; 95% CI, 0.710–2.928; P=0.311), and locoregional sites (HR, 1.471; 95% CI, 0.489–4.425; P=0.492) between groups.

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Variables	Total No. of patients	HR	95% CI	P-value
Sex				
Male	396	1.153	0.784–1.695	0.469
Female	188	0.750	0.408–1.378	0.355
Age				
<60	284	0.971	0.595–1.584	0.906
≥60	300	1.011	0.654–1.564	0.959
ASA score				
1	228	0.757	0.449–1.279	0.299
2	290	1.414	0.855–2.337	0.177
3	63	0.898	0.407–1.982	0.791
Extent of gastric resection				
Subtotal gastrectomy	376	0.942	0.618–1.438	0.783
Total gastrectomy	208	1.084	0.649–1.810	0.759
pT stage				
T2	84	1.302	0.424–3.994	0.644
T3	254	1.163	0.664–2.039	0.597
T4	222	0.875	0.570–1.344	0.543
pN stage				
N0	74	0.648	0.203–2.070	0.464
N1	89	0.978	0.311–3.074	0.969
N2	158	0.732	0.366–1.461	0.376
N3	263	1.230	0.811–1.864	0.329
AJCC 8th stage				
Stage II	193	1.050	0.420–2.623	0.916
Stage III	391	1.041	0.735–1.475	0.820
Tumor size (cm)				
≤5	285	1.362	0.759–2.443	0.300
>5	299	0.890	0.599–1.322	0.564

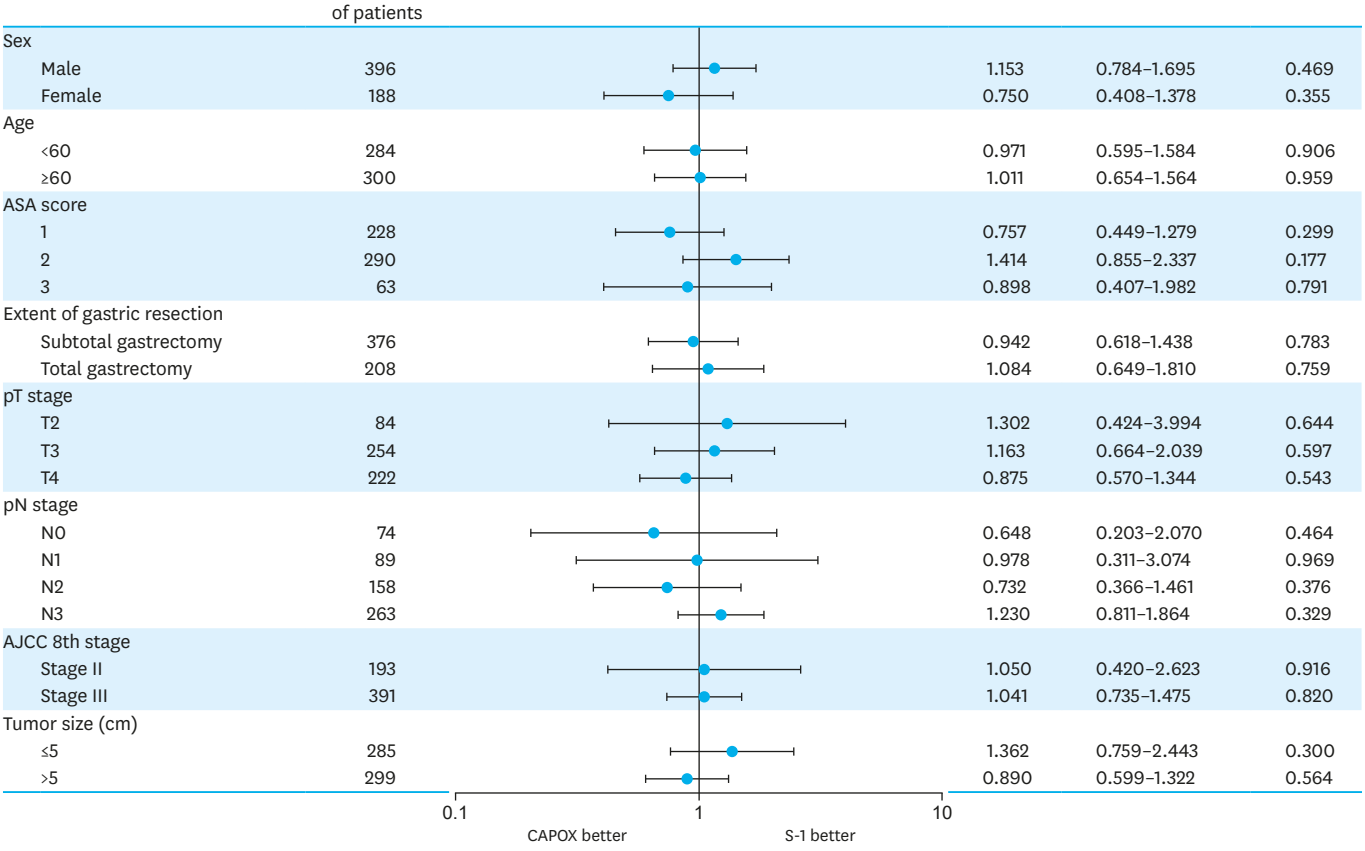

Fig. 3. Forest plot for subgroup analysis of disease-free survivals in S-1 and CAPOX groups.
CAPOX = capecitabine and oxaliplatin; S-1 = tegafur/gimeracil/oteracil; HR = hazard ratio; CI = confidence interval; ASA = American Society of Anesthesiologist; AJCC 8th, 8th edition of American Joint Committee on Cancer.

Table 4. Major sites of recurrence after adjuvant chemotherapy for gastric cancers

Sites*	S-1	CAPOX	HR	95% CI	P-value
Peritoneum	51 (11.8)	23 (14.8)	1.040	0.633–1.708	0.878
Hematogenous	34 (7.9)	11 (7.1)	0.813	0.398–1.659	0.568
Lymph nodes	45 (10.5)	10 (6.5)	1.442	0.710–2.928	0.311
Locoregional	11 (2.6)	5 (3.2)	1.471	0.489–4.425	0.492
Total No. of recurrences	141 (32.9)	49 (31.6)	-	-	-

Values are presented as number (%).
S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin; HR = hazard ratio; CI = confidence interval.
*Some patients had recurrence more than one site at first relapse.

Risk factors for recurrence

In both uni- and multivariate analysis, we entered pT and pN stages instead of the AJCC 8th stage. Univariate analysis of risk factors revealed that patient age, ASA score, extent of gastric resection, operation approach method, pT and pN stages, tumor size, lymphatic and vascular invasions, and completion of planned chemotherapy were significant predictors related to DFS. After adjustment for meaningful factors in multivariate analysis, pT (4 vs. 1) (HR, 11.667; 95% CI, 1.595–85.351; P=0.016), pN stage (0 vs. 3) (HR, 2.788; 95% CI, 1.502–5.174; P=0.001), and completion of planned chemotherapy (HR, 2.213; 95% CI, 1.618–3.028; P<0.001) were revealed as independent prognostic factors for DFS (**Table 5**).

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Table 5. Univariate and multivariate analysis of risk factors for disease-free survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥60)	1.433 (1.075–1.909)	0.014*	1.014 (0.736–1.396)	0.933
Sex (male)	1.201 (0.877–1.643)	0.253	-	-
BMI (>23)	1.014 (0.761–1.35)	0.927	-	-
ASA score (2 vs. 1)	1.207 (0.884–1.649)	0.237	-	-
ASA score (3 vs. 1)	1.840 (1.17–2.896)	0.008*	-	-
ASA score (4 vs. 1)	2.577 (0.357–18.594)	0.348	-	-
Extent of gastric resection (total)	1.538 (1.155–2.049)	0.003*	1.151 (0.835–1.585)	0.391
Operation approach method (open)	1.647 (1.025–2.647)	0.039*	1.132 (0.670–1.914)	0.643
pT stage (2 vs. 1)	5.133 (0.683–38.573)	0.112	5.260 (0.688–40.19)	0.110
pT stage (3 vs. 1)	7.555 (1.049–54.414)	0.045*	7.043 (0.959–51.719)	0.055
pT stage (4 vs. 1)	15.243 (2.127–109.253)	0.007*	11.667 (1.595–85.351)	0.016*
pN stage (1 vs. 0)	0.797 (0.385–1.651)	0.541	0.942 (0.428–2.074)	0.881
pN stage (2 vs. 0)	1.180 (0.638–2.183)	0.598	1.204 (0.613–2.364)	0.590
pN stage (3 vs. 0)	3.072 (1.766–5.341)	<0.001*	2.788 (1.502–5.174)	0.001*
Retrieved lymph nodes (>45)	0.846 (0.634–1.13)	0.258	-	-
Tumor size (cm) (>5)	1.864 (1.39–2.5)	<0.001*	1.376 (0.983–1.928)	0.063
Differentiation (P/S vs. W/M)	1.076 (0.781–1.481)	0.655	-	-
Differentiation (O vs. W/M)	1.050 (0.573–1.923)	0.876	-	-
Lauren classification (D vs. I)	1.053 (0.759–1.461)	0.755	-	-
Lauren classification (M vs. I)	1.064 (0.634–1.787)	0.814	-	-
Lymphatic invasion	1.598 (1.11–2.299)	0.012*	0.907 (0.589–1.396)	0.657
Vascular invasion	1.698 (1.257–2.292)	0.001*	1.222 (0.867–1.723)	0.252
Incompletion of planned chemotherapy	2.552 (1.913–3.406)	<0.001*	2.213 (1.618–3.028)	<0.001*

HR = hazard ratio; CI = confidence interval; ASA = American society of anesthesiologist; BMI = body mass index; Differentiation: W = well-differentiated; M = moderately-differentiated; P = poorly-differentiated; S = signet ring cell carcinoma; O = others; Lauren classification: D = diffuse; I = intestinal; M = mixed.
*Statistically significant with P<0.05.

DISCUSSION

We compared the long-term efficacy of S-1 and CAPOX AC regimens for stage II or III GC based on PSM analysis from a multicenter historical cohort study over 5 years after surgery. We did not identify any significant difference in over-5yr DFS between the 2 regimens. We also observed no significant differences between the 2 regimens in subgroup analysis. The pathologic stage and completion of planned chemotherapy were shown as independent prognostic factors for DFS.

Previous prominent prospective studies on AC for GCs, the ACTS-GC [1] and CLASSIC [2,7] trials, showed the efficacy of S-1 and CAPOX regimens compared with that of no chemotherapy. However, they did not directly compare the efficacies of both regimens. Therefore, the difference in efficacy between the 2 regimens remained unknown. A recent retrospective multicenter study showed that the CAPOX AC regimen was more effective than S-1 in patients with stage IIIB or IIIC GC based on 3-year DFS [3]. Another retrospective single-center study showed that CAPOX tended to be more effective than S-1 in patients with stage IIIC GC after D2 gastrectomy, although the adjuvant CAPOX and S-1 regimens did not show any significant difference in patients with stage III GC [8]. Consequently, the single-center study concluded that pathologic N stage and cycle completion as planned were meaningful prognostic factors for recurrence, comparable to the results of the multivariate analysis in the present study.

We did not find any differences in survival between the 2 AC regimens for GC. However, previous retrospective studies reported that CAPOX chemotherapy may be superior to S-1

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monotherapy in terms of efficacy on DFS [3]. This survival discrepancy might be due to the different AJCC stages, 7th or 8th, and the slight differences in planned AC completion rates between the past and present studies. A previous retrospective multicenter study investigated actual patient compliance to AC [9]. In line with this study, the actual completion rates of S-1 and CAPOX were 65.9% and 70.3%, respectively. In a retrospective multicenter observational study [3], the completion rates of planned AC were 79.76% and 76.37% in the S-1 and CAPOX groups, respectively, after PSM. We also performed PSM to reduce bias due to the retrospective nature of data collection, and observed planned AC completion rates of 68.53% in the S-1 group and 69.03% in the CAPOX group. Another potential cause of discrepancies in survival might be the somewhat small numbers of patients in the CAPOX group (43, 32, and 28 patients with stage IIIA, IIIB, and stage IIIC GC, respectively), compared with those in the S-1 group (106, 94, and 85 patients with stage IIIA, IIIB, and stage IIIC GC, respectively). In the present study, the HRs for GC recurrence of S-1 compared with those of CAPOX were below 1 in the subgroups of patients with stage III GC, at 0.873 (95% CI, 0.466–1.635; P=0.671) for stage IIIA, and 0.813 (95% CI, 0.482–1.371; P=0.437) for stage IIIC, although the HRs did not reach statistical significance. Additional large-scale, prospective studies are needed to confirm these differences in survival.

Recent studies have reported the use of other AC regimens, such as S-1 with oxaliplatin and taxane. The RESCUE-GC study aimed to elucidate the efficacy of S-1 alone compared with that of S-1 plus oxaliplatin for AC in patients with locally advanced GC after curative gastrectomy [10]. The JACCRO GC-07 study is a prospective randomized phase III study that aimed to assess the effect of postoperative S-1 plus docetaxel over S-1 alone in patients with stage III GC [11]. The analysis clarified the superiority of S-1 plus docetaxel (66%) over S-1 (50%) in terms of 3-year DFS with manageable adverse effects. AC regimens are expected to become more diverse. The differences in survival and adverse effects between these AC regimens require direct comparisons to determine the best choice of regimen. Two phase II studies, the J-CLASSIC and SOXaGC trials, analyzed the patient compliance and safety of CAPOX and S-1 plus oxaliplatin regimens [12,13], but they did not investigate oncologic outcomes as the primary end points. However, in another 2 phase II study, the observational study cohort was designed with somewhat small size of enrolled patients to analyze survival outcomes [14]. This ad hoc cohort study revealed that CAPOX and S-1 plus oxaliplatin regimens in the adjuvant setting have similar oncologic efficacy for patients with pathologic stage III GC. The findings of previous studies showed that doublet AC regimens might have comparable efficacies, whereas monotherapies tended to have inferior capability to suppress recurrence compared with doublet regimens [3,8]. To the best of our knowledge, the current propensity score-matched multicenter cohort study was the first report comparing long-term DFS outcomes between a monotherapy and a doublet regimen as an AC.

Our findings showed similar long-term oncologic outcomes despite the different regimens, indicating the need to consider factors other than chemotherapeutic regimens that may affect patient prognosis. For example, the duration of chemotherapy may explain the differences in 3- and 5-year oncologic outcomes of patients with GC [3]. Moreover, the long-term outcomes of GC patients might also be affected by factors related to GC (e.g., histologic classification, lymphatic or venous invasion, and c-erbB2 status).

Therefore, a nomogram should be established to extend the duration of AC according to the disease categories. On the basis of these factors, physicians may administer additional chemotherapeutic agents after the currently accepted AC in cases of highly aggressive GC.

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Additional strategies are needed to enhance compliance to complete AC in patients with intractable AGC.

In conclusion, although the present study was limited by its retrospective design, the PSM analysis in this multicenter cohort study clarified that the AC regimens S-1 and CAPOX did not show significant difference in terms of over-5yr DFS after curative gastrectomy in patients with stage II or III GC.

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