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Original Article

Long-Term Survival Outcomes of Elderly Patients Treated With S-1 or Capecitabine Plus Oxaliplatin for Stage II or III Gastric Cancer: A Multicenter Cohort Study

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ABSTRACT

Purpose: Tegafur/gimeracil/oteracil (S-1) and capecitabine plus oxaliplatin (CAPOX) are standard adjuvant chemotherapies (ACs) administered after gastrectomy to patients with stage II or III gastric cancer. However, the efficacy of AC in elderly patients remains unclear.

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Conflict of Interest

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

The objective of this retrospective multicenter cohort study was to compare the efficacies of S-1 and CAPOX AC in patients aged ≥70 years.

Materials and Methods: Nine hundred eighty-three patients who were treated with AC using S-1 (768 patients) or CAPOX (215 patients) were enrolled in this study. Each patient underwent AC after curative gastrectomy for stage II or III gastric cancer at one of 27 hospitals in the Republic of Korea between January 2012 and December 2013. Relapse-free survival (RFS) and overall survival (OS) were analyzed according to AC regimen and age group.

Results: Of the 983 patients, 254 (25.8%) were elderly. This group had a similar RFS (P=0.099) but significantly poorer OS (p=0.003) compared with the non-elderly group. Subgroup analysis of the non-elderly group revealed no AC-associated differences in survival. Subgroup analysis of the elderly group revealed significantly better survival in the S-1 group than in the CAPOX group (RFS, P<0.001; OS, P<0.001). Multivariate analysis revealed that the CAPOX regimen was an independent poor prognostic factor for RFS (hazard ratio [HR], 1.891; 95% confidence interval [CI], 1.072–3.333; P=0.028) and OS (HR, 2.970; 95% CI, 1.550–5.692; P=0.001).

Conclusions: This multicenter observational cohort study found significant differences in RFS and OS between S-1 and CAPOX AC among patients with gastric cancer aged ≥70 years.

Keywords: Adjuvant chemotherapy; Gastric cancer; Elderly; Survival; Recurrence

INTRODUCTION

Gastric cancer was the fifth most common cancer worldwide and the fourth leading cause of cancer-related death in 2020 [1], and the incidence is gradually increasing as the population ages [2]. A Japanese nationwide registry found that the median age of patients who underwent gastrectomy is 67 years [3]. The proportions of elderly patients who undergo gastrectomy for gastric cancer are approximately 28% (>70 years of age) in Korea [4] and 47% (>75 years of age) in Japan [5]. However, current guidelines for gastric cancer treatment are predominantly based on clinical trials of patients aged ≤75–80 years [6,7].

Two pivotal prospective randomized studies of adjuvant chemotherapy (AC) after D2 dissection in patients with advanced gastric cancer found beneficial effects for AC using tegafur/gimeracil/oteracil (S-1) or capecitabine plus oxaliplatin (CAPOX). However, subgroup analysis of the elderly population in the ACTS-GC study found that AC with S-1 did not improve relapse-free survival (RFS) or overall survival (OS) compared with surgery alone [8,9]. In the CLASSIC study, patients treated with CAPOX had significantly better RFS and similar OS compared with patients treated with surgery alone [9,10]. Evidence of the efficacy of AC for elderly patients is limited [9,11,12]. Thus, most clinicians have difficulty developing AC treatment plans for elderly patients because they have a higher incidence of comorbidities, greater risk of adverse events, and shorter life expectancies [13]. Most clinicians empirically choose monotherapy (S-1) for elderly patients and combination therapy (CAPOX) for younger patients [14].

This multicenter cohort study compared the survival outcomes of elderly patients who were treated with S-1 or CAPOX AC after curative gastrectomy for gastric cancer.

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MATERIALS AND METHODS

Patients

Retrospective data were collected from the medical records of 983 patients who underwent radical gastrectomy and D2 lymph node dissection. Each patient underwent surgery at one of 27 hospitals in the Republic of Korea between January 2012 and December 2013. After surgery, all patients were treated with AC for gastric cancer. The inclusion criteria were as follows: age ≥20 years, pathologic stage II or III gastric cancer after curative gastrectomy (R0) according to the American Joint Committee on Cancer staging system [15], and postoperative S-1 or CAPOX AC. The exclusion criteria were as follows: synchronous or metachronous cancer, neoadjuvant chemotherapy, tumor cells present on cytological examination of peritoneal wash fluid, and distant metastasis. We classified patients aged ≥70 years as elderly and patients aged <70 years as non-elderly. Each patient was assigned to 1 of 4 groups based on AC regimen and completion status: S-1 group with completion of AC, S-1 group without completion of AC, CAPOX group with completion of AC, and CAPOX group without completion of AC.

Study design

Medical records and clinical data were reviewed in May 2019. The primary endpoint was 5-year RFS after curative gastrectomy. RFS was defined as the time from the day of surgery to the day of disease relapse. OS was defined as the time from the day of surgery to the day of death from any cause. The Institutional Review Board of Severance Hospital, Yonsei University College of Medicine approved this study (4-2021-0754).

AC regimens

AC was administered according to the ACTS-GC and CLASSIC trial protocols [8,16]. Each patient in the S-1 group was administered the treatment at a dose of 40, 50, or 60 mg (based on body surface area) twice per day for 4 weeks, followed by a 2-week rest period. This 6-week S-1 treatment cycle was repeated for a total of 8 cycles over 12 months. Each patient in the CAPOX group was administered oral capecitabine (1,000 mg/m^2 twice daily on days 1–14 of each 3-week cycle) and intravenous oxaliplatin (130 mg/m^2 on day 1 of each 3-week cycle) for a total of 8 cycles over 6 months.

Survival outcomes

During the AC treatment period, each patient underwent abdominal computed tomography (CT) or endoscopy every 3–4 months. After completion of the 8 AC cycles, follow-up medical consultations, including history taking, physical examination, clinical evaluation, and abdominal CT with or without endoscopy, were performed every 3–4 months for the first 2 years and then every 6 months for the next 3 years. Annual or biennial follow-up assessments were performed starting at approximately 5 years post-surgery. If the findings at follow-up suggested cancer recurrence, abdominal ultrasound, chest CT, positron emission tomography, abdominal magnetic resonance imaging, and/or bone scans were performed.

Statistical analysis

IBM SPSS statistics version 25 software (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The Mann-Whitney U test or Student's t-test was used to compare independent continuous variables. The χ^2 test was used to compare independent categorical variables. RFS and OS were estimated using the Kaplan-Meier method, and survival differences between groups were assessed using the log-rank test. Risk factors associated

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with OS and RFS in elderly patients were identified using both univariate and multivariate Cox proportional hazards models. Statistical significance was set at P<0.05.

RESULTS

Clinicopathologic characteristics of elderly and non-elderly patients

Of the 983 patients, 254 (25.8%) were elderly. The results of the between-group comparisons (elderly vs. non-elderly) of clinicopathologic characteristics are presented in **Table 1**. In the elderly group, there were significantly higher proportions of patients who were women (P=0.021), with a low BMI (P=0.027), with a high American Society of Anesthesiologists (ASA) score (P<0.001), with a histologically differentiated type (well-differentiated or moderately differentiated adenocarcinoma, P=0.014), and with an intestinal-type Lauren classification (P=0.003). The elderly group had significantly lower rates of CAPOX administration (P<0.001) and planned chemotherapy completion (P<0.001).

Comparison of the clinicopathologic characteristics of the elderly patients in the S-1 and CAPOX groups

Of the 254 elderly patients, 225 (88.6%) were treated with S-1, and 29 (11.4%) were treated with CAPOX. The clinicopathological characteristics of the elderly patients in the 2 AC groups are presented in **Table 2**. When compared with the CAPOX group, the S-1 group was associated with smaller tumor size (P=0.004), differentiated type tumors (P=0.011), and an ASA score of 2 (P=0.022). The between-group difference in the completion rate of planned AC was not significant (52.4% vs. 48.3%, P=0.672).

Survival outcomes

The median and longest follow-up periods were 59.0 and 87.6 months, respectively. The survival curves of all patients stratified by age are shown in **Fig. 1**. The difference in RFS between elderly and non-elderly patients was not significant (**Fig. 1A**, P=0.099). However, we found a significant difference in OS between the 2 groups (**Fig. 1B**, P=0.003).

Survival curves for the non-elderly and elderly groups stratified by AC regimen are presented in **Fig. 2**. In the non-elderly patient group, the differences in RFS (**Fig. 2A**, P=0.281) and OS (**Fig. 2B**, P=0.570) were not significant, whereas in the elderly patient group, the differences in RFS (**Fig. 2C**, P<0.001) and OS (**Fig. 2D**, P<0.001) were significant.

The results of the analysis by cancer stage indicated that, compared with the CAPOX group, elderly patients with stage II cancer treated with S-1 had better RFS and OS (**Supplementary Fig. 1A and B**; P<0.001 and P<0.001, respectively). For patients with stage III cancer, the differences in RFS and OS between the S-1 and CAPOX groups were not significant (**Supplementary Fig. 1C and D**, P=0.104 and P=0.080, respectively).

The survival curves for elderly patients stratified by AC regimen and completion status are presented in **Supplementary Fig. 2**. Patients in the CAPOX group who did not complete AC had poor RFS and OS compared to those in the other group. The RFS and OS of patients who did not complete S-1 AC were similar to those of patients who completed CAPOX AC (P=0.632 and P=0.658, respectively).

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Table 1. Patient characteristics

Characteristics	Age <70 yr (n=729)	Age ≥70 yr (n=254)	P-value
Sex			0.021
Male	516 (70.8)	160 (63.0)	
Female	213 (29.2)	94 (37.0)	
Age (yr)	55.5±9.2	74.5±3.7	<0.001
BMI (kg/m²)	23.4±3.3	22.8±3.3	0.027
ASA score			<0.001
1	313 (43.1)	40 (15.7)	
2	364 (50.1)	148 (58.3)	
3	50 (6.9)	63 (24.8)	
4	0 (0)	3 (1.2)	
Extent of gastric resection			0.276
Subtotal gastrectomy	469 (64.3)	173 (68.1)	
Total gastrectomy	260 (35.7)	81 (31.9)	
Operative approach			0.737
Open	590 (80.9)	208 (81.9)	
Laparoscopic or robot	139 (19.1)	46 (18.1)	
T stage			0.324
pT1	40 (5.5)	8 (3.1)	
pT2	106 (14.5)	38 (15.0)	
pT3	351 (48.1)	116 (45.7)	
pT4	232 (31.8)	92 (36.2)	
N stage			0.101
pN0	161 (22.1)	42 (16.5)	
pN1	150 (20.6)	59 (23.2)	
pN2	178 (24.4)	54 (21.3)	
pN3	240 (32.9)	99 (39.0)	
TNM staging			0.055
II	358 (49.1)	107 (42.1)	
III	371 (50.9)	147 (57.9)	
Retrieved lymph nodes	46.6±19.1	44.6±18.7	0.142
Tumor size (cm)	5.7±3.3	6.1±3.3	0.074
Differentiation			0.014
Well or moderately	230 (31.6)	100 (39.4)	
Poorly or signet ring cell	448 (61.5)	146 (57.5)	
Other	51 (7.0)	8 (3.1)	
Lauren classification			0.003
Intestinal	242 (33.2)	104 (40.9)	
Diffuse	350 (48.0)	92 (36.2)	
Mixed	73 (10.0)	23 (9.1)	
Unknown	64 (8.8)	35 (13.8)	
Lymphatic invasion			0.142
Yes	444 (60.9)	172 (67.7)	
No	245 (33.6)	72 (28.3)	
Unknown	40 (5.5)	10 (3.9)	
Vascular invasion			0.151
Yes	219 (30.0)	93 (36.6)	
No	477 (65.4)	150 (59.1)	
Unknown	33 (4.5)	11 (4.3)	
AC regimen			<0.001
S-1	543 (74.5)	225 (88.6)	
CAPOX	186 (25.5)	29 (11.4)	
Completion of planned chemotherapy			<0.001
Yes	529 (72.6)	132 (52.0)	
No	200 (27.4)	122 (48.0)	

Data are shown as mean±SD or number (%).
BMI = body mass index; ASA = American Society of Anesthesiologists; pT = pathologic depth of invasion; pN = pathologic lymph node involvement; TNM = tumor-node-metastasis; AC = adjuvant chemotherapy; S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin.

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Table 2. Characteristics of elderly patients according AC regimen

Characteristics	S-1 (n=225)	CAPOX (n=29)	P-value
Sex			0.264
Male	139 (61.8)	21 (72.4)	
Female	86 (38.2)	8 (27.6)	
Age (yr)	73.0 (6.0)	73.0 (4.0)	0.218
BMI (kg/m^2)	22.7 (4.6)	21.6 (5.6)	0.756
ASA score			0.022
1	31 (13.8)	9 (31.0)	
2	138 (61.3)	10 (34.5)	
3	53 (23.6)	10 (34.5)	
4	3 (1.3)	0 (0)	
Extent of gastric resection			0.597
Subtotal gastrectomy	152 (67.6)	21 (72.4)	
Total gastrectomy	73 (32.4)	8 (27.6)	
Operative approach			0.096
Open	181 (80.4)	27 (93.1)	
Laparoscopic or robot	44 (19.6)	2 (6.9)	
T stage			0.971
pT1	8 (3.6)	0 (0)	
pT2	34 (15.1)	4 (13.8)	
pT3	102 (45.3)	14 (48.3)	
pT4	81 (36.0)	11 (37.9)	
N stage			0.264
pN0	38 (16.9)	4 (13.8)	
pN1	56 (24.9)	3 (10.3)	
pN2	47 (20.9)	7 (24.1)	
pN3	84 (37.3)	15 (51.7)	
TNM staging			0.092
II	99 (44.0)	8 (27.6)	
III	126 (56.0)	21 (72.4)	
Retrieved lymph node	41.0 (24.0)	43.0 (23.0)	0.811
Tumor size (cm)	5.0 (3.1)	7.0 (4.0)	0.004
Differentiation			0.011
Well or moderately	94 (41.8)	6 (20.7)	
Poorly or signet ring cell	126 (56.0)	20 (69.0)	
Other	5 (2.2)	3 (10.3)	
Lauren classification			0.334
Intestinal	96 (42.7)	8 (27.6)	
Diffuse	79 (35.1)	13 (44.8)	
Mixed	21 (9.3)	2 (6.9)	
Unknown	29 (12.9)	6 (20.7)	
Lymphatic invasion			0.625
Yes	152 (67.6)	20 (69.0)	
No	65 (28.9)	7 (24.1)	
Unknown	8 (3.6)	2 (6.9)	
Vascular invasion			0.118
Yes	78 (34.7)	15 (51.7)	
No	138 (61.3)	12 (41.4)	
Unknown	9 (4.0)	2 (6.9)	
Completion of planned chemotherapy			0.672
Yes	118 (52.4)	14 (48.3)	
No	107 (47.6)	15 (51.7)	

Values are presented as median (interquartile range) or number (%).
AC = adjuvant chemotherapy; S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin; BMI = body mass index; ASA = American Society of Anesthesiologists; pT = pathologic depth of invasion; pN = pathologic lymph node involvement; TNM = tumor-node-metastasis.

Univariate and multivariate analysis of prognostic factors for survival

Risk factors related to RFS were identified using a Cox regression model (**Table 3**). Univariate analysis revealed that total gastrectomy, stage, tumor size, differentiation,

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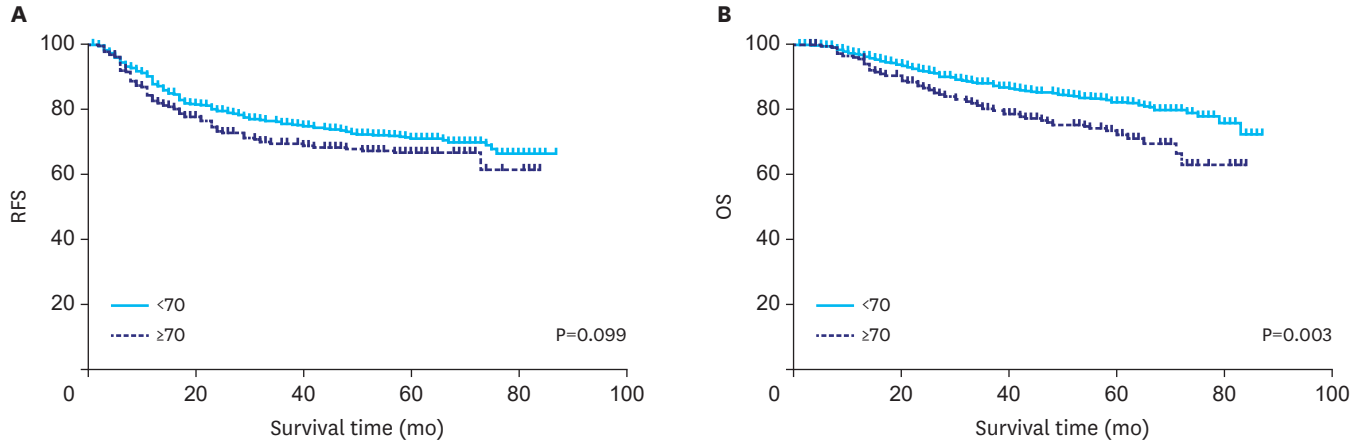

Fig. 1. RFS and OS of all patients with stage II and III gastric cancer according to age. (A) RFS. (B) OS.
RFS = relapse-free survival; OS = overall survival.

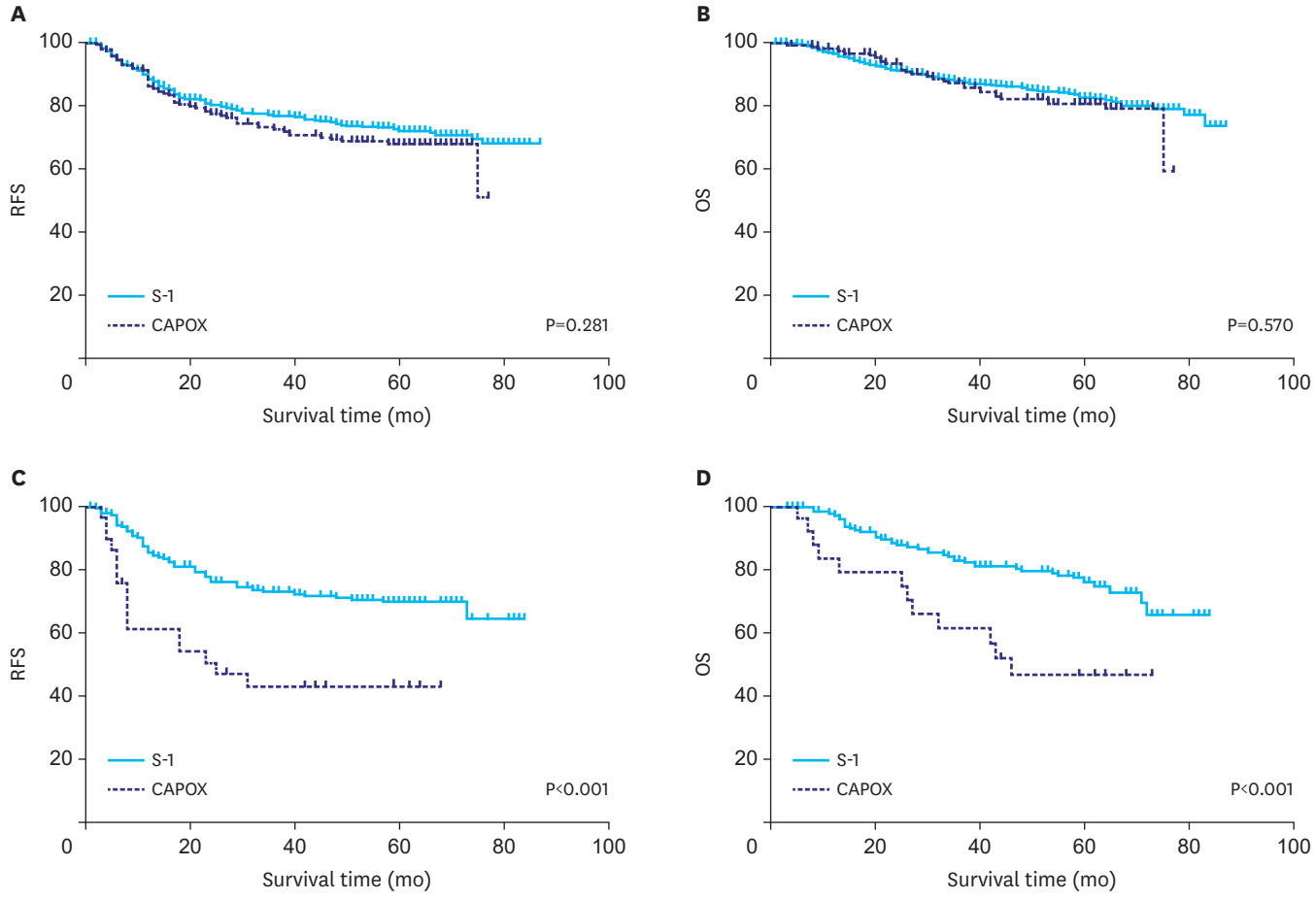

Fig. 2. Survival comparisons of elderly and non-elderly patient groups according to chemotherapy regimen. (A) RFS in non-elderly patients. (B) OS in non-elderly patients. (C) RFS in elderly patients. (D) OS in elderly patients.
S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin; RFS = relapse-free survival; OS = overall survival.

CAPOX administration, and completion of planned chemotherapy were associated with RFS (P<0.05). Multivariate analysis revealed that advanced stage, larger tumor size, CAPOX administration, and non-completion were independent risk factors for RFS.

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Table 3. Univariate and multivariate analysis of risk factors for RFS and OS in elderly patients

Risk factors	RFS (univariate)			RFS (multivariate)			OS (univariate)			OS (multivariate)		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Sex												
Female	Ref						Ref					
Male	1.061	0.668–1.685	0.803				0.957	0.547–1.673	0.877			
Age	1.038	0.980–1.099	0.206				1.085	1.015–1.158	0.016	1.100	1.024–1.182	0.009
BMI	0.993	0.929–1.062	0.847				0.980	0.904–1.064	0.635			
ASA score												
1	Ref						Ref					
2	1.066	0.550–2.066	0.849				0.954	0.436–2.087	0.906			
3	1.318	0.635–2.736	0.458				1.259	0.533–2.974	0.600			
4	2.550	0.565–11.510	0.224				2.084	0.260–16.701	0.489			
Extent of gastric resection												
Subtotal gastrectomy	Ref						Ref					
Total gastrectomy	1.718	1.096–2.693	0.018				1.098	0.618–1.915	0.751			
Operative approach												
Open	Ref						Ref					
Laparoscopic or robotic	0.574	0.296–1.116	0.102				0.682	0.322–1.445	0.318			
TNM staging												
II	Ref			Ref			Ref			Ref		
III	3.865	2.198–6.796	<0.001	3.116	1.746–5.560	<0.001	3.461	1.818–6.589	<0.001	3.502	1.822–6.730	<0.001
Tumor size	1.121	1.057–1.189	<0.001	1.070	1.006–1.138	0.031	1.034	0.943–1.133	0.479			
Differentiation												
Well or moderately	Ref						Ref					
Poorly or signet ring cell	1.016	0.638–1.617	0.946				1.360	0.773–2.392	0.289			
Other	2.860	1.110–7.370	0.030				1.328	0.308–5.724	0.703			
Lauren classification												
Intestinal	Ref						Ref					
Diffuse	1.231	0.739–2.051	0.425				1.805	0.600–1.960	0.788			
Mixed	1.059	0.464–2.418	0.892				0.758	0.262–2.194	0.609			
Lymphatic invasion	1.576	0.904–2.747	0.109				1.526	0.778–2.993	0.219			
Vascular invasion	1.325	0.830–2.114	0.238				1.078	0.600–1.936	0.803			
AC regimen												
S-1	Ref			Ref			Ref			Ref		
CAPOX	2.573	1.482–4.467	0.001	1.891	1.072–3.333	0.028	2.986	1.568–5.683	0.001	2.970	1.550–5.692	0.001
Completion of planned chemotherapy												
Yes	Ref			Ref			Ref			Ref		
No	1.824	1.166–2.852	0.008	1.645	1.050–2.577	0.030	1.903	1.111–3.258	0.019	1.609	0.933–2.774	0.087

RFS, relapse-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis; AC, adjuvant chemotherapy; S-1 = tegafur/gimeracil/oteracil; CAPOX = capecitabine plus oxaliplatin.

Univariate analysis of OS (**Table 3**) revealed that age, stage, CAPOX administration, and non-completion of planned chemotherapy were independent risk factors. Multivariate analysis identified older age, advanced cancer stage, and CAPOX administration as independent risk factors for OS.

DISCUSSION

This multicenter cohort study had several unique findings. First, although RFS survival was similar in the elderly and non-elderly groups, the elderly group had significantly poorer OS than the non-elderly group. This difference in OS might be due to the age difference between the 2 patient groups. Second, subgroup analysis of the non-elderly group showed that RFS and OS were not different for the 2 AC regimens. Third, subgroup analysis of the elderly group showed significantly better RFS and OS for S-1 AC. This survival benefit remained when the groups were stratified by stage (i.e., stages II and III). Among patients with stage

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II cancer, patients treated with S-1 AC had significantly better RFS and OS. Analysis of patients with stage III cancer revealed that those treated with S-1 AC had better RFS and OS, but the differences were not significant. Fourth, compared with CAPOX AC, S-1 AC was an independent factor for favorable RFS and OS.

The superior survival benefit of S-1 compared with CAPOX was in contrast to previous findings of a survival benefit for CAPOX AC (RFS) among elderly patients when compared with surgery only [10] and no survival benefit for S-1 (RFS or OS) when compared with surgery only [7]. This is the first real-world study to directly compare the efficacy of these AC regimens in elderly patients. The survival discrepancy between the previous and present studies might have been caused by differences in AC compliance among the elderly patients. Patients treated with CAPOX AC in the CLASSIC trial had a completion rate of 67%, and those treated with S-1 had a completion rate of 65.7% in the ACTS-GC trial [8,16]. In this study, the S-1 completion rate was higher than the CAPOX completion rate, although the difference was not statistically significant. AC compliance is a prognostic factor for recurrence [17]. An ACTS-GC trial post-hoc analysis showed that patients who completed AC had better survival than those who did not [18].

Toxicity is the most common reason for failure to complete chemotherapy. In the CLASSIC trial, 99% of patients treated with CAPOX AC experienced adverse events of grade one or more, and 56% of patients experienced adverse events of grade 3 or more [16]. In contrast, in the ACTS-GC trial [8], one common reason for withdrawal of S-1 administration was adverse events, including a relatively low incidence of anorexia grade 3 or higher (6.0%). Since old age is a risk factor for severe chemotherapy toxicity during AC [19], S-1 AC might be more beneficial than CAPOX AC for elderly patients with advanced gastric cancer. Elderly patients are a specific subgroup who requires a careful approach to improve outcomes. In elderly patients, age-related changes in pharmacokinetics and pharmacodynamics and the presence of comorbidities increase the risk of toxicity compared to younger patients [20].

Another reason for the better survival of the S-1 group compared with the CAPOX group could be attributed to differences in genetic characteristics and chemo-responsiveness. The results of a comprehensive molecular characterization using The Cancer Genome Atlas database revealed that the microsatellite instability-high (MSI-H) subtype of gastric cancer was diagnosed in relatively elderly patients (median age, 72 years) [21]. An MSI-H tumor study of the benefits of AC in large cohorts of patients with gastric cancer found that AC with fluoropyrimidine alone, such as S-1 or uracil and tegafur/leucovorin, had a significant survival benefit compared with fluoropyrimidine and platinum, including 5-fluorouracil plus cisplatin or CAPOX [22].

This study had some limitations, which were mostly associated with its retrospective design. First, medical records did not include detailed data on chemotherapy-related adverse events. Second, the number of elderly patients treated with CAPOX was low, which undermined the statistical power to identify some differences, especially for the stage III cancer analysis. Nonetheless, to our knowledge, this study is the first study to evaluate the real-world survival outcomes of AC using S-1 or CAPOX post-curative gastrectomy among elderly patients with stage II or III gastric cancer.

In conclusion, the RFS of the elderly group of patients was similar to that of the non-elderly group. We also found a significant difference between AC with S-1 and CAPOX AC in terms of RFS and OS in elderly patients, indicating that S-1 may be a better AC regimen choice after

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curative gastrectomy in elderly patients with stage II and III gastric cancer.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1

Survival comparison in elderly patients according to chemotherapy. (A) RFS in elderly patients with stage II. (B) OS in elderly patients with stage II. (C) RFS in elderly patients with stage III. (D) OS in elderly patients with stage III.

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Supplementary Fig. 2

Survival comparison in elderly patients according to chemotherapy regimen and completion status of adjuvant chemotherapy. (A) RFS in elderly patients. (B) OS in elderly patients.

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