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Analysis of outcomes according to start timing of adjuvant chemotherapy in patients with gastric cancer: a retrospective nationwide cohort study

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Abstract

Background: Gastrectomy with D2 lymph node dissection followed by adjuvant chemotherapy (AC) with S-1 or capecitabine/oxaliplatin (CAPOX) is the standard treatment for stage II and III gastric cancer (GC). However, there is no established guideline for the start timing of AC.

Methods: We analyzed data from the Korean Health Insurance Review and Assessment Service on 19 140 GC patients who received AC with S-1 (n = 10 442) or CAPOX (n = 8698) between January 2014 and December 2018. Patients were categorized based on AC initiation timing: within 6 weeks (n = 12 843), 6-8 weeks (n = 5386), and >8-16 weeks (n = 911).

Results: Initiating AC within 6 weeks significantly improved 5-year disease-free survival (DFS) and overall survival (OS) compared to later initiation, with consistent findings across both S-1 and CAPOX groups (all $P < .005$). These associations remained significant in multivariable analysis and after propensity score matching (all $P < .0001$). However, this nationwide big-data analysis has limitations, including potential survival status misclassification and the absence of some important variables such as pathologic stage, performance status, and postoperative complications.

Conclusion: To optimize outcomes, AC for GC should be initiated within 6 weeks after gastrectomy, provided patients have fully recovered.

Key words: adjuvant; chemotherapy; start timing; gastric cancer.

Implications for practice

There is no established guideline for the timing of adjuvant chemotherapy (AC) initiation in gastric cancer. We analyzed data from 19 140 patients who underwent AC from the Korean Health Insurance Review and Assessment Service. Patients who started AC within 6 weeks showed superior disease-free survival and overall survival. These results recommend starting AC within 6 weeks post-surgery for optimal outcomes, contingent on patient recovery.

Introduction

Gastric cancer (GC) is the sixth most common newly diagnosed malignancy and the fourth most common cause of cancer death worldwide.[1] In addition, GC occurs frequently in East Asia and is one of the most common malignancies in Korea.[2-4]

While surgery has been the mainstay of curative therapy for GC,[5-8] adjuvant chemotherapy (AC) has been the standard treatment for patients with stage II and III GC after gastrectomy with D2 lymph node dissection in East Asian countries.[7-13] Moreover, 1-year S-1 and 6-month capecitabine/oxaliplatin (CAPOX) are the established regimens of AC for GC and reimbursable in the Korean National Health Insurance System based on two pivotal phase III trials, ACTS-GC and CLASSIC.[9,10,12,13]

The ACTS-GC and CLASSIC trials enrolled patients within 6-7 weeks after surgery, while some studies investigated the relationship between the start timing of AC for GC and the survival outcomes, with conflicting results.[9,10,14-27] Moreover,

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there is no definite guideline on the timing of initiating AC for GC after surgery. Therefore, we aimed to investigate the treatment outcomes according to the timing of AC using nationwide big-data analysis in the Korean Health Insurance Review and Assessment Service (HIRA).

Methods

Design and study population

We extracted data on patients with a C16 diagnosis code of GC (International Classification of Diseases, 10th edition) between January 2014 and December 2018 from the HIRA database.[28] The Republic of Korea has a National Health Insurance system that provides healthcare coverage to all citizens. Healthcare providers must submit claims to HIRA for review. Therefore, this database included almost all GC patients treated during the period in the Republic of Korea. First, we identified patients who underwent gastrectomy followed by chemotherapy with either S-1 or CAPOX within 16 weeks after gastrectomy and had at least 16 weeks of follow-up period. We excluded patients with a history of surgical gastric resection before gastrectomy, neoadjuvant chemotherapy, or switched regimens between S-1 and CAPOX during treatment. Finally, we followed the selected patients up to December 31, 2020. We classified them into 3 groups according to their starting time of chemotherapy: patients within 6 weeks, those from 6 to 8 weeks, and those from 8 to 16 weeks. The study protocol was approved by the Ajou University Hospital Institutional Review Board (Approval No. AJOUIRB-EXP-2021-627). The requirement for informed patient consent was waived due to the use of a deidentified dataset.

Definition of risk factors and primary outcomes

The comorbidities were identified by primary or secondary diagnosis code and defined if patients had diagnosis codes at least 2 times during one year prior to the date of gastrectomy. The examined comorbidities (ICD-10) were as follows: diabetes mellitus (E10-E14), hypertension (I10-I15), coronary arterial occlusive disease (I25), cerebrovascular accident (ICD-10: I64-I66), chronic kidney disease (N18), liver cirrhosis (K74.6), and chronic obstructive pulmonary disease (J43-J44). On the other hand, the history of other cancers (C-codes except C16) was investigated throughout the entire period in each patient since January 2014.

We operationally defined the death event if patients did not have any medical records for more than one year because the death status of patients was unavailable due to the nature of HIRA data. Therefore, the death date was defined as the date of the last medical record. In addition, the recurrence event was operationally defined if patients received any other chemotherapy during or after completion of S-1 or CAPOX, excluding the switch between S-1 and CAPOX during treatment. Disease-free survival (DFS) was defined as the time from surgery to the recurrence date (starting date of another regimen) or the death date, while overall survival (OS) was defined as the time from surgery to the death date. Data on the survivors were censored at the date of the last medical record.

Statistical analysis

Baseline characteristics among the 3 groups were compared using the Chi-squared test and Kruskal-Wallis test. The DFS and OS curves were drawn using the Kaplan-Meier methods, and the differences in those survival curves were compared by the log-rank test. The log-rank test for all pairwise group comparisons was adjusted by Tukey-Kramer's studentized range test. The DFS and OS rates at 1, 3, and 5 years were estimated with a 95% confidence interval (CI) by the Kaplan-Meier estimator. The proportional hazard assumptions were tested by Schoenfeld residuals. Cox proportional hazard regression analysis was performed to assess the risk of death or disease. The hazard ratio (HR) was estimated and adjusted by age, sex, chemotherapeutic regimen, number of comorbidities, and history of cancer in the multivariable analysis.

In addition, we performed propensity-score matching (PSM) at a ratio of 1:1 nearest-neighbor matching algorithm to minimize any confounding biases that might be entailed in observational studies. We matched the patients who started AC within 6 weeks to those from 6 to 8 weeks with the following matching variables: age, sex, chemotherapeutic regimen, number of comorbidities, and history of cancer. With this matched cohort, we presented the patients' characteristics with a standardized mean difference before and after PSM to show the balance of covariates. Moreover, the Kaplan-Meier curves of the patients within 6 weeks and from 6 to 8 weeks were plotted, and the differences in the DFS and OS curves were tested with the log-rank test. Each analysis mentioned above was performed for all patients, patients starting S-1, and those starting CAPOX, respectively. All statistical analyses were 2-sided and performed using the SAS software version 9.4 (SAS Institute) with a statistical significance of $P < .05$.

Results

Patients

A total of 81 550 patients with GC who underwent gastrectomy were identified from January 2014 to December 2018. Among them, the data of 20 377 patients who received chemotherapy with S-1 or CAPOX were analyzed. In addition, 954 patients who received chemotherapy 16 weeks after gastrectomy or had a follow-up period less than 16 weeks after gastrectomy were excluded for the exclusion of patients treated with palliative chemotherapy or avoidance of immortal time bias. Furthermore, 100 patients with a history of surgical gastric resection before gastrectomy were excluded. In addition, 62 patients who switched between S-1 and CAPOX during treatment were excluded due to the difficulty in distinguishing chemotherapeutic drug intolerance from recurrence, as well as the potential inability to accurately estimate the effect of each regimen. Moreover, 121 patients treated with neoadjuvant chemotherapy were excluded. Consequently, a total of 19 140 patients were included in this study analysis (Supplementary Figure S1).

The median age of the patients was 62 years, which increased significantly as the initiation of AC was delayed. Male patients were predominant (n = 13 201, 69.0%), and more patients were treated with S-1 (n = 10 442, 54.6%). Most comorbidities, including previous malignancies, were significantly more frequent in patients who received AC 8 weeks after gastrectomy, except for cerebrovascular accident and liver cirrhosis (Table 1).

Patient outcomes

With a median follow-up duration of 3.6 years, the 5-year DFS rates were 63%, 57%, and 47% for the patients who started within 6 weeks, from 6 to 8 weeks, and more than 8 weeks after surgery (Supplementary Table S1). In terms of

Table 1. Patients' characteristics.

Characteristics	All	Groups[a]			*P*-value
		weeks < 6	6 ≤ weeks ≤ 8	8 < weeks ≤ 16	
N	19 140	12 843	5386	911	—
Age at gastrectomy, years, median (range)	62(77)	60(77)	64(73)	67(57)	<.0001[b]
Age ≥ 70	5322(27.8)	3132(24.4)	1812(33.6)	378(41.5)	<.0001
Sex, male	13 201(69.0)	8799(68.5)	3733(69.3)	669(73.4)	.0066
Regimen					
S-1	10 442(54.6)	6983(54.4)	2872(53.3)	587(64.4)	<.0001
CAPOX	8698(45.4)	5860(45.6)	2,514(46.7)	324(35.6)	
DM	3427(17.9)	2149(16.7)	1074(19.9)	204(22.4)	<.0001
HTN	6323(33.0)	4089(31.8)	1883(35.0)	351(38.5)	<.0001
CAOD	354(1.9)	215(1.7)	108(2.0)	31(3.4)	.0006
CVA	159(0.8)	102(0.8)	47(0.9)	10(1.1)	.574
CKD	157(0.8)	82(0.6)	61(1.1)	14(1.5)	.0002
LC	66(0.3)	40(0.3)	20(0.4)	6(0.7)	.208
COPD	420(2.2)	256(2.0)	132(2.5)	32(3.5)	.0033
Other cancers	2338(12.2)	1429(11.1)	755(14.0)	154(16.9)	<.0001

Data are presented as *N* (%).
[a]Start timing of adjuvant chemotherapy from surgery.
[b]Kruskal-Wallis test.
Abbreviations: CAOD, coronary arterial occlusive disease (ICD-10: I25); CAPOX, capecitabine/oxaliplatin; CKD, chronic kidney disease (ICD-10: N18); COPD, chronic obstructive pulmonary disease (ICD-10: J43-J44); CVA, cerebrovascular accident (ICD-10: I64-I66); DM, diabetes mellitus (International Classification of Diseases, Tenth Revision (ICD-10): E10-E14); HTN, hypertension (ICD-10: I10-I15); LC, cirrhosis of liver (ICD-10: K74.6); Other cancers (ICD-10: C-codes except C16).

DFS according to the start timing of AC, the patients who started AC within 6 weeks were significantly superior to the other groups of patients ($P < .0001$), while there was no significant difference between those from 6 to 8 weeks and more than 8 weeks (Supplementary Tables S1 and S2, Figure 1).

The five-year OS rates were 72%, 66%, and 53% according to the delay of AC in all patients (Supplementary Table S3). The OS also significantly demonstrated superior outcomes in patients who started AC within 6 weeks than the other groups of patients ($P < .0001$), without significant difference between those from 6 to 8 weeks and more than 8 weeks (Supplementary Tables S3 and S4, Figure 2).

The univariable and multivariable analyses for DFS and OS are summarized in Table 2. In the multivariable analysis, the patients who initiated AC from 6 to 8 weeks or more than 8 weeks had significantly poor DFS (6 ≤ weeks ≤ 8: HR 1.18, 95% CI 1.12-1.24, $P < .0001$ / 8 < weeks ≤ 16: HR 1.70, 95% CI 1.54-1.87, $P < .0001$). The patients who were 70 years or older (HR 1.37, 95% CI 1.29-1.45, $P < .0001$), patients treated with CAPOX regimen (HR 1.67, 95% CI 1.59-1.75, $P < .0001$), and patients with previous cancer history (HR 1.23, 95% CI 1.15-1.32, $P < .0001$) had significantly poor DFS outcomes.

The OS also revealed similar results in the multivariable analysis compared with DFS, except for the significantly poor outcome in male patients (HR 1.06, 95% CI 1.00-1.13, $P = .042$). The patients who started AC from 6 to 8 weeks or more than 8 weeks also showed independently significantly poor OS (6 ≤ weeks ≤ 8: HR 1.21, 95% CI 1.14-1.29, $P < .0001$ / 8 < weeks ≤ 16: HR 1.91, 95% CI 1.72-2.12, $P < .0001$).

Analysis of survival outcomes after PSM

PSM was performed in the patients who started AC within 6 weeks and those from 6 to 8 weeks. The patients' characteristics were well-balanced, with 5386 patients in each group (Table 3). DFS and OS showed similar outcomes with the analyses in all patients before PSM. Both DFS and OS were significantly superior in the patients who started AC within 6 weeks compared with those from 6 to 8 weeks in all patients (both, $P < .0001$) and those treated with S-1 (Figures 3 and 4). However, there was no significant difference in the OS outcome between the patients who started AC with CAPOX within 6 weeks and those between 6 and 8 weeks (HR 1.10, 95% CI 0.99-1.21, $P = .078$), with inferior DFS in patients who treated between 6 and 8 weeks (HR 1.12, 95% CI 1.03-1.22, $P = .0067$) (Figures 3 and 4).

Discussion

Although adjuvant treatment for locally advanced GC is widely used worldwide, the optimal timing of initiation of AC remains undefined. While there have been several reports on the relationship between the timing of AC and the survival outcomes of GC patients, these studies included patients treated with heterogeneous chemotherapeutic regimens and applied various cutoff reference timings from surgery, with conflicting results (Supplementary Table S5).[14-27] Most Western studies have not revealed a significant association between the start timing of AC and the outcomes of patients.[14,23,24] For example, Greenleaf et al reported that starting AC later than 8 or 12 weeks after resection was not associated with worse OS, according to the National Cancer Database in the United States.[14] On the other hand, inferior outcomes related to the delay of chemotherapy start have been reported in several Eastern studies.[17,18,20,21,26,27] A Japanese study retrospectively investigated 401 GC patients receiving AC with S-1 and reported worse OS in patients who started AC more than 8 weeks after surgery, while there was no significant difference

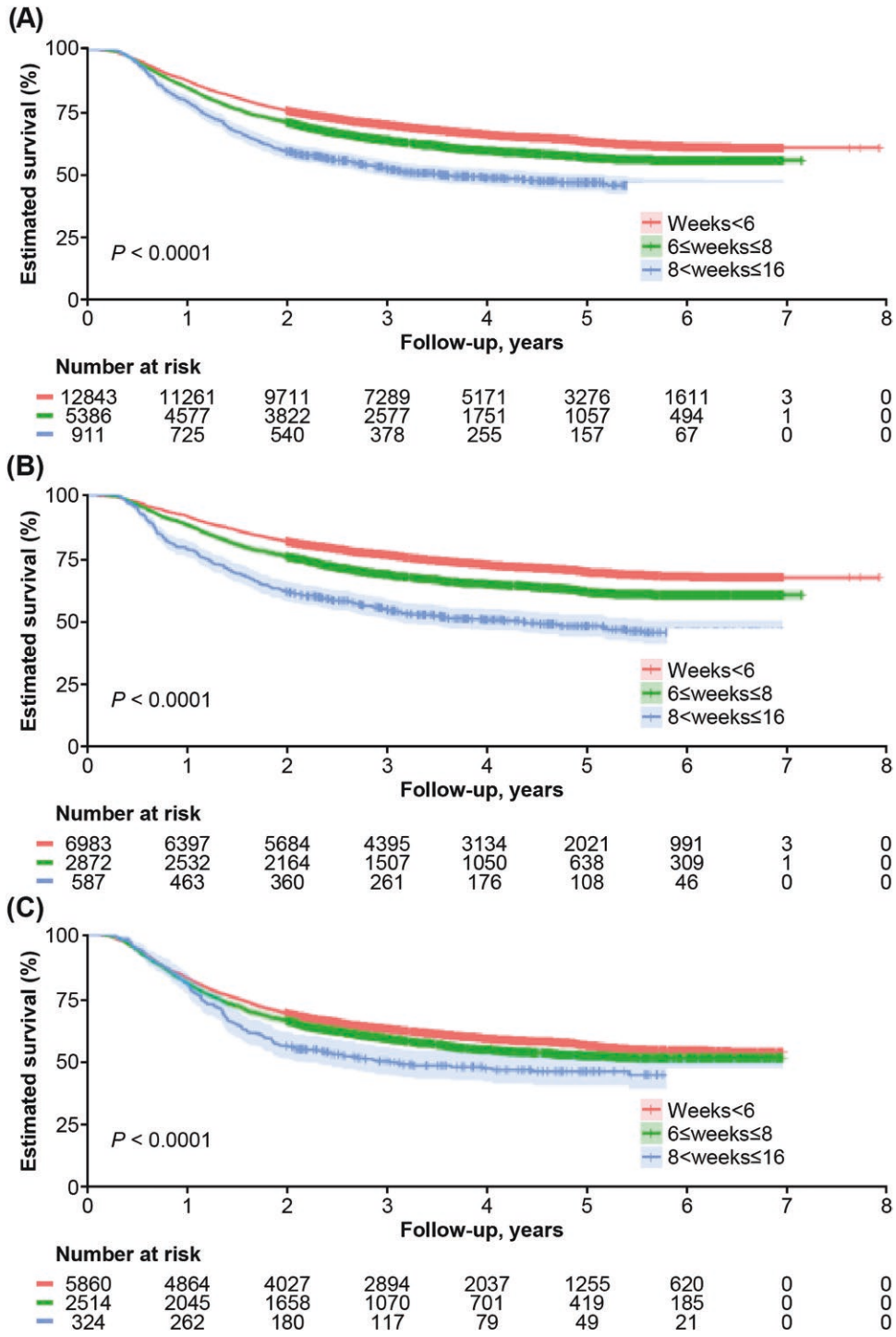

Figure 1. Disease-free survival curve for each group in (A) all patients, (B) patients starting S-1, and (C) patients starting capecitabine/oxaliplatin.

between patients who initiated within 6 weeks and those in 6 to 8 weeks.[17] Furthermore, a meta-analysis showed that AC per 4-week delay caused worse survival outcomes in GC patients.[16] Although the contradictory findings between Western and Eastern countries are difficult to explain, the establishment of extended lymphadenectomy (D2 dissection) as the standard of care in Eastern countries, such as Korea and Japan, may be a contributing factor.[13] In Eastern countries, although starting AC within 6 to 8 weeks after surgery is usually recommended,[16,17,19] there is no definite guideline with high-level evidence to support it. Therefore, to define the best start timing of AC in GC, we conducted this study for GC patients receiving S-1 and CAPOX, standard AC regimens in East Asian countries, using big data from Korea's HIRA.[9,10,12,13] The CLASSIC trial initiated AC at 4-7 weeks after surgery, while the Japanese guidelines recommend starting AC within 6 weeks.[10,13,29] Moreover, a retrospective study from Korea on the timing of AC that included patients treated with S-1 /CAPOX (38.1% of total) showed poor OS when treatment was initiated after 8 weeks.[21] Therefore, this study determined 6 and 8 weeks as the cutoff points for analysis of the start timing for AC in GC, respectively.

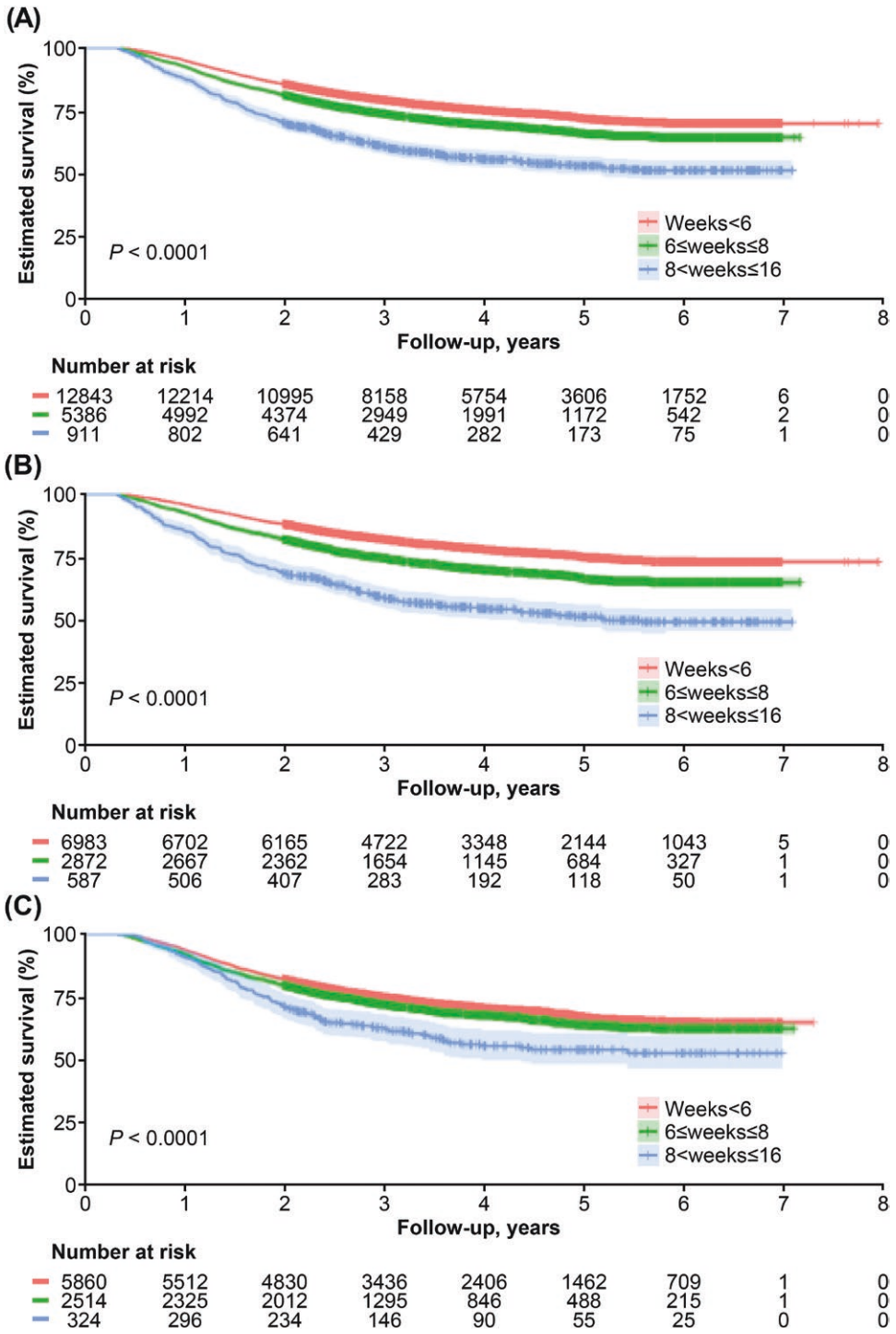

Figure 2. Overall survival curve for each group in (A) all patients, (B) patients starting S-1, and (C) patients starting capecitabine/oxaliplatin.

This study showed that the outcomes of patients were significantly better when AC was started within 6 weeks after surgery, while delayed initiation of AC was independently associated with poor DFS and OS. However, there was no statistically significant difference between the group with 6 to 8 weeks of AC and that with more than 8 weeks. A relatively small number of patients who started AC more than 8 weeks may explain these findings. In addition, there were significant differences in some characteristics, such as age and comorbidities, between patients who initiated AC within 6 weeks and those from 6 to 8 weeks, which might be related to the poor outcome of patients with delayed initiation of AC. Therefore, PSM was performed in the two groups with well-balanced characteristics. Although DFS and OS were also better in patients who initiated within 6 weeks in all patients and the S-1 group even after PSM, there was no significant difference in OS outcome in the CAPOX group. CAPOX is a commonly used palliative first-line chemotherapeutic regimen for GC patients.[30] We assumed that relatively more GC patients with palliative resection or stage IV might be included in the CAPOX group with relatively early initiation of chemotherapy compared with S-1, leading to the absence of a significant

Table 2. Univariable and multivariable analyses of disease-free survival and overall survival.

	DFS						OS					
	Univariable			Multivariable			Univariable			Multivariable		
Characteristics	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age												
<70	1			1			1			1		
≥70	1.21	1.15-1.28	<.0001	1.37	1.29-1.45	<.0001	1.53	1.45-1.62	<.0001	1.64	1.54-1.74	<.0001
Sex												
Female	1			1			1			1		
Male	1.04	0.97-1.11	.244	1.02	0.97-1.08	.358	1.07	1.01-1.13	.0259	1.06	1.00-1.13	.042
Regimen												
S-1	1			1			1			1		
CAPOX	1.53	1.46-1.60	<.0001	1.67	1.59-1.75	<.0001	1.26	1.19-1.33	<.0001	1.44	1.36-1.52	<.0001
Comorbidities												
0	1			1			1			1		
1	1.02	0.97-1.13	.373	0.98	0.93-1.04	.514	1.09	1.02-1.16	.0069	0.98	0.92-1.04	.491
≥2	1.05	0.97-1.08	.212	1.01	0.94-1.09	.855	1.13	1.04-1.23	.0041	0.99	0.91-1.08	.829
Other cancers												
No	1			1			1			1		
Yes	1.30	1.22-1.39	<.0001	1.23	1.15-1.32	<.0001	1.36	1.26-1.47	<.0001	1.26	1.17-1.36	<.0001
Groups[a]												
Weeks < 6	1			1			1			1		
6 ≤ weeks ≤ 8	1.23	1.17-1.29	<.0001	1.18	1.12-1.24	<.0001	1.28	1.21-1.36	<.0001	1.21	1.14-1.29	<.0001
8 < weeks ≤ 16	1.73	1.57-1.90	<.0001	1.70	1.54-1.87	<.0001	2.04	1.84-2.27	<.0001	1.91	1.72-2.12	<.0001

[a]Start timing of adjuvant chemotherapy from surgery.
Abbreviations: CAPOX, capecitabine/oxaliplatin; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; other cancers (ICD-10: C-codes except C16).

Table 3. Demographic characteristics between weeks <6 and 6 ≤weeks ≤8 groups before and after propensity score matching

Parameter	Before matching				After matching			
	weeks < 6 *N* = 12 843	6 ≤ weeks ≤ 8 *N* = 5386	SMD	*P*-value	Weeks < 6 *N* = 5,386	6 ≤ weeks ≤ 8 *N* = 5386	SMD	*P*-value
Age			0.205	<.001			0.010	.611
Age ≥ 70	3132 (24.4)	1812 (33.6)			1838 (34.1)	1812 (33.6)		
Age < 70	9711 (75.6)	3574 (66.4)			3548 (65.9)	3574 (66.4)		
Sex			0.017	.297			0.003	.349
Male	8799 (68.5)	3733 (69.3)			3687 (68.5)	3733 (69.3)		
Female	4044 (31.5)	1653 (30.7)			1699 (31.5)	1653 (30.7)		
Regimen			0.021	.201			0.059	.395
S-1	6983 (54.4)	2872 (53.3)			2917 (54.2)	2872 (53.3)		
CAPOX	5860 (45.6)	2514 (46.7)			2469 (45.8)	2514 (46.7)		
Comorbidities[a]			0.105	<.001			0.005	.683
≥ 2	1495 (11.6)	769 (14.3)			776 (14.4)	769 (14.3)		
1	3798 (29.6)	1711 (31.8)			1669 (31.0)	1711 (31.8)		
0	7550 (58.8)	2906 (54.0)			2941 (54.6)	2906 (54.0)		
Other cancers			0.087	<.001			0.031	.596
Yes	1429 (11.1)	755 (14.0)			735 (13.6)	755 (14.0)		
No	11414 (88.9)	4631 (86.0)			4651 (86.4)	4631 (86.0)		

Data are presented as *N* (%).
Abbreviations: CAPOX, capecitabine/oxaliplatin; SMD, standardized mean difference.
[a]Comorbidities include diabetes mellitus, hypertension, coronary arterial occlusive disease, cerebrovascular accident, chronic kidney disease, cirrhosis of liver, and chronic obstructive pulmonary disease.

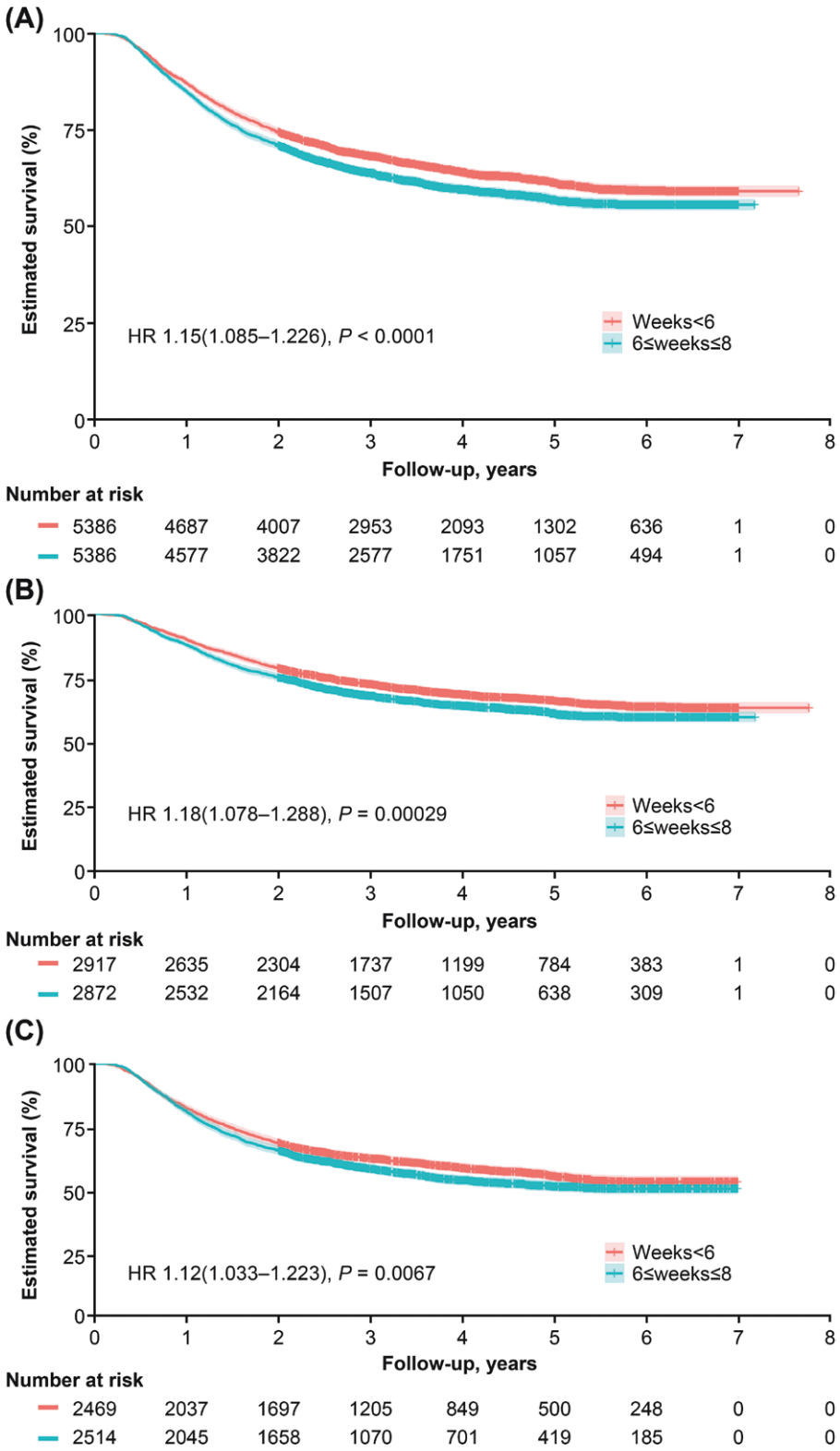

Figure 3. Disease-free survival curve with the matched cohort group in (A) all patients, (B) patients starting S-1, and (C) patients starting capecitabine/oxaliplatin.

difference in OS in the CAPOX group according to the start timing of chemotherapy. For example, among about 700 patients who received CAPOX/S-1 after gastrectomy in our institution, about 17% of patients in the CAPOX group and 7% of those in the S-1 group underwent palliative resection or were in stage IV, respectively (unpublished data).

To our knowledge, the present study is the first big-data analysis about the start timing of AC in GC patients in Eastern countries. Based on the results of analyzing real-world nationwide big data in this study, we recommend that AC should be started within 6 weeks from surgery if possible. However, this study has several limitations. First,

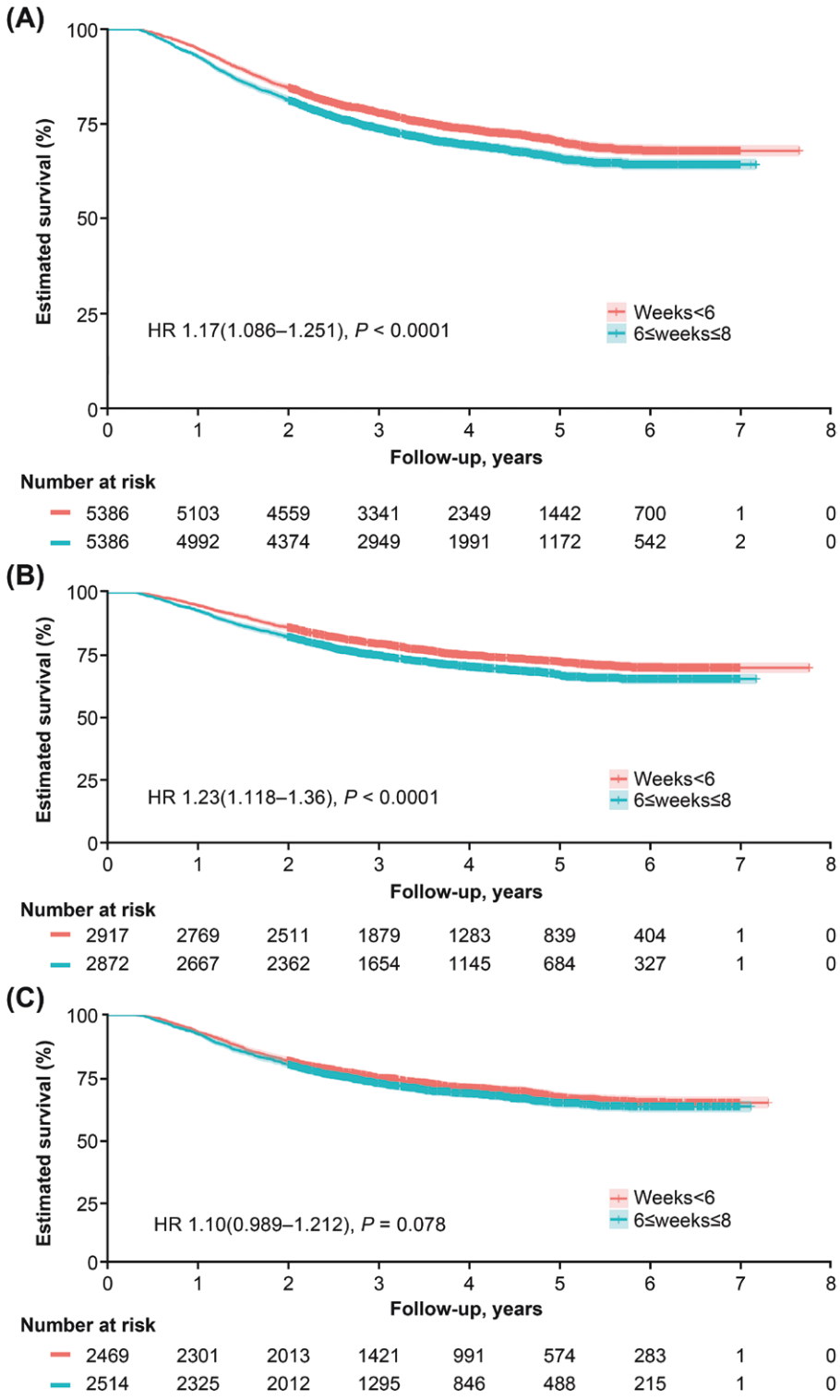

Figure 4. Overall survival curve with the matched cohort group in (A) all patients, (B) patients starting S-1, and (C) patients starting capecitabine/oxaliplatin.

death was operationally defined as the absence of medical records for over one year, due to the lack of exact death dates in the HIRA data. Therefore, patients who were alive but had no hospital visits for over one year might have been misclassified as dead, while those who died after January 2020 might have been recorded as alive due to data availability only through December 2020. However, defining death as the absence of medical records for over one year seems reasonable, given the comprehensive coverage of the HIRA database for nearly all individuals in Korea and the frequent healthcare use among Korean patients. The prolonged absence of claims in the HIRA database likely indicates death, particularly for those with chronic or severe conditions such as cancer.[31] Moreover, in Korea, nearly all cancer patients die in medical institutions rather than at home.[32] Additionally, a study from Korea demonstrated

the high validity of this operational definition of death.[33] Second, since recurrence was defined as the initiation of any other chemotherapy during or after completion of S-1 or CAPOX, patients who did not receive chemotherapy or were treated with radiotherapy or surgery alone after recurrence might not have been counted as events. However, because DFS includes both recurrence and death, and nearly all recurrent patients without chemotherapy die within a short period,[34] the impact on DFS estimation is likely minimal, except for a possible slight prolongation of time to event. Third, it was impossible to analyze important prognostic factors, such as pathologic stage and performance status, in the HIRA database. Fourth, this study cohort might have included patients who underwent palliative surgery or had stage IV disease despite complete resection, followed by chemotherapy (approximately 9.5% based on unpublished data from our institution). Fifth, the effects of postoperative complications, which are the major causes of delay in AC, were not analyzed, as it is difficult to define their scope, such as occurrence timing and duration, and to determine their association with surgery using the HIRA database. Nonetheless, it is worth noting that a few studies investigating the timing of AC and outcomes, including analyses of postoperative complications, did not report an independent association between complications and outcomes such as OS or relapse-free survival.[15,17,18,20] Sixth, with a median follow-up period of 3.6 years, the OS data might be somewhat immature. However, considering a previous study reporting a significant correlation between DFS and OS in AC for GC and the improvement of 3-year DFS by AC leading to a significant benefit of the 5-year OS in the CLASSIC trial,[10,13,35] this study's results from the analysis of both DFS and OS may have clinical relevance, with relatively enough follow-up time for DFS. Finally, the inclusion of comorbidities within one year before surgery might have led to their underestimation.

It is unclear whether the poor outcomes resulting from the delay of AC are attributed to the proliferation of micrometastasis during the waiting period or poor baseline status of the patients because AC might be delayed due to postoperative complications or poor general condition.[18] Although a randomized trial is needed to conclude whether earlier administration of AC is beneficial for GC patients, its implementation seems almost impossible due to ethical and practical issues. In addition, AC for GC may be delayed due to various reasons, such as postoperative complications, the overall health condition of the patients, referral and waiting times for AC, and patients' will.[18] Based on the results of the present study, efforts to minimize such delays seem to be necessary for the initiation of AC within 6 weeks after surgery.

Conclusion

AC with S-1 or CAPOX for GC showed the best outcomes when initiated within 6 weeks following surgery. Therefore, AC for GC should be started within 6 weeks after gastrectomy if patients have fully recovered.

Author contributions

Tae-Hwan Kim, Eunyoung Lee , Hyun Woo Lee, and Jin-Hyuk Choi (Conceptualization, Data curation). Tae-Hwan Kim , Eunyoung Lee , Hyun Woo Lee , Mi Sun Ahn , Yong Won Choi , Minsuk Kwon, Seok Yun Kang, and Jin-Hyuk Choi (Formal Analysis, Methodology, Resources). Tae-Hwan Kim, Eunyoung Lee, Hyun Woo Lee, and Jin-Hyuk Choi (Writing—original draft) and Tae-Hwan Kim and Jin-Hyuk Choi (Writing—review & editing), Tae-Hwan Kim, Eunyoung Lee , Hyun Woo Lee, and Jin-Hyuk Choi (Formal Analysis), Eunyoung Lee and Bumhee Park (Formal Analysis). All authors (Writing—review & editing).

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Conflicts of interest

J. -H. Choi received research funding from Roche and Sanofi. All other authors have declared no conflict of interest.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the confidentiality of the data of patient but are available from the corresponding author on reasonable request.

Ethical approval

This study was conducted in accordance with the principles expressed in the Declaration of Helsinki 1964 and later versions. The study protocols were approved by the institutional review board of Ajou University Hospital (IRB approval no. AJOUIRB-EXP-2021-627). Furthermore, the institutional review board of Ajou University Hospital decided to waive the informed consent for this study because it was a retrospective study using anonymized data.

Prior presentation

This study was presented in part as a poster at the European Society for Medical Oncology Congress 2023, Madrid, Spain, October 20-24.

Supplementary material

Supplementary material is available at *The Oncologist* online.

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