Optimal time interval from surgery to adjuvant chemotherapy in gastric cancer

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Abstract. The effect of adjuvant chemotherapy (AC) for resected gastric cancer is well established; however, delays in treatment and its impact on clinical outcomes have not yet been determined. The current study analyzed the survival rates based on time interval (TI) between surgery and AC administration to evaluate a potential association between the two variables. Patients diagnosed with stage II-III gastric adenocarcinoma between 2009 and 2016 at the Kyung Hee University Hospital were included. Patients' data including demographics, TNM stage, types of AC, and TI retrospectively collected from surgery to the start of AC. Patients were dichotomized based on the TI, which was predetermined at 3, 4, 5, 6, 7 or 8 weeks. Median disease-free survival (DFS) and overall survival (OS) were analyzed according to TI. In total, 172 patients were identified. The median follow-up duration was 40.8 (3-109) months. The median TI was 4.1 (2.1-9.8) weeks. DFS in patients with TI ≥4 weeks (n=106, 61.6%) was significantly lower compared with patients with TI <4 weeks (n=66, 38.4%), with a median DFS of TI < vs. ≥4 weeks of 8.1 vs. 6.0 years [hazard ratio (HR)=1.80, 95% confidence interval (CI): 1.067-3.045, P=0.0277]. OS was also significantly reduced in patients with TI ≥4 weeks, favoring TI <4 weeks [median OS of TI < vs. ≥4 weeks: Not reached (NR) vs. 7.0 years, HR=2.15, 95% CI: 1.173-3.939, P=0.0133]. Other predetermined TIs were not associated with survival outcomes. The current study demonstrated that AC within 4 weeks of surgery should be recommended for gastric cancer, and delays of >4 weeks may be detrimental to patients' survival.

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Introduction

Gastric cancer is one of the most common cancers worldwide (1). Its incidence varies by region, with a high representation in East Asia, Eastern Europe, and South America. Surgery is currently the sole curative treatment option for patients with advanced gastric cancer; however, a substantial number of patients experience disease recurrence (2,3). Adjuvant chemotherapy (AC) such as S-1 monotherapy or combination therapy with capecitabine and oxaliplatin (XELOX) has been the standard of treatment following gastrectomy with D2 dissection for pathologic stages II or III (4,5). However, the optimal time for postoperative chemotherapy initiation after surgery is yet to be established. A significantly short time interval (TI) between surgery and AC can affect the patient's recovery from surgery and is more likely to cause problems including surgical wound complications. In contrast, a long TI between surgery and AC leads to a high risk of cancer recurrence due to growth of microscopic metastases. In the real world, delays in AC administration after surgery are common for various medical conditions such as postoperative complications, a decline in the patient's physical status as well as other nonmedical reasons such as low patient compliance, delayed consultation with medical oncologist, or economic issues (6,7). In our hospital, AC is routinely administered within 4-6 weeks of surgery.

According to the 2017 Japan Gastric Cancer Guidelines, AC, particularly in the case of S-1 chemotherapy, is empirically recommended within 6 weeks of surgery (8). The Korean Practice Guidelines for Gastric Cancer 2018 were recently published following an evidence-based multidisciplinary approach, but did not include a recommended time point for the start of AC after gastrectomy (9). There were also no specific comments that focused on the time of AC administration in the pivotal phase 3 trials that have confirmed the role of AC in gastric cancer (10,11). In a recent phase 3 trial evaluating the role of perioperative chemotherapy with or without immunotherapy, a TI for AC was defined at 4-10 weeks following surgery (12). Due to the fact that a precise cutoff value has not been established for the delayed time in AC administration, we analyzed the survival rate according to a predefined TI between surgery and the start of AC and attempted to define

an optimal TI. In cases where delays were observed, we also addressed the reasons for this occurrence.

Patients and methods

Patients. Clinical data from patients diagnosed with stage II-III gastric adenocarcinoma who received AC after gastrectomy with D2 lymph node dissection between 2009 and 2016 in Kyung Hee University Hospital were reviewed retrospectively. Among these, patients eligible for analysis with accurate records were evaluated. Patients' data included demographics, TNM staging, types of chemotherapeutic agents, and TI between surgery and the start of AC. TI was defined as the period from the date of surgery to the start of AC. Staging of cancer was based on the guidelines established by the American Joint Committee on Cancer 7th edition. The protocol for the study was reviewed and approved by the Institutional Review Board (IRB) of Kyung Hee University Hospital (approval no. KHUH 2020-01-044). All analyses and writing of the manuscript were in accordance with the Declaration of Helsinki.

Data collection and statistical analyses. This study aimed to investigate the clinical effect of TI on disease recurrence and survival. Therefore, we first searched for variables that affected the clinical outcomes in these patients. We subsequently analyzed the impact of TI on disease recurrence and overall survival (OS) after adjusting for other variables using the Cox regression analysis. We investigated whether the initially planned AC was successfully completed, and reasons for delays in AC administration when TI was over 4 weeks were also determined. To compare the effect of TI between the two groups, the TIs were dichotomized based on the predetermined times of 3, 4, 5, 6, 7, or 8 weeks and on the median value of TI for each patient. OS was defined as the period from the date of surgery to the last follow-up or death from any cause. Disease-free survival (DFS) was defined as the period from the date of surgery to the time of cancer recurrence or death from any cause. Survival outcomes were estimated using the Kaplan-Meier survival curves. A log-rank test was performed when a significant difference between the survival curves for each of the groups was observed. In case of the effect of the types of adjuvant chemotherapy on the survival outcomes, firth's penalized maximum likelihood bias reduction method for Cox regression was used. When statistically significant factors were observed in the univariate analysis, multivariate analysis using a Cox regression model were performed. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 23 package (International Business Machines Corporation) and R 3.5.3 software (https://cran.r-project.org).

Results

Patients characteristics. A total of 172 patients were identified in this study. Among these, 97 patients (56.4%) were diagnosed with stage II gastric adenocarcinoma and 75 patients (43.6%) with stage III gastric adenocarcinoma. All patients included in this study underwent surgical resection with D2 lymph node dissection. The median age of the patient population was 51.5 years, with a higher proportion of male patients (n=124, 72%). Six types of chemotherapy were used as follows: XELOX (capecitabine and oxaliplatin), TS-1, FP (5-fluorouracil plus cisplatin), TS-1/Cisplatin, FOLFOX (oxaliplatin, leucovorin plus 5-fluorouracil) and doxifluridine in 27.9, 50.0, 13.9, 3.4, 2.9, and 1.7% of patients, respectively. The median follow-up duration was 40.8 (range, 3-109) months. Recurrence was observed in a total of 68 patients (39.5%), with most of the patients presenting with distant metastases (n=62 out of 68, 91.1%). Patients' characteristics are summarized in

Table I. Patient characteristics.

Variables	N	%
Age (year)		
Median (range)	51.5	(21-82)
<60	88	51.2
≥60	84	48.8
Sex		
Male	124	72.1
Female	48	27.9
Stage		
II	97	56.4
III	75	43.6
Type of adjuvant chemotherapy		
XELOX	48	27.9
TS-1	86	50.0
FP	24	13.9
TS-1/Cisplatin	6	3.4
FOLFOX	5	2.9
Doxifluridine	3	1.7
Median (range)	4.1	(2.1-9.8)
Recurrence		
No	104	60.4
Yes	68	39.6
Pattern of recurrence[a]		
Loco-regional	6	8.9
Distant	62	91.1
Death		
No	116	67.4
Yes	56	32.6
Planned adjuvant chemotherapy was completed		
No	98	57.0
Yes	74	43.0
Total	172	100

XELOX, oxaliplatin plus capecitabine; FP, cisplatin plus 5-fluorouracil; FOLFOX, oxaliplatin plus leucovorin plus 5-fluorouracil. [a]The percentage of each pattern of recurrence was calculated based on the number of patients (n=68) who had disease recurrence rather than the total number of the patient population (n=172).

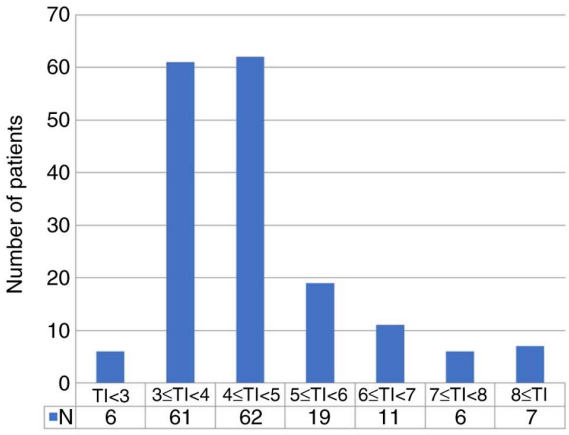

Figure 1. Patients' distribution according to time interval. TI, time interval; N, number of patients.

Table I, and TI distribution is shown in Fig. 1. The median TI was 4.1 (range, 2.1-9.8) weeks. Based on this observation, we compared the groups based on TI <4 weeks (n=66, 38.4%) and TI ≥4 weeks (n=106, 61.6%). The majority of patients (n=123, 71.5%) had received chemotherapy within 3 to 5 weeks of surgery, with few patients receiving chemotherapy within 3 weeks or after 8 weeks.

Clinical factors affecting survival outcomes. Following a univariate analysis, the clinical factors that showed a significant effect on the survival outcome included tumor stage and TI. The median DFS for patients with stage III gastric adenocarcinoma was significantly shorter than that for patients with stage II gastric adenocarcinoma [4.3 years vs. not reached (NR), respectively; hazard ratio (HR)=2.22, P=0.0013, Fig. 2A]. OS showed a similar statistical trend toward patients with stage II vs. III gastric adenocarcinoma (NR vs. 7.0 years, respectively; HR=2.01, P=0.0098, Fig. 2B). Similarly, a TI of greater than or less than 4 weeks had a significant impact on patients' survival. Patients who started chemotherapy 4 weeks or more after surgery showed a significantly shorter median DFS compared to patients who had started chemotherapy within 4 weeks of surgery (6.0 vs. 8.1 years, respectively; HR=1.80, P=0.0277, Fig. 3A). The median OS in patients with TI ≥4 weeks was also shorter than that in patients with TI <4 weeks (7.0 vs. NR years, HR=2.15, P=0.0133, Fig. 2B). Other clinical factors such as sex, age, and whether the planned chemotherapy was completed had no significant effect on either DFS or OS (Table II). After adjusting for the effect of tumor stage in the multivariate analysis, TI ≥4 weeks still showed a significantly worse effect on reducing both DFS and OS (DFS: HR=1.737, P=0.040; OS: HR=1.939, P=0.018, Table III). In addition to the median value of TI (4 weeks), we also compared DFS and OS based on a different TI from 3 to 8 weeks. However, only a TI of 4 weeks discriminated between DFS and OS.

Reasons for delayed adjuvant chemotherapy. Reasons for delays in the administration of chemotherapy included postoperative complications (i.e., intra-abdominal abscesses, anastomotic site leakage, paralytic ileus, or wound infections), inadequate physical condition to start chemotherapy (i.e., general weakness or poor oral intake), and others (i.e., low patient compliance, economic status, or delays due to patient's unavailability). Considering the retrospective nature of this study, obtaining the reasons for delaying AC was challenging. However, the most common causes for delays of longer than 4 weeks in administering AC were surgical complications (n=29/105, 26.6%), followed by a poor general condition by the patient (n=13/105, 12.3%). All reasons for delayed AC are listed in Table IV. For surgical complications, the types of complications were investigated in more detail (Supplementary Table). The median DFS of patients who experienced surgical complication was insignificantly shorter than that of patients without surgical complication (7.3 vs. 8.1 years, HR=1.34, P=0.326). The median OS also tended to be numerically shorter without statistical significance in patients who experienced postoperative complications than that in patients who did not, although the median values in both groups were not reached (HR=1.52, P=0.185).

Discussion

AC is typically administered to eradicate residual cancer and invisible micrometastases that may remain after surgery. Previous studies using animal models have shown that surgical resection of primary tumors increased the number of circulating tumor cells and promoted the proliferation of residual cells (13). Surgery has also been shown to promote the production of oncogenic growth factors such as transforming growth factor-α and to significantly reduce the immunotherapeutic effect of interleukin-2 and lymphokine-activated killer cells (14). Cellular proliferation of cancer cells progresses rapidly initially and then progressively. Therefore, when the tumor burden is minimal following surgery, it is expected that AC should be administered as soon as possible. However, a significantly early AC start can affect the patient's recovery such as wound healing and may cause adverse effects when the patient's general condition has not been fully recovered. Conversely, beginning AC significantly late can increase the risk of recurrence due to regrowth of microscopic or indolent foci of viable tumor cells. As a result, several studies have evaluated the optimal timing for AC administration, particularly in patients with colon or breast cancer.

In colon cancer, early AC administration has been shown to improve OS compared to late administration, using various time points from 60 days to 8 weeks (15,16). Another study showed that AC started within 4 to 8 weeks improved survival compared to later starts of longer than 8 weeks (17). A previous meta-analysis has also shown that relative OS decreases by 14% for every 4-week delay in the initiation of AC (18). Early AC within 20 days improved DFS, whereas initiation of AC within 21 days of surgery was not associated with OS or DFS in patients with early breast cancer, suggesting there is some complexity and ambiguity in the optimal time of AC after tumor resection surgery (19,20). Similar reports in gastric cancer are insufficient; thus, the appropriate timing of AC administration in patients with gastric cancer is yet to be established. In a Korean retrospective study, AC within 28 days led to significant improvement in 10-year OS, suggesting the early initiation of AC after gastrectomy (21). However, the

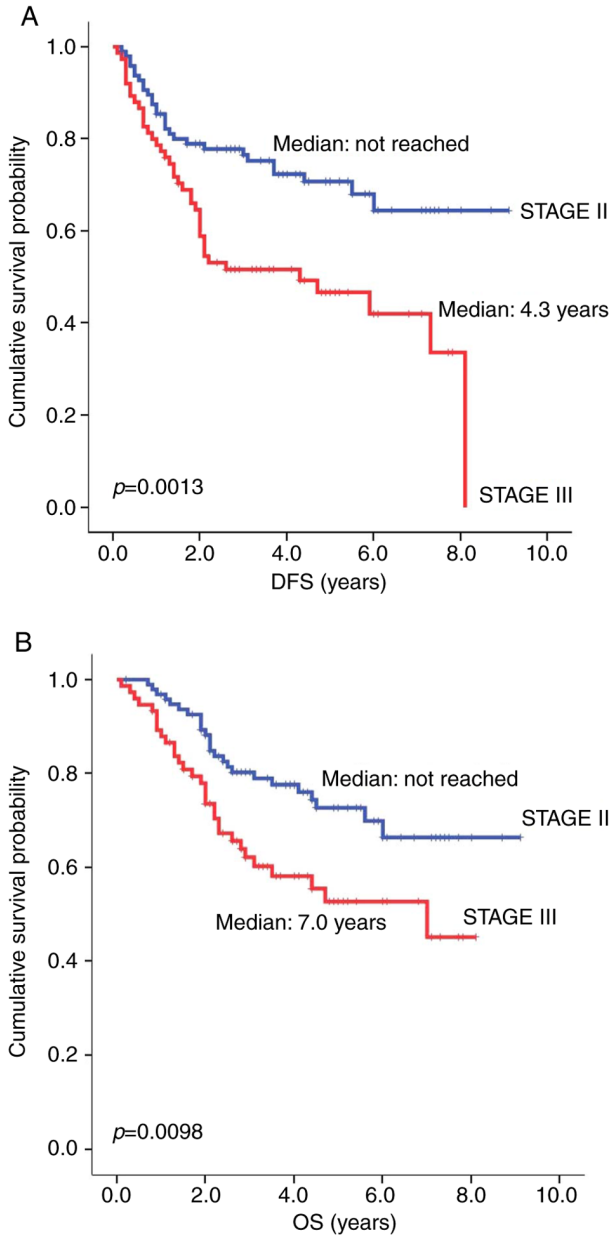

Figure 2. (A) Disease-free survival and (B) overall survival according to staging, II vs. III.

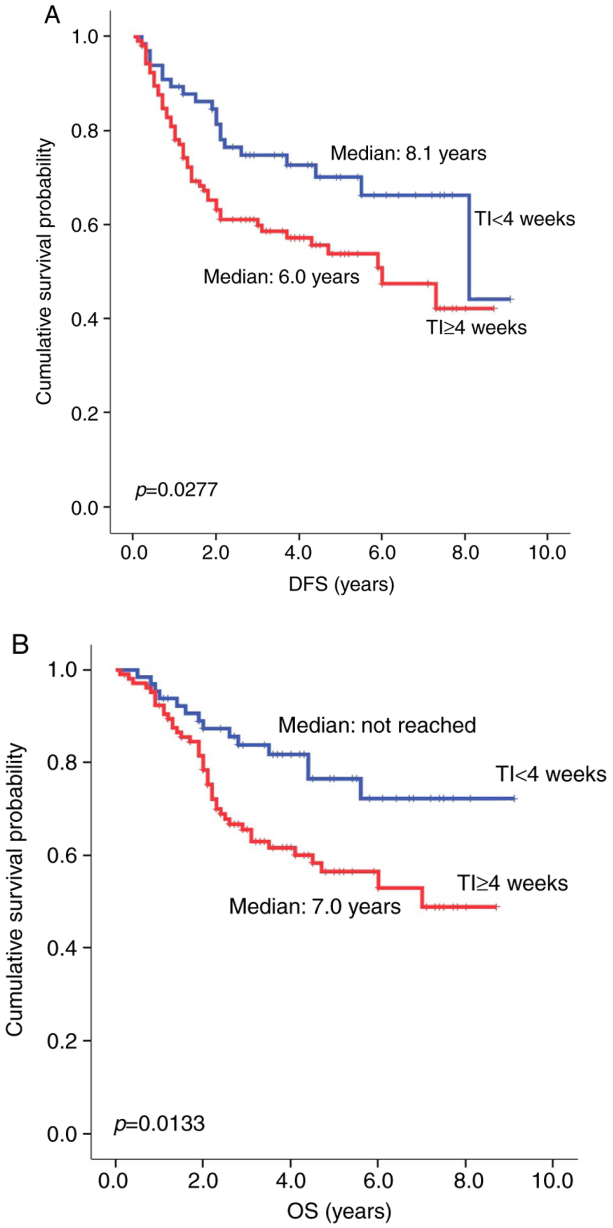

Figure 3. (A) Disease-free survival and (B) overall survival according to the time interval, less than 4 weeks compared to 4 weeks or more.

chemotherapeutic agents in the study (5-FU, mitomycin C, and polysaccharide-K) are not the standard agents used recently. Another Korean study showed AC administered within 8 weeks instead of 4 weeks of surgery improved survival outcomes (22). Interestingly, the results of the analysis of subgroups who were able to start AC within 4 weeks because of minimally invasive surgery (i.e., laparoscopic or robot-assisted gastrectomy) showed a significantly better OS and relapse-free survival compared to subgroups who started AC after 4 weeks. Conversely, other reports showed no survival benefit for patients who received AC within 4 weeks of surgery (23). A study in Taiwan showed that starting AC within 8 weeks of a gastrectomy resulted in an improved 5-year recurrent-free survival rate, possibly contributing to an improved OS (24). Another study on AC using S-1 chemotherapy, from Japan, found that the timing of AC was not associated with OS (25). However, others reported that S-1 administration within 6 weeks of surgery was associated with a decrease in recurrence rates and an increase in survival time (26). A recent meta-analysis showed a survival benefit when AC was started within 6 to 8 weeks of surgery. However, when AC was started after 8 weeks, a 20% increased risk of death was observed (27). Notwithstanding, this meta-analysis did not evaluate solely gastric cancer, but also included other types of cancer such as colorectal or pancreatic cancer. Taken together, it is important to set an optimal TI for AC delivery, despite differences in patient's recovery after surgery, surgery methods, types of AC, and tumor patterns. It has been not exactly known why the results of previous studies are inconsistent with each other. Considering that prospective comparative studies have not yet been conducted, it is inevitable to interpret them in consideration of the number of samples, methods of statistical analysis, and potential biases in each study. However, as reported in the

Table II. Univariate analysis of disease-free survival and overall survival based on clinical factors.

		DFS		OS	
Variable	N	HR (95% CI)	P-value	HR (95% CI)	P-value
Age			0.3672		0.7545
<60	88	1		1	
≥60	84	1.56 (0.97-2.53)		1.35 (0.80-2.29)	
Sex			0.657		0.4181
Male	124	1		1	
Female	48	1.60 (0.97–2.53)		1.27 (0.72–2.24)	
Stage			0.0013[a]		0.0098
II	97	1		1	
III	75	2.22 (1.37-3.60)		2.01 (1.18-3.40)	
Type of adjuvant chemotherapy[a]					
XELOX	48	1		1	
TS-1	86	0.60 (0.34-1.08)	0.0872	0.65 (0.34-1.27)	0.2059
FP	24	1.29 (0.65-2.57)	0.4723	1.67 (0.80-3.49)	0.1760
TS-1/cisplatin	6	0.90 (0.27-3.00)	0.8594	1.34 (0.41-4.46)	0.6303
FOLFOX	5	0.86 (0.22-3.33)	0.8315	0.65 (0.11-3.85)	0.6330
Doxifluridine	3	0.42 (0.03-6.15)	0.5274	0.55 (0.03-9.67)	0.6798
Planned adjuvant chemotherapy was completed			0.0969		0.2675
No	98	1		1	
Yes	74	1.50 (0.93–2.43)		1.35 (0.80–2.28)	
Time interval			0.0277		0.0133
<4 weeks	67	1		1	
≥4 weeks	105	1.8 (1.067-3.045)		2.15 (1.173-3.939)	

[a]Firth's penalized maximum likelihood bias reduction method for Cox regression was used. DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; XELOX, oxaliplatin plus capecitabine; FP, cisplatin plus 5-fluorouracil; FOLFOX, oxaliplatin plus leucovorin plus 5-fluorouracil; NA, not applicable.

Table III. Multivariate analysis of DFS and OS based on stage and TI of 4 weeks.

	DFS		OS	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Stage (III vs. II)	2.163 (1.331-3.515)	0.002	1.939 (1.143-3.290)	0.014
Time interval (<4 weeks vs. ≥4 weeks)	1.737 (1.026-2.939)	0.040	1.939 (1.143-3.290)	0.018

DFS, disease-free survival; OS, overall survival; HR, hazard ration; CI, confidential interval; TI, time interval.

aforementioned study (22) that early AC within 4 weeks due to minimally invasive surgical technique led a better survival outcomes, it may be reasonable to recommend starting AC as early as possible (i.e., within 4 weeks) as long as the patient's condition improves sufficiently after surgery and there is no reason to delay the administration of AC.

In this study, we dichotomized the TI as less than vs. equal or more than 4 weeks based on the median value of TI within our study population (4.1 months). Additionally, we further examined the effect of various TIs set arbitrarily every 1 week to evaluate whether there were significant differences based on the different TIs. We found that OS and DFS were greater in the group with a TI lower than 4 weeks than those in the group with a TI higher than 4 weeks. In addition to TI, TNM stage was another significant factor that affected patients' survival in our multivariate analysis (stage III vs. II, HR=2.22. 95% CI: 1.37-3.60). This is consistent with the results from previous studies (10,11,20) and may suggest that our study population provides a significant representation of the general population in terms of disease characteristics and the natural course of disease, despite the retrospective nature of our cohort. Therefore, the significance of the 4-week TI obtained in this

Table IV. Reasons for delayed chemotherapy (≥4 weeks).

Reason for delayed chemotherapy	N (%)
Postoperative complications (i.e., intra-abdominal abscess, anastomosis site leakage, ileus, wound infection)	29 (51)
Inadequate condition to start chemotherapy (i.e., general weakness, poor oral intake)	13 (23)
Other conditions requiring hospitalization, excluding postoperative complications	12 (21)
Personal condition (i.e., low patient's compliance, economic status, delayed due to foreign residence)	3 (5)
Total	57 (100)

study may be considered as a reliable TI for the general population as well. Additionally, this study included solely patients who received gastrectomy with D2 lymph node dissection, unlike previous studies that included patients undergoing both D1 and D2 dissections. Since D2 dissection has become a standard technique, our study may be more appropriately applied to the real-world clinical practice (28,29).

Besides its retrospective nature, our study has some limitations. First, preexisting comorbidity data for patients were missing. Comorbidities are important factors to consider as they can affect the recovery from surgery, start of chemotherapy, and patients' long-term survival. We were not able to investigate the effects of comorbidities in this instance. However, as patients included here were sufficiently healthy to withstand a radical surgery, even if other comorbidities were observed, it is possible to assume that the overall health status of our patients was satisfactory. In addition to the comorbidities that had already been diagnosed, it has been found that postoperative complications have a significantly negative impact on survival, including both on OS and disease-specific mortality, in patients with gastric cancer (30). In fact, when comparing HR, there was a tendency of worse long-term survival outcomes according to the immediate postoperative complications. The fact that statistical significance was not observed in this study population might be related to the insufficient sample size. Second, although the Korean study mentioned earlier showed the association between the possibility of early AC and minimally invasive surgical procedures, we did not investigate the surgical methods used. A study reported that a laparoscopic approach was associated with a reduced recovery time and allowed for a shortened TI to AC administration (31). Other studies have shown that this approach was not associated with the time of AC start and that although it allowed for earlier discharge following surgery, its benefits did not last longer than in open surgery post-discharge (23). Third, 98 of the 172 patients (57%) did not complete the planned AC. However, these patients were equally distributed in both groups of patients with TI ≥4 weeks and <4 weeks; hence, the potential effect might be offset. Finally, a selection bias may be present in our data considering that this study was conducted in a single center and with a small number of patients.

In conclusion, this study suggests that AC should be initiated within 4 weeks of surgery with D2 resection in patients with gastric cancer. Delays longer than 4 weeks in AC administration for any reason may be detrimental to patients' survival.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CHM designed the study. GTA and CHM collected patient data and performed the initial statistical analysis. SJJ performed the detailed statistical analysis. GTA was a major contributor in writing the manuscript. CHM supervised the written manuscript. SKB, HJK and JJH provided the clinical information for patients included in the analysis. SKB, HJK and JJH interpreted the results and wrote the first draft of the discussion section. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The current study was approved by Kyung Hee University Hospital IRB (approval no. KHUH 2020-01-044).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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