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Original Article

Effect of Early Adjuvant Chemotherapy on Survival of Advanced Gastric Cancer Patients: a Propensity Score-matched Analysis

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ABSTRACT

Purpose: Generally, adjuvant chemotherapy (AC) should be initiated as soon as possible after surgery to eradicate microscopic cancer cells. In this study, we investigated the effect of early AC on the survival of stage II/III gastric cancer patients.
Materials and Methods: Four hundred sixty patients who received AC (S-1 or XELOX) for pathologic stage II/III gastric cancer at Seoul National University Bundang Hospital between January 2008 and December 2014 were included. Patients were divided into 2 groups: early AC administration (within 4 weeks) and late AC administration (more than 4 weeks). Patients in the early AC group (n=174) were matched 1:1 with patients in the late AC group (n=174) by propensity scoring to adjust for clinical differences. Three-year relapse-free survival (RFS) was evaluated according to the timing of AC.
Results: Three-year RFS was 98.1% in stage IIA (n=109), 85.0% in stage IIB (n=83), 87.4% in stage IIIA (n=96), 83.5% in stage IIIB (n=91), and 62.5% in stage IIIC (n=81). After propensity score matching, RFS was similar between early and late AC groups (hazard ratio [HR],1.04; 95% confidence interval [CI], 0.62–1.74; P=0.889). Pathologic stage and histological type were independent prognostic factors of RFS (HR, 2.05; 95% CI, 1.06–3.96; P=0.033 and HR, 2.61; 95% CI, 1.42–4.80; P=0.002, respectively).
Conclusions: Early initiation of AC within 4 weeks does not affect survival rates in stage II/III gastric cancer.

Keywords: Stomach neoplasms; Chemotherapy; Adjuvant drug therapy; Survival rate; Propensity score

INTRODUCTION

Curative resection, including surgical resection of the primary tumor and lymph node dissection, is the main treatment for gastric cancer; however, curative resection alone does not prevent recurrence. Patients who undergo curative D2 gastrectomy for pathologic stage II or III gastric cancer are subsequently treated with adjuvant chemotherapy (AC) [1,2]. The effectiveness of AC after curative gastrectomy has been verified in large clinical trials in East Asia [3,4].

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

Since surgical resection itself can cause immunosuppression in patients, AC should be initiated as soon as possible after surgery to eradicate microscopic cancer cells. For gastric cancer, the Japanese Gastric Cancer Association guidelines recommend initiating AC within 6 weeks after surgery and most clinicians initiate AC according to the guidelines [5]. However, the optimal timing of AC for gastric cancer remains unclear. A Korean study reported that initiating AC after 8 weeks was associated with a worse prognosis [6]. However, 2 studies performed in western countries reported that the timing of the initiation of AC did not affect survival [7,8].

Laparoscopic gastrectomy for gastric cancer was first reported in 1994 [9], and since then this approach has been shown to have many of the benefits associated with minimally invasive surgery, including accelerated recovery, early return to normal bowel function, reduced postoperative pain, and early discharge from hospital [10]. Delays in the initiation of AC are usually caused by surgical complications or poor general condition [11]. However, the advantages of the laparoscopic approach (LA), such as faster recovery or lower complication rates, may affect the timing of initiation of AC. Regarding pancreatic and colorectal cancers, several reports have highlighted the impact of the LA on the initiation of AC [12,13], but only one study has evaluated this issue in gastric cancer patients [14].

The present study aimed to evaluate the effect of early AC on survival and the factors associated with delayed initiation of AC in stage II/III gastric cancer.

MATERIALS AND METHODS

Study design

This retrospective study included patients with pathologic stage II or III gastric cancer who underwent curative gastrectomy with D2 lymph node dissection at Seoul National University Bundang Hospital between January 2008 and December 2014. At 3–4 weeks after surgery, patients were referred to a medical oncologist, who confirmed the patients' recovery status and then made a decision regarding the timing of initiation and regimen of AC. Two types of AC were used in this study: oral fluoropyrimidine (S-1) for 1 year or capecitabine plus intravenous oxaliplatin (XELOX) for 6 months. Patients with recurrence during AC treatment were excluded.

A propensity score-matched analysis was performed to adjust for significant differences in the clinicopathologic characteristics of patients (age, sex, surgical approach, body mass index, American Society of Anesthesiologists [ASA] score, type of operation, the extent of lymphadenectomy, hospital stay, postoperative complications, histological type, and pathologic stage). After propensity score matching using the nearest neighbor matching method, patients who received AC within 4 weeks (n=174) were matched 1:1 with 174 patients selected from 286 patients who received AC after more than 4 weeks [15].

Study objectives

The primary objective of this study was relapse-free survival (RFS), defined as the time from surgery to the first recurrence or death from same cancer and all treatment-related deaths. In our institution, most patients received AC within 6 weeks according to current guidelines. We hypothesized that earlier AC administration (within 4 weeks) than that stipulated in the guidelines (within 6 weeks) would have a positive effect on RFS. In addition, the

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clinicopathologic characteristics and RFS data were compared according to AC regimen (S-1, XELOX). The secondary outcome was to determine the factors associated with late initiation of AC in multivariable analysis.

Data collection

Patient data were collected from electronic medical records. Clinicopathologic features, including age, sex, tumor-node-metastasis (TNM) stage, tumor histology, surgical extent and technique, postoperative complications, chemotherapy regimen, and timing of AC, were analyzed. TNM staging followed the 7th edition American Joint Committee on Cancer classification. Postoperative complications, including wound infection, leakage, and intestinal obstruction, occurring within 30 days of surgery were evaluated according to the Clavien-Dindo classification. For the analysis of World Health Organization (WHO) classification, papillary, well differentiated, and moderately differentiated types were classified as the differentiated group, whereas poorly differentiated, mucinous, and poorly cohesive types were classified as the undifferentiated group.

Statistical analysis

Patients were classified into 2 groups according to the time from surgery to the initiation of AC: early AC administration (within 4 weeks) and late AC administration (more than 4 weeks). The baseline characteristics of each group were compared using the χ^2 or Fisher's exact tests. The Kaplan-Meier method was used to estimate the 3-year RFS rate, and differences between survival curves were tested using the log-rank test. To assess the effect of timing of AC on survival independently of other confounding factors, a multivariable Cox proportional hazards model was applied by incorporating the prognostic factors identified in the univariable log-rank test. Independent predictive factors for late initiation of AC were identified using logistic regression analysis. All variables with $P<0.2$ in univariable analysis and timing of AC were included in multivariable analysis. A P-value threshold of 0.05 was considered statistically significant. All statistical analyses were performed with R software (R Foundation for Statistical Computing, Vienna, Austria; http://cran.r-project.org/).

Ethical statement

Approval for the study was obtained from the Institutional Review Board of Seoul National University Bundang Hospital (B-1612/373-107). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and National) and with the Helsinki Declaration of 1964 and later versions.

RESULTS

Patient characteristics

A total of 460 patients with stage II or III gastric cancer were included in this study. Of those who received chemotherapy, 174 (37.8%) started AC within 4 weeks after gastrectomy and 286 (62.2%) started chemotherapy more than 4 weeks after surgery. The baseline characteristics of the patients are shown in **Table 1**. Sex, surgical approach, ASA score, surgical extent and technique, tumor histology, TNM stage, and AC regimen were not significantly different between the 2 groups. Patients older than 70 years were more likely to receive AC after 4 weeks ($P<0.001$). Postoperative complications of grade II or higher occurred in 6 (3.4%) patients in the early group and 66 (23.1%) in the late group ($P<0.001$). The median hospital stay was 6 days in the early group and 7 days in the late group ($P<0.001$). The distribution of time to

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Table 1. Patient characteristics

Time to CTx	≤4 wk (n=174)	>4 wk (n=286)	P-value
Age (yr)			<0.001
<70	157 (90.2)	213 (74.5)	
≥70	17 (9.8)	73 (25.5)	
Sex			0.459
Female	53 (30.5)	98 (34.3)	
Male	121 (69.5)	188 (65.7)	
Surgical approach			0.165
Laparoscopy	126 (72.4)	188 (65.7)	
Open	48 (27.6)	98 (34.3)	
Body mass index (kg/m^2)	24.1 (2.9)	23.4 (3.1)	0.030
ASA performance status			0.227
1	99 (56.9)	140 (49.0)	
2	64 (36.8)	128 (44.8)	
3	11 (6.3)	18 (6.3)	
Type of operation			0.105
Distal gastrectomy	122 (70.1)	178 (62.2)	
Total gastrectomy	52 (29.9)	108 (37.8)	
Combined resection: yes	25 (14.4)	46 (16.1)	0.718
Extent of lymphadenectomy			0.898
D1+	27 (15.5)	47 (16.4)	
D2	147 (84.5)	239 (83.6)	
Retrieved lymph node	58 (46–72)	59 (48–76)	0.831
Hospital stays (day)	6 (5–7)	7 (5–9)	<0.001
Complications within 30 days (grade II or more): yes	6 (3.4)	66 (23.1)	<0.001
Histological type			1.000
Differentiated	53 (30.5)	88 (30.8)	
Undifferentiated	121 (69.5)	198 (69.2)	
Stage			0.715
II	75 (43.1)	117 (40.9)	
III	99 (56.9)	169 (59.1)	
CTx regimen			0.056
S-1	111 (63.8)	208 (72.7)	
XELOX	63 (36.2)	78 (27.3)	

Data shown are number (%), mean (SD), or median (IQR).
CTx = chemotherapy; ASA = American Society of Anesthesiologists; SD = standard deviation; IQR = interquartile range.

initiation of AC is shown in **Fig. 1**. The median interval between surgery and AC was 5 weeks (range, 2–9 weeks). Ninety percent of patients (n=414) received AC within 6 weeks.

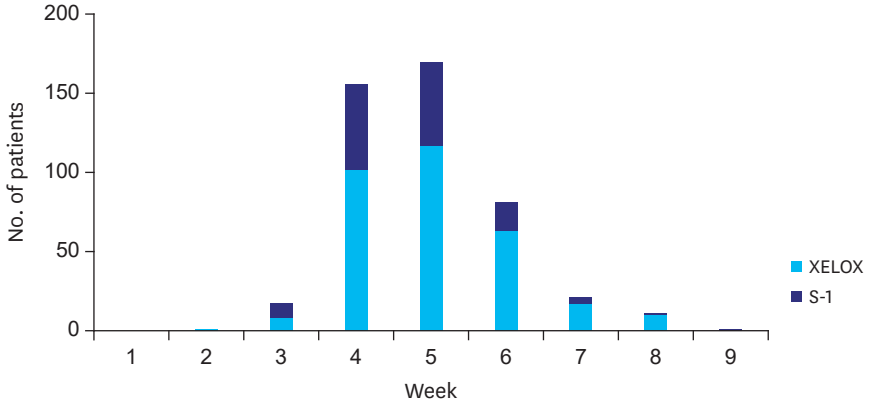

Fig. 1. The distribution of time to initiation of AC. The median interval between surgery and AC was 5 weeks (range, 2–9 weeks).
AC = adjuvant chemotherapy.

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Table 2. Patient characteristics after propensity score matching

Time to CTx	≤4 wk (n=174)	>4 wk (n=174)	P-value
Age (yr)			1.000
<70	157 (90.2)	156 (89.7)	
≥70	17 (9.8)	18 (10.3)	
Sex			0.645
Female	53 (30.5)	58 (33.3)	
Male	121 (69.5)	116 (66.7)	
Surgical approach			0.556
Laparoscopy	126 (72.4)	120 (69.0)	
Open	48 (27.6)	54 (31.0)	
Body mass index (kg/m^2)	24.1 (2.9)	23.7 (2.9)	0.263
ASA performance status			0.370
1	99 (56.9)	96 (55.2)	
2	64 (36.8)	72 (41.4)	
3	11 (6.3)	6 (3.4)	
Type of operation			1.000
Distal gastrectomy	122 (70.1)	123 (70.7)	
Total gastrectomy	52 (29.9)	51 (29.3)	
Combined resection: yes	25 (14.4)	19 (10.9)	0.420
Extent of lymphadenectomy			1.000
D1+	27 (15.5)	28 (16.1)	
D2	147 (84.5)	146 (83.9)	
Retrieved lymph node	58 (46–72)	57.5 (47–74)	0.945
Hospital stays (day)	6 (5–7)	6 (5–7)	0.586
Complications within 30 days (grade II or more): yes	6 (3.4)	5 (2.9)	1.000
Histological type			1.000
Differentiated	53 (30.5)	52 (29.9)	
Undifferentiated	121 (69.5)	122 (70.1)	
Stage			0.666
II	75 (43.1)	80 (46.0)	
III	99 (56.9)	94 (54.0)	
CTx regimen			0.209
S-1	111 (63.8)	123 (70.7)	
XELOX	63 (36.2)	51 (29.3)	

Data shown are number (%), mean (SD), or median (IQR).
CTx = chemotherapy; ASA = American Society of Anesthesiologists; SD = standard deviation; IQR = interquartile range.

Table 2 summarizes the clinicopathologic characteristics of the 2 groups after propensity score matching. Each group included 174 patients, and there were no significant differences between the basic characteristics of the 2 groups. The early AC administration group was well matched to the late AC group for all variables.

Survival outcomes

The median duration of follow-up in all 460 patients was 48 months (range, 3–101 months). The 3-year RFS was 98.1% in stage IIA (n=109), 85.0% in stage IIB (n=83), 87.4% in stage IIIA (n=96), 83.5% in stage IIIB (n=91), and 62.5% in stage IIIC (n=81) (**Fig. 2**).

Factors associated with RFS after propensity score matching are shown in **Table 3**. In univariable analysis, patients with open approach, undifferentiated histological type, and pathologic stage III showed worse RFS (hazard ratio [HR], 1.82; 95% confidence interval [CI], 1.08–3.07; P=0.024; HR, 2.03; 95% CI, 1.05–3.92; P=0.035; and HR, 2.83; 95% CI, 1.55–5.17; P=0.001; respectively). The timing of AC (>4 weeks, HR, 1.04; 95% CI, 0.62–1.74; P=0.889) was not significantly associated with RFS. In multivariable analysis, independent prognostic factors were undifferentiated histological type and pathologic stage III (HR, 2.05; 95% CI, 1.06–3.96; P=0.033 and HR, 2.61; 95% CI, 1.42–4.80; P=0.002, respectively).

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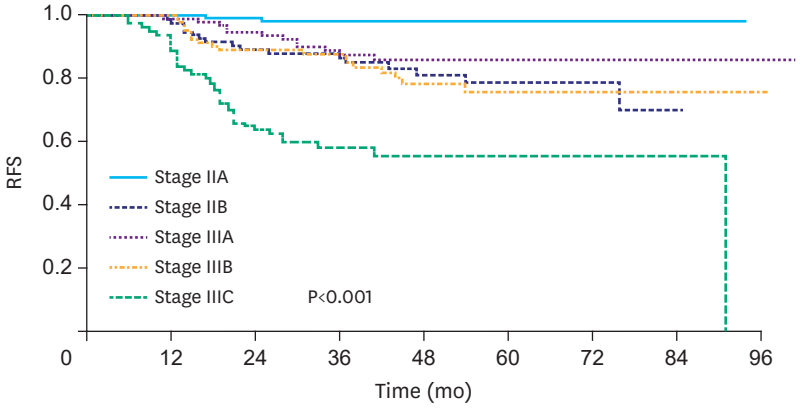
Table 3. Univariable and multivariable analysis of prognostic factors for RFS after propensity score matching

Variable	No. of patients	Univariable		Multivariable	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)					
<70	313	1	-		
≥70	35	1.12 (0.48–2.61)	0.793		
Sex					
Female	111	1	-		
Male	237	1.28 (0.72–2.28)	0.395		
Surgical approach					
Laparoscopy	246	1	-	1	-
Open	102	1.82 (1.08–3.07)	0.024	1.62 (0.95–2.74)	0.075
Body mass index (kg/m^2)		1.05 (0.96–1.15)	0.279	-	-
Type of operation					
Distal gastrectomy	245	1	-		
Total gastrectomy	103	1.34 (0.78–2.30)	0.296		
Complications within 30 days (grade II or more)					
No	337	1	-		
Yes	11	1.14 (0.28–4.69)	0.852		
Histological type					
Differentiated	105	1	-	1	-
Undifferentiated	243	2.03 (1.05–3.92)	0.035	2.05 (1.06–3.96)	0.033
Stage					
II	155	1	-	1	-
III	193	2.83 (1.55–5.17)	0.001	2.61 (1.42–4.80)	0.002
Time to CTx (wk)					
≤4	174	1	-	1	-
>4	174	1.04 (0.62–1.74)	0.889	1.05 (0.62–1.75)	0.866

RFS = relapse-free survival; HR = hazard ratio; CI = confidence interval; CTx = chemotherapy.



No. at risk									
Stage IIA	109	106	105	92	73	36	17	4	0
Stage IIB	83	82	74	60	40	25	15	1	0
Stage IIIA	96	93	87	66	50	30	14	4	1
Stage IIIB	91	91	80	65	36	22	14	9	4
Stage IIIC	81	76	50	30	17	14	5	4	0

Fig. 2. RFS according to pathologic stage. The 3-year RFS was 98.1% in stage IIA (n=109), 85.0% in stage IIB (n=83), 87.4% in stage IIIA (n=96), 83.5% in stage IIIB (n=91), and 62.5% in stage IIIC (n=81).
RFS = relapse-free survival.

Subgroup analysis according to AC regimen

We divided patients into 2 groups according to AC regimen: S-1 group and XELOX group. The baseline characteristics of each subgroup showed a similar distribution to that of the total study group (**Supplementary Tables 1** and **2**). However, patients older than 70 years or

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Table 4. Univariable and multivariable analysis of logistic regression analysis of late initiation of CTx

Variable	No. of patients	Univariable		Multivariable	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Age (yr)					
<70	370	1	-	1	-
≥70	90	3.17 (1.84–5.74)	<0.001	2.78 (1.57–5.13)	<0.001
Sex					
Female	151	1	-		
Male	309	0.84 (0.56–1.26)	0.400		
Surgical approach					
Laparoscopy	314	1	-	1	-
Open	146	1.37 (0.91–2.08)	0.136	1.17 (0.75–1.83)	0.487
Body mass index (kg/m^2)		0.93 (0.88–0.99)	0.031	0.94 (0.87–1.00)	0.057
Type of operation					
Distal gastrectomy	300	1	-	1	-
Total gastrectomy	160	1.42 (0.95–2.14)	0.086	1.02 (0.66–1.59)	0.921
Complications within 30 days (grade II or more)					
No	388	1	-	1	-
Yes	72	8.40 (3.85–22.11)	<0.001	7.99 (3.59–21.33)	<0.001
Histological type					
Differentiated	141	1	-		
Undifferentiated	319	0.99 (0.65–1.48)	0.944		
Stage					
II	192	1	-		
III	268	1.09 (0.75–1.60)	0.644		

CTx = chemotherapy; OR = odds ratio; CI = confidence interval.

those diagnosed with stage II were less likely to receive the XELOX regimen. Of the patients in the XELOX group (n=122), 86.5% were diagnosed with stage III cancer. Factors associated with RFS are shown in **Supplementary Tables 3** and **4**. In the S-1 group, stage III was the only independent prognostic factor of RFS (HR, 2.25; 95% CI, 1.19–4.24; P=0.012). In the XELOX group, there was no significant factor affecting RFS after multivariable analysis. The timing of AC was not significantly associated with RFS in either group.

Factors associated with late initiation of AC

The factors associated with late initiation of AC (more than 4 weeks after surgery) were analyzed by logistic regression (**Table 4**). On multivariable analysis, independent factors were old age and postoperative complications (odds ratio [OR], 2.78; 95% CI, 1.57–5.13; P<0.001 and OR,7.99; 95% CI, 3.59–21.33; P<0.001, respectively).

DISCUSSION

AC after gastrectomy with D2 dissection is the standard treatment for advanced gastric cancer in eastern countries. The Japanese Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial showed a survival benefit following 1 year of postoperative administration of S-1 monotherapy [4], and the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial conducted in Korea and China revealed improved survival with XELOX [3]. Based on this, S-1 and XELOX regimens are currently covered by National Health Insurance in Korea. The Japanese Gastric Cancer Association guidelines recommend initiation of AC within 6 weeks of surgery [5]; however, the actual timing of AC in clinical practice is delayed in patients with postoperative complications or in those with a poor general condition requiring recovery.

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In the present study, 90% of patients received AC within 6 weeks. Because of the relatively low rate of postoperative complications, patients were able to receive AC according to the guideline. Therefore, we divided the timing of AC by 4 weeks. There was no significant difference in survival according to the timing of AC after propensity score matching. However, undifferentiated histological type and pathologic stage III had a negative effect on RFS. Similar results were obtained in subgroup analysis according to AC regimen.

A large breast cancer trial showed that early AC within 3 weeks was more effective than late chemotherapy concerning RFS and overall survival (OS) [16]. Unlike gastrointestinal surgery, patients undergoing breast surgery do not require a long recovery period or a long time to resume a normal diet. A delayed start of AC after resection of colorectal cancer is reported to be responsible for impaired clinical outcomes [17,18]. However, recent studies reported conflicting results. One of the largest series evaluating the impact of AC in colorectal cancer showed that a delay in the initiation of AC has a minor impact on survival. On Cox regression analysis, only pathologic stage, angiolymphatic invasion, histological grade, emergency surgery, preoperative therapy, and age were significant factors influencing OS [19]. The interval between surgery and AC was not significant.

In gastric cancer, Arrington et al. [20] compared the outcomes of stage II/III surgically-resected gastric cancer patients who received neoadjuvant therapy (± postoperative chemotherapy) with those who received AC and reported no difference in OS between the 2 treatment groups. In later studies, 2 Korean reports demonstrated the effect of AC timing. Park et al. [6] reported worse RFS and OS rates in patients who initiated AC after 8 weeks. They also showed that stage III gastric patients who received early AC within 4 weeks survived longer than those who received late AC. Similarly, Kang et al. [21] reported that patients who started AC within 4 weeks had better outcomes. In Japan, Yamamoto et al. [22] suggested that beginning S-1 within 6 weeks of surgery is associated with a favorable prognosis. In contrast, Fujitani et al. [23] showed that time to initiation of S-1 within 6 weeks does not have an impact on survival outcome. The results of a phase III study comparing sequential FOLFIRI followed by docetaxel/cisplatin versus 5-fluorouracil monotherapy (Intergroup Trial of Adjuvant Chemotherapy in Adenocarcinoma of the Stomach; ITACA-S) showed that delayed initiation of AC had no detrimental effect on RFS and OS, whereas treatment completion had a protective effect [7]. Therefore, they suggested that it is reasonable to provide sufficient time after surgery to restore the patient's general condition with the aim of completing AC. Greenleaf et al. [7] also 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.

Consistent with previous studies, the present study revealed that early AC administration within 4 weeks had no positive effect on survival. In the XELOX group, most patients were diagnosed with stage III cancer, and there was also no significant difference between the early and late groups. These results suggest that sufficient time should be provided after surgery to allow for recovery of bowel function and intestinal absorption. The recovery period is important because gastrectomy has a significant impact on food intake. Early initiation of AC before full recovery did not have a positive effect on survival.

LA has advantages with respect to early recovery and fewer complications; therefore, we hypothesized that LA had a positive effect on the early initiation of AC. Recently, Kaito et al. [14] reported that independent factors associated with delayed initiation of AC (>6 weeks) were morbidity, open surgery, and postoperative weight loss in a case-matched comparison

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study of laparoscopic vs. open surgery. In the present study, independent prognostic factors associated with delayed initiation of AC were old age and postoperative complications. LA was not associated with the timing of AC. Although LA allows early discharge after surgery, its benefits do not persist any longer than those of open approach after discharge.

The present study had several limitations. The retrospective and single-institution design may lead to patient selection bias. In addition, consultation with medical oncologists usually occurred at 3–4 weeks after surgery, regardless of the individual condition of each patient. However, the advantage of this study is that the AC regimens were standardized into 2 types, and the surgical procedure was also standardized in the single institution.

In conclusion, early initiation of AC within 4 weeks does not affect survival rates in stage II/III gastric cancer.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Characteristics of S-1 adjuvant CTx patients

Click here to view

Supplementary Table 2
Characteristics of XELOX adjuvant CTx patients

Click here to view

Supplementary Table 3
Univariable and multivariable analysis of prognostic factors for RFS in S-1 adjuvant CTx patients

Click here to view

Supplementary Table 4
Univariable and multivariable analysis of prognostic factors for RFS in XELOX adjuvant CTx patients

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