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의학석사 학위논문

Effect of early adjuvant chemotherapy on survival of advanced gastric cancer patients: A propensity-score matched analysis

진행성위암환자에서 수술 후 항암요법의 시작 시기가 생존률에 미치는 영향: 성향점수매칭을 통한 분석

서울대학교 대학원
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Abstract

Effect of early adjuvant chemotherapy on survival of advanced gastric cancer patients: A propensity-score matched analysis

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Background: Generally, adjuvant chemotherapy (AC) should be started 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.

Methods: Between January, 2008 and December, 2014, 460 patients who received AC (S-1 or XELOX) for pathologic stage II/III gastric cancer at Seoul National University Bundang Hospital were included. Patients were divided into two groups: early AC administration (within 4 weeks) and late AC administration (more than 4 weeks). Patients who received AC early (n=174) were matched 1:1 with patients who received AC late (n=174) by propensity scoring to adjust for clinical differences. Three-year disease free survival (DFS) was evaluated according to the timing of AC.

Results: Three-year DFS 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, DFS was similar between early and late AC groups (HR=1.04, 95% CI=0.62–1.74, p=0.889). Pathologic stage and histological type were independent prognostic factors of DFS (HR=2.05, 95% CI=1.06–3.96, p=0.033; HR=2.61, 95% CI=1.42–4.80, p=0.002). Independent factors of late AC administration were old age and postoperative complications [odds ratio (OR)=2.78, 95% CI=1.57

–5.13, p<0.001; OR=7.99, 95% CI=3.59-21.33, p<0.001].

Conclusions: Early initiation of AC within 4 weeks does not affect survival rates of stage II/III gastric cancer patients.

Keywords: Stomach Neoplasms; Chemotherapy, Adjuvant; Survival Rate; Propensity Score

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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 pathological 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].

Since surgical resection itself can cause immunosuppression in patients, AC should be started as soon as possible after surgery to eradicate microscopic cancer cells. In 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, two 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. In pancreatic and colorectal cancers, several reports have highlighted the impact of LA on the initiation of AC [12, 13], but only one study has evaluated this issue in gastric cancer patients [14].

The aims of the present study were 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 pathological 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 checked 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 as follows: 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 matching was used to adjust for significant differences in the clinicopathologic characteristics of patients [age, sex, surgical approach, body mass index (BMI), American Society of Anesthesiologists (ASA) score, type of operation, extent of lymphadenectomy, hospital stay, postoperative complication, 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 more than 4 weeks [14]. Approval for the study was obtained from the Institutional Review Board of Seoul National University Bundang Hospital (B-1612/373-107).

Study Objectives

The primary objective of this study was disease free survival (DFS), defined as the time from surgery to the first recurrence of disease. In our institution, most patients received AC within 6 weeks according to current guidelines. Our hypothesis was that earlier AC administration (within 4 weeks) than that stipulated in the guidelines (within 6 weeks) would have a positive effect on DFS. In addition, the clinicopathologic characteristics and DFS 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 the 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 WHO classification, papillary, well differentiated, and moderately differentiated types were classified as the differentiated group, and poorly differentiated, mucinous, and poorly cohesive types were classified as the undifferentiated group.

Statistical analysis

Patients were classified into two groups according to the time from surgery to the initiation of AC as follows: early AC administration (within 4 weeks) and late AC administration (more than 4 weeks). The baseline characteristics of each group were compared using the chi square or Fisher's exact test. The Kaplan–Meier method was used to estimate the 3-year DFS 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, the multivariable Cox proportional hazards model was applied by incorporating the significant 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 $p<0.20$ 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 (http://cran.r-project.org/).

Results

Patient characteristics

A total 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 two groups. Patients older than 70 years were more likely to receive AC over 4 weeks ($p<0.001$). Postoperative complications of grade II or more 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 7days in the late group ($p<0.001$). The distribution of time to initiation of AC is shown in Fig. 1. The median interval between surgery and AC was 5 weeks (range, 2–9 weeks). 90% of patients (n=414) received AC within 6 weeks.

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

Table 1. Patient characteristics

Time to CTx	≤4 W (n = 174)	>4 W (n = 286)	p value
AGE, n (%)			<0.001
- <70 yr	157 (90.2)	213 (74.5)	
- ≥70 yr	17 (9.8)	73 (25.5)	
SEX, n (%)			0.459
- Female	53 (30.5)	98 (34.3)	
- Male	121 (69.5)	188 (65.7)	
Surgical approach, n (%)			0.165
- Laparoscopy	126 (72.4)	188 (65.7)	
- Open	48 (27.6)	98 (34.3)	
Mean body mass index (SD), kg/m^2	24.1 (2.9)	23.4 (3.1)	0.030
ASA performance status, n (%)			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, n (%)			0.105
- Distal gastrectomy	122 (70.1)	178 (62.2)	
- Total gastrectomy	52 (29.9)	108 (37.8)	
Combined resection: yes, n (%)	25 (14.4)	46 (16.1)	0.718
Extent of lymphadenectomy, n (%)			0.898
- D1+	27 (15.5)	47 (16.4)	
- D2	147 (84.5)	239 (83.6)	
Median retrieved lymph node (IQR)	58 (46-72)	59 (48-76)	0.831
Median hospital stay (IQR), day	6 (5-7)	7 (5-9)	<0.001
Complications within 30 day (Grade II or more): yes, n (%)	6 (3.4)	66 (23.1)	<0.001
Histological type, n (%)			1.000
- Differentiated	53 (30.5%)	88 (30.8%)	
- Undifferentiated	121 (69.5%)	198 (69.2%)	
Stage, n (%)			0.715
- II	75 (43.1)	117 (40.9)	
- III	99 (56.9)	169 (59.1)	
CTx regimen, n (%)			0.056
- S-1	111 (63.8)	208 (72.7)	
- XELOX	63 (36.2)	78 (27.3)	

CTx chemotherapy, *W* weeks, *IQR* interquartile range, *ASA* American Society of Anesthesiologists

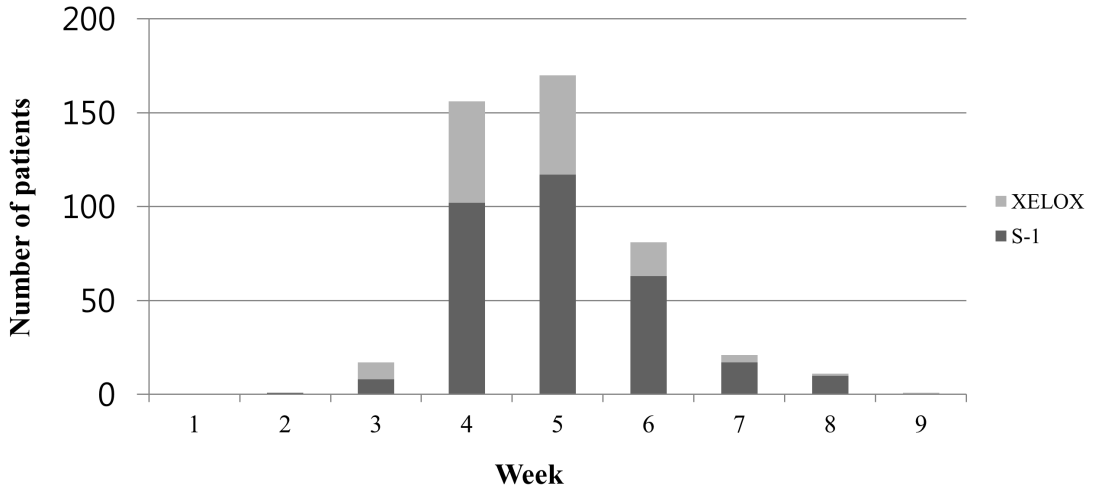

Figure 1. The distribution of time to initiation of adjuvant chemotherapy. The median interval between surgery and AC was 5 weeks (range, 2–9 weeks).

Table 2. Patient characteristics after propensity-score matching

Time to CTx	≤4 W (n = 174)	>4 W (n = 174)	p value
AGE, n (%)			1.000
- <70 yr	157 (90.2)	156 (89.7)	
- ≥70 yr	17 (9.8)	18 (10.3)	
SEX, n (%)			0.645
- Female	53 (30.5)	58 (33.3)	
- Male	121 (69.5)	116 (66.7)	
Surgical approach, n (%)			0.556
- Laparoscopy	126 (72.4)	120 (69.0)	
- Open	48 (27.6)	54 (31.0)	
Mean body mass index (SD), kg/m^2	24.1 (2.9)	23.7 (2.9)	0.263
ASA performance status, n (%)			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, n (%)			1.000
- Distal gastrectomy	122 (70.1)	123 (70.7)	
- Total gastrectomy	52 (29.9)	51 (29.3)	
Combined resection: yes, n (%)	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%)	
Median retrieved lymph node (IQR)	58 (46-72)	57.5 (47-74)	0.945
Median hospital stay (IQR), day	6 (5-7)	6 (5-7)	0.586
Complications within 30 day (Grade II or more): yes, n (%)	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)	

CTx chemotherapy, *W* weeks, *IQR* interquartile range, *ASA* American Society of Anesthesiologists

Survival outcomes

The median duration of follow-up in the total 460 patients was 48 months (range 3–101 months). The 3-year DFS 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) (Figure 2).

Factors associated with DFS 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 DFS [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; HR=2.83, 95% CI=1.55-5.17, p=0.001]. The timing of AC (>4 week, HR=1.04, 95% CI=0.62–1.74, p=0.889) was not significantly associated with DFS. 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; HR=2.61, 95% CI=1.42–4.80, p=0.002).

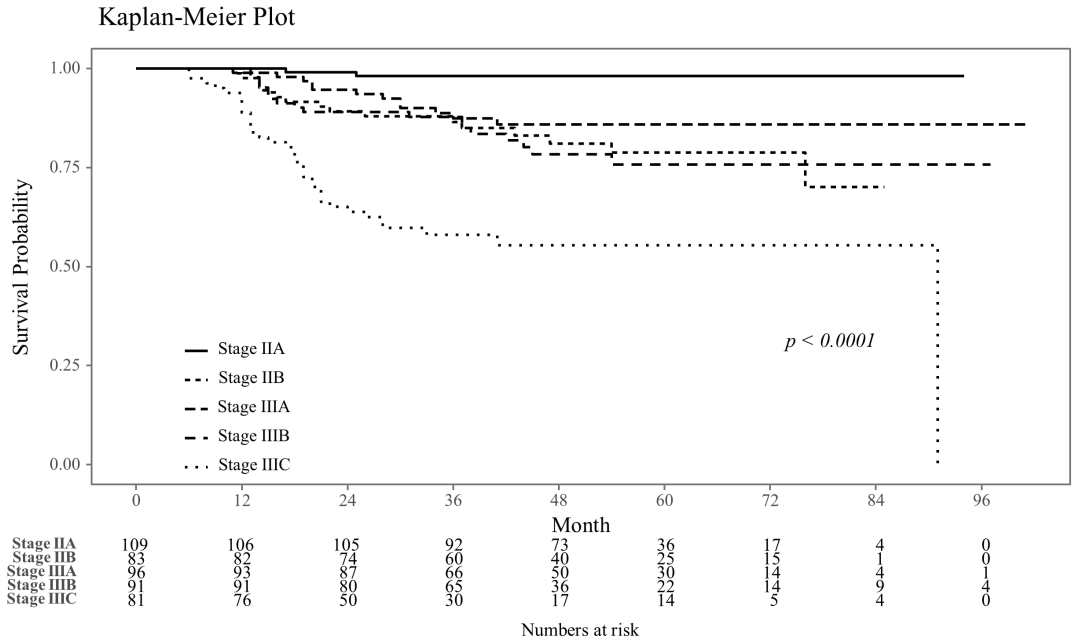

Figure 2. Disease free survival according to pathologic stage. The 3-year disease free survival was 98.1% in stage IIA (n=109), 85.0% in stage IIB (n=83), 87.4% in stage IIIA (n=96), 83.5% in stage IIIB (n=91), and 62.5% in stage IIIC (n=81).

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

	No. of patients	Univariable		Multivariable	
		HR (95% CI)	p value	HR (95% CI)	p value
AGE					
- <70 yr	313	1			
- ≥70 yr	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		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 day (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					
- ≤4 W	174	1		1	
- >4 W	174	1.04 (0.62–1.74)	0.889	1.05 (0.62-1.75)	0.866

DFS disease free survival, *HR* hazard ratio, *CI* confidence interval, *CTx*, Chemotherapy, *W* weeks

Subgroup analysis according to AC regimen

We divided patients into two 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 (Table 4, 5). However, patients older than 70 years or diagnosed with stage II were less likely to receive XELOX regimen. 86.5% of patients in the XELOX group (n=122) were diagnosed with stage III. Factors associated with DFS are shown in Table 6 and 7. In the S-1 group, stage III was the only independent prognostic factor of DFS (HR=2.25, 95% CI=1.19-4.24, p=0.012). In the XELOX group, there was no significant factor affecting DFS after multivariable analysis. The timing of AC was not significantly associated with DFS in either group.

Table 4. Characteristics of S-1 adjuvant chemotherapy patients

Time to CTx	≤4 W (n = 111)	>4 W (n = 208)	p value
AGE, n (%)			0.001
- <70 yr	99 (89.2)	149 (71.6)	
- ≥70 yr	12 (10.8)	59 (28.4)	
SEX, n (%)			0.398
- Female	33 (29.7)	73 (35.1)	
- Male	78 (70.3)	135 (64.9)	
Surgical approach, n (%)			0.678
- Laparoscopy	78 (70.3)	140 (67.3)	
- Open	33 (29.7)	68 (32.7)	
Mean body mass index (SD), kg/m^2	24.2 (2.8)	23.5 (3.0)	0.021
ASA performance status, n (%)			0.438
- 1	60 (54.1)	105 (50.5)	
- 2	41 (36.9)	90 (43.3)	
- 3	10 (9.0)	13 (6.2)	
Type of operation, n (%)			0.730
- Distal gastrectomy	76 (68.5)	137 (65.9)	
- Total gastrectomy	35 (31.5)	71 (34.1)	
Combined resection: yes, n (%)	20 (18.0)	29 (13.9)	0.424
Extent of lymphadenectomy, n (%)			1.000
- D1+	20 (18.0)	38 (18.3)	
- D2	91 (82.0)	170 (81.7)	
Median retrieved lymph node (IQR)	56 (42.5-70.5)	57 (47-69.5)	0.501
Median hospital stay (IQR), day	6 (5-7)	6 (5-8)	0.021
Complications within 30 day (Grade II or more): yes, n (%)	5 (4.5%)	48 (23.1%)	<0.001
Histological type, n (%)			0.572
- Differentiated	40 (36.0)	67 (32.2)	
- Undifferentiated	71 (64.0)	141 (67.8)	
Stage, n (%)			0.587
- II	63 (56.8)	110 (52.9)	
- III	48 (43.2)	98 (47.1)	

CTx chemotherapy, *W* weeks, *IQR* interquartile range, *ASA* American Society of Anesthesiologists

Table 5. Characteristics of XELOX adjuvant chemotherapy patients

Time to CTx	≤4 W (n = 63)	>4 W (n = 78)	p value
AGE, n (%)			0.138
- <70 yr	58 (92.1)	64 (82.1)	
- ≥70 yr	5 (7.9)	14 (17.9)	
SEX, n (%)			1.000
- Female	20 (31.7)	25 (32.1)	
- Male	43 (68.3)	53 (67.9)	
Surgical approach, n (%)			0.094
- Laparoscopy	48 (76.2)	48 (61.5)	
- Open	15 (23.8)	30 (38.5)	
Mean body mass index (SD), kg/m^2	23.8 (2.9)	23.4 (3.5)	0.528
ASA performance status, n (%)			0.081
- 1	39 (61.9)	35 (44.9)	
- 2	23 (36.5)	38 (48.7)	
- 3	1 (1.6)	5 (6.4)	
Type of operation, n (%)			0.021
- Distal gastrectomy	46 (73.0)	41 (52.6)	
- Total gastrectomy	17 (27.0)	37 (47.4)	
Combined resection: yes, n (%)	5 (7.9)	17 (21.8)	0.043
Extent of lymphadenectomy, n (%)			1.000
- D1+	7 (11.1)	9 (11.5)	
- D2	56 (88.9)	69 (88.5)	
Median retrieved lymph node (IQR)	65 (52.5-79.5)	70 (50-89)	0.371
Median hospital stay (IQR), day	6 (5-7)	7 (6-12)	<0.001
Complications within 30 day (Grade II or more): yes, n (%)	1 (1.6)	18 (23.1)	0.001
Histological type, n (%)			0.503
- Differentiated	40 (36.0)	67 (32.2)	
- Undifferentiated	71 (64.0)	141 (67.8)	
Stage, n (%)			0.135
- II	12 (19.0)	7 (9.0)	
- III	51 (81.0)	71 (91.0)	

CTx chemotherapy, *W* weeks, *IQR* interquartile range, *ASA* American Society of Anesthesiologists

Table 6. Univariable and multivariable analysis of prognostic factors for DFS in S-1 adjuvant chemotherapy patients

	No. of patients	Univariable		Multivariable	
		HR (95% CI)	p value	HR (95% CI)	p value
AGE					
- <70 yr	248	1			
- ≥70 yr	71	1.54 (0.79–2.99)	0.204		
SEX					
- Female	106	1			
- Male	213	0.92 (0.50–1.70)	0.799		
Surgical approach					
- Laparoscopy	218	1		1	
- Open	101	1.77 (0.99–3.16)	0.054	1.46 (0.80–2.64)	0.216
Body mass index		0.95 (0.86–1.05)	0.332		
Type of operation					
- Distal gastrectomy	213	1			
- Total gastrectomy	106	1.11 (0.60–2.03)	0.744		
Complications within 30 day (Grade II or more)					
- No	266	1			
- Yes	53	0.72 (0.31–1.70)	0.455		
Histological type					
- Differentiated	107	1			
- Undifferentiated	212	1.20 (0.64–2.24)	0.575		
Stage					
- II	173	1		1	
- III	146	2.45 (1.32–4.55)	0.004	2.25 (1.19-4.24)	0.012
Time to CTx					
- ≤4 W	111	1		1	
- >4 W	208	1.45 (0.76–2.77)	0.254	1.43 (0.75-2.72)	0.278

DFS disease free survival, *HR* hazard ratio, *CI* confidence interval, *CTx* Chemotherapy, *W* weeks

Table 7. Univariable and multivariable analysis of prognostic factors for DFS in XELOX adjuvant chemotherapy patients

	No. of patients	Univariable		Multivariable	
		HR (95% CI)	p value	HR (95% CI)	p value
AGE					
- <70 yr	122	1			
- ≥70 yr	19	1.59 (0.70–3.62)	0.269		
SEX					
- Female	45	1			
- Male	96	0.96 (0.48–1.91)	0.904		
Surgical approach					
- Laparoscopy	96	1		1	
- Open	45	1.77 (0.92–3.40)	0.086	1.77 (0.92–3.40)	0.086
Body mass index		1.02 (0.92–1.12)	0.747		
Type of operation					
- Distal gastrectomy	87	1		1	
- Total gastrectomy	54	1.85 (0.97–3.53)	0.061	1.85 (0.97–3.53)	0.061
Complications within 30 day (Grade II or more)					
- No	122	1			
- Yes	19	0.97 (0.38–2.50)	0.957		
Histological type					
- Differentiated	34	1		1	
- Undifferentiated	107	1.79 (0.74–4.29)	0.194	1.79 (0.74–4.29)	0.194
Stage					
- II	19	1			
- III	122	2.08 (0.64–6.77)	0.225		
Time to CTx					
- ≤4 W	63	1		1	
- >4 W	78	1.12 (0.58–2.15)	0.741	1.12 (0.58-2.15)	0.741

DFS disease free survival, *HR* hazard ratio, *CI* confidence interval, *CTx* Chemotherapy, *W* weeks

The factors associated with late initiation of AC

The factors associated with late initiation of AC (over 4 weeks after surgery) were analyzed by logistic regression (Table 8). In multivariable analysis, independent factors were old age and postoperative complications [odds ratio (OR)=2.78, 95% CI=1.57–5.13, $p<0.001$; OR=7.99, 95% CI=3.59-21.33, $p<0.001$].

Table 8. Univariable and multivariable analysis of logistic regression analysis of late initiation of adjuvant chemotherapy

	No. of patients	Univariable		Multivariable	
		OR (95% CI)	p value	OR (95% CI)	p value
AGE					
- <70 yr	370	1		1	
- ≥70 yr	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		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 day (Grade II or more)					
- No	388	1		1	
- Yes	72	8.4 (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		

OR odds ratio, *CI* confidence interval

Discussion

AC after gastrectomy with D2 dissection is the standard treatment for advanced gastric cancer in Eastern countries. The Japanese ACTS-GC trial showed a survival benefit following 1 year of postoperative administration of S-1 monotherapy [4], and the 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.

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 guidelines. 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 DFS. 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 AC with respect to DFS 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 the opposite results. One of the largest series evaluating the impact of AC in colorectal cancer showed that a delay in the initiation 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. 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 two treatment groups [20]. In later studies, two Korean reports demonstrated the effect of AC timing. Park et al. reported worse DFS and OS rates in patients who initiated AC after 8 weeks [5]. 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. reported that patients who started AC within 4 weeks had better outcomes [21]. In Japan, Yamamoto et al. suggested that beginning S-1

within 6 weeks of surgery is associated with a favorable prognosis [22]. By contrast, Fujitani et al. showed that time to initiation S-1 within 6 weeks does not have an impact on survival outcome [23]. 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 DFS 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. 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 [6].

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 of patients were diagnosed with stage III, there was also no significant difference between two timing cohort. These results suggest that enough time should be provided after surgery to allow for recovery of bowel function and intestinal absorption. The recovery period is very 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. 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 study of laparoscopic vs. open surgery [13]. 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 OA 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 two types, and the surgical procedure was also standardized in the single institution.

In conclusion, an early initiation of AC within 4 weeks does not affect survival rates in stage II/III gastric cancer. The advantages of LA may not persist after discharge and may disappear 4 weeks after surgery.

Compliance with ethical standards

Conflict of interest

The authors were awarded a research grant from Seoul National University Bundang Hospital (Grant No.: 02-2016-024).

Ethical statement

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.

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국문초록

연구배경: 이론적으로 수술 후 항암요법은 미세 암세포의 박멸을 위해 수술 후 가능한 빨리 시행해야만 한다. 본 연구에서는 진행성위암환자에서 수술 후 항암요법의 시작 시기가 생존률에 미치는 영향을 분석하였다.

연구방법: 2008년 1월부터 2014년 12월까지 분당서울대학교병원에서 진행성 위암으로 수술을 받은 후 항암요법(S-1 혹은 XELOX)을 받은 460명의 환자를 대상으로 연구를 진행하였다. 연구대상자는 4주 이전에 항암요법을 시행한 군과 4주 이후에 항암요법을 시행한 군으로 나누었다. 항암요법을 일찍 시작한 174명의 환자들을 항암요법을 늦게 시작한 환자들과 성향점수로 매칭하였다. 3년 무병 생존률은 항암요법의 시기에 따라 분석하였다.

결과: 3년 무병 생존률은 IIA기에서 98.1%, IIB기에서 85.0%, IIIA기에서 87.4%, IIIB기에서 83.5%, IIIC기에서 62.5%였다. 성향점수 매칭한 결과, 무병 생존률은 항암요법의 시기와 관련성을 보이지 않았다. 수술 후 병기와 조직학적 분류가 무병생존률의 독립적인 예후 인자였다. 항암요법의 시작 시기와 관계된 독립적 요인은 연령과 수술 후 합병증이었다.

결론: 수술 후 4주 이내에 항암요법을 시작하는 것은 생존률에 영향을 미치지 않는다.