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Original Article

Who Can Perform Adjuvant Chemotherapy Treatment for Gastric Cancer? A Multicenter Retrospective Overview of the Current Status in Korea

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ABSTRACT

Purpose: To investigate the current status of adjuvant chemotherapy (AC) regimens in Korea and the difference in efficacy of AC administered by surgical and medical oncologists in patients with stage II or III gastric cancers.
Materials and Methods: We performed a retrospective observational study among 1,049 patients who underwent curative resection and received AC for stage II and III gastric cancers between February 2012 and December 2013 at 29 tertiary referral university hospitals in Korea. To minimize the influence of potential confounders on selection bias, propensity score matching (PSM) was used based on binary logistic regression analysis. The 3-year disease-free survival (DFS) rates were compared between patients who received AC administered by medical oncologists or surgical oncologists.
Results: Between February 2012 and December 2013 in Korea, the most commonly prescribed AC by medical oncologists was tegafur/gimeracil/oteracil (S-1, 47.72%), followed by capecitabine with oxaliplatin (XELOX, 16.33%). After performing PSM, surgical oncologists (82.74%) completed AC as planned more often than medical oncologists (75.9%), with statistical significance (P=0.036). No difference in the 3-year DFS rates of stage II (P=0.567) or stage III (P=0.545) gastric cancer was found between the medical and surgical oncologist groups.
Conclusions: S-1 monotherapy and XELOX are a main stay of AC, regardless of whether the prescribing physician is a medical or surgical oncologist. The better compliance with AC

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

by surgical oncologists is a valid reason to advocate that surgical oncologists perform the treatment of AC for stage II or III gastric cancers.

Keywords: Gastric cancer; Adjuvant chemotherapy

INTRODUCTION

Although gastric cancer has showed a decreased prevalence in the past decade, it remains the third leading cause of cancer-related deaths [1]. This mortality might be owing to the still-high recurrence rate in advanced cases [2,3]. Therefore, adjuvant chemotherapy (AC) is an important component of the treatment modalities for advanced gastric cancer (AGC) [4,5]. Prior to 2013, various chemotherapeutic regimens were applied in AC for stage II and III gastric cancer in Korea. However, based on the results of two prominent randomized controlled trials demonstrating the efficacy of AC, tegafur/gimeracil/oteracil (known as S-1) chemotherapy or capecitabine with oxaliplatin (XELOX) chemotherapy are the regimens currently administered as standard treatment [6,7]. To align with this paradigm, the Korean government began reimbursement for S-1 chemotherapy on January 1, 2013. The XELOX regimen was also included in the national reimbursement program on March 1, 2013. These policies have strongly affected the trend of AC in Korea because both S-1 monotherapy and the XELOX regimen satisfy conditions of economic reasonability as well as oncological legitimacy.

This phenomenon implies that the chemotherapeutic regimen is not determined by the personal assumption of the oncologists after the governmental reimbursements have been provided for S-1 or XELOX regimen. Along with this transition, some important issues have arisen in the clinical field of AGC. Above all, the question of who can properly perform AC was raised. In Korea, the subject who performs chemotherapy differs between institutes, because their infrastructure is also diverse. Surgical oncologists prescribe chemotherapeutic drugs in some institutions whereas in others, medical oncologists prescribe these medications.

Another issue involves the necessity of a nationwide survey in which the current status of AC can be objectively reviewed. Although many researchers have expected S-1 or XELOX to displace other chemotherapeutic regimens, no observational studies to investigate the current status of AC have been conducted in Korea. Therefore, our study group, the Surgical Oncology Forum (SOF) study group, performed a nationwide survey regarding AC for AGC. Our study results are expected to provide an answer to the question of who can most appropriately administer AC for patients with stage II or III gastric cancer.

MATERIALS AND METHODS

Patients and study design

This trial was conducted at 29 tertiary referral university hospitals in Korea. We performed a retrospective study among 1,898 patients who underwent curative resection and received AC for AGC without adjacent organ invasion between February 2012 and December 2013. Patients' medical records in each hospital and survival status were retrospectively reviewed in May 2016. Patients who fulfilled the following criteria were eligible for inclusion in this study: 1) histologically proven adenocarcinoma; 2) patients who underwent gastrectomy with D2 lymphadenectomy and R0 surgery; 3) patients aged between 20 and 75 years; 4) no

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preoperative chemotherapy, radiotherapy, or immunotherapy; 5) patients with pathologic stage II or stage III gastric cancer receiving XELOX or S-1 chemotherapy within 8 weeks after surgery; 6) no synchronous or metachronous malignancy; and 7) more than 15 lymph nodes examined in the final pathologic evaluation. According to the eligibility, we excluded 810 patients who failed to meet these criteria. Another 39 patients were excluded because we could not find the records indicating which department had administered adjuvant chemotherapy for these patients. Finally, data of 1,049 patients were retrospectively reviewed for comparative analysis.

To compare the oncologic outcomes of AC administered by surgical and medical oncologists, the 3-year disease-free survival (DFS) rate was determined. Stages of gastric adenocarcinoma were determined according to tumor, node, and metastasis (TNM) classification of malignant tumors established in the 7th edition of the American Joint Committee on Cancer (AJCC) staging manual [8]. To analyze the effect of each variable on recurrence while reducing selection bias caused by unbalanced covariates in an observational study, we performed propensity score matching (PSM) in which the parameters were patients' age, sex, American Society of Anesthesiologists (ASA) physical status classification score, extent of gastrectomy, operative method, T stage, N stage, AJCC 7th stage, retrieved lymph nodes, tumor size, Lauren's classification, lymphatic invasion, vascular invasion, and AC regimens.

Approval to perform research on human subjects in this study was provided by the Institutional Review Board (IRB) of each hospital (IRB No. ED14245 at the institution of the corresponding author).

Chemotherapeutic regimens

When administering S-1 monotherapy, patients with a body surface area less than 1.25 m^2 received 80 mg daily; those with body surface area 1.25 m^2 or more but less than 1.5 m^2 received 100 mg daily; and patients with body surface area 1.5 m^2 or more received 120 mg daily for 4 weeks, followed by 2 weeks of no chemotherapy. A total of 8 cycles (12 months) were needed for S-1 monotherapy.

The XELOX regimen consisted of 3-week cycles of oral capecitabine (1000 mg/m^2 twice daily on days 1 to 14 of each cycle) plus intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle). It took 8 cycles (6 months) to complete the XELOX chemotherapy.

Follow-up

For follow-up of the clinical outcomes, history taking, physical examination, serum tumor marker evaluation, simple chest radiograph, gastroduodenoscopy, and abdominal computed tomography (CT) scan were performed at intervals of 3–6 months. When signs or symptoms indicated a possible recurrence or development of a new gastric cancer, investigations were then performed to determine whether the patient was disease free. When necessary, abdominal ultrasonic examination, chest CT scan, whole body bone scan, and positron emission tomography scan were additionally performed. The 3-year DFS rates were retrospectively investigated using medical records from each hospital.

Statistical analysis

Clinicopathologic characteristics between patients who received S-1 chemotherapy (S-1 group) and XELOX chemotherapy (XELOX group) were compared using a 2-sample t-test for quantitative variables and χ^2 test for qualitative variables. To minimize the influence of

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potential confounders on selection bias, PSM was used based on binary logistic regression. Confounding variables were entered into the propensity score model, including age, sex, ASA score, extent of gastrectomy, operation method, T stage, N stage, stage according to the 7th AJCC staging system, retrieved lymph nodes, tumor size, Lauren's classification, lymphatic invasion, and vascular invasion. One-to-three matching between groups was performed using the nearest-neighbor matching method. In PSM, the value of caliper size was 0.1 and the seed number was 34567 in PSM. For nominal values, the χ^2 or Fisher's exact tests were used after PSM.The primary endpoint of this study was the 3-year DFS rate. DFS was calculated from the operation date to the date of last follow-up, the date of recurrence, or the date of death from any cause. The Kaplan-Meier method was used to estimate the 3-year DFS rate, with 95% confidence intervals (CIs). Log-rank or Breslow tests were used to compare DFS rates between patients who received AC administered by a medical oncologist (medical oncologist group) or by a surgical oncologist (surgical oncologist group). The hazard ratio (HR) for recurrence in the surgical oncologist group, using the medical oncologist group as reference, and 95% CIs were calculated using a Cox proportional hazards model.

All data analyses were conducted by a medical statistician using SPSS software for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided. Statistical significance was considered with $P<0.05$.

RESULTS

Baseline clinical data of regimens administered by medical and surgical oncologists

The kinds of AC regimen for stage II and III gastric cancers are presented in **Fig. 1**, according to the department that prescribed chemotherapy. Based on the regimen data before and after approval of AC by Korean insurance in 2013, both medical and surgical oncologists prescribed numerous regimens. Of these, the most commonly prescribed regimen by medical oncologists was S-1 (47.72%) followed by XELOX (16.33%). Surgical oncologists also mostly prescribed S-1 (54.45%), followed by doxifluridine (15.74%) and XELOX (12.51%).

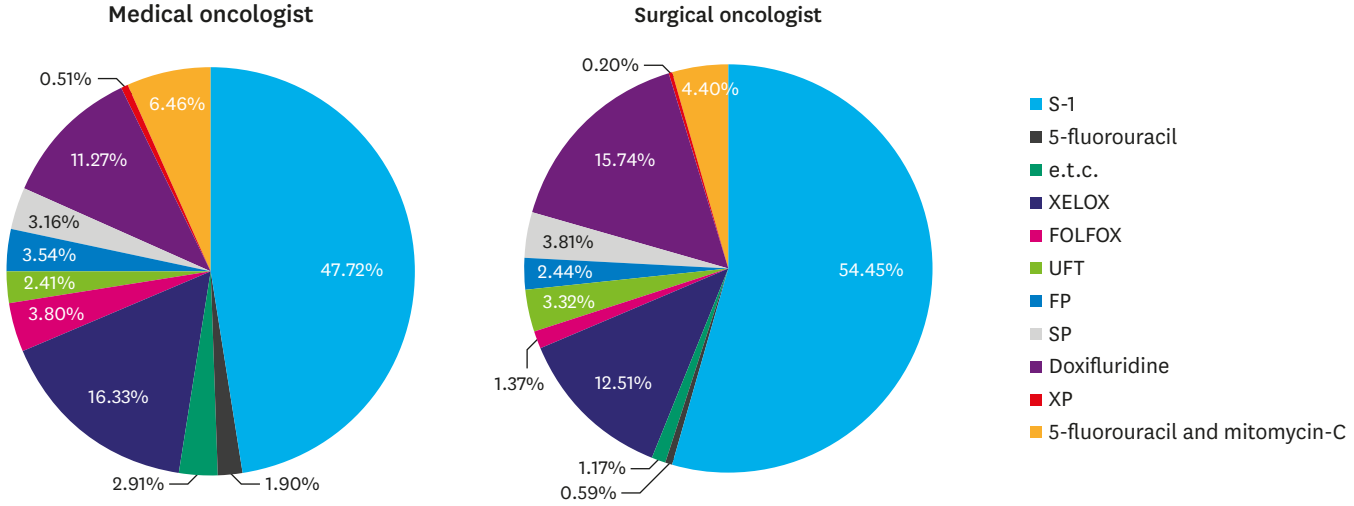

Fig. 1. Regimens of adjuvant chemotherapy for stage II and III gastric cancer, according to the prescribing department.
S-1 = tegafur/gimeracil/oteracil; FOXFOX = 5-fluorouracil, folinic acid, and oxaliplatin; UFT = tegafur/uracil; XP = capecitabine and cisplatin; XELOX = capecitabine and oxaliplatin; FP = 5-fluorouracil and cisplatin; SP = S-1 and cisplatin.

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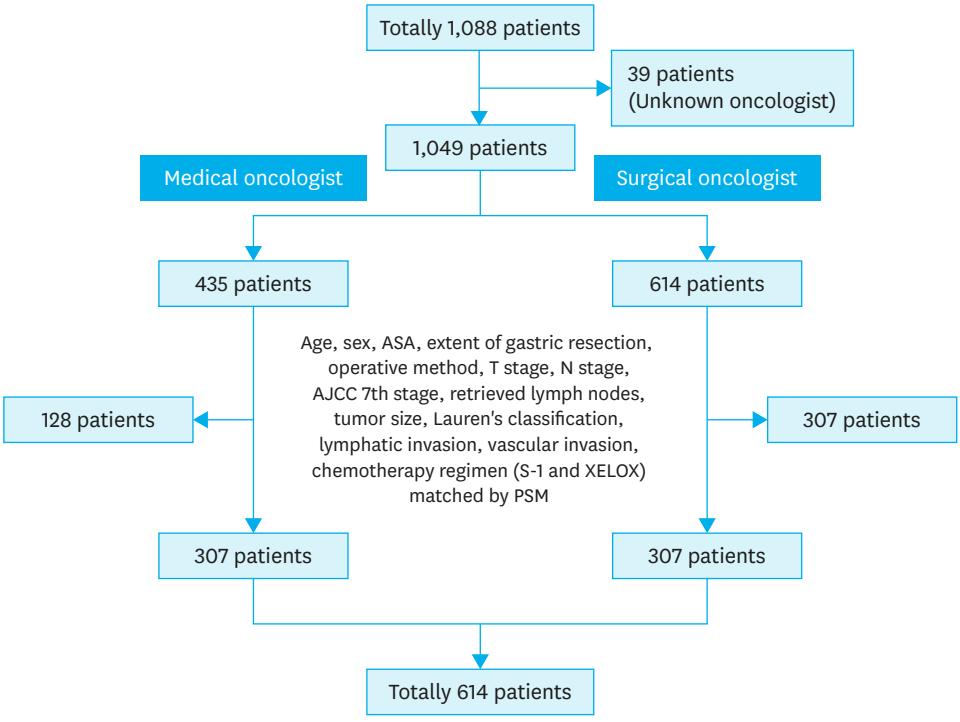

Fig. 2. Flowchart of PSM.
PSM = propensity score matching; ASA = American Society of Anesthesiologists; T = tumor; N = node; AJCC = American Joint Committee on Cancer; S-1 = tegafur/gimeracil/oteracil; XELOX, capecitabine and oxaliplatin.

PSM analysis

PSM was performed for 1,049 patients after excluding 39 patients for whom the prescribing oncology department was unknown (**Fig. 2**). AC regimens were selected for those patients who were prescribed only two regimens, S-1 and XELOX. After PSM, 307 patients were assigned to each group (medical oncologist and surgical oncologist groups). As shown in **Table 1**, surgical oncologists (82.74%) completed AC as planned more often than medical oncologists (75.9%), with statistical significance (P=0.036).

DFS after propensity score matching

After PSM, no difference was found in the 3-year DFS rates in stage II (P=0.567) or stage III cancers (P=0.545) between the medical and surgical oncologist groups (**Fig. 3**). In addition, there was no significant difference between the 2 oncologist groups with respect to HR in stage II and III cancers (**Table 2**).

DISCUSSION

In the present study, we found that the regimens of AC that were prescribed by medical and surgical oncologists in Korea from February 2012 to December 2013 were slightly different. In addition, the characteristics of patients receiving AC differed in the medical and surgical oncologist groups. After PSM analysis, surgical oncologists showed better compliance with AC than did medical oncologists; however, the 3-year DFS rates were not significantly different between them. The differences between AC regimens may have affected compliance with the AC plan in the 2 groups.

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Table 1. Characteristics of patients included in the medical or surgical oncologist groups, after propensity score matching analysis

Variables	Medical oncologists (n=307)	Surgical oncologists (n=307)	P-value
Age (y)	57.76±10.19	58.36±10.49	0.475
Sex			0.448
Male	202 (65.8)	193 (62.87)	
Female	105 (34.2)	114 (37.13)	
BMI	22.94±3.01	22.7±3.28	0.351
ASA score			0.795
1	127 (41.37)	126 (41.04)	
2	155 (50.49)	154 (50.16)	
3	25 (8.14)	26 (8.47)	
4	0 (0)	1 (0.33)	
Extent of resection			0.672
Distal gastrectomy	198 (64.5)	203 (66.12)	
Total gastrectomy	109 (35.5)	104 (33.88)	
Operation method			0.170
Open	259 (84.36)	246 (80.13)	
Laparoscopy	48 (15.64)	61 (19.87)	
T stage			0.294
T1	13 (4.23)	13 (4.23)	
T2	34 (11.07)	49 (15.96)	
T3	155 (50.49)	154 (50.16)	
T4	105 (34.2)	91 (29.64)	
N stage			0.911
N0	60 (19.54)	67 (21.82)	
N1	67 (21.82)	67 (21.82)	
N2	75 (24.43)	73 (23.78)	
N3	105 (34.2)	100 (32.57)	
AJCC 7th stage			0.374
Stage II	138 (44.95)	149 (48.53)	
Stage III	169 (55.05)	158 (51.47)	
Retrieved lymph nodes	46.52±18.19	48.75±18.88	0.135
Tumor size	5.76±3.01	5.55±3.17	0.411
Lauren classification			0.074
Intestinal	130 (42.35)	157 (51.14)	
Diffuse	145 (47.23)	127 (41.37)	
Mixed	32 (10.42)	23 (7.49)	
Lymphatic invasion			0.499
Yes	112 (36.48)	104 (33.88)	
No	195 (63.52)	203 (66.12)	
Vascular invasion			0.284
Yes	213 (69.38)	225 (73.29)	
No	94 (30.62)	82 (26.71)	
Chemotherapy Regimens			0.167
S-1	220 (71.66)	235 (76.55)	
XELOX	87 (28.34)	72 (23.45)	
Completion of planned chemotherapy			0.036*
Yes	233 (75.9)	254 (82.74)	
No	74 (24.1)	53 (17.26)	

BMI = body mass index; ASA = American Society of Anesthesiologists; T = tumor; N = node; AJCC = American Joint Committee on Cancer; S-1 = tegafur/gimeracil/oteracil; XELOX = capecitabine and oxaliplatin.
*Statistically significant with P<0.05.

There are 2 prominent prospective studies on S-1 and XELOX, which indicate ACTS GC and CLASSIC trials [5,7]. The completion rates of cycles in the S-1 and XELOX regimens were 65.8% and 67%, respectively. These two studies showed no difference in completion rates between these 2 regimens. The results for 5-year overall survival (OS) and 5-year DFS of the S-1 regimen trial were 71.7% and 65.4%, respectively. The results in the XELOX regimen trial were 78% and 68% for 5-year OS and 5-year DFS, respectively. However, the two studies were

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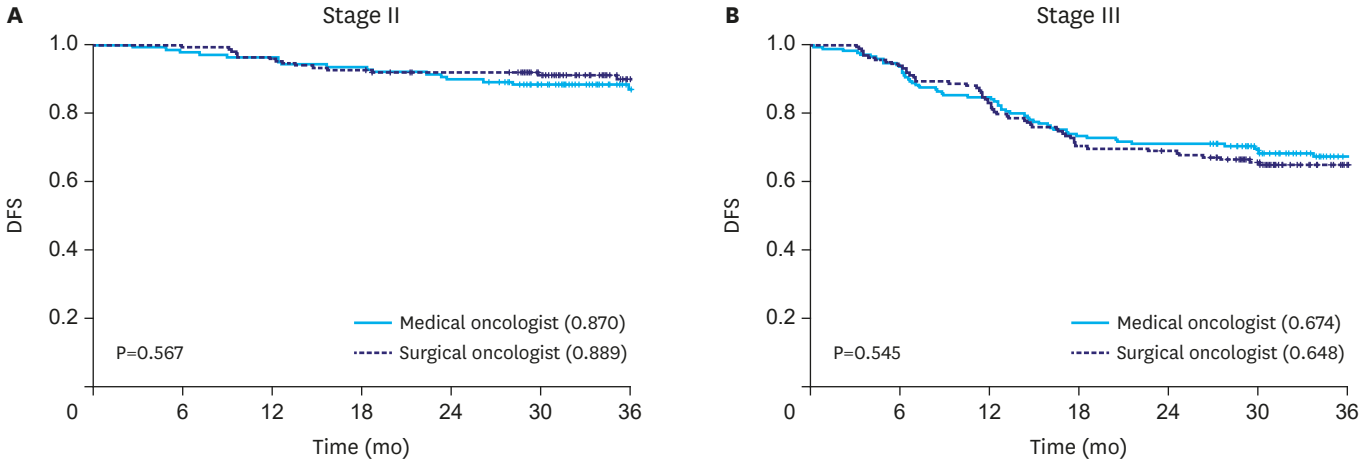

Fig. 3. DFS in patients with gastric cancer, analyzed by department administering adjuvant chemotherapy.
DFS = disease-free survival.

not head-to-head comparisons between the S-1 and XELOX regimens and thus cannot be considered a direct comparison of the completion and survival rates in these 2 regimens.

Recently, a retrospective single-center study reported that the 3-year DFS was higher in the S-1 treatment group than in the XELOX group (66.6% vs. 59.1%, respectively); however, the difference was not statistically significant (P=0.636) [9]. The 3-year OS in the S-1 and XELOX groups was 75.6% and 69.6%, respectively, with no significant difference (P=0.495). For patients with stage IIIC disease, the 3-year OS was 55.2% in the XELOX group and 39.0% in the S-1 group (HR, 0.50; 95% CI, 0.23±1.10; P=0.075). The findings of that study revealed that adjuvant XELOX therapy was not superior to S-1 for stage III gastric cancer in terms of survival, although there was a statistically non-significant trend toward better survival in stage IIIC gastric cancer. In a multivariate analysis of our study, the N stage (HR, 5.639; 95% CI, 1.297±24.522; P=0.021) and cycle completion as planned (HR, 5.734; 95% CI, 3.007±10.936; P<0.001) were independent predictors of OS.

Several reports have documented the importance of compliance with chemotherapy. In the REductive Gastrectomy for Advanced Tumor in Three Asian countries (REGATTA) trial, a significant interaction between treatment effect and tumor location was found [10]. Gastrectomy plus chemotherapy was associated with significantly worse OS in patients with upper-third tumors. The median number of chemotherapy cycles was reduced after gastrectomy in patients with upper-third tumors to half that of chemotherapy alone. Poor compliance with chemotherapy after gastrectomy accounted for worse OS than with chemotherapy alone. In addition, compliance with chemotherapy after gastrectomy was found

Table 2. Comparison of HRs in the surgical oncologist group, with the medical oncologist group as reference, for recurrence of gastric cancer

Stages	HR	95% CI	P-value
All	1.002	0.723–1.390	0.988
Stage II			
Stage IIA	1.870	0.571–6.122	0.301
Stage IIB	0.535	0.216–1.326	0.177
Stage III			
Stage IIIA	1.228	0.550–2.741	0.617
Stage IIIB	1.616	0.822–3.176	0.164
Stage IIIC	0.711	0.398–1.269	0.248

HR, hazard ratio; CI, confidence interval.

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to be inversely associated with the amount of postoperative body weight loss, which is generally more evident after total gastrectomy than after any other type of gastrectomy [11]. One study reported the risk factors for poor compliance with adjuvant S-1 chemotherapy for gastric cancer [12]. Of 359 patients, 252 (70.2%) continued adjuvant S-1 until 1 year after surgery. Older age (>65 years) and postoperative complications (Clavien-Dindo grade III or higher) correlated significantly with low compliance in S-1 for 12 months (P=0.008 and P=0.042, respectively). However, the type of gastrectomy or body weight loss at 1 month after surgery did not affect either 12-month compliance or the cumulative continuation rate of S-1. This study showed that older age and postoperative infectious complications were independent risk factors for poor compliance with adjuvant S-1 chemotherapy for gastric cancer.

Various complications that can occur after gastrectomy or during AC should be well managed to maximize AC compliance. The latest Japanese guidelines recommend that AC is to be started within 6 weeks of surgery after sufficient recovery [13]. Most prospective trials for gastric cancers recommend initiation of AC within 6–8 weeks of surgical intervention [5,7]. During that period, treatment of the symptoms of post-gastrectomy syndrome (PGS) occurring immediately after surgery is also necessary. Therefore, when administering AC, chemotherapy-related adverse events caused by each regimen and various symptoms of PGS after surgery should be fully noted and treated effectively, regardless of who administered AC [14,15].

Diarrhea occurring during AC may be due to side effects of chemotherapy or it may be a symptom of dumping syndrome shortly after surgery [16,17]. It is important to know whether diarrhea persists after stopping the chemotherapy or after eating a large quantity of food or carbohydrates. The causes of diarrhea should be treated after an accurate diagnosis. Vomiting may be directly related to the side effects of chemotherapy, or it may be caused by paralytic ileus or mechanical obstruction after surgery [18,19]. If vomiting continues, a thorough physical examination should be carried out. In addition, imaging studies should be conducted when necessary. Symptoms of peripheral neuropathy such as a tingling sensation in the hands or feet may be an adverse effect of chemotherapy or may be caused by megaloblastic anemia after total gastrectomy [20,21]. Megaloblastic anemia improves with administration of vitamin B-12, whereas peripheral neuropathy from adverse effects does not. In addition, peripheral neuropathy after oxaliplatin administration deteriorates during cold exposure. It is necessary to identify the precise cause of peripheral neuropathy symptoms so as to provide appropriate treatment.

In Korea, multidisciplinary approaches to the treatment of gastric cancers are emerging. The staffing situation and treatment system may differ among institutions. The choice of which medical professional should prescribe AC is best made after consideration of the individual staffing situation at each institution. Medical oncologists who administer AC should always be vigilant for symptoms of PGS, and surgical oncologists should be familiar with chemotherapy-related side effects. For the best outcomes, it is critical to correctly perform differential diagnosis and treatment when symptoms occur during the administration of AC in the immediate post-gastrectomy period.

In conclusion, we found that between February 2012 and December 2013, S-1 was prescribed the most in Korea, followed by XELOX. This tendency is in line with the current oncology consensus, which corresponds to 2 recent randomized controlled trials; therefore, S-1 monotherapy and XELOX remain a main stay of AC, regardless of the prescribing oncologist. This may be the reason why the 3-year DFS did not differ between patients receiving AC administered by medical and surgical oncologists in our multicenter study. Furthermore,

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our data showed better compliance with AC by surgical oncologists, although this result did not reach the prognostic difference for stage II or III disease; this would be one reason to advocate that AC for AGC given by surgical oncologists is not inferior to that administered by medical oncologists.

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