Does the timing of adjuvant chemotherapy for gastric cancer influence patient outcome?

SEOK YUN KANG[1,*], MI SUN AHN[1,*], GA WON SONG[1], YONG WON CHOI[1], HYUN WOO LEE[1], SEONG HYUN JEONG[1], JOON SEONG PARK[1], YONG KWAN CHO[2], SANG UK HAN[2], SEUNG SOO SHEEN[3], JAE HO HAN[4] & JIN-HYUK CHOI[1]

[1]*Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, Korea,* [2]*Department of Surgery, Ajou University School of Medicine, Suwon, Korea,* [3]*Section of Clinical Epidemiology and Biostatistics in Clinical Trial Center, Ajou University School of Medicine, Suwon, Korea and* [4]*Department of Pathology, Ajou University School of Medicine, Suwon, Korea*

To the Editor,

Gastric cancer is the second most common cause of cancer-related deaths worldwide, despite a gradual decrease in incidence [1]. Although curative resection is the standard treatment for patients with locally advanced gastric cancer, it is associated with a high recurrence rate and poor survival [2]. Adjuvant chemotherapy has now become a standard therapy for patients with stage II/III gastric cancer, as demonstrated by the results of several meta-analyses and recent phase III trials [2–5]. Nevertheless, there is no report about the optimal timing for starting adjuvant chemotherapy for gastric cancer after surgical resection.

According to population-based or cohort studies and meta-analyses of colorectal and breast cancer, a delay in the start of adjuvant chemotherapy is usually associated with poor cancer-specific and overall survival (OS) rates, indicating that early initiation of adjuvant therapy results in better outcomes [6–12].

Patients and methods

Study population

We retrospectively identified patients treated with 5-fluorouracil (5-FU), mitomycin-C (MMC) and polysaccharide-K (PSK) (FM-PSK) adjuvant chemotherapy following curative resection at Ajou University Hospital, Suwon, Korea, between November 1996 and December 2004.

The criteria for eligibility were histologically proven gastric adenocarcinoma, curative resection [13], extended lymph node dissection (D2 dissection), and pathological stage II or III according to the 7th edition of American Joint Committee on Cancer (AJCC).

This research protocol was approved by the Institutional Review Board of Ajou University Hospital.

Adjuvant chemotherapy

In this study, data on all the patients who received FM-PSK chemotherapy with duration of 24 weeks

*Seok Yun Kang and Mi Sun Ahn contributed equally to this work as first authors.
Correspondence: J.-H. Choi, Department of Hematology-Oncology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon, 443-380, Korea. Tel: +82 31 2194920. Fax: +82 31 2195983. E-mail: jhchoimd@ajou.ac.kr

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were analyzed. Detailed protocols of chemotherapy and follow-up after treatment were previously described [14,15]. The chemotherapy was started according to the discretion of surgeons and medical oncologists.

The patients were divided into early or late initiation group using two predefined time points, median day from surgery to the start of chemotherapy and 28 days: time from surgery to chemotherapy before median day (early group), on and after median day (late group); time from surgery to chemotherapy before 28 days (group A), 28 days or longer (group B).

Statistical analysis

OS was calculated using the Kaplan-Meier method. OS was defined as the time from the day of operation to death. The differences between the survival curves were tested by using the log-rank test. The Fisher's exact test was used to compare different groups for categorical variables. The Cox proportional-hazards regression model was used to determine the joint effects of several variables on survival. Factors with p-values <0.1 in the univariate analysis were included in the model. All statistical analyses were performed two-sided with SPSS for Windows 13.0 software.

Results

Patient characteristics

A total 410 patients with stage II or III gastric cancer received FM-PSK adjuvant chemotherapy after curative resection between November 1996 and December 2004. The median time interval between surgery and chemotherapy was 21 days (7–80 days). Twenty-seven patients (6.6%) experienced re-admission or prolonged hospitalization before starting chemotherapy due to postoperative complications.

Of the total 410 patients, 178 (43.4%) started chemotherapy within 21 days of surgery (early group) and 232 (56.6%) started chemotherapy 21 days or more after surgery (late group). In addition, 333 patients (81.2%) began chemotherapy within 28 days of surgery (group A), and 77 (18.8%) began treatment 28 days or more after surgery (group B). Fifty patients (12.2%) started chemotherapy ≤ 14 days after surgery, and 12 (2.9%) began treatment ≥ 42 days after surgery.

There were no significant differences in baseline clinicopathological characteristics between the early and late group except a higher proportion of total gastrectomy (28.7% vs. 39.7%; $p=0.022$), and postoperative complications (0% vs. 11.6%; $p<0.0001$) in the late group. The baseline characteristics were also well balanced between group A and B except for a higher proportion of postoperative complications in group B (Supplementary Table I to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1000467).

Overall survival

At the time of analysis, the median follow-up duration was 150 months (97–195 months) for the survivors and no patient was lost to follow-up for survival status.

There was no difference in OS between the early (<21 days after surgery) and late (≥ 21 days after surgery) groups (10-year OS; 57.3% vs. 51.4%; $p=0.409$; Supplementary Table II to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1000467). However, the OS was significantly inferior in group B (≥ 28 days after surgery) compared with group A (<28 days after surgery) (10-year OS; 38.8% vs. 57.5%; $p=0.003$; Supplementary Table II to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1000467, Figure 1A). In

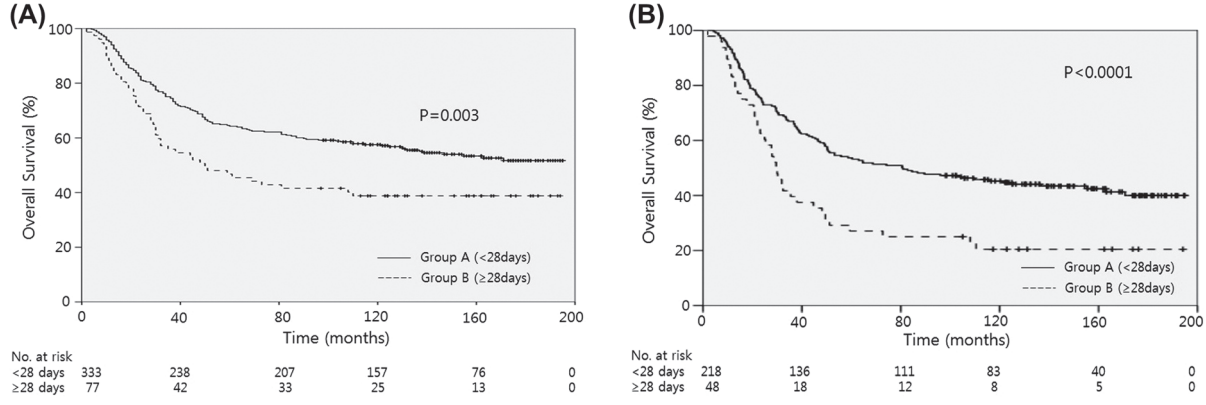

Figure 1. (A) Overall survival by interval between surgery and the start of adjuvant chemotherapy; group A (<28 days) versus group B (≥ 28 days). (B) Overall survival by interval between surgery and the start of adjuvant chemotherapy (group A vs. group B) in stage III.

addition, inferior 10-year OS in group B was observed in stage III (20.5% vs. 45.2%; $p < 0.0001$; Figure 1B), but not in stage II (69.0% vs. 80.8%; $p = 0.326$). Very early initiation of chemotherapy (≤ 14 days after surgery) was not associated with improved OS (10-year OS; 54.0% vs. 54.0%; $p = 0.918$). In multivariate analysis, independent prognostic factors of poor outcome were old age ($p < 0.0001$), large tumor size ($p = 0.035$), Borrmann type IV ($p = 0.002$), and advanced stages ($p < 0.0001$). In addition, initiation of adjuvant chemotherapy 28 days or more after surgery was also an independent prognostic factor of inferior OS ($p = 0.008$; HR 1.57; 95% CI 1.12–2.19).

Discussion

In the present study period, adjuvant chemoimmunotherapy using 5-FU, MMC, and PSK was used for most stage II or III gastric cancer patients at our institution, based on a report by Nakazato et al., in which the addition of PSK to FM adjuvant chemotherapy improved OS compared with FM alone [16]. Furthermore, mitomycin-based adjuvant chemotherapy regimens demonstrated improved OS compared with surgery alone in several studies [3,17,18]. Therefore, the FM-PSK used in the present study could be considered as a reasonable regimen for adjuvant chemotherapy during the period when the study patients had been treated. The outcome of our study cohort is comparable to that of adjuvant treatment studies in other Korean institutions [19,20].

In breast and colorectal cancers, many studies have demonstrated poor outcome of patients when adjuvant chemotherapy was initiated later than 4–12 weeks after surgery [6,8–12]. However, in routine clinical practice, it is not always possible to start adjuvant chemotherapy according to a regular schedule for a number of reasons, such as unexpected operation-related complications, slow recovery of performance status, time period for pathological assessment of specimens, the place of residence, and the time for referral to oncologists [9,11]. In breast and colorectal cancers, previous studies revealed that adjuvant chemotherapy usually began 4–7 weeks after surgery [6,7,10,11]. On the contrary, in the present study, the median time interval between surgery and the start of chemotherapy was 21 days, with a very low proportion of patients (2.9%) starting chemotherapy ≥ 6 weeks after surgery. This relatively short interval from surgery to the initiation of chemotherapy can be explained by the practice pattern for gastric cancer treatment in Korea. First, gastric cancer surgery is usually performed in university hospitals, in which a patient is referred to a medical oncologist as soon as the pathology results are reported. Second, surgeons and medical oncologists have tended to start adjuvant chemotherapy as early as possible [21]. Third, postoperative complication rates are generally very low compared with Western countries because of advanced surgical techniques [2,21].

The present study revealed that patients who started adjuvant chemotherapy 28 days or more after surgery had a significantly poor outcome. It is difficult to determine whether the association between the delay of chemotherapy initiation and poor outcome was attributable to the proliferation of micrometastasis resulting from the delay of chemotherapy or other patient-specific conditions related to the delay of chemotherapy. In the present study cohort, outcome-related factors, such as age, operation type, stage, and tumor size, did not differ significantly between group A and B except for a higher proportion of postoperative complications in group B (≥ 28 days after surgery). Moreover, the presence of postoperative complications itself was not associated with poor OS.

To our knowledge, this is the first report about the effect of the interval between surgery and the initiation of adjuvant chemotherapy on OS in gastric cancer. In addition, our study cohort consisted of a relatively large, homogeneous study population treated with D2 dissection and a uniform chemotherapy regimen with a fairly long follow-up period for survival status, analyzing all patients eligible for the study.

However, the present study has several limitations. First, all the patients in the study were from single institution. Second, detailed investigation of several patient-related factors, such as socioeconomic status and the change of performance status after surgery, was almost impossible due to the retrospective nature of the study. Third, this study did not analyze patients treated with S1 or capecitabine/oxaliplatin regimen currently established as the standard treatment after D2 dissection in Eastern Asian countries [4,5]. Finally, the number of patients who initiated chemotherapy after 28 days or more was relatively small (18.8%). However, implementation of randomized trials of the timing for adjuvant chemotherapy in gastric cancer would be almost impossible due to practical and ethical reasons. Therefore, to validate the results of the current study and to elucidate the exact cause of the association between the delay of chemotherapy and poor outcome, a retrospective study with a larger sample size or a prospective observational study using patient cohorts treated with S1 or capecitabine/oxaliplatin adjuvant chemotherapy is desirable.

Gastric cancer has different characteristics from other malignancies, such as breast cancer, in terms

of the initiation of adjuvant chemotherapy. First, abdominal surgery requires a relatively long recovery period [8]. Second, it takes a longer time to resume a normal diet after gastric cancer surgery. Third, chemotherapy-induced nausea and vomiting may occur more frequently in gastrectomy patients. The results of the present study, especially the lack of benefit of very early ($\leq$14 days after surgery) chemotherapy initiation, suggest that patients may be encouraged to have a sufficient recovery time of 3–4 weeks before initiating adjuvant chemotherapy in gastric cancer.

In conclusion, it does not seem to be necessary to initiate adjuvant chemotherapy too early after gastric cancer surgery. However, it is desirable to start treatment within four weeks after surgery if patients have fully recovered, especially in those with stage III.

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Supplementary material available online

Supplementary Tables I and II to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.1000467.