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Time interval between surgery and adjuvant chemotherapy in patients with gastric cancer after gastrectomy: a population-based cohort study using a nationwide claim database

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Chi Hoon Maeng, Hoseob Kim and Mina Kim

Abstract

Background: Adjuvant chemotherapy can reduce recurrence rates by eradicating microscopic metastases which may persist after curative resection. However, the optimal time interval (TI) between the surgery and chemotherapy remains controversial.

Objectives: This study investigated the optimal TI between surgery and chemotherapy.

Design: A population-based cohort study using a nationwide claims database.

Methods: The data were obtained from the Korean National Health Insurance Service (NHIS) of Korea. We included patients who underwent gastrectomy between 2013 and 2018. To determine the optimal cutoff point of TI, a restricted cubic spline Cox regression model was established, and categorized the population into three groups based on TI: the early (⩽20 days), the late (⩾35 days), and the reference group (21–34 days), and with the reference group having the lowest mortality and recurrence. Propensity score matching was performed for each group. The primary outcomes were disease-free survival (DFS) and overall survival (OS).

Results: After excluding ineligible participants, 6602 patients were included. The median DFS and OS did not differ significantly between the early and reference groups ($p = 0.7258$ and $p = 0.6056$, respectively). In comparison between the late and reference groups, it was significantly lower in the late group ($p = 0.0079$). Five-year DFS rates were 77.6% and 81.3% in the late and reference groups, respectively. The late group showed worse OS than the reference group ($p = 0.0336$). Five-year OS rates were 82.1% and 85.0% in the late and reference groups, respectively. In the multivariable analysis, DFS in the late group retained inferiority [adjusted hazard ratio (aHR): 1.138, 95% confidence interval (CI): 1.003–1.292, $p = 0.045$]. OS showed a worse trend without significance compared to the reference group (aHR: 1.138, 95% CI: 0.984–1.317, $p = 0.0805$).

Conclusion: Adjuvant chemotherapy after gastrectomy in patients with gastric cancer should be initiated within 5 weeks of surgery. A delay of more than 5 weeks may have a detrimental effect on the subsequent disease course.

Plain language summary

When is the best time to start adjuvant chemotherapy after stomach cancer surgery?

After a patient undergoes surgery for stomach cancer, if it is stage 2 or 3, they will receive chemotherapy for a certain period of time to reduce the possibility of recurrence. However, physicians are not clear about when it is best to start chemotherapy after surgery. The

Correspondence to:
Chi Hoon Maeng
Division of Medical Oncology–Hematology, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University College of Medicine, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, South Korea
mchihoon@khu.ac.kr

Hoseob Kim
Mina Kim
Department of Data Science, Hanmi Pharmaceutical Co., Ltd, Seoul, South Korea

study aimed to find out the best time interval between surgery and chemotherapy for patients with gastric cancer. We used data from a nationwide claims database in Korea and included patients who underwent gastrectomy between 2013 and 2018. The population has categorized the population into three groups based on the time interval: early (⩽ 20 days), late (⩾ 35 days), and reference group (21-34 days). We made statistical adjustments to minimize heterogeneity for each patient during the analysis. After excluding ineligible participants, 6,602 patients were included in the study.

As a result of the analysis, it was observed that the possibility of recurrence was significantly increased for patients in the late group compared to the reference group. The probability of survival without recurrence for 5 years (5-year disease-free survival) was 77.6% and 81.3%, respectively. Meanwhile, there was no difference in the recurrence rate between the early group and the reference group. Since recurrence of cancer can ultimately lead to death, we examined the possibility for all-cause mortality and could observe a similar pattern of association with recurrence probability. The late group had a lower survival rate than the reference group (82.1% vs. 85.0%, respectively). However, there was no statistically significant difference between these two numbers. Even in a statistical model adjusting other clinical factors, the recurrence rate in the late group was still found to be significantly high compared to the reference group. In conclusion. the results showed that adjuvant chemotherapy after gastrectomy in patients with gastric cancer should be initiated within five weeks of surgery. A delay of more than five weeks may have a detrimental effect on the patient's health.

Keywords: adjuvant chemotherapy, claim database, gastric cancer, recurrence, survival

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Introduction

Gastric cancer is a major type of cancer with high incidence and mortality rates worldwide, particularly in Eastern Asia, including Korea.[1,2] Pivotal results from the FNCLCC ACCORD-07 trial investigating 5-fluorouracil (5-FU) plus cisplatin, and the MAGIC trial (employing ECF: epirubicin, cisplatin, and 5-FU) have established perioperative chemotherapy as the standard treatment for resectable gastric cancer.[3,4] More recently, perioperative FLOT (5-FU, leucovorin, cisplatin, and docetaxel) has emerged as the new standard chemotherapy based on the German FLOT4-AIO trial.[5] On the other hand, adjuvant chemotherapy after gastrectomy has become the standard of care for patients with resectable gastric cancer, particularly in Asia. Within the adjuvant setting, capecitabine plus oxaliplatin (CAPOX) or S-1 monotherapy is the most acceptable chemotherapeutic option worldwide, although treatment intensification, such as S-1 plus docetaxel, has recently been proven effective in advanced stages.[6] Adjuvant chemotherapy can reduce the recurrence rate by eradicating microscopic metastases that may persist after curative resection. Therefore, if adjuvant chemotherapy is initiated too late after surgery, residual cancer cells may grow sufficiently to cause metastasis. However, early initiation of adjuvant chemotherapy after surgery may cause surgical complications, such as delayed wound healing. It is also possible that the patient did not recover after surgery enough to receive adjuvant chemotherapy. However, the optimal time interval (TI) remains controversial. There is no recommendation for the time point of initiation of adjuvant chemotherapy after gastrectomy in the Korean guidelines for gastric cancer.[7] Newly published Japanese Gastric Cancer Treatment guidelines do not specify when to start adjuvant chemotherapy, either.[8] This was the same for the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines published in the West.[9] We previously reported that disease-free survival (DFS) and overall survival (OS) significantly decreased when adjuvant

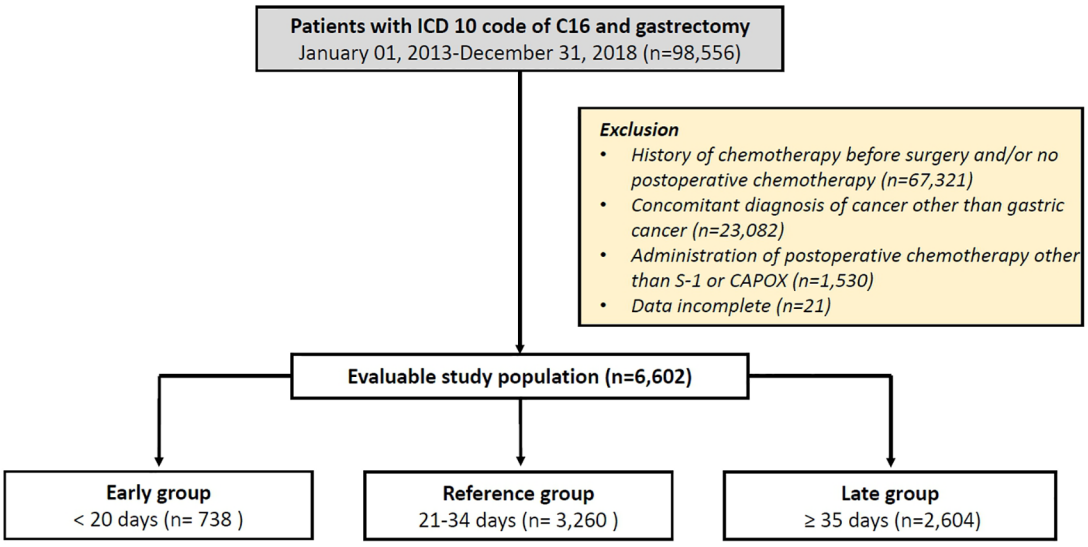

Figure 1. A flow diagram of study population selection.

chemotherapy was delayed for more than 4 weeks after surgery, favoring an optimal TI of less than 4 weeks.[10] However, the results were based on a single-center experience. Also, instead of presenting a single time point (i.e. ⩾ *versus* <4 weeks), deriving an appropriate time range (i.e. within 4–6 weeks) would be reasonable and more useful for real-world practice. Therefore, we explored appropriate TI using nationwide claims data to overcome the limitations of the previous study and verify the reproducibility.

Methods

Study population and data source

Korean National Health Insurance Service (K-NHIS) data were used to identify the optimal TI for adjuvant chemotherapy in patients with gastric cancer. All residents of South Korea are mandatory subscribers to nationwide insurance because the K-NHIS, managed by the Korean government, exclusively covers the entire Korean population. The K-NHIS database consists of primary and secondary diagnosis statements as defined by the International Classification of Disease 10th revision (ICD-10) codes, general specifications (i.e. age and sex), pharmaceutical prescriptions, medical utilization, and death information.[11] For this study, patients who had been diagnosed with gastric cancer (C16) and had undergone gastrectomy simultaneously were screened from 1 January 2013 to 31 December 2018. Individuals who underwent gastrectomies before 2013 were excluded from the study. Figure 1 shows the patient selection process. Among the initial population of 98,556 patients, we excluded patients based on the following criteria: (1) patients who received chemotherapy before surgery and did not receive any chemotherapy after surgery; (2) patients who had a diagnosis of other cancers, which was defined as patients with an ICD code other than gastric cancer (C16); (3) patients who received postoperative chemotherapy other than S-1 or CAPOX; and (4) patients who had incomplete or missing data. To avoid immortal time bias, patients who survived for <3 months after diagnosis were excluded as conditional landmarks.[12] Ultimately, 6602 patients were included in the analysis. We report this study in line with the Strengthening the Reporting of Observational Studies in Epidemiology Statement.[13]

Demographic factors at baseline and comorbidities

In this study, demographic information about patients included age, sex, and income (bottom 30% *versus* above 30%) at enrollment. Comorbidities were identified based on the following ICD-10 codes: hypertension (I10–I13, I15), diabetes mellitus (E10–E14), dyslipidemia (E78), chronic kidney disease (N18), and stroke (I63–I64), respectively. Finally, the Charlson comorbidity index (CCI) was calculated using Quan's algorithm.[14]

Clinical variables

The type of adjuvant chemotherapy (S-1 *versus* CAPOX) was identified. TI was defined as the period between surgery and the initiation of adjuvant chemotherapy. Considering that the data were based on health insurance claims data, the following operational definition was used to establish the predefined variables during data collection. Adjuvant chemotherapy was defined as the initiation of S-1 or CAPOX treatment within 3 months of surgery. Adjuvant CAPOX was defined to be administered if capecitabine and oxaliplatin were administered on the same day or at intervals of up to 1 week. To determine whether adjuvant S-1 was completed as planned, the period from the first administration start date to the last end date, based on a total planned period of 336 days, was completed between 30 days before and 60 days after adjuvant S-1 was considered complete because of the possibility of chemotherapy delay. In the case of CAPOX, if the number of oxaliplatin prescriptions was 8, the planned treatment was defined as complete, and if it was 7 or fewer, it was considered incomplete. If the prescription of chemotherapeutic agents was identified again after adjuvant S-1 or CAPOX was administered, it was defined as a recurrent case after surgery, and the patient received palliative first-line chemotherapy. Similarly, if the prescription of other chemotherapies was detected during adjuvant S-1 or CAPOX, this was considered a case of recurrence during adjuvant chemotherapy, and a switch to palliative first-line chemotherapy was made. DFS was defined as the period from the date of surgery to the start of first-line chemotherapy. Although we could not determine the actual date of radiologically or clinically confirmed recurrence, the definition of DFS was adopted because palliative chemotherapy was initiated in cases of recurrence. OS was defined as the period from the date of surgery to the date of death. Data were not collected from patients who did not undergo chemotherapy, even if they relapsed. Stages (II or III) of each subject were not available for any subject.

Ethical statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Kyung Hee University Hospital. The IRB Board waived the need for consent (Approval Number: KHUH 2019-08-031). All the personal information of the participants was anonymized and de-identified.

Statistical analysis

Categorization of TI group. To determine the optimal cutoff point of TI between surgery and adjuvant chemotherapy, a restricted cubic spline Cox regression model was established using four knots at the 5th, 23rd, 68th, and 84th percentiles based on the lowest Akaike information criteria.[15–17] The threshold was derived from the model after we ascertained the bottom with a 95% CI below a hazard ratio (HR) of 1.0. This threshold was used to categorize the population into three distinct groups based on TI: early, reference, and late group, with the reference interval group having the lowest mortality and recurrence.[17]

Basic and survival analysis. To minimize heterogeneity between the reference group and the early and late groups, a one-to-one propensity score matching (PSM) analysis was performed. In consideration of the limitations in variables available from health insurance claims data, compared to those obtainable from data of individual medical records, we collected variables anticipated to influence patients' clinical outcomes from the available data to conduct PSM, including age, sex, region where patients received adjuvant chemotherapy, and CCI. After PSM, baseline characteristics are presented as a median (range) or number (percentage). Variables such as age, sex, region where the patients received adjuvant chemotherapy, and CCI were used to construct a multivariable model. Survival analysis, including the Kaplan–Meier method with the log-rank test, was estimated to certify the difference and risk of mortality and events of first-line chemotherapy, and HRs and 95% confidence intervals were described. Finally, subgroup analyses were performed according to age, sex, planned adjuvant chemotherapy, CCI group, and type of adjuvant chemotherapy, which were confirmed by p values for interaction analysis. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and STATA16. Statistical significance was set at $p < 0.05$ significant.

Results

Patient characteristics

Descriptive patient characteristics are summarized in Table 1. Among a total of 6602 patients, three groups were categorized as early group (TI $\leqslant$ 20 days, $n = 738$), reference group (TI 21–34 days, $n = 3260$), and late group (TI $\geqslant$ 35 days,

Table 1. Descriptive patient characteristics.

Characteristics	Total		Early group		Reference group		Late group		*p* Value
	N	%	*N*	%	*N*	%	*N*	%	
Age (year)									
<65	4001	60.6	440	59.6	2146	65.8	1415	54.3	<0.0001
⩾65	2601	39.4	298	40.4	1114	34.2	1189	45.7	
Median (range)	61 (17–93)		61 (30–88)		59 (17–93)		63 (22–92)		
Sex									
Male	4468	67.7	509	69.0	2180	66.9	1779	68.3	0.3640
Female	2134	32.3	229	31.0	1080	33.1	825	31.7	
Income									
Low income	1302	19.7	170	23.0	607	18.6	525	20.2	0.0403
High income	5191	78.6	558	75.6	2591	79.5	2042	78.4	
Missing	109	1.7	10	1.4	62	1.9	37	1.4	
Type of chemotherapy									
S-1	4199	63.6	590	79.9	2037	62.5	1572	60.4	<0.0001
CAPOX	2403	36.4	148	20.1	1223	37.5	1032	39.6	
Completion of planned adjuvant chemotherapy									
No	1798	27.2	197	26.7	776	23.8	825	31.7	<0.0001
Yes	4804	72.8	541	73.3	2484	76.2	1779	68.3	
CCI									
0–3	6313	95.6	704	95.4	3126	95.9	2483	95.4	0.5772
⩾4	289	4.4	34	4.6	134	4.1	121	4.6	
Comorbidity									
Hypertension	2426	36.7	268	36.3	1178	36.1	980	39.1	0.0143
Diabetes	1352	20.5	149	20.2	590	18.1	613	23.5	<0.0001
Dyslipidemia	1038	15.7	92	12.5	497	15.2	449	17.2	0.0041
Chronic kidney disease	73	1.1	3	0.4	28	0.9	42	1.6	0.0036
Stroke	320	4.8	31	4.2	143	4.4	146	5.6	0.0663
Total	6602	100.0	738	100.0	3260	100.0	2604	100.0	

CAPOX, capecitabine plus oxaliplatin; CCI, Charlson comorbidity index.

$n = 2604$), respectively. The median age of the total population was 61 (17–93) years, and male patients were 67.7%. The distribution of each clinical variable was balanced after one-to-one PSM between the early and reference groups, and the late and reference groups, respectively (Supplemental Tables 1 and 2). The median follow-up duration was 4.47 (range, 0.1–8.0) years.

Survival outcomes according to TI

The model-derived thresholds indicated that the period between 14 and 34 days exhibited the lowest HR below 1.0. However, given that initiating adjuvant chemotherapy around 14 days post-surgery is very rare in practice, we have pragmatically categorized the TIs into the following groups based on TI: early group (⩽20 days), reference group (21–34 days), and late group (⩾35 days), with the reference group exhibiting the lowest mortality (Supplemental Figure 1). Before PSM, the three groups (early, reference, and late group) showed statistically different DFS ($p < 0.0001$) and OS ($p < 0.0001$) (Supplemental Figures 2 and 3). After PSM, the median DFS did not differ significantly between the early and reference groups ($p = 0.7258$) [Figure 2(a)]. Five-year DFS rates were 80.2% and 80.7% in the early and reference groups, respectively. When comparing the late and reference groups after PSM, the median DFS was significantly shorter in the late group ($p = 0.0079$) [Figure 2(b)]. Five-year DFS rates were 77.6% and 81.3% in the late and reference groups, respectively. OS showed a similar pattern after PSM. There was no significant difference between the early and reference groups ($p = 0.6056$) [Figure 3(a)]. Five-year OS rates were 85.8% and 85.3% in early and reference groups, respectively. The OS was worse in the late group than in the reference group ($p = 0.0336$) [Figure 3(b)]. Five-year OS rates were 82.1% and 85.0% in the late and reference groups, respectively. In the multivariable analysis, which was adjusted for other variables, including completion of planned chemotherapy and type of adjuvant chemotherapy, adjusted HRs (aHRs) for DFS and OS (early *versus* reference group) did not show significant differences (aHR: 0.965, 95% CI: 0.761–1.222, $p = 0.7659$ for DFS and aHR: 0.818, 95% CI: 0.616–1.088, $p = 0.1679$ for OS). Age >65 years, incomplete adjuvant chemotherapy, and XELOX (*versus* S-1) increased the likelihood of worse DFS and OS (Table 2). In the comparison of the late and reference groups, aHRs for DFS were significantly increased in the late group (aHR: 1.138, 95% CI: 1.003–1.292, $p = 0.045$). However, aHR for OS was non-significantly higher in the late group compared to the reference group (aHR: 1.138, 95% CI: 0.984–1.317, $p = 0.0805$). Age >65 years, incomplete duration of adjuvant chemotherapy, and treatment with XELOX (*versus* S-1) and CCI (⩾4 *versus* 0–3) were significantly unfavorable factors for OS, whereas the effect of CCI on DFS showed similar but not significant results (Table 3).

Subgroup analysis

Subgroup analysis of DFS between the early and reference groups showed no differences among the subgroups [Supplemental Figure 4(a)]. A similar pattern was observed in the subgroup comparing the DFS between the late and reference groups [Supplemental Figure 4(b)]. When comparing OS between the early and reference groups, none of the subgroups showed any differences or interactions [Supplemental Figure 5(a)]. Subgroup analysis of OS between the late and reference groups also showed no significant interactions across the variables [Supplemental Figure 5(b)].

Discussion

In this population-based study, we investigated the optimal TI between surgery and the initiation of adjuvant chemotherapy. In the results, there was no significant impact on survival outcomes of recurrence and all-cause mortality between the early (TI ⩽ 20 days) and reference groups (TI 21–34 days), whereas the late group (TI ⩾ 35 days) showed worse DFS as well as non-significant inferior OS. This finding could be interpreted as delaying adjuvant chemotherapy for >5 weeks after surgery, which may have an adverse effect on patient survival, especially DFS. Considering that the growth kinetics of tumor cells follow the Gompertzian model, prompt initiation of postoperative chemotherapy following radical surgery to eradicate possible microscopic metastasis is reasonable, even though the evidence supporting this hypothesis is sparse. Several studies have reported appropriate TI between surgery and the initiation of adjuvant chemotherapy in various types of cancer, including gastric cancer. In a cohort study of a pancreatic cancer population, survival outcomes were best when adjuvant chemotherapy was initiated within 28–59 days after surgery.[17] If the disease started earlier or later than this period, worse mortality rates were observed. In a study of patients with stage III colon cancer, a TI of <8 weeks was recommended.[18] In gastric cancer, adjuvant chemotherapy delayed for more than 28 days after surgery is reportedly associated with poorer outcomes.[19] By contrast, another study showed that early initiation of adjuvant chemotherapy within or after 3 weeks did not have a significant effect on survival.[20] When TI was based on 4 weeks, a delay of more than 4 weeks showed worse OS than that in the group that initiated adjuvant chemotherapy within 4 weeks. These findings are consistent with our results because

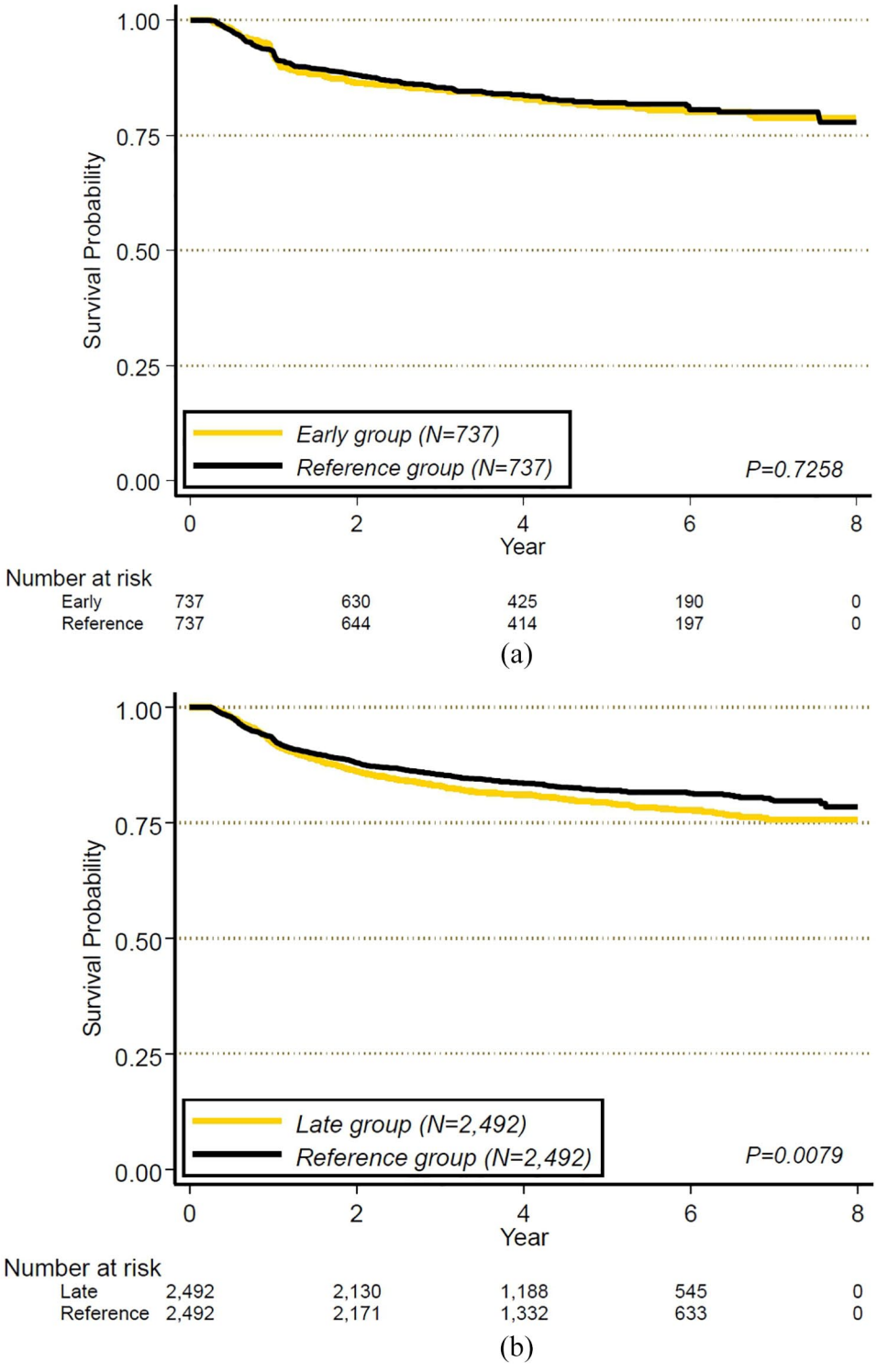

Figure 2. Disease-free survival between the early and reference groups (a) and between the late and reference groups (b).

the early group (TI less than 3 weeks) showed similar outcomes to the reference group, and the late group, in which patients started adjuvant chemotherapy after 5 or more weeks, had poorer DFS. Several other studies present similar or conflicting results, such as whether there is a significant effect on survival according to a given TI, such as at 6 or 8 weeks.[21–23] All these studies had

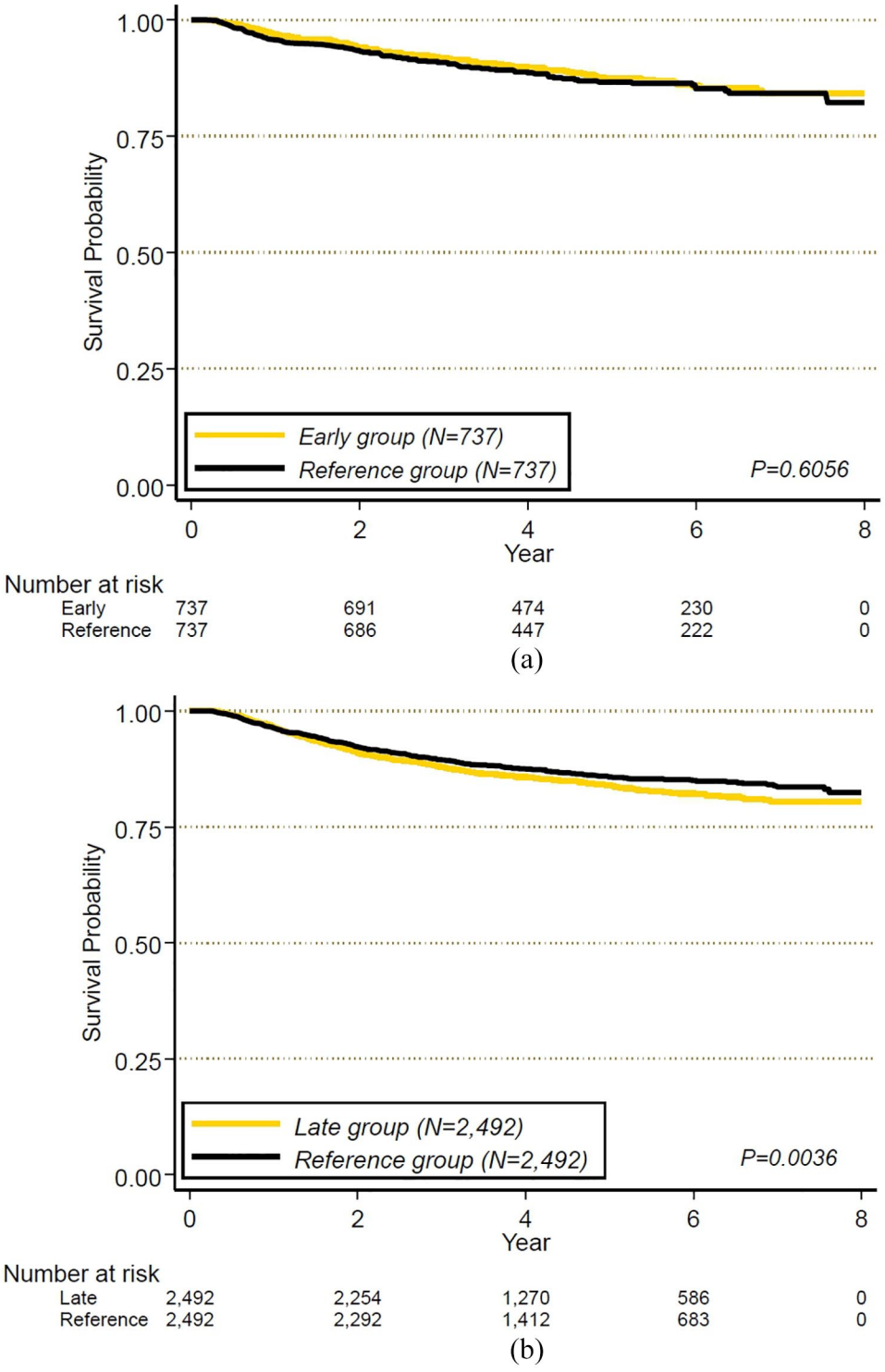

Figure 3. Overall survival between the early and reference groups (a) and between the late and reference groups (b).

a retrospective design with a small sample size, limiting the credibility of the results. However, our data are more convincing in that we targeted a much larger nationwide cohort. In addition, our results are more practical because we presented the TI as the range of the most appropriate time, rather than a binary distinction divided by a single time point.

Table 2. Comparison between early *versus* reference group: multivariable analysis for DFS and OS.

Characteristics	DFS						OS					
	HR	95%CI	*p* Value	aHR	95%CI	*p* Value	HR	95%CI	*p* Value	aHR	95%CI	*p* Value
Age (⩾65 *versus* <65 years)	2.149	1.693–2.726	<0.0001	1.884	1.462–2.429	<0.0001	3.171	2.353–4.273	<0.0001	2.838	2.068–3.896	<0.0001
Sex (male *versus* female)	0.77	0.602–0.983	0.0362	0.832	0.649–1.066	0.1452	0.895	0.664–1.208	0.4685	1.012	0.748–1.370	0.937
Completion of planned adjuvant chemotherapy (yes *versus* no)	0.295	0.233–0.374	<0.0001	0.332	0.261–0.424	<0.0001	0.203	0.152–0.271	<0.0001	0.238	0.177–0.319	<0.0001
CCI (⩾4 *versus* 0–3)	1.419	0.843–2.388	0.1873	1.331	0.788–2.248	0.2849	1.473	0.801–2.708	0.2123	1.352	0.732–2.497	0.3355
Type of chemotherapy (CAPOX *versus* S-1)	1.307	0.99–1.727	0.059	1.721	1.287–2.300	0.0002	1.497	1.082–2.072	0.0149	2.197	1.564–3.088	<0.0001
TI (early *versus* reference)	1.049	0.829–1.329	0.6885	0.965	0.761–1.222	0.7659	0.929	0.700–1.234	0.6111	0.818	0.616–1.088	0.1679

aHR, adjusted hazard ratio; CAPOX, capecitabine plus oxaliplatin; CCI, Charlson comorbidity index; CI, confidence interval; DFS, disease-free survival; HR, crude hazard ratio; OS, overall survival.

Table 3. Comparison between late *versus* reference group: multivariable analysis for DFS and OS.

Characteristics	DFS						OS					
	HR	95%CI	*p* Value	aHR	95%CI	*p* Value	HR	95%CI	*p* Value	aHR	95%CI	*p* Value
Age (⩾65 *versus* <65 years)	1.973	1.736–2.242	<0.0001	1.951	1.707–2.230	<0.0001	2.834	2.433–3.301	<0.0001	2.795	2.385–3.276	<0.0001
Sex (male *versus* female)	1.156	1.005–1.328	0.0417	1.207	1.049–1.388	0.0084	1.144	0.976–1.342	0.0976	1.219	1.038–1.431	0.0156
Completion of planned adjuvant chemotherapy (yes *versus* no)	0.306	0.270–0.348	<0.0001	0.323	0.284–0.367	<0.0001	0.276	0.239–0.320	<0.0001	0.298	0.258–0.346	<0.0001
CCI (⩾4 *versus* 0–3)	1.619	1.254–2.090	0.0002	1.267	0.978–1.640	0.0727	2.068	1.585–2.698	<0.0001	1.536	1.173–2.011	0.0018
Type of chemotherapy (CAPOX *versus* S-1)	1.17	1.030–1.329	0.016	1.473	1.289–1.683	<0.0001	1.032	0.891–1.197	0.6715	1.438	1.233–1.677	<0.0001
TI (late *versus* reference)	1.165	1.027–1.322	0.018	1.138	1.003–1.292	0.045	1.177	1.018–1.361	0.028	1.138	0.984–1.317	0.0805

aHR, adjusted hazard ratio; CAPOX, capecitabine plus oxaliplatin; CCI, Charlson comorbidity index; CI, confidence interval; DFS, disease-free survival; HR, crude hazard ratio; OS, overall survival.

It should be noted that, unlike DFS, OS in the late group was inferior without statistical significance. When analyzing the effect of the initiation point of adjuvant chemotherapy on survival, it is important to identify whether DFS, which is directly related to recurrence, or OS, which is related to all-cause mortality, are appropriate surrogate markers. Although OS is the ultimate parameter in oncological clinical trials, the primary and direct effects of the timing of adjuvant chemotherapy may be closer to disease recurrence than all-cause mortality. Thus, pivotal studies examining the role of perioperative chemotherapy set DFS, or progression-free survival, as the primary endpoint.[24–26] Analysis of the long and varied disease courses after recurrence using a large-scale cohort can be difficult. Therefore, the complexity and diversity of each patient's subsequent treatment after recurrence may have diluted the observed differences in DFS. The reasons for the absence of significant differences in DFS and OS between the early and reference groups remain unclear. Initially, the restricted cubic spline Cox regression model used to identify the TI range associated with the lowest mortality included TI of 14–34 days, as previously mentioned. However, patients within this specific interval were not included in our reference group for the aforementioned pragmatic reason. Therefore, it might be possible that the inclusion of some patients with relatively favorable prognoses in the early group, defined as having a TI of less than 21 days, may have diluted the differences observed between this group and the reference group.

Another independent factor was identified in the multivariable analysis. Regarding DFS and OS in the late group, patients who were 65 years or older, did not complete the planned adjuvant chemotherapy, and received CAPOX (compared with S-1) showed worse outcomes. Those with four or more CCI-designated diseases had a worse OS. These findings, except for the chemotherapy regimen CAPOX, seem to be unquestionably and generally acceptable, as these factors are related to negative features for optimal treatment. The effect of CAPOX compared to that of S-1 was unexpected and will be further addressed in our next study.

Our study had several limitations. First, although the all-cause mortality of the participants in our study was officially confirmed in the database, the operational definition of disease recurrence may not completely capture the actual status because a subset of patients had recurrent disease but did not receive any treatment. Therefore, the recurrence rates in our study population may have been underestimated. However, because the population was quite large, there is a possibility that the degree of underestimation may be evenly distributed in each group. Therefore, we believe that our results are valid. Second, information on the pathological stage of the participants, which has a significant effect on recurrence and death, could not be obtained owing to the lack of information in the K-NHIS database. Third, similarly to the information on staging, this study did not intricately consider clinical variables such as the type of surgery or the presence and type of postoperative complications, which have a significant impact on the outcome analysis. Due to the nature of this analysis, which relied on large-scale health insurance claims data rather than detailed patient medical records, these critical clinical variables were not incorporated into our results despite their importance. This limitation underscores a gap between the granularity of insurance claims data and the detailed clinical insights that individual patient records might provide, highlighting an area for future research to bridge this divide for a more comprehensive analysis. Despite these limitations, we believe the results of our analysis are powerful, particularly because it employs a nationwide large population that has not been previously explored for this topic.

Conclusion

In conclusion, adjuvant chemotherapy after gastrectomy in patients with gastric cancer should be initiated within 5 weeks of surgery. A delay of more than 5 weeks may have a detrimental effect on the subsequent disease course.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Kyung Hee University Hospital. The IRB has granted a waiver of consent (Approval Number: KHUH 2019-08-031). All personal information of subjects was anonymized and de-identified.

Consent for publication

Not applicable since this study was based on a national data registry of the anonymized cohort.

Author contributions

Chi Hoon Maeng: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration.

Hoseob Kim: Data curation; Formal analysis; Investigation; Methodology; Resources; Software.

Mina Kim: Formal analysis; Software; Validation.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are contained within the article and is available on request to the corresponding author, Chi Hoon Maeng.

ORCID iD

Chi Hoon Maeng https://orcid.org/0000-0002-4450-3350

Supplemental material

Supplemental material for this article is available online.

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