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ORIGINAL ARTICLE

Early initiation of fluorouracil-based adjuvant chemotherapy improves survival in patients with resectable gastric cancer

Jing-Lei Qu, Xiu-Juan Qu, Xin Li, Jing-Dong Zhang, Yue-E Teng, Bo Jin, Ming-Fang Zhao, Ping Yu, Jing Liu, Dong-Yang Li, Yun-Peng Liu

Department of Medical Oncology, The First Hospital of China Medical University, No. 155 North Nanjing Street, Heping District, Shenyang 110001, China.

Summary

Purpose: *Several clinical trials have suggested that adjuvant chemotherapy improves the survival of patients with resected gastric cancer, but the optimal time at which to initiate postoperative adjuvant chemotherapy has not been studied. This study investigated the association between time to adjuvant chemotherapy and survival in gastric cancer.*

Methods: *We retrospectively identified 266 patients with stage IB-IIIC gastric cancer who received fluorouracil-based adjuvant chemotherapy after radical gastrectomy. Overall survival (OS) was compared between patients grouped according to time from surgery to adjuvant chemotherapy (<45 and ≥45 days). The Cox proportional hazards model was used to analyze the effects of time to initiation of chemotherapy and other clinical covariates on survival.*

Results: *Of 266 patients, 141 (53%) started adjuvant chemotherapy within 45 days after surgery and 125 (47%) started adjuvant chemotherapy more than 45 days after surgery. The 3-year OS rates were 81.2 and 65.8% for patients starting chemotherapy within 45 days and after 45 days, respectively (p=0.006). Multivariate analysis identified early initiation of adjuvant chemotherapy, completion of the planned chemotherapy, and early-stage disease as favorable prognostic factors in terms of OS (p<0.05). Subgroup analysis suggested that starting chemotherapy within 45 days after surgery was associated with significant OS benefit compared with initiation of chemotherapy after 45 days from surgery in most subgroups.*

Conclusions: *This retrospective analysis suggests that delaying adjuvant chemotherapy for longer than 45 days after surgery may be associated with poorer survival in patients with resected gastric cancer.*

Key words: *adjuvant chemotherapy, gastric cancer, overall survival, time to initiation*

Introduction

Gastric cancer is the second leading cause of cancer-related mortality worldwide, with a 5-year survival rate of <20% [1]. Although surgery is the cornerstone of management for patients with stage I-III gastric cancer, a considerable proportion of patients still experience disease relapse despite curative resection. Large randomized clinical trials and meta-analyses recently demonstrated that postoperative adjuvant chemotherapy using fluorouracil (FU)-based regimens improved survival in patients with gastric cancer [2-5]. Adjuvant chemotherapy using FU-based treatments is therefore routinely recommended after radical surgery for gastric cancer. The widespread adoption of adjuvant chemotherapy for patients with gastric cancer has emphasized the need to address various factors affecting the efficacy of chemotherapy, such as the optimal timing of treatment. However, the optimal time from surgery to the start of adjuvant chemotherapy for gastric cancer

Correspondence to: Yun-Peng Liu, MD, PhD. Department of Medical Oncology, The First Hospital of China Medical University, No. 155 North Nanjing Street, Heping District, Shenyang 110001, China. Tel: +86 24 83282312; Fax: +86 24 83282543, E-mail: cmuliuyunpeng@hotmail.com
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has not been reported.

Adjuvant chemotherapy is thought to reduce the cancer recurrence rate and improve survival by eliminating micrometastases after surgery. However, removal of the primary tumor and the process of wound healing may increase the number of circulating tumor cells, stimulate the release of growth factors, and induce an immunosuppressive effect, all of which might accelerate the growth of metastatic deposits [6,7]. From a biological point of view, chemotherapy should thus commence as soon as practical after surgical resection. Clinical trials of adjuvant chemotherapy in gastric cancer generally define a time period of 28-60 days between surgery and adjuvant chemotherapy for enrollment [2,3,8-10], but there is no direct evidence to support the idea that delaying adjuvant chemotherapy for longer than 28-60 days may have a detrimental effect on survival. Several studies in patients with colorectal, breast and pancreatic cancers have shown an association between time to initiation of adjuvant chemotherapy and survival [11-15]. However, a population-based study failed to show any significant association between time to adjuvant chemotherapy and survival in patients with non-small cell lung cancer [16]. The association between the timing of adjuvant chemotherapy and survival thus remains to be clarified.

There is wide variation in clinical practice in the interval between surgery and chemotherapy. There may be several reasons for delaying adjuvant chemotherapy, including surgical complications, comorbid conditions, and non-disease-related factors, such as administrative problems and the need for patients to gather information, consider their options, and make a decision. Although disease-related reasons are generally beyond our control, system- and patient-related factors could be adjusted through training and patient education. In order to maximize the anticipated benefit of adjuvant therapy, it is therefore important to determine the correlation between time to initiating adjuvant chemotherapy for gastric cancer and survival. No prospective randomized trials have addressed this issue, and we therefore performed a retrospective study to compare the outcomes of starting chemotherapy before or after 45 days from surgery in patients with gastric cancer, using multivariate analysis to account for the effects of known prognostic factors.

Methods

Patients

This retrospective study was reviewed and approved by the institutional review board of the First Hospital of China Medical University. Written informed consent was obtained from all the participants before enrollment. All patients received adjuvant chemotherapy after radical gastrectomy with D1 or D2 lymphadenectomy and had histologically-confirmed stage IB-IIIC gastric cancer, according to the American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma (7th Edn) [17]. Other inclusion criteria were as follows: all patients surviving beyond 6 months after surgery, who had the opportunity to benefit from adjuvant chemotherapy; received at least four cycles of FU-based adjuvant chemotherapy; initiated adjuvant chemotherapy within 120 days after surgery; had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; had no double-cancer history; and had not received neoadjuvant chemotherapy or adjuvant radiation therapy. Patients with gastroesophageal junction cancer, patients who were lost to follow-up or died within 6 months of diagnosis, those who delayed chemotherapy because of disease-related factors (surgical complications) and comorbid conditions, and those who experienced relapse during adjuvant chemotherapy were excluded from the study. Patients who received at least six cycles of treatment were considered as having completed the planned chemotherapy. A total of 266 patients between May 2004 and March 2013 met the inclusion criteria and were analyzed in this study.

Patients were divided into two cohorts according to time from the date of surgery to the date of adjuvant chemotherapy: patients who received adjuvant chemotherapy within 45 days after surgery (early treatment group) and those who received adjuvant chemotherapy more than 45 days after surgery (late treatment group).

Statistics

The primary analysis involved evaluation of the association between the time to adjuvant chemotherapy initiation and OS, which was calculated from the time of surgery until death or the last follow-up visit. Differences in patient characteristics at diagnosis between the two groups were analyzed by x^2 test. Kaplan-Meier curves were used to describe patient survival, and differences between survival curves were tested by two-tailed log-rank test. Various clinicopathological variables were analyzed by univariate and multivariate analyses with respect to their prognostic significance for OS, and hazard ratios (HRs) were estimated with 95% confidence intervals (95% CI). Multivariate analysis was performed by forward stepwise addition with removal of covariates found to be associated with survival in univariate models ($p<0.10$). The following variables were examined: age (<65 vs ≥65 years), sex, stage of disease (stage IB+II vs stage III), grade (well and moderately differentiated vs poorly differentiated

Table 1. Demographic and clinical characteristics of patients by time to initiation of chemotherapy

Characteristics	*All (N=266) N (%)*	*<45 d (N=141) N (%)*	*≥ 45 d (N=125) N (%)*	*p value*
Age at diagnosis, years (median, range)	56 (26-77)	54 (26-76)	57 (30-77)	0.272
<65	220 (82.7)	120 (85.1)	100 (80.0)	
≥65	46 (17.3)	21(14.9)	25 (20.0)	
Gender				0.458
Male	193 (72.6)	105 (74.5)	88 (70.4)	
Female	73 (27.4)	36 (25.5)	37 (29.6)	
Chemotherapy regimen				0.330
FU monochemotheray	25 (9.4)	12 (8.5)	13 (10.4)	
FU plus oxaliplatin	200 (75.2)	103 (73.0)	97 (77.6)	
Other FU-based combinations	41 (15.4)	26 (18.4)	15 (12.0)	
AJCC stage				0.961
IB	11 (4.1)	5 (3.5)	6 (4.8)	
II	75 (28.2)	39 (27.7)	36 (28.8)	
IIIA	51 (19.2)	29 (20.6)	22 (17.6)	
IIIB	56 (21.1)	30 (21.3)	26 (20.8)	
IIIC	73 (27.4)	38 (27.0)	35 (28.0)	
Tumor stage				0.194
T1	6 (2.3)	3 (2.1)	3 (2.4)	
T2	24 (9.0)	10 (7.1)	14 (11.2)	
T3	63 (23.7)	28 (19.9)	35 (28.0)	
T4	173 (65.0)	100 (70.9)	73 (58.4)	
Nodal status				0.683
N0	71 (26.7)	39 (27.7)	32 (25.6)	
N1	49 (18.4)	29 (20.6)	20 (16.0)	
N2	66 (24.8)	34 (24.1)	32 (25.6)	
N3	80 (30.1)	39 (27.7)	41 (32.8)	
Histology grade				0.803
G1-G2	70 (26.3)	38 (27.0)	32 (25.6)	
G3-G4	196 (73.7)	103 (73.0)	93 (74.4)	
Lymph node dissection				0.899
D1	27 (10.2)	14 (9.9)	13 (10.4)	
D2	239 (89.8)	127 (90.1)	112 (89.6)	
Completion of adjuvantchemotherapy				0.909
Yes	203 (76.3)	108 (76.6)	95 (76.0)	
No	63 (23.7)	33 (23.4)	30 (24.0)	

FU: fluorouracil, AJCC: American Joint Committee on Cancer, G1: well differentiated, G2: moderately differentiated, G3: poorly differentiated, G4: undifferentiated

and undifferentiated), lymph node dissection (D1 vs D2), completion of the planned chemotherapy (yes vs no), and time to initiation of chemotherapy (<45 vs ≥45 days). Statistical analyses were carried out using SPSS 16.0 (SPSS Inc., Chicago, Ill, USA). A two-sided value of $p<0.05$ was used to indicate significance.

Results

Patient characteristics

A total of 266 eligible patients were included in the study. Patients were administered at least

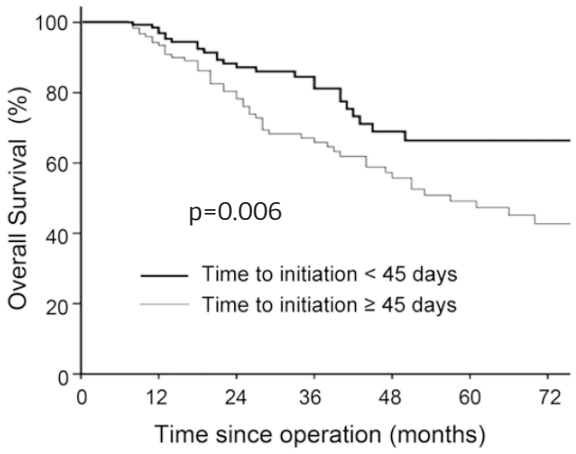

Figure 1. Kaplan-Meier overall survival by time to initiation of adjuvant chemotherapy in all patients (N=266). p=0.006.

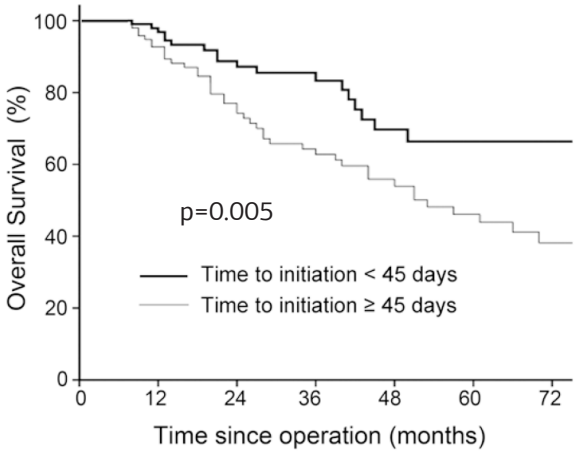

Figure 2. Kaplan-Meier overall survival by time to initiation of adjuvant chemotherapy in the FU plus oxaliplatin subgroup (N=200). p=0.005.

four cycles of FU monochemotherapy, FU plus oxaliplatin, or other FU-based chemotherapy combinations, and each cycle was repeated every 21 days. Time to adjuvant chemotherapy ranged from 12-115 days (median 42.5). Of the 266 patients, 141 patients (53%) received adjuvant chemotherapy within 45 days after surgery and 125 patients (47%) received adjuvant chemotherapy after 45 days. Seventy-six percent of patients completed at least six cycles of treatment. The main reasons for early termination of treatment were patient refusal for further treatment and treatment-related complications.

The demographic and clinical characteristics of the patients are shown in Table 1. Characteristics were equally distributed between the two groups. The median age was 56 years (range 26-77), and there were 193 male and 73 female patients. Sixty-eight percent of patients had stage III disease, 65% had T4 tumors, 30% had more than six lymph node metastases (N3), 74% had poorly differentiated tumors, and 90% underwent gastrectomy with D2 lymph node dissection. The median follow-up time was 28 months (range 7-139).

Survival analysis

The OS rates for all 266 enrolled patients were 73.5% at 3 years post-surgery and 56.9% at 5 years. The 3-year OS rates for patients who initiated adjuvant chemotherapy within 45 days after surgery and those who initiated adjuvant chemotherapy after 45 days were 81.2% and 65.8%, respectively (p=0.006). Kaplan-Meier curves for OS are illustrated in Figure 1. In the subset of patients who received FU plus oxaliplatin combined chemotherapy, the 3-year OS rates for the early and late treatment groups were 83.3% and 62.7%,

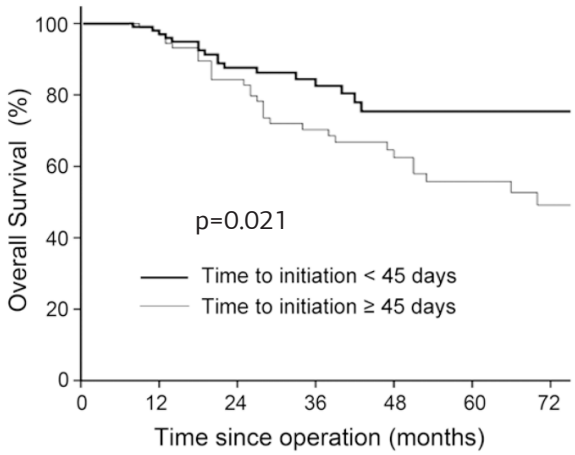

Figure 3. Kaplan-Meier overall survival by time to initiation of adjuvant chemotherapy in patients who completed the planned treatment (N=203). p=0.021.

Table 2. Univariate and multivariate analysis for overall survival (N=266)

Factors	*Univariate analysis*			*Multivariate analysis*		
	HR	*95% CI*	*p value*	*HR*	*95% CI*	*p value*
Age at diagnosis (years)						
<65	1.000					
≥65	1.680	0.996-2.834	0.052			
Gender						
Male	1.000					
Female	1.277	0.776-2.102	0.336			
AJCC stage						
I+II	1.000			1.000		
III	4.752	2.364-9.553	<0.001	4.923	2.447-9.905	<0.001
Histology grade						
G1-G2	1.000			1.000		
G3-G4	1.756	0.965-3.198	0.065	1.755	0.964-3.194	0.066
Lymph node dissection						
D1	1.000					
D2	0.740	0.379-1.445	0.378			
Completion of adjuvant chemotherapy						
Yes	1.000			1.000		
No	2.281	1.415-3.678	0.001	2.158	1.328-3.505	0.002
Time to initiation of chemotherapy (days)						
<45	1.000			1.000		
≥45	1.933	1.194-3.128	0.007	1.771	1.086-2.889	0.022

For abbreviations see footnote of Table 1

respectively (Figure 2). Early treatment was associated with an HR for mortality of 0.466 (95% CI=0.269-0.810, p=0.007) vs the late treatment group. However, in the subset of patients who received FU±non-platinum therapy, there was no significant survival difference between the two groups (HR 0.807, 95% CI=0.282-2.307, p=0.689). In patients who completed the planned chemotherapy, early treatment was also associated with better survival compared with the late treatment group (HR 0.506, 95% CI=0.281-0.913, p=0.024), with 3-year OS rates of 82.5% and 70.3%, respectively (Figure 3). However, in patients who did not complete the planned treatment, there was no significant survival advantage of early over late treatment (HR 0.703, 95% CI=0.299-1.652, p=0.418). Subgroup analysis was undertaken according to age, sex, stage, histologic grade and lymphadenectomy. Consistent with the overall patient population, patients who started chemotherapy within 45 days of surgery had a significantly better, or a tendency towards a better OS compared with those who started after 45 days in almost all subgroups (Figure 4).

Prognostic factors

Table 2 summarizes the results of the Cox proportional hazards regression analyses of factors associated with OS. Univariate analysis showed that time to initiation of adjuvant chemotherapy, completion of the planned chemotherapy, and disease stage were significantly correlated with OS. Multivariate analysis identified early initiation of adjuvant chemotherapy, completion of the planned chemotherapy, and early-stage disease as favorable prognostic factors in terms of OS. Compared with patients who initiated adjuvant chemotherapy within 45 days after surgery, those who initiated adjuvant chemotherapy after 45 days had poorer OS (HR=1.771, 95% CI=1.086-2.889; p=0.022). Patients who terminated chemotherapy early had a significantly poorer outcome, with an HR for OS of 2.158 (95% CI=1.328-3.505; p=0.002), compared with those who completed the planned chemotherapy.

Discussion

The issue of time to adjuvant chemotherapy has been addressed in patients with a variety of tumors, including colorectal, breast, non-small cell lung, and pancreatic cancers [11-16]. A recent meta-analysis reported that a 4-week increase in time to adjuvant chemotherapy was associated with a significant decrease in OS among patients with colorectal cancer [18]. A retrospective analysis of patients with early breast cancer demonstrated that OS was significantly better in patients

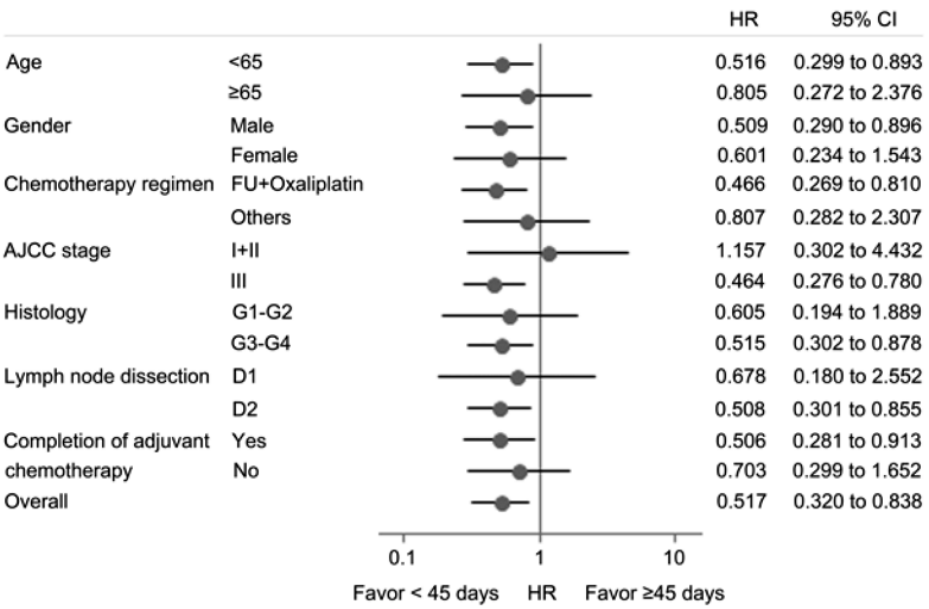

Figure 4. Hazard ratios (HRs) for death and 95% confidence intervals (CIs) in subgroup analyses.

who initiated adjuvant treatment within 44 days after surgery, compared with patients who initiated adjuvant treatment after 44 days [13]. However, no published reports have provided insight into the optimal timing between surgical resection of gastric cancer and initiation of adjuvant chemotherapy. Recent large-scale randomized controlled trials of adjuvant chemotherapy after gastrectomy (ACTS GC trial and CLASSIC trial) defined the time from surgery to enrollment as 42 days [2,3]. The results of these trials indicated a survival benefit of adjuvant chemotherapy for resected gastric cancer compared with surgery alone. We therefore chose 45 days as the clinical cut-off point to distinguish between early and late chemotherapy in terms of effect on OS. The present study demonstrated that patients who received FU-based adjuvant chemotherapy within 45 days after surgery had significantly better OS than those who received adjuvant chemotherapy after 45 days. Furthermore, multivariate analysis showed that earlier initiation of adjuvant chemotherapy was an independent prognostic factor for OS. Subgroup analysis indicated that early treatment favored survival in most subgroups. Based on these results, we suggest that adjuvant chemotherapy should be initiated within 45 days after surgery in patients with resected gastric cancer.

Many preclinical cancer studies have supported the early initiation of adjuvant chemotherapy. The release of circulating growth factors and growth of metastases were accelerated after removal of the primary tumor in animal models [19]. A mathematical model predicted that the effectiveness of a given chemotherapeutic regimen was inversely proportional to the tumor burden [20]. It follows from these results that there is a time window after surgery, beyond which adjuvant chemotherapy would fail to eradicate the micrometastases. Studies have shown that tumor burden at the time of adjuvant chemotherapy was associated with the proliferative activity of tumors, which was correlated in turn with the grade of tumor differentiation [21]. In the present study, early initiation of chemotherapy was associated with better OS than later treatment in patients with poorly differentiated tumors, though there was no difference between early and late treatments in patients with well and moderately well differentiated tumors. Our results thus support the view that adjuvant treatment should start as soon as possible after surgery in patients with highly malignant tumors.

Previous retrospective analyses of time to adjuvant chemotherapy initiation have had some limitations, including lack of information on treatment cycles, which is relevant, given that the duration of chemotherapy has been reported to affect survival. Recent combined analyses investigating the effects of timing and duration of adjuvant chemotherapy on survival produced inconsistent results [15,22,23]. Murakami et al. reported that time to initiation of adjuvant chemotherapy was associated with disease free survival

(DFS) independent of duration of chemotherapy and other clinical covariates in patients with pancreatic carcinoma [15]. In contrast, a report from the ESPAC-3 study recently showed that completion of all six cycles of the planned adjuvant chemotherapy, rather than early initiation, improved survival in patients with pancreatic carcinoma after resection [22]. Moreover, Ahmed et al. reported that early discontinuation, but not the timing of adjuvant therapy, affected survival in patients with high-risk colorectal cancer [23]. It is therefore necessary to consider the number of chemotherapy cycles when analyzing the association between time to initiate chemotherapy and survival. However, there are currently no recommendations regarding the optimal duration of adjuvant chemotherapy for gastric cancer. In a previous report, we observed that the number of cycles of adjuvant chemotherapy was an independent prognostic factor for patients with gastric cancer, and that six cycles of treatment might represent an efficacy plateau [24]. In the present study, all patients enrolled received at least four cycles of adjuvant chemotherapy, and patients who received at least six cycles of treatment were defined as having completed the planned chemotherapy. Our results showed that early initiation and completion of the planned treatment were both independent prognostic factors in multivariate analysis. In the subset of patients who completed at least six cycles of chemotherapy, initiation of therapy within 45 days was associated with favorable OS compared with initiation of therapy after 45 days ($p<0.05$). However, in patients who terminated chemotherapy early, initiation of therapy within 45 days showed no significant survival benefit, possibly because of the small sample size. In practice, however, it is not possible to know at the start of treatment whether or not a patient will go on to complete the planned chemotherapy, and ensuring early initiation of chemotherapy is thus the first step in maximizing the anticipated benefit of adjuvant therapy.

The subset of patients with stage III disease showed an overall reduction in mortality of 54% ($p=0.004$) in patients who started early adjuvant chemotherapy compared with those who started late. However, there was no significant difference in survival between the two groups in patients with early-stage disease. Chen et al. reported no survival benefit from postoperative adjuvant chemotherapy in patients with stage II gastric cancer [25]. The effectiveness of adjuvant chemotherapy in patients with early-stage gastric cancer thus remains controversial, and large randomized controlled studies are needed to evaluate the effects of adjuvant chemotherapy and optimal timing of treatment in these patients.

The present study had some limitations. It was a retrospective study with no randomization and no control over known and unknown prognostic factors, such as reasons for adjuvant chemotherapy delay, which may have influenced the observed results. For patients who require chemotherapy, artificially prolonging the time to initiation of treatment is unethical, and it is therefore unlikely that a prospective trial of early vs late chemotherapy would be acceptable. Evaluation of the optimal timing of adjuvant chemotherapy therefore needs to rely on rigorously designed retrospective studies with large sample sizes. In addition, patients who delayed chemotherapy because of surgical complications and comorbid conditions were excluded from the present study, which might have reduced the impact of potential confounders on survival to some extent.

In conclusion, we retrospectively analyzed the optimal timing of adjuvant chemotherapy in gastric cancer patients after radical gastrectomy. Early initiation of chemotherapy within 45 days of surgery was associated with better survival, and time to initiation of treatment was identified as an independent prognostic factor for OS. To the best of our knowledge, this study is the first to explore the optimal timing of FU-based adjuvant chemotherapy in patients with resectable gastric cancer. These results provide valuable insight into the strategy of postoperative adjuvant chemotherapy for gastric cancer, and will help to optimize treatment planning and the benefits of adjuvant therapy. Further studies are needed to confirm the association between the timing of chemotherapy and survival, especially in specific patient subgroups.

Acknowledgements

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