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ORIGINAL ARTICLE

Time to initiation or duration of S-1 adjuvant chemotherapy; which really impacts on survival in stage II and III gastric cancer?

Kazumasa Fujitani[1] · Yukinori Kurokawa[2] · Atsushi Takeno[3] · Shunji Endoh[4] · Takeshi Ohmori[5] · Junya Fujita[6] · Makoto Yamasaki[2] · Shuji Takiguchi[2] · Masaki Mori[2] · Yuichiro Doki[2] · On behalf of the Osaka University Clinical Research Group for Gastroenterological Surgery

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Abstract

Background Surgical resection with S-1 adjuvant chemotherapy (AC) is the standard of care for stage II–III gastric cancer (GC). However, it is unclear if time to initiation and duration of S-1 AC impact on survival.

Methods A multi-institutional GC database identified 498 patients who were treated with S-1 AC after D2 or more extended radical surgery for stage II–III gastric cancer. Patients were divided into four groups according to the interval between surgery and initiation of AC and the duration of AC as follows: group A ($n = 226$), who received AC earlier (≤6 weeks) and for longer (≥6 months) after surgery; group B ($n = 160$), who received AC later (>6 weeks) and for longer after surgery; group C ($n = 46$), who received AC earlier but for a shorter period (<6 months) after surgery; and group D ($n = 66$), who received AC later and for a shorter period after surgery. Prognostic factors for overall survival (OS) were investigated using multivariate analysis.

Results The 5-year OS was 69.5%. Pathological stage II disease (hazard ratio (HR), 0.334; 95% confidence interval (CI), 0.215–0.499), with an OS of 85.8% versus 60.5% for stage III disease, as well as a longer duration (≥6 months) of S-1 (HR, 0.498; 95% CI, 0.355–0.706), with an OS of 74.3% versus 53.0% for a shorter duration (<6 months) of S-1, were identified as significant prognostic factors for long-term survival. Time to initiation was not associated with OS.

Conclusions A duration of S-1 AC of ≥6 months, but not time to initiation within 6 weeks, impacts on OS in stage II–III gastric cancer.

Keywords S-1 adjuvant chemotherapy · Stage II–III gastric cancer · Time to initiation · Duration · Overall survival

Introduction

Gastric cancer is the third leading cause of cancer-related death and the fifth most common cancer diagnosed worldwide [1]. Gastrectomy with D2 lymph node dissection is now the standard radical treatment in the West [2] and the East. However, approximately 40–80% of these patients will ultimately relapse and die of their cancer after gastrectomy alone, making adjunctive therapy an important component of treatment [3–9]. In the United States and Europe, postoperative chemoradiotherapy [4] and perioperative chemotherapy [5, 6] are the current standard treatments for patients with resectable advanced gastric cancer. In East Asia, adjuvant chemotherapy (AC), postoperative S-1 monotherapy for 1 year, or capecitabine with oxaliplatin for 6 months following curative surgery, is the standard of care for pathological stage II and III gastric cancer after D2 or more extended lymphadenectomy [7–9].

✉ Yukinori Kurokawa
ykurokawa@gesurg.med.osaka-u.ac.jp

[1] Department of Surgery, Osaka Prefectural General Medical Center, Osaka, Japan

[2] Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2-E2, Yamadaoka, Suita, Osaka 565-0871, Japan

[3] Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan

[4] Department of Surgery, Higashi-Osaka Medical Center, Higashi-Osaka, Japan

[5] Department of Surgery, Osaka Police Hospital, Osaka, Japan

[6] Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan

The aim of AC is to eradicate micrometastases in a proportion of patients who would otherwise experience cancer recurrence after radical surgery. AC is usually planned to start as soon as possible after surgery, as clinical trials that showed a survival benefit with AC [4, 7, 9] had AC initiation within 3–7 weeks of gastrectomy. However, in practice, not all patients can initiate AC in this time frame. Some face delays in AC due to postoperative complications, comorbid conditions, personal decisions regarding AC, or health system logistic factors such as delays in referral or waiting times.

Little is known about whether initiating AC beyond the time window specified by clinical trials could achieve similar survival benefits. Furthermore, it is not known if a longer duration of AC could offset the effects of delaying AC in terms of overall survival (OS). Therefore, we sought to address whether time to initiation and duration of S-1 adjuvant chemotherapy impact on OS in stage II and III gastric cancer by performing a retrospective analysis of a large multi-institutional gastric cancer database.

Patients and methods

Study population

A review of the gastric cancer database established for another multi-institutional retrospective study involving 21 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery identified 517 patients with pathological stage II and III primary gastric adenocarcinoma who underwent S-1 AC after microscopically curative distal or total gastrectomy with D2 or more extensive lymph node dissection between January 1, 2008 and December 31, 2010. Patients treated with neoadjuvant therapy were excluded from the study. Nineteen patients with recurrence during S-1 adjuvant treatment within 6 months of surgery were excluded from the cohort of 517 patients. The remaining 498 patients were our target population. Data on relevant prognostic factors were extracted. Pathological depth of tumor invasion (pT), lymph node metastasis (pN), and tumor stage were classified according to the Japanese Classification of Gastric Carcinoma [10]. Histopathology of the tumor was in accordance with the Lauren classification. Postoperative infectious complications, including anastomotic leakage, pancreatic fistula, abdominal abscess, wound infection, and pneumonia, were evaluated according to the Clavien–Dindo classification [11, 12]. Patients were categorized into four groups according to the interval between surgery and initiation of AC and the duration of AC: group A ($n = 226$), who received AC earlier ($\leq$6 weeks) and for longer ($\geq$6 months) after surgery; group B ($n = 160$), who received AC later (>6 weeks) and for longer after surgery; group C ($n = 46$), who received AC earlier but for a shorter period (<6 months) after surgery; and group D ($n = 66$), who received AC later and for a shorter period after surgery. Institutional review board approval of the original study protocol was obtained at each participating hospital.

Survival analysis

All the patients were followed for a minimum of 5 years or until death. None were lost to follow-up. OS was defined as the time from the date of surgery to the date of death from any cause or last follow-up. Univariate analysis was used to assess the association between each clinicopathological factor and OS. Multivariate analysis was performed to identify variables independently associated with OS. Postoperative deaths were not excluded from the survival analysis.

Statistical analysis

Continuous variables are presented as median (IQR), where IQR is the interquartile range. Statistical analyses were performed using the chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. Survival rates were calculated according to the Kaplan–Meier method and differences were evaluated using the log-rank test. A Cox proportional hazards model was used to identify prognostic factors for OS. All statistical analyses were performed using JMP Pro software version 11.0.0 (SAS Institute, Cary, NC). A p value <0.05 was considered to indicate statistical significance.

Results

Patient characteristics

Among the 498 patients, 180 (36.1%) had stage II disease and 318 (63.9%) had stage III disease. The clinical and histopathological tumor characteristics of the 498 patients are summarized in Table 1 by group. There were no differences in sex, histology, pT, pN, tumor stage, type of gastrectomy, and American Society of Anesthesiologists—physical status (ASA-PS) score. There were differences in age, surgical approach, and postoperative infectious complications. S-1 adjuvant treatment was started within 6 weeks of surgery in 272 patients (54.6%). The distribution of time to initiation of AC is shown in Fig. 1. The median interval between surgery and AC was 6 weeks (range, 2–20 weeks). Ten patients started AC 20 weeks after surgery with a median administration period of 6.5 (IQR, 3.0–12.8) months. S-1 adjuvant treatment lasted for 6 months or longer in 386 patients (77.5%). The distribution of the duration of AC

Table 1 Patient characteristics categorized by time to initiation and duration of S-1 adjuvant chemotherapy

Characteristic	Group A duration ≥6 M initiation ≤6 W ($n = 226$)	Group B duration ≥6 M initiation >6 W ($n = 160$)	Group C duration <6 M initiation ≤6 W ($n = 46$)	Group D duration <6 M initiation >6 W ($n = 66$)	p value
Age, median (IQR)	64 (59–71)	69 (62–74)	70 (62–75)	70 (65–74)	<0.0001
Sex					
Male	159	110	33	48	0.9369
Female	67	50	13	18	
Histology					
Intestinal	82	75	20	30	0.1767
Diffuse	144	85	26	36	
Pathological depth of tumor invasion					
T2	36	24	11	4	0.2301
T3	84	61	10	28	
T4a	99	73	24	32	
T4b	7	2	1	2	
Pathological lymph node metastasis					
N0	28	22	6	3	0.4180
N1	70	44	14	19	
N2	60	45	10	14	
N3	68	49	16	30	
Pathological tumor stage					
II	82	65	16	17	0.2109
III	144	95	30	49	
Resection type					
TG	76	69	19	33	0.0645
DG	150	91	27	33	
Surgical approach					
Open	203	150	44	66	0.0283
Laparoscopic	23	10	2	0	
Infectious complications					
Grades 0–1	209	121	42	39	<0.0001
Grades 2–3	17	39	4	27	
ASA-PS					
1–2	210	148	39	56	0.0838
3	16	12	7	10	

M months, *W* weeks, *IQR* interquartile range, *TG* total gastrectomy, *DG* distal gastrectomy, *ASA-PS* American Society of Anesthesiologists—physical status

is shown in Fig. 2. The median duration was 12 months (range, 1–24 months). Fifteen patients received AC for more than 24 months, with a median duration of 29 (IQR, 28–51) months.

Recurrence and survival outcome

Relapse occurred in 168 (33.7%) patients. By group, the recurrence rate was 30.1% in group A, 30.6% in group B, 32.6% in group C, and 54.6% in group D, with a significant difference between groups A, B, C, and D ($p = 0.0020$). Death occurred in 157 (31.5%) patients. The 5-year OS rate was 69.5%; by pathological stage, it was 85.8% for stage II and 60.5% for stage III tumors ($p < 0.0001$). The 5-year OS rate was 76.4% in group A, 71.4% in group B, 63.8% in group C, and 45.5% in group D, with a significant difference between groups ($p < 0.0001$), as shown in Fig. 3. There was no difference in the median duration of AC between groups A (12 months with an IQR of 11–13 months) and B (12 months with an IQR of 11–13 months).

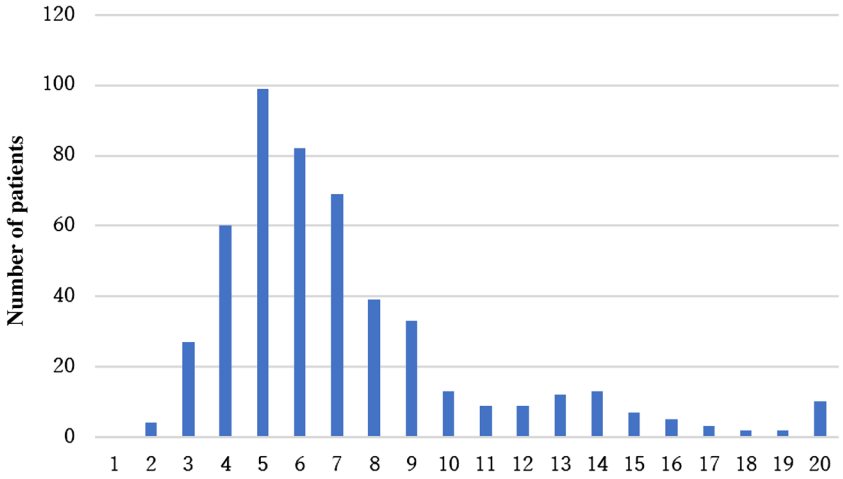

Fig. 1 Time to initiation of adjuvant chemotherapy (weeks). This graph shows the distribution of time to starting S-1 adjuvant chemotherapy for all patients

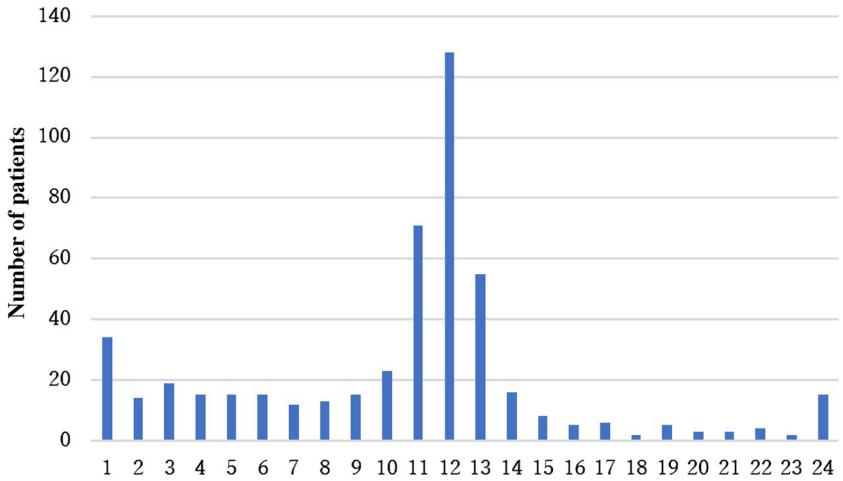

Fig. 2 Duration of adjuvant chemotherapy (months). This graph shows the distribution of S-1 adjuvant chemotherapy duration for all patients

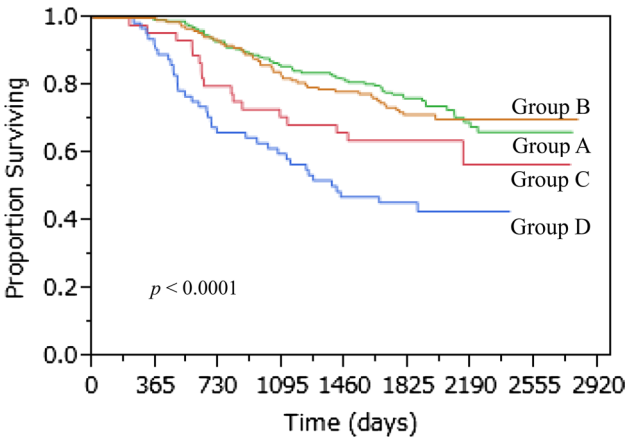

Fig. 3 Kaplan–Meier estimates of the survival probabilities by group

Prognostic factors

Factors that were significantly associated with OS in the univariate analysis were histology, pathological tumor stage, type of gastrectomy, postoperative infectious complications, and duration of S-1 treatment (Table 2). In the multivariate analysis, pathological stage II disease [hazard ratio (HR), 0.334; 95% confidence interval (CI), 0.215–0.499] and longer duration of S-1 treatment (HR, 0.498; 95% CI, 0.355–0.706) were independent favorable prognostic factors. In both univariate and multivariate analyses, time to initiation of adjuvant S-1 was not associated with OS.

Discussion

Gastric cancer clinical trials demonstrating that adjuvant therapy confers a survival benefit [4, 7, 9] generally required treatment to be initiated within 3–7 weeks of definitive surgery, beyond which patients were no longer eligible to participate. Therefore, a routine clinical assumption is that AC should commence as soon as practical. In addition, AC is often assumed to have little or no benefit beyond a certain time frame from surgery, such as the often quoted 12 weeks. However, there is no persuasive evidence to support either

Table 2 Univariate and multivariate analyses of prognostic factors

Characteristics	Univariate analysis			Multivariate analysis		
	No. of patients	HR	*p* value	HR	95% CI	*p* value
Age						
≥65 years	302	1.173	0.3362	1.039	0.741–1.472	0.8246
<65 years	196					
Sex						
Male	350	1.083	0.6521	1.043	0.727–1.517	0.8235
Female	148					
Histology						
Intestinal	207	0.715	0.0447	0.727	0.513–1.021	0.0657
Diffuse	291					
Pathological tumor stage						
II	180	0.310	<0.0001	0.334	0.215–0.499	<0.0001
III	318					
Resection type						
TG	197	1.388	0.0395	1.124	0.813–1.551	0.4775
DG	301					
Infectious complications						
Grades 0–1	411	0.579	0.0031	0.709	0.481–1.063	0.0943
Grades 2–3	87					
ASA-PS						
1–2	453	0.646	0.0718	0.852	0.531–1.441	0.5329
3	45					
Duration of S-1						
≥6 M	386	0.440	<0.0001	0.498	0.355–0.706	0.0001
<6 M	112					
Time to initiation of S-1						
≤6 W	272	0.733	0.0511	0.843	0.602–1.181	0.3213
>6 W	226					

HR hazard ratio, *CI* confidence interval, *TG* total gastrectomy, *DG* distal gastrectomy, *ASA-PS* American Society of Anesthesiologists—physical status, *M* months, *W* weeks

assumption, especially in patients with gastric cancer. In practice, there are often delays in commencing adjuvant therapy, and not all patients could initiate treatment within these time frames due to postoperative complications, poor performance status, and compromised nutritional status. It is not known whether delaying treatment affects long-term survival. It is also unknown whether durable AC is required for a survival benefit. These questions have not been subjected to a randomized controlled trial. It is unlikely that such a trial will be performed due to low operability and potential ethical problems. Therefore, we undertook this study to assess whether time to initiation and duration of S-1 AC impact on long-term survival in stage II and III gastric cancer.

The 5-year OS rate was 69.5% in our patients. When stratified by pathological stage, the rate was 85.8% for stage II and 60.5% for stage III ($p < 0.0001$). These results are consistent with the results of the ACTS-GC trial that showed a 5-year OS rate of 71.7% for all S-1 cohorts, 84.2% for stage II, 67.1% for stage IIIA, and 50.2% for stage IIIB [8]. Factors that were independently associated with favorable OS were pathological stage II disease and durable S-1 treatment ≥6 months. Time to initiation of adjuvant S-1 was not associated with OS.

The proper timing for AC in gastric cancer has not been fully evaluated. The latest Japanese guideline [13] recommends initiating AC within 6 weeks of surgery merely because that is the timeframe in which chemotherapy was initiated in randomized AC trials. Recently, two retrospective studies suggested a correlation between early initiation of AC, within 6–8 weeks after surgery, and better survival [14, 15]. However, in one study with a small sample size of 113 patients [14], those who suffered a recurrence within 1 year were excluded from the study, which suggests that biologically aggressive tumors were excluded. This exclusion criterion might have led to the conclusion that duration of AC is not a significant prognostic factor. In another study [15], the small proportion of patients (4.3%) who received

delayed AC (>8 weeks) were not suitable for detailed analysis. In addition, the chemotherapy regimen was significantly imbalanced in favor of the early (≤8 weeks) initiation cohort, who received more potent combination regimens. Furthermore, postoperative infectious complications, which are well-known negative prognosticators [16–18], and duration of chemotherapy were not included in the multivariate analysis of prognostic factors for OS. Other recent retrospective studies [19, 20] did not find a survival benefit with early initiation of AC. A delay in starting AC beyond 8 or 12 weeks after surgery did not have a significant impact on OS in patients undergoing curative resection for stage I–III gastric cancer, even when stratified by pathological stage [19, 20]. For other types of cancer such as colorectal and breast cancer, there are also pros and cons regarding the impact of early initiation of AC on OS [21–25]. These findings suggest a significant benefit with AC, even when delayed. In this study, 54 patients (10.8%) initiated S-1 treatment more than 12 weeks after surgery. Their 5-year OS rate was 56.2%, compared with 71.2% in the other 444 patients who initiated AC within 12 weeks ($p = 0.0606$), which suggests that it would be better not to start AC too late, though there is no desperate need to start AC within 6 weeks as in the clinical trials.

The recommended duration of AC for solid tumors ranges from 6 to 12 months. In particular, 6 months of treatment were considered necessary for breast and colon cancer [26–31], while 6 or 12 months were considered necessary for gastric cancer in the CLASSIC trial or ACTS-GC trial, respectively [7, 9]. In this study, durable S-1 treatment lasting ≥6 months and pathological stage II disease were independently associated with favorable OS. There was no difference in time to initiation between patients with and without durable S-1 treatment (6 versus 7 weeks). Although most retrospective studies of cases of colorectal, breast, and gastric cancer do not evaluate treatment duration or compliance as potential prognostic factors, completion of all planned treatment cycles of AC was demonstrated to be the only significant prognosticator of long-term survival in a prospective phase III study of pancreatic cancer [32]. It is reasonable to assume that patients with a longer duration of AC may have a potentially longer OS. When our patient cohort was stratified by pathological stage, the survival benefit of a longer S-1 treatment duration persisted for stage III gastric cancer but not for stage II disease. On multivariate analysis, longer duration of S-1 treatment (HR, 0.479; 95% CI, 0.331–0.702) was the only independent favorable prognostic factor for stage III gastric cancer (data not shown). In contrast, neither duration nor time to initiation of S-1 treatment was significant, whereas intestinal histology (HR, 0.403; 95% CI, 0.161–0.923) was the only independent favorable prognostic factor for stage II disease (data not shown). In addition, it is relevant to explore the possibility that any survival advantage of early AC initiation is offset by early discontinuation of adjuvant treatment. However, even when excluding 34 patients who could not tolerate S-1 treatment for more than 1 month after surgery, the survival benefit of pathological stage II disease (HR, 0.341; 95% CI, 0.211–0.526) and longer duration of S-1 treatment (HR, 0.482; 95% CI, 0.332–0.711) persisted, whereas time to initiation of S-1 treatment was still not associated with OS (data not shown).

Our study has several limitations. First, our analysis is limited by its nonrandomized and retrospective nature, which may have introduced patient selection bias. Second, compliance and the relative dose intensity of S-1 AC, which may be key determinants of survival, were not evaluated. However, we believe that our results are relevant because a randomized clinical trial that is designed to answer this question would be unrealistic and unethical, especially for stage III disease. To the best of our knowledge, this study includes the largest number of patients receiving adjuvant S-1 treatment ever reported. In addition, the patients were relatively homogeneous, with limited stage II and III gastric cancer and a single surgical procedure, standardized D2 dissection, used in all patients.

In conclusion, we demonstrated that delaying the initiation of S-1 AC was not associated with worse survival; adverse outcomes occurred only when AC was discontinued within 6 months. Thus, physicians have enough time and opportunity after surgery to commence AC when appropriate. Every effort should be made to secure durable S-1 adjuvant treatment for at least 6 months for stage II–III gastric cancer, although the optimal treatment duration remains unclear.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Institutional and National) and with the Helsinki Declaration of 1964 and later versions.

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