Prognostic effect of postoperative duration until adjuvant chemotherapy and cumulative S-1 dose in gastric cancer

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Abstract

Background

Adjuvant chemotherapy (AC) following curative gastrectomy for stage II/III gastric cancer (GC) is recommended in Japan. However, for various reasons, patients cannot always start AC at the appropriate time. This study was designed to investigate the effect of the postoperative duration until adjuvant chemotherapy (PDAC) and cumulative S-1 dose on prognosis.

Methods

Between 2008 and 2014, 76 consecutive GC patients who underwent postoperative S-1 monotherapy were enrolled in this study.

Results

Postoperative complications of Clavien–Dindo grade II or higher and postoperative peak C-reactive protein of 8 mg/dl or higher were significantly associated with delayed AC. The cut-off value of PDAC selected to most effectively stratify prognosis was 7 weeks. For relapse-free survival (RFS), patients with $PDAC \geq 7$ weeks had an insignificantly poorer prognosis than those with $PDAC < 7$ weeks ($p = 0.017$, 5-year RFS: $PDAC \geq 7$ weeks vs. $PDAC < 7$ weeks, 48.5% vs. 77.0%). A multivariate analysis showed that $PDAC \geq 7$ weeks [$p = 0.007$; hazard ratio (HR) 3.99 (95% CI: 1.46–11.5)] and cumulative S-1 dose $> 12,000$ mg [$p = 0.033$; HR 0.38 (95% CI: 0.14–0.93)] were independent prognostic factors. In patients with a cumulative S-1 dose $\geq 12,000$ mg, there were no prognostic differences between patients with and without $PDAC \geq 7$ weeks.

Conclusions

7 weeks after surgery could be an indicator starting AC. A cumulative S-1 dose of more than 12,000 mg might be a key dose for diminishing the poor prognostic effects of delaying AC.

Background

Gastric cancer is the fourth most commonly diagnosed cancer and the third most common cause of cancer-related death worldwide [1]. Treatment for gastric cancer has been enhanced by improvements in surgical procedures and perioperative management [2–6]. Although surgical resection mainly involves macroscopic tumor resection and lymphadenectomy, the oncologic effect of surgical treatment is often limited to the local control. Therefore, perioperative therapy has been recommended to clear remaining microscopic metastasis [7].

The ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) study and its 5-year follow-up results demonstrated that adjuvant chemotherapy (AC) with S-1 monotherapy following curative gastrectomy with lymphadenectomy significantly improved relapse-free survival and overall survival

rates. Therefore, AC following curative gastrectomy has been recommended as the standard treatment in Japan for stage II/III gastric cancer since 2014 (JGCTG 2014) [8, 9].

The ACTS-GC study proved the beneficial prognostic effect of starting S-1 treatment within 6 weeks of undergoing curative surgery. However, patients cannot always start AC at the appropriate time following surgery due to various clinical issues that can result in delayed recovery. The prognostic effect of any delay with regard to AC remains controversial [10, 11]. Even if the prognosis may be affected by a delay in starting AC, until now there has been no definite cut-off value for the postoperative duration following curative surgery with which to stratify the prognosis [12]. Moreover, it is not clear whether a sufficient total S-1 dose during AC could affect the prognosis or diminish the poor prognostic effect resulting from a delay in starting AC.

In this study, we investigated the clinical significance of the postoperative duration until adjuvant chemotherapy (PDAC) and the total cumulative S-1 dose, with particular reference to the prognosis. The results of our study suggest a crucial indicator starting AC. Our study also suggested that the cumulative S-1 dose might be key to diminishing any poor prognostic effect, even if there is a delay in starting AC.

Methods

Patients and surgical procedures

This study was approved by the Kyoto Prefectural University of Medicine, Japan, and was therefore performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all patients to participate in the research. A total of 214 consecutive patients underwent curative gastrectomy with lymphadenectomy for stage II or III GC at our institute between January 2008 and December 2014. Of these 214 patients, 97 patients received S-1 monotherapy as AC. We excluded 21 patients from the study because of neoadjuvant chemotherapy (n = 2), insufficient follow-up (n = 1), recurrence during AC (n = 8), remnant GC (n = 3), and multiple carcinomas (n = 7). As a result, we retrospectively investigated 76 consecutive patients who received S-1 AC (**Fig. 1**).

Patients with clinical stage IA (clinical T1 and clinical N0 GC) underwent D1+ lymphadenectomy, while those with clinical stage IIA or higher underwent D2 or D2+ lymphadenectomy. All patients underwent macroscopic curative resection (R0); resected specimens were examined by pathologists and evaluated in accordance with the Japanese classification of GC [13]. Dissected lymph nodes were fixed in buffered formalin and embedded in paraffin prior to pathological examination. Pathologists in our institution examined embedded lymph nodes by sectioning slices in the plane of the largest node dimension to confirm the presence of metastasis. Clinicopathological findings from these patients were determined retrospectively on the basis of their hospital records.

Follow-up after curative gastrectomy followed by AC

Postoperative follow-up was performed in the outpatient clinic every three months following surgery. Blood chemistry was also measured every three months. Endoscopic examinations were performed annually, and computed tomography (CT) examinations were performed every three-to-six months for five years after surgery. The average follow-up period was 52.7 months.

AC was begun in the outpatient clinic following discharge. The dose of S-1 was determined according to a patient's body surface area (BSA). Specifically, patients with $BSA < 1.25 \text{ m}^2$ received 80 mg per day; patients with $1.25 \text{ m}^2 \leq BSA < 1.5 \text{ m}^2$ received 100 mg per day; and patients with $1.5 \text{ m}^2 \leq BSA$ received 120 mg per day. The cumulative S-1 dose received by each patient during AC was calculated from their hospital records.

Statistical analysis

Statistical analyses were conducted using JMP version 10 (SAS Institute Inc., Cary, NC). The Mann–Whitney U test for unpaired data comprising continuous variables was used to compare clinicopathological variables. For the analysis of survival, Kaplan–Meier survival curves were constructed for groups based on univariate predictors, and differences between the groups were tested using a generalized Wilcoxon test. The Cox proportional hazards model was used for further evaluations of multivariate survival analysis. A p-value < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of GC patients after curative gastrectomy followed by S-1 AC

Table 1 shows the clinical characteristics of GC patients who received curative gastrectomy followed by S-1 AC. The mean age of the patients was 62.9 years. Of 76 patients, 47 (61.8%) were male and 29 (38.2%) were female; 30 patients were at pStage IIA, 17 patients were at pStage IIB, 17 patients were at pStage IIIA, and 12 patients were at pStage IIIB. Total gastrectomy was performed in 30 patients (39.5%), distal gastrectomy in 44 patients (57.9%), and proximal gastrectomy was performed in two patients (2.6%) for curative resection dependent on the location of the tumor. A total of 19 patients (25.0%) underwent D1+ lymphadenectomy based on their clinical stage, while the remaining patients performed D2 or D2+ lymphadenectomy [13].

Cut-off value of PDAC to stratify the prognosis and correlation between PDAC and clinicopathological factors

We performed a minimum p-value analysis for relapse-free survival (RFS) using various cut-off values for PDAC, as shown in **Fig. 2**. The cut-off value of 7 weeks post-surgery was confirmed to be the upper-limit to stratify the prognosis ($p = 0.017$; 5-year RFS: PDAC ≥ 7 weeks vs. PDAC < 7 weeks; 48.5 % vs. 77.0 %). Although there were no significant differences in 5-year overall survival (OS) rates, patients in the PDAC ≥ 7 weeks group had a poorer prognosis than those in the PDAC < 7 weeks group ($p = 0.49$; 5-year OS: PDAC ≥ 7 weeks vs. PDAC < 7 weeks; 74.3 % vs. 80.7 %). (**Fig. 3**).

Cut-off value of cumulative S-1 dose to stratify the prognosis and combined survival curves using PDAC and cumulative S-1 dose factors

To clarify the clinical effect of cumulative S-1 dose, we performed a minimum p-value analysis for RFS using various cut-off values of cumulative S-1 dose (data not shown). A cut-off value of 12,000 mg was confirmed to stratify the prognosis most ($p = 0.006$; 5-year RFS: cumulative S-1 dose $\geq 12,000$ mg vs. $< 12,000$ mg; 84.7 % vs. 52.4 %).

Next, we compared survival curves between four groups: 1) PDAC ≥ 7 weeks / total S-1 dose $\geq 12,000$ mg; 2) PDAC < 7 weeks / total S-1 dose $\geq 12,000$ mg; 3) PDAC ≥ 7 weeks / total S-1 dose $< 12,000$ mg; and 4) PDAC < 7 weeks / total S-1 dose $< 12,000$ mg. With regard to patients who received a cumulative S-1 dose $< 12,000$ mg, there was a significant prognostic difference between the PDAC ≥ 7 -weeks group and the PDAC < 7 -weeks group for RFS ($p = 0.040$; 5-year RFS: PDAC ≥ 7 weeks vs. PDAC < 7 weeks; 25.0 % vs. 66.3 %). However, in patients who received a cumulative S-1 dose $> 12,000$ mg there was no prognostic difference between the PDAC ≥ 7 -weeks group and PDAC < 7 -weeks group for RFS ($p = 0.64$; 5-year RFS: PDAC ≥ 7 weeks vs. PDAC < 7 weeks; 85.7 % vs. 84.4 %). (**Fig. 4**)

Comparison of PDAC with clinicopathological factors

Next, we evaluated correlations between PDAC and clinicopathological factors using the Mann–Whitney U test. As shown in **Table 2**, a high peak in the C-reactive protein (CRP) cut-off value of 8 mg/dl or above was significantly associated with a delay in starting S-1 AC. In addition, the incidence of postoperative complications (Clavien–Dindo classification $\geq$ II) tended to be linked to longer PDAC ($p = 0.065$). There were no other significant differences between the groups with regard to other clinicopathological factors.

Univariate and multivariate analysis using Cox's proportional hazard model

To elucidate the prognostic factors for recurrence-free survival, univariate and multivariate analysis using Cox's proportional hazard model were performed. As shown in **Table 2**, age, gender, BMI, histological type, a postoperative peak CRP of ≥ 8 mg/dl, complications of Clavien–Dindo grade II or higher, pT-stage, pN-stage, cumulative S-1 dose, and PDAC were selected as clinical variables. The multivariate analysis showed that PDAC ≥ 7 weeks [$p = 0.007$; hazard ratio (HR) 3.99 (95% CI: 1.46–11.5)] and cumulative S-1 dose $> 12,000$ mg [$p = 0.033$; HR 0.38 (95% CI: 0.14–0.93)] were independent prognostic factors.

Discussion

There have been few reports of prognostic effects with regard to PDAC and the extent of S-1 treatment in AC [11, 12, 14]. In this study, we clearly demonstrated that a PDAC ≥ 7 weeks and a cumulative S-1 dose of more than 12,000 mg were independent prognostic factors in GC patients undergoing AC following curative gastrectomy. Moreover, in patients who received a cumulative S-1 dose of more than 12,000 mg, we showed that there were no prognostic differences between patients who had a PDAC of more than or less than 7 weeks. PDAC ≥ 7 weeks. Our results strongly suggested that a cumulative S-1 dose of more

than 12,000 mg is a crucial indicator and might be the key dose for diminishing the poor prognostic effects arising from a delay in AC.

Concerning PDAC, we clearly demonstrated that 7 weeks was the best cut-off value to stratify the prognosis of patients with pStage II/III gastric cancer ($p = 0.017$; 5-year RFS: PDAC ≥ 7 weeks vs. PDAC < 7 weeks; 48.5 % vs. 77.0 %). From an oncological perspective, to eliminate microscopic metastasis it appears that AC should be started immediately following curative gastrectomy. PDAC has been reported to be an independent prognostic factor in other types of cancer, with various cut-off values suggested, including 12 weeks [10] and 8 weeks in colon cancer [15-17] and 13 weeks (91 days) in breast cancer [18]. With regard to gastric cancer, various cut-off values of PDAC have been reported as prognostic factors, ranging from 4 to 8 weeks [12, 16, 19-21]. Our PDAC cut-off value of 7 weeks could also be a candidate indicator. Future studies are warranted, and big data analysis might be needed to determine the best cut-off value for clinical settings.

Regarding the cumulative S-1 dose, we also demonstrated that a cumulative S-1 dose of more than 12,000 mg was an independent prognostic factor for RFS [$p = 0.033$; HR 0.38 (95% CI: 0.14–0.93)]. The Japanese phase 3 randomized trial (JCOG1104 [OPAS-1]) revealed that four courses of S-1 AC were inferior to eight courses of S-1 AC for achieving RFS of pStage II gastric cancer, highlighting the importance of the duration of AC [22]. Fujitani et al. also reported that S-1 AC with a duration of more than 6 months could have a prognostic impact in patients with gastric cancer [11]. These results could be a crucial indicator of the importance of S-1 AC duration. However, the S-1 dose intensity in each patient is considerably different in clinical practice, and is indeed not as high as shown in previous reports [8, 23, 24]. Therefore, we suggest that the cumulative S-1 dose is also a pivotal factor, in addition to the PDAC of S-1.

The most striking finding in the present study was that there were no prognostic differences for RFS between patients with PDAC ≥ 7 weeks and those with PDAC < 7 weeks ($p = 0.64$; 5-year RFS: PDAC ≥ 7 weeks vs. PDAC < 7 weeks; 85.7 % vs. 84.4 %). Specifically, these results suggested that a cumulative S-1 dose of more than 12,000 mg might diminish the poor prognostic effect associated with a delay in AC. Similar results were also reported that S-1 AC of more than 6 months [11] and S-1 AC with a relative dose intensity of more than 64.6 % [12] have more prognostic impact than PDAC. Although which factors have the optimal impact on prognosis is unclear, we enhance on the cumulative S-1 dose. As shown by our results, patients could not always begin AC at the appropriate time because of various clinical issues, such as a high serum CRP level or postoperative complications. To avoid postoperative complications [25] and achieve low postoperative CRP levels [26], less invasive surgery is a pivotal surgical goal from a prognostic perspective. Nevertheless, if these issues are encountered and AC cannot be initiated with sufficient S-1 dose intensity, administering high cumulative S-1 dose treatment even after a long PDAC could be a valuable strategy that could potentially rescue high-risk patients with these issues.

This study had some limitations: the results were obtained from a retrospective evaluation of a small number of patients at a single institute. A large-scale, multicenter cohort study is necessary to confirm the

significance of PDAC and cumulative S-1 dose.

Conclusions

Patients with early initiation of AC had better prognosis than those with delayed initiation. 7 weeks could be a crucial indicator starting AC, and a cumulative S-1 dose of more than 12,000 mg might be a key dose for diminishing the poor prognostic effects of delaying AC.

Declarations

Acknowledgements

Not applicable.

Ethical approval and consent to participate

This study was designed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine. All patients received sufficient explanation of the study, and written informed consent was obtained.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution:

YT and SK designed this work. SK, KN, TA, TK, HK, RM, AS, YK, HI, TK, HF, KO, EO acquired clinical data and critically reviewed this manuscript. YT and SK analyzed data and wrote the paper.

Abbreviations

GC: gastric cancer; AC: adjuvant chemotherapy; PDAC: postoperative duration until adjuvant chemotherapy; RFS: relapse-free survival; ACTS-GC: Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer

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Tables

Table 1 Clinicopathological characteristics of patients who received S-1 monotherapy as adjuvant chemotherapy.

Variable		n	%
Total		76	
Gender	Male	47	62%
	Female	29	38%
Age (years)	≥ 70	55	72%
	< 70	21	28%
BMI ^a (kg/m ²)	≥ 18.5	69	91%
	< 18.5	7	9%
Tumor location	Upper	24	32%
	Middle	32	42%
	Lower	20	26%
pT category ^b	T1	6	8%
	T2	12	16%
	T3	39	51%
	T4	19	25%
pN category ^b	N0	27	36%
	N1	12	16%
	N2	21	28%
	N3	16	21%
pStage ^b	IIA	30	39%
	IIB	17	22%
	IIIA	17	22%
	IIIB	12	16%
Histopathological type	Differentiated	30	39%
	Undifferentiated	46	61%
Operation	Total gastrectomy	30	39%
	Distal gastrectomy	44	58%
	Proximal gastrectomy	2	3%
Lymphadenectomy	D1+	19	25%
	D2 or D2+	57	75%

^a BMI: body mass index,

^b Classification of Gastric Carcinoma.

Table 2 Comparison of PDAC with clinicopathological factors.

Variable		n	PDAC ^a (days)			p-value ^c
			□ mean	±	SD ^b	□
Gender	Male	47	□ 41.6	±	12.8	□ 0.992
	Female	29	□ 46.3	±	24.5	□
Age (years)	≥ 70	21	□ 42.0	±	11.6	□ 0.857
	< 70	55	□ 43.9	±	20.2	□
BMI ^d (kg/m ²)	≥ 18.5	69	□ 41.9	±	12.7	□ 0.907
	< 18.5	7	□ 58.4	±	44.8	□
ASA-PS ^e	1	49	□ 44.1	±	20.2	□ 0.841
	≥2	27	□ 42.2	±	14.1	□
GPS ^f score	0	68	□ 42.8	±	14.0	□ 0.282
	≥ 1	8	□ 48.6	±	40.2	□
PNI ^g score	≥ 48	54	□ 42.6	±	14.5	□ 0.684
	< 48	22	□ 45.4	±	25.4	□
pStage	II	47	□ 42.3	±	14.1	□ 0.945
	III	29	□ 45.1	±	23.5	□
Histological type	Differentiated	30	□ 41.9	±	10.7	□ 0.663
	Undifferentiated	46	□ 44.4	±	21.8	□
Surgical approach	Open	59	□ 45.0	±	19.5	□ 0.224
	Laparoscopy	17	□ 37.8	±	11.5	□
Post-operative peak CRP ^h (mg/dl)	≥8	44	□ 46.3	±	20.1	□ 0.046
	< 8	32	□ 39.4	±	14.6	□
Complication (C-D ⁱ ≥ II)	Positive	9	□ 54.0	±	21.2	□ 0.065
	Negative	67	□ 42.0	±	17.4	□

^a PDAC: postoperative duration until adjuvant chemotherapy, ^b Mann-Whitney U test analysis,

^c SD: standard deviation, ^d BMI: body mass index,

^e ASA-PS: Physical status proposed by the American Society of Anesthesiologists (ASA),

^f GPS: Glasgow prognostic score, ^g PNI: prognostic nutritional index,

^h CRP: C-reactive protein, ⁱ C-D: Clavien-Dindo classification

Table 3 Univariate and multivariate analysis using Cox's proportional hazard model.

Variable	n	Univariate ^a <i>p</i> value	Multivariate ^b				
			HR ^c	95% CI ^d		<i>p</i> -value	
Total	76						
Gender							
Male vs. Female	47 vs. 29	0.128					
Age (years)							
≥ 70 vs. < 70	21 vs. 55	0.165					
BMI (kg/m ²)							
≥ 18.5 vs. < 18.5	69 vs. 7	0.090					
pT category ^e							
pT1-3 vs. pT4	57 vs. 19	0.048	4.14	1.47	- 12.14	0.008	
pN category ^e							
pN0 vs. pN1-2	27 vs. 49	0.038	2.95	1.08	- 10.32	0.034	
Histological type							
Differentiated vs. Undifferentiated	30 vs. 46	0.899					
Postoperative peak-CRP (mg/dl)							
≥ 8 vs. < 8	44 vs. 32	0.933					
Complication (C-D>II) ^f							
Positive vs. Negative	9 vs. 67	0.637					
PDAC (weeks)							
≥ 7 vs. < 7	20 vs. 56	0.017	3.99	1.46	- 11.51	0.007	
Cumulative S-1 dose (mg)							
≥12,000 vs. < 12,000	40 vs. 36	0.006	0.38	0.14	- 0.93	0.033	

^a Analyzed by Log Rank (Mantel-Cox) test.

^b Analyzed by Cox's proportional hazard model.

^c HR: hazard ratio, ^d CI: confidence interval.

^e Japanese Classification of Gastric Carcinoma.

^f Clavien-Dindo Classification

Figures

Figure 1

A total of 97 patients underwent S-1 monotherapy as adjuvant chemotherapy for stage II/III gastric cancer between 2008 and 2014. Of these, 21 patients were excluded from the study for the reasons listed in the main text. Data for the remaining 76 consecutive patients were obtained from their hospital records and retrospectively analyzed.

Figure 2

Cut-off values of the postoperative duration until adjuvant chemotherapy (PDAC) The cut-off value of PDAC to stratify relapse-free survival (RFS) rates the most effectively in pStage II/III gastric cancer was 7 weeks post-surgery ($p = 0.017$).

Figure 3

Comparison of 5-year relapse-free survival (RFS) rates (a) Patients with PDAC ≥ 7 weeks had a significantly poorer relapse-free survival (RFS) rate than patients with PDAC < 7 weeks (5-year RFS: 48.5 % vs. 77.0 %, $p = 0.017$). (b) The patients with PDAC ≥ 7 weeks had a poorer overall survival (OS) rate than patients with PDAC < 7 weeks (5-year OS: 74.3 % vs. 80.7 %, $p = 0.49$).