International Journal of Clinical Oncology (2019) 24:1190–1196
https://doi.org/10.1007/s10147-019-01468-0

ORIGINAL ARTICLE

Late start and insufficient S-1 dose in adjuvant chemotherapy can lead to poor prognosis in stage II/III gastric cancer

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Received: 13 February 2019 / Accepted: 7 May 2019 / Published online: 18 May 2019

Abstract

Background How the interval between surgery and S-1 adjuvant chemotherapy (ACT), and S-1 relative dose intensity (RDI) affect prognosis in patients with stage II/III gastric cancer who undergo gastrectomy with D2 lymph node dissection followed by S-1 ACT is unclear.

Methods We enrolled 95 patients with histopathologically confirmed gastric adenocarcinoma treated with gastrectomy with D2 dissection, followed by S-1 ACT.

Results Per ROC analysis, we used 32 days as the optimal cut-off interval to divide patients into the delayed group (started ACT ≥ 32 days) and the non-delayed group (< 32 days). Their 5-year overall survival (OS) rates differed significantly (delayed: 54.2%, non-delayed: 85.4%; $P < 0.0001$). Per ROC analysis of patients without recurrence within 1 year post-surgery, patients were divided into the high RDI (RDI^{High}; ≥ 64.6%) and low RDI (RDI^{Low}; < 64.6%) groups. Their 5-year OS rates differed significantly (RDI^{High}: 76.9%, RDI^{Low}: 63.7%; $P = 0.012$). In multivariate analysis, RDI and interval before starting ACT were independent prognostic indicators. Five- year OS rates by subgroups were RDI^{High}/non-delayed: 84.0%, RDI^{High}/delayed: 66.8%, RDI^{Low}/non-delayed: 100%, and RDI^{Low}/delayed: 48.2% ($P < 0.0001$).

Conclusions Early initiation and sufficient RDI for S-1 ACT can improve the prognosis of patients with stage II/III gastric cancer.

Keywords Adjuvant chemotherapy · Gastric cancer · Prognosis · Recurrence · S-1

Introduction

The prognosis for patients with gastric cancer (GC) has been improved by better diagnostic techniques and better intraoperative and postoperative care. Worldwide, however, an estimated 1,300,000 new GC diagnoses, and 819,000 deaths from GC, occurred in 2015, placing GC fifth among cancer incidences and third among causes of cancer deaths [1, 2].

Gastrectomy with regional lymph node dissection is the mainstay curative treatment for GC. However, many GC patients experience recurrence even after complete tumor removal (R0 resection). Recurrence usually arises from micrometastases that cannot be detected by ordinary diagnostics, including ultrasonography, computed tomography, and positron emission tomography. Therefore, perioperative therapy has been recommended to clear microscopic tumors. Cunningham et al. demonstrated that a perioperative regimen of epirubicin, cisplatin, and fluorouracil significantly improved progression-free and overall survival (OS) [3]. Adjuvant chemotherapy (ACT) is also usually performed after surgery to prevent recurrence. The principle of ACT is that circulation of anticancer drugs throughout the entire body via the bloodstream can control micrometastases and prevent recurrence. The effectiveness of postoperative ACT in preventing recurrence has been shown in patients with GC who underwent curative surgeries. Nakajima et al. found a significant survival benefit for postoperative ACT with uracil and tegafur in patients with serosa-negative, node-positive GC [4]. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) also showed a survival benefit from ACT after D2 gastrectomy compared with surgery alone for patients with stage II/III GC [5]. The Japanese Gastric Cancer Treatment

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Guideline recommends ACT with S-1 for a year after gastrectomy with D2 dissection for stage II/III GC, based on the results of ACTS-GC [6]. Capecitabine–oxaliplatin-based ACT also reportedly improves 3-year disease-free survival significantly after gastrectomy with D2 dissection for stage II/III GC [7]. These results strongly indicate that ACT is an indispensable component of recurrence prevention for resected advanced GC.

Because gastrectomy reduces decreases stomach volume, some patients' postoperative nutritional status is worse than their preoperative nutritional status, which can results in late initiation and insufficient ACT intake after their surgeries. In this regard, Aoyama et al. showed that weight loss, which is common after gastrectomy, is the most important risk factor for noncompliance with S-1 ACT in patients with stage II/III GC who have undergone D2 gastrectomies [8]. However, how late initiation of S-1 ACT and insufficient intake of S-1 affect the prognoses of stage II/III GC patients are unclear. The current study investigated the effects of late S-1 ACT initiation and insufficient S-1 intake on prognosis in patients with stage II/III GC.

Materials and methods

Patients

We retrospectively enrolled 95 patients with stage II/III GC who underwent curative gastrectomies (R0 resections) and S-1 ACT at our institution between January 2001 and April 2013. T1N3 and T3N0 patients were not included in the current study. The institutional review board of our institution approved of the study (approval number: 19A025). The informed consent requirement was waived. Patients' clinicopathologic findings were determined according to the Japanese Classification of Gastric Carcinoma [9]. All patients underwent either distal partial, proximal partial, or total gastrectomy with regional lymph node dissection. No patients underwent radiation therapy or neoadjuvant chemotherapy. Patients were periodically checked for early recurrence by diagnostic imaging (chest X-ray, upper gastrointestinal endoscopy, ultrasonography, and/or computed tomography). Causes of death and patterns of recurrence were determined by reviewing medical records, including laboratory data, ultrasonography, computed tomography, scintigrams, peritoneal punctures, and laparotomies, or by the direct inquiry of family members.

Treatment schedule

The Japanese Gastric Cancer Treatment Guideline recommends starting ACT with S-1 within 6 weeks post-surgery for patients with stage II/III GC [6]. Therefore, patients with stage II/III GC are usually scheduled to visit outpatient clinic 5 to 6 weeks after operation to start adjuvant chemotherapy with S-1. The S-1 dose was based on body surface area (BSA). Patients with a BSA of < 1.25 m^2 received 80 mg daily; those with a BSA of 1.25–1.5 m^2 received 100 mg

Table 1 Relationships between the interval before starting S-1 adjuvant chemotherapy after operation and clinicopathological variables in patients with gastric cancer

Variable	Interval (days)	*P* value
Age		0.78
< 70 ($n=53$)	37.6 ± 15.5	
≥ 70 ($n=42$)	40.3 ± 24.7	
Gender		0.041
Male ($n=71$)	41.2 ± 21.3	
Female ($n=24$)	31.8 ± 13.5	
Tumor size		0.13
< 5 cm ($n=43$)	43.0 ± 24.4	
≥ 5 cm ($n=52$)	35.4 ± 14.9	
Histology[a]		0.81
Differentiated ($n=40$)	40.6 ± 25.8	
Undifferentiated ($n=55$)	37.5 ± 14.6	
Depth of invasion		0.82
T2/T3 ($n=71$)	38.8 ± 21.3	
T4 ($n=24$)	38.8 ± 16.1	
Lymph node metastasis		0.23
N0/N1 ($n=40$)	35.5 ± 14.6	
N2/N3 ($n=55$)	41.2 ± 23.0	
Lymphatic invasion		0.86
Ly0/Ly1 ($n=32$)	38.1 ± 17.1	
Ly2/Ly3 ($n=63$)	39.2 ± 21.5	
Venous invasion		0.077
V0/V1 ($n=46$)	37.2 ± 23.5	
V2/V3 ($n=49$)	40.4 ± 16.1	
Stage of disease		0.3
II ($n=45$)	36.2 ± 15.1	
III ($n=50$)	41.2 ± 23.4	
Approach		0.0004
Open ($n=65$)	36.2 ± 22.0	
Laparoscopy ($n=30$)	44.5 ± 13.3	
Gastrectomy		0.82
Total ($n=37$)	38.0 ± 16.4	
Proximal and diastal ($n=58$)	39.3 ± 22.2	
Postoperative complication[b]		0.023
Absent ($n=58$)	33.9 ± 11.3	
Present ($n=37$)	46.5 ± 27.3	

All results are expressed as the mean ± SD

[a]Differentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma

[b]Present, postoperative complication of grade II and more according to Clavien-Dindo classification

daily; and those with a BSA of > 1.5 m^2 received 120 mg daily. Patients received S-1 for 28 days every 6 weeks for 12 months. Relative dose intensity (RDI) was defined as the actual dose divided by the planned dose. Toxic effects were evaluated according to the Common Terminology Criteria for Adverse Events V4.0.

Statistical analysis

Differences among the post-surgical interval before starting S-1 ACT (PSI), S-1 RDI, and clinicopathological variables were evaluated using the Mann–Whitney U test. The Youden index was calculated using receiver operating characteristic (ROC) analysis to determine optimal cutoffs for PSI and RDI of S-1 in survival analyses. Survival curves were calculated according to the Kaplan–Meier method. Differences between curves were identified using the log-rank test. Univariate analysis of factors considered prognostic of overall survival (OS) were performed using Cox's proportional hazards model. Multivariate analyses of factors considered prognostic of OS were based on Cox's proportional hazards model and a stepwise procedure. $P < 0.05$ was considered to be significant. GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA) and Stat View (Abacus Concepts, Inc., Berkeley, CA, USA) software were used for the statistical analyses.

Results

Mean PSI was 38.8 days (range 10–167 days). Table 1 shows correlations between PSI and patients' clinicopathological variables. Mean PSIs were significantly longer for male patients, those who underwent laparoscopic gastrectomies, and those with postoperative complications than for female patients ($P = 0.041$), those who underwent open gastrectomies ($P = 0.0004$), and those without postoperative complications ($P = 0.023$), respectively. As ROC analysis for OS indicated that the optimal PSI cut-off time was 32 days (AUC = 0.56, $P = 0.33$), we divided patients into the delayed group (≥ 32; $n = 36$) and the non-delayed group (< 32; $n = 59$). Their 5-year OS rates differed significantly (delayed: 54.2%, non-delayed: 85.4%; $P < 0.0001$; Fig. 1a). Their 5-year relapse-free survival (RFS) rates also differed significantly (delayed: 54.6%, non-delayed: 77.3%; $P = 0.0053$; Fig. 1b).

Among the 95 patients, S-1 ACT was terminated in 8 patients due to recurrence within 1 year after initiating treatment. Those 8 patients were excluded in the subsequent analysis. Mean RDI was 68.4% (range 3.1–135.7) in the remaining 87 patients. Table 2 shows correlations between RDI and patients' clinicopathological variables. The RDI was significantly higher in patients < 70 years of age and those without adverse effects than in elderly patients aged ≥ 70 years ($P = 0.014$) and those with adverse effects ($P = 0.0003$), respectively. The RDI was also significantly higher in non-delayed group than in delayed group ($P = 0.031$).

As ROC analysis for OS indicated that the optimal RDI cut-off was 64.6% (AUC = 0.59, $P = 0.18$), we divided patients into the high RDI (RDI^{High}; ≥ 64.6%; $n = 56$) and low RDI (RDI^{Low}; < 64.6%; $n = 31$) groups. Their 5-year OS rates differed significantly (RDI^{High}: 76.9%, RDI^{Low}: 63.7%; $P = 0.012$; Fig. 2a). Their 5-year RFS rates also differed significantly (RDI^{High}: 79.4%, RDI^{Low}: 49.4%; $P = 0.0012$; Fig. 2b). Univariate analysis indicated that depth of invasion, lymphatic invasion, type of gastrectomy, PSI, and RDI were significantly associated with OS (Table 3). Multivariate analysis was performed using all covariates included in univariate analysis and indicated that RDI and PSI were independent prognostic indicators (Table 3). Figure 3 shows

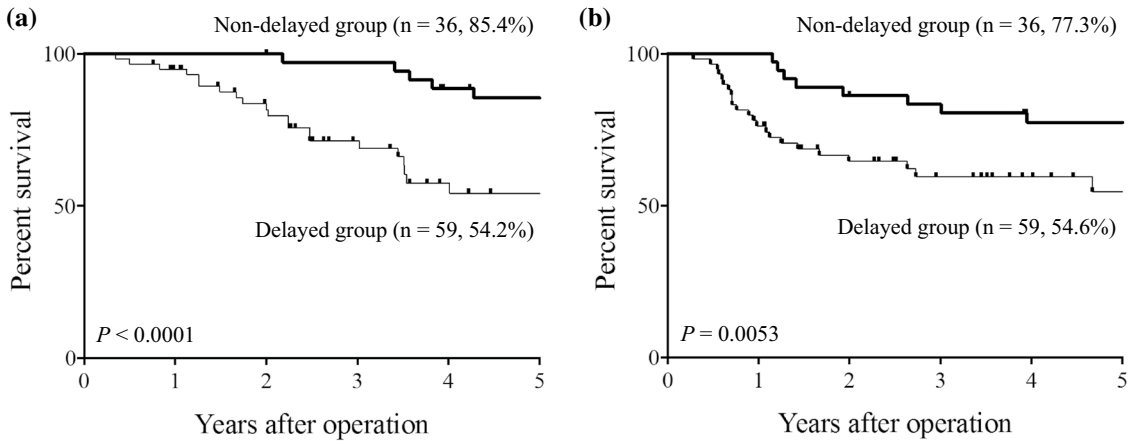

Fig. 1 Overall survival curves (**a**) and relapse-free survival curves (**b**) by the interval between undergoing gastrectomy and starting S-1 adjuvant chemotherapy

our cohort's survival curves according to PSI and RDI. Their 5-year survival rates by subgroup differed significantly, at RDI^{High}/non-delayed: 84.0%, RDI^{High}/delayed: 66.8%, RDI^{Low}/non-delayed: 100%, and RDI^{Low}/delayed: 48.2% ($P < 0.0001$; Fig. 3). In the subgroup analysis, furthermore, the prognosis of RDI^{High}/delayed group was significantly better than that of RDI^{Low}/delayed group ($P = 0.044$). The prognosis of RDI^{High}/non-delayed tended to be better than that of RDI^{High}/delayed group ($P = 0.072$).

Discussion

Recurrence usually arises from residual micrometastases. Surgery induces inflammation and suppression of cell-mediated immunity, which is likely to induce the growth of those residual cancer cells. In fact, studies in animal models suggest that surgery may increase numbers of circulating tumor cells and potentially the growth of metastatic deposits. In addition, this increase in metastatic growth is considered to correlate with increased angiogenesis and enhanced production of oncogenic growth factors [10–13], which implies that the postsurgical condition encourages growth of residual cancer cells, which eventually results in recurrence. A meta-analysis associated a 4-week delay before ACT with significantly decreased OS and disease-free survival in patients with colorectal cancers [14]. In addition, ACT initiated > 61 days after surgery was associated with adverse outcomes among patients with stage II breast cancer [15]. These findings indicate that ACT should be initiated promptly after curative surgery to prevent recurrence. Most clinical trials mandate that ACT begins within 6–8 weeks after surgery.

The Japanese Gastric Cancer Treatment Guideline also recommends starting ACT with S-1 within 6 weeks post-surgery for patients with stage II/III GC [6]. Based on this recommendation, Yamamoto et al. demonstrated that the prognosis of advanced GC was significantly related to the start of S-1 adjuvant treatment within 6 weeks after surgery for patients with stage II/III GC [16]. However, because the optimal time to start ACT has not been the subject of a randomized controlled trial, no data has shown the appropriate PSI. In the current study, we demonstrated that delayed initiation of S-1 ACT worsened prognosis of stage II/III GC patients. Most importantly, ROC analysis indicated that optimal PSI cutoff value was 32 days in the current study, indicating that initiating ACT after 32 days of operation worsened the prognosis of GC patients. Therefore, our results support the recommendation by the Japanese Gastric Cancer Treatment Guideline. On the other hand, mean PSIs were significantly longer in patients who underwent laparoscopic gastrectomies than in those who underwent open gastrectomies. The frequencies of postoperative complication of

Table 2 Relationships between S-1 relative dose intensity and clinicopathological variables in gastric cancer patients who did not have recurrence within 1 year after operation

Variable	Relative dose intensity	*P* value
Age		0.014
< 70 (*n* = 49)	75.7 ± 36.7	
≥ 70 (*n* = 38)	58.9 ± 36.6	
Gender		0.53
Male (*n* = 64)	70.4 ± 36.8	
Female (*n* = 23)	62.7 ± 39.3	
Tumor size		0.38
< 5 cm (*n* = 39)	66.2 ± 38.5	
≥ 5 cm (*n* = 48)	71.0 ± 36.7	
Histology[a]		0.91
Differentiated (*n* = 36)	66.7 ± 40.3	
Undifferentiated (*n* = 51)	69.6 ± 35.5	
Depth of invasion		0.52
T2/T3 (*n* = 66)	68.7 ± 38.8	
T4 (*n* = 21)	67.3 ± 33.3	
Lymph node metastasis		0.89
N0/N1 (*n* = 37)	69.8 ± 36.2	
N2/N3 (*n* = 50)	67.4 ± 38.6	
Lymphatic invasion		0.22
Ly0/Ly1 (*n* = 29)	75.3 ± 37.1	
Ly2/Ly3 (*n* = 58)	65.0 ± 37.4	
Venous invasion		0.4
V0/V1 (*n* = 44)	72.7 ± 36.0	
V2/V3 (*n* = 43)	64.0 ± 38.7	
Stage of disease		0.8
II (*n* = 42)	66.8 ± 39.2	
III (*n* = 45)	69.9 ± 36.1	
Approach		0.2
Open (*n* = 58)	72.1 ± 36.0	
Laparoscopy (*n* = 29)	61.0 ± 39.7	
Gastrectomy		0.36
Total (*n* = 32)	64.3 ± 38.0	
Proximal and diastal (*n* = 55)	70.8 ± 37.2	
Postoperative complication[b]		0.9
Absent (*n* = 54)	68.7 ± 36.1	
Present (*n* = 33)	67.9 ± 40.0	
Adverse effect[c]		0.0003
Absent (*n* = 37)	83.2 ± 32.6	
Present (*n* = 50)	57.4 ± 37.2	
PSI		0.031
Delayed group (*n* = 52)	61.4 ± 38.1	
Non-delayed group (*n* = 35)	78.8 ± 34.3	

All results are expressed as the mean ± SD

PSI post-surgical interval before starting S-1 adjuvant chemotherapy

[a]Differentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma

[b]Present, postoperative complication of grade II and more according to Clavien-Dindo classification

[c]Present, adverse effect of grade II and more according to the Common Terminology Criteria for Adverse Events V4.0

grade 2 and more according to Clavien-Dindo classification were 36.7% and 26.2% in patients who underwent laparoscopic gastrectomies and in those who underwent open gastrectomies, respectively. In the current study, PSI was significantly longer in patients with CDC grade 2/3/4 compared with those without postoperative complication and those with CDC grade 1. Therefore, it is likely that the high frequency of postoperative complication observed in patients who underwent laparoscopic gastrectomies is responsible for the late initiation of ACT.

Because the aim of ACT is to eradicate micrometastatic tumor cells, continuing chemotherapy for a minimal length of time is essential to ensure that these cells are eradicated. The recommended duration of ACT for solid tumors ranges from 6 to 12 months. In particular, 6 months of treatment are necessary for breast and colon cancers, whereas the ACTS-GC trial indicated that 12 months were necessary for GC [5]. However, the optimal duration of ACT for GC is still unclear. Receiving S-1 treatment for one year can be difficult because of adverse effects. In fact, ACTS-GC showed that only 65.8% of the patients allocated to their S-1 arm could continue their treatment for an entire year [5]. The current study also found that RDI was significantly less in patients with adverse effects than in those without adverse effects. Therefore, we determined the optimal RDI cutoff value to improve prognosis of GC patients, and found that prognosis of patients with ≥ 64.6% RDI was significantly better than that of patients with < 64.6% of RDI, which indicates that treatment should be continued for at least 6 months to achieve ≥ 64.6% RDI.

In ACT for GC patients, patients received S-1 for 28 days every 6 weeks for 12 months. The S-1 dose was based on BSA. Modification of administration period and reduced S-1 dose are sometime required due to adverse effects. In this regard, we previously demonstrated that alternate-day S-1 administration improved compliance and led to fewer adverse effects [17]. Therefore, alternate-day S-1 ACT could be a more sustainable option for patients with stage II/ III GC to achieve ≥ 64.6% S-1 RDI.

In multivariate analysis, both RDI and PSI were independent prognostic indicators. In fact, our results demonstrated that prognosis of patients with both late initiation of S-1 treatment and insufficient S-1 RDI was extremely poor. On the other hand, prognosis of patients with late initiation of S-1 treatment improved if sufficient S-1 RDI was achieved. The prognosis of patients with ≥ 64.6% RDI was significantly better than that of patients with < 64.6% of RDI in patients with late initiation of S-1 treatment in the current study. The main reason for late initiation of postoperative ACT is postoperative complications. Furthermore, the presence of postoperative inflammatory complication reportedly worsens prognosis in GC patients [18]. Therefore, to prevent recurrence, achieving ≥ 64.6% S-1 RDI in late-initiating patients seems especially important. On the other hand, the prognosis of RDI^{Low}/non-delayed group was extremely good in the current study. It is likely that early initiation of S-1 treatment after operation make it possible to kill residual cancer cells before they grow, which results in the prevention of recurrence. Therefore, less than 64.6% S-1 RDI might be enough to prevent recurrence in early-initiating patients. Since the number of patients in RDI^{Low}/non-delayed group was so small in this study, however, the results must be confirmed in a large-scale trial.

Our study had a few limitations. First, it had the bias associated with retrospective studies. Second, our study cohort was rather small, which may have particularly affected our ROC calculations for optimal cut-off values for PSI and RDI. Therefore, the results must be confirmed in a large-scale, prospective, randomized, controlled trial.

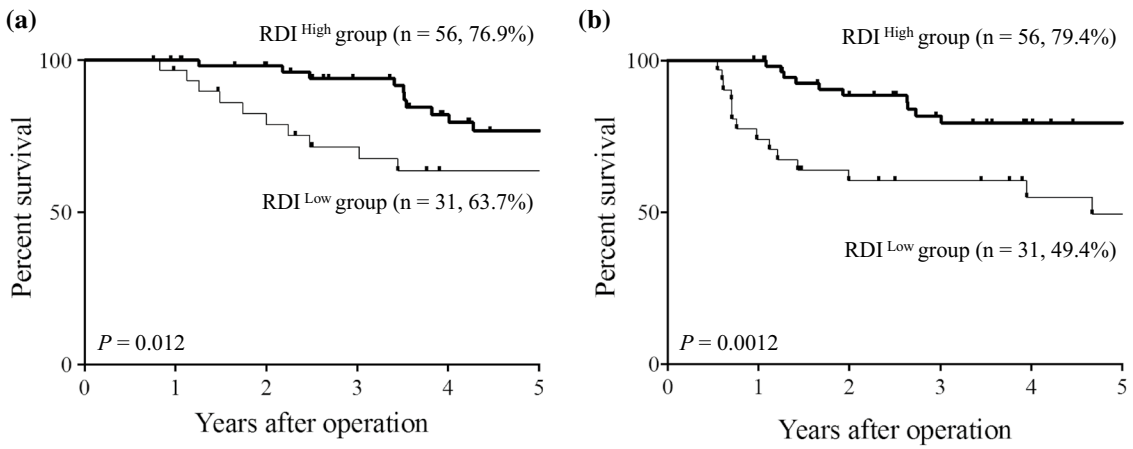

Fig. 2 Overall survival curves (**a**) and relapse-free survival curves (**b**) by relative S-1 dose intensity

Table 3 Univariate and multivariate analyses of factors prognostic of overall survival in stage II/III gastric cancer patients who underwent S-1 adjuvant chemotherapy

Variables	Univariate analysis			Multivariate analysis		
	P value	HR[h]	95% CI[i]	P value	HR	95% CI
Age[a]	0.24	1.02	0.98–1.07			
Gender (female vs. male)	0.13	2.16	0.79–5.88			
Depth of invasion (T2–T4)[b]	0.036	2.01	1.05–3.88	0.0014	2.941	1.52–5.691
Lymph node metastasis (N0–N3)[c]	0.065	1.48	0.98–2.25			
Lymphatic invasion (Ly0–Ly3)[d]	0.012	2.15	1.19–3.90			
Venous invasion (V0–V3)[e]	0.37	1.24	0.78–1.97			
Histology (differentiated vs. undifferentiated)[f]	0.99	1.00	0.45–2.22			
Tumor size[a]	0.39	1.06	0.92–1.23			
Serum concentration of preoperative CEA[a]	0.75	1.01	0.96–1.06			
Serum concentration of preoperative CA19-9[a]	0.45	1.00	0.99–1.01			
Body weight loss rate[a]	0.10	1.09	0.98–1.22	0.026	1.129	1.014–1.256
Approach (laparoscopy vs. open)	0.80	1.14	0.42–3.08			
Gastrectomy (total vs. proximal and distal)	0.048	2.22	1.01–4.90			
Lymph node dissection (D0/1 vs. D2 and more)	0.13	1.89	0.83–4.33			
PSI[g] (delayed vs. Non-delayed)	0.0008	5.26	2.00–13.84	0.0002	6.711	2.494–17.86
Relative dose intensity (non-completion vs. completion)	0.016	2.67	1.20–5.92	0.02	2.743	1.172–6.417

The depth of invasion, lymph node metastasis, lymphatic invasion, and venous invasion were used as numeric characters

[a]Continuous variable

[b]Depth of invasion: T2, tumor invasion of the muscularis propria; T3, tumor invasion of the subserosa; T4, tumor penetration of the serosa or tumor invasion of adjacent organs

[c]Lymph node metastasis: N0, no regional lymph node metastasis; N1, metastasis in 1–2 regional lymph nodes; N2, metastasis in 3–6 regional lymph nodes; N3, metastasis in 7 or more regional lymph nodes

[d]Lymphatic invasion: Ly0–Ly3, grade of lymphatic invasion

[e]Venous invasion: V0–V3, grade of venous invasion

[f]Differentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma

[g]Post-surgical interval before starting S-1 adjuvant chemotherapy

[h]*HR* hazard ratio

[i]*CI* confidence interval

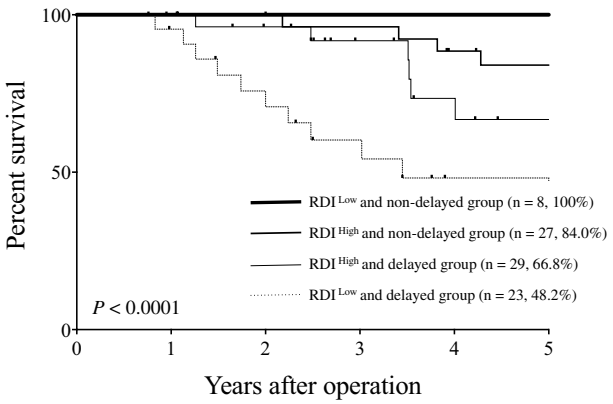

Fig. 3 Overall survival curves according to both the interval between undergoing gastrectomy and starting S-1 adjuvant chemotherapy, and relative S-1 dose intensity

In conclusion, our study indicates that early initiation and sufficient RDI of S-1 as ACT are important to prevent post-surgical recurrence for patients with stage II/III gastric cancer.

Acknowledgement We thank Marla Brunker, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Compliance with Ethical Standards

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

Ethical approval All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards.

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