

# Phase II Feasibility Study of Adjuvant Chemotherapy With Docetaxel/Cisplatin/S-1 Followed By S-1 For Stage III Gastric Cancer

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## Research Article

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# Abstract

## *Background*

To evaluate the feasibility, safety, and efficacy of postoperative adjuvant chemotherapy with docetaxel/cisplatin/S-1 (DCS) following S-1 therapy in patients with stage III gastric cancer after curative gastrectomy.

## *Methods*

Patients with stage III gastric cancer who underwent D2 gastrectomy were enrolled. Adjuvant chemotherapy was initiated within 8 weeks of gastrectomy. The first cycle of chemotherapy consisted of S-1 monotherapy (day 1–14), followed by a 7-day rest period. Cycles 2 and 3 consisted of the following: S-1 (day 1–14) administration, followed by a 14-day rest period, and an intravenous infusion of cisplatin and docetaxel on days 1 and 15. After 2 cycles, S-1 was administered for up to 1 year.

## *Results*

Thirty patients were enrolled between 2013 and 2017. Febrile neutropenia of grade 3 or higher was the most common hematological toxicity with 4 patients (13.3%). Other hematological toxicities of grade 3 or higher were as follows: neutropenia in 3 (10.0%), leukopenia in 3 (10.0%), and anemia in 2 (6.7%). Most frequent non-hematological toxicity of grade 3 was anorexia (n=4, 13.3%) and general fatigue (n=3, 10.0%); no grade 4 non-hematological toxicities were observed. Twenty-five patients (83.3%) completed 2 cycles of DCS treatment and 18 (60.0%) completed subsequent S-1 treatment for 1 year. The relative dose intensity of docetaxel and cisplatin was 0.86 and that of S-1 was 0.88.

## *Conclusion*

The DCS regimen can be acceptable as an adjuvant chemotherapy and offers an effective postoperative treatment option for stage III gastric cancer patients.

*Trial registration number.* UMIN000012785

*Date of registry.* 08/01/2014

# Introduction

Postoperative adjuvant chemotherapy for gastric cancer has been used to eradicate minimal residual disease. In particular, patients with advanced gastric cancer, who are at a high risk of recurrence even after curative resection, require effective postoperative adjuvant chemotherapy to prolong survival. In 2006, the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), which was a phase III trial, conducted a two-arm study comparing the effects of 1-year adjuvant chemotherapy with S-1 and surgery alone, after curative gastrectomy for stage II or III gastric cancer. This study demonstrated a survival

benefit of adjuvant chemotherapy with S-1; the 5-year survival rate was 71.7% in the S-1 group and 61.1% in the surgery alone group, with a hazard ratio (HR) of 0.669 (95% confidence interval (CI): 0.54–0.828) [1]. Based on these results, adjuvant treatment with S-1 has become the standard treatment for stage II/III gastric cancer patients who have undergone radical surgery, according to the 13th edition of the General Rules for Gastric Cancer Treatment [2]. Meanwhile, a subgroup analysis for stage IIIB disease showed that patients in the S-1 group were associated with better overall survival (OS) than patients who underwent surgery alone, regardless of sex, age, or histology, with an HR of 0.791 (95% CI: 0.52–1.205); however, there was no statistically significant survival benefit [3]. These results may be affected by the limitations in the number of patients enrolled in the subgroup analysis; therefore, further improvement in adjuvant chemotherapy for stage IIIB gastric cancer patients is needed. Many exploratory clinical trials and several phase III studies have been conducted in Japan and overseas to clarify the safety, feasibility, and efficacy of the postoperative administration of S-1 in combination with other anti-cancer agents for advanced gastric cancer [4–6]. However, compliance with adjuvant chemotherapy is challenging because of postoperative physical decline in patients [7, 8]. Various phase II and phase III trials of preoperative chemotherapy are currently ongoing with the aim of improving the treatment outcome of gastric cancer; however, no favorable results with high-quality evidence have been reported [9, 10].

In this study, we conducted a phase II trial to evaluate the feasibility, safety, and efficacy of postoperative adjuvant therapy with docetaxel/cisplatin/S-1 (DCS) following S-1 therapy in patients with stage IIIA, IIIB, and IIIC gastric cancer after R0 gastrectomy.

## Materials And Methods

### Inclusion and exclusion criteria

Patients who met the following eligibility criteria were enrolled in this study: (1) histologically confirmed stage IIIA, IIIB, or IIIC gastric cancer [11]; (2) patients receiving curative gastrectomy with a D2 lymph node dissection or greater [12]; (3) macroscopic tumor type was neither Borrmann type 4 nor large ( $\geq 8$  cm) type 3; (4) no prior chemotherapy or radiation therapy, including treatment for other types of cancer; (5) performance status of 0–1 on Eastern Cooperative Oncology Group classification; (6) no gastric stump cancer; (7) no esophageal invasion or invasion of  $\leq 3$  cm; (8) able to receive chemotherapy within 4–8 weeks after surgery; (9) aged between 25 and 75 years; (10) sufficient oral intake; (11) adequate organ function (white blood cell [WBC] count  $\geq 3,500/\text{mm}^3$  and  $< 12,000/\text{mm}^3$ , neutrophil count  $\geq 2,000/\text{mm}^3$ , hemoglobin level  $\geq 9.0$  g/dl, platelet count  $\geq 100,000/\text{mm}^3$ , total bilirubin level  $\leq 1.5$  mg/dl, aspartate transaminase (AST) and alanine aminotransferase (ALT) levels  $\leq 100$  IU/l; (12) creatinine level  $\leq 1.2$  mg/dl, creatinine clearance  $> 60$  ml/min in the Cockcroft-Gault equation; and (13) written informed consent provided by the patient to participate in the study.

The following patients were excluded: (1) synchronous or metachronous (within 5 years) duplication cancers other than carcinoma in situ; (2) contraindications to S-1, cisplatin, and docetaxel; (3) current treatment with systemic steroids; (4) continued use of flucytosine, phenytoin, or warfarin; (5) a history of

serious drug hypersensitivity; (6) serious comorbidities (intestinal paralysis, intestinal obstruction, interstitial pneumonia or pulmonary fibrosis, neuropathy, uncontrolled diabetes, heart failure, renal failure, or hepatic failure, etc.); (7) severe mental disorders; (8) history of myocardial infarction or unstable angina pectoris within 6 months; (9) diarrhea (watery stool); (10) pregnancy or breastfeeding; (11) hepatitis B surface antigen positivity; and (12) those deemed ineligible for this study by the investigator or sub-investigator.

This study was approved by the Shimane University Institutional Committee on Ethics and was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Studies. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry, number 000012785. Written informed consent was obtained from the patients prior to the study.

### **Patient characteristics**

Thirty patients were enrolled in this study between March 2013 and December 2017. The characteristics of the patients are summarized in Table 1. There were 26 men and 4 women, with a median age of 69 years (range, 51–79 years). Total gastrectomy, proximal gastrectomy, and distal gastrectomy were performed in 12 patients (40%), 2 patients (6.7%), and 16 patients (53.3%), respectively. Histologically, 2 patients (6.7%) had well-differentiated adenocarcinoma, 12 (40%) had moderately differentiated adenocarcinoma, and 16 (53.3%) patients had undifferentiated adenocarcinoma. In regard to cancer staging, 12 patients (40.0%) had stage IIIA, 9 patients (30.0%) had stage IIIB, and 9 patients (30.0%) had stage IIIC.

### **Treatment schedule**

Adjuvant chemotherapy was initiated 4–8 weeks after the gastrectomy. The first cycle of chemotherapy consisted of S-1 monotherapy, which was administered twice daily at the following oral doses based on the patient's body surface area (BSA): 40 mg ( $BSA < 1.25 \text{ m}^2$ ), 50 mg ( $BSA \geq 1.25 \text{ m}^2$ ), or 60 mg ( $BSA \geq 1.5 \text{ m}^2$ ), from day 1 to day 14, followed by a 7-day rest. Cycles 2 and 3 adhered to the following schedule: oral administration of S-1 (same dose as that of the first cycle) twice daily from day 1 to day 14, a 14-day rest, followed by intravenous infusion of cisplatin at  $35 \text{ mg/m}^2$  for 2 hours and intravenous infusion of docetaxel at  $35 \text{ mg/m}^2$  for 2 hours on days 1 and 15. After 2 cycles, S-1 was administered for up to 1 year. To avoid cisplatin-induced renal dysfunction, adequate hydration with normal saline ( $> 2000 \text{ ml}$ ) was administered on days 1 and 15.

Antiemetic analgesics were routinely prescribed to prevent nausea and vomiting. On day 1, all patients received aprepitant 125 mg orally 60 min before cisplatin infusion plus intravenous palonosetron (0.75 mg) and dexamethasone (12 mg) approximately 30 minutes prior to receiving cisplatin. On days 2 and 3, all patients received oral aprepitant 80 mg once daily after breakfast. Rescue antiemetics, such as 5-hydroxy-tryptamine-3 (5-HT<sub>3</sub>) receptor antagonists, were prescribed to treat prominent, unbearable

nausea and vomiting. These prophylactic antiemetics were used in accordance with the Japan Society of Clinical Oncology Guidelines for Antiemetics in Oncology 2010 [13].

## **Toxicity assessment**

The patient's symptoms and physical examination results were obtained. The assessment and grading of blood test were done according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0

([https://ctep.cancer.gov/protocoldevelopment/electronic\\_applications/ctc.htm#ctc\\_40](https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40)).

Subsequent chemotherapy was postponed if a patient did not meet the following criteria: WBC count  $\geq 3,000 \text{ mm}^3$ , neutrophil count  $\geq 1,500 \text{ mm}^3$ , hemoglobin level  $\geq 8.0 \text{ g/dl}$ , platelet count  $\geq 75,000 \text{ mm}^3$ , total bilirubin level  $\leq 1.5 \text{ mg/dl}$ , AST and ALT levels  $\leq 100 \text{ IU/l}$ , and creatinine concentration  $< 1.2 \text{ mg/dl}$ . After confirming non-hematological toxicities, body temperature, general fatigue, anorexia, stomatitis, diarrhea, watery eyes, and neuropathy were graded (0 or 1) for adjuvant chemotherapy, and other non-hematological toxicities were graded as 2 or lower.

The dose of S-1 was reduced by 20 mg/day when any adverse events mentioned above were observed during the previous cycle. Patients in whom the dose of S-1 was already reduced to 80 mg per day were withdrawn from the study when adverse events reoccurred. The doses of docetaxel and cisplatin were reduced from 35 to 20 mg/m<sup>2</sup> in case of any adverse events. Moreover, if patients could not resume subsequent cycles within 4 weeks due to toxicities, they were withdrawn from the study.

## **Follow-up**

During the study, physical examination, complete blood cell counts, and biochemical examination were performed on the first day of each chemotherapy cycle, and every 3 months thereafter. Computed tomography was performed every 6 months for the first 3 years, and yearly thereafter.

## **Statistical analysis**

The primary endpoint of this study was the completion rate of two courses of S-1 in combination with DCS chemotherapy. Secondary endpoints were OS, recurrence-free survival (RFS), cumulative 1-year S-1 completion rate, and the safety of the chemotherapy regimen. OS was defined as the time from registration to the date of death from any cause. RFS was defined as the interval from registration until objective tumor recurrence. OS and PFS were estimated using the Kaplan-Meier method. Data for patients who remained event-free at clinical time were censored on the day they were last reviewed. Relative dose intensity (RDI) was defined as the administered dose divided by the planned dose.

All statistical analyses were conducted using JMP software for Windows (version 14.0; SAS Institute, Cary, NC, USA).

## **Results**

## Toxicity

Table 2 summarizes the adverse events observed in this study. Febrile neutropenia of grade 3 or higher was the most common hematological toxicity which was associated with 4 patients (13.3%). Other hematological toxicities, which were grade 3 or higher, were as follows: neutropenia in 3 patients (10.0%), leukopenia in 3 patients (10.0%), and anemia in 2 patients (6.7%). The most frequent non-hematological toxicity of grade 3 or higher was anorexia, which was observed in 4 patients (13.3%), followed by general fatigue in 3 patients (10.0%).

Granulocyte-colony-stimulating factor (G-CSF) and antibiotics were required for 4 patients who had febrile neutropenia of grade 3 or higher. All chemotherapy-related toxicities were resolved with appropriate care, and treatment-related deaths were not observed in this study. Non-hematological toxicities were generally mild, and grade 4 patients were not observed.

## Treatment compliance

Table 3 summarizes treatment compliance in this study. Twenty-five patients (83.3%) completed two cycles of the DCS treatment, and 18 patients (60.0%) completed subsequent S-1 treatment for 1 year. Dose reduction of DCS was required in 6 patients (20.0%). The second DCS cycle was delayed in 4 patients owing to several reasons, such as general fatigue (n=2, 6.7%) and anorexia (n=2, 6.7%). The dose of S-1 was reduced in 6 patients (20.0%), mainly due to a grade 3 or higher neutropenia (n=2, 6.7%) and anorexia (n=4, 13.3%).

The RDI of docetaxel and cisplatin was 0.86, and the RDI of S-1 for the DCS treatment was 0.88.

One patient withdrew from the study because the patient refused subsequent chemotherapy due to disagreeable toxicities.

## Survival analysis

The median follow-up period was 1335 days (range, 684–2639). All patients were followed-up for at least 3 years from the date of registration. At the time of the date cut-off on December 31, 2020, 10 patients had died of primary disease, 2 patients survived with recurrence, and the remaining 18 remained well without recurrence.

The 1-, 2-, and 3-year OS rates were 100%, 93% (95% CI: 79.8–99.5), and 72.1% (95% CI: 53.3–85.4), respectively (Figure 1a). The 1-, 2-, and 3-year RFS rates were 86.7% (95% CI: 69.4–94.9), 66.7% (95% CI: 48.3–81.0), and 63.3% (95% CI: 45.1–78.3), respectively (Figure 1b).

## Discussion

In the present study, we investigated whether the DCF chemotherapy regimen is safe to be administered as postoperative adjuvant therapy with acceptable toxicity in patients who underwent R0 resection for

gastric cancer. Adjuvant chemotherapy after curative surgery is beneficial in reducing recurrence and improving OS in patients with resectable gastric cancer [1, 14, 15]. However, strict consideration should be given to tolerability of patients and safety of the regimen when administering multidrug adjuvant chemotherapy since postoperative patients are often physically weak, [16–18] and gastrectomy-induced decline in tolerability to chemotherapy may limit intensive adjuvant treatment. Therefore, attention towards neoadjuvant chemotherapy (NAC) is increasing; however, effective NAC regimens with high-quality evidence are yet to be developed [19, 20]. Further refinement and modification of postoperative regimens without compromising the patient's quality of life is important to improve the clinical outcome of patients with gastric cancer.

In Japan, the standard regimens considered as adjuvant chemotherapy for gastric cancer are S-1 for pathological stage II and docetaxel plus S-1 for stage III patients, based on the results of the ACTS-GC [1, 3] and START-II trials [20], respectively. The ACTS-GC trial revealed that 66.4% of the enrolled patients were tolerable to S-1 alone for 1 year. While the START-II trial was conducted to prove the superiority of administering postoperative S-1 plus docetaxel over S-1 alone for pathological stage III gastric cancer patients; it revealed that 234 (69%) of the 320 patients tolerated the originally planned 6 doses of docetaxel treatment, with a dose reduction in 94 patients (28%). Regarding patient compliance with S-1, administration of S-1 for 1 year persisted in 168 patients (49%) in the S-1 plus docetaxel group and 195 patients (56%) in the S-1 alone group. In the present study, a relatively high tolerance for DCS treatment was also observed, that is, 25 (83.3%) patients completed two courses of DCS and 18 (60.0%) patients subsequently received S-1 for 1 year; this was probably because docetaxel and cisplatin were administered biweekly in two divided doses, after anticipating a decrease in toxicity [21–23]. Takahari et al. [24] investigated the tolerability of adjuvant therapy with S-1 plus cisplatin in patients with stage III gastric cancer who underwent gastrectomy, based on the original protocol stating three courses of S-1 plus cisplatin followed by S-1 alone for 1 year after surgery. However, the protocol was revised due to the low completion rate of the study that was revealed in the interim evaluation; following which, S-1 alone was the first course and S-1 plus cisplatin were courses 2–4, finally followed by S-1 alone until 1 year after surgery. As a result, the completion rates of 3 courses of S-1 plus cisplatin therapy improved from 57% before revision to 81% after revision [24]. The S-1 plus cisplatin regimen was safer and better tolerated when cisplatin was administered after the second course of S-1, than administering cisplatin in the first course. In the present study, S-1 monotherapy was selected as the first course.

Sato et al. [25] and Nakayama et al. [22] reported that grade 3 and grade 4 neutropenia was observed in 77.4% and 42.9%, of patients after administering NAC with DCS, respectively. In our study, febrile neutropenia was the most common hematological toxicity, accounting for only 13.3% of cases. In addition, patients with grade 4 neutropenia or grade 3 or 4 febrile neutropenia required the use of G-CSF, with a short duration of neutropenia. In patients who required the use of G-CSF in the first cycle, the occurrence of neutropenia and febrile neutropenia was reduced in the second cycle because G-CSF was administered prophylactically to these patients. The most common grade 3 non-hematologic toxicities in our study were anorexia (13.3%) and general fatigue (10.0%). Grade 3 nausea was observed in only 3.3% of patients. Anorexia and nausea were usually tolerable and managed with a planned protocol of

prophylactic administration of antiemetics (5-HT<sub>3</sub> antagonists plus corticosteroids) during cisplatin administration. Notably, adjuvant chemotherapy was continued according to the protocol in most cases. In addition, most toxicities associated with chemotherapy were resolved by prolonging the onset of treatment, reducing the dose of anti-cancer drugs, or providing appropriate supportive care. As a result, there were no treatment-related deaths in this study.

Future directions for chemotherapeutic research include administering oxaliplatin, a platinum-based drug with reduced toxicity, for the gastrointestinal system and kidney. In addition, intensive management of chemotherapy-related adverse effects with prophylactic agents is necessary. Olanzapine is an atypical antipsychotic drug that inhibits neurotransmitter pathways known to be involved in nausea and vomiting [26, 27]. Evaluation of the efficacy of olanzapine in combination with standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting is warranted.

Although our study provided some useful information, several limitations need to be considered when interpreting the results of this study. First, our clinical trial may have enrolled relatively healthy patients, that is, there may be a selection bias related to performance status, age, and comorbidities. Second, the study was not sufficiently powered to identify specific populations that are more likely to derive benefits from DCS chemotherapy because of its small sample size. Third, we initially planned to recruit 10 patients per year; however, there were not enough patients diagnosed with stage III gastric cancer due to an unexpectedly low incidence of gastric cancer in Japan, which is probably due to *Helicobacter pylori* eradication and the widespread use of gastric cancer screening [28, 29]. Therefore, the study required a longer time to enroll eligible patients, and the chemotherapy regimen recommended by the Japanese Guidelines for the Treatment of Gastric Cancer was revised during the study period [30].

In conclusion, our phase II study revealed that the DCS regimen can be acceptable as adjuvant chemotherapy in terms of safety and toxicity, and may offer a viable postoperative treatment option for patients with stage III gastric cancer.

## Declarations

**Ethics approval and consent to participate:** This study was performed in line with the principles of the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Studies. Approval was granted by the Shimane University Institutional Committee on Ethics (28 September 2012). This study was registered with the University Hospital Medical Information Network Clinical Trials Registry.

Written informed consent was obtained from all individual participants included in the study.

**Consent to publish:** Patients signed informed consent regarding publishing their data.

**Availability of data and material:** The datasets used and analyzed 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's contributions:** NH was the lead author and surgeon for all of the patients. TM and SK were the co-surgeon. TY, RH, KT, YU and KI contributed patients and information on the patients. YT reviewed the paper and surgical technique. All authors read and approved the final manuscript.

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## Tables

Table 1. Baseline patient characteristics

Characteristics	No. of patients (%)
Median age year, (range)	69 (51-79)
Gender	
male	26 (86.7)
female	4 (13.4)
Median BMI, (range)	22.2 (15.3-28.5)
Primary lesion	
Upper	8 (26.7)
Middle	11 (36.7)
Lower	11 (36.7)
Type of gastrectomy	
Proximal	2 (6.7)
Distal	16 (53.3)
Total	12 (40.0)
Macroscopic type	
1	1 (3.3)
2	5 (16.7)
3	22 (73.3)
5	2 (6.7)
Differentiation	
well	2 (6.7)
mod	12 (40.0)
poor	16 (53.3)
Tumor stage	
3	14 (46.7)
4a	16 (53.3)
Nodal stage	
1	2 (6.7)
2	13 (43.3)
3a	12 (40.0)
3b	3 (10.0)
UICC stage	
IIIA	12 (40.0)
IIIB	9 (30.0)
IIIC	9 (30.0)

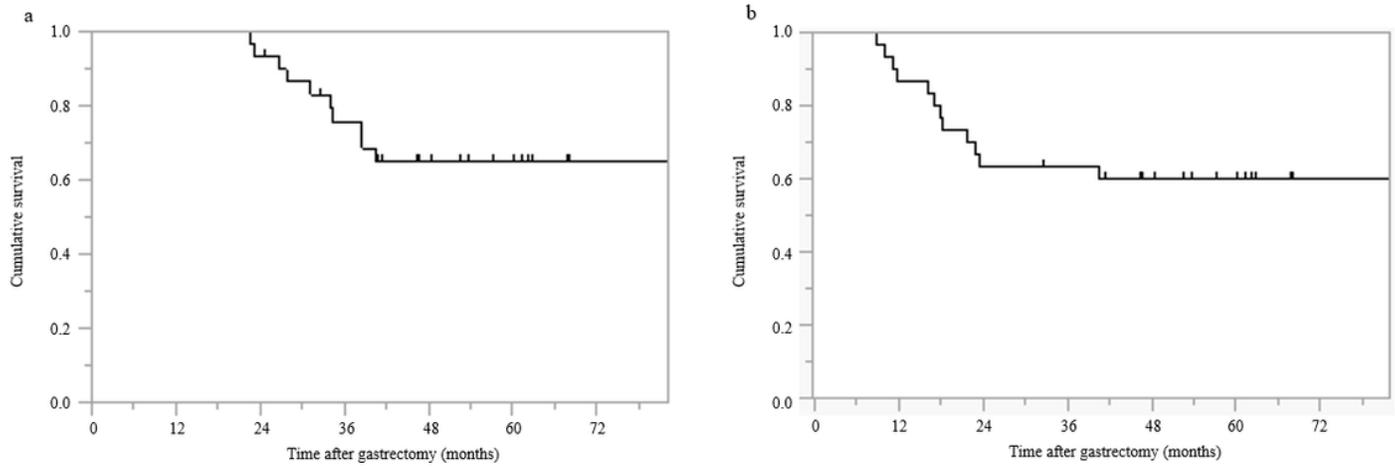
Table 2. Toxicity of adjuvant chemotherapy

Toxicity	No. of patients (%)	
	Grade 3 or higher	All
Hematological toxicity		
Neutropenia	3 (10.0)	14 (46.7)
Leukopenia	3 (10.0)	12 (40.0)
Anemia	2 (6.7)	10 (33.3)
Thrombocytopenia	0 0.0	8 (26.7)
Febrile neutropenia	4 (13.3)	4 (13.3)
Non-hematological toxicity		
Nausea	1 (3.3)	19 (63.3)
Diarrhea	1 (3.3)	6 (20.0)
Anorexia	4 (13.3)	22 (73.3)
Fatigue	3 (10.0)	23 (76.7)
Stomatitis	0 0.0	5 (16.7)
Abdominal distension	0 0.0	2 (6.7)
Alopecia	0 0.0	17 (56.7)
Dry skin	0 0.0	2 (6.7)
Dysgeusia	0 0.0	3 (10.0)
Skin pigmentation	0 0.0	4 (13.3)

Table 3. Compliance to adjuvant chemotherapy

	No. of patients (%)	
Cycle of DCS		
1	29	(96.7)
2	25	(83.3)
S-1 administration period (month)		
3	28	(93.3)
6	27	(90.0)
9	23	(76.7)
12	18	(60.0)

## Figures



**Figure 1**

The Kaplan-Meier estimates indicate overall survival (a) and relapse-free survival (b) after curative gastrectomy for stage III gastric cancer