

Outcome predictors for patients with stage II/III gastric cancer who undergo gastrectomy and S-1 adjuvant chemotherapy

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Received May 25, 2016; Accepted February 13, 2017

DOI: 10.3892/ol.2017.6286

Abstract. Predictors of survival in patients with stage II/III gastric cancer (GC) who received tegafur/gimeracil/oteracil (S-1) adjuvant chemotherapy (ACT) subsequent to gastrectomy were examined. Additionally, the association between dose intensity of S-1 and survival rate was investigated. A total of 62 patients with stage II/III gastric cancer were retrospectively evaluated, each of whom had received a curative D2 gastrectomy and S-1 ACT. The relative performance (RP; administered/planned S-1 doses $\times 100\%$), body mass index (BMI), prognostic nutritional index (PNI) and body weight (BW) were calculated, and the association of survival with these factors and other clinicopathological parameters was examined. The 1-year treatment continuation rate for S-1 was 94.2%, excluding patients who experienced cancer recurrences during their ACT year. The initial S-1 reduction rate was 38.7%. Patients with stage II/IIIA disease exhibited significantly improved 5-year overall survival rates compared with patients with stage IIIB GC, 81.6/73.7 vs. 33.8% ($P < 0.01$). No association between RP and survival was observed. BMI, BW and PNI were significantly decreased following surgery compared with preoperative states. In the univariate analysis, postoperative BW loss (BMI loss), pathological stage and >7 lymph node metastases were significantly associated with outcome ($P < 0.05$); in the multivariate analysis, postoperative

BW loss $>10.6\%$ and pathological stages were independent prognostic factors for survival. Continuing S-1 ACT for the full year exhibited a greater effect on survival compared with dosage. Early postoperative nutritional deterioration may decrease the survival rates in these patients.

Introduction

Gastric cancer (GC) is the fifth most common type of malignancy in the world, with 952,000 incident cases estimated to have occurred in 2012 (1). The standard treatment for stage II/III GC in Japan is gastrectomy with extended (D2) lymphadenectomy plus postoperative tegafur/gimeracil/oteracil (S-1) adjuvant chemotherapy (ACT) for 1 year, according to the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) (2,3). However, 30.6% of patients undergo cancer recurrences, 65.8% continue their S-1 treatments for a full year and 46.5% of patients are administered reduced doses of their recommended regimens (2,3). The clinical parameters for continuing S-1 ACT in these patients has been the focus of several studies (4-6), as has the role of S-1 dose intensity in ACT subsequent to curative gastrectomy for advanced GC (7). However, the association between relative dose intensity or continuation of S-1 and patient survival has not been fully characterized.

The prognostic significance of a number of clinical parameters has been examined for patients with GC subsequent to radical surgery (8-15). Of these, the preoperative prognostic nutritional index (PNI) as a reflection of the immunological and nutritional condition of the patients has been associated with the outcomes of patients who undergo gastrectomy for a number of stages of GC (10,11,16,17). Although the association between body mass index (BMI) and postoperative complications has been investigated (18-22), the association between BMI and long-term survival subsequent to curative gastrectomy remains unclear (23-28). The association between BMI and outcome in patients who received ACT for colon cancer has been demonstrated (29), but not the analogous association for patients with gastric cancer.

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Abbreviations: ACT, adjuvant chemotherapy; BMI, body mass index; CCr, creatinine clearance; PNI, prognostic nutritional index; RP, relative performance; BW, body weight

Key words: gastric cancer, adjuvant chemotherapy, tegafur/gimeracil/oteracil, survival predictors

In the present study, the dose-response effects of S-1 ACT on survival in patients who received gastrectomy for GC were clarified, and other clinical factors that affected their survival were analyzed, including BMI and PNI as nutritional parameters.

Patients and methods

Data collection involved a survey of original medical records and drug information databases of Nara Hospital, Kindai University School of Medicine (Ikoma, Japan). Patients with histologically confirmed primary gastric adenocarcinoma who had received curative gastrectomy with D2 lymphadenectomy and ACT with S-1 between January 2007 and December 2014 at Nara Hospital, Kindai University School of Medicine were enrolled and retrospectively evaluated. All patients exhibited adenocarcinoma histology, as demonstrated by endoscopic biopsies, with pathological stage II or III disease according to the Japanese Classification of Gastric Carcinoma (13th edition) (30); the TNM Classification of Malignant Tumors (7th edition) (31) was also used. Gastric adenocarcinomas can be divided into two major histological types, diffuse and intestinal type according to the Lauren classification (32). Patients received S-1 beginning between 4 and 8 weeks after surgery, typically at a standard dose of S-1 of 80 mg/m²/day for 4 weeks, followed by 2 weeks of no chemotherapy. This 6-week cycle was repeated during the first year following surgery. A 3-week regimen of 80 mg/m² S-1 for 2 weeks, followed by a 1-week rest, was also permitted. Certain patients received S-1 dose decreases, according to the criteria outlined in the ACTS-GC study (3), but decisions to decrease or cease S-1 ACT were entrusted to the patients and their physicians. Almost all patients in whom cancer recurrence was detected during their year of S-1 ACT were transferred to second-line chemotherapy, which included CPT-11, cisplatin and taxanes.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0) (33). The present study was approved by the ethical review committee of Nara Hospital, Kindai University School of Medicine. Median follow up time was 44.76 months, ranging between 13.5-92 months. Written informed consent was obtained from all patients. The concept of the present study is available on the Nara Hospital website (<http://www.kindainara.com/act/goannai.pdf>).

Clinical and nutritional parameters. Clinical and pathological parameters were evaluated from medical records, and postoperative prognostic factors with S-1 adjuvant therapy were analyzed. The relative performance (RP) value was evaluated instead of the relative dose intensity. RP value was calculated as (administered S-1 dose)/(planned S-1 administration dose) x100%. The overall survival (OS) rates were compared between low- and high-RP groups. Creatinine clearance (CCr), was calculated using the formula developed by Cockcroft and Gault (34). PNI was evaluated and calculated as [10x serum albumin value (g/dl)] + (0.005x peripheral lymphocyte counts), using serum albumin (mg/dl) level and peripheral lymphocyte counts (counts/mm³)

Table I. Clinicopathological characteristics of patients in the present study (n=62).

Factor	n
Sex	
Male	41
Female	21
Mean age, years	64.9
Tumor location in stomach	
Upper	17
Middle	21
Lower	24
Pathological type ^a	
Intestinal	22
Diffuse	40
Depth of tumor invasion (pT) ^b	
T1	2
T2	11
T3	18
T4a	28
T4b	3
Pathological nodal status ^c	
N0	7
N1	23
N2	32
No. of lymph node metastasis (pN) ^c	
0 (N0)	7
1-2 (N1)	15
3-6 (N2)	12
≥7 (N3)	27
Final pathological stage ^c	
II	21
IIIA	20
IIB	21
Surgery type	
Total gastrectomy	21
Distal gastrectomy	41

^aLauren classification (32); ^bTNM Classification of Malignant Tumours (7th edition) (31); ^cJapanese Classification of Gastric Carcinoma (13th edition) (30). p, pathological; T, tumor; N, node.

assessed between 1 and 2 months after surgery (35), and BMI (kg/m²) was calculated as weight in kg/ (height in m)². Body weight (BW), BMI and PNI were evaluated between 2 and 4 weeks before, and between 1 and 2 months after, surgery. Postoperative BW and BMI losses were calculated between 1 and 2 months after surgery as (postoperative value-preoperative value)/preoperative value x100%). As BW loss and BMI loss were the same values, we evaluated only BW loss. The threshold values for postoperative BW loss (BMI loss), PNI, CCr and number of metastatic lymph nodes were decided by receiver operating characteristic (ROC) curves for OS. Other clinical and pathological prognostic

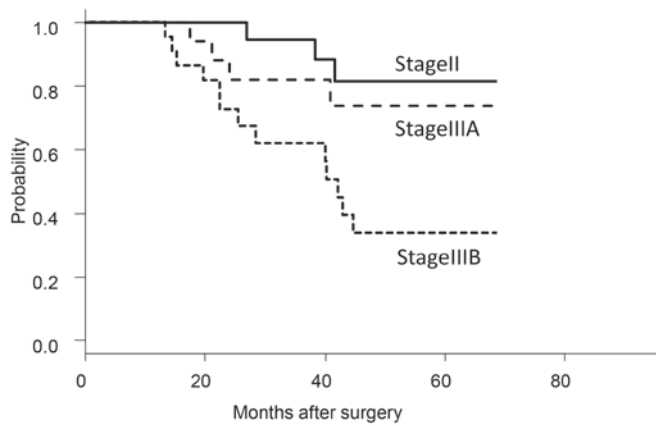


Figure 1. Patients with stage II-III A disease exhibited significantly improved 5-year overall survival compared with patients with stage IIIB disease ($P<0.01$).

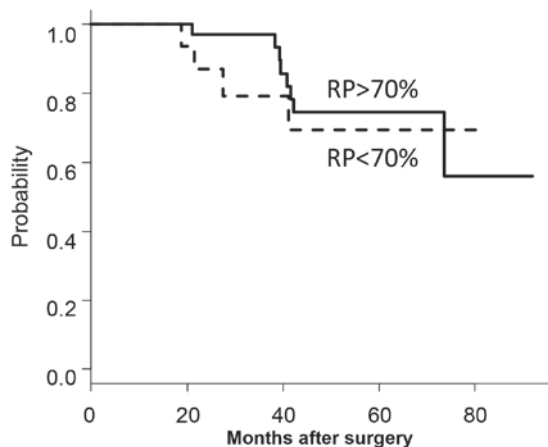


Figure 2. Overall survival by RP value for patients who underwent gastrectomies and S-1 adjuvant chemotherapy. Survival rates did not significantly differ by RP subsequent to exclusion of patients who experienced recurrences between 6 and 12 months after surgery. RP, relative performance.

factors included age, sex, type of gastrectomy and tumor stage (pStage) were also evaluated.

Statistical analysis. OS was defined as time between surgery and patient mortality or the last available information pertaining to vital status. Differences between cumulative survival rates of the patient groups were calculated using a log-rank test for comparison using Kaplan-Meier survival curves. $P<0.05$ was considered to indicate a statistically significant difference. PNI, BMI, BW were expressed as the mean \pm standard deviation. The Wilcoxon signed rank test was used for comparison between preoperative and postoperative PNI, BMI and BW. Time-dependent survival ROC curves were used to evaluate the sensitivity and specificity of postoperative BW loss, CCr, PNI and number of metastatic lymph nodes for predicting the 3-year OS rate (36). The Youden index was used to determine optimal threshold values for postoperative BW loss, BMI loss, CCr, number of metastatic lymph nodes and PNI. Patients were divided into two subgroups, above and below the threshold values, for each factor. Factors were also subjected to univariate and

multivariate analyses, using Cox's proportional hazard model, against OS. Statistical analyses used JMP (version 11; SAS, Tokyo, Japan). Survival ROC was analyzed using R software (version 3.1.1; R Project for Statistical Computing, Vienna, Austria).

Results

A total of 62 patients were enrolled in the present study (Table I), all of whom received S-1 ACT as outpatients, at 60-120 mg/day.

Survival. For the cohort of the present study, 3- and 5-year OS rates were 79.1 and 60.9%, respectively, but varied according to disease stage (Fig. 1). The stage II and IIIA groups exhibited significantly improved 5-year OS rates (stage II, 81.6%; stage IIIA, 73.7%) compared with that of the stage IIIB group (33.8%; $P<0.01$).

Recurrence. Of the 62 patients, 25 (40.3%) experienced cancer recurrences. The sites of recurrence were peritoneal dissemination in 13 patients, liver in 5 patients, bone in 2 patients, lymph nodes in 4 patients, and lung in 1 patient.

ROC curves and threshold values. ROC survival curves were used to determine optimal threshold values for favorable OS in the factors under investigation. The threshold values were: PNI, 48 [area under curve (AUC), 0.637; true positive (TP), 0.96; false positive (FP), 0.57]; CCr, 70 ml/min (AUC, 0.541; TP, 0.72; FP, 0.485); BW loss, 10.6% (AUC, 0.612; TP, 0.669; FP, 0.255) and number of metastatic lymph nodes, 7 (AUC, 0.733; TP, 0.645; FP, 0.183). The analyses of ROC curves used a 3-year endpoint and maximum Youden index.

As the ROC curves did not produce an optimal threshold value for BMI, it was set at 23 kg/m² according to the WHO Expert Consultation (37); the RP threshold value was set at 70% according to the ACTS-GC subset report (6). Patients were defined as those above or below each threshold and the two groups were compared.

RP value and survival. Of the 62 patients, 24 were administered decreased S-1 doses within the first 3 cycles, at their or their physicians' decision, for an initial reduction rate of 38.7%. A total of 3 patients elected to end their S-1 ACT regimens following 3 or 4 cycles (patient refusal); these patients did not exhibit cancer recurrences. The 1-year treatment continuation rate was 79.0%, including patients who exhibited recurrences during S-1 ACT and were referred to second-line chemotherapies. Among the patients who did not exhibit recurrences, the 1-year treatment continuation rate was 94.2%.

Of the 62 patients, 36 exhibited RP values of $>70\%$, including 12 patients who possessed 100% RPs, and 26 patients exhibited RP values of $<70\%$. A total of 16 patients in the $<70\%$ RP group were lost to follow-up due to toxicity, and 10 for cancer recurrence leading to second-line chemotherapy between 6 and 12 months after surgery. The 5-year OS rate of the $>70\%$ RP group (74.6%) was significantly increased compared with the $<70\%$ RP group (41.2%; $P<0.01$). However, as the 10 patients who had stopped their S-1 ACT

regimens due to recurrence between 6 and 12 months after surgery and were on second-line therapies were excluded, no significant difference between the 5-year OS rates for the >70% RP group (74.7%) and the <70% RP group was identified (69.3%; $P=0.642$; Fig. 2).

Nutritional parameters prior to and subsequent to surgery. Preoperative values were significantly decreased subsequent to surgery for BMI (20.69 ± 2.811 vs. 22.79 ± 2.97 kg/m²; $P<0.001$), BW (55.01 ± 9.94 vs. 60.68 ± 10.94 kg; $P<0.001$) and PNI (48.36 ± 4.26 vs. 50.36 ± 4.12 ; $P<0.001$; Fig. 3).

Prognostic factors for OS. In the univariate analysis (Table II), BW loss between 1 and 2 months after surgery, pStage and number of lymph node metastases were of significant prognostic value ($P<0.05$). In multivariate analysis, BW loss between 1 and 2 months after surgery, and pStage were identified to be independent prognostic factors ($P<0.05$, Table III).

Discussion

The present retrospective study was designed to evaluate the clinical prognostic factors of OS, including the nutritional parameters in gastrectomy patients who receive ACT with S-1 for GC in Nara Hospital. As described in the ASTS-GC reports, a 1-year regimen of S-1 ACT was effective for stage II and stage IIIA GC, but not stage IIIB disease, according to subset analysis (2,3). In the present study, 94.2% of patients continued S-1 when the 10 patients who experienced cancer recurrence within the 1-year ACT period were excluded. However, the 38.7% of patients who decreased their S-1 doses within the first 3 cycles were included. The OS rate of the present study was similar to that of the ACTS-GC report, except for stage IIIB disease (2,3).

It was revealed that, even if the S-1 dose was reduced, patients who continued to receive it for the recommended year exhibited a significant survival benefit. The lowest dose of S-1 administered in the present study was 60 mg/day, for which a sufficient clinical effect has not been established; however, it should be established in the future. It is expected that more effective types of adjuvant therapy may be established in the near future for stage III disease. According to the ACTS-GC results [unpublished data, noted in (6)], improved survival was noted with 1-year continuation of S-1 ACT and RP values >70%. In the present study, the high and low RP groups did not significantly differ in OS when the patients with between 6 and 12-month postsurgical recurrences, i.e., those on second-line regimens, were excluded. Physicians in hospital settings may have decreased their patients' S-1 doses out of concern for toxic effects, which may have affected these numbers. Additionally, the present study involved relatively small numbers of patients, which may also have affected the results. However, no association between RP values and survival was observed in the present study. Additional examination may be required.

Pre- and postsurgical nutritional parameters were also evaluated. The deterioration in nutritional status subsequent to gastrectomy is induced by decreased food intake due to decreased capacity (38-40). Several nutritional parameters were markedly decreased subsequent to surgery in the present study. Body weight loss between 1 and 2 months after surgery

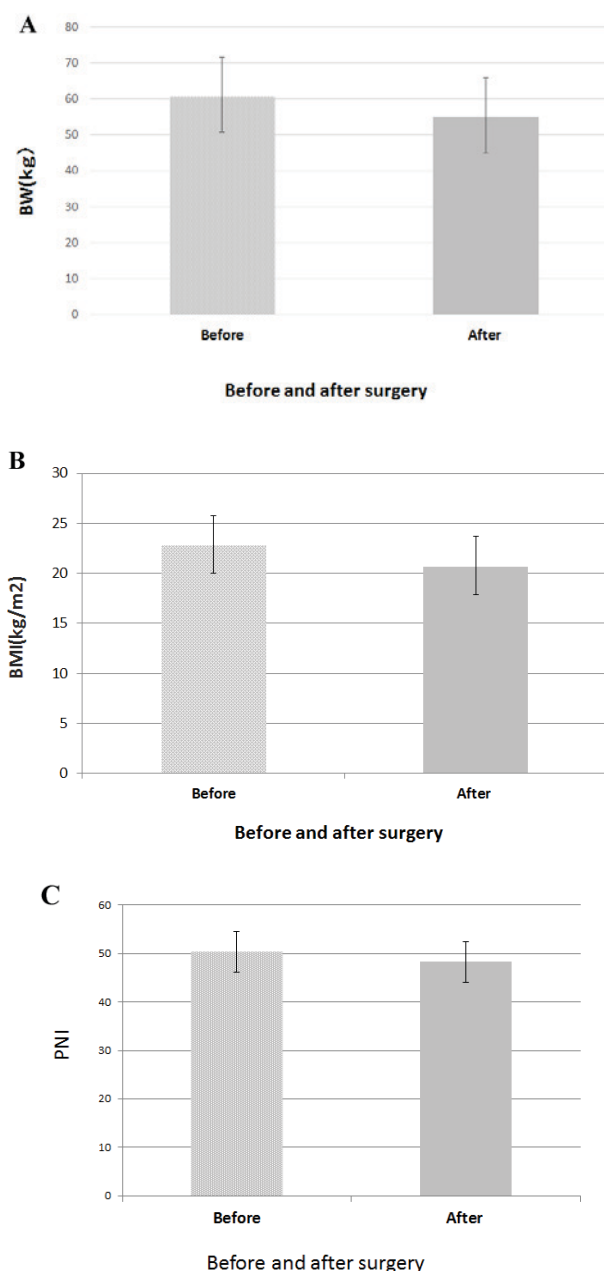


Figure 3. BW, BMI and PNI differences prior to and following surgery. (A) BW was significantly decreased at 1 and 2 months following gastrectomy compared with prior surgery ($P<0.01$). (B) BMI was significantly decreased at 1 and 2 months following gastrectomy compared with prior surgery ($P<0.01$). (C) PNI was significantly decreased at 1 and 2 months following gastrectomy compared with prior surgery ($P<0.01$). BW, body weight; BMI, body mass index; PNI, prognostic nutritional index.

was a significant prognostic factor in the multivariate analysis for patients who received S-1 ACT. The prognosis of patients with BW loss >10.6% between 1 and 2 months after surgery was poorer in the present study. Aoyama *et al* (5) demonstrated that BW loss of >15% at 1 month after surgery was the most important risk factor for compliance of S-1 ACT. Additionally, BW loss at presentation is associated with poor chemotherapy compliance and poor prognosis in gastrointestinal malignancies (41). A previous study from Korea revealed that weight loss at the first month of palliative chemotherapy predicted unfavorable survival outcomes in patients with

Table II. Univariate analysis of prognostic factors for overall survival in patients with gastric cancer who underwent neoadjuvant chemotherapy.

Characteristic	n	HR	95% CI	P-value
Age, years				
≥70	18	1.013	0.392-2.616	0.979
<70	44			
Sex				
Male	42	1.204	0.477-3.041	0.696
Female	20			
Type of gastrectomy				
Distal	41	0.596	0.242-1.472	0.263
Total	21			
pStage				
II	21	4.64	1.318-16.381	0.017
III	41			
Lymph node metastasis				
≥7	27	2.97	1.219-7.236	0.017
<7	35			
Creatinine clearance				
≥70	36	0.441	0.168-1.162	0.098
<70	26			
Postoperative BMI				
≥23	14	0.582	0.171-1.980	0.386
<23	38			
Postoperative PNI				
≥48	37	0.522	0.215-1.265	0.15
<48	21			
Preoperative BMI				
≥23	27	1.179	0.496-2.802	0.709
<23	35			
Preoperative PNI				
≥48	44	0.716	0.262-1.956	0.514
<48	18			
Body weight loss, %				
≥10.6	23	2.744	1.157-6.505	0.022
(BMI loss)				
<10.6	39			
RP, %				
≥70	36	0.752	0.226-2.506	0.643
<70	16			

BMI, body mass index; PNI, prognostic nutritional index; RP, relative performance, pStage, tumor stage; CI, confidence interval; HR, hazard ratio.

advanced GC (42). However, it was not possible to determine the potential association between S-1 continuation and body weight loss between 1 and 2 months after surgery owing to the high S-1 continuation in the present study; however, BW loss between 1 and 2 months after surgery is hypothesized to affect the prognosis of patients who receive S-1 ACT subsequent to gastrectomy. To the best of our knowledge, the present study

has provided the first evidence that BW loss between 1 and 2 months after surgery is associated with survival rate in patients with GC who received ACT. However, whether BW loss affects prognoses directly or indirectly, for example by decreasing the effectiveness of S-1, remains unclear. In any case, diminished nutritional status may worsen the prognosis of any patient with a serious illness, including gastric cancer.

Table III. Multivariate analysis of clinicopathological factors compared with overall survival in patients with gastric cancer who underwent neoadjuvant chemotherapy.

Factor	HR	95% CI	P-value
Age	0.980	0.927-1.036	0.980
pStage	5.236	1.447-18.95	0.012
BW loss subsequent to surgery	2.821	1.117-7.126	0.028

HR, hazard ratio; CI, confidence interval; pStage, tumor stage; BW, body weight.

The association between BMI and long-term outcome has been investigated with regard to certain malignancies (43,44), including a number of controversial studies evaluating BMI and GC prognosis (23-28). In the present study, preoperative and postoperative BMI of patients with stage II/III GC were evaluated, although no association between BMI and survival rates was identified.

Preoperative PNI is hypothesized to be a prognostic marker for a number of malignancies, including long-term survival for patients with GC (10,11,17,45). However, no association between either preoperative or postoperative PNI and survival in patients with GC who received S-1 ACT was demonstrated. As it was revealed that post-surgical BMI and BW loss were more reliable predictors of survival than PNI, the present study suggests that nutritional support subsequent to surgery improves survival rates in patients with stage II and III GC who expect to receive S-1 ACT.

In conclusion, 1-year continuation of S-1 ACT had an increased effect on survival compared with relative dose intensity, as demonstrated by RP value, for patients with stage II/III GC. Additionally, postoperative nutritional intervention may improve survival rates of these patients. A novel treatment strategy for stage III gastric cancer may be warranted.

Acknowledgements

The authors wish to thank the department's assistant, Mrs Akiko Kaku, and the pharmacologist, Mrs. Saori Nishiura, for their help with data collection from the patients.

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