Int J Clin Oncol (2017) 22:476–483
DOI 10.1007/s10147-017-1089-y

ORIGINAL ARTICLE

Postoperative weight loss leads to poor survival through poor S-1 efficacy in patients with stage II/III gastric cancer

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Received: 8 November 2016 / Accepted: 9 January 2017 / Published online: 7 February 2017

Abstract
Aims We previously demonstrated that body weight loss (BWL) at one month after gastrectomy, a common finding after surgery for gastric cancer, was an independent risk factor for the continuation of adjuvant chemotherapy with S-1. However, it is unclear whether BWL after gastrectomy leads to poor survival through poor compliance to adjuvant chemotherapy with S-1.
Methods We conducted this follow-up study in the same cohort as our previous study. Overall survival (OS) and recurrence-free survival (RFS) were examined in 103 patients who underwent curative D2 surgery and were pathologically diagnosed with stage II or III gastric cancer, and who received postoperative adjuvant chemotherapy with S-1 between June 2002 and December 2011.
Results The median follow-up period was 64.3 months. The 5-year OS rate in the patients with a BWL of <15% was 59.9%, while that in the patients with a BWL of ≥15% was 36.4% ($p = 0.004$). Univariate and multivariate analyses for OS demonstrated that pathological *T* factor and BWL were significant risk factors. On the other hand, the 5-year RFS rate was 56.4% in the BWL <15% group and 36.4% in the BWL ≥15% group ($p = 0.016$), while univariate and multivariate analyses for RFS demonstrated that BWL was a marginally significant risk factor.
Conclusions Severe postoperative BWL, which is closely related with poor S-1 compliance, is an important risk factor for survival. It merits testing if preventing BWL improves survival of gastric cancer patients who receive S-1 adjuvant chemotherapy.

Keywords Gastric cancer · Adjuvant chemotherapy · Body weight loss · Overall survival

Introduction

In 2012, there were 951,600 new cases of gastric cancer and 723,100 deaths occurred [1]. Complete resection is essential for cure of localized gastric cancer. At present, the standard treatments for locally advanced gastric cancer in Asia, Europe and the USA are D2 gastrectomy followed by adjuvant chemotherapy, surgery with pre- and postoperative chemotherapy, and surgery with postoperative chemoradiotherapy, respectively [2–6]. Thus, postoperative chemotherapy or chemoradiotherapy plays a crucial role in improving survival.

We recently reported that body weight loss (BWL) at one month after gastrectomy, a common finding after surgery for gastric cancer, was an independent risk factor for the continuation of adjuvant chemotherapy with S-1 [7]. The 6-month continuation rate of S-1 treatment was 66.4% in the patients with a BWL of <15 and 36.4% in the patients with a BWL of ≥15% ($p = 0.017$). Poor compliance to adjuvant chemotherapy might lead to poor survival [8]. Postoperative BWL might be prevented by perioperative care such as intensive enteral nutrition [9]. If BWL after gastrectomy has a prognostic impact through

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decreased compliance to adjuvant treatments, then surgeons must seriously consider perioperative care in patients undergoing gastric cancer surgery.

In order to clarify whether BWL after gastrectomy leads to poor survival through poor compliance to S-1, we conducted this follow-up study in the same cohort that was used to examine BWL after gastrectomy and compliance to adjuvant chemotherapy with S-1 [7].

Patients and methods

The details of the patients have been published previously [7]. In brief, the study examined the long-term outcomes of 103 patients who underwent curative D2 surgery for gastric cancer, who were diagnosed with stage II/III disease, who had a creatinine clearance rate of >60 ml/min, and who received adjuvant chemotherapy with S-1 at our institution between June 2002 and December 2011. All patients received distal or total gastrectomy with nodal dissection for gastric cancer [10, 11].

Postoperative care

As described in our previous report [12], the patients received perioperative care according to the ERAS protocol. In brief, oral intake was initiated on postoperative day (POD) 2, beginning with water and an oral nutritional supplement. Patients began to eat solid food on POD 3, starting with rice gruel and soft food on POD 3 and advancing in three steps to regular food intake on POD 7. Patients were discharged when they achieved adequate pain relief and soft food intake, returned to their preoperative mobility level, and exhibited normal laboratory data on POD 7.

Adjuvant treatment with S-1

The patients received S-1 chemotherapy at 80–120 mg/body per day according to their body surface area (BSA)—BSA <1.25 m^2/80 mg/day; BSA 1.25–1.5 m^2/100 mg/day; BSA >1.5 m^2/120 mg/day [2]. The planned period of S-1 treatment was either 1 year or 6 months according to the protocol of the phase III trial in which they were registered; the protocol of one phase III trial to confirm the efficacy of S-1 was 1 year, while that of the other phase III trial was 6 months [2, 13]. A consort diagram was shown in our previous report [7]. The time to S-1 treatment failure (TTF) defined the period between the day of S-1 treatment to 6 months after surgery or the day on which the physician decided to discontinue S-1 treatment due to adverse events, the patient's refusal to continue treatment (either due to adverse events or for other reasons), disease recurrence, or death.

Follow-up and statistical analyses

The patients were followed up at an outpatient clinic. The patients received no treatments other than adjuvant chemotherapy with S-1 until recurrence. Hematological tests and physical examinations were performed at least every 2–3 weeks during S-1 treatment, and at least every 6 months for 5 years after completion of S-1 treatment. The CEA and CA19-9 tumor marker levels were checked at least every 6 months for 5 years. Patients underwent a computed tomography examination every 6 months during the first 3 years after surgery, and then every year until 5 years after surgery.

BWL at 1 month after gastrectomy was defined as %BW loss = (preoperative body weight − body weight at 1 month after surgery) × 100/preoperative body weight. Each patient's preoperative body weight was measured 3–4 days before surgery.

Overall survival (OS) was defined as the period between surgery and death. Recurrence-free survival (RFS) was defined as the period between surgery and recurrence or death, whichever came first. Survival curves were calculated using the Kaplan–Meier method and compared by the log-rank test. Cox's proportional hazards model was used to perform univariate and multivariate survival analyses. A p value of <0.05 was considered to indicate statistical significance. The SPSS software program (v11.0 J Win, SPSS, Chicago, IL, USA) was used to perform all statistical analyses. This study was approved by the IRB Committee of the Kanagawa Cancer Center.

Results

A total of 286 patients underwent surgical resection and were pathologically diagnosed with stage II or III disease between June 2002 and December 2011. A flow diagram of 286 patients is shown in Fig. 1. The depth of invasion was deeper in the BWL >15% group (pT4, 10/11; 90.9%) than in the BWL <15% group (pT4, 60/92; 65.2%) ($p = 0.084$), while the incidence of nodal metastases was higher in the BWL <15% group (79/92; 85.9%) than in the BWL >15% group (6/11, 54.5%) ($p = 0.010$). Moreover, the incidence of total gastrectomy was higher in the BWL >15% group (10/11; 90.9%) than in the BWL <15% group (49/92; 53.3%) ($p = 0.017$). No patient showed a BWL >10% before surgery. The proportion of time to S-1 TTF at 6 months was 66.4 and 36.4% in the BWL ≥15 and BWL <15% groups, respectively [7].

The median follow-up period was 64.3 months (range 12–156.3 months). The 5-year survival rate was 59.9% in the BWL <15% group and 36.4% in the BWL ≥15% group (Fig. 2, $p = 0.004$). Each of the clinicopathological

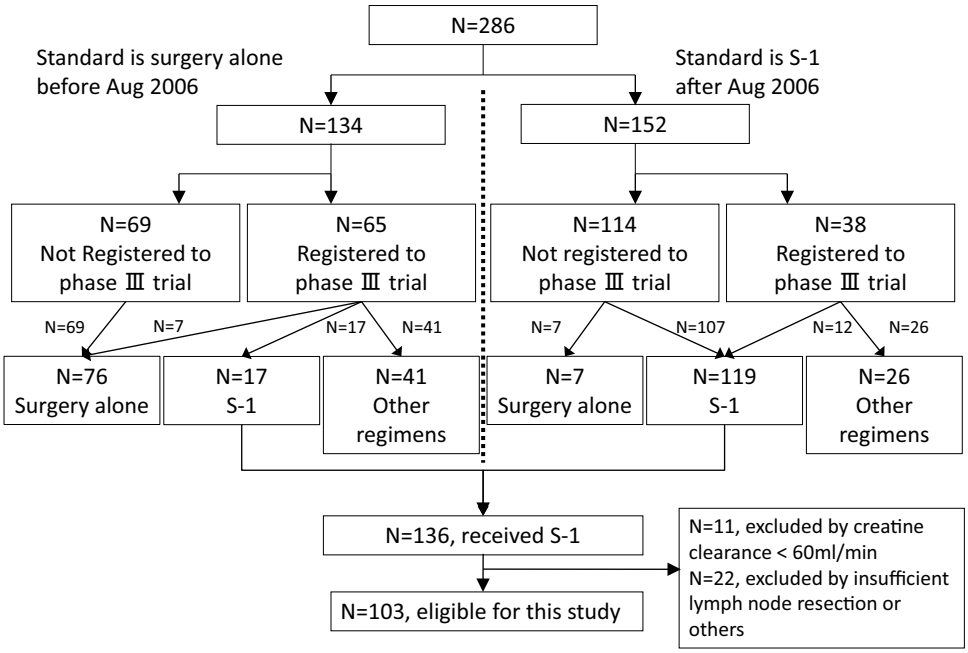

Fig. 1 Flow diagram of 286 patients

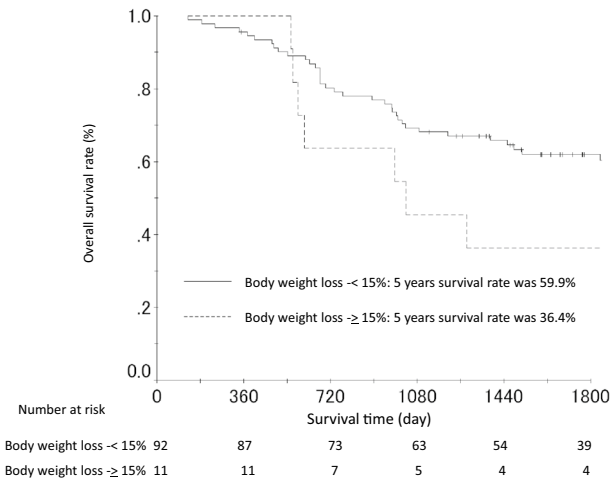

Fig. 2 Overall survival curves of patients in the BWL ≥15% and BWL <15% groups. *BWL* body weight loss

factors were categorized as shown in Table 1, and analyzed to determine their prognostic significance. Univariate and multivariate analyses for OS demonstrated that pathological *T* factor and BWL were significant risk factors. On the other hand, type of resection, other organ resection or postoperative morbidity were not selected as significant prognosticators in both univariate and multivariate analyses.

The 5-year RFS rate was 56.4% in the BWL <15% group and 36.4% in the BWL ≥15% group (Fig. 3, $p = 0.016$). Each of the clinicopathological factors was categorized as shown in Table 2 and was analyzed to determine their prognostic significance. Univariate and multivariate analyses for RFS demonstrated that BWL was a marginally significant risk factor. When comparing the sites of first relapse, the incidence of peritoneal recurrence was significantly higher in the BWL ≥15% group than in the BWL <15% group (Table 3). On the other hand, survival and the proportion of first-line, second-line and third-line treatments after recurrence were similar between the BWL <15% and BWL >15% groups.

The cause of death was also analyzed for all patients. The proportion of gastric cancer-related death was significantly higher in the BWL ≥15% group than in the BWL <15% group (hazard ratio 1.561 for ≥15 vs <15%, 95% CI 1.036–2.351, $p = 0.033$). The death rate due to other causes was slightly higher in the BWL ≥15% group than in the BWL <15% group; however, the difference did not reach statistical significance (hazard ratio 2.353 for ≥15% vs <15%, 95% CI 0.706–7.843, $p = 0.164$).

In the subgroup analysis, BWL >15% was not selected for multivariate analysis in both the total and distal gastrectomy groups. However, BWL >15% was a marginally significant risk factor for univariate analysis in the total gastrostomy group (hazard ratio 1.441; 95% CI 0.985–2.167) (Table 4). The *p* value of the total gastrostomy group was 0.079. On the other hand, BWL >15% was also a marginally significant risk factor for univariate analysis in the distal gastrostomy group (hazard ratio 2.063; 95% CI 0.734–6.798) (Table 5). However, the *p* value of the distal gastrostomy group was 0.170.

Discussion

We previously demonstrated that a BWL of ≥15% at 1 month after gastrectomy was a significant risk factor

Table 1 Univariate and multivariate Cox proportional hazards analyses of clinicopathological factors for overall survival

Factor	Number	Univariate			Multivariate		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)				0.054			
<70	76	1.000					
≥70	27	1.823	0.990–3.357				
Gender				0.985			
Female	33	1.000					
Male	70	1.006	0.541–1.872				
Pathological *T* factor				0.001			0.001
T3	33	1.000			1.000		
T4	70	4.991	1.967–12.62		5.184	2.021–13.299	
Pathological *N* factor				0.543			0.076
Negative	18	1.000			1.000		
Positive	85	1.284	0.573–2.876		2.129	0.925–4.898	
Postoperative infectious complications				0.255			
No	91	1.000					
Yes	12	1.600	0.712–3.593				
Type of gastrectomy				0.180			
DG	44	1.000					
TG	59	1.519	0.824–2.798				
Splenectomy				0.333			
No	72	1.000					
Yes	31	1.359	0.731–2.528				
Lymphovascular invasion				0.370			
Negative	15	1.000					
Positive	88	1.421	0.659–3.062				
Pathological type				0.356			
Differentiated	34	1.000					
Undifferentiated	69	1.355	0.711–2.584				
Body weight loss at 1 month after surgery (%)				0.015			0.036
<15	92	1.000			1.000		
≥15	11	1.572	1.090–2.267		1.499	1.027–2.188	

DG distal gastrectomy, *TG* total gastrectomy

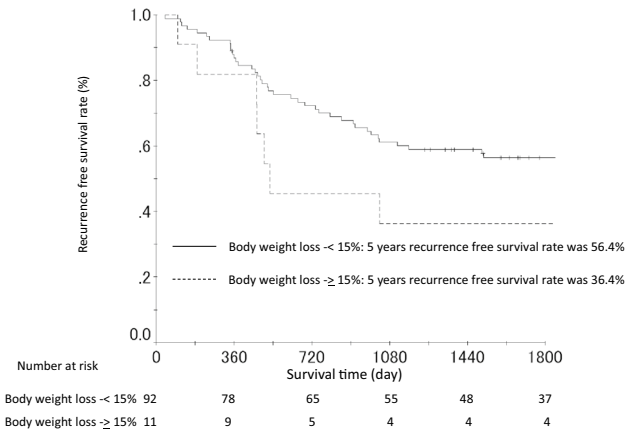

Fig. 3 Recurrence-free survival curves of patients in the BWL ≥15% and BWL <15% groups. *BWL* body weight loss

for the continuation of adjuvant chemotherapy with S-1 in patients with stage II/III gastric cancer [7]. However, it was unclear whether BWL impacted the survival of these patients. In this follow-up study, we firstly demonstrated that a BWL of ≥15% at 1 month after gastrectomy was a significant independent risk factor for both OS and RFS. Moreover, the patients with a BWL of ≥15% had significantly higher rates of peritoneal recurrence and gastric cancer-related death than those with a BWL of <15%. These results indicated that the patients with a BWL ≥15% at one month after gastrectomy had poor survival, in concordance with the insufficient efficacy of adjuvant chemotherapy with S-1. It merits testing if preventing BWL improves the survival of gastric cancer patients who receive S-1 adjuvant chemotherapy in the future.

Table 2 Univariate and multivariate Cox proportional hazards analysis of clinicopathological factors for recurrence-free survival

Factor	Number	Univariate			Multivariate		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)				0.398			
<70 years	76	1.000					
≥70 years	27	1.388	0.649–2.970				
Gender				0.517			
Female	33	1.000					
Male	70	1.215	0.674–2.190				
Pathological *T* factor				<0.001			0.001
T3	33	1.000			1.000		
T4	70	4.912	2.089–11.550		5.183	2.181–12.319	
Pathological *N* factor				0.419			0.066
Negative	18	1.000			1.000		
Positive	85	1.390	0.625–3.091		2.143	0.952–4.823	
Postoperative infectious complications				0.204			
No	91	1.000					
Yes	12	1.693	0.751–3.816				
Type of gastrectomy				0.227			
DG	44	1.000					
TG	59	1.476	0.785–2.776				
Splenectomy				0.292			
No	72	1.000					
Yes	31	1.380	0.758–2.511				
Lymphovascular invasion				0.411			
Negative	15	1.000					
Positive	88	1.376	0.643–2.941				
Pathological type				0.477			
Differentiated	34	1.000					
Undifferentiated	69	1.247	0.679–2.291				
Body weight loss at 1 month after surgery (%)				0.058			0.087
<15	92	1.000			1.000		
≥15	11	1.445	0.988–2.113		1.379	0.955–1.991	

DG distal gastrectomy, *TG* total gastrectomy

Table 3 Comparison of recurrence sites between the BWL <15% and BWL ≥15% groups

	BWL <15% (%)	BWL ≥15% (%)	*p* value
Peritoneal recurrence	19.6% (18/92)	54.5% (6/11)	0.009
Lymph node recurrence	8.7% (8/92)	0% (0/11)	0.309
Hematological recurrence	9.8% (9/92)	18.1% (2/11)	0.394
Total	38.0% (35/92)	63.6% (7/11)	0.103

BWL body weight loss

There are several possible reasons why BWL at 1 month after gastrectomy affected the survival of the stage II and III gastric cancer patients. It is most likely that the patients with severe weight loss received little benefit from adjuvant chemotherapy with S-1. The previous study demonstrated that half of the patients who had a BWL of ≥15% terminated S-1 during the first course due to adverse events or because the patient refused further treatment as a result of the adverse events [7]. Similar results have been reported in patients with metastatic gastrointestinal malignancies [14]. Andreyev et al. found that patients with BWL at the initial diagnosis had a worse outcome when undergoing palliative chemotherapy. They demonstrated that patients with BWL received significantly less chemotherapy and developed more toxicities. In addition, weight loss was correlated with shorter failure-free survival ($p < 0.0001$, hazard ratio 1.25) and OS ($p < 0.0001$, hazard ratio 1.63), a decreased response ($p = 0.006$), and a reduced quality of

Table 4 Univariate and multivariate Cox proportional hazards analyses of clinicopathological factors for overall survival in total gastrectomy

Factor	Number	Univariate			Multivariate		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)				0.407			
<70	43	1.000					
≥70	16	1.383	0.643–2.977				
Gender				0.679			
Female	20	1.000					
Male	39	1.181	0.537–2.601				
Pathological *T* factor				0.023			0.023
T3	12	1.000			1.000		
T4	47	10.094	1.372–74.29		10.094	1.372–74.29	
Pathological *N* factor				0.661			
Negative	13	1.000					
Positive	46	1.223	0.497–3.011				
Postoperative infectious complications				0.513			
No	49	1.000					
Yes	10	1.351	0.549–3.325				
Splenectomy				0.263			
No	28	1.000					
Yes	31	1.366	0.833–2.887				
Lymphovascular invasion				0.625			
Negative	11	1.000					
Positive	48	1.253	0.507–3.098				
Pathological type				0.246			
Differentiated	18	1.000					
Undifferentiated	41	1.657	0.706–3.887				
Body weight loss at 1 month after surgery (%)				0.079			
<15	49	1.000					
≥15	10	1.441	0.985–2.167				

life ($p < 0.0001$) and performance status ($p < 0.0001$). On the other hand, BWL >15% was not selected for multivariate analysis in the subgroup analysis in both the total and distal gastrectomy groups. However, a BWL of >15% was a marginally significant risk factor for univariate analysis in the total gastrostomy group (hazard ratio 1.441; 95% CI 0.985–2.167). The *p* value of the total gastrostomy group was 0.079. It might be a new important risk factor of survival. Furthermore, a BWL of >15% was also a marginally significant risk factor for univariate analysis in the distal gastrostomy group (hazard ratio 2.063; 95% CI 0.734–6.798, $p = 0.170$); however, the *p* value of the distal gastrostomy group was 0.170. Moreover, when comparing the sites of first relapse in the present study, peritoneal recurrence was more frequent in the patients with a BWL of ≥15% than in the patients with a BWL of <15%, which suggests that S-1 was not effective in patients with severe weight loss. The ACTS-GC trial indicated that S-1 could improve patient survival by preventing peritoneal metastases [2]. In cases where adjuvant chemotherapy with S-1 is insufficient due to severe BWL, the chemotherapy might not provide a sufficient prophylactic effect to prevent peritoneal metastasis.

On the other hand, the difference in survival in the patients with mild weight loss and those with severe weight loss was 23.5% at 5 years after surgery, which might be higher than that expected by the S-1 efficacy in the ACTS-GC trial [2]. In the ACTS-GC trial, the survival difference at 5 years between the patients in the S-1 group and the patients in the surgery-alone group was only 10.6%. Moreover, in the present study, the difference in RFS in the patients with mild weight loss and those with severe weight loss was 20.0% at 5 years after surgery, while in the ACTS-GC trial, the difference at 5 years between the S-1 group and the surgery-alone group was 12.3% [2]. Thus, the difference in RFS was also greater in the present study than

Table 5 Univariate and multivariate Cox proportional hazards analyses of clinicopathological factors for overall survival in distal gastrectomy

Factor	Number	Univariate			Multivariate		
		HHR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)				0.078			
<70	34	1.000					
≥70	10	2.454	0.903–6.669				
Gender				0.424			
Female	15	1.000					
Male	29	1.483	0.564–3.901				
Pathological *T* factor				0.020			0.020
T3	21	1.000	1.000		1.000		
T4	23	3.788	1.232–11.643		3.788	1.232–11.643	
Pathological *N* factor				0.887			
Negative	5	1.000					
Positive	39	1.113	0.254–4.879				
Postoperative infectious complications				0.336			
No	42	1.000					
Yes	2	1.591	0.208–12.169				
Lymphovascular invasion				0.571			
Negative	4	1.000					
Positive	40	1.539	0.346–6.847				
Pathological type				0.908			
Differentiated	16	1.000					
Undifferentiated	28	1.061	0.391–2.875				
Body weight loss at 1 month after surgery (%)				0.170			
<15	43	1.000					
≥15	1	2.063	0.734–6.798				

that expected from the ACTS-GC trial. This discrepancy suggests that a BWL of ≥15% might be associated, not only with cancer-related death, but also with a higher risk of non-cancer death. In the present study, the death rate due to other causes was slightly higher in the patients with a BWL of ≥15% than in the patients with a BWL of <15%, but the difference was insignificant. Thus, we cannot conclude that high incidence of deaths due to other causes was a major cause of the poor survival observed in the patients with severe BWL. Migita et al. evaluated the impact of the prognostic nutritional index on the long-term outcomes of 548 patients with gastric cancer who underwent gastrectomy [15]. They found that a low preoperative immunonutritional status was associated with a higher risk of non-cancer death. In the future, a study with a population of sufficient size should be performed to clarify whether deaths due to other causes increased in the patients with a BWL of ≥15% at one month after gastrectomy.

There are some limitations associated with this study. First, this is a retrospective single-center study. Moreover, the background of the patients, such as pathological *T* factor, pathological *N* factor, and type of gastrectomy, were different between the BWL >15% and BWL <15% groups. Second, there is a possibility of selection bias in this series. (1) All patients who were registered to the adjuvant phase III trial were randomly assigned to surgery alone, S-1, or other chemotherapeutic regimens; therefore, there was no selection bias among these. (2) One-hundred and fourteen patients were not registered in the trial after August 2006. Only 7 of these patients rejected S-1 chemotherapy even though the physicians recommended S-1 because of the standard treatment. (3) Sixty-nine patients were not registered in the trial before August 2006. None of those patients received S-1 because standard treatment was surgery alone. On the other hand, 65 patients were registered in the trial and 17 were assigned to S-1. There may be a selection bias in these 17 patients, because only patients who fulfilled the strict eligibility criteria were entered into the trial. However, this proportion is not high. In addition, all patients in this study initiated S-1 adjuvant chemotherapy within 6 weeks. Therefore, the patients developing severe morbidity were not included in this study. Third, the periods of S-1 administration were different. As mention above, this study contained three groups—(1) patients

serving as a test arm of the ACTS-GC trial, (2) those serving as a test arm of SAMIT trial, and (3) those in general clinical practice. The patients who were registered to the ACTS-GC trial received S-1 treatment for 1 year after surgery. The patients who were registered to the SAMIT trial between February 2004 and April 2007 received S-1 treatment for 6 months after surgery, while the patients who were registered to the SAMIT trial between May 2007 and September 2009 received the same S-1 treatment as those registered to the SAMIT trial between February 2004 and April 2007, and this protocol continued for 12 months, because the SAMIT was amended in May 2007 based on the report of the ACTS-GC. The remaining patients (those in clinical practice) received S-1 treatment for 12 months following the protocol of the ACTS-GC after the results of ACTS-GC were reported. However, the incidence of BWL in the treatment groups or planned S-1 treatment periods was not statistically different (data not shown).

In summary, severe postoperative BWL, which is closely related with poor S-1 compliance, is an important risk factor for survival. It merits testing if preventing BWL improves the survival of gastric cancer patients who receive S-1 adjuvant chemotherapy in the future.

Acknowledgements This work was supported, in part, by the non-governmental organization, Kanagawa Standard Anti-cancer Therapy Support System, Uehara Memorial Foundation, the Yasuda Medical Foundation, and Takeda Medical Foundation. The authors express their sincere gratitude to Ms. Yuka Fujita, Ms. Natsumi Sato, and Ms. Rika Takahashi for their excellent data management in this study.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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