Weight loss at the first month of palliative chemotherapy predicts survival outcomes in patients with advanced gastric cancer

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Abstract

Background Weight loss during chemotherapy is a significant prognostic factor for poor survival in patients with advanced gastric cancer (AGC). However, in most studies, weight loss was measured at the end of chemotherapy, limiting its clinical use. In this study, we evaluated whether weight loss during the first month of chemotherapy could predict survival outcomes in patients with AGC.

Methods We analyzed 719 patients with metastatic or recurrent AGC who were receiving palliative chemotherapy. We calculated the initial body mass index (BMI), percent weight loss after 1 month of chemotherapy (ΔW_{1m}), percent weight loss after last administration of chemotherapy (ΔW_{end}), and average weight loss per month during chemotherapy ($\Delta W/m$). We correlated these data with overall survival (OS) by receiver-operating characteristic (ROC) curves and Kaplan-Meier curves, and performed a subgroup analysis using Cox regression.

Results The probabilities of longer OS had stronger correlations with $\Delta W/m$ and ΔW_{1m} than with ΔW_{end} or BMI. A significant positive correlation between ΔW_{1m} and $\Delta W/m$ ($r^2 = 0.591$, $p < 0.001$) was observed. Median OS of

patients with ΔW_{1m} more than 3 % was significantly shorter than in patients with less weight loss (OS: 9.7 vs. 16.3 months, $p < 0.001$). Subgroup analysis revealed that ΔW_{1m} accompanied poor survival irrespective of other clinical characteristics.

Conclusion Weight loss at the very first month of palliative chemotherapy could predict unfavorable survival outcomes in AGC.

Keywords Weight loss · Chemotherapy · Survival · Prognostic factor · Gastric cancer

Introduction

The relationships between cancer mortality and weight loss before or during chemotherapy have also been reported in various cancers, including gastric cancer [1–7]. Weight loss before diagnosis has been explained by a tumor burden with hypermetabolism and cytokines that induce host cachexia. Overall weight loss during chemotherapy may also be associated with reduced tolerance of the treatment, resulting in reduced administration of chemotherapy [1–4].

However, the clinical application of body weight changes to predict clinical outcomes has not been investigated, since weight change before diagnosis cannot be accurately considered because of recall bias. Further, total weight change during the chemotherapy period can be measured only after the end of all courses of chemotherapies, and this information cannot be used as a predictor of outcome or giving a chance of intervention for that in patients receiving palliative chemotherapy for advanced gastric cancer (AGC).

In this study, we evaluated the possibility of early prediction of clinical outcomes by assessing weight loss during palliative chemotherapy in AGC. For this, we assumed

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that the rate of weight change over time was approximately consistent throughout the chemotherapy period, meaning that average weight loss during all the course of treatment could be estimated by only measuring weight loss in the very early phase of treatment. We hypothesized that weight loss after 1 month of palliative chemotherapy could early predict survival in patients with AGC.

Methods

Patients

This study is a retrospective analysis of de-identified patient-level data collected from medical charts. Patients who received the first-line chemotherapy for AGC at Seoul National University Hospital, Republic of Korea, from September 2004 to March 2014 were included for analysis. Eligibility criteria included men or women older than 18 years of age; histologically confirmed recurrent or metastatic AGC; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; and recorded measurements of body weights at the beginning of the first cycle, after 1 month of chemotherapy, and at the last cycle of palliative first-line chemotherapy. Patients with a short duration (<6 months) of follow-up without confirmed death were excluded from the study. For one or more missing data of body weight, 428 patients were

excluded from the analysis. A total of 719 AGC patients treated with palliative chemotherapy were included in the analysis (Fig. 1a).

Body weight measurement and clinical variables

A schematic overview of the study protocol is illustrated in Fig. 1b. We considered body weight on the first day of the first cycle, 1 month after the start of first cycle, and after the last cycle of first-line palliative chemotherapy concluded. Body weight 1 month after the start of first cycle was practically measured at the second visit of a 3-week regimen or third visit of a 2-week regimen, but weight measured after more than 2 months (60 days) was not allowed. Body weight was measured by the same device for all patients after fasting more than 8 h since, we also planned to draw their blood before the outpatient clinic. Height was also measured on the first day of the first cycle. We calculated four variables: body mass index at the start of first cycle chemotherapy (BMI_i), percent weight loss after the end of chemotherapy (ΔW_{end}), percent weight loss after 1 month of chemotherapy ($\Delta W_{1\text{m}}$), and average weight loss per month during chemotherapy ($\Delta W/\text{m}$). $\Delta W_{1\text{m}}$ and $\Delta W/\text{m}$ were calculated by dividing the difference in weight by the exact time that weight was measured after 1 month and after the end of chemotherapy, respectively. Overall survival (OS) and progression-free survival (PFS) were calculated as the time from the date of first administration of palliative chemotherapy to the date of either death or

Fig. 1 CONSORT diagram and schematic overview of definitions of weight change. Flow chart of patients in the study is illustrated (a). We calculated the body mass index at the first cycle (BMI_i), percent weight loss after the end of chemotherapy (ΔW_{end}), percent weight loss after 1 month of chemotherapy ($\Delta W_{1\text{m}}$), and average weight loss

per month during chemotherapy ($\Delta W/\text{m}$). $\Delta W_{1\text{m}}$ and $\Delta W/\text{m}$ were calculated by dividing the difference in weight by the total time that weight was measured (b). AGC advanced gastric cancer, SNUH Seoul National University Hospital

the final follow-up visit and to the date of disease progression confirmed by imaging modality, respectively. Imaging studies were all reviewed for the tumor response evaluation according to the RECIST 1.1 criteria [8]. The pathology of the tumor was obtained from the medical records. We defined human epidermal growth factor receptor 2 (HER2)-positive status according to the ToGA trial [9], which identified HER2 immunohistochemistry 3+ or HER2 fluorescent in situ hybridization-positive status using the PathVysion HER2 DNA probe kit (Abbott Laboratories, Green Oaks, IL).

Statistical analysis

We examined the ability of ΔW_{1m} to predict OS and PFS. To assess whether BMI, ΔW_{end} , ΔW_{1m} , and $\Delta W/m$ affected OS or PFS, patients were divided into two groups by cutoff point of OS of 12 months and PFS of 6 months, which were established based on median survivals of previous studies [10, 11] and median survivals of the current study. The optimal cutoff values for each variable for discriminating between a positive and negative result were determined using receiver-operating characteristic (ROC) curve analyses. To further evaluate the discrimination performance of weight change for predicting survival, we calculated the area under the curve (AUC) and compared the correlated ROC curve under nonparametric assumptions with the DeLong test [12]. The chi-square test was used to determine the nature of the associations between optimal cutoff points and clinicopathologic parameters. Kaplan-Meier estimates and Cox regression analyses of OS were conducted. Results were considered significant when p values were less than 0.05. Analyses were completed with STATA version 12 (Stata-Corp LP, College Station, TX).

Ethics

The study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (H-1306-007-493). All studies were conducted according to guidelines for biomedical research specified in the Declaration of Helsinki.

Results

Patient characteristics

The general characteristics of all enrolled patients are listed in Table 1. Median follow-up duration was 48.2 [95 % confidence interval (CI) 14.9–93.9] months. A total of 719 patients received palliative chemotherapy, and 666 (92.6 %) patients were treated with a combination regimen of fluoropyrimidine and platinum. Median OS and PFS

were 13.5 (95 % CI 12.4–14.8) and 6.4 (95 % CI 6.1–6.7) months, respectively. The mean time of weight measurement after 1 month of chemotherapy was 1.3 months (standard deviation 0.44 months).

ROC curve analysis of the ability of weight change to predict survival outcomes

We performed an analysis of ROC curves to determine whether weight change predicts a favorable survival outcome and to define the optimal cutoff values for discriminating patients with good and poor outcomes. Figure 2 shows the ROC curves of BMI, ΔW_{end} , ΔW_{1m} , and $\Delta W/m$ for discriminating OS shorter than 12 months (Fig. 2a) and PFS shorter than 6 months (Fig. 2b). Although BMI did not predict shorter survivals, all three variables associated with weight change significantly predicted shorter OS and PFS. The AUC for shorter OS by $\Delta W/m$ was significantly higher than by ΔW_{end} (0.642 vs. 0.596, $p < 0.001$) or ΔW_{1m} (0.642 vs. 0.603, $p = 0.009$). The AUC for shorter OS by ΔW_{1m} was not significantly different with ΔW_{end} ($p = 0.687$). The AUCs for shorter PFS by $\Delta W/m$, ΔW_{1m} , and ΔW_{end} had similar trends to those of OS and had statistical significance (AUCs: 0.639, 0.601, and 0.569, respectively). The optimal cutoff values of ΔW_{1m} for predicting shorter OS and PFS were 2.9 and 2.8 %, respectively, and we defined that of 3.0 % for practical convenience. The optimal cutoff values for $\Delta W/m$ for predicting shorter OS and PFS were both 1.0 %.

Patient characteristics according to significant weight loss during the first month of chemotherapy

Clinicopathologic characteristics of the patients included in our analysis are summarized in Table 1. Compared to the weight-preserved group ($\Delta W_{1m} < 3$ %; $N = 524$), patients with significant weight loss after the first month of chemotherapy ($\Delta W_{1m} \geq 3$ %; $N = 195$) were significantly younger, had worse performance status, more diffuse-type Lauren classification, more HER2-negative pathology, a higher number of involved organs, and more peritoneal seeding at initial presentation. They had a higher proportion of initially metastatic disease and signet ring cell feature pathology, although these findings were not statistically significant.

Survival analysis according to weight loss during the first month and average weight loss per month during all courses of chemotherapy

We first attempted to identify whether weight loss at the first month was correlated with average weight loss measured at the end of chemotherapy. ΔW_{1m} and $\Delta W/m$ were

Table 1 Patient characteristics

	Total <i>N</i> = 719	$\Delta W_{1m} \geq 3$ % <i>N</i> = 195	$\Delta W_{1m} < 3$ % <i>N</i> = 524	<i>p</i> value
Age				
Median (range)	59 (21–89)	57 (21–89)	60 (22–86)	0.006
<60 years old, <i>N</i> (%)	352 (49.0)	105 (53.9)	247 (47.1)	
≥ 60 years old, <i>N</i> (%)	367 (51.0)	90 (46.2)	277 (52.9)	0.110
Sex				
Male, <i>N</i> (%)	508 (70.7)	138 (70.8)	370 (70.6)	
Female, <i>N</i> (%)	211 (29.4)	57 (29.2)	154 (29.4)	0.967
ECOG				
0, <i>N</i> (%)	86 (12.0)	18 (9.2)	68 (13.0)	
1, <i>N</i> (%)	568 (79.0)	148 (75.9)	420 (80.2)	
2, <i>N</i> (%)	65 (9.0)	29 (14.9)	36 (6.9)	0.002
Palliative setting				
Initially metastatic, <i>N</i> (%)	479 (66.6)	139 (71.3)	340 (64.9)	
Recurrent, <i>N</i> (%)	240 (33.4)	56 (28.7)	184 (35.1)	0.106
Tumor location				
GEJ, <i>N</i> (%)	63 (8.8)	17 (8.7)	46 (8.8)	
Other stomach, <i>N</i> (%)	656 (91.2)	178 (91.3)	478 (91.2)	0.980
Pathology type				
Adenocarcinoma, <i>N</i> (%)	577 (80.2)	148 (75.9)	429 (81.9)	
Signet ring cell, <i>N</i> (%)	125 (17.4)	42 (21.5)	83 (15.8)	
Other types, <i>N</i> (%)	17 (2.4)	5 (2.6)	12 (2.3)	0.189
Contains signet ring cell feature, <i>N</i> (%) ^a	189 (26.3)	61 (31.3)	128 (24.4)	0.061
Lauren				
Intestinal, <i>N</i> (%)	102 (37.4)	17 (25.0)	85 (41.5)	
Diffuse, <i>N</i> (%)	137 (50.2)	45 (66.2)	92 (44.9)	
Mixed, <i>N</i> (%)	34 (12.5)	6 (8.8)	28 (13.7)	0.010
HER2				
HER2 checked, <i>N</i> (%)	549 (76.4)	152 (78.0)	397 (75.8)	0.540
HER2 positive, <i>N</i> (%)	143 (26.1)	29 (19.1)	114 (28.7)	0.021
Metastasis				
Number of involved organs, mean $\pm$ SE	2.3 $\pm$ 0.03	2.5 $\pm$ 0.07	2.2 $\pm$ 0.04	0.001
Involved organs <3, <i>N</i> (%)	468 (65.1)	114 (58.5)	354 (67.6)	
Involved organs ≥ 3 , <i>N</i> (%)	251 (34.9)	81 (41.5)	170 (32.4)	0.023
Metastatic site				
Peritoneal seeding, <i>N</i> (%)	414 (57.6)	131 (67.2)	283 (54.0)	0.001
Peritoneal seeding with ascites, <i>N</i> (%)	190 (26.4)	60 (30.8)	130 (24.8)	0.107
Lymph node, <i>N</i> (%)	345 (48.0)	97 (49.7)	248 (47.3)	0.564
Liver, <i>N</i> (%)	172 (23.9)	45 (23.1)	127 (24.2)	0.746
Bone, <i>N</i> (%)	65 (9.0)	17 (8.7)	48 (9.2)	0.854
Others, <i>N</i> (%)	128 (17.8)	42 (21.5)	86 (16.4)	0.110
Chemotherapy regimen				
Fluoropyrimidine + Platinum, <i>N</i> (%)	666 (92.6)	179 (91.8)	487 (92.9)	
+ Trastuzumab, <i>N</i> (%) ^b	88 (12.2)	18 (9.2)	70 (13.4)	0.133
Taxane + Platinum, <i>N</i> (%)	30 (4.2)	10 (5.1)	20 (3.8)	
Others, <i>N</i> (%)	23 (3.2)	6 (3.1)	17 (3.2)	0.734
Treatment response				
CR, <i>N</i> (%)	19 (2.6)	2 (1.0)	17 (3.2)	
PR, <i>N</i> (%)	222 (30.9)	42 (21.5)	180 (34.4)	

Table 1 continued

	Total $N = 719$	$\Delta W_{1m} \geq 3\%$ $N = 195$	$\Delta W_{1m} < 3\%$ $N = 524$	p value
SD, N (%)	358 (49.8)	105 (53.9)	253 (48.3)	
PD, N (%)	103 (14.3)	41 (21.0)	62 (11.8)	
Not evaluable, N (%)	17 (2.4)	5 (2.6)	12 (2.3)	0.001
Objective response, N (%) ^c	241 (33.5)	44 (22.6)	197 (37.6)	0.001

ΔW_{1m} percent weight loss after 1 month of chemotherapy, CR complete response, $ECOG$ Eastern Cooperative Oncology Group performance status, GEJ esophagogastric junction, $HER2$ human epidermal growth factor receptor 2, PD progressive disease, PR partial response, SD stable disease

^a Contains signet ring features: number of patients who had either pure signet ring cell carcinoma (i.e., poorly cohesive carcinoma) or adenocarcinoma containing signet ring features

^b Trastuzumab was added to a combination regimen of fluoropyrimidine plus platinum

^c Objective response: complete response plus partial response

Fig. 2 Predictive value of weight loss during chemotherapy. Receiver-operating characteristic curves of body mass index at the initiation of the first cycle (BMli), percent weight loss after the end of chemotherapy (ΔW_{end}), percent weight loss after 1 month of

chemotherapy (ΔW_{1m}), and average weight loss per month during chemotherapy ($\Delta W/m$) predicted overall survival shorter than 12 months (a) and progression-free survival shorter than 6 months (b)

positively correlated ($r^2 = 0.591$, $p < 0.001$; Fig. 3a). Next, we divided patients into four groups based on cutoff values for predicting survival (ΔW_{1m} of 3 % and $\Delta W/m$ of 1 %). In patients with preserved weight during the first month ($\Delta W_{1m} < 3\%$; $N = 524$; right upper quadrant of Fig. 3a), 417 (79.6 %) had preserved average weight loss per month during chemotherapy ($\Delta W/m < 1\%$). Of these patients, 249 (59.7 %) had OS longer than 12 months. However, in patients with significant weight loss during the first month ($\Delta W_{1m} \geq 3\%$, $N = 195$), 159 (81.5 %) patients had significantly increased average weight loss per month during chemotherapy ($\Delta W/m \geq 1\%$; left lower quadrant of Fig. 3a). Of these patients, 40 (25.2 %) had OS

longer than 12 months. To confirm the survival difference of groups, we performed a Kaplan-Meier survival analysis of patients grouped by significant weight loss during the first month ($\Delta W_{1m} \geq 3\%$). Median OS was 8.9 (95 % CI 7.8–10.3) months in patients with $\Delta W_{1m} \geq 3\%$ compared with 15.3 (95 % CI 14.2–16.7) months in those with $\Delta W_{1m} < 3\%$ [hazard ratio (HR) 0.66, 95 % CI 0.54–0.79, $p < 0.001$; Fig. 3b].

Patients with preserved weight during the first month but increased average weight loss per month during chemotherapy ($N = 107$; 20.4 %; right lower quadrant of Fig. 3a) had a relatively unfavorable prognosis. Of these patients, only 44 (41.1 %) had OS longer than 12 months,

Fig. 3 Survival analysis according to weight loss at the first month of chemotherapy. Scatter plot of percent weight loss after the first month and average weight loss per month during chemotherapy (**a**). The red line indicates the fitted value calculated by linear regression. The blue dot indicates patients with OS longer than 12 months, and the yellow

dot indicates patients with OS shorter than 12 months. Kaplan-Meier curves for OS of two groups divided by weight loss (cutoff value: 3%) after 1 month of chemotherapy (**b**). Kaplan-Meier curves for OS of four groups divided by $\Delta W1m$ and $\Delta W/m$ (cutoff values: 3 and 1%, respectively; **c**)

which was significantly lower than 59.7% of patients who preserved average weight loss per month during chemotherapy ($p = 0.001$). Meanwhile, only 36 (18.5%) patients with weight loss during the first month recovered average weight loss per month during chemotherapy (left upper quadrant of Fig. 3a). Interestingly, 21 (58.3%) patients in this group had OS longer than 12 months. Kaplan-Meier survival analysis of four groups showed that the median OS of patients with both weight loss during the first month and increased average weight loss per month during chemotherapy was 7.8 (95% CI 7.1–9.3) months, which was significantly shorter than other groups ($p < 0.001$; Fig. 3c). A small number of patients recovered weight after the first month, and they had a prolonged OS of 21.3 (95% CI 11.3–27.7) months ($p < 0.001$). Patients with preserved weight during the first month had considerably favorable

survival outcomes, with median OSs of 11 (95% CI 8.4–14.1) months in patients with increased average weight loss per month during chemotherapy and 15.9 (95% CI 15–18.1) months in patients with recovered average weight loss per month during chemotherapy. PFS of the same groups showed similar patterns to OS (data not shown).

The clinicopathologic characteristics of patients divided into four groups on the basis of cutoff values for $\Delta W1m$ and $\Delta W/m$ are listed at Supplementary Table 1. In patients who experienced significant weight loss at the first month, those who recovered average weight loss per month during chemotherapy were older, had fewer signet ring features, had more HER2 positivity, and were exposed to trastuzumab compared with those who eventually had increased average weight loss per month during chemotherapy.

Subgroup analysis of OS and PFS by weight loss at the first month

A predictive value of weight loss at the first month of chemotherapy could be observed irrespective of clinico-pathologic characteristics such as age, gender, performance status, metastatic setting, signet ring feature pathology, HER2-positivity, initial BMI, and number or site of metastases and response to chemotherapy for both OS (Fig. 4a) and PFS (Fig. 4b). Univariate and multivariate Cox survival analyses for OS are provided in Table 2. Multivariate analysis showed that weight loss at the first month of chemotherapy adversely affected OS ($p = 0.004$). Performance status, HER2-negativity, peritoneal metastasis, lymph node metastasis, liver metastasis, and bone metastasis also adversely affected OS.

Discussion

We observed that significant weight loss at the very first month of palliative chemotherapy was correlated with shorter OS and PFS irrespective of any other clinico-pathologic characteristics in AGC.

Weight loss at initial disease presentation, as well as during chemotherapy, is well defined as a poor prognostic factor in most types of cancer, especially gastrointestinal malignancies [1, 2, 5]. However, defining the exact cutoff value of weight change before diagnosis is difficult, since it is hard to estimate the timing of healthy or precancerous status, and recall bias is possible. We investigated weight changes after treatment rather than weight changes before diagnosis to eliminate difficulties in obtaining accurate measurements.

BMI at initial presentation was measured and analyzed, but it failed to predict clinical outcomes in our model. Reported associations between BMI and cancer-related survival in gastric cancer are controversial [13, 14], and previous reports are based on results from patients with gastric cancer, including early stage disease, which can be cured by resection. For this study, we only included patients who were diagnosed in the advanced unresectable stage. The finding suggests that the amount or rate of weight change might play a more important role than initial BMI in predicting survival in AGC under chemotherapy.

An association between weight change during chemotherapy and OS in AGC has been reported [1, 2]. Recent reports showed that significant weight loss of more than

Fig. 4 Subgroup analysis according to weight loss at the first month of chemotherapy. Forest plot of hazard ratios (HR) and 95 % confidence intervals (CI) for overall survival (a) and progression-free survival (b) assessed by subgroup factors. ΔW_{1m} : percent weight loss after 1 month of chemotherapy; CR complete response, DM diabetes

mellitus, ECOG Eastern Cooperative Oncology Group performance status, HER2 human epidermal growth factor receptor 2, PD progressive disease, PR partial response, SD stable disease, SRC signet ring cell

Table 2 Univariate and multivariate Cox analysis of overall survival

Overall survival	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	<i>p</i> value	HR (95 % CI)	<i>p</i> value
$\Delta W_{1m} \geq 3 \%$	1.52 (1.27–1.84)	<0.001	1.39 (1.11–1.73)	0.004
Age ≥ 60	0.94 (0.80–1.11)	0.487	0.83 (0.67–1.03)	0.086
Female gender	0.99 (0.83–1.19)	0.945	0.88 (0.70–1.10)	0.257
ECOG ≥ 2	2.86 (2.16–3.79)	<0.001	2.34 (1.65–3.29)	<0.001
Metastatic (not recurrent)	1.27 (1.06–1.52)	0.008	1.17 (0.91–1.49)	0.222
GEJ location	0.76 (0.56–1.04)	0.097	0.89 (0.62–1.29)	0.546
Signet ring feature pathology	1.59 (1.31–1.92)	<0.001	1.24 (0.98–1.57)	0.068
HER2-negative	1.70 (1.34–2.16)	<0.001	1.92 (1.48–2.48)	<0.001
Involved organs ≥ 3	1.55 (1.30–1.85)	<0.001	0.87 (0.64–1.19)	0.384
Peritoneal metastasis	1.44 (1.21–1.71)	<0.001	1.53 (1.18–1.99)	0.002
Lymph node metastasis	1.04 (0.88–1.23)	0.642	1.31 (1.01–1.70)	0.041
Liver metastasis	1.11 (0.91–1.35)	0.315	1.84 (1.40–2.44)	<0.001
Bone metastasis	1.97 (1.48–2.63)	<0.001	2.03 (1.38–2.99)	<0.001

ΔW_{1m} percent weight loss after 1 month of chemotherapy, ECOG Eastern Cooperative Oncology Group performance status, GEJ esophagogastric junction, HER2 human epidermal growth factor receptor 2

3 % at the end of chemotherapy is associated with poor survival in AGC [2]. However, the clinical application of weight loss during chemotherapy as a prognostic factor is limited since the final weight at the end of chemotherapy cannot be estimated in the middle of treatment.

In this study, we attempted to define a clinically relevant predictive value for weight change during chemotherapy and to compare other variables that influence survival. We calculated the rate of weight change, which has not been reported in previous studies, rather than the total amount of weight change. Based on this, we hypothesized that measuring weight change after only 1 month of chemotherapy could predict clinical outcomes of treatment in AGC. ROC analysis revealed that average weight loss per month during chemotherapy ($\Delta W/m$) and weight loss after 1 month of chemotherapy (ΔW_{1m}) better predicted survival outcomes than weight change during the entire course of chemotherapy (ΔW_{end}) when analyzed with optimal cutoff values of 1.0 and 3.0 % for $\Delta W/m$ and ΔW_{1m} , respectively. Most patients who had weight loss after 1 month also experienced weight loss at the end of chemotherapy ($r^2 = 0.591$, $p < 0.001$), and they had worse survival outcomes. Equally, most patients who experienced weight preservation at the first month also showed weight preservation through the last cycle of chemotherapy and had better survival outcomes.

However, the intraindividual variation in the weight measurement should be taken into consideration for correct interpretation of this result. Because weight was measured only once in each outpatient visit, random error from within-subject variability might attenuate the slope of the regression line in Fig. 3a toward the null [15]. Although

quantification of the random error in weight measurement was impossible since the repeated measure data were unavailable, the impact of the random error in subsequent survival analysis could be evaluated through the effect from possible misclassification of patients due to dichotomization of ΔW_{1m} by the cutoff value from the ROC analysis.

Because the measuring device was consistent during the study periods, diurnal weight change as well as different time of measurement was regarded as the main source of within-subject measurement variation, whose range was known to be $\pm 0.5 \%$ in the normal population [16–18]. When the diurnal weight change range of $\pm 0.5 \%$ was assumed among our participants, 62 patients (8.6 % of a total of 719 patients) with ΔW_{1m} from 2.5 to 3.5 % might have the risk of being misclassified because of measurement error. In survival analysis, patients with ΔW_{1m} 3.0–3.5 % and ΔW_{1m} 2.5–3.0 % had a very similar prognosis to patients with $\Delta W_{1m} > 3.5 \%$ and $\Delta W_{1m} < 2.5 \%$, respectively. After exclusion of patients with ΔW_{1m} from 2.5 to 3.5 %, furthermore, the association between the weight loss group ($\Delta W_{1m} > 3.5 \%$) and preserve group ($\Delta W_{1m} < 2.5 \%$) remained statistically significant. These findings indirectly demonstrated that the random errors in weight measurement were small enough to justify use of the threshold value of 3 %.

Patients who experienced significant weight loss at the first month of chemotherapy had poor performance status, high tumor burden, and peritoneal seeding, which might contribute to poor survival; however a subgroup analysis showed that weight loss had a significant adverse prognostic value, irrespective of those factors. This finding

might also eliminate the confounding effect of malignant ascites as a contributor to weight change. Therefore, we conclude that weight loss of greater than 3 % at the very first month of chemotherapy is an independent prognostic factor for survival in AGC.

In our study, patients who experienced weight loss at the first month but eventually recovered or preserved weight during all courses of chemotherapies showed good survival outcomes. This group of patients had more HER2-positive gastric cancer, which can be exploited with trastuzumab to prolong survival [9]. Our finding implies that even patients with initial weight loss can recover weight and experience a favorable prognosis if they receive appropriate treatment. Although it might be unclear that the effort to preserve weight during chemotherapy leads to good prognosis since this study was an observational study, several strategies have been suggested for managing weight loss of cancer patients during treatment. Nutritional intervention for patients with significant weight loss has been attempted, but meta-analyses have shown no differences in mortality, although improved quality of life was observed [19, 20]. Various strategies for weight maintenance, other than nutritional support, have also been evaluated. Antiinflammatory therapy including thalidomide was investigated and reportedly attenuated weight loss [21], and exercise training improved physical performance [22]. However, none of these studies demonstrated prolonged survival. More effective strategies to block weight loss during chemotherapy are needed. Recent findings have shown that reduced muscle mass or sarcopenia is prevalent in cancer patients treated with chemotherapy and is correlated with adverse events and poor survival [23–25], and efforts to recover the composition of the muscle-fat ratio has been suggested [26]. A recent report showed that parathyroid-hormone-related protein was a key mediator of hyperactivity of brown fat and sarcopenia [27]. Correction of sarcopenia should be further investigated in terms of improving the prognosis of patients with significant weight loss.

This study collected and analyzed data retrospectively; however, we clearly showed a prognostic value of weight change in the early phase of chemotherapy. We also investigated the rate of weight change as a variable for predicting clinical outcomes. A relatively large sample size enabled us to achieve sufficient statistical power for the current analysis.

In conclusion, weight loss at the very first month of palliative chemotherapy was an early predictor for survival outcomes in AGC. New strategies to manage or overcome early weight loss are warranted to improve the prognosis of patients with AGC.

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