Impact of postoperative reduced skeletal muscle on prognosis after recurrence in gastric cancer

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Abstract. Little is known about the association between sarcopenia development after gastrectomy and gastric cancer prognosis after recurrence. The present study retrospectively examined the effects of decreased psoas muscle index (PMI) on post-recurrence prognosis after gastrectomy. A total of 67 patients with gastric cancer recurrence were included in the present study. PMI at pre-operation and recurrence were calculated, and 25 patients whose PMI reduction rate value was lower than the cutoff values (male=0.766 and female=0.704) were classified into the sarcopenia group and 42 patients into the non-sarcopenia group. There were no significant differences between the groups regarding age, sex, pathological stage, and nutrition and inflammation indices at the time of recurrence. Post-recurrence overall survival (OS) was significantly shorter in the sarcopenia group compared with the non-sarcopenia group (P<0.001). The post-recurrence survival rate was significantly worse in the sarcopenia group compared with the non-sarcopenia group (P<0.001). In multivariate analysis, sarcopenia (HR=5.04) and the total courses of chemotherapy after recurrence (HR=3.88) were independent unfavorable prognostic factors. In conclusion, sarcopenia and fewer total courses of post-recurrence chemotherapy were poor prognostic factors after gastric cancer recurrence. To improve prognosis, preventing sarcopenia development after gastrectomy is required.

Introduction

Despite ongoing advances in diagnostics, operative technique, and treatment strategy for the decades, gastric cancer remains one of the most common cancers in the world and a lethal disease (1). Gastrectomy for gastric cancer is essential for improving the survival rate, it may cause persistent functional disorders such as reduced amount of oral intake, insulin resistance, increased protein catabolism, and metabolic changes, leading to weight loss and the development of sarcopenia (2). It is reported that preoperative sarcopenia has been associated with long-term prognosis as well as short-term outcomes such as the development of postoperative pneumonia, poor activities of daily living, longer hospital stay, and the incidence of postoperative complications (3-10), which may restrict the following treatment options (11). Treatment option for patient with recurrence of gastric cancer after gastrectomy is limited to chemotherapy or best supportive care. It is known that sarcopenia could influence on pharmacokinetics of chemotherapy which could be associated with adverse effects of chemotherapy in several cancers (4). However, little is known about the effects of reduced skeletal muscle volume after gastrectomy on prognosis and treatment strategy after the recurrence of gastric cancer. In the present study, we investigated the effects of reduced skeletal muscle volume after gastrectomy on the treatment and prognosis in patients with recurrent gastric cancer.

Materials and methods

Patients. The study protocol was approved by the Institutional Review Board of National Defense Medical College (Saitama, Japan). Of the 553 patients who underwent radical gastrectomy for gastric cancer at the National Defense Medical College between 2011 and 2016, 67 patients who had gastric cancer recurrence were included in this study. We retrospectively evaluated the clinicopathological findings, serum albumin levels, C-reactive protein (CRP), total cholesterol, and neutrophil and lymphocyte counts at the time of preoperative and recurrence of gastric cancer. In addition, the neutrophil-lymphocyte ratio (NLR), the CRP-albumin ratio (CAR), the controlling nutrition status (CONUT) score, the prognostic nutritional index (PNI), and the modified Glasgow prognostic (mGPS) score were calculated as markers of nutrition or inflammation.

The tumor pathological findings were recorded in accordance with the third English edition of the Japanese Classification of Gastric Carcinoma, edited by the Japanese Gastric Cancer Association (12). All patients were followed-up using an oncologically appropriate plan on a per-patient basis.

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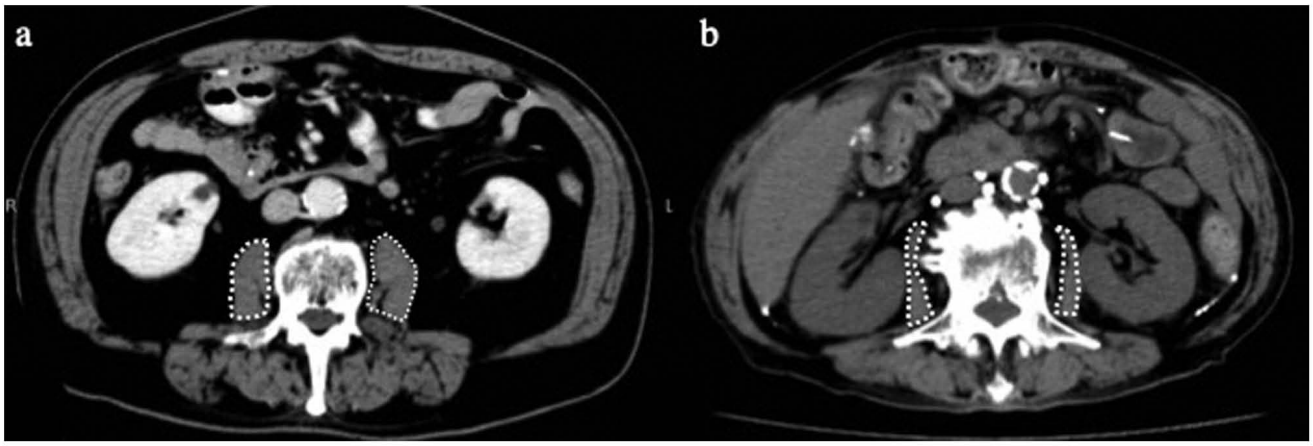

Figure 1. Sarcopenia was defined as the case with less PMI reduction rate value than the sex-specific cut-off values. The psoas muscle mass was measured using a manually traced area as presented by the dotted line. (a) non-sarcopenia case and (b) sarcopenia case. PMI, psoas muscle index.

For patients with stage II or III disease, postoperative adjuvant chemotherapy with S-1 (80 mg/m^2/day) was recommended for 1 year. In 45 cases of pathological stage II or III gastric cancer patients, 26 cases (57.8%) received adjuvant chemotherapy. There was no significant correlation between age and receiving adjuvant chemotherapy.

Definition of sarcopenia. The psoas muscle index (PMI: cm^2/m^2) was calculated from CT images (Aquilion 64; Toshiba Medical Systems) and the psoas muscle cross-sectional area at the third lumbar vertebra (L3) normalized length preoperatively and at the recurrence of gastric cancer by a physician who was blinded to the clinicopathological characteristics of the patients (Fig. 1) (13,14). The reduction rate of PMI from the preoperative value to that at the recurrence of gastric cancer was calculated. The patients were divided into two groups by the cutoff value using area under the receiver operating characteristic curves (ROC); the sarcopenia group (n=25 patients) had less than the cutoff value of the reduction rate of PMI (male=0.766 and female=0.704), and the non-sarcopenia group (n=42 patients) had more than the cutoff value (Fig. 2). The median value of the total cohort was 0.793.

Statistical analyses. All statistical analyses were performed using the JMP® Pro 14.0.0 software package (SAS Institute Inc.). The Student's t-test and Pearson's Chi-square test were performed, as appropriate. A receiver operating characteristics (ROC) curve was constructed to estimate the optimal cutoff value of the reduction of PMI. Survival rates were obtained by the Kaplan-Meier method, and the statistical significance was determined by the log-rank test.

Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. The data are expressed as mean ± standard deviation. A P-value of <0.05 was considered statistically significant.

Results

Patient characteristics. Patients' clinical factors at the recurrence of gastric cancer and pathological factors diagnosed from resected specimens are shown in Table I. There were no significant differences in age, sex, Charlson Comorbidity Index score, and surgical procedure including reconstruction methods between the two groups. The sarcopenia group had a higher body weight and body mass index (BMI) than did the non-sarcopenia group. In addition, the reduction rates of body weight and BMI due to the recurrence of gastric cancer in the sarcopenia group were higher than those of the non-sarcopenia group. There was no significant difference in the pathological factors between the two groups except for tumor depth. The NLR, CAR, CONUT score, PNI, and mGPS at the recurrence of gastric cancer were not significantly different between the two groups (Table II). There was no significant difference in the time between gastrectomy and recurrence, the number of patients who received adjuvant chemotherapy and chemotherapy after the recurrence, the number of discontinued chemotherapies due to adverse effect, the number of chemotherapy regimens after recurrence, the kind of basic chemotherapy after recurrence, and the total courses of chemotherapies between the two groups. The sarcopenia group had a significantly shorter OS from recurrence than did the non-sarcopenia group (median survival time, interquartile range: 118, 43.5-180.5 vs. 300, 133.8-636.3 days, P<0.001).

Prognostic factors. The survival rate from the time of recurrence in the sarcopenia group was significantly worse than that in the non-sarcopenia group (3-year OS 6.0% vs. 21.0%, P<0.001; Fig. 3). Univariate and multivariate analyses that might affect the survival rate from the time of the recurrence of gastric cancer were shown in Table III. Univariate analysis demonstrated that the total courses of chemotherapy after recurrence <5 [hazard ratio (HR)=3.82], sarcopenia (HR=2.66), NLR ≥3.0 (HR=2.63), and PNI ≤40 (HR=2.59) were significantly associated with the prognosis after recurrence. The sarcopenia group more frequently had peritoneal recurrence, which didn't affect prognosis.

Multivariate analysis revealed that sarcopenia at the recurrence (HR=5.04) and the total courses of chemotherapy after recurrence (HR=3.88) were independent unfavorable prognostic factors.

Table IV shows univariate and multivariate analysis for the OS from the time at recurrence among the difference time

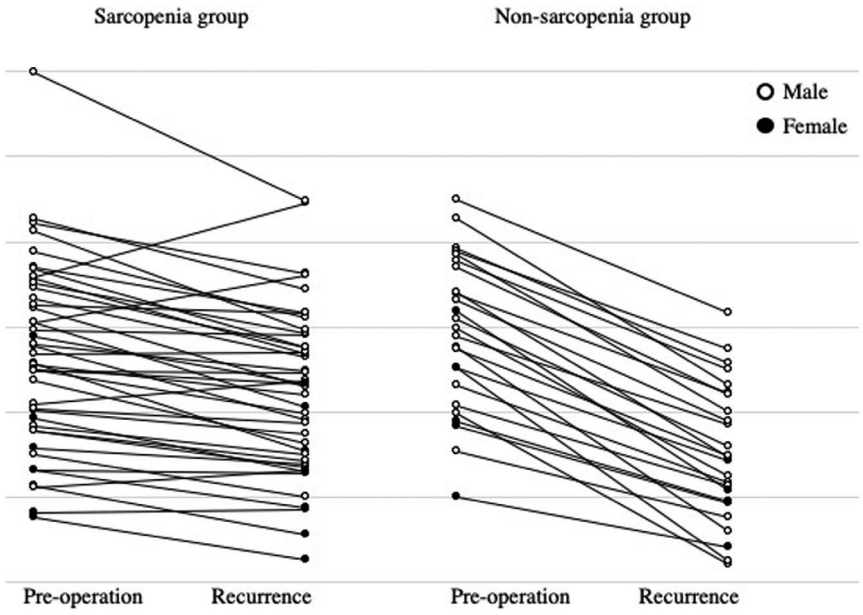

Figure 2. Changes in PMI from preoperative to recurrence in all patients; the sarcopenia group exhibited <cutoff value of the reduction rate of PMI (male=0.804 and female=0.733), and the non-sarcopenia group exhibited >the cutoff value. Open circles represent male cases and filled circles represent female cases. PMI, psoas muscle index.

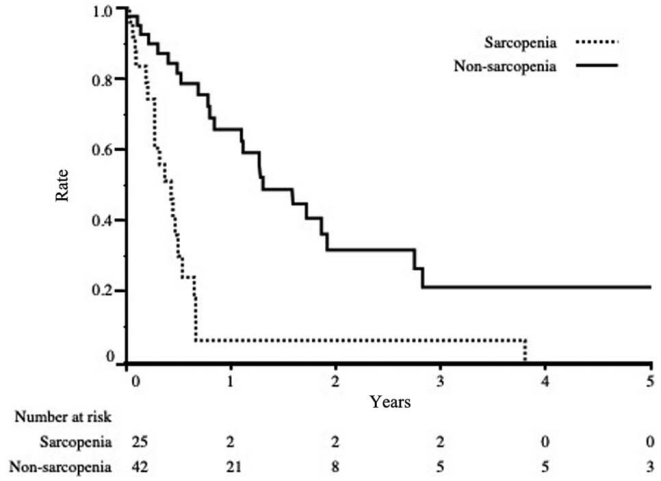

Figure 3. The overall survival from the time of recurrence. Log-rank test, P<0.05.

of sarcopenia. Sarcopenia at the recurrence and the reduction rate of PMI from surgery to the recurrence were selected as the independent poor prognostic factors via multivariate analysis, but preoperative sarcopenia was not.

Discussion

In the present study, we demonstrated that the high reduction rate of PMI from the preoperative value to that at the recurrence of gastric cancer and the fewer courses of chemotherapy performed after recurrence were independently associated with poor prognosis after the recurrence.

Since Rosenberg has reported the concept of sarcopenia in 1997, and many studies have evaluated the associations between sarcopenia and clinical factors, such as poor quality of life, aspiration pneumonia, osteoporosis, swallowing function, and respiratory function (15). In patients with malignancies, sarcopenia is more likely to be developed due to increased protein catabolism, inflammatory reactions, metabolic abnormalities, and poor oral intake and may be associated with cancer cachexia. Many recent studies have shown that the frequency of serious postoperative complications was high and the long-term prognosis was poor in gastric cancer patients with preoperative sarcopenia (5-7,9,10). In addition, postoperative loss of the muscle mass affects the continuation rate of postoperative adjuvant chemotherapy, especially in the elderly, because of increased severe adverse events (16,17). However, no study has evaluated the relationship between prognosis after the recurrence and the reduction of skeletal muscle mass after gastrectomy. This study indicated that the reduction of PMI was a risk factor of poor OS after the recurrence of gastric cancer, which is consistent with a previous report that skeletal muscle loss during postoperative adjuvant chemotherapy is associated with poor prognosis (18).

We also demonstrated that patients who failed to continue chemotherapy more than five courses after the recurrence of gastric cancer had a poor prognosis. There are several factors affecting the continuity of chemotherapy after the recurrence, i.e., adverse events, age, performance status, the amounts of oral intakes, economic problem, and other social circumstances (19). Physicians can intervene the continuity of chemotherapy by providing appropriate nutritional management and preventing loss of skeletal muscle mass at the time of recurrence, which may be associated with longer survival after the recurrence of gastric cancer.

Preoperative exercises and nutritional support programs were effective for increasing total caloric intake, protein, and grip strength, maintaining skeletal muscle volume and

Table I. Patient's clinicopathological factors.

Characteristic	Sarcopenia (n=25, 37.3%)	Non-Sarcopenia (n=42, 62.7%)	Total (n=67)	P-value
Age	72.1±7.8	70.0±8.6	70.8±8.3	0.393
Sex				0.718
Male	20	32	52	
Female	5	10	15	
Body weight (kg)				
Preoperatively	55.4±8.9	59.5±9.8	57.9±9.6	0.082
At the time of recurrence	46.2±8.1	51.2±7.9	49.3±8.3	0.014[a]
Recurrence/preoperatively	0.8±0.1	0.9±0.1	0.9±0.1	0.422[b]
Body mass index (kg/m^2)				
Preoperatively	21.3±2.9	22.6±3.2	22.1±3.1	0.071
At the time of recurrence	17.7±2.2	19.5±2.6	18.8±2.6	0.010[a]
Recurrence/preoperatively	0.8±0.1	0.9±0.1	0.9±0.1	0.338
Psoas muscle index				
Preoperatively	3.9±0.9	3.7±1.1	3.8±1.0	0.223
At the time of recurrence	2.5±0.8	3.2±1.0	3.0±1.0	0.005[a]
Recurrence/Preoperatively	0.6±0.1	0.9±0.1	0.8±0.2	<0.001[a]
CCI score 2≤				0.630
Yes	6	8	14	
No	19	34	53	
Tumor location U/M/L				0.579
U	11	15	26	
M	9	12	21	
L	5	15	20	
Histology int/dif/other				0.210
Int	14	18	32	
Dif	8	22	30	
Other	3	2	5	
Tumor depth				0.418
pT1	4 (16.0%)	3 (7.1%)	7 (10.5%)	
pT2	3 (12.0%)	3 (7.1%)	6 (9.0%)	
pT3	7 (28.0%)	19 (45.2%)	26 (38.8%)	
pT4	11 (44.0%)	17 (40.5%)	28 (41.8%)	
Lymph node metastasis				0.978
pN0	5 (20.0%)	8 (19.1%)	13 (19.4%)	
pN1	4 (16.0%)	8 (19.1%)	12 (17.9%)	
pN2	6 (24.0%)	11 (26.2%)	17 (25.4%)	
pN3	10 (40.0%)	15 (35.7%)	25 (37.3%)	
Pathological cancer stage				0.267
pStageI	3 (12.0%)	3 (7.2%)	6 (9.1%)	
pStageII	6 (24.0%)	12 (28.6%)	18 (27.3%)	
pStageIII	16 (64.0%)	27 (64.3%)	43 (63.6%)	
Lymphatic invasion				0.613
Ly0	2	5	7	
Ly1	23	37	60	
Venous invasion				0.429
V0	4	4	8	
V1	21	38	59	
DG/TG/other				0.161
DG	6	19	25	
TG	17	22	39	
Other	2	1	3	

Table I. Continued.

Characteristic	Sarcopenia (n=25, 37.3%)	Non-Sarcopenia (n=42, 62.7%)	Total (n=67)	P-value
Open/laparoscopy				0.161
Open	18	23	41	
Laparoscopy	7	19	26	
Billroth-I/Roux-en-Y/other				0.130
Billroth-I	6	15	21	
Roux-en-Y	2	27	44	
Other	17	0	2	
Recurrence pattern				0.455
Peritoneal	9 (36.0%)	9 (7.1%)	18 (26.9%)	
Hematogenous	6 (24.0%)	17 (7.1%)	23 (34.3%)	
Lymph node	6 (24.0%)	11 (7.1%)	17 (25.4%)	
Local	2 (8.0%)	1 (7.1%)	3 (4.5%)	
Other	2 (8.0%)	4 (45.2%)	6 (8.9%)	

U, upper third; M, middle third; L, lower third; Int, intestinal type; Dif, diffuse type; DG, Distal gastrectomy; TG, Total gastrectomy; CCI, Charlson comorbidity index; [a]P<0.05. Data are expressed as the mean ± standard deviation.

Table II. Patient's characteristics at the time of recurrence of gastric cancer.

Characteristic	Sarcopenia (n=25, 37.3%)	Non-Sarcopenia (n=42, 62.7%)	Total (n=67)	P-value
Neutrophil lymphocyte ratio				
Preoperatively	3.0±2.4	3.5±2.8	3.3±2.6	0.828
At the time of recurrence	4.2±3.1	4.6±4.7	4.5±4.1	0.589
CAR				
Preoperatively	0.3±0.4	0.1±0.2	0.2±0.3	0.213
At the time of recurrence	0.7±1.0	0.5±0.6	0.6±0.8	0.474
CONUT score				
Preoperatively	2.3±1.1	2.5±1.3	2.4±1.2	0.597
At the time of recurrence	4.8±2.8	3.0±1.7	3.9±2.5	0.062
Prognostic nutritional index				
Preoperatively	37.2±9.5	35.9±13.3	36.4±11.7	0.746
At the time of recurrence	39.7±7.5	43.7±9.0	42.1±8.6	0.114
Modified GPS score				
Preoperatively	0.4±0.7	0.5±0.7	0.5±0.7	0.927
At the time of recurrence	1.2±0.7	1.0±0.6	1.1±0.7	0.180
Adjuvant chemotherapy				0.874
Yes	8	16	24	
No	17	26	43	
Discontinued adjuvant chemotherapy due to adverse effect	6 (75.0%)	10 (62.5%)	16 (66.7%)	0.540
Duration from gastrectomy to recurrence (day)	572.9±513.2	444.8±331.0	492.6±409.5	0.484
Chemotherapy after recurrence				0.729
Yes	12	22	34	
No	13	20	33	
1st line regimen after recurrence				0.100
Pyrimidine fluoride	8	20	28	
Taxane	2	2	4	
Other	2	0	2	

Table II. Continued.

Characteristic	Sarcopenia (n=25, 37.3%)	Non-Sarcopenia (n=42, 62.7%)	Total (n=67)	P-value
Number of chemotherapy regimens after recurrence	1.6±0.8	1.7±1.0	1.7±0.9	0.855
Total courses of chemotherapy after recurrence	3.7±2.4	7.5±5.6	6.3±5.1	0.092
Discontinued chemotherapy due to adverse effect	6 (50.0%)	7 (31.8%)	13 (38.2%)	0.297
Overall survival from the recurrence of gastric cancer (day)	169.0±52.8	492.9±83.4	372.0±58.8	<0.001

CAR, C-reactive protein Albumin ratio; CONUT, controlling nutrition status; GPS, Glasgow Prognostic Score. Data are expressed as the mean ± standard deviation.

Table III. Prognostic factor for the overall survival from the time at recurrence.

	Univariate analysis			Multivariate analysis		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Age ≥70 years old	1.69	0.91-3.22	0.096			
Body weight reduction rate ≥Median	1.24	0.67-2.28	0.490			
Body mass index reduction rate ≥Median	1.21	0.65-2.23	0.530			
CCI score ≥2	0.90	0.37-1.92	0.802			
Tumor depth ≥pT3	0.71	0.35-1.66	0.404			
Lymph node metastasis ≥pN2	1.65	0.88-3.24	0.117			
Lymphatic invasion Ly1	0.99	0.45-2.62	0.984			
Venous invasion V1	0.95	0.43-2.52	0.908			
Neutro Lymph ratio ≥3.0	2.63	1.28-5.53	0.008[a]	1.48	0.40-5.01	0.544
CONUT score ≥4	2.26	0.90-6.20	0.084			
Prognostic Nutritional Index ≤40	2.59	1.23-5.50	0.012[a]	1.25	0.33-5.01	0.746
modified GPS score ≥1	1.91	0.90-4.70	0.097			
Sarcopenia Yes	4.18	2.17-8.07	<0.001[a]	5.04	1.28-22.61	0.021[a]
Adjuvant chemotherapy No	1.05	0.58-1.93	0.872			
Recurrence site Peritoneal	1.49	0.75-2.80	0.246			
Chemotherapy after recurrence No	1.32	0.71-2.43	0.376			
Chemotherapy regimen after recurrence Pyrimidine fluoride	0.45	0.16-1.59	0.192			

Table III. Continued.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Number of regimens after recurrence <2	1.13	0.50-2.58	0.762			
Total courses of chemotherapy after recurrence <5	3.82	1.33-11.42	0.013[a]	3.88	1.19-13.69	0.025[a]

HR, hazard ratio; CI, confidence interval; CRP, C-reactive protein; CONUT, controlling nutrition status; GPS, Glasgow Prognostic Score; CCI, Charlson comorbidity index. [a]P<0.05.

Table IV. Univariate and multivariate analysis for the overall survival from the time at recurrence among the difference time of sarcopenia.

		Univariate analysis			Multivariate analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Sarcopenia by skeletal muscle mass reduction rate	Yes	4.18	2.17-8.07	<0.001[a]	3.05	1.44-6.48	0.004[a]
Preoperative sarcopenia	Yes	0.93	0.51-1.73	0.813	0.80	0.39-1.67	0.551
Sarcopenia at the time of recurrence	Yes	3.58	1.78-7.42	<0.001[a]	3.05	1.30-7.31	0.010[a]

HR, hazard ratio; CI, confidence interval. [a]P<0.05.

improving postoperative outcomes in patients with gastric cancer (19,20). However, there were few reports on the effects of postoperative nutritional supports on the postoperative development of sarcopenia and outcome. In addition, it has been reported that subtotal gastrectomy for the upper third of gastric cancer had advantages over total gastrectomy in terms of maintaining weight and nutritional status (20,21). Thus, it will be essential to ensure thorough nutritional management after surgery, as well as surgical procedures, for maintaining skeletal muscle volume and nutritional status at the recurrence of gastric cancer.

In the present study, we also evaluated the NLR, CAR, PNI, CONUT, and mGPS at the recurrence of gastric cancer, which were well known to be preoperative prognostic markers in various malignancies (22-26). We demonstrated that these markers were not associated with prognosis when the values at the recurrence were used, indicating the importance of preoperative value but not at the recurrence.

We compared the clinical importance of the sarcopenia preoperatively, at the recurrence, and the reduction rate of PMI from surgery to the recurrence. Sarcopenia at the recurrence and the reduction rate of PMI from surgery to the recurrence were selected as the independent poor prognostic factors by multivariate analysis.

This study has several potential limitations. The retrospective design of the study and relatively small number of patients in this study may have resulted in bias. In addition, we did not evaluate the relation of amounts of oral intake and the exercise after gastrectomy to the occurrence of gastric cancer, which made it difficult to determine whether skeletal muscle loss was caused by eating disorder after gastrectomy or with the progression of cancer.

In conclusion, fewer total courses of chemotherapy after recurrence and sarcopenia were poor prognostic factors for patients with gastric cancer recurrence. Our data suggested that prospective interventional study to prevent the reduction of skeletal muscle volume should be promising for improving survival after the recurrence of gastric cancer.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors contributions

KK, HT, HS, YIt, YIs, ST, YK and HU contributed to the study conception and design. Material preparation and data collection and analysis were performed by KK. The first draft of the manuscript was written by KK and HT, and all

authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures followed were in accordance with the Helsinki Declaration of 1964 and later versions. The study protocol was approved by the Institutional Review Board of the National Defense Medical College, and written informed consent was obtained from every patient.

Patient consent for publication

Informed consent for publication was obtained from every patient.

Competing interests

The authors declare that they have no competing interests.

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