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Psoas muscle depletion during preoperative chemotherapy for advanced gastric cancer has a negative impact on long-term outcomes after gastrectomy

Nobutoshi Horii[1] 🟢 | Takashi Kosaka[1] | Ryo Fujiwara[1] | Sho Sato[1] | Hirotoshi Akiyama[1] | Chikara Kunisaki[2] | Itaru Endo[1]

[1] Department of Gastroenterological Surgery, Yokohama City University, Graduate School of Medicine, Yokohama, Japan

[2] Department of Surgery, Gastroenterological Center, Yokohama City University, Yokohama, Japan

Correspondence
Nobutoshi Horii, MD, Yokohama City University, Department of Gastroenterological Surgery, 3–9 Fukuura, Kanazawa-Ku, Yokohama 236-0004, Japan.
Email: horiinobushi1029@gmail.com

Yokohama City University, Department of Gastroenterological Surgery, 3–9 Fukuura, Kanazawa-Ku, Yokohama 236-0004, Japan

Abstract

Aim: The significance of sarcopenia in cancers has been widely recognized. However, few studies have focused on chronological changes in sarcopenia in cancer patients. This study aimed to clarify the clinical significance of changes in the psoas muscle area before and after preoperative chemotherapy.

Methods: This study included 39 patients who underwent gastrectomy followed by preoperative chemotherapy for advanced gastric cancer between January 2010 and December 2016 in our hospital. The psoas muscle area was measured at the umbilical level before and after chemotherapy, and the relationship between its chronological changes and the long-term prognosis was examined.

Results: Patients were classified into two groups according to changes in the psoas muscle area before and after preoperative chemotherapy: remarkable muscle depletion and normal groups. No significant differences were observed in clinicopathological factors. Notably, the remarkable muscle depletion group included significantly more male patients ($P = .018$) and showed a high weight loss rate ($P < .001$). Although no significant difference was observed in the recurrence-free survival between the two groups ($P = .484$), overall survival was significantly worse in the remarkable muscle depletion group ($P < .001$). Multivariate analysis for prognosis revealed that pathological stage III or higher ($P = .022$) and decreased psoas muscle area ($P = .038$) were independent prognostic factors.

Conclusions: The present findings suggest that psoas muscle depletion during preoperative chemotherapy is a prognostic factor for poor long-term outcomes in patients who underwent gastrectomy followed by preoperative chemotherapy for advanced gastric cancer.

KEYWORDS
gastric cancer, preoperative chemotherapy, psoas muscle, psoas muscle index, sarcopenia

1 | INTRODUCTION

Gastric cancer remains common in Japan, although the incidence has been decreasing.[1] The promotion and progress of screening for early gastric cancer have contributed to the early discovery and improvement of the prognosis.[2] However, the prognosis of advanced gastric cancer (AGC) has room for improvement, and one such method is preoperative chemotherapy (POC) for resectable AGC.[3,4]

Sarcopenia has been observed in various pathological conditions and is caused by numerous factors.[5,6] Accumulating evidence indicates that sarcopenia is a prognostic factor for worse short-term and long-term outcomes in several cancers, including gastric cancer.[7-9] Many studies have reported the clinical significance of sarcopenia in gastric cancer.[8-11] However, in most of these studies, sarcopenia was defined by measuring the skeletal muscle mass and strength at a single time point,[7-11] and few studies have focused on changes in the skeletal muscle and strength in patients with gastric cancer.

Skeletal muscle depletion during neoadjuvant chemotherapy for esophageal cancer[12] and ovarian cancer[13] is reportedly an adverse prognostic factor for short- and long-term outcomes. However, similar studies have not been conducted for gastric cancer. Therefore, this study aimed to determine the clinical significance of changes in the psoas muscle area before and after preoperative chemotherapy.

2 | MATERIALS AND METHODS

2.1 | Patients and methods

Between January 2010 and December 2016, a series of 38 patients with resectable AGC who underwent POC were enrolled in this retrospective study. POC was indicated for AGC patients who experienced clinically positive lymph node metastasis or para-aortic lymph node metastasis and no other organ metastases. Therefore, patients with a few para-aortic lymph node metastases that were considered resectable lesions were included in this study. POC included two courses of one of the following regimens:

1. DCS – TS-1, cisplatin, and docetaxel therapy (40 mg/m^2 docetaxel + 40 mg/m^2 cisplatin + 80 mg/m^2 S-1).
2. DS – TS-1 and docetaxel therapy (40 mg/m^2 docetaxel + 80 mg/m^2 S-1).
3. XP – capecitabine and cisplatin therapy (1000 mg/m^2 capecitabine + 80 mg/m^2 cisplatin).
4. SP – TS-1 and cisplatin (40 mg/m^2 cisplatin + 80 mg/m^2 S-1).

Eleven patients underwent DCS therapy, 19 underwent DS therapy, five underwent XP therapy, and three underwent SP therapy. The regimen was selected according to each patient's condition, lifestyle, and intention after sufficient explanation. This retrospective study was approved by the ethics committee of Yokohama City University (B181200029). The ethics approval, consent to use medical records
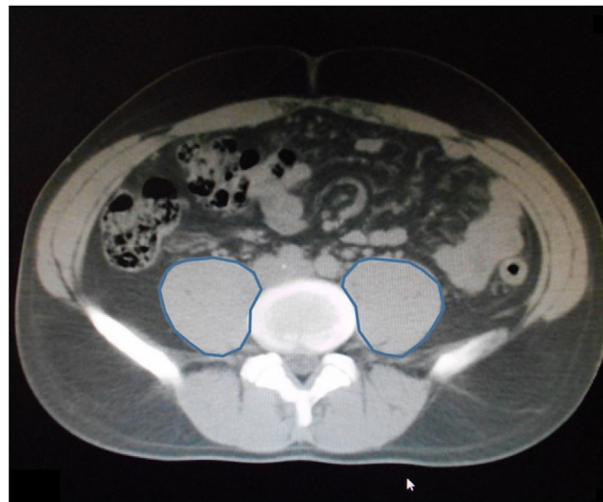

FIGURE 1 Contrast-enhancement computed tomography image of the bilateral psoas muscles at the level of the umbilicus. Blue lines indicate the manual tracing of the psoas muscles [Colour figure can be viewed at wileyonlinelibrary.com]

and electronic data, and consent for publication were obtained from the Ethics Committee of Yokohama City University.

To determine the clinical stage, the following tests were performed within a month before POC: gastroduodenoscopy, upper gastrointestinal barium study, contrast-enhancement computed tomography (CECT), and diagnostic laparoscopy. The response after POC was evaluated according to the Response Evaluation Criteria in Solid Tumors Guideline (RECIST1.1).[14] Gastrectomy was performed 2 months after POC. Clinicopathological variables were collected based on the clinical and pathological records. Psoas muscle changes at the umbilical level were evaluated by CECT findings (Figure 1), and postoperative complications were assessed with the Clavien-Dindo classification system.[15-16]

2.2 | Imaging analysis

All computed tomography (CT) imaging before and after POC was performed with a multi-detector CT scanner (Aquilion CXL, Canon Medical Systems, Otawara, Japan; Aquilion PRIME, Canon Medical Systems, Otawara, Japan; and SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany). Skeletal muscle mass was evaluated using the psoas muscle area (cm^2) and the psoas muscle index (PMI) at the level of the umbilicus. The bilateral psoas muscle area was evaluated using manual tracings (Figure 1). The PMI was calculated by normalizing these cross-sectional areas to height (cm^2/m^2).[17,18]

The decrease in the proportion of the psoas muscle area was determined using a receiver operating characteristic (ROC) curve. Moreover, as an evaluation of skeletal muscle mass at one time point, PMI was measured before and after chemotherapy, and the cut-off value was similarly determined by a ROC curve with overall survival (OS) as the dependent variable.

TABLE 1 Patient characteristics

	Total (n = 38)
Age at diagnosis (years)	
Median (IQR)[a]	64 (44-78)
Sex n (%)	
Male	28 (74)
Female	10 (26)
Serum albumin level (g/dl) before POC	
Median (IQR)	4.3 (3.5-4.8)
Serum albumin level (g/dl) after POC	
Median (IQR)	3.8(2.2-4.4)
ASA score n (%)	
1	15 (40)
2	23 (60)
PNI before POC	
Median (IQR)	51.6 (44.6-57.2)
PNI after POC	
Median (IQR)	47.8 (30.5-57.8)
mGPS n (%) before POC	
0	38 (100)
mGPS n (%) after POC	
0	25(66)
1	10(26)
2	3 (8)
BMI (kg/m^2) before POC	
Median (IQR)	22.7 (17.1-30.4)
BMI (kg/m^2) after POC	
Median (IQR)	21.7 (16.3-27.1)
Tumor main location n (%)	
Upper	12 (32)
Middle	15 (40)
Lower	11(28)
Clinical stage (stage J)	
II	18 (47)
III	13 (34)
IV	7 (19)
Pathological stage (stage J)	
I	10 (26)
II	12 (32)
III	15 (39)
IV	1 (3)
Pathological stage (TNM)	
I	9 (25)
II	14 (36)
III	14 (36)
IV	1 (3)

(Continues)

TABLE 1 (Continued)

	Total (n = 38)
CEA (ng/dL) before POC	
Median (IQR)	11.0 (1.1-855)
CEA (ng/dL) after POC	
Median (IQR)	2.1 (0.3-7.5)
CA19-9 (mU/L) after POC	
Median (IQR)	9.0 (1.0-150)
CA19-9 (mU/L) before POC	
Median (IQR)	11.0 (1-118)
Effects of POC	
PR	12 (32)
SD	26 (68)
POC Regimen	
DS	19 (39)
DCS	11 (29)
XP	5 (13)
SP	3 (8)
Adverse events related to POC	
Grade I or 0	17 (45)
Grade II	9 (24)
Grade III	11 (29)
Grade IV	1 (9)
Surgical procedure n (%)	
Total gastrectomy	17 (45)
Partial gastrectomy	21 (55)
Operation time (min)	
Median (IQR)	263 (167-422)
Operative blood loss (mL)	
Median (IQR)	400 (100-1510)
PMI (cm^2/m^2) before POC	
Median (IQR)	
Male	6.7(4.7-9.7)
Female	6.0(3.8-8.2)
PMI (cm^2/m^2) after POC	
Median (IQR)	
Male	6.4(3.7-8.8)
Female	5.5(3.6-7.6)
Postoperative complications n (%)	
Clavien-Dindo grade II	6 (16)
Clavien-Dindo grade III	5 (13)

[a]Abbreviations: ASA score, American Society of Anesthesiologists classification score; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DS: TS-1 and docetaxel therapy DCS: TS-1, cisplatin, and docetaxel therapy IQR: interquartile range; mGPS, modified Glasgow prognostic score; PMI, psoas muscle index; PNI, prognostic nutritional index; POC: Preoperative chemotherapy; Post-op, postoperative; PR: Partial response; SD: Stable disease; SP: TS-1 and cisplatin therapy; Stage J: Stage according to the Japanese 14th handling rules; TNM: Stage according to the 8th TNM classification.; XP: capecitabine and cisplatin therapy.

TABLE 2 Comparison of patient backgrounds between the normal and remarkable psoas muscle loss groups

TABLE 2 (Continued)

	RD group (n = 8)	N group (n = 30)	P-value
Age (years)			
Median (IQR)[a]	64 (44-78)	61 (45-75)	.916
Sex n (%)			
Male	8 (100)	20 (63)	.018
Female	0 (0)	10 (27)	
Serum albumin level (g/dL) before POC			
Median (IQR)	4.4 (4.0-4.7)	4.2 (3.5-4.8)	.057
Serum albumin level (g/dL) after POC			
Median (IQR)	4.3 (3.2-4.8)	3.9 (3.5-4.5)	.388
ASA score n (%)			
1	3 (38)	12 (40)	.897
2	5 (62)	18 (60)	
PNI before POC			
Median (IQR)	52.5 (48.9-56.3)	51.3 (44.6-57.3)	.223
PNI after POC			
Median (IQR)	47.5 (38.3-57.0)	47.8 (30.5-57.0)	.691
mGPS n (%) after POC			
0	3 (38)	22 (73)	.063
1 or 2	5 (62)	98 (17)	
BMI (kg/m^2) before POC			
Median (IQR)	23.2 (20.3-29.5)	22.2 (17.1-30.4)	.691
BMI (kg/m^2) before POC			
Median (IQR)	20.0 (18.7-26.6)	21.5 (16.3-27.1)	.691
Body weight loss rate (%)			
Median (IQR)	6.2 (0-14)	2.6 (-6-10)	<.001
Tumor main location n (%)			
U area	2 (25)	10 (33)	.780
M area	4 (50)	11 (36)	
L area	2 (25)	9 (31)	
Clinical stage (J stage)			
II	4 (50)	14 (47)	.887
III	3 (37)	10 (33)	
IV	1 (13)	6 (20)	
Pathological stage (J stage)			.157
I	2 (25)	8 (28)	
II	1 (12.5)	11 (36)	
III	4 (50)	11 (36)	
IV	1 (12.5)	0 (0)	
Pathological stage(TNM)			.164
I	1 (12.5)	8 (28)	
II	2 (25)	12 (40)	
III	4 (50)	10 (33)	
IV	1 (12.5)	0 (0)	
CEA (ng/dL) before POC			
Median (IQR)	2.4 (1.1-6.5)	2.0 (0.5-7.5)	.691
CEA (ng/dL) after POC			
Median (IQR)	2.9 (1.0-8.0)	2.4 (1.1-6.5)	.691
CA19-9 (mU/L) before POC			.818
Median (IQR)	17 (1-32)	9 (1-150)	
CA19-9 (mU/L) after POC			.571
Median (IQR)	12(1-55)	11 (1-118)	
Effects of POC			
PR	3 (37)	9 (30)	.688
SD	5 (63)	21 (70)	
POC Regimen			.620
DS	5 (63)	14 (46)	
DCS	2 (24)	9 (30)	
XP	1(13)	4 (13)	.302
SP	0 (62)	3 (11)	
Adverse events related to POC			.050
0 or 1	6 (75)	19 (63)	
Grade 2 or worse adverse events	2 (25)	11 (37)	
Surgical Procedure n(%)			.256
Total gastrectomy	3 (38)	18 (60)	
Partial gastrectomy	5 (62)	12 (40)	
Operation time (min)			
Median (IQR)	258 (191-297)	270 (167-422)	.691
Operative blood loss (mL)			
Median (IQR)	344 (233-1097)	459 (100-1510)	.818
PMI (cm^2/m^2) before POC			
Median (IQR)			
Male	7.3 (5.7-8.4)	6.7 (4.7-9.7)	1.000
Female	None	6.0(3.8-8.2)	
PMI (cm^2/m^2) after POC			
Median (IQR)			
Male	5.9 (3.7-7.0)	6.4 (3.7-8.8)	.678
Female	None	5.5 (3.6-7.6)	
Post-op complication ≥ C-D grade 2			
Yes n (%)	2 (25)	9 (30)	.779

(Continues)

(Continues)

TABLE 2 (Continued)

	RD group (n = 8)	N group (n = 30)	P-value
Post-op complication ≥ C-D grade 3			
Yes n (%)	1 (13)	4 (13)	.950

^aAbbreviations: ASA score, American Society of Anesthesiologists classification score; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; DS: TS-1 and docetaxel therapy DCS: TS-1, cisplatin, and docetaxel therapy IQR: interquartile range; J stage: Stage according to the Japanese 14th handling rules: mGPS, modified Glasgow prognostic score; N: normal group; PMI, psoas muscle index; PNI, prognostic nutritional index; POC: Preoperative chemotherapy; Post-op, postoperative; PR: Partial response; RD: remarkable psoas muscle loss group; SD: Stable disease; SP: TS-1 and cisplatin therapy; TNM: Stage according to 8th TNM classification.; XP: capecitabine and cisplatin therapy.

Patients whose psoas muscle areas decreased by 15% or more during POC were defined as the remarkable muscle depletion (RD) group, and other patients were classified into the normal (N) group. Similarly, the cutoff value of 15% was determined by a ROC curve with OS as the dependent variable.

2.3 | Analyzed parameters

The OS and recurrence-free survival (RFS) rates after gastrectomy for AGC were evaluated for the patients and classified with respect to the decrease in the proportion of the psoas muscle area during POC. OS and RFS were defined as overall survival and recurrence-free survival measured after surgery, respectively. In addition, the following variables were analyzed as prognostic factors: patient age, sex, body mass index (BMI), Onodera's prognostic nutritional index (PNI),[19] modified Glasgow prognostic score (mGPS),[20] American Society of Anesthesiologists Classification score (ASA score), the regimen of POC, the adverse events of chemotherapy determined with reference to the Common Terminology Criteria for Adverse Events version 4.0, the effectiveness of POC evaluated according to RECIST1.1,[14] serum carcinoembryonic antigen level, serum carbohydrate antigen 19-9 level, surgical procedure, clinical and pathological stage (determined based on Japan's 14th edition of the Gastric Cancer Handling Regulations[21]), pathological stage (determined according to the 8th edition of the classification released by Union for International Cancer Control), operation duration, amount of bleeding during the operation, and postoperative complications. The severity of postoperative complications was assessed by the Clavien-Dindo classification system.[15–16] Regarding the clinical stage before POC, the number of metastasis-positive lymph nodes was not described in our database. Therefore, it was impossible to convert from the stages according to the Japanese handling rules[21] to those according to the 8th TNM classification. Regarding the clinical stages before POC, only those according to the Japanese handling rules[21] are described.

2.4 | Statistical analyses

Data are presented as median (range) or number (percentage). The differences were assessed with Mann-Whitney U tests for numerical variables and Fischer's exact probability tests for categorical variables. Survival was assessed using Kaplan-Meier life tables, and differences in survival were evaluated with Gehan-Breslow-Wilcoxon tests. A two-tailed P-value < .05 was considered significant. Statistical analyses were performed with SPSS commercial statistics software, version 22 (IBC, Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics

Baseline characteristics of the 38 patients who participated in this study are summarized in Table 1. The median patient age was 64 (44-78) years. All patients had an ASA score of one or two. Mean body weights before and after POC were 61.2 (43.5-88.0) kg and 57.5 (40.0-88.0) kg, respectively (P < .001). BMI before and after POC was 22.7 kg/m^2 (17.1-30.4) and 21.7 kg/m^2 (16.3-27.1), respectively (P = .001). The psoas areas before and after POC were 18.7 (8.9-29.8) cm^2 and 17.0 (8.0-25.8) cm^2, respectively (P < .001). The PMI before and after POC was 6.57 (3.84-9.74) cm^2/m^2 and 6.21 (3.30-8.89) cm^2/m^2, respectively (P < .001). The main location of the tumor was determined using the gastric barium test according to the Japanese gastric cancer handling regulations.[21]

Comparisons between the RD and N groups are shown in Table 2. No significant differences were observed in many patient factors, and the RD group included only men. Moreover, the body weight loss rate during POC was significantly higher in the RD group than in the N group. Although no statistically significant difference was observed, more adverse events related to POC were observed in the N group than in the RD group.

3.2 | RFS after gastrectomy

The RFS rate after gastrectomy for AGC was similar between the N and RD groups (P = .484; Figure 2A).

3.3 | OS after gastrectomy

The OS rate was significantly lower in the RD than in the N group (P < .001; Figure 2B). Of the 14 deaths, 13 died of cancer, and one died of aspiration pneumonia. The death from aspiration pneumonia occurred in the RD group.

Several other prognostic factors for OS were analyzed in the included patients. Univariate and multivariate analyses are summarized in Table 3. The univariate analyses showed that the rate of body weight loss of more than 10% (P = .001), RD group (P < .001),
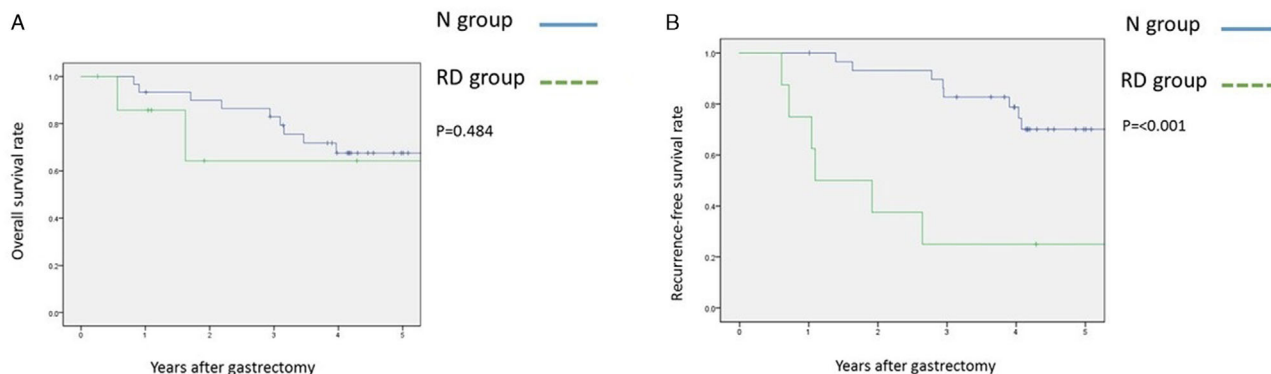
FIGURE 2 Comparison of survival of patients between the remarkable muscle depletion group and the normal group. A, recurrence-free survival; B, overall survival [Colour figure can be viewed at wileyonlinelibrary.com]

pathological stage III or IV ($P = .003$) determined by the Japanese handling rules,[21] and pathological stage III or IV ($P = .004$) determined by the 8th TMN classification were significantly associated with worse prognosis. As shown in Table 2, the patient distributions by stage III or IV and the TMN stage determined by the Japanese handling rules were similar. Therefore, stage III or IV determined by the TMN classification was excluded from the multivariate analysis as a confounding factor. Multivariate analysis was performed using three factors: weight loss, RD group, and stage III or higher determined by the Japanese handling rules.

RD group ($P = .036$) and pathological stage III or IV determined by the Japanese handling rules ($P = .031$) were associated with poor prognosis after gastrectomy for AGC. Similarly, prognostic evaluation using PMI was performed for the assessment of skeletal muscle mass at one time point. The PMI cutoff values were set using a ROC curve, and patients with low PMI were classified as the low PMI group before and after POC (PMI cutoffs before POC: men, 6.2; women, 4.7; PMI cut-offs after POC: men, 5.9; women, 5.4). However, no correlation between PMI calculated from skeletal muscle mass at one time point and the long-term prognosis was observed.

4 | DISCUSSION

To our knowledge, this is the first report suggesting an association between reduced psoas muscle area during POC and prognosis in AGC. No significant differences were observed in clinicopathological factors between the RD and N groups; however, the RD group included significantly more male patients and showed a high weight loss rate. OS was significantly worse in the RD group, and the multivariate analysis revealed that pathological stage III or higher and decreased psoas muscle area were independent prognostic factors.

Sarcopenia is a prognostic factor for several malignant diseases, including gastric cancer; however, it is often evaluated by assessing skeletal muscle mass or strength at a single time point, and a few studies have observed muscle mass or strength changes.[7-11] Although studies have reported changes in skeletal muscle mass during POC in patients with ovarian cancer and esophageal cancer,[22,12] there

was no similar report on gastric cancer. In addition, many studies have investigated sarcopenia in gastric cancer,[7-11] but few studies have focused on muscle mass changes. In this study, PMI was used as an indicator of skeletal muscle mass at a single time point, and its association with prognosis was examined. We found that PMI was not a prognostic factor. Therefore, although it is necessary to pay attention to skeletal muscle mass at one time point in patients undergoing POC, the changes in skeletal muscle mass or strength should equally be considered. Moreover, PMI tended to be higher in men than in women before and after POC, suggesting that there is a sex difference in PMI; the findings are consistent with those in previous studies.[17,18] The method of PMI evaluation in this study was considered appropriate. As shown in Table 1, the reduction in PMI was noticeable among women. However, the fact that there were more males in the RD group might be responsible for the observation of a significant reduction in the iliopsoas muscle exclusively among males. Although this study did not reveal any cause for skeletal muscle loss, we found that males were more likely to have skeletal muscle loss; therefore, caution is required when administering POC in male patients. Moreover, in this study, BMI and PNI were used as indicators of nutritional condition, and no significant association was observed between BMI or PNI and poor prognosis. Therefore, the iliopsoas muscle might be a potential target for assessing nutritional immunological status that cannot be judged only by the conventional nutritional immunity index.

Gastric cancer was originally considered a disease that is prevalent in men,[1] and there is a sex difference in the long-term prognosis after gastric cancer surgery.[23] Consistently, a comparison of the patient's background between the RD and N groups revealed that the RD group exclusively included male patients with poor prognosis, probably leading to a statistically significant difference in prognosis between the RD and N groups. In addition, the only death not caused by cancer occurred in the RD group (aspiration pneumonia). Notably, sarcopenia has been suspected to be associated with respiratory function.[11] Therefore, not only cancer immunity but also the systemic function might be reduced in the RD group, thereby leading to a significant difference in the OS between the RD and N groups. In fact, although not significantly different, there were more patients with high mGPS after

TABLE 3 Univariate and multivariate analyses for overall survival

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI[a]	P-value	Odds ratio	95% CI[a]	P-value
Age ≥ 70 years	1.124	0.376-3.357	.834			
Male	1.711	0.568-5.154	.334			
ASA score 2	1.668	0.522-5.329	.383			
PNI before POC < 49	1.032	0.323-3.292	.958			
PNI before POC < 44	0.970	0.303-3.102	.959			
mGPS 1 or 2 after POC	02.119	0.743-6.046	.151			
BMI before POC < 21 kg/m^2	0.667	0.185-2.403	.533			
BMI after POC < 21 kg/m^2	2.298	0.796-6.631	.113			
Body weight loss rate ≥ 10%	5.302	1.836-15.314	.001	3.578	0.673-16.917	.135
RD group	5.689	1.938-16.751	<.001	4.307	1.087-17.074	.038
Main tumor location U area	0.711	0.238-2.128	.540			
Clinical stage III or IV(J stage)	1.989	0.653-5.836	.223			
Pathological stage III or IV(J stage)	5.109	1.563-16.701	.003	4.400	1.145-16.917	.031
Pathological stage III or IV(TMN)	5.651	1.739-18.363	.004			
CEA ≥ 5 ng/dl before POC	1.555	0.348-6.956	.560			
CEA ≥ 5 ng/dl after POC	1.681	0.563-5.018	.347			
CA19-9 ≥ 20 mU/l before POC	2.242	0.624-8.060	.204			
CA19-9 ≥ 20 mU/l after POC	1.577	0.439-5.667	.482			
Effect of POC: SD	0.964	0.439-5.667	.482			
POC adverse events ≥ grade 2	1.437	0.481-4.290	.514			
Total gastrectomy	1.189	0.411-3.434	.751			
Operation time > 240 min	1.202	0.377-3.837	.756			
Operation blood loss > 500 mL	0.662	0.222-1.979	.457			
Low PMI group before POC	1.700	0.567-5.093	.338			
Low PMI group after POC	1.391	0.482-4.011	.540			
POC complication ≥ C-D grade 3	0.480	0.063-3.762	.470			

[a]Abbreviations: ASA score, American Society of Anesthesiologists classification score; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; H group, high intramuscular adipose content group; J stage: Stage according to the Japanese 14th handling rules, mGPS, modified Glasgow prognostic score; PMI, psoas muscle index; PNI: prognostic nutritional index; Po complication ≥ C-D grade 3, postoperative complication as Clavien-Dindo grade 3 or more severe; POC: Preoperative chemotherapy; RM group: Remarkable muscle steatosis group; SD: Stable disease; TNM: Stage according to the 8th TNM classification.

chemotherapy in the RD group; therefore, trophic immunity might be significantly deteriorated during POC in the RD group due to the progression of cancer or the effect of the chemotherapy. Moreover, the weight loss rate similarly tended to be significantly higher in the RD group, suggesting that weight loss accompanying skeletal muscle loss occurred during chemotherapy. A possible reason for skeletal muscle loss is decreased food consumption due to adverse events experienced during chemotherapy; however, the frequency of adverse events was not significantly different between the two groups. Notwithstanding, because the amount of food consumption was evaluated only through an outpatient interview, it is possible that patients in the RD group consumed a smaller amount of food than estimated by the outpatient interview. Therefore, a more detailed evaluation of food intake may be necessary in outpatient care.

In this study, no significant difference was observed in tumor-related factors and surgery-related factors between the RD and N groups. Although complications are widely known to adversely affect long-term prognosis,[23] no significant difference was found between the two groups in the incidence of complications. However, significant differences in long-term prognosis were found among the patients with similar postoperative short-term results, suggesting that the skeletal muscle loss during POC may adversely affect the long-term prognosis.

Although sarcopenia has been previously reported as a prognostic factor in various malignancies,[7–11] the underlying mechanism has not been fully clarified. Sarcopenia may be caused by the presence of cancer cells, and the accompanying chronic inflammation[24–26] may lead to skeletal muscle atrophy. In this study, the percentage of patients with high mGPS in the RD group after POC was high, suggesting that

chronic inflammation due to cancer might lead to reduced immune function and consequently worsened nutritional status.[24-25] In addition, cancer immunity might have declined due to decreased immune function, thereby leading to the deterioration in RFS and OS in the RD group.

This study suggests that preventing weight loss, including loss of the psoas muscle area during POC, may improve prognosis after gastrectomy. Although the cause of the decrease in the psoas muscle area is unclear in this study, it is possible that food intake was decreased in the RD group. As a preventive treatment for weight loss accompanied by loss of the psoas muscle area, the nutritional intervention was reported to be effective.[27-28] A study showed that eicosapentaenoic acid supplementation during POC was effective for skeletal muscle loss in cancer patients.[27] Moreover, enobosarm, an orally-active small-molecule agonist of the skeletal muscle androgen receptor, was reported to induce muscle anabolism and be effective in maintaining the muscle strength of patients with several cancers.[29] Therefore, we are considering nutritional interventions during chemotherapy based on these previous findings.[27-29] In addition, rehabilitation has been reported to be effective in the prevention of sarcopenia[30]; thus, further studies are needed to determine the effectiveness of intervention by rehabilitation in AGC patients.

This retrospective study has several limitations. First, the sample size was small. At our institution, there is doubt about the value of POC for AGC currently, and no active POC has been performed. Further studies with a larger sample size are needed to confirm the present findings. Second, the POC regimens, clinical stage, and postoperative treatments were heterogeneously observed. A third limitation is the extended observation period. Excluding two patients for whom follow-up could not be performed, ten of the patients underwent surgery <5 years ago. For these patients, postoperative observation would gain additional insights into the usefulness of the reduction in psoas muscle depletion during POC.

The fourth limitation is the reliability of PMI. PMI has been reported to correlate with the skeletal muscle mass of patients,[31] and the method of PMI evaluation is supposedly appropriate. However, in recent years, the concept of intramuscular adipose tissue content (IMAC), which assesses the quality of skeletal muscle as a method of evaluation for sarcopenia, has been reported. In addition, for liver diseases,[17] IMAC has been used as a prognostic factor, but PMI has not.[17] Similarly, PMI has been reported to be inadequate as a predictor of postoperative prognosis after hepatectomy for colorectal liver metastasis.[32] Therefore, further studies are needed to investigate the potential diagnostic applications of not only PMI but also IMAC in gastric cancer.

The fifth limitation of this study is the appropriateness of the cut-off values for PMI and PMI reduction rates used in this study. Presently, there is no consensus on proper PMI values for healthy individuals. In this study, the sarcopenia group was defined using the cut-off values derived from the ROC curve. The ROC curve is considered a reasonable way of determining the cutoff value.[33] We hope that the evaluation of sarcopenia using the reduction rate of PMI will be generally established in the future.

In conclusion, psoas muscle depletion during POC may be associated with worse long-term survival outcomes. Further prospective studies, including a large number of homogenous AGC patients, are needed to establish a strategy that would avoid the reduction in skeletal muscle.

CONFLICT OF INTEREST
The authors declare that no conflict of interest.

PATIENT CONSENT STATEMENT
Patients provided informed consent before participating in the study.

AUTHOR CONTRIBUTIONS
HN contributed to the manuscript concept, surgery, literature retrieval, and writing. TK and HA participated in the surgery, patient data collection, and manuscript drafting and writing. CK and EI drafted the manuscript. All the authors have read and approved the manuscript.

DATA AVAILABILITY STATEMENT
The datasets used and analyzed in this study are not publicly available (to maintain privacy) but can be made available by the corresponding author on reasonable request.

ORCID
Nobutoshi Horii https://orcid.org/0000-0002-6347-476X

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