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ORIGINAL SCIENTIFIC REPORT

# Postoperative Skeletal Muscle Loss Predicts Poor Prognosis of Adenocarcinoma of Upper Stomach and Esophagogastric Junction

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## Abstract

*Background* The relationship between postoperative changes in muscle mass and the prognosis of malignancies remains controversial. We aimed to determine whether a decrease in skeletal muscle mass after surgical resection can predict long-term outcomes in patients with adenocarcinoma of upper stomach (AUS) and esophagogastric junction (AEGJ).

*Methods* We reviewed 146 patients who underwent curative surgery for AUS and AEGJ. We assessed the skeletal muscle index pre- and post-surgery and 6 months postoperatively. The rate of decrease in skeletal muscle index (SMI) was calculated and its relationship with clinicopathological factors and prognosis was analyzed.

*Results* Among the 146 patients studied, 115 underwent re-assessment of SMI 6 months postoperatively. The mean decrease in SMI was more prominent in patients with recurrence than in those without recurrence (19.0 ± 2.3 vs. 7.4 ± 0.9%, respectively, $P < 0.0001$). AUS and AEGJ patients with a >19% decrease in SMI showed significantly lower 5-year overall survival and recurrence-free rates than those with a <19% decrease in SMI (recurrence-free survival: 33.4 vs. 89.2%, respectively, $P < 0.0001$; overall survival: 40.6 vs. 90.0%, respectively, $P < 0.0001$). Multivariate analyses indicated that a ≥19% decrease in SMI could predict poor overall survival independently in patients with AUS and AEGJ ($P = 0.0070$).

*Conclusions* A ≥19% postoperative decrease in SMI was substantially associated with poor survival in patients with AUS and AEGJ.

## Introduction

Patients undergoing esophagectomy and gastrectomy as surgical treatment for upper gastrointestinal malignancies are known to develop postoperative malnutrition [1]. These patients often show a postoperative reduction in body weight and loss of muscle mass. The number of studies about muscle mass and outcomes in various types of malignancies is increasing [2–9]. In 1989, Rosenberg [10] referred to the progression of systematic decrease in muscle with aging or atrophy as sarcopenia. Sarcopenia has been suggested as a new medical condition and is recognized as a risk factor for diminished quality of life, functional limitation, and ultimately death [11, 12]. This type of

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malnutrition is usually more severe in patients with upper than lower gastric cancer. Patients who undergo total gastrectomy have a lower caloric intake and need a greater number of meals per day to retain a sufficient nutritional condition, which, however, is invariably poorer than that in patients who undergo subtotal gastrectomy [13, 14].

We focused on adenocarcinoma of upper stomach (AUS) and esophagogastric junction (AEGJ) and previously reported that preoperative loss of skeletal muscle was substantially associated with poor overall survival (OS) after surgery for AUS and AEGJ [15]. On the other hand, recent studies have shown that postoperative loss of muscle mass is associated with recurrence of hepatocellular carcinoma [16], as well as poorer OS in patients with metastatic renal cell carcinoma [17], urothelial carcinoma [18], and esophageal cancer [19]. However, very few studies have analyzed the effects of decrease in muscle mass after surgery in gastrointestinal tumors.

Several inflammation-based prognostic scores have been reported as predictive biomarkers for survival in patients with various cancers. Representative biomarkers include the prognostic nutritional index (PNI), the neutrophil–lymphocyte ratio (NLR), the platelet–lymphocyte ratio (PLR), the prognostic index (PI), the controlling nutritional status (CONUT) score, and the C-reactive protein (CRP)/albumin (Alb) ratio [20–23]. Although these biomarkers have demonstrated prognostic value in patients with several types of malignant tumors [20–25], the causality between decrease in skeletal muscle mass after surgery and these prognostic scores remains unresolved.

In this study, we focused on decrease in skeletal muscle mass after surgical resection in AUS and AEGJ patients and analyzed whether muscle mass reduction is related to the prognosis of these carcinomas. We also assessed the above-mentioned predictive scores in AUS and AEGJ patients and analyzed the relationship between these biomarkers and changes in skeletal muscle mass after surgical resection.

## Materials and methods

### Patients

This retrospective analysis included patients with AUS and AEGJ with a histopathologically proven diagnosis of adenocarcinoma. All patients have undergone surgical resection at the Department of Surgery and Science, Kyushu University between January 2005 and March 2016.

Patients with other types of tumors such as squamous cell carcinoma were omitted from the present study. Among the 157 patients enrolled, 11 who underwent non-curative or palliative surgery were omitted. Eventually, total 146 AUS and AEGJ patients were qualified for analysis (Fig. 1). We used the Siewert classification for tumor area [25]. We categorized tumors of Siewert types I, II, and III as AEGJ and those located >5 cm below the esophagogastric junction in the upper third of the stomach as AUS [15]. Based on this classification, 87 and 59 patients were classified as AUS and AEGJ, respectively.

The present study was categorized as retrospective cohort study, and was approved by the Institutional Review Board of Kyushu University (27-192).

### Assessment of skeletal muscle mass

The area of skeletal muscle was measured using preoperative computed tomography (CT) images retrospectively. The cross-sectional area of the skeletal muscle mass was measured by manually outlining the transversus abdominis, quadratus lumborum, psoas, erector spinae, and external and internal oblique muscles of the abdomen and the rectus abdominis muscle at the 3rd lumbar vertebra level on the CT images [2, 15, 26–28]. The SMI was calculated using the formula: (cross-sectional area of the total skeletal muscle at the 3rd lumbar vertebra level in $cm^2$)/(height [m] $\times$ height [m]). Preoperative SMI was calculated using preoperative CT images. Preoperative CT was performed 1–2 weeks before surgery. Postoperative SMI was calculated by CT images filmed around 6 months (range 5–7 months) postoperatively. Of note, 6 patients who caused recurrence within 6 months and 25, whose postoperative CT images were unavailable within this period were omitted from the analysis. Thus, 115 patients were qualified for assessment of postoperative changes in SMI 6 months postoperatively (Fig. 1). The rate of variability in SMI was calculated using the formula: [(preoperative SMI $-$ postoperative SMI)/preoperative SMI] $\times$ 100, and this rate of variability was considered the rate of decrease in SMI.

### Prognostic biomarkers

We calculated the PNI, NLR, PLR, PI, CONUT score, and the CRP/Alb ratio. The baseline blood data were obtained within ten-odd days before the operation. The PNI was evaluated by the following formula: 0.005 $\times$ total count of lymphocyte (per $mm^3$) + 10 $\times$ serum albumin (g/dL) [20]. Calculation of the PI was dependent on the white blood cell count and the CRP level. The upper limits of reference ranges for the white blood cell count (11,000/$mm^3$) and the CRP level (0.1 mg/dL) were used as cut-off values [20]. The PI was 0 if both levels were lower than the cut-off values, and the PI was 1 if 1 of the 2 markers was higher than each cut-off value. The CONUT score was dependent on the total cholesterol level, serum albumin

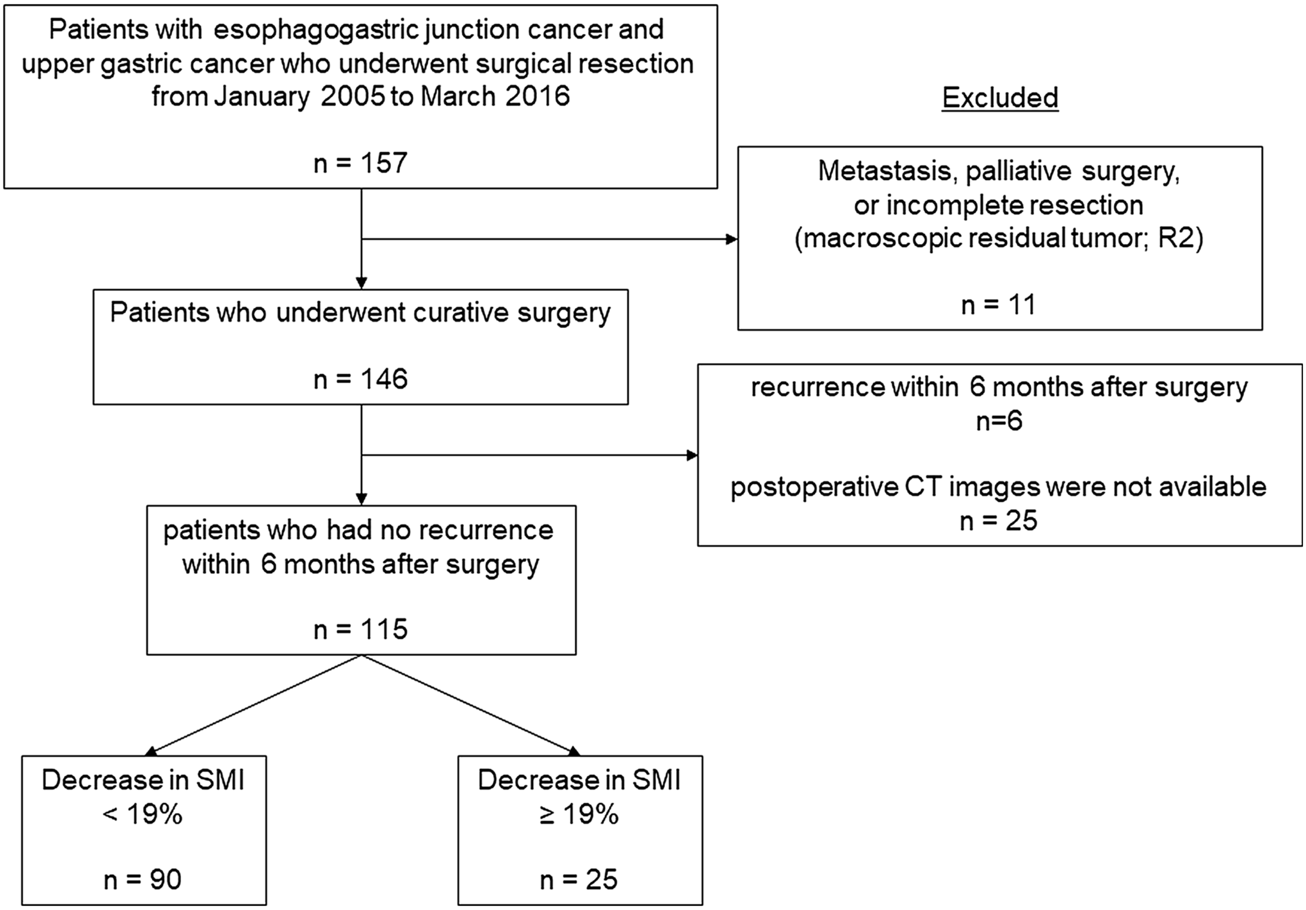



**Fig. 1** Flow chart showing the patient selection process

level, and total count of lymphocyte, as described previously [21]. The CRP/Alb ratio was calculated using the serum CRP and serum albumin level [23]. Receiver operating characteristic (ROC) curve analysis was performed to elicit the appropriate cut-off values of these predictive biomarkers (Supplementary Figure 1).

### Statistical analysis

Intergroup disparity in patient characteristics was analyzed using the unpaired *t* test or the Fisher exact test. Prognosis curves were plotted using the Kaplan–Meier method, and statistical variance was detected using the log-rank test. A Cox proportional hazard model was used to administer univariate and multivariate analyses. All *P* values were two-sided, and a *P* value <0.05 denoted statistically significant. ROC curve analysis was administered to decide the cut-off values of the various markers. The JMP PRO 13 software was adopted for all statistical analyses.

## Results

### Correlation between postoperative decrease in SMI and recurrence of AUS and AEGJ

We calculated the pre- and postoperative SMI in all 115 patients analyzed in the study, and decrease in skeletal muscle mass after surgical resection was evaluated. These values were compared between patients with recurrence (recurrence group) and those without recurrence (non-recurrence group). The mean rate of decrease in SMI was significantly higher in the recurrence than in the non-recurrence group (19.0 ± 2.3 vs. 7.4 ± 0.9%, respectively, $P < 0.0001$) (Fig. 2). ROC curve analyses were used and the most suitable cut-off value demonstrating a decrease in SMI related to OS was decided. The cut-off value was determined to be 19%, and the area under the curve (AUC) was 0.72340 (Supplementary Figure 1).

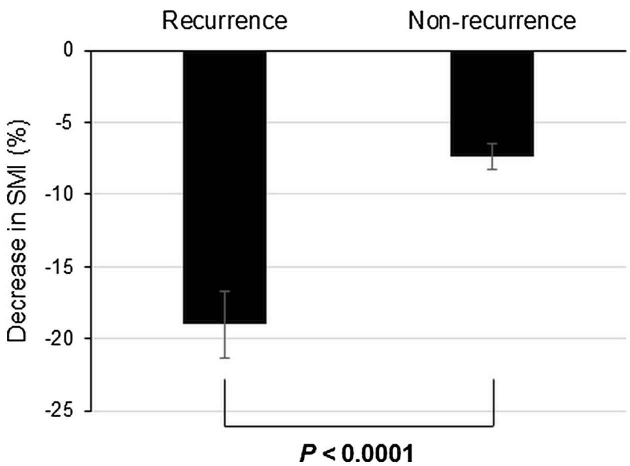



**Fig. 2** Comparison of the rate of decrease in SMI between the recurrence and the non-recurrence groups. The rate of decrease in SMI was calculated as the percentage of change in SMI using the formula: [(preoperative SMI − postoperative SMI)/preoperative SMI] × 100. Data are represented as means ± standard deviations. *SMI* skeletal muscle index

## Clinicopathological features in patients based on the postoperative decrease in SMI

Of the 115 patients analyzed, 25 (22%) showed a >19% decrease in SMI from baseline to 6 months after surgical resection. These 25 and the remaining 90 patients were categorized into 2 groups dependent on the cut-off value of the decrease in SMI, and their clinicopathological features were considered (Table 1).

In the eyes of tumor area, the percentage of AEGJ patients was higher in the group with a ≥19% decrease in SMI than in the group with a <19% decrease in SMI ($P = 0.0002$). Significant intergroup differences were observed with regard to P-stage, T-stage, and N-stage disease, and patients with a ≥19% decrease in SMI showed a tendency to present with more advanced cancers. Based on this result, the rate of postoperative adjuvant chemotherapy administered was also higher in the group showing a ≥19% decrease in SMI. All postoperative complications arised more frequently in patients with a ≥19% decrease in SMI ($P = 0.0131$), although the occurrence of severe complications (Clavien–Dindo [29, 30] grade ≥IIIa) was not associated with the decrease in SMI ($P = 0.2896$).

The above inflammation-based prognostic scores of each patient were calculated. The relationship between the decrease in SMI and the values of these biomarkers, but there were no significant correlation between any of these biomarkers and decreased SMI. In addition, although preoperative skeletal muscle mass was compared between the 2 groups, there were no significant intergroup differences in terms of preoperative SMI and the proportion of preoperative sarcopenia. On the other hand, the mean postoperative SMI was much lower in patients with a ≥19% decrease in SMI ($P < 0.0001$) (Table 1).

## Postoperative decrease in SMI and recurrence of AUS and AEGJ

We compared the rate of recurrence between patients with a ≥19% decrease in SMI and those with a <19% decrease in SMI to validate whether the postoperative decrease in SMI can predict the recurrence of AUS and AEGJ. The rate of recurrence was significantly higher in patients with a ≥19% decrease in SMI than in those with a <19% decrease in SMI ($P < 0.0001$) (Table 1).

## Postoperative prognosis based on the postoperative decrease in SMI

The survival rates were compared between patients with a ≥19% decrease in SMI and those with a ≤19% decrease in SMI. The 5-year recurrence-free survival (RFS) and OS rates were poorer in patients with a ≥19% decrease in SMI than in those with a <19% decrease in SMI (RFS: 33.4 vs. 88.4%, respectively, $P < 0.0001$; OS: 40.6 vs. 89.0%, respectively, $P < 0.0001$) (Fig. 3).

## Poor prognostic factors of AUS and AEGJ

Univariate and multivariate analyses were administered to find the independent prognostic factors for OS. ROC curve analyses showed that the appropriate cut-off values of the PNI, NLR, PLR, CONUT score, and CRP/Alb ratio were 45, 3.93, 170, 3, and 0.1, respectively, and the AUC values were 0.59119, 0.46809, 0.48632, 0.59245, and 0.60714, respectively (Supplementary Figure 1). Univariate analyses showed that the T-stage (T1–2 vs. T3–4) ($P < 0.0001$), N-stage (N0–1 vs. N2–3) ($P < 0.0001$), intraoperative blood loss volume ≥ 500 mL ($P = 0.0062$), adjuvant chemotherapy ($P < 0.0001$), PI = 1 (vs. PI = 0) ($P = 0.0223$), CONUT score ≥ 3 (vs. < 3) ($P = 0.0032$), preoperative sarcopenia (vs. non-sarcopenia) ($P = 0.0033$), and a ≥19% postoperative decrease in SMI ($P < 0.0001$) were related to OS in AUS and AEGJ patients. These 8 factors, as well as age ≥ 65 years, postoperative complication, PNI < 45, and the CRP/Alb ratio ($P = 0.0767$, 0.0750, 0.0565, and 0.1407, respectively) were included in the multivariate analyses and observed that only a decrease in SMI was an independent predictor for OS in AUS and AEGJ patients ($P = 0.0070$) (Table 2).

**Table 1** Clinicopathological features according to decrease in SMI

| Factor | Decrease in SMI | | *P* value |
|---|---|---|---|
| | <19% (*n* = 90) | ≥19% (*n* = 25) | |
| Sex | | | |
| Male | 62 (68.9) | 19 (76.0) | 0.6227 |
| Female | 28 (31.1) | 6 (24.0) | |
| Age | 64.1 (35–91) | 62.5 (43–80) | 0.5346 |
| Tumor area | | | |
| AEGJ | 30 (33.3) | 19 (76.0) | 0.0002 |
| AUS | 60 (66.7) | 6 (24.0) | |
| P-stage | | | |
| I | 46 (51.1) | 6 (24.0) | 0.0223 |
| II–III | 44 (48.9) | 19 (76.0) | |
| Pt | | | |
| T1–T2 | 51 (56.7) | 7 (28.0) | 0.0133 |
| T3–T4 | 39 (43.3) | 18 (72.0) | |
| pN | | | |
| N0 | 56 (62.2) | 8 (32.0) | 0.0114 |
| N1–N3 | 34 (37.8) | 17 (68.0) | |
| Serum albumin (g/dl) | 4.1 (2.8–5.0) | 4.1 (2.6–5.0) | 0.6020 |
| CRP (mg/dL) | | | |
| <0.3 | 74 (82.2) | 22 (88.0) | 0.7611 |
| ≥0.3 | 16 (17.8) | 3 (12.0) | |
| Surgical procedure | | | |
| Total gastrectomy | 85 (94.4) | 25 (100.0) | 0.5838 |
| Proximal gastrectomy | 5 (5.6) | 0 (0.0) | |
| All postoperative complications | | | |
| No | 68 (75.6) | 12 (48.0) | 0.0131 |
| Yes | 22 (24.4) | 13 (52.0) | |
| Severe complications (CD grade ≥ IIIa) | | | |
| No | 82 (91.1) | 21 (84.0) | 0.2896 |
| Yes | 8 (8.9) | 4 (16.0) | |
| Neoadjuvant chemotherapy | | | |
| No | 85 (94.4) | 24 (96.0) | 1.0000 |
| Yes | 5 (5.6) | 1 (4.0) | |
| Adjuvant chemotherapy | | | |
| No | 64 (71.1) | 8 (32.0) | 0.0008 |
| Yes | 26 (28.9) | 17 (68.0) | |
| PNI | 50.0 (31–130) | 54.5 (29–122) | 0.0826 |
| NLR | 2.50 (0.3–8.0) | 2.28 (0.1–5.4) | 0.4855 |
| PLR | 154 (15–500) | 133 (9–352) | 0.2105 |
| PI | 0.06 (0–1) | 0.16 (0–1) | 0.0868 |
| CONUT score | 1.37 (0–8) | 1.32 (0–10) | 0.9008 |
| CRP/Alb ratio | 0.07 (0–1.22) | 0.05 (0–0.62) | 0.5246 |
| Preoperative SMI ($cm^2/m^2$) | 47.6 (30–65) | 50.4 (34–81) | 0.1302 |
| Postoperative SMI ($cm^2/m^2$) | 44.8 (29–67) | 37.5 (23–63) | <0.0001 |
| Preoperative sarcopenia | | | |
| No | 66 (73.3) | 19 (76.0) | 1.0000 |
| Yes | 24 (26.7) | 6 (24.0) | |
| Recurrence | | | |
| No | 80 (88.9) | 16 (64.0) | <0.0001 |
| Yes | 10 (11.1) | 9 (36.0) | |

Data are presented as *n* (%) with the exception of age and serum albumin, which are presented as mean (range)

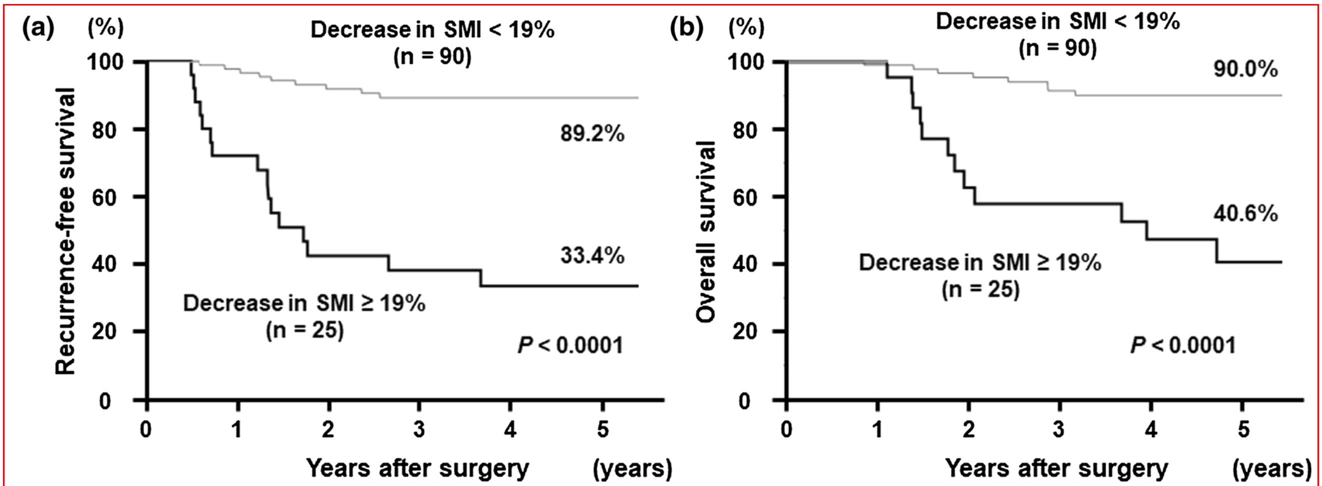
*SMI* skeletal muscle index, *AEGJ* adenocarcinoma of esophagogastric junction, *AUS* adenocarcinoma of upper stomach, *CRP* C-reactive protein, *CD* Clavien–Dindo classification, *PNI* prognostic nutritional index, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *PI* prognostic index, *CONUT* controlling nutritional status

## Discussion

In this study, the degree of decrease in SMI was more remarkable in AUS and AEGJ patients showing recurrence than in those without recurrence. The 5-year OS and RFS rates were poorer in patients with a ≥19% decrease in SMI than in those with a <19% decrease in SMI significantly. Multivariate analyses designated that a ≥19% postoperative decrease in SMI could predict poor OS in AUS and AEGJ patients independently.

With respect to upper gastrointestinal tumors, the previous studies have proposed that preoperative loss of muscle is not correlated with worse long-term outcomes after surgery in patients who have undergone surgical resection for gastric carcinoma, whereas preoperative sarcopenia is substantially associated with poor survival rates in patients who have undergone surgery for esophageal carcinoma, AEGJ, and AUS [15, 31, 32]. These results indicate that the degree of surgical invasion in patients with esophageal carcinoma, AEGJ, and AUS is larger than that in patients with carcinoma of distal stomach. The extent of surgical invasion might reinforce the influence of sarcopenia on prognosis of cancers. Park et al. [19] showed that a decrease in the psoas muscle area (PMA) after surgery is associated with a negative prognostic effect on OS in patients who underwent surgical resection for esophageal carcinoma. Park used the mean decrease of 10% as a cut-off value. In our study, ROC analysis was used to decide the cut-off values of various parameters. The appropriate cut-off value should be elucidated by the accumulation of further studies.

The percentage of patients with AEGJ and the occurrence of postoperative complications were more frequently




| Number at risk | | | | | |
|---|---|---|---|---|---|
| < 19% | 86 | 73 | 69 | 56 | 41 |
| ≥ 19% | 18 | 11 | 10 | 8 | 6 |

| Number at risk | | | | | |
|---|---|---|---|---|---|
| < 19% | 87 | 77 | 70 | 56 | 41 |
| ≥ 19% | 23 | 14 | 12 | 10 | 6 |

**Fig. 3** Postoperative survival in patients with a ≥19% decrease in SMI and in those with a <19% decrease in SMI: **a** recurrence-free survival and **b** overall survival of all studied patients. The 5-year recurrence-free and overall survival rates were significantly lower in patients with a ≥19% decrease in SMI than in those with a <19% decrease in SMI ($P < 0.0001$). *SMI* skeletal muscle index

**Table 2** Univariate and multivariate analyses for overall survival

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| Male (vs. female) | 1.329 (0.520–4.068) | 0.5696 | – | |
| Age ≥ 65 years (vs. < 65 years) | 2.187 (0.920–5.536) | 0.0767 | 1.050 (0.308–3.372) | 0.9353 |
| AEGJ (vs. AUS) | 1.417 (0.606–3.310) | 0.4153 | – | |
| T-stage (T3–4 vs. T1–2) | 22.17 (4.621–397.6) | <0.0001 | 3.219 (0.420–67.58) | 0.2823 |
| N-stage (N1–3 vs. N0) | 30.17 (6.270–541.8) | <0.0001 | 6.594 (0.856–146.1) | 0.0732 |
| IBL ≥ 500 ml (vs. < 500 ml) | 3.355 (1.419–8.226) | 0.0062 | 0.896 (0.253–3.060) | 0.8605 |
| Postoperative complication | 2.222 (0.920–5.318) | 0.0750 | 1.395 (0.414–4.843) | 0.5879 |
| Adjuvant chemotherapy | 8.226 (3.035–28.65) | <0.0001 | 1.939 (0.513–8.663) | 0.3363 |
| PNI < 45 (vs. ≥ 45) | 2.463 (0.974–5.851) | 0.0565 | 1.637 (0.089–13.17) | 0.6889 |
| NLR ≥ 3.93 (vs. < 3.93) | 0.920 (0.147–3.173) | 0.9098 | – | |
| PLR ≥ 170 (vs. < 170) | 1.901 (0.749–4.532) | 0.1684 | – | |
| PI = 1 (vs. PI = 0) | 4.465 (1.278–12.15) | 0.0223 | 2.965 (0.497–18.68) | 0.2310 |
| CONUT score ≥ 3 (vs. < 3) | 4.646 (1.754–11.22) | 0.0032 | 2.417 (0.228–54.20) | 0.4886 |
| CRP/Alb ≥ 0.1 (vs. CRP/Alb < 0.1) | 2.260 (0.739–5.774) | 0.1407 | 0.334 (0.045–1.602) | 0.1846 |
| Sarcopenia (vs. non-sarcopenia) | 3.725 (1.569–8.949) | 0.0033 | 2.779 (0.801–10.24) | 0.1064 |
| Decrease in SMI ≥ 19% | 7.323 (3.067–18.16) | <0.0001 | 4.890 (1.537–17.50) | 0.0070 |

*HR* hazard ratio, *CI* confidence interval, *AEGJ* adenocarcinoma of esophagogastric junction, *UGC* adenocarcinoma of upper stomach, *IBL* intraoperative blood loss, *PNI* prognostic nutritional index, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *PI* prognostic index, *CONUT* controlling nutritional status, *CRP* C-reactive protein, *Alb* albumin, *SMI* skeletal muscle index

in patients with a ≥19% decrease in SMI than in those with a <19% decrease in SMI ($P = 0.0002$ and 0.0131, respectively). Operative invasion is usually more severe in patients with AEGJ than that observed with AUS. In addition, the recovery of the patient's physical condition might be delayed if postoperative complication occurred.

These factors could influence the postoperative progression of decrease in skeletal muscle mass. However, multivariate analysis designated that a $\geq$19% postoperative decrease in SMI was identified as a singular independent prognostic factor for OS, whereas tumor area and postoperative complications did not show a significant causality (Table 2).

In the present study, we have a limitation. This study was a single-institutional and retrospective study. However, determining the importance of a decrease in SMI after surgery by performing prospective controlled trials is considered difficult or impractical. Moreover, few studies which were publicized the clinical significance of postoperative changes in skeletal muscle mass of gastrointestinal malignancies. Therefore, accumulation of clinical data from retrospective studies analyzing various types of cancers from many hospitals could be meaningful. The findings from this current study provide useful data regarding the value of changes in the skeletal muscle mass after surgery.

Our study has indicated that there was a strong causality between loss of skeletal muscle after surgical resection and poor prognosis in AUS and AEGJ patients. However, a question that remains unresolved is whether the loss of muscle mass is an effect or a cause of disease progression. Our study showed that patients with a $\geq$19% decrease in SMI demonstrated the tendency to present with cancers at a more advanced stage (Table 1). Cancer cells usually grow rapidly and may cause nutritional disorders and loss of skeletal muscle mass. However, several studies have suggested that a few myokines secreted by muscle cells can suppress colon tumorigenesis [33] or inhibit mammary cancer cell growth [34]. These results indicate that support of nutrition and increase in skeletal muscle mass may contribute to the suppression of tumorigenesis through the action of myokines; however, further investigation is required to conclusively establish these causal relationships.

## Conclusions

A $\geq$19% postoperative decrease in SMI was substantially associated with poor outcomes in AUS and AEGJ patients who had undergone surgical resection. The present data indicate that close attention should be paid in AUS and AEGJ patients who demonstrate a progression of decrease in muscle after surgical resection.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare that there is no conflict of interest.

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