ORIGINAL ARTICLE

# Prognostic Significance of Skeletal Muscle Loss During Early Postoperative Period in Elderly Patients with Esophageal Cancer

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Running title: Skeletal muscle loss after esophagectomy

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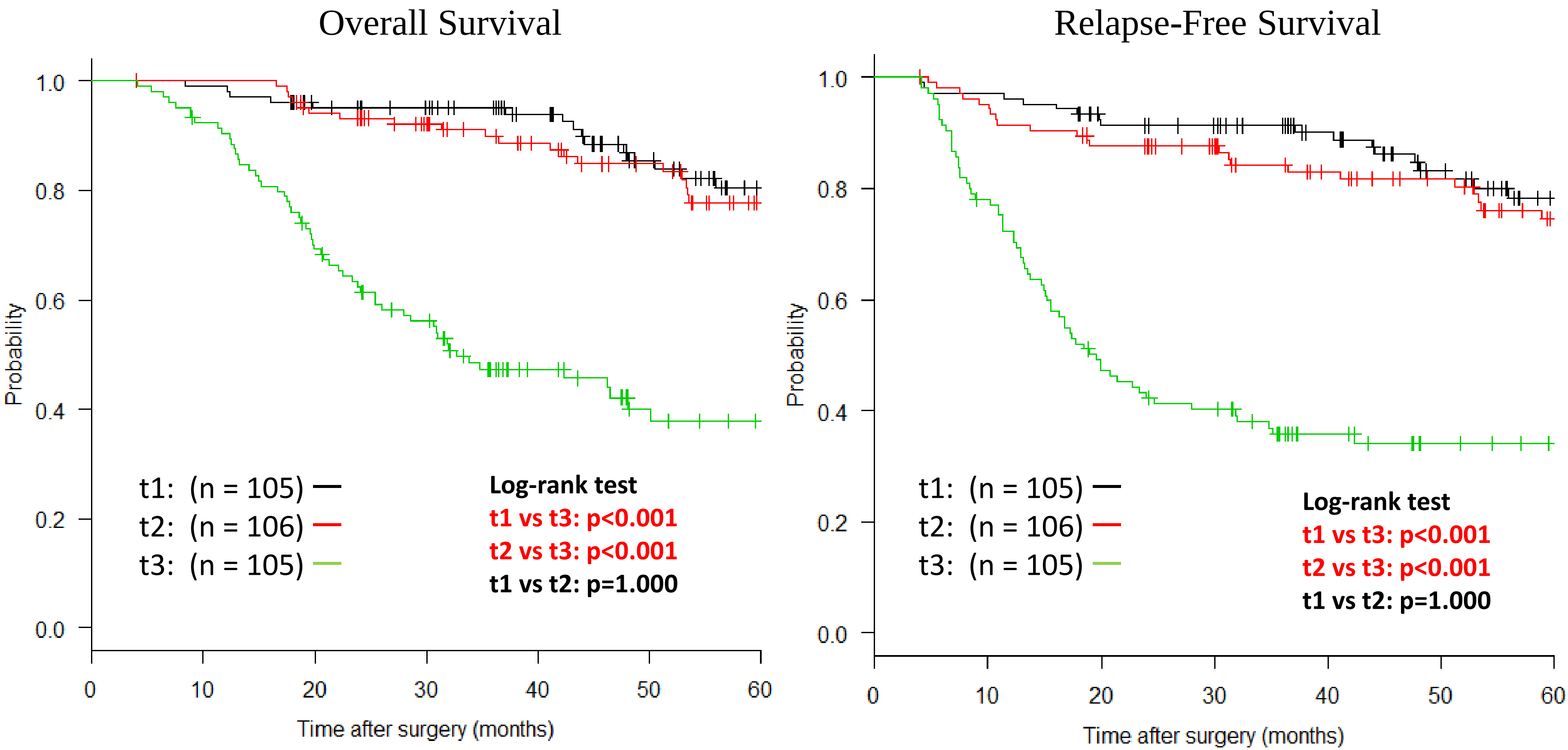
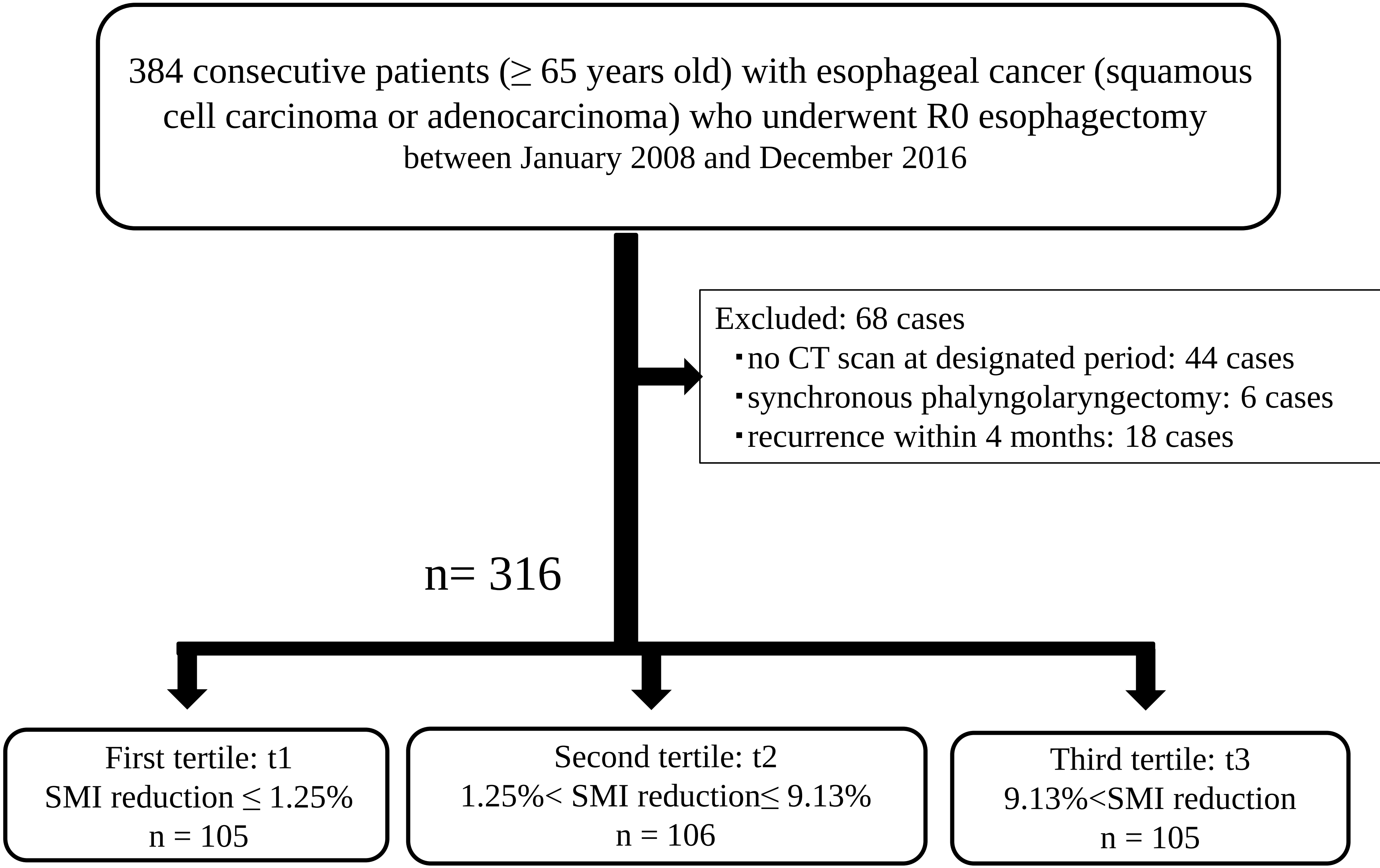

Overall Survival
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time after surgery (months)
t1: (n = 105)
t2: (n = 106)
t3: (n = 105)
Log-rank test
t1 vs t3: p<0.001
t2 vs t3: p<0.001
t1 vs t2: p=1.000
Relapse-Free Survival
Probability
Time after surgery (months)
t1: (n = 105)
t2: (n = 106)
t3: (n = 105)
Log-rank test
t1 vs t3: p<0.001
t2 vs t3: p<0.001
t1 vs t2: p=1.000

Figure 1a

Table 1. Clinicopathologic, operative and postoperative backgrounds of patients

| Variables | Total N=316 | LR N=211 | MR N=105 | p-value |
|---|---|---|---|---|
| Age | 71.0±4.4 | 70.8±4.2 | 71.3±4.8 | 0.46 |
| Gender | | | | 0.87 |
| Male | 265 (83.9) | 176 (83.4) | 89 (84.8) | |
| Female | 51 (16.1) | 35 (16.6) | 16 (15.2) | |
| BMI* (kg/m$^2$) | 21.6±3.0 | 21.8±3.0 | 21.3±3.0 | 0.10 |
| SMI** (cm$^2$/m$^2$) | 52.3±7.4 | 52.4±7.5 | 52.1±7.4 | 0.75 |
| Preoperative sarcopenia*** | 109 (34.5) | 68 (32.2) | 41 (39.0) | 0.26 |
| ASA-PS# | | | | 0.17 |
| 1 | 79 (25) | 57 (27) | 22 (21) | |
| 2 | 228 (72.2) | 146 (69.2) | 82 (78.1) | |
| 3 | 9 (2.8) | 8 (3.8) | 1 (1) | |
| Preoperative treatment | | | | 0.77 |
| None | 150 (47.5) | 98 (46.4) | 52 (49.5) | |
| Chemotherapy | 144 (45.6) | 99 (46.9) | 45 (42.9) | |
| Chemoradiation/Radiation | 22 (7.0) | 14 (6.6) | 8 (7.6) | |
| Histologic subtype | | | | 0.071 |
| Squamous cell carcinoma | 285 (90.2) | 195 (92.4) | 90 (85.7) | |
| Adenocarcinoma | 31 (9.8) | 16 (7.6) | 15 (14.3) | |
| Tumor location | | | | 0.14 |
| Upper third | 40 (12.7) | 25 (11.8) | 15 (14.3) | |
| Middle third | 133 (42.1) | 97 (46) | 36 (34.3) | |
| Lower third | 143 (45.3) | 89 (42.2) | 54 (51.4) | |
| Type of esophagectomy | | | | 0.26 |
| McKeown | 274 (86.7) | 187 (86.6) | 87 (82.9) | |
| Ivor-Lewis | 33 (10.4) | 19 (9) | 14 (13.3) | |
| Transhiatal | 7 (2.2) | 3 (1.4) | 4 (3.8) | |
| Cervical | 2 (0.6) | 2 (0.9) | 0 (0) | |
| Operation time (min) | 535.0±112.5 | 539.6±111.9 | 525.6±113.7 | 0.30 |
| Blood loss (ml) | 373.7±315.6 | 354.9±308.3 | 411.4±328.1 | 0.028 |
| Complications | | | | |
| Anastomotic leakage | 22 (7.0) | 15 (7.1) | 7 (6.7) | 1.0 |
| RLNP## | 63 (19.9) | 43 (20.4) | 20 (19) | 0.88 |
| Pneumonia | 97 (30.7) | 64 (30.3) | 33 (31.4) | 0.90 |
| Depth of penetration | | | | 0.97 |
| pT0/1 | 166 (52.5) | 112 (53.1) | 54 (51.4) | |
| pT2 | 49 (15.5) | 32 (15.2) | 17 (16.2) | |
| pT3 | 96 (30.4) | 64 (30.3) | 32 (30.5) | |
| pT4 | 5 (1.6) | 3 (1.4) | 2 (1.9) | |
| Lymph node metastasis | | | | 0.023 |
| pN0 | 174 (55.1) | 124 (58.8) | 50 (47.6) | |
| pN1 | 91 (28.8) | 57 (27.0) | 34 (32.4) | |
| pN2 | 38 (12.0) | 26 (12.3) | 12 (11.4) | |
| pN3 | 13 (4.1) | 4 (1.9) | 9 (8.6) | |
| Pathologic stage | | | | 0.37 |
| pStage 0 | 5 (1.6) | 5 (2.4) | 0 | |
| pStage I | 132 (41.8) | 91 (43.1) | 41 (39.0) | |
| pStage II | 92 (29.1) | 59 (28.0) | 33 (31.4) | |
| pStage III | 70 (22.2) | 47 (22.3) | 23 (21.9) | |
| pStage IV | 17 (5.4) | 9 (4.3) | 8 (7.6) | |

Data expressed as number (%) or Mean±Standard deviation, *BMI Body mass index, **SMI skeletal mass index, ***Preoperative sarcopenia SMI<52.4 cm/m$^2$ in male and SMI<38.5 cm/m$^2$ in female
#ASA-PS American Society of Anestheologists-physical status, ##RLNP Recurrent laryngeal nerve palsy.

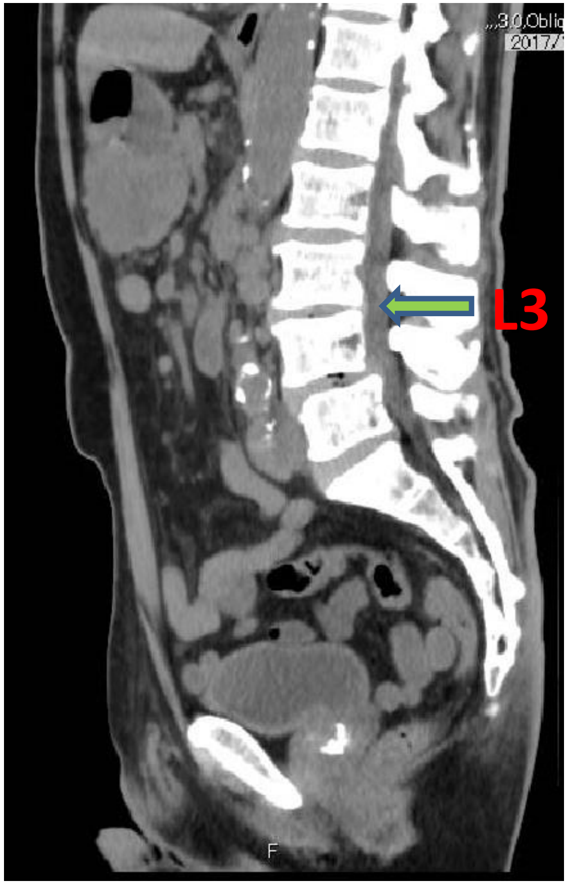


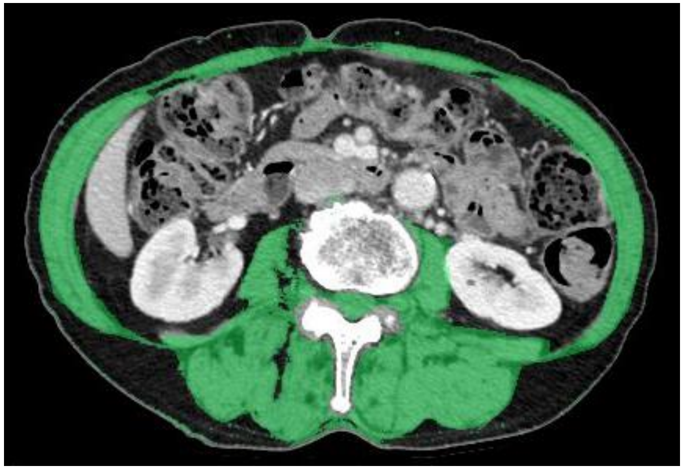

Supplemental Figure 1

Supplemental Table 1. Risk factors including SMI reduction rate divided by quartiles for overall survival

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | Hazard ratio (95% CI) | p-value | Hazard ratio (95% CI) | p-value |
| Age (year), per 1 year | 1.108 (1.063-1.155) | <0.001 | 1.105 (1.062-1.150) | <0.001 |
| Gender(male) | 2.167 (1.093-4.297) | 0.027 | 2.164 (1.083-4.324) | 0.029 |
| Pathological findings | | | | |
| pT, 3 or 4 | 2.462 (1.655-3.641) | <0.001 | 2.322 (1.314-4.102) | 0.004 |
| pN, positive | 2.149 (1.436-3.215) | <0.001 | 1.027 (0.588-1.793) | 0.923 |
| pStage, III or IV | 2.376 (1.600-3.526) | <0.001 | 1.475 (0.728-2.989) | 0.281 |
| SMI reduction (quartiles)* | | | | |
| q1 (≤-0.22%), reference | 1.000 | - | 1.000 | - |
| q2 (-0.21～5.57%) | 0.424 (0.248-0.725) | 0.002 | 0.869 (0.414-1.825) | 0.711 |
| q3 (5.58～11.03%) | 0.598 (0.363-0.985) | 0.044 | 1.561 (0.757-3.218) | 0.228 |
| q4 (≥11.04%) | 7.112 (4.726-10.700) | <0.001 | 8.326 (4.365-15.880) | <0.001 |

*SMI skeletal mass index



Supplemental Figure 2

Table 2. Univariate and multivariate analysis of risk factors for overall survival

| Variables | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | p-value | Hazard ratio (95% CI) | p-value |
| Age (year), per 1 year | 1.108 (1.063-1.155) | <0.001 | 1.116 (1.072-1.162) | <0.001 |
| Gender (male) | 2.167 (1.093-4.297) | 0.027 | 1.955 (0.951-4.019) | 0.068 |
| Preoperative BMI* ($kg/m^2$), per 1 $kg/m^2$ | 0.907 (0.850-0.968) | 0.003 | | |
| Preoperative SMI** ($cm^2/m^2$), per 1 $cm^2/m^2$ | 0.981 (0.956-1.006) | 0.14 | | |
| Preoperative sarcopenia*** | 2.138 (1.442-3.170) | <0.001 | 1.831 (1.203-2.788) | 0.005 |
| ASA-PS#, ≥ 3 | 0.787 (0.247-2.506) | 0.69 | | |
| Cancer type (Adenocarcinoma) | 1.637 (0.930-2.881) | 0.087 | | |
| Preoperative Treatment, present | 1.074 (0.725-1.590) | 0.72 | | |
| Pathological findings | | | | |
| pT, 3 or 4 | 2.462 (1.655-3.641) | <0.001 | 2.229 (1.456-3.413) | <0.001 |
| pN, positive | 2.149 (1.436-3.215) | <0.001 | 1.650 (1.075-2.531) | 0.022 |
| pStage, III or IV | 2.376 (1.600-3.528) | <0.001 | | |
| Operation time, per 1minute | 0.998 (0.996-0.999) | 0.021 | | |
| Blood loss, per 1 ml | 1.001 (1.000-1.001) | 0.018 | 1.000 (0.999-1.001) | 0.11 |
| Morbidity | | | | |
| Anastomotic leakage | 1.238 (0.642-2.457) | 0.54 | | |
| RLNP## | 1.044 (0.632-1.725) | 0.87 | | |
| Pneumonia | 1.290 (0.855-1.944) | 0.23 | | |
| BMI change, per 1% | 0.999 (0.974-1.024) | 0.92 | | |
| SMI reduction, massive | 4.767 (3.176-7.152) | <0.001 | 5.405 (3.514-8.314) | <0.001 |

*BMI Body mass index, **SMI skeletal mass index, *** Preoperative sarcopenia SMI<52.4 $cm/m^2$ in male and SMI<38.5 $cm/m^2$ in female, # ASA-PS, American Society of Anesthesiologists-physical status, ## RLNP Recurrent laryngeal nerve palsy.

Table 3. Univariate and multivariate analysis of risk factors for relapse-free survival

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | Hazard ratio (95% CI) | p-value | Hazard ratio (95% CI) | p-value |
| Age (year), per 1 year | 1.091 (1.051-1.133) | <0.001 | 1.106 (1.063-1.150) | <0.001 |
| Gender (male) | 1.989 (1.069-3.700) | 0.030 | | |
| Preoperative BMI* ($kg/m^2$), per 1 $kg/m^2$ | 0.916 (0.863-0.973) | 0.004 | | |
| Preoperative SMI** ($cm^2/m^2$), per 1 $cm^2/m^2$ | 0.979 (0.956-1.002) | 0.074 | | |
| Preoperative sarcopenia*** | 2.282 (1.584-3.287) | <0.001 | 1.933 (1.323-2.823) | <0.001 |
| ASA-PS[#], ≥ 3 | 0.720 (0.227-2.284) | 0.58 | | |
| Cancer type (Adenocarcinoma) | 1.847 (1.104-3.092) | 0.020 | 1.796 (1.041-3.096) | 0.035 |
| Preoperative Treatment, present | 1.326 (0.919-1.913) | 0.13 | 1.390 (0.914-2.116) | 0.12 |
| Pathological findings | | | | |
| pT, 3 or 4 | 2.498 (1.736-3.594) | <0.001 | 2.063 (1.384-3.075) | <0.001 |
| pN, positive | 2.367 (1.627-3.442) | <0.001 | 1.905 (1.286-2.823) | 0.001 |
| pStage, III or IV | 2.511 (1.738-3.629) | <0.001 | | |
| Operation time, per 1minute | 0.999 (0.997-1.000) | 0.071 | | |
| Blood loss, per 1 ml | 1.001 (1.000-1.001) | 0.033 | | |
| Morbidity | | | | |
| Anastomotic leakage | 1.421 (0.763-2.647) | 0.27 | | |
| RLNP[##] | 1.042 (0.659-1.648) | 0.86 | | |
| Pneumonia | 1.308 (0.892-1.918) | 0.17 | | |
| BMI change, per 1% | 0.992 (0.970-1.016) | 0.54 | | |
| SMI reduction, massive | 4.818 (3.303-7.028) | <0.001 | 5.070 (3.414-7.532) | <0.001 |

*BMI Body mass index, **SMI skeletal mass index, *** Preoperative sarcopenia SMI<52.4 $cm/m^2$ in male and SMI<38.5 $cm/m^2$ in female, [#]ASA-PS, American Society of Anesthesiologists-physical status, [##] RLNP Recurrent laryngeal nerve palsy.

Table 4. Risk factors for massive SMI reduction

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | Odds ratio (95% CI) | p-value | Odds ratio (95% CI) | p-value |
| Age (year) per 1 year | 1.030 (0.977-1.080) | 0.28 | | |
| Gender (male) | 1.110 (0.581-2.110) | 0.76 | | |
| Preoperative BMI* ($kg/m^2$), per 1 $kg/m^2$ | 0.945 (0.873-1.020) | 0.16 | 0.931 (0.860-1.010) | 0.082 |
| Preoperative SMI** ($cm^2/m^2$), per 1 $cm^2/m^2$ | 0.995 (0.964-1.030) | 0.75 | | |
| Preoperative sarcopenia*** | 1.350 (0.828-2.190) | 0.23 | | |
| ASA-PS[#], ≥ 3 | 0.787 (0.247-2.506) | 0.69 | 0.216 (0.026-1.790) | 0.16 |
| Cancer type (Adenocarcinoma) | 2.030 (0.962-4.290) | 0.063 | 2.160 (1.010-4.650) | 0.048 |
| Preoperative Treatment, present | 1.074 (0.725-1.590) | 0.72 | | |
| Pathological findings | | | | |
| pT, 3 or 4 | 1.030 (0.624-1.700) | 0.91 | | |
| pN, positive | 1.570 (0.979-2.510) | 0.061 | 1.700 (1.050-2.750) | 0.032 |
| pStage, III or IV | 1.160 (0.690-1.950) | 0.58 | | |
| Complications, present | | | | |
| Anastomotic leakage | 0.933 (0.368-2.364) | 0.89 | | |
| RLNP[##] | 0.919 (0.509-1.660) | 0.78 | | |
| Pneumonia | 1.053 (0.635-1.746) | 0.84 | | |

*BMI Body mass index, **SMI skeletal mass index, *** Preoperative sarcopenia SMI<52.4 $cm/m^2$ in male and SMI<38.5 $cm/m^2$ in female, [#] ASA-PS, American Society of Anesthesiologists-physical status, [##] RLNP Recurrent laryngeal nerve palsy.

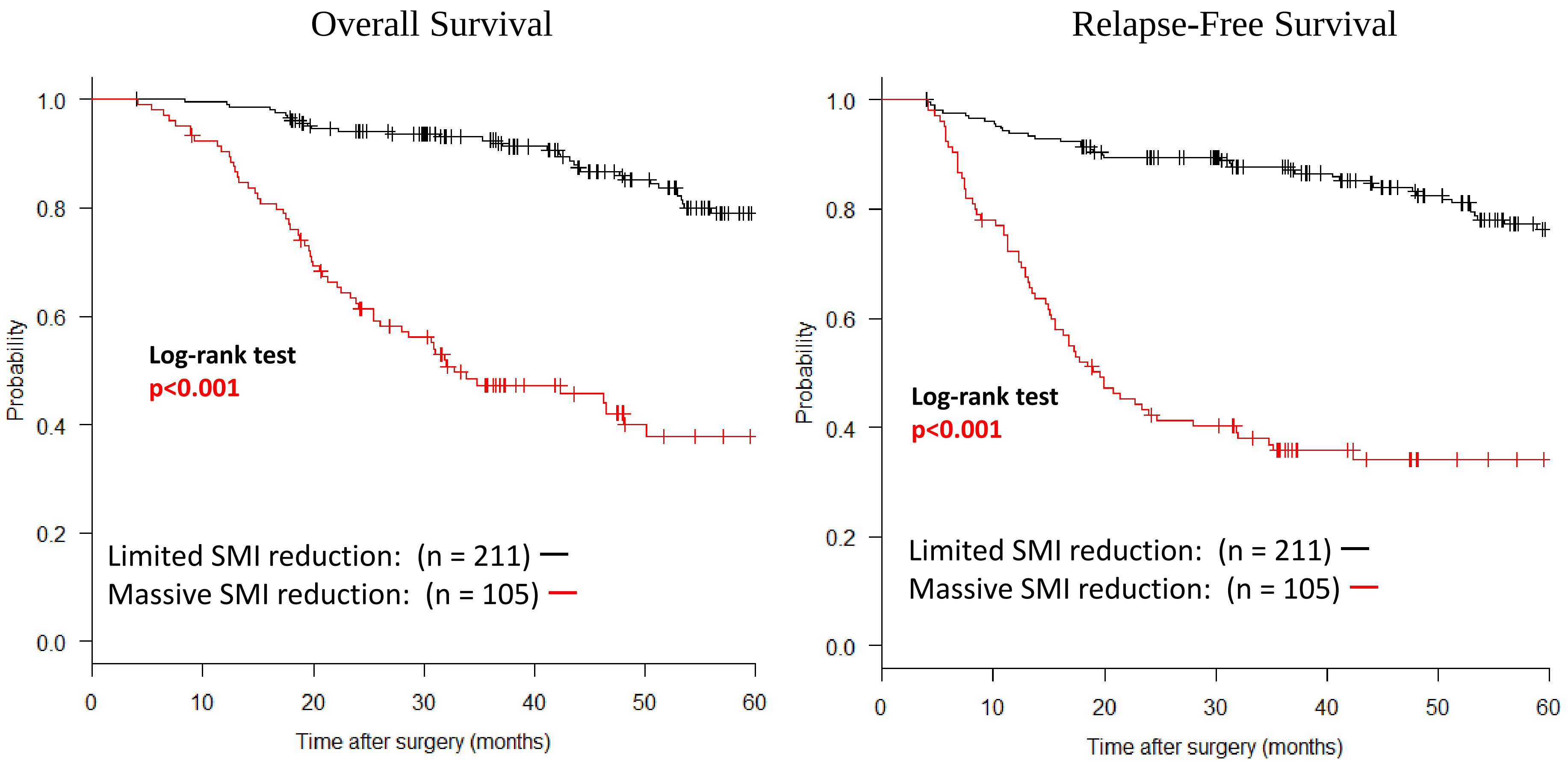

Overall Survival
Relapse-Free Survival
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Time after surgery (months)
Log-rank test
p<0.001
Limited SMI reduction: (n = 211)
Massive SMI reduction: (n = 105)

Figure 1b

**Synopsis**

We investigated an influence of skeletal muscle loss during the early postoperative period on the prognosis in elderly patients who underwent oncologic esophagectomy. The existence of massive skeletal muscle reduction (>9.13%) was an independent predictor of worse prognosis and recurrence.

**ABSTRACT**

**Background**: Skeletal muscle loss during the early postoperative period frequently occurs during post-esophagectomy. Preoperative sarcopenia is a known prognostic factor. However, the prognostic significance of postoperative skeletal muscle loss remains unclear. To clarify the impact of skeletal muscle loss during the early postoperative period on the prognosis of elderly patients undergoing esophagectomy.

**Methods**: We included 316 patients (age ≥ 65) who underwent esophagectomy. The skeletal muscle index (SMI) at the third lumber vertebra's bottom level was measured using computed tomography (CT) pre-surgery and 4 months after surgery. The SMI reduction rate, patient's prognosis, and recurrence rates were evaluated.

**Results**: The SMI reduction rates in tertiles were <1.25% in the first tertile (t1, n = 105), between 1.25% and 9.13% in the second tertile (t2, n = 106), and >9.13% in the third tertile (t3, n = 105). Both relapse-free survival (RFS) and overall survival (OS) in t3 were significantly worse than those in t1 and t2 ($p < 0.001$). Therefore, we defined t3 as the massive reduction (MR) group and t1 and t2 as the limited reduction (LR) group. By univariate analysis, both RFS and OS were significantly poorer in the MR group than in LR. By multivariate analysis, the massive skeletal muscle loss during the early postoperative period was an independent factor for both RFS and OS.

**Conclusions**: Early postoperative skeletal muscle loss predicts both recurrence and poor

survival.

## INTRODUCTION

Esophagectomy for esophageal cancer is highly invasive and poses a high risk for postoperative morbidity and mortality [1,2]. Additionally, esophageal cancer is known to have a high recurrence rate and a poor prognosis [3-5]. Sarcopenia, which is defined as the progressive and generalized loss of skeletal mass and strength [6], has been reported to be a predictor of postoperative respiratory complications after esophagectomy [7]. It has been recently shown that preoperative low skeletal muscle mass represents a factor for poor prognosis in esophageal cancer patients >65 years [8]. Furthermore, several recent studies have found that loss of skeletal muscle mass during neoadjuvant therapy was linked to a worse prognosis [9,10].

During the early postoperative period, it has been shown that esophagectomized patients commonly undergo body weight loss [11]. However, only few studies investigated the changes in skeletal muscle mass during the early post-esophagectomy period. To date, the influence of skeletal muscle loss on the prognosis of esophagectomized patients remains unclear. Earlier reports in cancer patients have directly correlated the skeletal muscle volume at the level of the third lumber vertebra (L3) with the entire body skeletal muscle mass [12,13]. On the basis of these findings, changes in the skeletal muscle mass can be evaluated by comparing preoperative and postoperative computed tomography (CT) images.

The purpose of this retrospective study is to clarify whether the skeletal muscle loss during the early postoperative period influenced recurrence and survival post-esophagectomy for esophageal cancer.

## MATERIALS AND METHODS

*Patients*

We enrolled in the present study 384 consecutive patients (≥65 years old) with esophageal cancer who underwent R0 esophagectomy at The Cancer Institute Hospital of Japanese Foundation for Cancer Research (Tokyo, Japan). The study period was between January 2008 and December 2016. A total of 68 patients were excluded from the study. The exclusion criteria were as follows: patients who did not undergo CT both within 3 months pre-surgery or 4 months post-surgery, patients who underwent simultaneous pharyngolaryngectomy, and patients who experienced tumor recurrence within 4 months. Finally, 316 patients were eligible (Supplemental Figure 1). Clinicopathological data, including patient background, tumor stage, histopathological features, postoperative complications, survival, and recurrence. Preoperative sarcopenia was defined as SMI < 52.4 $cm^2/m^2$ in male and SMI < 38.5 $cm^2/m^2$ in female, according to Prado's criteria [14]. Tumor stage was defined as the pathological stage and classified according to the 7th TNM classification of the Union for International Cancer Control [15]. The study protocol was approved by our institutional review board (2018-1175).

*Measurement of skeletal muscle index (SMI)*

CT scan was performed within 3 months pre-surgery and 4 months post-surgery (Light Speed, General Electric, Milwaukee, WI). SMI assessment was performed using the synapse VINCENT image analysis system (Fujifilm Medical, Tokyo, Japan). An axial image at the level of L3 was used for the measurement (Supplemental Figure 2). We measured the cross-sectional area of the total skeletal muscle volume ($cm^2$), and then, the SMI ($cm^2/m^2$) was calculated using the following formula: total skeletal muscle volume (L3)/height $(m)^2$. Additionally, the SMI reduction rate was calculated as follows: (pre-SMI − post-SMI)/pre-SMI × 100%.

*Statistical analysis*

Data were shown as the mean ± standard deviation or number (%). Survival analysis was performed using the Kaplan–Meier method. The statistical difference was evaluated using the log-rank test. We used the Cox proportional hazards model to clarify the covariates' effects on survival. We considered as statistically significant a probability level of 0.05. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). This platform is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [16].

## RESULTS

*SMI reduction and patients' survival*

We planned on estimating the prognostic significance of the SMI reduction rate. We first divided the patients into quartiles according to the percentiles of SMI reduction rate. We then compared the risk for overall survival (OS) using both known risk factors and each quartile, since the cut-off value of the SMI reduction rate has not been decided. As described in Supplemental Table 1, multivariate Cox proportional hazard analysis with all variables showed that the risk for OS increased with age, pT $\geq$ 3, and the fourth quartile of SMI reduction. Additionally, our results suggest that hazard ratio increased in the third quartile, which ranged between 50 and 75 percentile. On the basis of these findings, we classified the patients into tertiles based on the percentiles of SMI reduction rate. Specifically, the first tertile (t1, n = 105) had an SMI reduction rate of <1.25%, the second tertile (t2, n = 106) had an SMI reduction rate between 1.25% and 9.13%, and the third tertile (t3, n = 105) had an SMI reduction rate of >9.13%. Figure 1a shows the overall and relapse-free survivals (RFS) among the tertiles. We found that the survivals of t3 were significantly poorer than those of t1 and t2. We then defined t3 as "massive SMI reduction (MR) group" and t1–2 as "limited SMI reduction (LR) group." Figure 1b describes the overall and RFSs between the groups. We found that the MR group's survival was significantly poorer than that of the LR group.

*Difference in the clinicopathologic, operative, and postoperative findings*

Table 1 shows the patients' clinicopathologic, operative, and postoperative backgrounds. The mean age was 71.1 years, and 83.9% was male. There were no significant differences in the clinicopathologic, operative, and postoperative findings between the groups with the exception of blood loss and pN status. Blood loss was significantly greater in the MR group than in the LR ($p = 0.028$), and the prevalence of node positive cases was significantly higher in the MR group than in the LR ($p = 0.023$).

*Effect of SMI massive reduction and other factors on OS and RFS*

The prognostic factors for OS according to Cox proportional hazard analysis were shown in Table 2. Univariate revealed that age, gender, preoperative BMI, preoperative sarcopenia, pT ≥ 3, pN ≥ 1, pStage ≥ III, operation time, blood loss, and massive SMI reduction were significant variables influencing a worse OS. Multivariate analysis demonstrated that the significant factors were the following: age [$p < 0.001$, HR 1.116, 95% CI 1.072–1.162], preoperative sarcopenia [$p = 0.005$, HR 1.831, 95% CI 1.203–2.788], pT ≥ 3 [$p < 0.001$, HR 2.229, 95% CI 1.456–3.413], pN ≥ 1 [$p = 0.022$, HR 1.650, 95% CI 1.075–2.531], and massive SMI reduction [$p < 0.001$, HR 5.405, 95% CI 3.514–8.314].

As shown in Table 3, univariate analysis revealed that the significant risk factors for recurrence were age, gender, preoperative BMI, preoperative sarcopenia, cancer type (adenocarcinoma), pT ≥ 3, pN ≥ 1, pStage ≥ III, blood loss, and massive SMI reduction.

Multivariate analysis demonstrated that the independent factors were as follows: age [$p < 0.001$, HR 1.106, 95% CI 1.063–1.150], preoperative sarcopenia [$p < 0.001$, HR 1.933, 95% CI 1.323–2.823], cancer type [$p = 0.035$, HR 1.796, 95% CI 1.041–3.096], pT ≥ 3 [$p < 0.001$, HR 2.063, 95% CI 1.384–3.075], pN ≥ 1 [$p = 0.001$, HR 1.905, 95% CI 1.286–2.823], and massive SMI reduction [$p < 0.001$, HR 5.070, 95% CI 3.414–7.532]. Neither preoperative BMI nor preoperative sarcopenia was associated with MR, although preoperative sarcopenia was significantly associated with BMI ($p<0.0001$).

*Risk factors of massive SMI reduction*

Our results showed that massive reduction of SMI worsened both OS and RFS. Specifically, we investigated the risk factors of massive SMI reduction using a logistic regression model (Table 4). Univariate analysis found no significant risk factor, and cancer type (adenocarcinoma) and pN ≥ 1 tended to associate with massive SMI reduction. However, multivariate analysis demonstrated that pN ≥ 1 and cancer type (adenocarcinoma) correlated with massive SMI reduction (pN ≥ 1 [$p = 0.032$, OR 1.700, 95% CI 1.050–2.750] and cancer type [$p = 0.048$, OR 2.160, 95% CI 1.010–4.650], respectively).

## DISCUSSION

In the present study, we found that massive SMI reduction during the early postoperative period after esophagectomy negatively influenced tumor recurrence and survival in elderly patients with esophageal cancer. Sarcopenia is a well-known prognosticator of elderly cancer patients, including those with esophageal cancer. However, our study is the first to demonstrate the influence of early postoperative skeletal muscle loss on the prognosis of elderly esophageal cancer patients.

Body weight loss during the early postoperative period is frequently observed among patients who underwent esophagectomy. A prospective cohort study revealed that 63.7% of patients suffered from weight loss more than 10% in 6 months after esophagectomy [17], while two retrospective studies showed mean weight loss rates of 10.95% [18] and 12.9% one year post-esophagectomy [19]. Numerous potential causative factors for weight loss post-esophagectomy can be taken into account. A significant link is reported between appetite loss, eating difficulties, and odynophagia with postoperative weight loss [17], while preoperative weight and vocal cord palsy were reported to be independent risk factors for severe postoperative weight loss [19]. Pyloroplasty's absence is reported to be the sole risk factor for >10% weight loss one year post-esophagectomy [18]. Several studies showed that post-esophagectomy patients experience a severe decrease in ghrelin secretion [20,21] and a significant increase in plasma glucagon-like peptide-a, which induces early satiety [11].

The extent of body weight loss post-esophagectomy differs among individuals, and the absence of weight loss was reported to be an independent factor associated with 5-year survival

[22]. In the present study, we revealed that SMI at 4 months after esophagectomy differed among the elderly and found the massive reduction of SMI was an independent worse prognostic factor. None of the patients included in the study underwent pyloroplasty. Furthermore, postoperative complications, including recurrent laryngeal nerve palsy, didn’t affect the extent of SMI reduction.

The presence of sarcopenia has been reported to be an independent predictor of lower disease-free survival and OS among patients with many types of cancer [14,23,24]. Also in our study, sarcopenia was an independent factor for both OS and RFS. It is reported that loss of skeletal muscle mass during neoadjuvant chemoradiotherapy was predictive of postoperative mortality in stage III–IV subgroups [10]. A correlation between decreased skeletal muscle mass following neoadjuvant therapy and poor prognosis was also reported [25]. Additionally, skeletal muscle mass during neoadjuvant treatment but not preoperative sarcopenia correlated with worse OS [9]. Recent studies have reported on the negative prognostic impact of postoperative skeletal muscle loss in numerous cancer types including gastric [26], non-small cell lung [27,28], urothelial [29], renal [30], rectal [31], and esophageal [32].

To date, the mechanism of association between loss of skeletal muscle and poor prognosis in cancer patients remains unclear. One possible explanation is that tumor-derived cytokines impair myogenesis. It is reported that Proteolysis Inducing Factor from cancer cells induces skeletal muscle wasting through the activation of the ubiquitin-mediated pathway [33,34].

TNF-α produced by immune cells affected the decrease of skeletal muscle by suppressing MyoD messenger RNA [35], while TNF-α, IL-1, and IL-6 from malignant tumors affected cachexia [36]. The existence of a microscopic residual tumor may be a cause of skeletal muscle wasting. In this study, the prevalence of node-positive cases was significantly higher in the MR group than in the LR. Especially, the prevalence of pN3 was much higher in the MR group than in the LR. It is reported that the probability of systemic disease exceeded 50% when 3 or more positive nodes were present and approached 100% when 8 or more were present [37]. Therefore, the MR group is estimated to include more patients with systemic disease.

The operative blood loss was significantly greater in the MR group than in the LR. We could not find out the factors possibly affecting blood loss, such as the operative approach, the type of esophagectomy, and the extent of lymph node dissection, between the groups. Although meta-analysis revealed autologous blood transfusion was associated with significantly worse long-term survival in patients undergoing esophagectomy [38], the prevalence of patients who underwent blood transfusion was comparable between the groups.

The prevalence of adenocarcinoma was significantly higher in the MR group than in the LR group. In this study, the surgical procedures were similar between adenocarcinoma and squamous cell carcinoma (SCC), and the incidence of lymph node metastasis was similar between them (48.9% vs. 44.6%). However, the prevalence of pN2 or pN3 tended to be higher in adenocarcinoma (29.0%) than in SCC (14.7%) ($p = 0.067$), suggesting that there were more patients with systemic disease in adenocarcinoma than in SCC [37]. That might be why there were more patients with adenocarcinoma in the MR group than in the LR.

Recently, skeletal muscle has been identified as a secretory organ [39]. Specifically, muscle fibers produce, express, and release cytokines and other peptides. Additionally, muscle fibers communicate with other organs (e.g., adipose tissue, liver pancreas, and brain). Additionally, the skeletal muscle contains a high number of leukocytes. Specifically, the latter comprise various cell types, including the following: CD8+ cytotoxic T cells, regulatory T cells, neutrophils, and eosinophils. Such cells act as the muscle immune system [40]. When skeletal muscle mass is lost, the immunity of cancer patients is impaired, leading to cancer recurrence. On the basis of this knowledge, it is thought that interventions to preserve skeletal muscle volume after esophagectomy may improve elderly patients' survival.

Numerous studies which investigated the effect of post-discharge enteral feeding failed to demonstrate the improvement of postoperative weight loss [41, 42]. Anamorelin is an orally active, high-affinity, selective ghrelin-receptor agonist. Two recent RCTs demonstrated that anamorelin significantly increased lean body mass in advanced non-small cell lung carcinoma cachexic patients [43]. Meanwhile, the postoperative use of rikkunshito, a traditional Japanese herbal medicine, was reported to increase the acyl ghrelin level after a 48-week treatment. Furthermore, it has been shown to improve body weight loss post-esophagectomy [44]. Interventions modulating serum ghrelin levels may successfully minimize skeletal muscle loss post-esophagectomy.

Several limitations can be found in our study. First, this was a retrospective and conducted in a single institution. Second, no standard method was used in SMI evaluation, and the cut-off value of the SMI reduction rate differed among the studies. Further multicenter prospective studies are required to confirm our results. Additionally, there is the need to evaluate the efficacy of the intervention to minimize SMI reduction and methodology standardization in SMI evaluation among the institutes.

## CONCLUSION

We observed that massive SMI reduction was significantly correlated with recurrence and poor prognosis in elderly patients who underwent curative esophagectomy for esophageal cancer. We believe that early postoperative skeletal muscle loss represents a useful predictor of both recurrence and poor survival.

## ACKNOWLEDGMENTS

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## Figure legends

Fig 1. Kaplan-Meier curves stratified by SMI reduction rate. a: Overall survival and relapse-free survival, classified into tertiles depending on the SMI reduction rate. Survival was significantly worse in group t3 than in other groups. b: Overall survival and relapse-free survival, stratified by massive or limited SMI reduction. Overall survival and relapse-free survival was significantly worse in massive SMI reduction group than in limited SMI reduction group.

Supplemental Fig 1. Study population.

Supplemental Fig 2. The method to assess skeletal muscle mass (green area); skeletal muscle index = skeletal muscle mass / height$^2$ (cm$^2$ / m$^2$)