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# Effect of Muscle Mass Loss After Esophagectomy on Prognosis of Oesophageal Cancer

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**Abstract.** *Background/Aim: To assess the prognostic effect of muscle loss after esophagectomy and before discharge. Patients and Methods: This study retrospectively analysed 159 consecutive patients with oesophageal and gastroesophageal junction cancer who underwent esophagectomy between August 2011 and October 2015. Body composition was evaluated one week before surgery and at discharge using a bioelectrical impedance analyser. Results: The median rate of muscle mass loss (RMML) was 4.38% (range=−3.3 to +18.8). Patients with increased RMML had significantly poorer outcomes of overall survival than those with decreased RMML (p=0.015). On multivariate analysis, RMML [≥4.38, hazard ratio (HR)=2.033, 95% confidence interval (CI)=1.018-5.924, p=0.044) and pathological tumour depth (≥2, HR=3.099, 95%CI=1.339-7.172, p=0.008) were selected as independent prognostic factors. Conclusion: RMML after esophagectomy is indicative of poor prognosis in patients with esophageal cancer.*

Oesophageal cancer (EC) is the sixth most frequent cause of cancer death worldwide (1). EC has a poor prognosis despite recent advances in therapeutic strategies, including surgery, chemotherapy, radiotherapy, and combined therapies (2). Identifying novel measures of prognosis is important for improving long-term outcomes in patients with EC.

Recent reports suggest that the preoperative presence of sarcopenia, characterised by the progressive and generalised loss of skeletal muscle mass and strength, is an independent predictor of overall survival in patients with EC (3-5). Alternatively, muscle mass loss (MML) during neoadjuvant treatments worsens long-term outcomes after surgery in patients with EC (6, 7). It has been shown that postoperative MML leads to poor survival of cancer patients, including gastric, bladder, rectum, and lung cancer (8-11). However, the effect of postoperative MML on long-term outcomes remains unclear in patients with EC.

The aim of the present study was to reveal whether MML in the period between esophagectomy and discharge had an effect on long-term outcomes in patients with EC.

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*Key Words:* Muscle mass loss, oesophageal cancer, esophagectomy.

## Patients and Methods

*Patient data*. This study was approved by the Research Ethics Committee of the Kanagawa Cancer Center prior to initiating the study (approval number: Epidemiological Study-2019-140). Overall, 167 consecutive patients diagnosed with EC, who underwent esophagectomy between August 2011 and October 2015 at Kanagawa Cancer Center, were selected from the clinical database. Inclusion criteria included: 1) patients with a pathological diagnosis of squamous cell carcinoma or adenocarcinoma and 2) patients who had undergone curative resection (R0). The exclusion criteria included: 1) patients that died prior to discharge and 2) patients with a pathological diagnosis of T4 or Stage IV according to the International Union against Cancer (UICC 7th edition) (12).

*Neoadjuvant treatment*. Patients with clinical stage II or III EC had usually undergone preoperative chemotherapy or chemoradiotherapy as the standard therapy. The standard regimen of preoperative therapy was 2 cycles of cisplatin and 5-fluorouracil. Some patients were enrolled in clinical trials and had undergone other treatment regimens.

*Surgical procedure*. The surgical treatment was determined according to the Guidelines for Diagnosis and Treatment of Carcinoma of the Esophagus (13). In principle, 2 fields lymph node

dissection was indicated for tumours in the middle thoracic to abdominal oesophagus, while 3 fields dissection was applied for upper thoracic tumours. Reconstruction was performed using a gastric tube placed through the posterior mediastinal route or retrosternal route.

*Perioperative care*

i) Preoperative management: For patients who could not tolerate a liquid diet, parenteral nutrition therapy with nasal feeding tube was administered until the time of surgery. Otherwise, patients were permitted to eat until midnight on the day before surgery.

ii) Intraoperative management: During the surgical procedure, a tube of enteral nutrition was placed in all patients for early initiation of enteral nutrition.

iii) Postoperative management: All patients received uniform perioperative management based on the ERAS program (14). Enteral nutrition was introduced using jejunostomy from postoperative day (POD) 1. Oral intake was initiated on POD 6, beginning with water and gelatinous foods. The patients began to eat solid food on POD 9, starting with rice porridge and soft food, and progressing in 3 steps to regular food intake. Patients were discharged when they had achieved adequate pain relief and soft food intake, returned to their preoperative mobility level, and exhibited normal laboratory data between POD 12-15.

Physical activity was initiated with the aid of an expert physiotherapist from POD 1. Typically, patients started walking from POD 1 with the help of the physiotherapist who accompanied them during the walking task until POD 2. After that, walking distance was extended according to each patient's physical condition. Patients who could not perform the walking task implemented training tasks with the physiotherapist to increase muscle strength.

*Data collection*. All data, including patient age, sex, American Society of Anesthesiologists physical status (ASA-PS), operative time (min), blood loss (ml), and serum C-reactive protein (CRP) levels were retrieved from the clinical database of the Kanagawa Cancer Center. Histopathological examination and staging were performed on the resected specimens according to the International Union against Cancer (UICC) TNM 7th edition (12). Postoperative complications were defined as grade 2 or greater according to the Clavien-Dindo classification (15).

*Measurement of muscle mass*. The segmental body composition was measured using the Tanita MC-190EM bioelectrical impedance analyser (Tanita, Tokyo, Japan). Body weight and composition were analysed within 1 week prior to surgery and at discharge. The rate of muscle mass loss (RMML) was defined as follows: RMML= (preoperative muscle mass-muscle mass at discharge)× 100/preoperative muscle mass.

*Follow-up after surgery*. The patients were followed for at least 5 years after surgery or until death. Blood tests, including tumour markers, were performed every 3 months for the first year and every 6 months thereafter. Computed tomography of the neck, chest, and abdomen was performed every 6 months, while upper gastrointestinal endoscopy was performed once a year.

*Evaluation and statistical analysis*. Overall survival was defined as the period between the date of surgery and death. Recurrence-free survival was defined as the period between the date of surgery and recurrence or death, whichever occurred first.

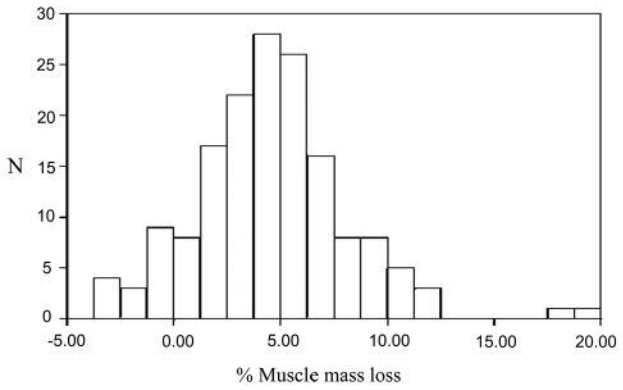



Figure 1. *Distribution of rate of loss of muscle mass (RMML). Based on the median RMML (4.38), patients were categorised in one of 2 groups, increased RMML and decreased RMML.*

Patients were divided into 2 groups based on the RMML by cut-off median, as performed in previous studies (6, 16). Continuous parameters were tested for normality using Shapiro-Wilk's test, and deemed normally distributed if $p>0.05$. For comparing normal scalar variables between the 2 groups, independent samples Student's t test was used, while the Mann-Whitney *U*-test was used for non-normal variables. Categorical variables were analysed using Pearson $\chi^2$ test. The Kaplan-Meier method was used to calculate the survival rates, and the log-rank test was used for comparisons of the survival rates. Cox proportional hazards regression models were used to analyse the hazard ratios for the overall survival. Two-tailed *p*-values <0.05 were considered as significant. All statistical analyses were performed using SPSS® 24.0 (SPSS Inc, Chicago, IL, USA).

## Results

*Comparison of the clinicopathological characteristics among the 2 groups presenting increased and decreased RMML, respectively*. Overall, 159 patients were examined in this study. Distribution of the RMML is shown in Figure 1. The patients were divided into 2 groups based on the median RMML (4.38), namely increased RMML group and decreased RMML group. The clinicopathological characteristics of the patients in each of the 2 groups (increased and decreased RMML) is shown in Table I. There was no difference in age, gender, neoadjuvant chemotherapy, ASA-PS, histological type, operation time, blood loss, and pathological tumour depth between the 2 groups. Pathological lymph node metastasis in the group with increased RMML was more advanced than in the group with decreased RMML ($p=0.005$). The incidence of postoperative complications was 25 cases (31%) in the group with decreased RMML and 37 cases (49%) in the group with increased RMML. The rate of postoperative complications was significantly higher in the group with increased RMML ($p=0.044$). Particularly, the rate of anastomotic leakage was

significantly higher in the group with increased RMML. Although not significant, the peak serum CRP levels in the period between surgery and discharge tended to be higher in the group with increased RMML than in the group with decreased RMML. Frequently, the duration of postoperative hospital stay was greater in the group with increased RMML than in the group with decreased RMML.

*Survival analyses*. The median follow-up period was 43.0 months and ranged between 6.6 and 81.7 months. The group with increased RMML presented significantly poorer outcomes in both overall and relapse-free survival than the group with decreased RMML (Figures 2, 3). On univariate analysis, pathological tumour depth, pathological lymph node metastasis, and the RMML were significantly associated with poor overall survival. On multivariate analysis, the RMML [hazard ratio (HR)=2.033, 95% confidence interval (CI)=1.018-5.924, $p$=0.044], and pathological tumour depth (HR=3.099, 95%CI=1.339-7.172, $p$=0.008) were selected as independent prognostic factors (Table II).

## Discussion

Our findings indicate that during the period between surgery and discharge, MML is a marker of poor prognosis in patients with EC. To date, this is the first report that demonstrates the effect of perioperative RMML on prognosis in patients with EC.

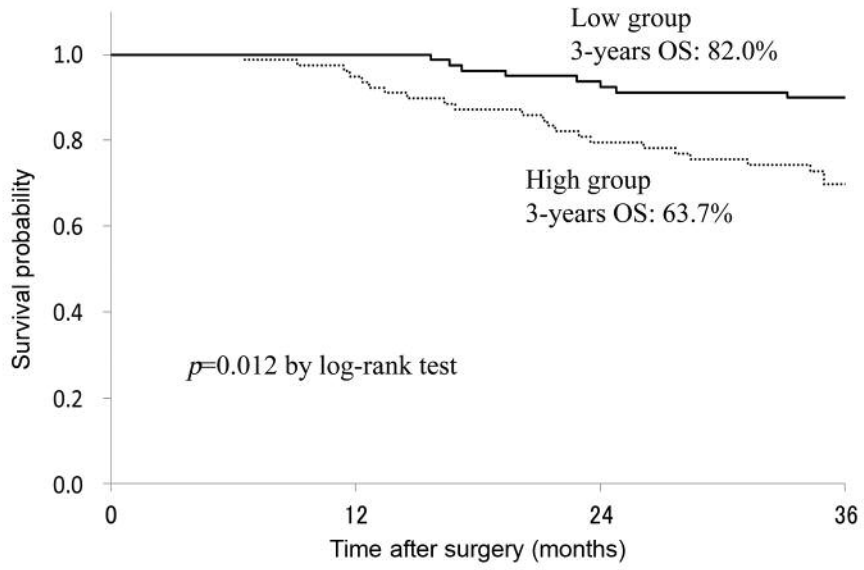
Recently, several studies have reported that changes in body composition are important for predicting all-cause mortality of patients with cancer (17, 18). Mayanagi *et al*. (2017) have reported that loss in total muscle cross-sectional area preoperatively and 4 months postoperatively negatively affected cancer recurrence and survival (19). Lee *et al*. (2018) have revealed that muscle mass and decreased body mass index were associated with an increased risk of cancer death (20). Moreover, MML is related to physical activity, and it was reported that reduced physical activity promotes cancer progression (21, 22). Reduced muscle mass is associated with aberrant energy homeostasis, impaired cell growth, immune dysfunction due to inadequate myokines, and impaired amino acid metabolism (23, 24). Alternatively, increased physical activity resulting in increased muscle mass may improve immune function against cancer recurrence (25).

Based on our results and previous reports, we predicted that a substantial decrease in muscle mass was associated with poor long-term outcomes postoperatively and prior to discharge. In this study, the postoperative peak serum CRP levels were greater in the group with increased RMML than in the group with decreased RMML. CRP is regarded as a biochemical marker of systemic inflammatory response (26). Indeed, there are reports that postoperative infections may enhance the growth of micrometastases (27, 28). Thus, postoperative

Table I. *Relationship between rate of loss of muscle mass and clinicopathological characteristics*.

| | Rate of loss of muscle mass | | |
|---|---|---|---|
| | Low (n=80) | High (n=79) | $p$-Value |
| Age, years, mean±SD | 67.0±6.5 | 66.0±7.1 | 0.382 |
| Gender, n (%) | | | |
| Male | 66 (83) | 67 (85) | 0.694 |
| Female | 14 (18) | 12 (15) | |
| Neoadjuvant treatment, n (%) | | | |
| Absent | 32 (40) | 29 (37) | 0.670 |
| Present | 48 (60) | 50 (63) | |
| ASA-PS, n (%) | | | |
| 1 | 13 (16) | 13 (16) | 0.972 |
| 2 | 67 (84) | 66 (84) | |
| Histological type, n (%) | | | |
| Squamous cell carcinoma | 77 (96) | 72 (91) | 0.184 |
| Adenocarcinoma | 3 (4) | 7 (9) | |
| Operation time, min, mean±SD | 408.8±69.8 | 414.2±64.5 | 0.613 |
| Blood loss, ml, mean±SD | 515.5±466.4 | 501.9±262.5 | 0.822 |
| Pathological tumour depth, n (%) | | | |
| 0 | 2 (3) | 3 (4) | 0.856 |
| 1 | 37 (46) | 32 (41) | |
| 2 | 9 (11) | 11 (14) | |
| 3 | 32 (40) | 33 (42) | |
| Pathological lymph node metastasis, n (%) | | | |
| 0 | 41 (51) | 26 (33) | 0.005 |
| 1 | 30 (38) | 26 (33) | |
| 2 | 6 (8) | 19 (24) | |
| 3 | 3 (4) | 8 (10) | |
| All postoperative complication, n (%) | | | |
| Absent | 55 (69) | 42 (51) | 0.044 |
| Present | 25 (31) | 37 (49) | |
| Anastomotic leakage, n (%) | | | |
| Absent | 70 (87) | 58 (74) | 0.025 |
| Present | 10 (13) | 21 (26) | |
| Pneumonia, n (%) | | | |
| Absent | 69 (86) | 65 (82) | 0.492 |
| Present | 11 (14) | 14 (18) | |
| Recurrent laryngeal nerve paralysis, n (%) | | | |
| Absent | 77 (96) | 77 (97) | 0.660 |
| Present | 3 (4) | 2 (3) | |
| Others, n (%) | | | |
| Absent | 73 (91) | 72 (91) | 0.980 |
| Present | 7 (9) | 7 (9) | |
| Peak CRP level after surgery, n (%) | | | |
| <15 mg/dl | 72 | 60 | 0.018 |
| ≥15 mg/dl | 8 | 19 | |
| Postoperative hospital stay, day mean±SD | 19.7±12.8 | 24.2±16.5 | 0.052 |

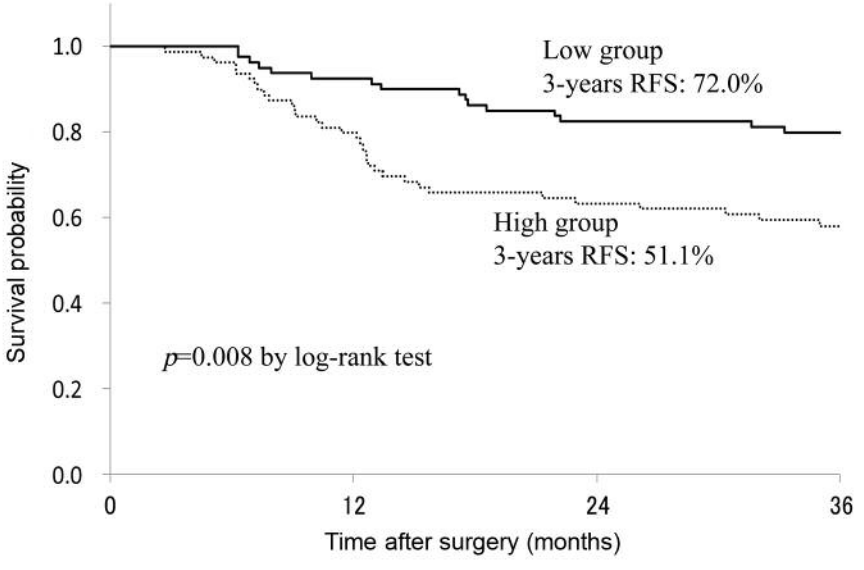
ASA-PS: American Society of Anaesthesiologists Physical Status; CRP: C-reactive protein.




Number at risk

| | | | | |
|---|---|---|---|---|
| Low group | 80 | 80 | 76 | 72 |
| High group | 79 | 75 | 63 | 56 |

Figure 2. *The overall survival curves of the group presenting decreased RMML and the group with increased RMML. The group with increased RMML revealed significantly poorer outcomes in overall survival than the group with decreased RMML.*




Number at risk

| | | | | |
|---|---|---|---|---|
| Low group | 80 | 74 | 66 | 64 |
| High group | 79 | 63 | 50 | 46 |

Figure 3. *The recurrence-free survival curves of the groups with increased and decreased RMML. The group with increased RMML revealed significantly poorer outcomes in relapse-free survival than the group with decreased RMML.*

Table II. *Univariate and multivariate analyses for overall survival.*

| | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|
| | Number | HR | 95%CI | *p*-Value | HR | 95%CI | *p*-Value |
| Age, years | | | | | | | |
| ≤66 | 81 | 1.000 | | | | | |
| ≥67 | 78 | 1.213 | 0.640-2.301 | 0.554 | | | |
| Gender | | | | | | | |
| Male | 133 | 1.000 | | | | | |
| Female | 26 | 1.207 | 0.531-2.746 | 0.653 | | | |
| ASA-PS | | | | | | | |
| 1 | 26 | 1.000 | | | | | |
| 2/3 | 133 | 2.521 | 0.775-8.203 | 0.124 | 1.792 | 0.542-5.924 | 0.339 |
| Histological type | | | | | | | |
| Squamous cell carcinoma | 149 | 1.000 | | | | | |
| Adenocarcinoma | 10 | 1.218 | 0.375-3.961 | 0.743 | | | |
| Pathological tumour depth | | | | | | | |
| T0/T1 | 74 | 1.000 | | | | | |
| T2/T3 | 85 | 3.892 | 1.781-8.505 | 0.001 | 3.099 | 1.339-7.172 | 0.008 |
| Pathological lymph node metastasis | | | | | | | |
| N0 | 67 | 1.000 | | | | | |
| N1/2/3 | 92 | 2.668 | 1.262-5.640 | 0.010 | 1.448 | 0.641-3.273 | 0.373 |
| Postoperative complication | | | | | | | |
| Absent | 97 | 1.000 | | | | | |
| Present | 62 | 1.246 | 0.653-2.375 | 0.504 | | | |
| Postoperative hospital stay, day | | | | | | | |
| ≤15 | 99 | 1.000 | | | | | |
| ≥16 | 60 | 1.272 | 0.668-2.424 | 0.464 | | | |
| Rate of loss of muscle mass | | | | | | | |
| Low | 80 | 1.000 | | | | | |
| High | 79 | 2.309 | 1.178-4.525 | 0.015 | 2.033 | 1.018-5.924 | 0.044 |

ASA-PS: American Society of Anaesthesiologists Physical Status; HR: hazard ratio; CI: confidence interval.

complications resulting in systemic inflammation that increases CRP may be risk factors for cancer recurrence in patients with EC (29). In the postoperative period, as cancer recurrence results from the growth of invisible tumour cells, postoperative infections might enhance the growth of micrometastases (27, 28). These mechanisms may be associated with poor long-term outcomes due to decreased muscle mass in the postoperative period before discharge. Moreover, the group with increased RMML presented a significantly higher incidence of postoperative complications than the group with decreased RMML, especially anastomotic leakage. Indeed, patients with anastomotic leakage require fasting. In our study, parenteral nutrition was administered to patients with anastomotic leakage using a tube of enteral nutrition; however, this method may be insufficient for the prevention of muscle mass reduction. Indeed, adequate calorie administration by parenteral nutrition is sometimes difficult due to diarrhoea or abdominal pain from increased motility of the small intestine. An inadequate supply of protein and energy results in protein energy malnutrition (30). Currently, we are working on more effective nutritional supports and early rehabilitation for reducing MML postoperatively.

Our study presents several limitations. First, this was a single-centre, retrospective study with a reduced number of patients without randomisation. Second, the muscle mass was analysed using a bioelectrical impedance analyser, which is not typically used for examination after esophagectomy. Bioelectrical impedance included muscle mass, as well as liver and kidney mass. Indeed, the mass of visceral organs would not be changed by surgery, and the major contributor to the change in lean body mass would be muscle; however, the bioelectrical impedance analyser cannot directly measure muscle mass. Therefore, the results of the present study need to be validated by computed tomography (CT) measurements. Finally, MML is only one aspect of functional depletion. Other parameters, such as loss of muscle function and strength, were not measured in this study.

In conclusion, our findings demonstrated that a postoperative increase in RMML before discharge had a negative effect on long-term outcomes. Considering the mechanism responsible for postoperative MML, prevention of postoperative complications leading to systemic inflammation, as well as postoperative nutrition and early rehabilitation may improve long-term prognosis.

## Conflicts of Interest

All Authors have no conflicts of interest or financial ties to disclose regarding this study.

## Authors' Contributions

Concept and study design were conducted by Y. Shimoda, T. Yamada and T. Oshima. Data collection and literature search were done by Y. Shimoda, K. Koumori, H. Watanabe, and H. Osakabe. Data analysis and interpretation were done by Y. Shimoda, T. Yamada and T. Oshima. Interpretation of data was done by all 17 investigators. Drafting the article and figure were done by Y. Shimoda, T. Yamada and T. Oshima. Finally, this article was revised and approved by all 17 investigators. Thus, all Authors actively participated in this study.

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