Abstract. Background: Esophageal cancer often involves direct invasion of adjacent organs and patient survival rates are low. Sarcopenia has been reported to be associated with a poor prognosis in several types of malignancies. However, the impact of sarcopenia on the long-term survival of patients with unresectable locally advanced esophageal cancer remains unclear. Patients and Methods: A total of 48 patients undergoing definitive chemoradiotherapy at our Institution from October 2012 to December 2015 were enrolled; their data were compared according to patient skeletal muscle index (SMI): low SMI (sarcopenia group), n=34; normal SMI (non-sarcopenia group), n=14. Results: There were no significant differences in the incidence of severe adverse events and dose reduction rate between the two groups. The incidence of nutritional support was significantly higher in the groups with sarcopenia than in the non-sarcopenia group (44.1% vs. 7.1%, p=0.077). Response rates were significantly lower in the sarcopenia group than in the non-sarcopenia group (43.8% vs. 78.6%, p=0.025). The overall survival rate in the group with sarcopenia was significantly lower than that in the non-sarcopenia group (3-year: 36.95% vs. 63.9%, p=0.018). Conclusion: Sarcopenia prior to treatment may worsen the long-term survival of patients with unresectable locally advanced esophageal cancer. Further well-designed prospective trials are needed to estimate whether adequate nutritional support has a favorable impact on therapeutic outcomes in this population.

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Key Words: Sarcopenia, esophageal cancer, prognosis, nutritional support.

Impact of Sarcopenia in Patients with Unresectable Locally Advanced Esophageal Cancer Receiving Chemoradiotherapy

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Esophageal cancer is the eighth most common cancer in the world and a growing epidemic, with approximately 460,000 new diagnoses, and resulting in 380,000 deaths worldwide annually (1, 2). The prognosis of esophageal cancer remains poor with a 5-year overall survival rate of less than 20% (3, 4). Although curative surgery is a treatment for patients with resectable esophageal cancer, approximately 50% of patients have unresectable locally advanced tumor invading the adjacent organs or radiographically visible metastases (5). The standard treatment for unresectable locally advanced esophageal cancer is definitive chemoradiotherapy (6), but survival rates remain low.

Currently, sarcopenia, that is defined as the severe depletion of skeletal muscle mass and strength, is considered the most relevant phenotype of cachexia and has been linked to poor prognosis in several types of cancer (7-9). With respect to patients with esophageal cancer, it has been reported that sarcopenia is related to dose-limiting toxicity during neo-adjuvant chemotherapy and high anastomotic leakage rates (7, 10).

However, the impact of sarcopenia prior to treatment on the long-term prognosis of patients with unresectable locally advanced esophageal cancer remains unclear. Therefore, this retrospective single-institution study aimed to evaluate the impact of pretreatment sarcopenia as a prognostic factor in patients with unresectable locally advanced esophageal cancer receiving definitive chemoradiotherapy.

Patients and Methods

Patients. From October 2012 to December 2015, a series of 48 patients diagnosed with unresectable locally advanced esophageal cancer underwent definitive chemoradiotherapy at the Department of Surgery, Gastroenterological Center, Yokohama City University and its related institution. For all patients, tumors were confirmed histologically as squamous cell carcinoma. This retrospective study protocol conformed to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board for the Use of
Chemoradiotherapy. From October 2012, patients with unresectable esophageal cancer initially underwent therapy with 5-fluorouracil plus cisplatin with radiotherapy. Patients under the age of 75 years were treated with concurrent chemoradiotherapy and patients over the age of 75 years were treated with sequential chemoradiotherapy tin order to avoid severe adverse events. Cisplatin was administered at a dose of 70 mg/m² by slow drip infusion on days 1 and 29. 5-fluorouracil was administered at a dose of 700 mg/m² per day by continuous infusion for 24 h on days 1-4 and days 29-32 in concurrent chemoradiotherapy or days 1-5 and days 29-33 in sequential chemoradiotherapy. Two liters of hydration was administered by continuous infusion for 24 h on days 1-5 and days 29-33.

Radiation therapy was delivered with megavoltage equipment (6 MV) with anterior- and posterior-opposed fields up to 40 Gy to the primary tumor and regional lymph node area followed by a booster dose of 20 Gy to the primary tumor and locally enlarged lymph nodes using an oblique-opposed technique to exclude the spinal cord. Radiation therapy was performed 5 days per week at 2 Gy/day.

After initial chemoradiotherapy, patients without complete remission underwent docetaxel plus cisplatin therapy as a second-line chemotherapy. Docetaxel was administered at a dose of 60 mg/m² on day 1 and cisplatin was administered at a dose of 60 mg/m² on day 1. Two liters of hydration was administered by continuous infusion for 24 h on days 1-4. Each course lasted three weeks and was repeated until disease progression.

For third-line chemotherapy, a twice-daily dose of 40 mg/m² S-1 was administered orally for four consecutive weeks. This was followed by a drug-free-interval of 2 weeks. The cycles of chemotheraphy were repeated until obvious progression of disease.

For fourth-line chemotherapy, paclitaxel was administered at a dose of 100 mg/m² on days 1, 8, 15, 22, 29, and 36. This was followed by a drug-free-interval of two weeks. Each course was repeated until progression of disease or until the patient refused treatment.

During the treatment, blood tests were carried out at least twice a week. Chemoradiotherapy or chemotherapy was discontinued if grade 3 or 4 adverse events determined by Common Terminology Criteria Events (CTCAE) version 4.0 (11) occurred, but resumed when symptoms improved. The tumor response was assessed using the Response Evaluation Criteria in Solid Tumors Guideline (RECIST version 1.1) 1 month after chemoradiotherapy (12). When a tumor showed a complete response (CR), two additional courses of the same chemotherapy were performed and the patients were followed up in the short-term with an esophagastroduodenoscopy and CT scan every 3-6 months.

Skeletal muscle tissue measurement. Skeletal muscle tissue areas were measured by the SYNAPSE VINCENT system (Fuji Film Co., Ltd., Tokyo, Japan). Computed tomographic scans taken before and after chemoradiotherapy were evaluated. The area covered by skeletal muscle was calculated from pixels in the density range of −29 to +150 Hounsfield units (HUs). Two adjacent axial images within the same series at the level of the third lumbar vertebrae (L3) in the inferior direction were selected for analysis of the total muscle cross-sectional area (cm²) and averaged for each patient. The muscle area normalized by the square of the patient’s height (m²) was defined as the skeletal muscle index (SMI) (cm²/m²) (9). Pre-defined cut-offs for sarcopenia (≤52.4 cm²/m² for men and ≤38.5 cm²/m² for women) were used to define sarcopenia (10, 13) and patients were subsequently divided into groups with and without sarcopenia. This index was calculated on the day before chemoradiotherapy.

Nutritional support. Amounts of oral intake energy (OIE) and nutritionally supported energy (NSE) were calculated from medical records over a 1-week hospitalization period for first-line chemoradiotherapy. First, total energy expenditure (TEE) of all patients was calculated using the Harris-Benedict equation and the activity factor was calculated as 1.2. Nutritional support was administered for the patients with poor oral intake (OIE/TEE <0.6) by administration of semi-digestive state nutrients for patients without obstruction by tumor, and elemental diet via enteral feeding tube for patients with obstruction by tumor. Nutritional support was administered before the start of chemoradiotherapy, and continued throughout the whole period of chemoradiotherapy.

Patient data. Clinical data for all cases were collected from the prospectively maintained database at our Institution. The pathological classification was based on the esophageal cancer TNM (tumor-node metastasis) staging system of the Union for International Cancer Control (eighth edition) (14). Glasgow Prognostic Scores (GPSs) were assessed from blood tests carried out the day before chemoradiotherapy started. Patients with serum C-reactive protein >10 mg/l and hypoalbuminemia (<35 g/l) were given a score of 2, those with only one of these biochemical abnormalities a score of 1, and those with neither of these abnormalities a scored of 0 (15). Neutrophil lymphocyte ratio (16) and prognostic nutritional index (PNI) (17) were also calculated on the day before chemoradiotherapy.

Statistical analysis. Continuous data are expressed as the median (range). Data of different groups were compared using Wilcoxon test. Categorical data were analyzed using chi-square test. Overall survival rates from the start of treatment were calculated according to Kaplan–Meier method, and differences between groups were tested for significance using the log-rank test. Multivariate survival analysis and the calculation of hazard ratios used a model of Cox proportional hazards regression including covariates that gave values of p<0.10 in univariate survival analysis. All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA). Differences with probability values of p<0.05 were considered as significant.

Results

Patient characteristics. Patient characteristics in the sarcopenia group (n=34) and the non-sarcopenia group (n=14) are shown in Table I. A total of 34 patients (70.8%) had invasion of the trachea or left main bronchus, nine patients (18.8%) had invasion of the aorta and 10 patients (20.8%) had invasion of other areas (recurrent nerve, carotid artery, lung, and vertebra) which were considered unresectable invaded organs. No patient had distant metastasis, and tumor in every patient was diagnosed as stage IIIC in the TNM classification (14).

There were no significant differences in patient characteristics other than body mass index (BMI). The BMI provided by patients was calculated on the day before chemoradiotherapy.
was lower in the group with sarcopenia than in the group without [18.4 (13.3-25.0) versus 22.8 (17.8-27.4) kg/m², p=0.001]. There were no differences in tumor factors between the two groups.

Response to chemoradiotherapy and adverse events. There were no significant differences in the incidence of severe adverse events or the dose reduction rate between the two groups (Table II). Discontinuation of chemoradiotherapy tended to be more frequent in the group with sarcopenia (11.8% versus 0%, p=0.088). Reasons for discontinuation were perforation of aorta, severe diarrhea and neutropenia, cancer death during chemoradiotherapy, and drug allergy in one case each in the sarcopenia group. Response rates

Table I. Patient characteristics of both sarcopenia and non-sarcopenia groups.

| Variable                          | Sarcopenia group (n=34) | Non-sarcopenia group (n=14) | p-Value |
|-----------------------------------|-------------------------|----------------------------|---------|
| Gender: M/F, n (%)                | 23 (67.7%)/11 (32.4%)   | 9 (64.3%)/5 (35.7%)         | 0.823   |
| Age (years)                       | 65.5 (41-79)            | 70.0 (53-77)                | 0.097   |
| Comorbidity, n (%)                |                         |                            |         |
| Cardiovascular disease            | 2 (5.9%)                | 0 (0%)                     | 0.234   |
| Pulmonary disease                 | 2 (5.9%)                | 0 (0%)                     | 0.234   |
| Diabetes mellitus                 | 3 (8.8%)                | 1 (7.1%)                   | 0.846   |
| PNI*                              | 48.8 (36.5-59.2)        | 49.7 (43.8-55.9)           | 0.919   |
| BMI (kg/m²)                       | 18.4 (13.3-25.0)        | 22.8 (17.8-27.4)           | 0.001   |
| BSA (m²)                          | 1.77 (1.30-2.13)        | 1.70 (1.29-2.04)           | 0.439   |
| GPS, n (%)                        |                         |                            | 0.963   |
| 0                                 | 23 (67.7%)              | 10 (71.4%)                 |         |
| 1                                 | 8 (23.5%)               | 3 (21.4%)                  |         |
| 2                                 | 3 (8.8%)                | 1 (7.1%)                   |         |
| CRP (mg/dl)*                      | 0.373 (0.024-8.677)     | 0.628 (0.033-3.527)        | 0.786   |
| Alb (mg/dl)*                      | 4.15 (3.1-4.8)          | 4.15 (3.4-4.6)             | 0.665   |
| NLR*                              | 3.31 (1.41-15.9)        | 3.13 (1.14-7.05)           | 0.461   |
| Tumor size (mm)*                  | 60.0 (30-120)           | 60.0 (20-92)               | 1.000   |
| Invaded organ, n (%)              |                         |                            |         |
| Trachea/main bronchus             | 23 (67.6%)              | 12 (85.7%)                 | 0.182   |
| Aorta                             | 6 (17.6%)               | 3 (21.4%)                  | 0.767   |
| Other                             | 8 (23.5%)               | 2 (14.3%)                  | 0.461   |
| Lymph node metastasis, n (%)      | 12 (85.7%)              | 31 (91.2%)                 | 0.583   |
| SCC (ng/ml)*                      | 1.65 (0.6-15.1)         | 1.3 (0.6-10.6)             | 0.615   |

PNI: Prognostic nutritional index, GPS: Glasgow prognostic score, NLR: neutrophil:lymphocyte ratio, BMI: body mass index, BSA: body surface area, CRP: C-reactive protein, Alb: albumin, SCC: squamous cell carcinoma *Data are median (range).

Table II. Adverse effects, response to chemoradiotherapy and administration of subsequent chemotherapy of both the sarcopenia and the non-sarcopenia groups.

| Variable                          | Sarcopenia group (n=34) | Non-sarcopenia group (n=14) | p-Value |
|-----------------------------------|-------------------------|----------------------------|---------|
| Grade 3 or 4 AE, n (%)            | 5 (14.7%)               | 3 (21.4%)                  | 0.577   |
| Dose reduction, n (%)             | 9 (26.5%)               | 6 (42.9%)                  | 0.273   |
| Discontinuation, n (%)            | 4 (11.8%)               | 0 (0%)                     | 0.088   |
| RT dose (Gy)*                     | 59.4 (19.8-68.4)        | 59.4 (50.4-61)             | 0.945   |
| Response, n (%)                   |                         |                            |         |
| CR                                | 3 (8.8%)                | 4 (28.6%)                  | 0.092   |
| CR + PR                           | 14 (43.8%)              | 11 (78.6%)                 | 0.025   |
| Subsequent chemotherapy           |                         |                            |         |
| 2nd line                          | 19 (55.9%)              | 10 (71.4%)                 | 0.310   |
| 3rd line                          | 7 (20.6%)               | 5 (35.7%)                  | 0.271   |
| 4th line                          | 4 (11.8%)               | 1 (7.1%)                   | 0.633   |

AE: Adverse effect. PR: partial response. CR: complete response. RT: radiotherapy. *Data are median (range).
[complete response (CR) and partial response (PR)] were
significantly lower in the sarcopenia group than in the non-
sarcopenia group (43.8% versus 78.6%, p=0.025). Moreover,
the CR rate tended to be lower in the sarcopenia group (8.8%
versus 28.6%, p=0.092). After CR was confirmed, four
patients (two patients in each group) experienced recurrence:
two had local recurrence and two had distant metastasis.
There were no differences in administration of follow-up
chemotherapy between the two groups.

Nutritional support for both groups. As previously described,
nutritional support was administered for patients with poor
oral intake. Both the incidence of nutritional support and
nutritionally supported energy administration was significantly
higher in the sarcopenia group than the non-sarcopenia group.
Total intake energy, and the proportion of both body weight
change and SMI change during chemoradiotherapy were not
significantly different (Table III).

Overall survival. Overall survival rates of both groups are
shown in Figure 1. The overall survival rate was significantly
worse in the group with sarcopenia (at 3 years: 36.95% vs.
63.9%, p=0.018).

Prognostic factors for overall survival. Univariate analysis
for overall survival showed that male gender, discontinuation
of chemoradiotherapy, being a non-responder, and having
sarcopenia were significantly associated with poor overall
survival (Table IV).

The Cox proportional hazard regression model for overall
survival showed that being male and being a responder were
independent prognostic factors for poor overall survival in
these patients. However, sarcopenia was rejected as an
independent prognostic factor (Table V).

Discussion

This retrospective study showed that patients with
unresectable locally advanced esophageal cancer with
sarcopenia had worse responses to chemoradiotherapy and
poorer overall survival than the those without sarcopenia.
Although patients with sarcopenia received nutritional
support to an equivalent level to patients without sarcopenia,
this support appears to have had no effect.

Recently, data obtained from various large databases have
linked sarcopenia to a poor prognosis in patients with
gastrointestinal cancer (9). In addition, there is significant
evidence showing that sarcopenia is independently associated
with poor response to cancer therapy in pancreatic (18), breast
(19), colorectal (13, 20), and renal-cell (21), and hepatic (22)
cancer. Sarcopenia carries a high risk of morbidity (23-26) and
confers poor long-term survival after resection of esophageal
cancer (27-29). However, there is very little evidence showing
the correlation between sarcopenia and long-term outcomes in
patients with unresectable esophageal cancer undergoing
chemoradiotherapy. Harada et al. reported that patients with
esophageal cancer without lymph involvement had poor long-
term outcomes, however, their study included both
chemoradiotherapy and esophageal resection cases (7). To our knowledge, our retrospective study is the first report that shows the impact of sarcopenia on patients with unresectable locally advanced esophageal cancer. The mechanisms by which skeletal muscle depletion shortens the survival of patients with malignant cancer remain unclear. In the current study, the response rates were worse in the sarcopenia group than the non-sarcopenia group, which indicates that tumors in the sarcopenia group had poorer sensitivity to chemoradiotherapy despite nutritional support. In addition, a recent study has putatively linked skeletal muscle depletion to molecular phenotypic changes in factors such as tumor necrosis factor alpha, interleukin-6, and insulin-like growth factor 1 (7). Sarcopenia is considered the most relevant phenotypic feature of cancer cachexia, and thus might reflect the high malignancy of advanced esophageal cancer and lead to poor long-term results (7, 30). In addition, sarcopenia is a prominent feature of malnutrition due to cancer progression. Undernutrition has been reported to be as frequent as 79% in patients with advanced esophageal cancer before starting treatment (31). In these patients, anorexia and dysphagia are the main factors

### Table IV. Univariate analysis for overall survival.

| Variable                      | N   | 3-Year survival (%) | MST (months) | HR    | 95% CI          | p-Value |
|-------------------------------|-----|---------------------|--------------|-------|-----------------|---------|
| Gender                        |     |                     |              |       |                 |         |
| Female                        | 16  | 70.0                | NR           | 1     | 1.498-10.47     | 0.0039  |
| Male                          | 32  | 35.0                | 16.8         | 3.691 | 1.961-6.996     | 0.0009  |
| Adverse effect                |     |                     |              |       |                 |         |
| Grade 1, 2                    | 40  | 40.9                | 17.8         | 1     | 0.155-1.936     | 0.4816  |
| Grade 3,4                     | 8   | 62.5                | NR           | 0.659 | 0.340-1.277     | 0.340   |
| Dose reduction                |     |                     |              |       |                 |         |
| Yes                           | 15  | 57.5                | NR           | 1     | 0.764-5.825     | 0.1732  |
| No                            | 33  | 16.8                | 39.4         | 1.920 | 0.764-5.825     | 0.1732  |
| Discontinuation of CRT        |     |                     |              |       |                 |         |
| Yes                           | 4   | 0                   | 4.0          | 5.873 | 0.662-47.52     | 0.0234  |
| No                            | 44  | 47.9                | 24.8         | 1     | 1.329-18.59     | 0.0234  |
| CR                            |     |                     |              |       |                 |         |
| Yes                           | 7   | 64.3                | NR           | 0.383 |                 |         |
| No                            | 41  | 42.1                | 16.8         | 1     | 0.061-1.313     | 0.1408  |
| PR/CR                         |     |                     |              |       |                 |         |
| Yes                           | 25  | 60.2                | 60.2         | 0.389 |                 |         |
| No                            | 21  | 24.4                | 24.4         | 1     | 0.161-0.919     | 0.0317  |
| SCC                           |     |                     |              |       |                 |         |
| ≥1.5                          | 22  | 35.5                | 17.8         | 1.596 |                 |         |
| <1.5                          | 21  | 58.9                | 39.2         | 1     | 0.250-1.528     | 0.3022  |
| GPS                           |     |                     |              |       |                 |         |
| 0                             | 33  | 46.9                | 24.8         | 1     |                 |         |
| 1 or 2                        | 15  | 42.4                | 20.2         | 1.264 | 0.483-3.986     | 0.6136  |
| BMI                           |     |                     |              |       |                 |         |
| ≥10%                          | 12  | 32.1                | 17.8         | 1.310 |                 |         |
| <10%                          | 36  | 49.5                | 20.2         | 1     | 0.472-3.159     | 0.5788  |
| NLR                           |     |                     |              |       |                 |         |
| ≥2.5                          | 34  | 41.2                | 24.8         | 1.246 |                 |         |
| <2.5                          | 14  | 46.7                | 20.2         | 1     | 0.516-3.463     | 0.6384  |
| PNI                           |     |                     |              |       |                 |         |
| ≥40                           | 45  | 45.0                | NR           | 1     | 0.037-3.202     | 0.6756  |
| ≤40                           | 3   | 50.0                | 20.2         | 0.668 |                 |         |
| BMI                           |     |                     |              |       |                 |         |
| ≥20                           | 27  | 43.5                | 12.2         | 1.741 |                 |         |
| ≤20                           | 11  | 49.2                | 24.8         | 1     | 0.759-4.198     | 0.1913  |
| Muscle depletion during CRT   |     |                     |              |       |                 |         |
| ≥10%                          | 12  | 32.1                | 17.8         | 1.310 |                 |         |
| <10%                          | 36  | 49.5                | 20.2         | 1     | 0.472-3.159     | 0.5788  |

MST: Median survival, HR: hazard ratio, CI: confidence interval, NR: not reached (>50% patients surviving at study end), GPS: Glasgow prognostic score, NLR: neutrophil:lymphocyte ratio, PNI: prognostic nutritional index, PR: partial response, CR: complete response, BMI: body mass index, SCC: squamous cell carcinoma.

Sato et al: Sarcopenia in Esophageal Cancer

June 1, 2023
A previous study reported an association between sarcopenia and dose-limiting toxicity during neoadjuvant chemotherapy for esophageal cancer (10). Moreover, sarcopenia was reported to be associated with a high risk of adverse events during chemotherapy for metastatic breast and colorectal carcinoma (19, 20, 36). The reason for the frequent adverse events was that in a patient with a small lean compartment, a high drug dose is distributed in a small volume. Recent studies have shown that skeletal muscle volume decreases after neoadjuvant chemotherapy (37, 38), and 43.6% of patients show more than 10% of body weight volume decreases after neoadjuvant chemotherapy (37, 38), indicating skeletal muscle depletion routinely and to establish adequate nutritional support for patients with unresectable esophageal cancer before chemoradiotherapy. Thirdly, this was a single-institution study and the number of patients was small. Therefore, a multi-institutional study with more patients should be conducted.

In conclusion, sarcopenia may worsen the long-term prognosis of patients with unresectable locally advanced esophageal cancer. It is necessary to conduct a well-designed prospective trial to determine whether adequate nutritional support has a favorable impact on therapeutic outcomes in this population.

Conflicts of Interest

None.

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