in vivo *32*: 603-610 (2018)
doi:10.21873/invivo.11282

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

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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.

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

Human Subjects at the Yokohama City University School of Medicine (approval number: B180100023).

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/m^2 by slow drip infusion on days 1 and 29. 5-fluorouracil was administered at a dose of 700 mg/m^2 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 days1-5 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/m^2 on day 1 and cisplatin was administered at a dose of 60 mg/m^2 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/m^2 S-1 was administered orally for four consecutive weeks. This was followed by a drug-free-interval of 2 weeks. The cycles of chemotherapy were repeated until obvious progression of disease.

For fourth-line chemotherapy, paclitaxel was administered at a dose of 100 mg/m^2 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 esophagogastroduodenoscopy 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 (cm^2) and averaged for each patient. The muscle area normalized by the square of the patient's height (m^2) was defined as the skeletal muscle index (SMI) (cm^2/m^2) (9). Pre-defined cut-offs for sarcopenia (≤52.4 cm^2/m^2 for men and ≤38.5 cm^2/m^2 for women) were used to define sarcopenia (10, 13) and patients were subsequently divided into groups with and without saropenia. 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

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/m^2)	18.4 (13.3-25.0)	22.8 (17.8-27.4)	0.001
BSA (m^2)	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).

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/m^2, 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 III. *Nutritious status of the sarcopenia and non-sarcopenia groups.*

Variable	Sarcopenia group (n=34)	Non-sarcopenia group (n=14)	*p*-Value
Number of patients receiving nutritional support, n (%)	15 (44.1%)	1 (7.1%)	0.007
Nutritionally supported energy (kcal) (mean±SD)	564.4±789.0	107.1±400.9	0.017
Total intake energy (kcal) (mean±SD)	1513.6±367.1	1430.1±380.1	0.488
Body weight (%)*	98.9 (86.8-113.6)	98.7 (88.2-107.0)	0.696
SMI (%)*	99.1 (80.7-115.4)	93.7 (77.1-108.2)	0.250

SMI: Skeletal muscle index.*Data are median (range) difference between the start and end of chemoradiotherapy.

[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).

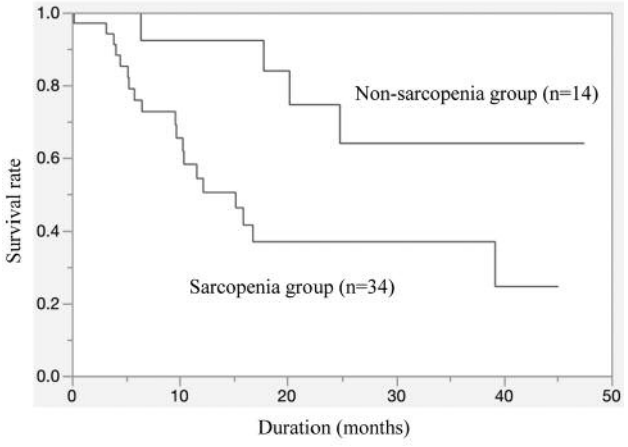

Figure 1. *Overall survival in patients with and without sarcopenia with unresectable locally advanced esophageal cancer treated with definitive chemoradiotherapy. The difference in overall survival between the sarcopenia group (n=34) and the non-sarcopenia group (n=14) was significant (36.95% vs. 63.9%, p=0.018).*

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

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		
Male	32	35.0	16.8	3.691	1.498-10.47	0.0039
Adverse effect						
Grade 1, 2	40	40.9	17.8	1		
Grade 3,4	8	62.5	NR	0.659	0.155-1.936	0.4816
Dose reduction						
Yes	15	57.5	NR	1		
No	33	16.8	39.4	1.920	0.764-5.825	0.1732
Discontinuation of CRT						
Yes	4	0	4.0	5.873		
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	0.483-2.986	0.6136
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	3	50.0	20.2	0.668		
≥40	45	45.0	NR	1	0.037-3.202	0.6756
Sarcopenia						
Yes	34	37.0	15.2	3.474		
No	14	63.9	NR	1	1.283-12.17	0.0125
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.

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 cheoradiotherapy 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 V. *Multivariate analysis for overall survival.*

Variable	HR	95% CI	*p*-Value
Gender			
Male	4.293	1.446-15.92	0.0075
Female	1		
Discontinuation of CRT			
Yes	3.249	0.476-13.60	0.1954
No	1		
PR/CR			
Yes	0.253	0.096-0.656	0.0050
No	1		
Sarcopenia			
Yes	2.326	0.813-8.374	0.1202
No	1		

HR: Hazard ratio, CI: 95% confidence interval, PR: partial response, CR: complete response, CRT: chemoradiotherapy.

involved in the onset of undernutrition (32). Basically, limitation of oral intake can be caused by tumor obstruction. Undernutrition has been reported as a factor predictive of treatment discontinuation and poor outcomes in patients treated at the palliative stage (33-35). In the current study, there was no significant difference in nutritional status measurements, such as PNI and albumin level between groups. Sarcopenia might be an independent nutritional indicator which affects the long-term prognosis in patients with unresectable esophageal cancer.

A previous study reported an association between sarcopenic obesity 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 loss during definitive chemoradiotherapy for advanced esophageal cancer (39). Patients undergoing chemotherapy for gastrointestinal cancer who experience weight loss usually suffer more frequent and severe toxicities (33). In our study, patients with sarcopenia had a lower BMI combined with weight loss before chemotherapy. However, there was no significant difference in the incidence of severe toxicities or dose reduction between groups. Patients in the sarcopenia group received nutritional support appropriately and there were no differences in total energy intake, body weight loss, and SMI change between the two groups. Therefore, positive nutritional support may prevent severe weight loss, muscle depletion, and severe adverse events in patients with unresectable esophageal cancer who cannot maintain sufficient oral intake. As a result, pretreatment sarcopenia lost its role as an independent prognostic factor for overall survival in this population.

There were some limitations to this study. Firstly, it was a retrospective study. Secondly, nutritional support was administered to 44.1% patients in the sarcopenia group; however, the usefulness of nutritional support for patients with sarcopenia is still unclear. Moreover, the volume of nutritional support required to achieve adequacy is unknown. It is necessary to evaluate 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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Received January 5, 2018
Revised February 13, 2018
Accepted February 20, 2018