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**Original Article**

# Clinical mechanism of muscle mass loss during neoadjuvant chemotherapy in older patients with esophageal cancer: a prospective cohort study

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*SUMMARY.* **In older patients with locally advanced esophageal cancer (LAEC), loss of skeletal muscle mass during neoadjuvant chemotherapy (NAC) is associated with poor clinical outcomes. This study aimed to investigate factors associated with loss of skeletal muscle mass during NAC in older patients with LAEC. This was a single-center exploratory prospective cohort study. Consecutive patients aged ≥65 years with LAEC scheduled for curative esophagectomy after NAC were enrolled between October 2021 and December 2023. As a primary endpoint, loss of skeletal muscle mass index (ΔSMI: pre-NAC minus post-NAC value) was calculated from computed tomography images before and after NAC. Significant pre-NAC and during-NAC factors with ΔSMI were detected with a multivariate regression model. Statistical significance was considered as two-tailed $P<0.05$. A total of 69 patients were analyzed. The mean age was 72.9 years, and 53 (77%) were male. Mean SMI before and after NAC was 43.1 and 40.9 cm$^2$/m$^2$, and mean ΔSMI was 2.2 cm$^2$/m$^2$. In multivariate analysis, ΔSMI was associated with increased sitting time during NAC (per 1 min/day, adjusted coefficient 0.007, 95% confidence interval [CI] 0.001 to 0.013, $P=0.016$), decreased Geriatric Nutritional Risk Index during NAC (per 1 score, adjusted coefficient −0.146, 95% CI −0.213 to −0.013, $P=0.002$), and worsening decreased appetite during NAC (vs. no worsening, adjusted coefficient 1.571, 95% CI 0.279 to 2.862, $P=0.018$). It was hypothesized that the inactivity-related mechanism and malnutrition-related mechanism are important for skeletal muscle mass loss during NAC in older patients with LAEC.**

*KEY WORDS*: **chemotherapy, esophageal cancer, geriatrics, nutrition, rehabilitation.**

## INTRODUCTION

Death caused by gastrointestinal cancer was reported to account for more than one-third (35%) of all cancer-related deaths in 2018.[1] In particular, locally advanced esophageal cancer (LAEC) has a poor prognosis, with a reported 5-year survival rate of <70%.[2] One of the global standard treatments for patients with LAEC is esophagectomy following neoadjuvant chemotherapy (NAC).[2,3] However, esophagectomy following NAC has negative impacts on physical function, skeletal muscle mass, and quality of life[4–6] because this multidisciplinary cancer treatment is one of the most intense and demanding treatments available. The number of patients aged ≥65 years with LAEC has recently increased

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globally.[7] During cancer treatment, these older patients carry several risks for complications, adverse events, and dependence in daily life.[8,9] Therefore, there is an international need for evidential information to develop novel supportive care to prevent complications and adverse events of esophagectomy following NAC and to improve clinical outcomes, including health-related quality of life, in older patients with LAEC.[10]

Skeletal muscle mass has an impact on physical function, disability, and quality of life, important factors in older patients with cancer.[11,12] It was reported that the loss of skeletal muscle mass during NAC not only causes long-term delayed recovery of skeletal muscle mass but also negatively impacts postoperative pneumonia and 3-year survival rate through preoperative progression of physical frailty in older patients with LAEC.[4,13] However, there is not only no positive clinical trial of effect of prehabilitation during NAC to prevent the loss of skeletal muscle mass but also no research on the clinical mechanism of the loss of skeletal muscle mass during NAC in older patients with LAEC. Such information regarding clinical mechanisms contributes to the development of novel supportive care to prevent skeletal muscle mass loss and the progression of physical frailty during chemotherapy in older patients with cancer. This prospective cohort study aimed to investigate factors associated with loss of skeletal muscle mass during NAC in older patients with LAEC and thereby determine the clinical mechanism.

## METHODS

### Design and participants

This was a single-center exploratory prospective cohort study in a Japanese national cancer center. A total of 80 patients aged ≥65 years with clinical stage IB, II, III, or IV esophageal cancer without distant organ metastasis (Union for International Cancer Control tumor–node–metastasis [UICC–TNM] classification, 8th edition), who were scheduled for curative esophagectomy after NAC at the National Cancer Center East Hospital in Japan between October 2021 and December 2023 without untreated or undertreated duplicate cancer upon starting NAC, were consecutively included. Exclusion criteria were alteration of the treatment such as changing to chemoradiotherapy because of progression tumor during NAC, using a feeding tube in nutritional therapy, dropout of NAC, and clinical decline. This study was approved by the Research Ethics Committee of the National Cancer Center (2021-179) in accordance with the Declaration of Helsinki. All participants received verbal and written explanations regarding study procedures and signed an informed consent form upon agreement to participate.

### NAC and surgery

The NAC regimen was cisplatin + fluorouracil (FP), oxaliplatin + leucovorin + fluorouracil (FOLFOX), or docetaxel + cisplatin + fluorouracil (DCF). The FP regimen consisted of cisplatin (80 mg/m$^2$) on day 1 and fluorouracil (800 mg/m$^2$) on days 1–5 of a 21-day cycle. The FOLFOX regimen consisted of oxaliplatin (85 mg/m$^2$), leucovorin (200 mg/m$^2$), and a bolus of fluorouracil (400 mg/m$^2$) on day 1 and fluorouracil (2400 mg/m$^2$) on days 1–2 of a 21-day cycle. The DCF regimen consisted of docetaxel (70 mg/m$^2$) on day 1, cisplatin (70 mg/m$^2$) on day 1, and fluorouracil (750 mg/m$^2$) on days 1–5 of a 21-day cycle. Patients were scheduled to undergo two courses of FP, four courses of FOLFOX, or three courses of DCF, decided upon by oncologists according to the patients' physical condition and disease stage. Esophagectomy with three-field lymph node dissection was performed via open or minimally invasive surgery. The extent of lymph node dissection was similar for open thoracotomy and minimally invasive thoracoscopy. Esophageal reconstruction was usually performed via the substernal route using a gastric tube. In cases with a history of laparotomy, open surgery was performed.

### Skeletal muscle mass loss during NAC

The skeletal muscle mass index (SMI[14]) was used as a skeletal muscle mass indicator, which was calculated from computed tomography (CT) images at the level of L3. CT was performed twice in clinical practice, within 1 month before NAC and within 2 weeks after the last cycle of NAC. The cross-sectional area (−29 to 150 Hounsfield units) on CT images was measured in the skeletal muscle area using SliceOmatic (Image Labo, Saitama, Japan).[14] The SMI was calculated as cross-sectional skeletal muscle area ÷ (height$^2$). The SMI loss (ΔSMI) was used a primary endpoint, which was calculated as pre-NAC minus post-NAC SMI.

### Progression of physical frailty during NAC

We measured a physical function indicator and a disability indicator to evaluate physical frailty. The incremental shuttle walking test (ISWT)[15] and World Health Organization Disability Assessment Schedule (WHODAS) version 2.0,[16] within 4 weeks before starting NAC and within 3 weeks after last cycle of NAC, were measured as physical function and disability. The decline in ISWT (ΔISWT = pre-NAC value − post-NAC value) and worsening of WHODAS (ΔWHODAS = post-NAC value − pre-NAC value) were calculated as progression of physical frailty.

### Baseline factors

We also obtained the following information before NAC: age, sex, body mass index (BMI), high Charlson comorbidity index (CCI, ≥1),[4] low-G8 (≤14) score,[17] high Cancer and Aging Research Group (CARG, ≥10) score,[18] clinical stage (≥III),[4] clinical T factor (≥3)[4] and clinical N factor (positive)[4] according to UICC–TNM classification 8th edition, high C-reactive protein (CRP, ≥0.5 mg/dL),[4] high neutrophil-to-lymphocyte ratio (NLR, ≥3.5),[4] percent vital capacity (%VC), percent forced expiratory volume in 1 second (%FEV), moderate to vigorous physical activity (MVPA) and sitting time evaluated using Global Physical Activity Questionnaire (GPAQ),[19] and Geriatric Nutritional Risk Index (GNRI).[20] All factors were measured within 4 weeks before starting NAC. Cachexia at pretreatment was defined as BMI <21 kg/m$^2$ and presence of subdomain: CRP >0.5 mg/dL or presence of anorexia (National Cancer Institute Patient-Reported Outcome Common Terminology Criteria for Adverse Events version 1 [PRO-CTCAE]),[21] considering the Asian Working Group for Cachexia criteria.[22]

### During-NAC and post-NAC factors

We obtained the following information after NAC: low average relative dose intensity (RDI, <85),[23] high histological response of NAC (≥1b),[24] change in ΔCRP, ΔNLR, Δ%VC, Δ%FEV, Δsitting time, ΔMVPA, ΔGNRI during NAC (Δ = post-NAC value − pre-NAC value), and presence of hematologic toxicity (grade ≥ 1) during NAC (NCI CTCAE version 5.0).[25] Aggravation of physical symptoms during NAC was evaluated with PRO-CTCAE,[21] defined as attaining a higher grade at post-NAC than at pre-NAC in each subdomain. All post-NAC values were measured within 3 weeks after last cycle of NAC. Pathological stage (≥III),[4] pathological T factor (≥3),[4] and pathological N factor (positive) according to UICC–TNM classification 8th edition, and postoperative complications including pneumonia, anastomosis leakage, recurrent nerve paralysis, and others (Clavien–Dindo classification grade [CD grade])[26] within 30 days after surgery were assessed.

### Statistics

Descriptive statistics are presented as the number of people (%) and mean (standard deviation). The difference in SMI between pre-NAC and post-NAC was analyzed with a paired *t* test. We investigated the associated pre-NAC and during-NAC factors with ΔSMI, the primary endpoint in the present study, using a multivariate regression model to hypothesize the mechanism of skeletal muscle mass loss during NAC. The sample size was interpreted as 80 included patients, considering 10% excursion rate and potential use of seven explanatory variables (biological baseline factors, tumor factor, inflammatory factor, cancer treatment factor, toxicity factor, physical activity factor, and malnutrition-related factor) in multivariate regression analysis, given that this is an exploratory cohort study. Biological baseline factors (age, sex, G8, CARG score), tumor factors (clinical stage, T and N factors), inflammatory factors (CRP, NLR, ΔCRP, ΔNLR), cancer treatment factors (regimen, RDI, histological response), toxicity factors (hepatotoxicity, physical symptoms), physical activity factors (MVPA, sitting time, ΔMVPA, Δsitting time), and nutrition factors (GNRI, ΔGNRI) were used as potential factors for loss of skeletal muscle mass[27–30] in univariate analysis. Significant factors associated with ΔSMI were detected with a multivariate regression model, using potential factors with *P* <0.1 in univariate analysis and confounding factors (age, sex, regimen of NAC, and pre-NAC SMI). The characteristics of the significant associated factors were analyzed using a one-way analysis of variance or $\chi^2$ test. If the significant factor was a continuous variable, patients were then divided into two groups using the median value. To confirm that skeletal muscle mass loss during chemotherapy in older patients is a true physical frailty indicator, the associations of ΔSMI with ΔISWT and ΔWHODAS were analyzed using a multivariate regression model adjusted for age, sex, pre-NAC SMI, G8, clinical stage, regimen of NAC, RDI, histological response, and change in MVPA and GNRI during NAC. Statistical significance was considered as two-tailed *P* <0.05. All analyses were performed with R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Significant factors associated with skeletal muscle mass loss

A total of 69 patients were analyzed (Fig. 1). The mean SMI before and after NAC was 43.1 (SD 7.8) and 40.9 (7.6) cm$^2$/m$^2$, respectively; there was a significant difference ($P < 0.001$). The mean ΔSMI was 2.2 (2.6) cm$^2$/m$^2$. The mean ISWT before and after NAC was 418.7 (136.7) and 353.5 (133.8) m, and the mean ΔISWT was 65.2 (71.4) m. The mean WHODAS score before and after NAC was 13.6 (3.8) and 16.2 (6.9), and the mean ΔWHODAS was 2.7 (2.0). The mean age was 72.9 years, and DCF, FP, and FOLFOX regimens were administered to 46 (67%), 4 (6%), and 19 (27%) patients, respectively (Table 1). The mean BMI was 21.9 (2.7) kg/m$^2$ before NAC and 21.3 (2.8) kg/m$^2$ after NAC. The numbers of patients with response grade 0, 1a, and 1b-3 were 4 (6%), 20 (29%), and 45 (65%), respectively. In multivariate analysis, significant factors associated with loss of SMI were Δsitting time (per 1 min/day, adjusted coefficient 0.007, 95% confidence interval 0.001 to 0.013, $P = 0.016$), ΔGNRI (per 1 score, adjusted coefficient: −0.146, 95% confidence interval −0.213 to −0.013, $P = 0.002$), and worsening decreased appetite (vs. no worsening, adjusted coefficient 1.571, 95%

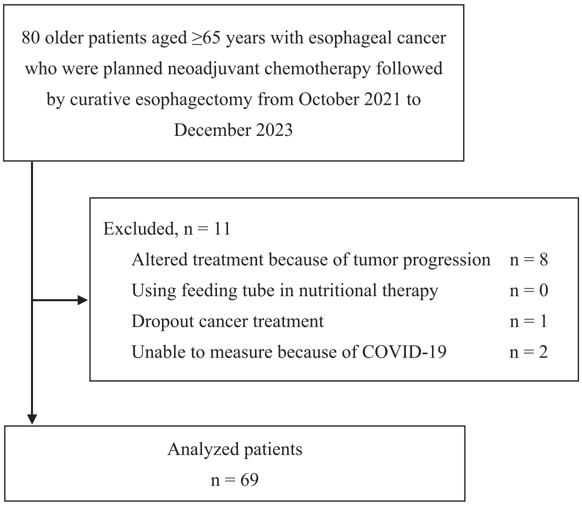


**Fig. 1** Recruitment flow diagram.

confidence interval 0.279 to 2.862, $P = 0.018$) (Table 1 and Fig. 2).

### Characteristics of significant factors associated with loss of skeletal muscle mass

There were significant differences in age, regimen, pre-NAC WHODAS, ΔMVPA, Δsitting time, ΔGNRI, ΔISWT, ΔWHODAS, ΔSMI, hematotoxicity of white blood cells (WBCs), presence of worsening mouth/throat sores, taste changes, shortness of breath, fatigue, number of worsening symptoms, and postoperative pneumonia between the groups of patients with non-large increase in sitting time (increase < median 60 min/week, $n = 34$) and large increase in sitting time (increase ≥ median 60 min/week, $n = 35$) (Table 2). There were significant differences in age, regimen, %VC, GNRI, ISWT, pre-NAC WHODAS, ΔCRP, Δsitting time, ΔGNRI, ΔISWT, ΔSMI, and hematotoxicity of WBCs between the groups of patients with non-large decrease in GNRI (score decrease <6.7, $n = 31$) and large decrease in GNRI (score decrease ≥6.7, $n = 30$) (Table 3). There were significant differences in Δsitting time, ΔISWT, ΔWHODAS, ΔSMI, presence of worsening difficulty in swallowing, mouth/throat sores, taste changes, decreased appetite, nausea, shortness of breath, fatigue, number of worsening symptoms, and postoperative pneumonia between the groups of patients with worsening appetite ($n = 46$) and no worsening appetite ($n = 23$) (Table 4).

### Confirmation of the association of skeletal muscle mass loss with physical frailty progression

Loss of SMI was confirmed to be significantly associated with ΔISWT (per 1 $cm^2/m^2$, adjusted coefficient 19.950, 95% confidence interval 14.299 to 25.601, $P < 0.001$) and ΔWHODAS (per 1 $cm^2/m^2$, adjusted coefficient 1.057, 95% confidence interval

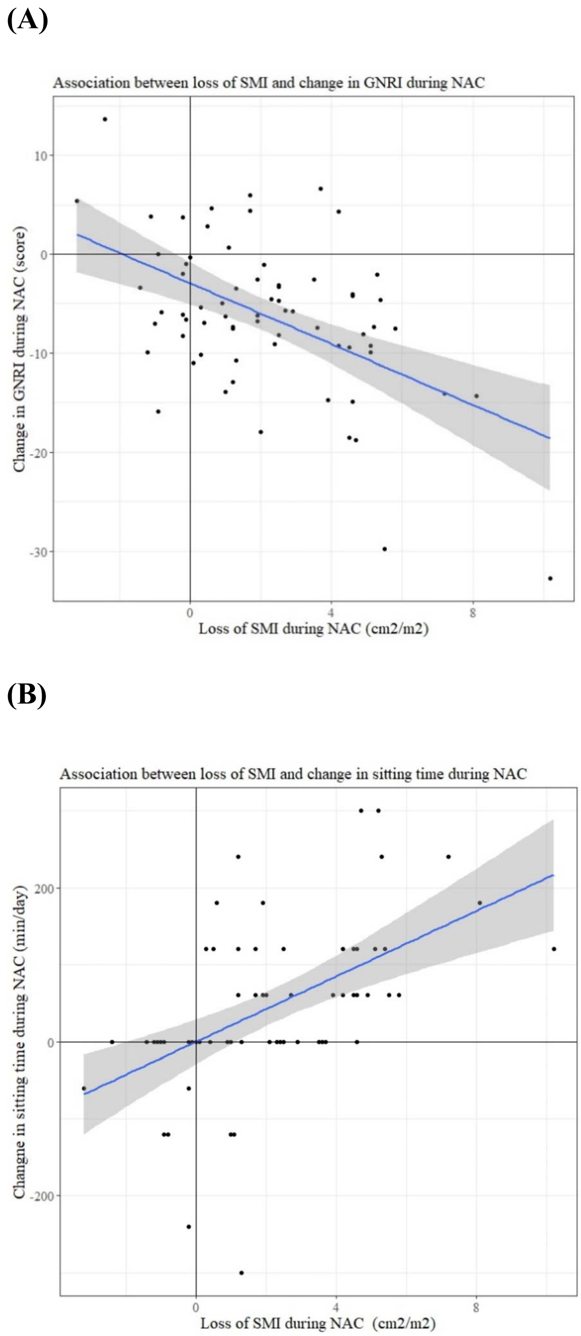


**Fig. 2** Association of loss of SMI with increase in sitting time and decrease in GNRI during NAC. Scatterplots and regression lines (gray areas: 95% confidence interval) of loss of SMI and increase in sitting time during NAC is indicated in (A), and loss of SMI and decrease in GNRI during NAC is indicated in (B).

0.553 to 1.560, $P < 0.001$), adjusted for age, sex, pre-NAC SMI, G8, clinical stage, regimen of NAC, RDI, histological response, and change in MVPA and GNRI during NAC (Table 5).

## DISCUSSION

This prospective cohort study is the first to investigate the factors associated with skeletal muscle mass loss during NAC in older patients with LAEC, with the

**Table 1** Association of all factors with skeletal muscle mass loss during NAC in univariate analysis

| Variables | | Values | Univariate analysis | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | | | β (95% CI) | P | β (95% CI) | \|B\| | VIF | P |
| Pre-NAC factors | Age (years) | 72.9 ± 4.4 | −0.092 (−0.232 to 0.049) | 0.197 | 0.028 (−0.102 to 0.159) | 0.049 | 1.576 | 0.665 |
| | Male | 53 (77%) | −0.242 (−1.227 to 1.711) | 0.743 | −1.200 (−2.609 to 0.208) | 0.199 | 1.714 | 0.093 |
| | DCF regimen | 46 (67%) | 0.967 (−0.328 to 2.263) | 0.141 | −0.429 (−1.653 to 0.794) | 0.079 | 1.613 | 0.485 |
| | SMI ($cm^2/m^2$) | 43.1 ± 7.8 | 0.083 (0.005 to 0.160) | 0.037* | 0.054 (−0.019 to 0.128) | 0.165 | 1.565 | 0.144 |
| | Low-G8 (≤14) | 41 (67%) | −0.839 (−2.140 to 0.461) | 0.200 | | | | |
| | High CARG (≥10) | 13 (21%) | −0.207 (−1.647 to 1.232) | 0.770 | | | | |
| | High CCI (≥1) | 25 (36%) | 0.728 (−0.551 to 2.007) | 0.260 | | | | |
| | cStage ≥III | 56 (81%) | 0.620 (−0.960 to 2.200) | 0.437 | | | | |
| | cT factor ≥ 3 | 50 (72%) | 0.125 (−1.264 to 1.513) | 0.859 | | | | |
| | cN factor positive | 59 (86%) | 0.772 (−0.981 to 2.534) | 0.383 | | | | |
| | High-CRP (≥0.5 mg/dL) | 19 (28%) | −0.350 (−1.736 to 1.037) | 0.620 | | | | |
| | High-NLR (≥3.5) | 36 (52%) | −0.271 (−1.512 to 0.969) | 0.660 | | | | |
| | Cachexia | 11 (16%) | −1.003 (−2.681 to 0.674) | 0.237 | | | | |
| | MVPA (min/week) | 384.6 ± 397.2 | −0.001 (−0.002 to 0.001) | 0.470 | | | | |
| | Sitting time (min/day) | 454.4 ± 212.6 | 0.001 (−0.002 to 0.004) | 0.501 | | | | |
| | GNRI (score) | 101.0 ± 9.5 | 0.029 (−0.037 to 0.094) | 0.380 | | | | |
| During-NAC factors | Low-RDI (<85%) | 44 (64%) | −0.345 (−1.634 to 0.943) | 0.590 | | | | |
| | High-response grade (≥1b) | 45 (65%) | 0.748 (−0.542 to 2.038) | 0.251 | | | | |
| | ΔCRP (mg/dL) | 0.40 ± 2.52 | 0.188 (−0.060 to 0.431) | 0.130 | | | | |
| | ΔNLR (ratio) | −1.79 ± 2.60 | −0.130 (−0.109 to 0.368) | 0.280 | | | | |
| | ΔMVPA (min/week) | −106 ± 348 | −0.001 (−0.003 to 0.001) | 0.200 | | | | |
| | Δsitting time (min/day) | 40 ± 105 | 0.012 (0.007 to 0.175) | <0.001** | 0.007 (0.001 to 0.013) | 0.288 | 1.303 | 0.016* |
| | ΔGNRI (score) | −6.3 ± 7.7 | −0.169 (−0.238 to −0.099) | <0.001** | −0.146 (−0.213 to −0.013) | 0.440 | 1.710 | <0.001** |
| | Presence of hematotoxicity | | | | | | | |
| | Decreasing Hb | 23 (33%) | 0.083 (−1.234 to 1.400) | 0.900 | | | | |
| | Decreasing WBC | 52 (75%) | 0.871 (−0.554 to 2.295) | 0.227 | | | | |
| | Decreasing plate | 8 (12%) | 0.928 (−0.997 to 2.8529) | 0.340 | | | | |
| | Neutropenia | 47 (68%) | 0.818 (−0.499 to 2.134) | 0.219 | | | | |
| | Febrile neutropenia | 8 (12%) | −0.811 (−2.739 to 1.117) | 0.400 | | | | |
| | Presence of worsening symptom | | | | | | | |
| | Difficulty swallowing | 12 (17%) | 1.669 (0.083 to 3.255) | 0.039* | 0.727 (−0.727 to 2.180) | 0.108 | 1.473 | 0.321 |
| | Mouth/throat sores | 23 (33%) | 1.491 (0.226 to 2.756) | 0.022* | −0.432 (−1.559 to 0.695) | 0.080 | 1.368 | 0.446 |
| | Taste changes | 35 (51%) | 1.978 (0.834 to 3.121) | <0.001** | 0.898 (−0.272 to 2.068) | 0.176 | 1.659 | 0.130 |
| | Decreased appetite | 23 (33%) | 2.450 (1.277 to 3.623) | <0.001** | 1.571 (−0.279 to 2.862) | 0.291 | 1.796 | 0.018* |
| | Nausea | 12 (17%) | 0.890 (−0.730 to 2.515) | 0.280 | | | | |
| | Vomiting | 4 (6%) | −0.217 (−2.872 to 2.438) | 0.870 | | | | |
| | Constipation | 22 (32%) | 0.684 (−0.637 to 2.005) | 0.310 | | | | |
| | Diarrhea | 10 (14%) | 0.515 (−1.243 to 2.273) | 0.560 | | | | |
| | Shortness of breath | 20 (29%) | 2.204 (0.946 to 3.462) | <0.001** | 0.367 (−1.140 to 1.874) | 0.065 | 2.266 | 0.627 |
| | Fatigue | 29 (42%) | 1.629 (0.486 to 2.822) | 0.008** | −0.969 (−2.346 to 0.408) | 0.188 | 2.240 | 0.164 |

*$P < 0.05$; **$P < 0.01$. Abbreviations: β, regression coefficient; CARG, Cancer and Aging Research Group; CI, confidence interval; CCI, Charlson comorbidity index; CRP, C-reactive protein; DCF, docetaxel + cisplatin + fluorouracil; %FEV, % force expiratory volume in 1 second; GNRI, geriatric nutritional risk index; Hb, hemoglobin; MVPA, moderate to vigorous physical activity; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; RDI, relative dose intensity; SMI, skeletal muscle mass index; %VC, % vital capacity; WBC, white blood cell.

**Table 2** Characteristics of the patients with large increase in sitting time during NAC (increase ≥60 min/day)

| Variables | | Large increase in sitting time $n = 35$ | Non-large increase in sitting time $n = 34$ | $P$ |
|---|---|---|---|---|
| Pre-NAC factors | Age (years) | 71.7 ± 4.1 | 74.2 ± 4.34 | 0.016** |
| | Male | 24 (69%) | 29 (85.3) | 0.174 |
| | DCF regimen | 29 (83%) | 17 (50.0) | 0.008* |
| | SMI ($cm^2/m^2$) | 44.0 ± 7.7 | 42.1 ± 7.9 | 0.303 |
| | Low-G8 (≤14) | 22 (63%) | 24 (71%) | 0.670 |
| | High CARG (≥10) | 8 (23%) | 9 (26%) | 0.945 |
| | High CCI (≥1) | 13 (37%) | 12 (35%) | 1.000 |
| | cStage ≥ III | 30 (86%) | 26 (76%) | 0.500 |
| | cT factor ≥ 3 | 27 (77%) | 23 (68%) | 0.540 |
| | cN factor positive | 32 (91%) | 27 (80%) | 0.282 |
| | Cachexia | 4 (11%) | 7 (21%) | 0.478 |
| | High-CRP (≥0.5 mg/dL) | 12 (34%) | 7 (21%) | 0.315 |
| | High-NLR (≥3.5) | 17 (49%) | 19 (56%) | 0.714 |
| | %VC (%) | 107.1 ± 16.5 | 107.3 ± 18.9 | 0.951 |
| | %FEV (%) | 78.8 ± 9.2 | 75.6 ± 14.6 | 0.287 |
| | MVPA (min/week) | 341 ± 349 | 429 ± 442 | 0.366 |
| | Sitting time (min/week) | 457 ± 230 | 468 ± 196 | 0.835 |
| | GNRI (score) | 100.4 ± 8.9 | 101.5 ± 10.2 | 0.651 |
| | ISWT (m) | 433 ± 150 | 403 ± 122 | 0.368 |
| | WHODAS (score) | 14.7 ± 4.7 | 12.4 ± 2.1 | 0.015* |
| During-NAC factors | Low-RDI (<85%) | 21 (60%) | 23 (68%) | 0.682 |
| | High-response grade (≥1b) | 22 (63%) | 23 (68%) | 0.869 |
| | ΔCRP (mg/dL) | 0.47 ± 2.84 | 0.33 ± 2.20 | 0.818 |
| | ΔNLR (ratio) | −1.36 ± 1.74 | −2.24 ± 3.23 | 0.164 |
| | Δ%VC (%) | −2.8 ± 10.9 | 2.9 ± 20.7 | 0.159 |
| | Δ%FEV (%) | −2.9 ± 10.6 | −3.1 ± 10.4 | 0.942 |
| | ΔMVPA (min/week) | −188 ± 343 | −21 ± 338 | 0.046* |
| | Δsitting time (min/day) | 123 ± 70 | −33 ± 73 | <0.001** |
| | ΔGNRI (score) | −8.6 ± 8.6 | −3.9 ± 6.0 | 0.010* |
| | Decline in ISWT (m) | 105 ± 69 | 24 ± 47 | <0.001** |
| | Worsening of WHODAS (score) | 4.4 ± 5.9 | 0.8 ± 2.1 | 0.002** |
| | Loss of SMI ($cm^2/m^2$) | 3.6 ± 2.3 | 0.7 ± 1.8 | <0.001** |
| | Presence of hematotoxicity | | | |
| | Decreasing Hb | 16 (46%) | 7 (21%) | 0.050 |
| | Decreasing WBC | 31 (89%) | 21 (62%) | 0.021* |
| | Decreasing plate | 5 (14%) | 3 (9%) | 0.740 |
| | Neutropenia | 28 (80%) | 19 (56%) | 0.059 |
| | Febrile neutropenia | 5 (14%) | 3 (9%) | 0.740 |
| | Presence of worsening symptom | | | |
| | Difficulty swallowing | 8 (23%) | 4 (12%) | 0.369 |
| | Mouth/throat sores | 18 (51%) | 5 (15%) | 0.003** |
| | Taste changes | 24 (69%) | 11 (32%) | 0.006** |
| | Decreased appetite | 15 (43%) | 8 (23%) | 0.148 |
| | Nausea | 8 (23%) | 4 (11%) | 0.369 |
| | Vomiting | 3 (9%) | 1 (3%) | 0.627 |
| | Constipation | 12 (34%) | 10 (29%) | 0.860 |
| | Diarrhea | 7 (20%) | 3 (9%) | 0.329 |
| | Shortness of breath | 18 (51%) | 2 (6%) | <0.001** |
| | Fatigue | 21 (60%) | 8 (23%) | 0.005** |
| | Number of worsening symptoms | 4.5 ± 2.9 | 2.1 ± 2.3 | <0.001** |
| Postoperative factors | pStage ≥ III | 15 (43%) | 14 (41%) | 1.000 |
| | pT factor ≥ 3 | 13 (38%) | 13 (38%) | 1.000 |
| | pN factor positive | 19 (56%) | 15 (44%) | 0.467 |
| | Complications CD grade ≥ III | 6 (17%) | 6 (18%) | 1.000 |
| | Anastomosis leakage | 4 (11%) | 1 (6%) | 0.696 |
| | Pneumonia | 13 (37%) | 4 (12%) | 0.030* |
| | Recurrent nerve paralysis | 12 (34%) | 7 (21%) | 0.315 |

*$P < 0.05$; **$P < 0.01$. Abbreviations: CARG, Cancer and Aging Research Group; CI, confidence interval; CCI, Charlson comorbidity index; CD, Clavien–Dindo classification; CRP, C-reactive protein; DCF, docetaxel + cisplatin + fluorouracil; %FEV, % force expiratory volume in 1 second; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; ISWT, incremental shuttle walking test; MVPA, moderate to vigorous physical activity; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; RDI, relative dose intensity; SMI, skeletal muscle mass index; %VC, % vital capacity; WBC, white blood cell; WHODAS, WHO Disability Assessment Schedule.

aim of hypothesizing the clinical mechanism of such loss of skeletal muscle mass during NAC. Currently, aging, disease and inflammation, physical activity, and nutrition are well known to lead to changes in skeletal muscle mass of older patients.[27] In the field of cancer, treatment-related factors such as mitochondrial toxicity and muscle atrophy, anorexia, nausea, and inactivity caused by chemotherapy,

**Table 3** Characteristics of the patients with large decrease in GNRI during NAC (score decrease ≥6.25)

| Variables | | Large decrease in GNRI $n = 34$ | Non-large decrease in GNRI $n = 35$ | $P$ |
|---|---|---|---|---|
| pre-NAC factors | Age (years) | 71.1 ± 3.42 | 74.7 ± 4.6 | 0.001** |
| | Male | 28 (82.4%) | 25 (71%) | 0.430 |
| | DCF regimen | 29 (85%) | 17 (49%) | 0.003** |
| | SMI ($cm^2/m^2$) | 44.3 ± 8.6 | 41.9 ± 6.8 | 0.197 |
| | Low-G8 (≤14) | 19 (56%) | 27 (77%) | 0.106 |
| | High CARG (≥10) | 6 (18%) | 11 (31%) | 0.294 |
| | High CCI (≥1) | 11 (32%) | 14 (40%) | 0.682 |
| | cStage ≥ III | 28 (82%) | 28 (80%) | 1.000 |
| | cT factor ≥ 3 | 23 (68%) | 27 (77%) | 0.540 |
| | cN factor positive | 30 (88%) | 29 (83%) | 0.770 |
| | Cachexia | 5 (15%) | 6 (17%) | 1.000 |
| | High-CRP (≥0.5 mg/dL) | 7 (21%) | 12 (34%) | 0.315 |
| | High-NLR (≥3.5) | 15 (44%) | 21 (60%) | 0.280 |
| | %VC (%) | 111.7 ± 18.6 | 102.9 ± 15.5 | 0.037* |
| | %FEV (%) | 78.3 ± 10.0 | 76.1 ± 14.0 | 0.449 |
| | MVPA (min/week) | 357 ± 330 | 411 ± 456 | 0.570 |
| | Sitting time (min/day) | 473 ± 236 | 451 ± 189 | 0.657 |
| | GNRI (score) | 103.4 ± 8.4 | 98.5 ± 10.0 | 0.030* |
| | ISWT (m) | 456 ± 150 | 382 ± 113 | 0.024* |
| | WHODAS (score) | 14.1 ± 4.7 | 13.0 ± 2.6 | 0.238 |
| During-NAC factors | Low-RDI (<85%) | 22 (65%) | 22 (63%) | 1.000 |
| | High-response grade (≥1b) | 25 (73%) | 20 (57%) | 0.240 |
| | ΔCRP (mg/dL) | 1.23 ± 2.51 | −0.41 ± 2.30 | 0.006** |
| | ΔNLR (ratio) | −1.45 ± 1.59 | −2.1 ± 3.29 | 0.287 |
| | Δ%VC (%) | 0.8 ± 20.8 | −0.8 ± 11.5 | 0.693 |
| | Δ%FEV (%) | −4.50 ± 10.5 | −1.56 ± 10.3 | 0.245 |
| | ΔMVPA (min/week) | −138 ± 369 | −74.6 ± 329 | 0.454 |
| | Δsitting time (min/week) | 76 ± 93 | 17 ± 111 | 0.020* |
| | ΔGNRI (score) | −11.8 ± 6.1 | −0.9 ± 4.7 | <0.001** |
| | Decline in ISWT (m) | 83 ± 83 | 48 ± 54 | 0.045* |
| | Worsening of WHODAS (score) | 3.6 ± 6.1 | 1.8 ± 2.9 | 0.123 |
| | Loss of SMI ($cm^2/m^2$) | 2.9 ± 2.8 | 1.4 ± 2.1 | 0.013* |
| | Presence of hematotoxicity | | | |
| | Decreasing Hb | 11 (32%) | 12 (34%) | 1.000 |
| | Decreasing WBC | 30 (88%) | 22 (63%) | 0.030* |
| | Decreasing plate | 4 (12%) | 4 (11%) | 1.000 |
| | Neutropenia | 27 (79%) | 20 (57%) | 0.084 |
| | Febrile neutropenia | 4 (12%) | 4 (11%) | 1.000 |
| | Presence of worsening symptom | | | |
| | Difficulty swallowing | 7 (21%) | 5 (14%) | 0.709 |
| | Mouth/throat sores | 14 (41%) | 9 (26%) | 0.268 |
| | Taste changes | 19 (56%) | 16 (46%) | 0.546 |
| | Decreased appetite | 11 (32%) | 12 (34%) | 1.000 |
| | Nausea | 6 (18%) | 6 (17%) | 1.000 |
| | Vomiting | 1 (3%) | 3 (9%) | 0.627 |
| | Constipation | 10 (29%) | 12 (34%) | 0.860 |
| | Diarrhea | 5 (15%) | 5 (14%) | 1.000 |
| | Shortness of breath | 14 (41%) | 6 (17%) | 0.053 |
| | Fatigue | 15 (44%) | 14 (40%) | 0.918 |
| | Number of worsening symptoms | 3.6 ± 3.2 | 3.0 ± 2.5 | 0.376 |
| Postoperative factors | pStage ≥ III | 16 (47%) | 13 (38%) | 0.555 |
| | pT factor ≥ 3 | 13 (38%) | 13 (38%) | 1.000 |
| | pN factor positive | 17 (50%) | 17 (50%) | 1.000 |
| | Complications CD grade ≥ III | 7 (21%) | 5 (14%) | 0.709 |
| | Anastomosis leakage | 2 (6%) | 4 (11%) | 0.696 |
| | Pneumonia | 11 (32%) | 6 (17%) | 0.235 |
| | Recurrent nerve paralysis | 11 (32%) | 8 (23%) | 0.540 |

*$P < 0.05$; **$P < 0.01$. Abbreviations: CARG, Cancer and Aging Research Group; CI, confidence interval; CCI, Charlson comorbidity index; CD, Clavien–Dindo classification; CRP, C-reactive protein; DCF, docetaxel + cisplatin + fluorouracil; %FEV, % force expiratory volume in 1 second; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; ISWT, incremental shuttle walking test; MVPA, moderate to vigorous physical activity; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; RDI, relative dose intensity; SMI, skeletal muscle mass index; %VC, % vital capacity; WBC, white blood cell; WHODAS, WHO Disability Assessment Schedule.

and cancer-related factors such as cachexia, are also well known to influence change in skeletal muscle mass.[28–30] However, there is no research on which factors truly impact skeletal muscle mass loss during NAC in older patients with LAEC from which to conjecture the actual clinical mechanism. We show in this study that loss of skeletal muscle mass during NAC was associated with increased

**Table 4** Characteristics of the patients with worsening appetite during NAC

| Variables | | Worsening appetite $n = 46$ | Non-worsening appetite $n = 23$ | $P$ |
|---|---|---|---|---|
| pre-NAC factors | Age (years) | 73.2 ± 4.5 | 72.8 ± 4.4 | 0.745 |
| | Male | 20 (87%) | 33 (72%) | 0.267 |
| | DCF regimen | 16 (70%) | 30 (65%) | 0.928 |
| | SMI ($cm^2/m^2$) | 44.2 ± 7.4 | 42.5 ± 8.0 | 0.401 |
| | Low-G8 (≤14) | 14 (61%) | 32 (70%) | 0.652 |
| | High CARG (≥10) | 6 (26%) | 11 (24%) | 1.000 |
| | High CCI (≥1) | 12 (52%) | 13 (28%) | 0.092 |
| | cStage ≥ III | 17 (74%) | 39 (85%) | 0.446 |
| | cT factor ≥ 3 | 15 (65%) | 35 (76%) | 0.505 |
| | cN factor positive | 18 (78%) | 41 (89%) | 0.397 |
| | Cachexia | 10 (21%) | 1 (4%) | 0.131 |
| | High-CRP (≥0.5 mg/dL) | 7 (30%) | 12 (26%) | 0.924 |
| | High-NLR (≥3.5) | 12 (52%) | 24 (52%) | 1.000 |
| | %VC (%) | 106.1 ± 16.6 | 107.7 ± 18.2 | 0.720 |
| | %FEV (%) | 76.6 ± 13.8 | 77.5 ± 11.4 | 0.766 |
| | MVPA (min/week) | 391 ± 435 | 381 ± 382 | 0.927 |
| | Sitting time (min/day) | 469 ± 182 | 458 ± 228 | 0.840 |
| | GNRI (score) | 103.4 ± 8.3 | 99.7 ± 9.9 | 0.132 |
| | ISWT (m) | 437 ± 152 | 409 ± 129 | 0.437 |
| | WHODAS (score) | 14.0 ± 3.0 | 13.3 ± 4.2 | 0.507 |
| During-NAC factors | Low-RDI (<85%) | 12 (52%) | 32 (70%) | 0.250 |
| | High-response grade (≥1b) | 17 (74%) | 28 (61%) | 0.421 |
| | ΔCRP (mg/dL) | 0.10 ± 1.39 | 0.55 ± 2.93 | 0.496 |
| | ΔNLR (ratio) | −1.74 ± 1.81 | −1.82 ± 2.94 | 0.906 |
| | Δ%VC (%) | −3.8 ± 10.4 | 1.9 ± 18.8 | 0.183 |
| | Δ%FEV (%) | −4.4 ± 10.4 | −2.3 ± 10.5 | 0.437 |
| | ΔMVPA (min/week) | −168 ± 275 | −75 ± 378 | 0.299 |
| | Δsitting time (min/week) | 99 ± 100 | 19 ± 100 | 0.003** |
| | ΔGNRI (score) | −7.5 ± 8.1 | −5.7 ± 7.5 | 0.349 |
| | Decline in ISWT (m) | 106 ± 76 | 44 ± 60 | <0.001** |
| | Worsening of WHODAS (score) | 5.3 ± 6.9 | 1.3 ± 2.4 | 0.001** |
| | Loss of SMI ($cm^2/m^2$) | 3.8 ± 2.4 | 1.4 ± 2.2 | <0.001** |
| | Presence of hematotoxicity | | | |
| | Decreasing Hb | 6 (26%) | 17 (37%) | 0.527 |
| | Decreasing WBC | 17 (74%) | 35 (76%) | 1.000 |
| | Decreasing plate | 4 (17%) | 4 (9%) | 0.506 |
| | Neutropenia | 16 (70%) | 31 (67%) | 1.000 |
| | Febrile neutropenia | 3 (13%) | 5 (11%) | 1.000 |
| | Presence of worsening symptom | | | |
| | Difficulty swallowing | 8 (35%) | 4 (9%) | 0.018* |
| | Mouth/throat sores | 13 (56%) | 10 (22%) | 0.009** |
| | Taste changes | 20 (87%) | 15 (33%) | <0.001** |
| | Decreased appetite | 23 (100%) | 0 (0%) | <0.001** |
| | Nausea | 8 (35%) | 4 (9%) | 0.018* |
| | Vomiting | 3 (13%) | 1 (2%) | 0.202 |
| | Constipation | 9 (39%) | 13 (28%) | 0.523 |
| | Diarrhea | 4 (17%) | 6 (13%) | 0.904 |
| | Shortness of breath | 13 (56%) | 7 (15%) | 0.001** |
| | Fatigue | 18 (78%) | 11 (24%) | <0.001** |
| | Number of worsening symptoms | 5.9 ± 2.3 | 2.0 ± 2.1 | <0.001** |
| Postoperative factors | pStage ≥ III | 10 (43%) | 19 (41%) | 1.000 |
| | pT factor ≥ 3 | 5 (23%) | 21 (46%) | 0.120 |
| | pN factor positive | 12 (54%) | 22 (52%) | 0.795 |
| | Complications CD grade ≥ III | 2 (9%) | 10 (22%) | 0.312 |
| | Anastomosis leakage | 2 (9%) | 4 (8%) | 1.000 |
| | Pneumonia | 10 (44%) | 7 (15%) | 0.023 |
| | Recurrent nerve paralysis | 7 (30) | 12 (26%) | 0.924 |

*$P < 0.05$; **$P < 0.01$. Abbreviations: CARG, Cancer and Aging Research Group; CI, confidence interval; CCI, Charlson comorbidity index; CD, Clavien–Dindo classification; CRP, C-reactive protein; DCF, docetaxel + cisplatin + fluorouracil; %FEV, % force expiratory volume in 1 second; GNRI, Geriatric Nutritional Risk Index; Hb, hemoglobin; ISWT, incremental shuttle walking test; MVPA, moderate to vigorous physical activity; NAC, neoadjuvant chemotherapy; NLR, neutrophil-to-lymphocyte ratio; RDI, relative dose intensity; SMI, skeletal muscle mass index; %VC, % vital capacity; WBC, white blood cells; WHODAS, WHO Disability Assessment Schedule.

sitting time among physical activity factors, decline in GNRI among nutritional factors, and appetite loss among physical symptom factors during NAC, with a dose-dependent relationship, in older patients with LAEC. Additionally, these inactivity-related mechanisms and malnutrition-related mechanisms including decline in GNRI and appetite loss were shown to perhaps be caused by a complex of intensity

**Table 5** Association of skeletal muscle mass loss with progression of physical frailty during NAC

| | Variables | Association with worsening WHODASΔ | | Association with decline in ISWTΔ | |
|---|---|---|---|---|---|
| | | $\beta$ (95% CI) | $P$ | $\beta$ (95% CI) | $P$ |
| Pre-NAC factors | Age (years) | −0.085 (−0.401 to 0.231) | 0.590 | −1.816 (−5.364 to 1.731) | 0.308 |
| | Male | 2.584 (−0.600 to 5.769) | 0.109 | 11.374 (−24.370 to 47.118) | 0.525 |
| | SMI before NAC ($cm^2/m^2$) | −0.027 (−0.213 to 0.158) | 0.767 | −0.179 (−2.259 to 1.901) | 0.863 |
| | Low-G8 (≤14) | 2.796 (0.126 to 5.466) | 0.040* | 23.525 (−6.440 to 53.491) | 0.121 |
| | cStage ≥ III | −2.237 (−5.427 to 0.954) | 0.165 | −37.865 (−73.673 to −2.057) | 0.039* |
| | DCF regimen | −1.545 (−4.267 to 1.176) | 0.259 | 13.321 (−17.223 to 44.866) | 0.385 |
| During-NAC factors | Low-RDI (<85%) | −0.198 (−2.466 to 2.069) | 0.861 | 19.204 (−6.247 to 44.654) | 0.136 |
| | High-response grade (≥1b) | 1.570 (−0.764 to 3.906) | 0.182 | −18.803 (−45.006 to 7.401) | 0.156 |
| | Change in MVPAΔ | 0.001 (−0.002 to 0.004) | 0.632 | −0.014 (−0.048 to 0.020) | 0.421 |
| | Change in GNRIΔ | −0.106 (−2.874 to 0.076) | 0.247 | −1.247 (−3.286 to 0.791) | 0.421 |
| | Loss of SMIΔ ($cm^2/m^2$) | 1.057 (0.553 to 1.560) | <0.001** | 19.950 (14.299 to 25.601) | <0.001** |

*$P < 0.05$; **$P < 0.01$. Abbreviations: $\beta$, regression coefficient; CI, confidence interval; DCF, docetaxel + cisplatin + fluorouracil; GNRI, geriatric nutritional risk index; MVPA, moderate to vigorous physical activity; NAC, neoadjuvant chemotherapy; SMI, skeletal muscle mass index.

of regimen, physical symptoms, and adverse events of NAC.

Mechanical stress to muscle fibers caused by physical activity, which could alter muscle mass volume via an alteration in the protein synthesis and degradation balance, is an important factor in changes in skeletal muscle mass.[31,32] In fact, increased sitting time along with decreased physical activity time was shown to be associated with skeletal muscle mass loss in older adults in a systematic review.[33] Therefore, in older patients with LAEC, decreased mechanical stress to muscle fibers with increased sitting time may be an especially important factor in the loss of skeletal muscle mass during NAC. In the present study, the group with a large increase in sitting time had significantly higher worsening rates of two chemotherapy-related physical symptoms that induce inactivity, namely, fatigue (60% vs. 23%) and shortness of breath (51% vs. 6%), in comparison with counterparts with no large increase in sitting time. The group with large increase in sitting time also had a significantly higher number of worsening symptoms during NAC than in the non-large increase group (mean 4.5 vs. 2.1 symptoms). Thus, the mechanism for increased sitting time may arise from chemotherapy-related physical symptoms and distress from multiple symptoms[34] that negatively impact skeletal muscle mass loss during NAC in older patients via decreased mechanical stress to muscle fibers.

Malnutrition-related mechanism during NAC was also one of the main mechanisms for skeletal muscle mass loss. The malnutrition-related mechanism may consist of two pathways, catabolism imbalance caused by chemotherapy and decreased food intake via appetite loss. Compared with the group with non-large decrease in GNRI, the patients with a large decrease in GNRI had significantly higher rates of decreasing WBCs (88% vs. 63%) and had larger increasing ΔCRP (mean 1.23 vs. −0.41 mg/dL) during NAC. It was previously reported that the DCF regimen specifically induced leukocytopenia (84% to 97%) with high incidence rates.[35,36] Additionally, the group with a large decrease in GNRI had an overwhelmingly higher rate of DCF regimen (85% vs. 49%) than counterparts with a non-large decrease in GNRI. In recent studies, a multiple anticancer drug regimen was reported to cause treatment-related myotoxicity, which directly impacts skeletal muscle by interference in signal transduction and dysregulation of anabolic–catabolic balance at the tissue level.[37] Thus, decline in GNRI may have reflected over-catabolism, such as protein wasting with infection and inflammation induced by hematotoxicity and treatment-related myotoxicity, from a high-intensity regimen such as the DCF regimen consisting of three anticancer drugs. Decreased food intake via appetite loss is also an important pathway for the malnutrition-related mechanism. Patients with worsening appetite during NAC had significantly higher rates of worsening difficulty in swallowing (35% vs. 9%), mouth/throat sores (56% vs. 22%), taste changes (87% vs. 33%), nausea (35% vs. 9%), shortness of breath (56% vs. 15%), and fatigue (78% vs. 24%) than those without worsening appetite. The appetite loss may also be caused by multiple factors, including swallowing, oral pain, dysgeusia, inactivity, and fatigue during NAC in the present study.

Tumor-related factors, including cachexia, clinical tumor stage, response to chemotherapy, and inflammatory and immune biomarkers, were not significant for loss of skeletal muscle mass during NAC in older patients. There may be two reasons for this. First, the subjects of the present study had non-metastatic resectable cancer. The stage of the tumor is an important factor for cancer cachexia because cancer cachexia is reported to be caused by increased catabolic mediators arising from tumor overexpression and tumor inflammation.[38] In metastatic unresectable esophageal cancer, the rate of cachexia was reported to be 52.9%.[39] In the present study, the rate of cachexia at baseline was 16% in patients with locally advanced esophageal cancer, implying that in this form of cancer the impact of cachexia on loss of skeletal muscle mass during NAC may be weak. Second, the rate of high (grade ≥ 1b) and poor (grade 0) response by chemotherapy was 64% and 6%, respectively, which means that tumor progression was relatively well controlled. Third, there was a diversity of physical vulnerability at baseline because of the older age of the subjects (mean age: 72.9 years). In fact, the rates of vulnerability were 67% in G8, 21% in CARG score, and 36% in CCI, meaning that the subjects were at high risk of toxicity by chemotherapy and had low resilience. Therefore, in older patients with locally advanced esophageal cancer, the change in lifestyle factors resulting from the toxicity of chemotherapy might regulate the loss of skeletal muscle mass during NAC rather than cachexia and tumor progression.

In older patients with cancer, skeletal muscle mass loss during chemotherapy is an important biomarker associated with postoperative complications, health outcomes, and prognosis, which reflected the preoperative physical frailty.[4,13,23] However, there is no global information on whether skeletal muscle mass during NAC truly reflects physical frailty in older patients. In the present study, skeletal muscle mass loss during NAC actually impacted progression of physical frailty during NAC, such as decline in ISWT and worsening of WHODAS score during NAC. To summarize the current study and previous literature, two main clinical mechanisms, namely, the inactivity-related mechanism and malnutrition-related mechanism, cause loss of skeletal muscle mass with physical frailty progression, which may negatively impact postoperative outcomes in older patients with LAEC[4,13,22] (Fig. 3). Hence, if appropriate prehabilitation during NAC to improve lifestyle factors, such as physical activity and nutrition status, is provided to these patients, not only skeletal muscle mass loss during NAC with progression of physical frailty but also poor postoperative outcomes may be preventable. In particular, our group with large increase in sitting time had not only significantly larger decline in ΔISWT (mean 105 vs. 24 m) and larger worse ΔWHODAS (mean 4.4 vs. 0.8 score) but also had a significantly higher rate of postoperative pneumonia (37% vs. 12%) compared with the group with non-large increase in sitting time. Therefore, increased sitting time may be especially important for skeletal muscle mass loss with progression of physical frailty not only during NAC but also for postoperative outcomes, which can also be considered as the critical target for the development of a novel supportive cancer care program during NAC in older patients with LAEC.

There are several limitations in the present study. First, it is a single-center observational study with a small sample size. The causality regarding the association of skeletal muscle mass loss with significant factors during NAC is unclear. The generalizability of these results needs to be confirmed by multicenter studies with larger sample sizes. Second, the present study did not focus on the molecular mechanism of skeletal muscle mass loss during NAC. Recent studies suggested that chemotherapy may cause loss of skeletal muscle mass through the myotoxic molecular mechanism.[29,37] Third, there is a lack of information regarding cachexia, malnutrition, and medication, including factors such as muscle strength, body weight loss percentage, polypharmacy, and SGLT2 inhibitors. Cachexia is possibly underestimated because of the lack of information on body weight loss percentage. Future studies need to investigate not only the clinical mechanism but also the molecular mechanism of skeletal muscle mass loss during chemotherapy in older patients with cancer. Finally, our study suggested a dose-dependent association between skeletal muscle mass loss and significant factors, but the optimal cutoff point of the significant factors for clinically defined loss of muscle mass was not clarified. The optimal cutoff point of significant factors will be a requirement for future interventional studies. However, the strong point of the present study is that it revealed significant factors associated with the clinical mechanism of skeletal muscle mass loss during chemotherapy using a prospective study design with informative assessments. As a result, it was suggested that loss of skeletal muscle mass is caused by the inactivity-related mechanism and malnutrition-related mechanism during NAC. Additionally, the inactivity-related mechanism may be especially important for skeletal muscle mass loss with progression of physical frailty during chemotherapy and the risk of postoperative pneumonia. Inactivity and partial physical symptoms including decreased appetite and fatigue can be improved by appropriate exercise therapy, nutritional therapy, and antiemetic drugs. Unfortunately, there is currently a lack of evidence and standard program of prehabilitation during NAC, so establishment of prehabilitation evidence should be a high research priority worldwide.[40,41] Altogether, this information will contribute to the development of a novel prehabilitation strategy during NAC and progress in exercise oncology during chemotherapy to improve health and clinical outcomes in geriatric oncology.

In conclusion, this prospective cohort study found an association of increasing sitting time, decreasing GNRI, and appetite loss during NAC with the loss of skeletal muscle mass during NAC in 69 older patients with LAEC. It was hypothesized that the inactivity-related mechanism and malnutrition-related mechanism during NAC are important clinical mechanisms

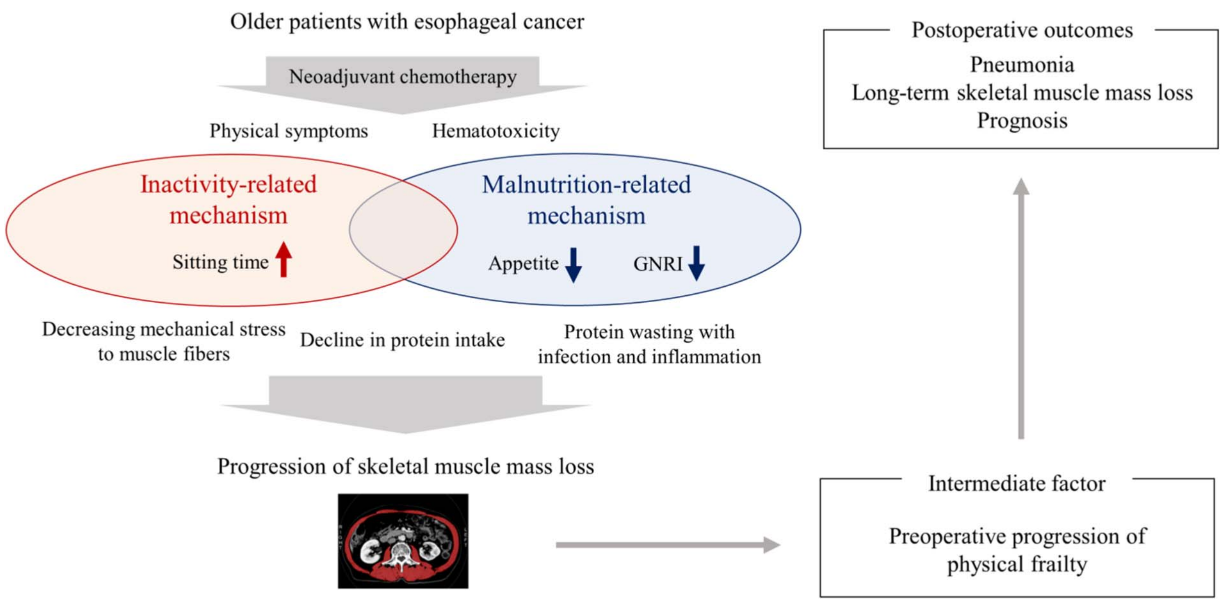


**Fig. 3** The mechanisms and clinical impacts of the skeletal muscle mass loss during neoadjuvant chemotherapy. The hypothesis that there are two main clinical mechanisms, namely the inactivity-related mechanism and malnutrition-related mechanism, causing loss of skeletal muscle mass and the skeletal muscle mass loss impacts postoperative outcomes through physical frailty progression in older patients with LAEC.

of skeletal muscle mass loss during NAC in older patients with LAEC.

## ABBREVIATIONS

CARG, Cancer and Aging Research Group
CCI, Charlson comorbidity index
CD, Clavien–Dindo classification
CRP, C-reactive protein
CTCAE, Common Terminology Criteria for Adverse Events
DCF, docetaxel + cisplatin + fluorouracil regimen
FEV, forced expiratory volume
FP, cisplatin + fluorouracil regimen
FOLFOX, oxaliplatin + leucovorin + fluorouracil regimen
GNRI, Geriatric Nutritional Risk Index
GPAQ, Global Physical Activity Questionnaire
ISWT, incremental shuttle walking test
LAEC, locally advanced esophageal cancer
MIS, minimally invasive surgery
MVPA, moderate to vigorous physical activity
NAC, neoadjuvant chemotherapy
NLR, neutrophil-to-lymphocyte ratio
RDI, average relative dose intensity
SMI, skeletal muscle mass index
VC, vital capacity
WHODAS, World Health Organization Disability Assessment Schedule

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## AUTHOR CONTRIBUTIONS

Tsuyoshi Harada (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Writing—original draft, Writing—review & editing), Tetsuya Tsuji (Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing—review & editing), Junya Ueno (Data curation, Investigation, Methodology, Supervision, Writing—review & editing), Nobuko Konishi (Data curation, Investigation, Writing—review & editing), Takumi Yanagisawa (Data curation, Investigation, Writing—review & editing), Nanako HIjikata (Data curation, Investigation, Project administration, Supervision, Writing—review & editing), Aiko Ishikawa (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing), Kakeru Hashimoto (Conceptualization, Methodology, Project administration, Writing—review & editing), Hitoshi Kagaya (Conceptualization, Project administration, Supervision, Writing—review & editing), Noriatsu Tatematsu (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing), Daisuke Kotani (Conceptualization, Data curation, Investigation, Methodology, Writing—review & editing), Takashi Kojima (Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing—review & editing), Sadamoto Zenda (Conceptualization, Methodology, Project administration, Supervision, Writing—review & editing), and Takeo Fujita (Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing—review & editing).

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