STROBE Statement—checklist of items that should be included in reports of observational studies

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|  | Item No. | Recommendation | Page  No. | Relevant text from manuscript |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | 2 | examined retrospectively as a case-control study. |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2,3 | BACKGROUND  Previous reports have focused on muscle mass as a prognostic factor in esophageal cancer.  AIM  To investigate how preoperative body type influenced the prognosis of patients with esophageal squamous cell carcinoma who underwent neoadjuvant chemotherapy (NAC) and surgery.  METHODS  The subjects were 131 patients with clinical stage II/III esophageal cancer who underwent subtotal esophagectomy after NAC. Skeletal muscle mass and quality were calculated from computed tomography images prior to NAC, and their statistical association with long-term outcomes was examined retrospectively as a case-control study.  RESULTS  The disease-free survival rates in the low psoas muscle mass index (PMI) group *vs* the high PMI group were 41.3% *vs* 58.8% (*P* = 0.036), respectively. In the high intramuscular adipose tissue content (IMAC) group *vs* the low IMAC group, the disease-free survival rates were 28.5% *vs* 57.6% (*P* = 0.021), respectively. The overall survival (OS) rates for low PMI *vs* high PMI were 41.3% *vs* 64.5% (*P* = 0.008), respectively, and for high IMAC *vs* low IMAC were 29.9% *vs* 61.9% (*P* = 0.024), respectively. Analysis of the outcomes of the OS rate revealed significant differences in those age 60 years or older (*P* = 0.018), pT3 or deeper (*P* = 0.021), or with lymph node metastasis-positivity (*P* = 0.006), aside from PMI and IMAC. Significant differences were noted from multivariate analysis in cases that were pT3 or deeper [hazard ratio (HR): 1.966, 95% confidence interval (CI): 1.089–3.550, *P* = 0.025), lymph node metastasis-positivity (HR: 2.154, 95%CI: 1.118–4.148, *P* = 0.022), low PMI (HR: 2.266, 95%CI: 1.282–4.006, *P* = 0.005), and high IMAC (HR:2.089, 95%CI: 1.036–4.214, *P* = 0.022).  CONCLUSION  Skeletal muscle mass and muscle quality before NAC in esophageal squamous cell carcinoma are significant prognostic factors of the OS. |
| Introduction | | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3,4 | Esophageal cancer continues to have a poor prognosis, with a low 5-year survival rate of 20%[1]. Poor prognostic factors are due to the tendency of the cancer to metastasize at an early stage[2,3] and to easily invade nearby vital organs such as the lungs, large blood vessels, heart, and trachea, indicating the cancer is already advanced at the time of diagnosis[1,4]. Therefore, the standard treatment is a combination of chemotherapy and radiotherapy in addition to surgery[5]. However, the prognosis remains poor.  In recent years, preoperative sarcopenia has been identified as a factor that reduces short-term postoperative prognosis and outcomes after gastrointestinal cancer surgery[6]. Sarcopenia is defined as the loss of function associated with muscle mass loss and quality[7]. Factors such as cancer status, underlying disease, advanced age, and sex are involved. Preoperative muscle mass loss has been reported as a postoperative complication or prognostic factor in gastric[8], hepatocellular[9], biliary[10], pancreatic[11], and colorectal cancers[12]. Recently, it has been suggested that, in addition to muscle mass, fatty degeneration of muscle and muscle quality changes affect prognosis[13]. Low skeletal muscle mass has been reported to influence the occurrence of postoperative respiratory complications in esophageal cancer[14-16] and is a factor in poor short-term outcomes[17,18].  Esophageal cancer is often complicated by preoperative nutritional deficits due to reduced oral intake caused by stenosis. Therefore, sarcopenia is often complicated preoperatively[19]. In addition, esophageal cancer surgery is highly invasive, which promotes catabolism creating a nutritional disadvantage[20]. Moreover, the multidisciplinary treatment combinations of chemotherapy and radiotherapy used with esophageal cancer can also contribute to nutritional impairment[21].  Multidisciplinary treatment for esophageal cancer is available in a variety of forms, including pre- and postoperative chemotherapy[22] and preoperative chemoradiotherapy[23,24]. The multidisciplinary approach is used in Europe and the United States for adenocarcinoma; in Japan and East Asian countries, however, this is more common for squamous cell carcinoma[4]. In Japan, preoperative chemotherapy and subtotal esophagectomy with three-field lymph node dissection is the standard treatment[5]. Therefore, assessing the impact of sarcopenia on short-term and long-term outcomes after esophageal cancer surgery requires a consistent examination of the disease and treatment context.  The present study included Japanese males with squamous cell carcinoma of the esophagus who underwent preoperative chemotherapy and subtotal esophagectomy with three-field lymph node dissection as the standard therapy. We examined the effect on long-term prognosis of changes in muscle mass and quality before preoperative chemotherapy. |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4 | The present study included Japanese males with squamous cell carcinoma of the esophagus who underwent preoperative chemotherapy and subtotal esophagectomy with three-field lymph node dissection as the standard therapy. We examined the effect on long-term prognosis of changes in muscle mass and quality before preoperative chemotherapy. |
| Methods | | | |  |
| Study design | 4 | Present key elements of study design early in the paper | 7 | Postoperative complications were defined according to the Clavien-Dindo classification[27], with Clavien-Dindo grade ≥ 3 defined as the presence of complications. For analysis of outcomes, OS and disease-free survival (DFS) rates were used. |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 | Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal cancer. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1). |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls  *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants | 5 | Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal cancer. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1). |
| (*b*)*Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed  *Case-control study*—For matched studies, give matching criteria and the number of controls per case | 5 | Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal cancer. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1). |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6 | Age, body mass index (BMI), Performance Status, and American Society of Anesthesiologists-Physical Status were determined from the medical records of the patients. The white blood cell count, neutrophil count, lymphocyte count, high sensitivity C-reactive protein level, and serum albumin level were investigated in preoperative blood chemistry data. From the following data, neutrophil-to-lymphocyte ratio (used as a nutrition index), Prognostic Nutritional Index, Geriatric Nutritional Risk Index, and modified Glasgow prognostic score were calculated as evaluation criteria. |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | *6* | *For skeletal muscle mass measurement, CT images before NAC were used. The bilateral psoas muscle areas were measured at the third lumbar vertebral level through tracing using Digital Imaging and Communications in Medicine viewer software, EV Invite® (PSP Corporation, Tokyo, Japan) (Figure 2). The value calculated by dividing the psoas muscle area by the square of the height was determined as the psoas muscle mass index (PMI) [= (cross-sectional area of bilateral psoas muscle)/(height)2 (cm2/m2)].*  *For skeletal muscle quality measurement using CT values, the bilateral multifidus muscles were traced at the third lumbar vertebral level (the same as the level of the psoas muscle cross-sectional area measurement), and the mean CT value of this region was calculated. In addition, subcutaneous fat was traced at four sites at the same level, and the mean CT value was determined. The mean CT value of the multifidus muscle was divided by the mean CT value of the subcutaneous fat at the four sites, and the calculated value was regarded as the intramuscular adipose tissue content (IMAC) [＝ mean CT value of bilateral multifidus muscle (HU)/mean CT value of four points of subcutaneous fat (HU)].* |
| Bias | 9 | Describe any efforts to address potential sources of bias | 6,7 | In this study, a receiver operating characteristic curve against overall survival (OS) was prepared using precalculated PMI with the optimum cutoff value of PMI set at 4 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with PMI < 4 and PMI ≥ 4 were designated as belonging to the low and high PMI groups, respectively, and compared.  Similarly, a receiver operating characteristic curve for IMAC was prepared, and the optimum cutoff value was set at 0.36 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with IMAC ≥ -0.36 and IMAC < -0.36 were designated as belonging to the high and low IMAC groups, respectively. |
| Study size | 10 | Explain how the study size was arrived at | 5 | Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal cancer. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1). |

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| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 6,7 | In this study, a receiver operating characteristic curve against overall survival (OS) was prepared using precalculated PMI with the optimum cutoff value of PMI set at 4 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with PMI < 4 and PMI ≥ 4 were designated as belonging to the low and high PMI groups, respectively, and compared.  Similarly, a receiver operating characteristic curve for IMAC was prepared, and the optimum cutoff value was set at 0.36 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with IMAC ≥ -0.36 and IMAC < -0.36 were designated as belonging to the high and low IMAC groups, respectively. |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 7 | For statistical analysis, SPSS® Statistics (Version 22.0; IBM Corp., Armonk, NY, United States) was used. All variables were presented as median values. In univariate analysis, continuous and non-continuous variables were analyzed using the Mann-Whitney *U* test and *χ2*test, respectively. Survival curves were prepared using the Kaplan-Meier method. For multivariate analysis, the log rank test was used, and analysis was performed using the Cox proportional hazards model. *P* values < 0.05 were regarded as significant. |
| (*b*) Describe any methods used to examine subgroups and interactions | 7 | For statistical analysis, SPSS® Statistics (Version 22.0; IBM Corp., Armonk, NY, United States) was used. All variables were presented as median values. In univariate analysis, continuous and non-continuous variables were analyzed using the Mann-Whitney *U* test and *χ2*test, respectively. Survival curves were prepared using the Kaplan-Meier method. For multivariate analysis, the log rank test was used, and analysis was performed using the Cox proportional hazards model. *P* values < 0.05 were regarded as significant. |
| (*c*) Explain how missing data were addressed | 5 | Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal cancer. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1). |
| (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed  *Case-control study*—If applicable, explain how matching of cases and controls was addressed  *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy | 5 | Of the 182 consecutive esophageal cancer patients who underwent esophagectomy between January 2009 and December 2013 at our hospital in Aomori, Japan, 131 were recruited for the study. In our hospital, one surgeon specializes in upper gastrointestinal surgery and performs 30 or more esophageal cancer surgeries per year. The selected subjects underwent subtotal esophagectomy with three-field lymph node dissection after completion of two courses of 5-fluorouracil plus cisplatin as neoadjuvant chemotherapy (NAC) for clinical stage II/III esophageal cancer. They had no residual tumors. Six patients with positive resection margins were excluded (Figure 1). |
| (*e*) Describe any sensitivity analyses | 6,7 | In this study, a receiver operating characteristic curve against overall survival (OS) was prepared using precalculated PMI with the optimum cutoff value of PMI set at 4 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with PMI < 4 and PMI ≥ 4 were designated as belonging to the low and high PMI groups, respectively, and compared.  Similarly, a receiver operating characteristic curve for IMAC was prepared, and the optimum cutoff value was set at 0.36 (area under the curve: 0.538, sensitivity: 61.0%, specificity: 78.3%). Patients with IMAC ≥ -0.36 and IMAC < -0.36 were designated as belonging to the high and low IMAC groups, respectively. |
| Results | | | | |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 7,8 | ***Patients’ characteristics***  The median age of the 131 patients was 64 years (range: 44-78 years), and the median BMI was 21.4 kg/m2 (range: 14.7-27.7 kg/m2). The clinical stages were stage II in 68 patients and stage III in 63 patients. The determination of the effect of NAC following the Response Evaluation Criteria in Solid Tumors guidelines was complete response in 2 patients, partial response in 79 patients, stable disease in 42 patients, and progressive disease in 8 patients. The rate of response to NAC was 61.8% compared with the disease control rate of 93.9%. The median postoperative number of hospitalization days was 18 d (range: 11-225 d); reoperation was performed on 4 patients (3.1%). There was no postoperative mortality at the hospital nor was there any mortality within 90 d following surgery. The median duration of postoperative follow-up was 60.9 mo (range: 3.9-100.3 mo).  The median PMI value was 4.94 (2.12-8.98). When the cases were classified setting the cutoff value of PMI at 4, the low and high PMI groups included 36 (27.5%) and 95 (72.5%) patients, respectively. In the between-group comparison, BMI and Geriatric Nutritional Risk Index was significantly lower in the low PMI group compared to the high PMI group, but no significant difference was noted for age, nutrition index, or chemotherapy response rates.  Similarly, in the comparison of IMAC, representing muscle quality, age was significantly higher in the high IMAC group. Details are presented in Table 1. |
| (b) Give reasons for non-participation at each stage | 7,8 | ***Patients’ characteristics***  The median age of the 131 patients was 64 years (range: 44-78 years), and the median BMI was 21.4 kg/m2 (range: 14.7-27.7 kg/m2). The clinical stages were stage II in 68 patients and stage III in 63 patients. The determination of the effect of NAC following the Response Evaluation Criteria in Solid Tumors guidelines was complete response in 2 patients, partial response in 79 patients, stable disease in 42 patients, and progressive disease in 8 patients. The rate of response to NAC was 61.8% compared with the disease control rate of 93.9%. The median postoperative number of hospitalization days was 18 d (range: 11-225 d); reoperation was performed on 4 patients (3.1%). There was no postoperative mortality at the hospital nor was there any mortality within 90 d following surgery. The median duration of postoperative follow-up was 60.9 mo (range: 3.9-100.3 mo).  The median PMI value was 4.94 (2.12-8.98). When the cases were classified setting the cutoff value of PMI at 4, the low and high PMI groups included 36 (27.5%) and 95 (72.5%) patients, respectively. In the between-group comparison, BMI and Geriatric Nutritional Risk Index was significantly lower in the low PMI group compared to the high PMI group, but no significant difference was noted for age, nutrition index, or chemotherapy response rates.  Similarly, in the comparison of IMAC, representing muscle quality, age was significantly higher in the high IMAC group. Details are presented in Table 1. |
| (c) Consider use of a flow diagram | 5 | Fig1 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 8 | Table1 |
| (b) Indicate number of participants with missing data for each variable of interest | 8 | Table1 |
| (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) | - | Not a COHORT study |
| Outcome data | 15\* | *Cohort study*—Report numbers of outcome events or summary measures over time | *-* | *Not a COHORT study* |
| *Case-control study—*Report numbers in each exposure category, or summary measures of exposure | *8* | *Table1* |
| *Cross-sectional study—*Report numbers of outcome events or summary measures | *-* | *Not a Cross-sectional study* |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 8,9 | ***Impact of muscle mass loss and muscle quality changes on DFS***  The 5-year DFS rates in the low and high PMI groups were 41.3% and 58.8%, respectively (*P* = 0.036). For IMAC, the 5-year DFS rates were 28.5% and 57.6% in the high and low IMAC groups, respectively (*P* = 0.021) (Figure 3).  ***Impact of muscle mass loss and muscle quality changes on OS***  The 5-year OS rates in the low and high PMI groups were 41.3% and 64.5%, respectively (*P* = 0.008), showing a significant difference between the two groups. Regarding IMAC, the 5-year OS rates of the high group *vs* low group were 29.9% and 61.9%, respectively (*P* = 0.024), which were significantly different (Figure 4).  Univariate analysis of the OS rate revealed significant differences in those age 60 or older (*P* = 0.018), pT3 or deeper (*P* = 0.021), and with lymph node metastasis-positivity (*P* = 0.006). When these factors were subjected to multivariate analysis using the Cox proportional hazards model, pT3 or deeper [hazard ratio (HR): 1.966, 95% confidence interval (CI): 1.089-3.550, *P* = 0.025], low PMI (HR: 2.266, 95%CI: 1.282-4.006, *P* = 0.005), and high IMAC (HR: 2.089, 95%CI: 1.036-4.214, *P* = 0.022) were significantly different and regarded as independent poor prognostic factors (Table 2). |
| (*b*) Report category boundaries when continuous variables were categorized | 8,9 | Table2 |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 8,9 | ***Impact of muscle mass loss and muscle quality changes on DFS***  The 5-year DFS rates in the low and high PMI groups were 41.3% and 58.8%, respectively (*P* = 0.036). For IMAC, the 5-year DFS rates were 28.5% and 57.6% in the high and low IMAC groups, respectively (*P* = 0.021) (Figure 3).  ***Impact of muscle mass loss and muscle quality changes on OS***  The 5-year OS rates in the low and high PMI groups were 41.3% and 64.5%, respectively (*P* = 0.008), showing a significant difference between the two groups. Regarding IMAC, the 5-year OS rates of the high group *vs* low group were 29.9% and 61.9%, respectively (*P* = 0.024), which were significantly different (Figure 4).  Univariate analysis of the OS rate revealed significant differences in those age 60 or older (*P* = 0.018), pT3 or deeper (*P* = 0.021), and with lymph node metastasis-positivity (*P* = 0.006). When these factors were subjected to multivariate analysis using the Cox proportional hazards model, pT3 or deeper [hazard ratio (HR): 1.966, 95% confidence interval (CI): 1.089-3.550, *P* = 0.025], low PMI (HR: 2.266, 95%CI: 1.282-4.006, *P* = 0.005), and high IMAC (HR: 2.089, 95%CI: 1.036-4.214, *P* = 0.022) were significantly different and regarded as independent poor prognostic factors (Table 2). |

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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 8,9 | Table2 |
| Discussion | | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 9 | The first finding of the present study was that lower skeletal muscle mass (low PMI) and changes in skeletal muscle quality (high IMAC) before preoperative chemotherapy had an impact on OS. |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 9 | However, unlike CT imaging before preoperative chemotherapy, these methods require additional examination and raise the issue of invasive radiation exposure[29]. These measurement methods are not standardized for measuring muscle mass[8,30]. In addition, it has been reported that it is difficult to standardize and assess muscle quality[31-33]. |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 9,10,11 | The first finding of the present study was that lower skeletal muscle mass (low PMI) and changes in skeletal muscle quality (high IMAC) before preoperative chemotherapy had an impact on OS. To assess skeletal muscle mass, a cross-sectional area of the psoas muscle at the level of the lumbar spine L3 in the abdominal CT images before preoperative chemotherapy was used. Dual-energy X-ray absorptiometry and bioelectrical impedance analysis are methods to measure skeletal muscle mass. However, unlike CT imaging before preoperative chemotherapy, these methods require additional examination and raise the issue of invasive radiation exposure[29]. These measurement methods are not standardized for measuring muscle mass[8,30]. In addition, it has been reported that it is difficult to standardize and assess muscle quality[31-33].  In this study, the cross-sectional area of the psoas muscle at the lumbar L3 level was used to assess muscle mass. Essentially, it was necessary to assess muscle mass by volume rather than area. The cross-sectional area of the psoas muscle is maximal at the level of the lumbar spine L3 and thus can be assessed as representative of the volume[34,35]. There are systematic reviews/meta-analyses of sarcopenia using a technique that measures skeletal muscle mass at L3 in patients undergoing abdominal surgery. The method used to measure muscle mass in this study was reasonable because it is cited as a factor affecting perioperative complications and prognosis in previous reports[6,36,37].  The same lumbar spine L3 level in CT images used to assess skeletal muscle mass was also used to assess skeletal muscle. We calculated the degree of fat content within the multifidus muscle in those CT images from the CT values. For this method, muscle quantity and quality were assessed at the same L3 level as abdominal CT imaging studies. The advantage was that no additional metrics were needed to assess changes in quality as a new parameter.  One modality of assessing muscle quality from CT images is the IMAC method[38,39], which evaluates the degree of fat content in muscle and quantifies the degree of fat degeneration. Fat degeneration of muscle has been reported to correlate with muscle weakness and loss of function[40,41]; for this reason, it can be used to assess muscle quality. In fact, muscle quality changes, determined by the IMAC method, have been reported as poor prognostic factors in nonalcoholic fatty liver disease[38], liver transplantation[42,43], hepatocellular carcinoma[44,45], pancreatic cancer[46], and cholangiocarcinoma diseases[13,47]. As mentioned above, it is reasonable to employ this same technique to assess the status of fatty degenerative changes in muscle and the relationship to the prognosis of patients undergoing preoperative chemotherapy for esophageal cancer.  In the present study, the results showed that a decrease in skeletal muscle mass and muscle quality changes affected OS. However, from previous reports on sarcopenia, the mechanism by which it affects the prognosis remains unclear. A cancer-bearing state is considered a systemic, chronic inflammatory condition. This may lead to the secretion of inflammatory cytokines interleukin (IL)-6, IL-8, tumor necrosis factor-alpha (TNF-α), and myostatin, and this may affect the entire body[48]. Increased secretion of the proinflammatory cytokine IL-6 itself and IL-6 mediated by TNF-α has been reported to reduce skeletal muscle mass[49]. It has also been reported that myostatin is a cytokine that potently reduces skeletal muscle, and its secretion increases in chronic inflammatory conditions, resulting in a decrease in skeletal muscle mass[50]. We consider that the combination of the effects of these cytokines leads to a malignant cycle of decreased skeletal muscle mass in a cancer-bearing state.  From an immunological point of view, IL-6, IL-8, and TNF-α cytokines are involved. IL-6 decreases the function of dendritic cells and T lymphocytes[51]. IL-8 and TNF-α also induce immunosuppressive myeloid-derived suppressor cells[52,53]. The actions of these cytokines are thought to suppress host immunity. Conversely, the secretion of IL-15, which is important for the maintenance of natural killer cell function, is reduced as a result of a decrease in the skeletal muscle, which is a secretory organ[54]. This inhibits the function of natural killer cells[55]. A decrease in IL-15 has been reported to increase adipose tissue[56], which may be linked to fat degeneration in muscle. We hypothesize that the chronic inflammatory state, which is a cancer-bearing state as described above, reduces skeletal muscle from inflammatory cytokines and, at the same time, suppresses immunity, which may worsen the prognosis.  Fat degeneration of muscle (a change in muscle quality) causes an increase in adipose tissue and the secretion of transforming growth factor-beta (TGF-β)[57]. It has been shown that TGF-β has an inhibitory effect on immune system cells such as T cells, B cells, natural killer cells, and dendritic cells, resulting in a suppression of immunity against cancer[58,59]. We presume that the long-term immunosuppressed state caused by the muscle mass loss and muscle quality changes may have resulted in a poor prognosis. These results suggest that muscle-strengthening interventions for patients with poor muscle composition may improve their prognosis in the future. |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 11 | Fat degeneration of muscle (a change in muscle quality) causes an increase in adipose tissue and the secretion of transforming growth factor-beta (TGF-β)[57]. It has been shown that TGF-β has an inhibitory effect on immune system cells such as T cells, B cells, natural killer cells, and dendritic cells, resulting in a suppression of immunity against cancer[58,59]. We presume that the long-term immunosuppressed state caused by the muscle mass loss and muscle quality changes may have resulted in a poor prognosis. These results suggest that muscle-strengthening interventions for patients with poor muscle composition may improve their prognosis in the future. |
| Other information | |  | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 21 | The authors declare having no conflicts of interest. |

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.