Original Article

# Sarcopenia following concurrent chemoradiotherapy for locally advanced esophageal squamous cell carcinoma

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**Background:** Multimodality treatment using chemotherapy, radiotherapy and surgery is standard practice for locally advanced esophageal squamous cell carcinoma (ESCC). Sarcopenia commonly occurs in patients with esophageal cancer. The effect of concurrent chemoradiotherapy (CCRT) on sarcopenia in patients with locally advanced ESCC remains unclear. We aimed to evaluate the effect of CCRT on sarcopenia in locally advanced ESCC.

**Methods:** This study included patients with locally advanced ESCC who received CCRT without surgery between 2011–2020. Sarcopenia was assessed using the skeletal muscle index (SMI) at the third lumbar vertebra (L3), which includes the psoas, paraspinal, and abdominal wall muscles, based on cross-sectional computed tomography (CT) scans before and after CCRT.

**Results:** In total, 213 patients with locally advanced ESCC who did not undergo esophagectomy after CCRT were included. Before CCRT, 178 patients (83.6%) had sarcopenia, while 35 patients (16.4%) did not. Moreover, 17 patients (48.6%) in the non-sarcopenia group developed sarcopenia after CCRT. The SMI significantly decreased after CCRT in both the sarcopenia and non-sarcopenia groups. The median overall survival (OS) was 12.6–15.7 months in all groups. The incidence of baseline sarcopenia showed no significant association with survival or CCRT-related toxicity. Male, high N-stage and decreasing body mass index (BMI) after CCRT were associated with poor survival prognosis.

**Conclusions:** Most patients with locally advanced ESCC had sarcopenia. Moreover, CCRT was associated with sarcopenia. Therefore, assessing sarcopenia before treatment and initiating interventions for prevention or treatment of sarcopenia may improve sarcopenia status.

**Keywords:** Sarcopenia; skeletal muscle index (SMI); chemoradiotherapy; esophageal squamous cell carcinoma (ESCC)

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## Introduction

Esophageal cancer is one of the most common gastrointestinal diseases and can easily spread to the adjacent organs and other parts of the body. Esophageal cancer is the eighth most commonly diagnosed cancer and is the sixth leading cause of cancer death worldwide (1). To improve outcome of treatment, multimodality using chemotherapy, radiotherapy, and surgery have been included.

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength (2). It commonly occurs in patients with cancer and chronic diseases. It is often associated with a range of adverse health outcomes, including reduced quality of life, disability, and mortality (3). Additionally, it is considered an important predictive factor for the prognosis of many cancers (4). Few studies have investigated sarcopenia in patients with locally advanced esophageal squamous cell carcinoma (ESCC) undergoing concurrent chemoradiotherapy (CCRT). In patients with esophageal cancer, sarcopenia can be easily assessed using cross-sectional computed tomography (CT) scans. The psoas, paraspinal, and abdominal wall muscles are measured at level 3 of the lumbar spine (L3), the standard skeletal position for measuring total muscle volume (5). Moreover, in patients with esophageal cancer, cross-sectional images of the thorax and upper abdomen, sectioned at the L3 level, are assessed before and after treatment to evaluate cancer stage and determine the treatment response.

However, the impact of CCRT on sarcopenia before or after treatment in patients with locally advanced ESCC remains unclear. Therefore, this study was conducted to determine the effect of CCRT on sarcopenia in patients with locally advanced ESCC. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-87/rc).

### Highlight box

**Key findings**

- This study had a large number of focused patients diagnosed with locally advanced esophageal squamous cell carcinoma (ESCC), having received concurrent chemoradiotherapy (CCRT) without surgery.

**What is known and what is new?**

- We have found a high prevalence of sarcopenia both before and after CCRT.
- However, patients with and without sarcopenia showed no significant association with survival nor CCRT-related toxicity.
- Male, high N-stage and decreasing body mass index after CCRT were associated with poor survival prognosis.

**What is the implication, and what should change now?**

- Sarcopenia is a major health problem and should be of concern in patients with locally advanced ESCC who have received CCRT.
- Therefore, assessing sarcopenia in patients before CCRT and beginning interventions, such as nutrition and exercise, may prevent further sarcopenia after CCRT.

## Methods

### *Data source and patient selection*

In this retrospective study, clinical data were collected from 213 patients with locally advanced ESCC who did not undergo esophagectomy after CCRT at Songklanagarind Hospital (Faculty of Medicine, Prince of Songkla University Hospital), between January 1, 2011, and December 31, 2020. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was approved by the Human Research Ethics Committee of the Faculty of Medicine of Songkla University (No. REC.63-278-10-4). Informed consent was waived because of the retrospective nature of the study.

The inclusion criteria consisted of the following: (I) squamous cell carcinoma confirmed by pathology; (II) Eastern Cooperative Oncology Group (ECOG) performance status 0–2; (III) received 2–4 cycles of cisplatin/5-FU or carboplatin/5-FU with concurrent radiotherapy at 41.4–50.4 Gy. The exclusion criteria consisted of the following: (I) multi-primary cancer; (II) insufficient imaging data; (III) M1 stage patients; (IV) esophagectomy. After screening according to the inclusion and exclusion criteria, 213 cases met the enrollment conditions. The study flow diagram of patients is shown in *Figure 1*. A total of 213 patients did not receive an esophagectomy after their CCRT for many reasons, they mostly decided they did not want surgery, they were unfit for surgery after their CCRT, they had underlying diseases which impact the risk of postoperative complications, or their disease had progressed to unresectable after their CCRT. The staging was based on the eighth edition of the American Joint Committee on Cancer (AJCC) clinical TNM (cTNM) staging standard for esophageal cancer (6). Locally advanced ESCC was defined as cT2, N0 (high risk lesions: lymphovascular invasion, ≥3 cm, poorly

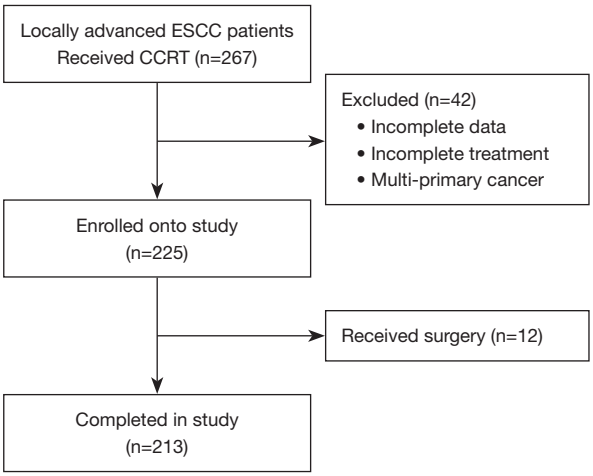


**Figure 1** Study flow diagram of patients. CCRT, concurrent chemoradiotherapy; ESCC, esophageal squamous cell carcinoma.

differentiated), M0 or cT1b-cT2, N+, M0 or cT3-T4a, any N, M0 (7).

### *Treatment and treatment outcomes*

The treatment methods for the study patients were as follows. After diagnosis, gastrostomy or jejunostomy was performed for nutritional support as 25–30 kcal/kg body weight per day (8). Patients then received CCRT following the National Comprehensive Cancer Network (NCCN) guideline, defined as 2–4 cycles of cisplatin/5-FU or carboplatin/5-FU with concurrent radiotherapy at 41.4–50.4 Gy (1.8–2.0 Gy/day) depending on the patient's dose (7). The skeletal muscle index (SMI) measurements were calculated from CT scans both pre-CCRT and post-CCRT 5–8 weeks after completion of CCRT (7). CCRT-related toxicity was evaluated according to the criteria of the World Health Organization (WHO) and Radiation Therapy Oncology Group (9).

### *SMI measurements*

The digital imaging and communications in medicine (DICOM) files were loaded into a program developed in MATLAB (MathWorks Inc., Natick, MA, USA) to select and segment the region of interest. The software implements semi-automatic segmentation using the well-known region growing method. Using this method, the seed point was placed within a selected region of the paravertebral muscle in the middle of L3. After the seed point is localized in a single layer, a contiguous pixel component is created within the outline of the segmentation (*Figure 2*).

The thresholds of the CT numerical values in the region were adjusted interactively. The outputs of the method were calculated area in square centimeters, the average of the CT number, and the standard deviation (SD) of the region. The results were exported to a table in an Excel file for further analysis. SMI at the L3 included the psoas, paraspinal, and abdominal wall muscles on cross-sectional CT scans before and after CCRT. The muscle area normalized by the square of the patient's height ($m^2$) was defined as SMI ($cm^2/m^2$). Sarcopenia was defined as an SMI of <43 $cm^2/m^2$ for body mass index (BMI) <25 $kg/m^2$ and <53 $cm^2/m^2$ for BMI ≥25 $kg/m^2$ in men and <41 $cm^2/m^2$ in women (2).

### *Statistical analysis*

For continuous variables, the mean and SD and median and interquartile range (IQR) were calculated. The chi-squared test and Fisher's exact test were used for comparisons between different categorical variables, and Student's *t*-test or the Wilcoxon rank sum test was used to analyze patient characteristics before and after CCRT. Cox analysis was used for survival, including potentially confounding variables. Statistical significance was set at $P<0.05$. All statistical analyses were performed using STATA software version 15 (StataCorp, College Station, TX, USA).

## Results

A total of 213 patients with locally advanced ESCC who did not undergo esophagectomy after CCRT were included in the study. The characteristics of the sarcopenia and non-sarcopenia groups before CCRT are presented in *Table 1*. Initially, 178 patients (83.6%) were in the sarcopenia group, and 35 patients (16.4%) were in the non-sarcopenia group. Moreover, 17 patients (48.6%) in the non-sarcopenia group developed sarcopenia after the CCRT. Patients with sarcopenia were older than those without. The prevalence of sarcopenia was significantly higher in men than in women. More than half of the participants had clinical stages cT3, any N, and M0 in both groups, with no differences in clinical stages, white blood cell counts, hematocrit levels, and creatinine levels between the groups. In contrast, levels of nutritional factors, weight, and BMI were significantly lower in the sarcopenia group.

A comparison of changes in SMI before and after CCRT

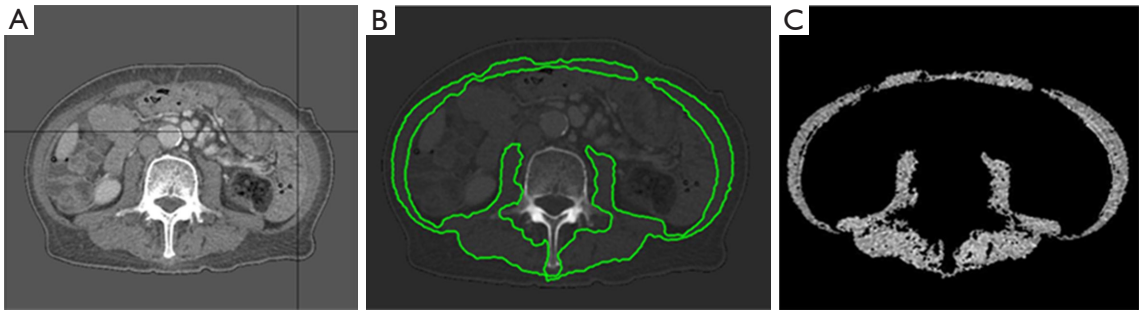


**Figure 2** SMI measurements. (A) A transverse CT scan section at the level of the third lumbar vertebra. (B) The green line area covered by the skeletal muscle (including the psoas, paraspinal, external oblique, internal oblique, transverse, and rectus abdominis muscles). (C) The skeletal muscle surface was calculated from pixels in the density range of –29 to +150 HU. Reprinted with permission from Sunpaweravong S, Vongcharoenpol T, Leelakiatpaiboon S, *et al.* Sarcopenia following concurrent chemoradiotherapy for locally advanced esophageal squamous cell carcinoma (abstract only). Clinical Nutrition ESPEN 2023;58:621. CT, computed tomography; SMI, skeletal muscle index.

**Table 1** Baseline characteristics of the study patients pre-CCRT

| Characteristics | Non-sarcopenia (n=35) | Sarcopenia (n=178) | P value |
|---|---|---|---|
| Age (years), mean (SD) | 58.1 (7.7) | 62.2 (9.6) | 0.02 |
| Sex, n (%) | | | 0.05 |
| Male | 35 (100.0) | 160 (89.9) | |
| Female | 0 (0.0) | 18 (10.1) | |
| Clinical stage, n (%) | | | 0.05 |
| cT2N0 | 0 (0.0) | 12 (6.7) | |
| cT1b-cT2N+ | 1 (2.8) | 8 (4.5) | |
| cT3, any N | 19 (54.3) | 118 (66.3) | |
| cT4a, any N | 15 (42.9) | 40 (22.5) | |
| ECOG, n (%) | | | 0.55 |
| 1 | 20 (57.1) | 92 (51.7) | |
| 2 | 15 (42.9) | 86 (48.3) | |
| Weight (kg), mean (SD) | 52.1 (7.3) | 48.5 (8.8) | 0.02 |
| BMI (kg/m$^2$), median (IQR) | 19.7 (17.8–21.5) | 17.9 (15.9–20.1) | <0.001 |
| WBC count (cells/μL), median (IQR) | 8,710 (7,460–10,970) | 8,530 (6,950–10,180) | 0.27 |
| Hct (%), mean (SD) | 37.4 (5.9) | 36.7 (5.4) | 0.50 |
| Creatinine level (mg/dL), mean (SD) | 0.86 (0.15) | 0.83 (0.17) | 0.28 |

BMI, body mass index; CCRT, concurrent chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; Hct, hematocrit; IQR, interquartile range; SD, standard deviation; WBC, white blood cell.

are presented in *Table 2*. SMI significantly decreased following CCRT in both the sarcopenia and non-sarcopenia groups by 3.8% (P<0.001) and 13.0% (P<0.001), respectively. Association of sarcopenia and adverse effects during CCRT are presented in *Table 3*. There were no significant differences in the adverse effects of CCRT between the groups.

The median overall survival (OS) is presented in *Table 4*.

**Table 2** Comparison of changes in SMI before and after CCRT

| Group | Pre-CCRT | Post-CCRT | Percent change | P value |
|---|---|---|---|---|
| Sarcopenia (n=178) | 34.0 (29.9, 38.6) | 32.6 (28.4, 36.4) | −3.8 (−14.0, 5.8) | <0.001 |
| Non-sarcopenia (n=35) | 46.7 (45.2, 49.9) | 40.9 (38.6, 45.1) | −13.0 (−20.9, −4.6) | <0.001 |

Data are presented as median (interquartile range). CCRT, concurrent chemoradiotherapy; SMI, skeletal muscle index.

**Table 3** Adverse events and CCRT-related toxicity

| Adverse events | Non-sarcopenia (n=35) | Sarcopenia (n=178) | P value |
|---|---|---|---|
| No serious side effects | 24 (68.6) | 90 (50.6) | 0.17 |
| Neutropenia | 5 (14.3) | 50 (28.1) | 0.13 |
| Febrile neutropenia | 0 (0.0) | 10 (5.6) | 0.37 |
| Anemia requiring blood transfusion | 2 (5.7) | 17 (9.6) | 0.54 |
| Nausea and vomiting requiring hospitalization | 4 (11.4) | 11 (6.2) | 0.28 |

Data are presented as n (%). CCRT, concurrent chemoradiotherapy.

**Table 4** Median OS of the participants

| Group | Median OS (95% CI), months | P value |
|---|---|---|
| Pre-CCRT | | 0.72 |
| Non-sarcopenia (n=35) | 15.7 (9.9–21.7) | |
| Sarcopenia (n=178) | 14.0 (13.1–17.4) | |
| Post-CCRT | | 0.71 |
| Non-sarcopenia (n=18) | 12.6 (11.3–37.8) | |
| Sarcopenia (n=195) | 14.4 (13.1–17.4) | |

CCRT, concurrent chemoradiotherapy; CI, confidence interval; OS, overall survival.

More than half of the patients in both groups died during follow-up. For sarcopenia before CCRT, OS did not differ between the groups. In addition, the presence of sarcopenia after CCRT did not affect OS. The analysis for survival, including potentially confounding variables, is presented in *Table 5*. According to this analysis, males had a poorer survival than females, N-stage 2 and 3 were worse than earlier stages, and decreasing BMI after CCRT was worse than increasing BMI after CCRT.

## Discussion

Patients with ESCC are likely to have sarcopenia at diagnosis due to aging, malnutrition from tumor obstruction, and the inflammatory process from cancer. To date, a definitive understanding of the course of sarcopenia after CCRT has not yet been established. We investigated the effects of sarcopenia on OS, CCRT-related toxicity, and SMI in patients with locally advanced ESCC before and after CCRT. In this study, 83.6% of the patients had sarcopenia before CCRT, while other studies showed a prevalence of sarcopenia ranging from 16% to 79% (10,11). Unlike studies in Asia, where the incidence of squamous cell carcinoma is higher than that of adenocarcinoma in Europe and the USA, studies in Japan have reported a sarcopenia prevalence of 57.7–70.8% (12,13). However, in Korea, the prevalence was reported to be 62.9–65.7% (14,15). The high prevalence of sarcopenia in this study might be explained by a more advanced stage of disease and lower socioeconomic status of patients than in previous studies.

Sarcopenia involves loss of muscle mass and function and is common in patients with cancer. It is a factor that indicates a poor prognosis (4). In our study, the SMI was significantly decreased in both the sarcopenia and non-sarcopenia groups after CCRT, by 3.8% and 13.0%, respectively. The Swiss Group for Clinical Cancer Research (SAKK) reported that neoadjuvant CCRT increased the prevalence of sarcopenia (16). Sarcopenia may be induced by esophageal cancer or one of the complications associated with treatment, as surgery, chemotherapy, and radiotherapy have been reported to contribute to muscle wasting by causing anorexia (11,15,16). Moreover, various circulating

**Table 5** Cox proportional hazards survival model for presence/absence of sarcopenia prior to CCRT

| Variable | Level | Hazard ratio | 95% CI | Wald P value | LR P value |
|---|---|---|---|---|---|
| Sarcopenia | No | 1 | | | 0.27 |
| | Yes | 1.27 | 0.82–1.97 | 0.28 | |
| Age | Per year | 1.00 | 0.98–1.01 | 0.63 | 0.63 |
| Sex | Female | 1 | | | 0.01 |
| | Male | 1.99 | 1.09–3.65 | 0.03 | |
| T-stage | 2 | 1 | | | 0.95 |
| | 3 | 1.07 | 0.64–1.80 | 0.79 | |
| | 4 | 1.09 | 0.61–1.96 | 0.76 | |
| N-stage | 0 | 1 | | | <0.001 |
| | 1 | 1.24 | 0.86–1.77 | 0.25 | |
| | 2 | 1.62 | 1.08–2.43 | 0.02 | |
| | 3 | 6.89 | 3.29–14.45 | <0.001 | |
| BMI post-CCRT | Per kg/m$^2$ | 0.90 | 0.85–0.95 | <0.001 | <0.001 |
| % SMI change | Per unit | 0.99 | 0.98–1.00 | 0.24 | 0.23 |

BMI, body mass index; CCRT, concurrent chemoradiotherapy; CI, confidence interval; LR, likelihood ratio; SMI, skeletal muscle index.

inflammatory mediators, such as tumor necrosis factor-α, interleukin-6 and C-reactive protein, have also been associated with excessive muscle proteolysis (17-19).

A few studies have shown the association between sarcopenia and poor prognosis; however, many factors affecting survival are still uncertain (20,21). To alleviate the confounding effect on survival outcome, we excluded patients who had undergone surgery. In this study, sarcopenia before and after CCRT had no significant association with overall OS. Similarly in other studies, no significant differences were found in OS between the two groups (4,14). We also found that male, high N-stage and decreasing BMI after CCRT were associated with poor survival prognosis.

In this study, patients with or without sarcopenia showed no significant association with CCRT-related toxicity. A study of unresectable locally advanced ESCC receiving CCRT by Sato *et al.* showed no significant differences in the incidence of severe adverse events and dose reduction rate between the two groups (13). Qu *et al.* also reported no statistically significant difference in the incidence of serious adverse events undergoing CCRT between the two groups of esophageal cancer patients (22). However, Panje *et al.* showed a significantly higher rate of grade ≥3 adverse events during neoadjuvant CCRT of locally advanced esophageal cancer than that in patients without sarcopenia (83.3% *vs.* 52.4%) (16). There are few studies on the adverse events of sarcopenia on CCRT in esophageal cancer patients, and more studies are still needed.

The strength of this study is the large numbers of focused patients with locally advanced ESCC who received CCRT without surgery. We have found a high prevalence of sarcopenia in both before and after CCRT. Further research should be conducted on whether implementing nutrition management and/or exercise treatment improves sarcopenia status or not in this condition. This study has several limitations. First, due to its retrospective nature, leading to some selection bias in which patients undergo treatments. Second, we adopted the definition of sarcopenia as muscle mass or SMI used in Western countries, and these cut-off values may be inappropriate for Thai patients with esophageal cancer, who generally have a smaller body frame.

## Conclusions

The prevalence of sarcopenia in patients with locally advanced ESCC was high and increased further after CCRT. Although CCRT-related toxicity and OS were not different between sarcopenia and non-sarcopenia groups. Sarcopenia

is a common problem and should be of concern in patients with locally advanced ESCC who receive CCRT. The role of sarcopenia in ESCC needs to be further studied and may help to provide optimal management before CCRT.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-87/rc

*Data Sharing Statement:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-87/dss

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-2025-87/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. This study was approved by the Human Research Ethics Committee of the Faculty of Medicine of Songkla University (No. REC.63-278-10-4), and informed consent was waived because of the retrospective nature of the study.



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