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Skeletal Muscle Loss Is an Imaging Biomarker of Outcome after Definitive Chemoradiotherapy for Locally Advanced Cervical Cancer

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Abstract

Purpose: This study investigates the association between body composition change during concurrent chemoradiotherapy (CCRT) and outcome in patients with locally advanced cervical cancer (LACC).

Experimental Design: Pre- and posttreatment CT images of 245 patients with LACC who were treated between 2004 and 2015 were analyzed. Skeletal muscle index (SMI) and density (SMD), subcutaneous adipose tissue index (SATI), and visceral adipose tissue index (VATI) were measured from two sets of CT images at the level of the L3 vertebra. Sarcopenia and a low SMD were defined using published cut-off points. Predictors of overall survival (OS) and cancer-specific survival (CSS) were analyzed using Cox regression models.

Results: The median follow-up was 62.7 (range, 7.3–152.3) months. Among the 245 patients, 127 (51.8%) had pretreatment sarcopenia, and 154 (62.9%) had a low SMD. SMI did not decrease significantly during CCRT, 0.6%/150 days [95% confidence interval (CI), −1.8–0.6; $P = 0.35$]. However, SMI loss during CCRT of >10.0%/150 days was independently associated with poorer OS (HR, 6.02; 95% CI, 3.04–11.93; $P < 0.001$) and CSS (HR, 3.49; 95% CI, 1.44–8.42; $P = 0.006$) when adjusted for FIGO stage, pathology, and treatment. Pretreatment sarcopenia and change of SMD, SATI, and VATI during CCRT were not associated with survival.

Conclusions: Skeletal muscle measurements could be imaging biomarkers to predict outcomes for patients with LACC in clinical practice. Further studies are needed to determine whether multimodal interventions can preserve skeletal muscle mass and thereby improve survival. *Clin Cancer Res; 24(20); 5028–36. ©2018 AACR.*

Introduction

Concurrent chemoradiotherapy (CCRT) is the mainstay of treatment for patients with locally advanced cervical cancer (LACC; refs. 1–3). During the course of CCRT, gastrointestinal toxicities could potentially contribute to weight loss, nutrient malabsorption, and even malnutrition in these patients (4, 5); therefore, the body composition including skeletal muscle and adipose tissue might change during CCRT, and this change could play a role in cancer outcomes (6, 7). Emerging evidence suggests that sarcopenia is associated with a poor prognosis and increased treatment-related toxicities in patients with metastatic and non-metastatic cancers (8–19). Adiposity was also an independent prognostic factor of outcomes according to three recent large studies (19–21). Longitudinal studies of body composition change during treatment (15–18) may provide a more comprehensive picture of how body composition is associated with outcomes. However, there is a paucity of data on the potential effect of skeletal muscle and adipose tissue change during CCRT on the outcomes of patients with LACC.

CT images could provide objective quantitative and qualitative measures of skeletal muscle and adipose tissue. The cross-sectional areas of skeletal muscle and adipose tissue on a single CT slice at the level of the third lumbar vertebra (L3) are strongly correlated with the total body skeletal muscle and fat masses (22–24). Muscle radiation attenuation is a radiological characteristic, and skeletal muscle with low radiation attenuation is suggestive of intramuscular adipose tissue infiltration and poor "quality" skeletal muscle (25). CT images are widely used in staging work-up, radiotherapy planning, and follow-up in patients with LACC (2, 3). Therefore, CT images are easily available for measuring body composition change during treatment, and hence, can be used as potential imaging biomarkers to predict outcomes in clinical practice (6, 26). Previous studies on the prognosis of LACC (27–32) have mainly focused on tumor-specific or treatment-related factors, such as International Federation of Gynecology and Obstetrics (FIGO) stage, nodal status, pathology, chemotherapy, and radiation field. However, the effect of body composition change during treatment remains unclear in patients with LACC.

We hypothesized that sarcopenia, skeletal muscle loss, and adipose tissue change during CCRT would affect patient outcomes. Therefore, this study aimed to evaluate the effect of body

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Translational Relevance

Body composition measures have an emerging role in predicting survival outcomes and treatment toxicity in patients with cancer. This article assessed the impact of body composition change during definitive concurrent chemoradiotherapy (CCRT) on outcomes in patients with locally advanced cervical cancer (LACC). Our results revealed that skeletal muscle loss during CCRT was an independent poor prognostic factor associated with reduced overall survival and cancer-specific survival. The adipose tissue at baseline or change during CCRT was not associated with outcomes. Hence, measurements of skeletal muscle change during treatment using routine CT images performed for staging, radiotherapy planning, and follow-up could be patient-specific imaging biomarkers to predict outcomes in clinical practice without additional cost; this could also help guide optimal treatment and supportive care based on individual body composition phenotypes to improve outcomes in the future.

composition change during CCRT on outcomes as well as the role of body composition measurement using routine CT images performed for staging, radiotherapy planning, and follow-up in clinical practice to determine patient-specific imaging biomarkers for predicting outcomes in LACC.

Materials and Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki. Our Institutional Review Board approved this retrospective study and waived the need for informed consent from the patients owing to the retrospective and observational nature of this study. Patients with biopsy-proven FIGO stage IB2–IVA cervical cancer who had received definitive radiotherapy or CCRT with curative intent at our institution between March 2004 and December 2015 were eligible. Demographic, disease, and treatment characteristics were obtained from the patients' medical records.

All patients received intensity-modulated radiotherapy consisting of six to nine coplanar fields using 6- or 10-MV photons. The standard radiation field was the pelvis. A prescribed dose of 45.0 to 50.4 Gy (1.8 Gy/fraction) was administered. Extended-field radiotherapy was considered for patients with positive pelvic lymph nodes or FIGO stage III–IVA disease. The dose to the involved pelvic lymph nodes was boosted to 59.4 Gy. The prescribed dose for each brachytherapy was 5.0 Gy to point A for six sessions. Chemotherapy consisted of weekly cisplatin (40 mg/m^2) administered concurrently with radiotherapy.

CT-based body composition analysis

Pre- and posttreatment CT images were retrieved for analysis. Posttreatment CT images were acquired within 3 months of radiotherapy. CT image parameters included the following: whether scans were contrast enhanced or unenhanced, 5-mm slice thickness, 120 kVp, and approximately 290 mA. The skeletal muscle and adipose tissue area measurement was conducted by analyzing CT scans at the L3 vertebra. The L3 vertebra was selected as a standardized landmark, as skeletal muscle and adipose tissue areas in a single CT image at the L3 correlate well with whole-body muscle and fat mass (23, 24). Two consecutive transverse CT images extending from L3 to the iliac crest were analyzed using Varian Eclipse software (Varian Medical Systems Inc.; ref. 33), which contains a number of tools that are useful for delineating and analyzing specific regions of interest. The skeletal muscle area includes the psoas, paraspinal, transversus abdominis, rectus abdominis, and internal and external oblique muscles. The skeletal muscle area was calculated by using Hounsfield unit (HU) thresholds of −29 and +150 (22, 23). The mean skeletal muscle radiation attenuation (HU) was reported as skeletal muscle density (SMD). Subcutaneous adipose tissue area was calculated from extramuscular tissue with a density between −190 and −30 HU and visceral adipose tissue from nonsubcutaneous tissue with a density between −150 and −50 HU (22). Tissue cross-sectional areas (cm^2) were calculated by summing the given tissue pixels and multiplying by the pixel surface area. Mean tissue areas for two consecutive images were calculated. One researcher, blinded to patient information, measured the body composition parameters. The intraobserver coefficient of variations were 1.1%, 1.5%, 1.1%, and 1.1% for skeletal muscle area, SMD, subcutaneous adipose tissue area, and visceral adipose tissue area, respectively, in a sample of 80 patients randomly selected from this cohort, which is consistent with previous articles in the literature (8, 10, 19, 20, 23, 34). Measurements of body composition parameters were highly reproducible (Supplementary Fig. S1). The cross-sectional areas of skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue were normalized for the patient height to calculate indexes (cm^2/m^2) for skeletal muscle (SMI), subcutaneous adipose tissue (SATI), and visceral adipose tissue (VATI).

Sarcopenia and a low SMD were defined according to the definition of Martin and colleagues (10). Sarcopenia was defined as an SMI of <41.0 cm^2/m^2 and a low SMD was defined as a mean attenuation of <41 HU in patients with a body mass index (BMI) of <25.0 kg/m^2 or <33 HU in patients with a BMI of ≥25.0 kg/m^2. The optimal cut-off values for SATI and VATI had not been well defined. Because body composition varies greatly among regions and ethnicities (35), we set our own cut-off values for SATI and VATI as performed by other studies with similar population sizes (12, 15). Cut-off values were set at the highest tertile for SATI and VATI.

Posttreatment skeletal muscle and adipose tissue change was assessed on the basis of the difference between the initial and follow-up CT images. Generally, the duration of the treatment course of radiotherapy ranged from 7 to 9 weeks, with follow-up CT images obtained within 3 months of radiotherapy (3). To account for variation in the exact scan interval duration, changes in the SMI, SMD, SATI, and VATI between the first and follow-up CT images were calculated as the change per 150 days to provide a standardized unit to allow comparisons between patients. Patients with a reduction or increase in the SMI of >10.0% were classified as having "SMI loss" or "SMI gain," respectively.

Statistical analysis

Continuous data are presented as the mean ± SD or median and range, where appropriate, and categorical data are presented as numbers and percentages. The distributions of patient and clinical characteristics between the sarcopenia and nonsarcopenia groups were compared using the χ^2 for categorical variables and independent t test for continuous variables. Paired t tests were

used to assess changes in skeletal muscle and adipose tissue. The McNemar test was used to test for significant differences in paired categorical data. Survival was measured from the date of treatment to the date of death or last follow-up. The Kaplan–Meier method was used to calculate actual rates, and the log-rank test was used to compare survival between the groups. Univariable and multivariable analyses were performed using Cox proportional hazards regression models. All variables with a $P < 0.05$ in the univariable analysis were included in the multivariable analysis. The probability of an event was expressed as an HR with 95% confidence intervals (CIs). Toxicity was assessed at each evaluation according to the Common Terminology Criteria for Adverse Events (version 3.0). The data were analyzed using IBM SPSS software (version 21.0; IBM Corp.). A $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

In total, 280 patients with biopsy-proven FIGO stage IB2–IVA cervical cancer who had received definitive radiotherapy or CCRT with curative intent were enrolled. Patients were excluded if they had small cell carcinoma ($n = 7$), an Eastern Cooperative Oncology Group performance status of ≥ 2 ($n = 10$), or missing posttreatment CT images ($n = 18$). Therefore, data for 245 patients were included in the final analysis.

Patient and tumor characteristics according to SMI category are summarized in Table 1. The mean age of all patients was 63.0 ± 12.7 years. A total of 127 patients (51.8%) had pretreatment sarcopenia and 154 patients (62.9%) had a low SMD. The pretreatment BMI, SATI, and VATI were significantly lower in the

Table 1. Patient and tumor characteristics ($N = 245$)

Characteristics	Overall ($n = 245$)	Sarcopenia ($n = 127$)	Nonsarcopenia ($n = 118$)	P
Age (years), mean ± SD	63.0 ± 12.7	62.7 ± 13.4	63.3 ± 12.0	0.72
ECOG performance status, *n* (%)				0.99
0	220 (89.8)	114 (89.8)	106 (89.8)	
1	25 (10.2)	13 (10.2)	12 (10.2)	
BMI (kg/m^2), mean ± SD	23.3 ± 4.1	22.5 ± 3.3	24.2 ± 4.7	0.002
WHO BMI categories, *n* (%)				0.006
Underweight (<18.5)	34 (13.9)	18 (14.2)	16 (13.6)	
Normal (18.5–24.9)	125 (51.0)	76 (59.8)	49 (41.5)	
Overweight (≥ 25)	86 (35.1)	33 (26.0)	53 (44.9)	
Body composition parameters				
SMI (cm^2/m^2), mean ± SD	39.6 ± 7.3	33.9 ± 4.3	45.8 ± 4.1	<0.001
SMD (HU), mean ± SD	34.9 ± 9.5	35.2 ± 9.0	34.5 ± 9.9	0.55
Low SMD[a], *n* (%)	154 (62.9)	81 (63.8)	73 (61.9)	0.76
SATI (cm^2/m^2), mean ± SD	59.1 ± 25.2	51.3 ± 22.4	67.5 ± 25.4	<0.001
Low SATI[b], *n* (%)	164 (66.9)	99 (78.0)	65 (55.1)	<0.001
VATI (cm^2/m^2), mean ± SD	35.5 ± 20.4	30.1 ± 18.4	41.3 ± 20.9	<0.001
Low VATI[b], *n* (%)	163 (66.5)	94 (74.0)	69 (58.5)	0.01
Smoking, *n* (%)				0.74
No (never smoked or quitted)	193 (78.8)	99 (78.0)	94 (79.7)	
Yes (current smoker)	52 (21.2)	28 (22.0)	24 (20.3)	
FIGO stage, *n* (%)				0.68
IB–II	184 (75.1)	94 (74.0)	90 (76.3)	
III–IVA	61 (24.9)	33 (26.0)	28 (23.7)	
Pathology, *n* (%)				0.57
Squamous cell carcinoma	215 (87.8)	110 (86.6)	105 (89.0)	
Adenocarcinoma	30 (12.2)	17 (13.4)	13 (11.0)	
PLN involvement, *n* (%)				0.20
Positive	110 (44.9)	52 (40.9)	58 (49.2)	
Negative	135 (55.1)	75 (59.1)	60 (50.8)	
Hb				0.08
≥10 mmol/L	202 (82.4)	110 (86.6)	92 (78.0)	
<10 mmol/L	43 (17.6)	17 (13.4)	26 (22.0)	
SCC-Ag level, *n* (%)				0.04
>10 ng/mL	86 (35.1)	37 (29.1)	49 (41.5)	
≤10 ng/mL	159 (64.9)	90 (70.9)	69 (58.5)	
Radiation field, *n* (%)				0.27
Extended-field radiotherapy	117 (47.8)	65 (51.2)	52 (44.1)	
Pelvic radiotherapy	128 (52.2)	62 (48.8)	66 (55.9)	
Chemotherapy, *n* (%)				0.74
Yes	212 (86.5)	109 (85.8)	103 (87.3)	
No	33 (13.5)	18 (14.2)	15 (12.7)	
CCRT weekly chemotherapy cycles, *n* (%)	$n = 212$	$n = 109$	$n = 103$	0.30
5–6	160 (75.5)	79 (72.5)	81 (78.6)	
1–4	52 (24.5)	30 (27.5)	22 (21.4)	
Overall treatment duration (day), median (range)	59 (43–79)	59 (44–79)	58 (43–79)	0.12
Median (range) follow-up, months	62.7 (7.3–152.3)	62.5 (10.6–151.4)	64.2 (7.3–152.3)	0.43

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin level; PLN, pelvic lymph node; SCC-Ag, squamous cell carcinoma antigen.
[a]BMI-specific cut-off values of low SMD according to Martin and colleagues.
[b]SATI <67.3 cm^2/m^2 and VATI <41.6 cm^2/m^2 were defined as low SATI and VATI, respectively.

Table 2. Change of body composition parameters during treatment ($N = 245$)

Variable	First CT scan Mean ± SD	Second CT scan Mean ± SD	Change per 150 days Mean	95% CI	P	Relative change per 150 days (%) Mean	95% CI	P
SMI (cm^2/m^2)								
Overall group	39.6 ± 7.6	39.3 ± 7.7	−0.3	−0.8 to 0.2	0.21	−0.6	−1.8 to 0.6	0.35
Sarcopenia	33.9 ± 4.3	33.9 ± 5.0	0.1	−0.5 to 0.6	0.84	0.3	−1.4 to 1.9	0.76
Nonsarcopenia	45.8 ± 4.1	45.0 ± 5.7	−0.7	−1.5 to 0.1	0.09	−1.5	−3.3 to 0.3	0.10
SMD (HU)								
Overall group	34.9 ± 9.5	33.8 ± 9.5	−1.2	−1.7 to −0.7	<0.001	−2.9	−4.4 to −1.3	<0.001
Sarcopenia	35.2 ± 9.0	34.2 ± 9.3	−1.2	−1.9 to −0.5	0.001	−3.2	−5.3 to −1.1	0.003
Nonsarcopenia	34.5 ± 9.9	33.4 ± 9.7	−1.2	−1.9 to −0.5	0.001	−2.5	−4.8 to −0.2	0.03
SATI (cm^2/m^2)								
Overall group	59.1 ± 25.2	57.3 ± 25.0	−1.9	−3.0 to −0.7	0.001	−2.7	−4.6 to −0.8	0.005
Sarcopenia	51.3 ± 22.4	49.7 ± 22.2	−1.8	−3.2 to −0.4	0.01	−3.1	−5.9 to −0.3	0.03
Nonsarcopenia	67.5 ± 25.4	65.6 ± 25.3	−2.0	−3.9 to −0.1	0.04	−2.4	−4.9 to 0.2	0.07
VATI (cm^2/m^2)								
Overall group	35.5 ± 20.4	34.2 ± 19.6	−1.4	−2.2 to −0.5	0.002	−1.6	−4.0 to 0.7	0.17
Sarcopenia	30.1 ± 18.4	29.4 ± 18.2	−0.8	−1.8 to 0.1	0.07	−0.5	−4.3 to 3.2	0.78
Nonsarcopenia	41.3 ± 20.9	39.5 ± 19.9	−1.9	−3.4 to −0.4	0.01	−2.8	−5.6 to −0.1	0.04

sarcopenia group than in the nonsarcopenia group. The cut-off values for low SATI and VATI were <67.3 and <41.6 cm^2/m^2, respectively. There were more patients with low SATI or VATI in the sarcopenia group.

Demographics, such as age, FIGO stage, nodal status, and radiation field, were comparable between the two groups. Thirty-three patients (13.5%) did not receive chemotherapy in this study, and there were no significant differences between the sarcopenia and nonsarcopenia groups. The mean age of the patients who did not receive chemotherapy was 77.0 ± 9.9 years. The reasons why these patients did not receive chemotherapy were as follows: (i) age ≥70 years with multiple underlying diseases ($n = 26$); (ii) poor renal function ($n = 4$); and (iii) refusal ($n = 3$). Treatment compliance was similar between the two groups in terms of overall treatment duration and chemotherapy cycles.

Body composition change during treatment

Table 2 summarizes the body composition changes during treatment. The median interval between pre- and posttreatment CT scans was 4.8 (range, 3.5–5.9) months. Patients lost an average of 0.6% (95% CI, −1.8–0.6; $P = 0.35$) of SMI per 150 days. The change in SMI was similar between the pretreatment sarcopenia and nonsarcopenia groups (0.3% vs. −1.5% per 150 days, respectively; $P = 0.16$). The SMD, SATI, and VATI decreased by 1.2 HU (95% CI, −1.7 to −0.7; $P < 0.001$) per 150 days, 2.7% (95% CI, −4.6 to −0.8; $P = 0.005$) per 150 days, and 1.6% (95% CI, −4.0–0.7; $P = 0.17$) per 150 days, respectively. The prevalence of sarcopenia increased from 51.8% ($n = 127$) at baseline to 60.0% ($n = 147$) at the time of the second CT scan ($P = 0.003$). Fifty (20.4%), 147 (60.0%), and 48 (19.6%) patients were diagnosed with SMI loss, stable SMI, or SMI gain, respectively.

Patient characteristics according to muscle change are shown in Supplementary Table S1. The reduction in SMD during treatment was significantly higher in the group with SMI loss than in the other two groups ($P = 0.03$). The SATI and VATI changes were not significantly different among the three groups. The number of patients with adenocarcinoma in the groups with SMI loss, stable SMI, and SMI gain was 13 (26.0%), 11 (7.5%), and 6 (12.5%), respectively ($P = 0.004$). The prevalence of SMI loss in patients with adenocarcinoma and squamous cell carcinoma was 43.3% ($n = 13$) and 17.2% ($n = 37$), respectively ($P = 0.003$). Patients with adenocarcinoma lost more SMI (−4.3% vs. −0.1%, respectively; $P = 0.03$) and SMD (−2.3 vs. −0.9 HU, respectively; $P = 0.04$) during treatment than patients with squamous cell carcinoma. The changes in SATI (−1.0% vs. −2.9%, respectively; $P = 0.52$) and VATI (−0.3% vs. −1.8%, respectively; $P = 0.66$) were not significantly different between patients with adenocarcinoma and squamous cell carcinoma.

Body composition change and survival

The median follow-up period was 62.7 (range, 7.3–152.3) months. The 5-year overall survival (OS) and cancer-specific survival (CSS) rates for all patients combined were 82.8% and 87.3%, respectively. The 5-year OS (82.6% vs. 83.0%, respectively; $P = 0.68$) and CSS (87.9% vs. 86.6%, respectively; $P = 0.84$) rates were comparable between the pretreatment sarcopenia and nonsarcopenia groups (Supplementary Fig. S2A and S2B). The 5-year OS and CSS rates for the groups with SMI loss, stable SMI, and SMI gain were 45.2%, 91.2%, and 95.6% (Fig. 1A, $P < 0.001$) and 59.8%, 92.6%, and 95.6% (Fig. 1B, $P < 0.001$), respectively. There were no significant differences in OS and CSS in the groups according to SMD (5-year OS: 80.9% vs. 86.1%; $P = 0.26$; 5-year CSS: 87.4% vs. 87.1%; $P = 0.84$), SATI (5-year OS: 79.6% vs. 89.3%; $P = 0.07$; 5-year CSS: 85.2% vs. 91.6%; $P = 0.15$), and VATI (5-year OS: 82.0% vs. 84.5%; $P = 0.68$; 5-year CSS: 86.6% vs. 88.5%; $P = 0.80$; Supplementary Fig. S2C–S2H). In a subgroup analysis, patients with SMI loss had significantly poorer OS and CSS in both the pretreatment sarcopenia and nonsarcopenia groups (Fig. 1C–F).

In univariable analysis, SMI change, SMD change, FIGO stage, radiation field, and pathology were predictors of OS and CSS (Supplementary Table S2). The use of chemotherapy was a predictor of OS, but not CSS. In a multivariable analysis adjusted for FIGO stage, pathology, and treatment, SMI loss was confirmed as an independent prognostic factor for OS (HR, 6.02; 95% CI, 3.04–11.93; $P < 0.001$) and CSS (HR, 3.49; 95% CI, 1.44–8.42; $P = 0.006$; Table 3). Pretreatment sarcopenia, SMD, SATI, and VATI were not associated with OS or CSS.

Patients in the SMI loss group had a significantly lower rate of extended-field radiotherapy and higher frequency of adenocarcinoma, which may have been a confounder associated with the

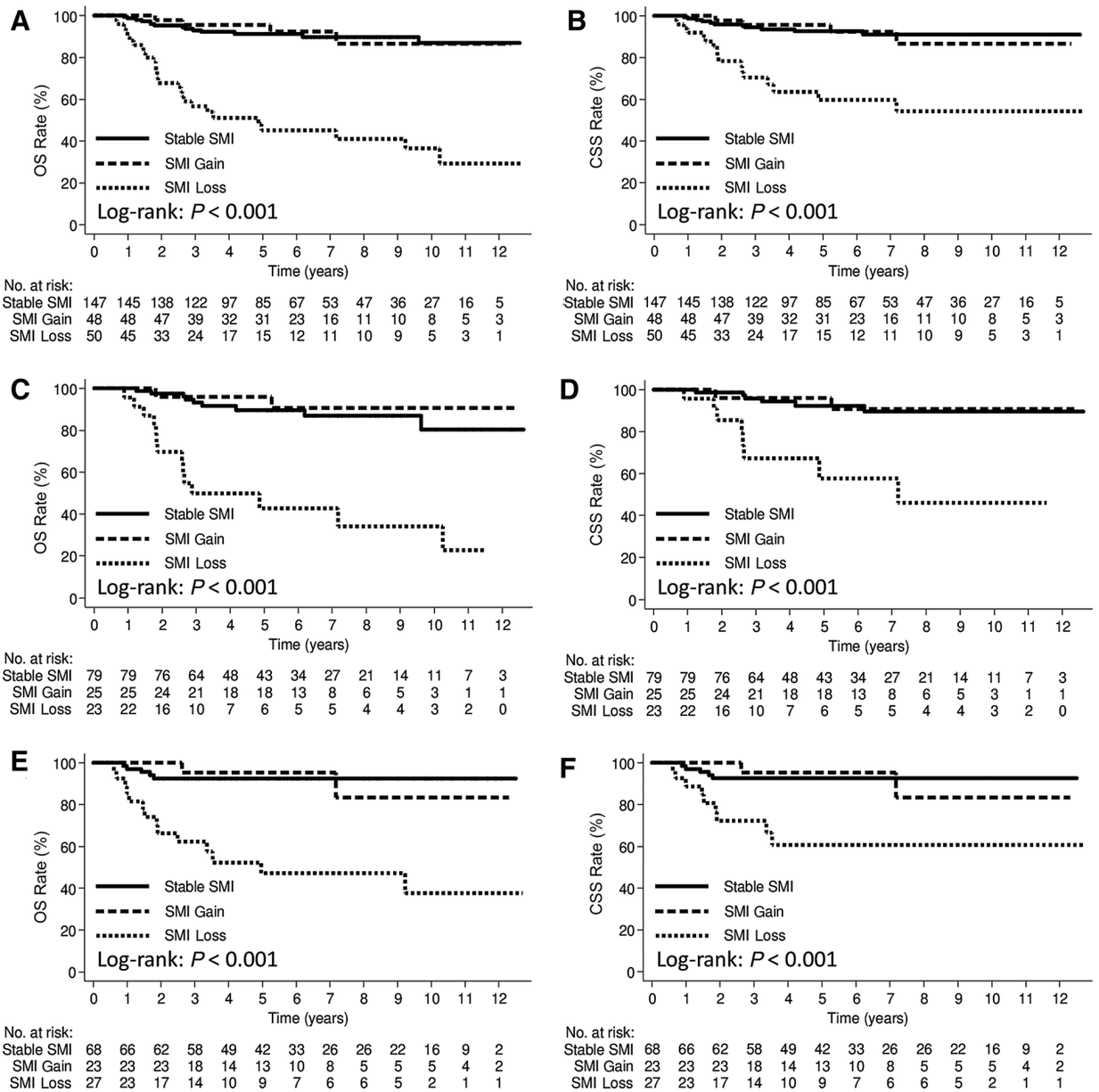

Figure 1.

Kaplan–Meier curve demonstrating OS and CSS according to skeletal muscle change groups for the overall (**A** and **B**), sarcopenia (**C** and **D**), and nonsarcopenia (**E** and **F**) patients.

inferior outcome. To further evaluate the effect of skeletal muscle loss during treatment in patients with squamous cell carcinoma, we conducted a subgroup analysis including only squamous cell carcinoma ($n = 215$). In these patients, SMI loss had significantly lower OS and CSS than stable SMI and SMI gain groups, while the OS and CSS rates remained not associated with SMD, SATI, and VATI (Supplementary Fig. S3). On multivariable analysis, SMI loss was an independent prognostic factor for OS (HR, 5.65; 95% CI, 2.65–12.02; $P < 0.001$) and CSS (HR, 3.23; 95% CI, 1.29–8.11; $P = 0.01$; Supplementary Table S3).

Toxicities

Acute toxicities according to SMI category are summarized in Table 4. No acute grade ≥3 gastrointestinal or genitourinary toxicities or treatment-related deaths occurred during or after treatment. Acute grade ≥3 hematologic toxicities occurred in 67 (52.8%) and 40 (33.9%) patients in the sarcopenia and nonsarcopenia groups, respectively ($P = 0.003$). The prevalence of grade ≥2 gastrointestinal and genitourinary toxicities and grade ≥3 hematologic toxicities were comparable in the groups according to SMI change, SATI, and VATI (Supplementary Table S4).

Table 3. Multivariable Cox proportional hazards model for OS and CSS ($N = 245$)

	OS		CSS	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***p***
SMI change, categorical				
SMI stable (±10.0%)	Reference		Reference	
SMI loss (>−10.0%)	6.02 (3.04–11.93)	<0.001	3.49 (1.44–8.42)	0.006
SMI gain (>+10.0%)	0.94 (0.31–2.87)	0.91	1.45 (0.44–4.82)	0.55
SMD change, per 1 HU increase	0.95 (0.87–1.03)	0.19	0.92 (0.82–1.05)	0.21
FIGO stage				
IB–II	Reference		Reference	
III–IVA	2.24 (1.19–4.22)	0.01	2.36 (1.14–4.92)	0.02
Radiation field				
Pelvic radiotherapy	Reference		Reference	
Extended-field radiotherapy	0.64 (0.32–1.31)	0.22	0.40 (0.16–0.99)	0.049
Pathology				
SCC	Reference		Reference	
Adenocarcinoma	2.30 (1.10–4.80)	0.03	2.20 (0.96–5.04)	0.06
Chemotherapy				
No	Reference			
Yes	0.36 (0.18–0.72)	0.004		

Abbreviation: SCC, squamous cell carcinoma.

Discussion

This study revealed that skeletal muscle loss during CCRT was an independent poor prognostic factor associated with reduced OS and CSS in patients with LACC. However, pretreatment sarcopenia and a low SMD were not independent poor prognostic factors, highlighting the importance of preserving skeletal muscle mass during CCRT. In addition, the SATI and VATI at baseline or change during CCRT were not associated with outcomes.

CT images could provide objective body composition measures and are widely used in staging, radiotherapy planning, and follow-up in patients with LACC. All patients in the current study underwent CT for radiotherapy planning and follow-up. Therefore, no additional radiation exposure was incurred in our evaluation of sarcopenia. The measurements were simple to perform using commercially available software, which did not add additional cost (33). In addition, previous studies (36, 37) have revealed that underweight patients with LACC (BMI < 18.5 kg/m^2) have a lower OS than normal weight or obese patients. However, in this study, pretreatment BMI was not associated with survival. One possible reason for the discrepancy is that BMI does not take into consideration the percentage of muscle and adipose masses, and the variation in body composition between patients with an identical BMI could be considerable (10). Optimal imaging biomarkers are integral for the routine management of patients with cancer (26). Therefore, measurements of body composition change during treatment using readily available CT images could be useful and practical imaging biomarkers to predict outcomes in clinical practice; this could also help guide optimal treatment and supportive care to improve outcomes in the future (6, 7).

To date, a consensus has not been reached regarding the optimal cut-off values for defining sarcopenia in patients with cancer. In this study, we defined sarcopenia according to the cut-off values for the SMI published by Martin and colleagues (10). These cut-off values were determined using the largest available dataset to date and are BMI specific. Prado and colleagues (8) also calculated cut-off values for the SMI. Their optimal cut-off value was lower (38.5 vs. 41.0 cm^2/m^2, respectively) than that published by Martin and colleagues (10). Both classifications have been widely validated for predicting survival in a number of external cohorts from Western and Asian populations (11–16, 18). If the patients in this study were classified according to the criteria of Prado and colleagues (8), then the proportion of patients diagnosed with pretreatment sarcopenia would decrease to 44.1% ($n = 108$), and the 5-year OS rate would remain similar between the sarcopenia and nonsarcopenia groups (Supplementary Fig. S4, 82.5% vs. 83.0%, respectively; $P = 0.78$). This finding suggests that at a specific time point, sarcopenia may be indicative of skeletal muscle loss. However, longitudinal studies of skeletal muscle change during treatment may provide a more comprehensive picture of how sarcopenia impacts on outcomes and toxicity. Daly and colleagues (16) reported that several factors may influence muscularity, including ethnicity, age, sex, obesity, socioeconomic factors, and dietary habits. To define the most robust diagnostic criteria for sarcopenia, international data repositories were needed and longitudinal changes during treatment may be taken into consideration in patients with cancer.

Table 4. Acute toxicities by SMI groups ($N = 245$)

	Pretreatment SMI			SMI change			
Toxicity	**Sarcopenia ($n = 127$)**	**Nonsarcopenia ($n = 118$)**	***P***	**SMI loss ($n = 50$)**	**SMI stable ($n = 147$)**	**SMI gain ($n = 48$)**	***P***
Grade 2 GI[a]	49 (38.6)	41 (34.7)	0.53	17 (34.0)	52 (35.4)	21 (43.8)	0.52
Grade 2 GU[a]	13 (10.2)	12 (10.2)	0.99	7 (14.0)	13 (8.8)	5 (10.4)	0.58
Grade ≥3 HT	67 (52.8)	40 (33.9)	0.003	23 (46.0)	67 (45.6)	17 (35.4)	0.44

NOTE: Data are expressed as the absolute number of events (%).

Abbreviations: GI, gastrointestinal; GU, genitourinary; HT, hematologic.

[a]No grade ≥3 acute GI or GU toxicities or treatment-related death occurred during or after treatment.

Our findings are supported by other studies. Kiyotoki and colleagues analyzed 60 patients with LACC with a median follow-up period of 33.5 months and reported iliopsoas muscle loss during CCRT was a poor prognostic factor, whereas the total skeletal muscle area loss was not associated with outcomes (17). However, Rutten and colleagues reported the weakness of psoas-only approach includes its low proportion of total trunk muscles (<10%), high measurement error, and weak correlation of psoas area with total lumbar muscle area. An assessment of psoas muscle area may be easier and quicker but is less sensitive to muscle change than the standard assessment of total skeletal muscle (38). Therefore, we evaluated the effect of sarcopenia by measuring the total muscle area at the L3 vertebral level because the total muscle area is more validated and widely used for patients with cancer (8–19). Although the average change in the SMI during CCRT was not significant in this study, the SMI loss was associated with poorer survival. In addition, patients with SMI loss had significantly poorer survival in both the sarcopenia and nonsarcopenia groups (Fig. 1C–F). These findings suggest that preventing skeletal muscle loss during CCRT might optimize the outcome of patients with LACC in both the sarcopenia and nonsarcopenia groups.

Knowledge of the mechanism that links skeletal muscle loss with poor survival is not well understood. In this study, the prevalence and extent of skeletal muscle loss were significantly higher for patients with adenocarcinoma than for those with squamous cell carcinoma. The clinical behavior, pattern of disease spread, and prognosis are more aggressive for adenocarcinoma than squamous cell carcinoma, and the optimal treatment for adenocarcinoma remains unknown (39, 40). Potentially, skeletal muscle loss may be one mechanism by which adenocarcinoma can detrimentally impact on outcomes. However, the number of patients with adenocarcinoma in this study meant we were unable to draw definitive conclusions. Furthermore, there were more patients receiving chemotherapy and extended-field radiotherapy in the groups with stable SMI and SMI gain than in the group with SMI loss. Previous studies (1, 29–32) have reported the benefits of chemotherapy and extended-field radiotherapy in patients with LACC. These differences in treatment could potentially confound the interpretation of our findings. However, a multivariable analysis of the overall cohort ($n = 245$) or only patients with squamous cell carcinoma ($n = 215$) adjusted for these factors confirmed that skeletal muscle loss was an independent prognostic factor for OS and CSS (Table 3; Supplementary Table S3). Optimal and structured supportive care to maintain skeletal muscle mass during CCRT may prevent the detrimental effects of skeletal muscle loss and improve the outcome of patients with LACC.

Adiposity was an independent prognostic factor of outcomes according to three recent large studies (19–21). In the current study, the pretreatment SATI and VATI were not associated with OS or CSS. Although the patients lost SATI and VATI during CCRT, the adipose change during CCRT was also not associated with OS and CSS. This discrepancy in the effect of adiposity on outcomes might be attributed to the small sample size, lack of optimal cancer-specific cutoffs associated with survival, or different evaluated cancer and treatment in the current study. A larger study with a consistent LACC population and treatment is needed to evaluate the actual effect of adiposity on outcomes in patients with LACC.

Previous studies (9, 41, 42) have reported that sarcopenia is a predictor of treatment-related toxicities. In this study, a greater proportion of patients in the sarcopenia group had acute grade ≥ 3 hematologic toxicities than in the nonsarcopenia group. This finding was consistent with previous studies, although the types of diseases and treatments differed (9, 41, 42). Chemotherapy and radiotherapy are both known to be myelosuppressive and could contribute to hematologic toxicity (43–45). Bone marrow–sparing radiotherapy could potentially reduce the incidence and severity of hematologic toxicities in patients with LACC (46). Potentially, bone marrow–sparing radiotherapy could be beneficial in preventing patients with sarcopenia from developing hematologic toxicities.

Our study has several limitations. First, given its retrospective design, measurements of food intake and physical activity were not available, which may influence muscle mass. Therefore, we were unable to identify a causal relationship between skeletal muscle loss and poor survival, only revealing an association between them. Second, our study included only Asian patients. Further studies on body composition change during CCRT in Western patients treated for LACC are needed to expand and generalize the findings of this study. Despite these limitations, the strength of this study is that patients received treatment from specialist radiation oncologists with a high level of consistency and high compliance of pre- and posttreatment CT images. The quality of care regarding the radiotherapy and chemotherapy administered to the patients in this study was consistent with the current standards of practice, and outcomes were comparable with previous studies (1). The follow-up period was also appropriate. Taken together, our findings contribute to the increasing body of research showing that outcomes are clearly associated with skeletal muscle loss. Moreover, we suggest that skeletal muscle change during treatment may provide a more comprehensive picture of how sarcopenia impacts on outcomes in patients with LACC. Further studies are needed to investigate the mechanism of skeletal muscle loss and whether interventions may attenuate or improve skeletal muscle mass during treatment and may lead to improved clinical outcomes. Dieli-Conwright and colleagues recently reported combined resistance and aerobic exercise significantly improved sarcopenic obesity in an ethnically diverse sample of sedentary, overweight, or obese survivors of breast cancer (47). A phase III clinical trial (NCT02330926) is underway across a number of international sites. It is possible that multimodal interventions, consisting of nutritional supplements and advice, home-based self-assisted exercise programs, and anti-inflammatory medications, could improve the outcomes of patients with cancer.

In conclusion, although the average change in the SMI during CCRT was not significant, skeletal muscle loss of >10.0% was independently associated with poor OS and CSS. The adipose tissue at baseline or change during CCRT was not associated with outcomes. By using existing CT images and readily available software, skeletal muscle assessments could be incorporated into the clinical setting as patient-specific imaging biomarkers to predict outcomes. Further studies are needed to investigate the mechanism of skeletal muscle loss and whether interventions may preserve skeletal muscle mass during treatment to help improve clinical outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J. Lee, S.-M. Hsu
Development of methodology: J. Lee
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Lee, M.-H. Wu, Y.-T. Jan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Lee, J.-B. Lin, F.-J. Sun
Writing, review, and/or revision of the manuscript: J. Lee, C.-L. Chang, S.-M. Hsu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Lee, C.-L. Chang, J.-B. Lin, M.-H. Wu, Y.-T. Jan
Study supervision: J. Lee, Y.-J. Chen

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