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Measurement of body composition via artificial intelligence-based volumetric technique and its prognostic implications in patients with cervical cancer

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Abstract

This study aimed to investigate the impact of sarcopenia and body composition on survival outcomes in Korean patients with early stage cervical cancer.

We retrospectively analyzed patients diagnosed with 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IB1-IIA2 cervical cancer and treated at the Seoul National University Hospital (SNUH).

Anonymized digital imaging and communications in medicine images of pre- and post-treatment computed tomography (CT) scans were uploaded to an artificial intelligence-based, commercially available software (DEEPCATCH v1.0.0.0; MEDICALIP Co. Ltd., Seoul, Korea). The software provides automatic volumetric segmentation of body components, labeling the abdominal waist between the lower end of the thoracic ribs and the upper end of the iliac crest, and measurement of the waist volume (cm^3) of each body component. The waist volume of skeletal muscle, abdominal visceral fat, and subcutaneous fat were quantified and normalized to the height in cubic meters. This software also provides automatic measurement of skeletal muscle area (cm^2) from the single cross-sectional CT image at the third lumbar vertebra body (L3) level. The skeletal muscle area was normalized to the height in square meters, producing L3 skeletal muscle index (SMI).

We defined L3 sarcopenia as L3 SMI <39.0 cm^2/m^2. We also defined volumetric sarcopenia based on the first quartile (Q1) value of volumetric SMI. Patients' clinicopathological characteristics and survival outcomes were

compared according to the presence of L3 sarcopenia and volumetric sarcopenia.

A total of 306 patients were included in the study. Using L3 SMI, no difference was found in progression-free survival (PFS) and overall survival (OS) between the sarcopenia and non-sarcopenia groups (P=0.415 and P=0.743, respectively). The L3 sarcopenia (<39.0 cm^2/m^2) group had a significantly lower body mass index (BMI) (22.1 vs. 24.8 kg/m^2; P<0.001) and a higher proportion of underweight (7.1% vs. 1.2%; P=0.001), compared to the non-sarcopenia (≥39.0 cm^2/m^2) group. Age, histologic type, stage, risk group, clinical cervical tumor size, and adjuvant treatment were similar between the two groups. In multivariable analysis, L3 sarcopenia was not associated with patients' PFS (adjusted hazard ratio [aHR], 0.896; 95% confidence interval [CI], 0.504-1.591; P=0.707) and OS (aHR, 1.225; 95% CI, 0.416-3.604; P=0.712).

Next, based on the Q1 value of volumetric SMI, 76 and 230 patients were assigned to the volumetric sarcopenia (<181.5 cm^3/m^3) and volumetric non-sarcopenia (≥181.5 cm^3/m^3) groups, respectively. Age, histologic type, stage, risk group, clinical cervical tumor size, pathologic cervical tumor size, and adjuvant treatment were similar between the two groups. The volumetric sarcopenia group showed significantly worse PFS (3-year survival rate, 78.3% vs. 88.7%; P=0.039) and OS (5-year survival rate, 90.0% vs. 97.6%; P=0.031) than did the volumetric non-sarcopenia group. In multivariable analysis adjusting for clinicopathologic factors, volumetric sarcopenia was identified as a poor prognostic factor for PFS (aHR, 1.922; 95% CI, 1.053-3.506;

P=0.033), but not OS (aHR, 2.863; 95% CI, 0.965-8.496; *P*=0.058).

Next, we compared the pre- and post-treatment body composition (n=192). Initially, the volumetric sarcopenia patients who gained total fat during treatment showed significantly worse PFS (3-year survival rate, 64.8% vs. 86.6%; *P*=0.014) than did the others; although OS (*P*=0.050) is not very obvious, there are differences. Multivariable analysis revealed that initial volumetric sarcopenia with total fat gain during primary treatment was associated with worse PFS (aHR, 2.565; 95% CI, 1.118-5.885; *P*=0.026).

In conclusion, volumetric sarcopenia before treatment increased the recurrence rates in Korean patients with early stage cervical cancer. Furthermore, patients with initial volumetric sarcopenia and total fat gain during primary treatment were at a high risk of disease recurrence.

Keyword: cervical cancer; body composition; body mass index; sarcopenia; muscle, visceral fat; prognosis; survival.

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1. Introduction

Cervical cancer is the fourth most common malignant tumor in women and is a major health problem worldwide. According to GLOBOCAN statistics 2020, more than 604,127 women are diagnosed with cervical cancer every year, and 341,831 women die from it worldwide [1]. Cervical cancer has the fourth highest incidence rate (6.5%) mortality rate (7.7%) among cancers in women [1]. In recent years, owing to the presence of effective screening tools and human papilloma virus vaccination, the incidence of cervical cancer has decreased gradually. According to the Surveillance, Epidemiology, and End Results data from the United States, in 2021, there were 14,480 newly diagnosed cervical cancer patients and 4,290 related deaths [2]. According to SEER data in 2020 among the newly diagnosed cervical cancer patients, 44% were in the early stage of diagnosis, and their 5-year survival rate was 91.8% [3]. However, the incidence rate of cervical cancer in Korea, China, and other Asian countries is still significantly higher than that in Western countries. According to the Korean cancer registry statistics, there will be 3,148 newly diagnosed cases and 801 deaths in South Korea in 2020 [4]. When calculated as population percentages, these values are significantly higher than the incidence and mortality rates of cervical cancer in the United States.

Obesity is a state of excessive fat accumulation, and may be associated with the development and survival of cancer [5,6]. Based on the body mass index (BMI) suggested by the World Health Organization (WHO) for Asian

populations, overweight (≥23.0 kg/m^2 and <25.0 kg/m^2) and obesity (≥25.0 kg/m^2) were identified as risk factors for breast cancer [7,8]. Obesity plays an important role in hormone-dependent cancer, and the incidence rates of gynecologic cancers such as endometrial cancer, ovarian cancer, and breast cancer are positively correlated with obesity. The association between obesity and these cancers may be explained by mechanisms involving sex hormones, insulin resistance, and some adipokines [9]. In most studies, obesity has an adverse effect on survival rate. In 2017, the World Health Organization published the news that obesity or overweight is associated with cancer in 13 human parts. Especially esophageal cancer or endometrial cancer, obesity or overweight, more than 3 times higher than normal risk, showing a high correlation [10].

Cervical cancer is also related with hormone risk factors, partly; therefore, obesity and cervical cancer also have a certain association [11]. Previous studies have shown that obesity may increase the risk of cervical cancer [12]. Obesity not only increases the incidence rate of cervical cancer, but also increases patient mortality [11]. In the past, we used BMI as an index to analyze the relationship between obesity and cancer, but in recent years, we found a phenomenon called the “obesity paradox.” In the United States, the overall mortality risk of overweight (BMI, ≥25.0 kg/m^2 and <30.0 kg/m^2) and grade I obesity (BMI, ≥30.0 kg/m^2 and <35.0 kg/m^2) patients after cancer diagnosis is generally lower, and the risk of death increases when the BMI of patients is ≥35 kg/m^2 [13].

Meanwhile, researchers have reported that BMI is not a good

representative of obesity and cannot distinguish the number and distribution of muscle and specific adipose tissue (viscera, subcutaneous, and intramuscular) [14-22]. The WHO expert consultation meeting concluded that the percentage of body fat in Asian people is generally higher than that of Western persons of the same age, sex, and BMI, and the trend of abdominal obesity is greater than that of Western persons [23]. The average or median BMI of Asian people is lower than that of Western people (thus, the distribution of BMI shifts to the left); therefore, BMI cannot be used as a single index to study the risk and prognostic factors of cervical cancer [23].

Sarcopenia has recently been reported as a poor prognostic factor for various cancers. Sarcopenia is characterized by the loss of skeletal muscle mass and function, which occurs not only in older adults but also in patients with cancer [24]. Low muscle mass was associated with a higher risk of recurrence, overall and cancer-specific mortality, surgical complications, and treatment-related toxicity [13]. In recent years, according to the research and analysis results of other cancers, it has been concluded that sarcopenia after hepatectomy is closely related to the prognosis of liver cancer [25], which is closely related to the recurrence risk, postoperative complications, and sarcopenia is a useful imaging biomarker for predicting preoperative nutritional risk, postoperative complications, and long-term outcomes in elderly colorectal cancer patients [26]. Sarcopenia is a risk factor for mortality among female early breast cancer patients also [27].

However, its use in cervical cancer management remains controversial. Some studies have shown that sarcopenia is a prognostic factor for locally

advanced cervical cancer patients who undergo chemoradiotherapy [28]. In contrast, other studies reported that sarcopenia is not a prognostic factor in cervical cancer patients receiving concurrent chemoradiation therapy (CCRT) or radiotherapy (RT) [29]. Unlike in other cancers, the role of sarcopenia in cervical cancer is just emerging, and the related literature is limited, especially for early stage cervical cancer. In recent years, researchers have unanimously believed that single index obesity or sarcopenia is not significant for the study of cancer prognosis, and it needs to be Integrated with the systematic analysis of body components. Therefore, in the treatment of cervical cancer patients, integrative analysis of fat, muscle, and other body components is necessary for a comprehensive analysis.

Body composition refers to the distribution of fat, muscle, bone, and water in the human body. CT is widely used because it can measure the body composition. In this technique, the area of skeletal muscle and adipose tissue measured on the horizontal cross-sectional image of L3 represents the body composition of the individual [30]. In addition, the latest technology allows the volume of each component to be measured.

To date, there are few studies on body composition analysis of patients with cervical cancer, and mainly focus on advanced patients, in order to evaluate its impact on prognosis. There is little information about the impact of longitudinal changes in body composition on the prognosis of patients with early stage cervical cancer. However, in recent years, the incidence rate of cervical cancer is increasing in younger populations. More emphasis should be placed on the evaluation of the therapeutic efficacy or prognostic factors of

early stage cervical cancer.

It is not clear which body components are preferentially affected during cervical cancer treatment. Therefore, the purpose of this study was to explore the impact of obesity, muscle loss, and body composition on the prognosis of patients with early stage cervical cancer in Korea, and the impact of body composition changes on survival outcomes.

2. Materials and Methods

This retrospective cohort study was conducted after obtaining approval from the Institutional Review Board of Seoul National University Hospital (SNUH; No. H-2012-061-117).

2.1. Study population

From the cervical cancer cohort database of SNUH in South Korea, we identified and collected patients who met the following conditions: (1) patients aged 20 years or older at the time of diagnosis; (2) patients diagnosed with cervical cancer who were treated at SNUH between January 2007 and December 2019; (3) patients diagnosed with stage IB1 to IIA2, according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system; (4) patients who underwent Q-M classification type B-C radical hysterectomy and pelvic lymphadenectomy; and (5) those for whom baseline CT imaging was performed in the process of diagnosis and treatment.

Patients with the following conditions were excluded: (1) those who were diagnosed with other cancers before being diagnosed with cervical cancer, (2) those with insufficient cliniocopathological data, (3) those lost to follow-up during treatment, and (4) those for whom we were unable to obtain baseline CT scans (**Figure 1**).

2.2. CT image analysis

Anonymized pre- and post-treatment CT digital imaging and communications in medicine images were uploaded to commercially available software for whole-body composition analysis (DEEPCATCH v1.0.0.0; MEDICALIP Co. Ltd., Seoul, Korea). The software provides automatic volumetric segmentation of body components into seven classes, including muscle, abdominal visceral fat, and subcutaneous fat, with an average segmentation accuracy of 97% compared with manual segmentation, already validated [31]. After segmentation, the software automatically labeled the abdominal waist between the lower end of the thoracic ribs and the upper end of the iliac crest, which was compatible with WHO's waist definition [31]. In our studies one body radiologist with 15 years of experience in body CT interpretation confirmed the results of automatic segmentation and labeling. Subsequently, the waist volume (cm^3) of muscle, abdominal visceral fat, and subcutaneous fat were quantified and normalized to the height in cubic meters. This software also provides automatic measurement of skeletal muscle area (cm^2) from the single cross−sectional CT image at the L3 level. The skeletal muscle area was normalized to the height in square meters (**Figure 2**).

2.3. Data collection

We collected the clinicopathologic features of the patients, such as age at diagnosis, BMI, surgical approach, histologic type, radicality of hysterectomy, para-aortic lymphadenectomy, FIGO stage, tumor size and pathologic risk

factors, risk group, and adjuvant treatment.

BMI was calculated at diagnosis and after initial treatment. According to the Asian population standard proposed by the WHO, patients were divided into four groups according to BMI for analysis [32].

If the tumor was visible, the size was measured by colposcopy or by preoperative magnetic resonance imaging (MRI). If the tumor was not visible, the size was measured by preoperative MRI or by examining the uterine specimens after radical hysterectomy.

After surgery, patients who had lymph node metastasis, positive resection margin, or paremetrium involvement were classified as the high-risk group. According to the Sedlis criteria, patients with intermediate risk factors were classified into the intermediate-risk group. High-risk and intermediate-risk patients received adjuvant CCRT or RT after the operation.

Surveillance frequency for symptom review and examination depends on stage and adjuvant therapy [33]. After completing the initial treatment (hysterectomy and adjuvant treatment), patients with early stage cervical cancer consulted a doctor every 3 months in the first 2 years, and every 6 months for the next 3 years. Thereafter, as recommended [34], the patients visited a doctor every year.

We determined the progression or recurrence of the disease from imaging studies based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [35]. PFS refers to the time interval between the beginning of treatment and disease progression. OS was defined as the time interval between the date of diagnosis and the date of death from any cause or the end

of the study.

2.4. Statistical analyses

The pre- and post-treatment BMI and body composition of the study population were compared using the paired t-test. We calculated each patient's change in BMI and the volume of body composition components as follows:

$$\Delta x\ (\%) = \frac{x_{Post\text{-}treatment} - x_{Pre\text{-}treatment}}{x_{Pre\text{-}treatment}} \times 100$$

.

The characteristics and survival outcomes of the two groups were compared. We used student's t-test or Mann–Whitney U test to compare continuous variables, and Pearson's chi-square test or Fisher's exact test to compare categorical variables. Pearson's correlation coefficient test was used to calculate the correlation value. Kaplan–Meier methods and log-rank tests were used for the survival analysis. In multivariable analysis, we used the Cox proportional hazards model to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). IBM SPSS software (version 25.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. We considered a *P* value <0.05, as statistically significant.

3. Results

3.1. Characteristics of the study population

In total, 306 patients with early cervical cancer were included in this analysis. **Table 1** describes the clinicopathologic features of the patients. Patients who were classified as overweight according to the Asian BMI standard accounted for 19% of the study population, while obese patients accounted for 34% of the population, 9.5% of whom also had diabetes. Squamous cell carcinoma was the most common histological type (74.2%), and 64.1% of the patients had 2009 FIGO stage IB1. All patients underwent hysterectomy, including 30 patients with RT only and 157 patients with CCRT. There were 125 patients with a pathological surgical tumor size of ≥40 mm. The median clinical cervical tumor size was 26.5 mm, while the median pathological cervical tumor size was 34.0 mm.

3.2. Baseline body composition analysis

Table 2 depicts the patients' baseline body composition. The median value of L3 SMI was 39.4 cm^2/m^2. In terms of waist body composition, the median value of volumetric SMI was 206.5 cm^3/m^3. Other measured and calculated body composition values are also presented in **Table 2**.

Each patient's baseline BMI was positively correlated with L3 SMI

(Pearson's correlation coefficient r=0.249; *P*<0.001), volumetric SMI (r=0.423; *P*<0.001), volumetric total fat index (r=0.812; *P*<0.001), and volumetric visceral fat index (r=0.726; *P*<0.001) (**Figure 3**). All patients were classified into four groups based on the BMI criteria suggested by the WHO for the Asian population. Underweight patients (n=12) showed worse PFS than the others (n=294), however, statistical significance was not observed (*P*=0.079).

We defined sarcopenia as SMI <39.0 cm^2/m^2. Using L3 SMI, no difference was found in PFS and OS between the sarcopenia and non-sarcopenia groups (*P*=0.415 and *P*=0.743, respectively) (**Figure 4A, B**).

The L3 sarcopenia (<39.0 cm^2/m^2) group had a significantly lower BMI (22.1 vs. 24.8 kg/m^2; *P*<0.001) and a higher proportion of underweight (7.1% vs. 1.2%; *P*=0.001), compared to the non-sarcopenia (≥39.0 cm^2/m^2) group. Age, histologic type, stage, risk group, clinical cervical tumor size, and adjuvant treatment were similar between the two groups. (**Table 3**).

In multivariable analysis, L3 sarcopenia was not associated with patients' PFS (aHR, 0.896; 95% CI, 0.504-1.591; *P*=0.707). Meanwhile, parametrial invasion (aHR, 3.058; 95% CI, 1.556-6.011; *P*=0.001) and lymph node metastasis (aHR, 3.122; 95% CI, 1.704-5.722; *P*<0.001) were associated with worse PFS (**Table 4**).

In multivariable analysis of OS, L3 sarcopenia was not a poor prognostic factor for OS (aHR, 1.225; 95% CI, 0.416-3.604; *P*=0.712). Meanwhile, parametrial invasion (aHR, 4.226; 95% CI, 1.154-15.475; *P*=0.030) were associated with worse OS (**Table 5**).

Based on the Q1 value of volumetric SMI, 76 and 230 patients were assigned to the volumetric sarcopenia (<181.5 cm^3/m^3) and volumetric non-sarcopenia (≥181.5 cm^3/m^3) groups, respectively. The volumetric sarcopenia group had a significantly lower BMI (22.1 vs. 23.9 kg/m^2; *P*<0.001) and a higher rate of underweight (7.9% vs. 2.6%; *P*=0.001), as compared to the volumetric non-sarcopenia group. Age, histologic type, stage, risk group, clinical cervical tumor size, pathologic cervical tumor size, and adjuvant treatment were similar between the two groups. (**Table 6**).

The volumetric sarcopenia group showed a significantly worse 3-year PFS rate (78.3% vs. 88.7%; *P*=0.039) and 5-year OS rate (90.0% vs. 97.6%; *P*=0.031), than the volumetric non-sarcopenia group (**Figure 4C, D**).

As shown in **Table 7**, in terms of L3 sectional body composition, the sarcopenia group showed significantly less SMI (36.4 cm^2/m^2 vs. 40.3 cm^2/m^2; *P*=0.002). For waist body composition, the sarcopenia group showed significantly less volumetric SMI(161.5 cm^3/m^3 vs. 220.3 cm^3/m^3; *P*<0.001).

In multivariable analysis, volumetric sarcopenia was identified as a poor prognostic factor for PFS (aHR, 1.922; 95% CI, 1.053-3.506; *P*=0.033) (**Table 8**). Meanwhile, non-squamous cell carcinoma (aHR, 2.001; 95% CI, 1.020-3.926; *P*=0.044), tumor size (aHR, 1.939; 95% CI, 1.056-3.561; *P*=0.033), parametrial invasion (aHR, 3.031; 95% CI, 1.561-5.889; *P*=0.001) and lymph node metastasis (aHR, 3.223; 95% CI, 1.770-5.869; *P*<0.001) were associated with worse PFS.

For OS, multivariable analysis revealed that volumetric sarcopenia was not associated with patients' OS (aHR, 2.863; 95% CI, 0.965-8.496; *P*=0.058).

Meanwhile, parametrial invasion (aHR, 4.323; 95% CI, 1.186-15.749; *P*=0.026) were associated with worse OS (**Table 9**).

3.3. Changes in body composition

Of the 306 patients who underwent body composition analysis, 114 patients did not receive CT scans within 1 month after completion of primary treatment. Th remaining 192 patients underwent subsequent analysis on changes in body composition.

First, we compared patients' pre-treatment and post-treatment BMIs. As post-treatment BMI data were missing in all the patients who did not receive adjuvant treatment (n=66) and 11 of 126 patients who received adjuvant treatment, only 115 patients underwent this analysis. During primary treatment, most patients experienced decrease of BMI (median Δ, -2.7%). In terms of changes in body composition, decrease of total fat volume was the most outstanding (median Δ, -9.1%) (**Figure 5**).

In correlation analyses, the extent of total fat volume (r=0.468; *P*<0.001) and visceral fat volume change (r=0.416; *P*<0.001) were positively correlated with BMI change, while the extent of waist muscle volume change was not correlated with BMI change (r=0.173; *P*=0.065) (**Figure 6**).

In survival analyses, no differences in PFS and OS were observed between the BMI loss and gain groups (*P*=0.975 and *P*=0.687, respectively) (**Figure 7**).

Figure 8 depicts the extent of changes in body composition components

(skeletal muscle, total fat, and visceral fat volumes) during the primary treatment of 192 patients.

Overall, the patients experienced significant decrease in waist skeletal muscle (P<0.001), total fat (P=0.009), and visceral fat (P<0.001) volumes (**Table 10**). The median values of Δ skeletal muscle, Δ total fat, and Δ visceral fat were -3.9%, -5.3%, and -3.1%, respectively. Changes in skeletal muscle volume were not associated with patients' FIGO stage, pathologic risk group, adjuvant treatment, and baseline BMI. However, the volumetric non-sarcopenia group showed significantly greater loss of skeletal muscle volume, as compared to the volumetric sarcopenia group (Δ skeletal muscle, median, -4.5 vs. 1.2; P=0.003).

There were no correlations between baseline BMI and changes in the three body composition components, namely, skeletal muscle, total fat, and visceral fat (**Figure 9**). Correlation analyses revealed that Δ skeletal muscle volume was significantly associated with Δ total fat volume (Pearson's correlation coefficient r=0.556; P<0.001), and Δ visceral fat volume (Pearson's correlation coefficient r=0.352; P<0.001). In addition, Δ total fat volume was significantly associated with Δ visceral fat volume (Pearson's correlation coefficient r=0.861; P<0.001) (**Figure 10**).

Next, we conducted survival analyses according to the changes in total fat volume and visceral fat volume. While no differences in PFS and OS were observed between the visceral fat gain and loss groups, the total fat gain group showed a trend towards worse PFS (3-year survival rate, 79.3% vs. 87.0%; P=0.071), compared to the total fat loss group. However, similar OS was

observed between the total fat gain and loss groups (*P*=0.148) (**Figure 11**).

Table 11 presents patients' clinicopathologic characteristics in the total fat gain and loss groups. Patients in the total fat gain group received open surgery (33.8% vs. 59.3%; *P*=0.001) and para-aortic lymphadenectomy (18.9% vs. 41.5%; *P*=0.001) less frequently, compared to those in the total fat loss group However, other characteristics were similar between the two groups(**Table 11**).

In multivariable analysis, total fat volume gain during primary treatment was identified as an independent poor prognostic factor for PFS (aHR, 2.250; 95% CI, 1.117-4.532; *P*=0.023) (**Table 12**). Meanwhile, non-squamous cell carcinoma (aHR, 3.830; 95% CI, 1.760-8.333; *P*=0.001), minimal invasive surgery (aHR, 2.256; 95% CI, 1.045-4.871; *P*=0.038), parametrial invasion (aHR, 3.215; 95% CI, 1.476-7.006; *P*=0.003 and lymph node metastasis (aHR, 2.291; 95% CI, 1.099-4.774; *P*=0.027) were associated with worse PFS. Owing to the small event number, we could not conduct multivariable analysis for OS.

Then combine baseline volumetric SMI with total fat volume change. Initially, the volumetric sarcopenia patients who gained total fat during treatment showed significantly worse PFS (3-year survival rate, 64.8% vs. 86.6%; *P*=0.014) than others (**Figure 12**). Although OS (*P*=0.050) is not very obvious, there are differences, but because the number of events is small, only PFS is used for additional analysis.

As shown in **Table 13**, there were no differences in age, BMI, stage, histological type, tumor size, pathologic risk factors and adjuvant treatment

between initially volumetric sarcopenia with total fat volume gain group and others groups.

In multivariable analysis, baseline volumetric sarcopenia with total fat gain during primary treatment was identified as an independent poor prognostic factor for PFS (aHR, 2.565; 95% CI, 1.118-5.885; *P*=0.026) (**Table 14**). With that, non-squamous cell carcinoma (aHR, 3.884; 95% CI, 1.739-8.499; *P*=0.001), parametrial invasion (aHR, 2.716; 95% CI, 1.263-5.837; *P*=0.010) and lymph node metastasis (aHR, 2.128; 95% CI, 1.020-4.438; *P*=0.044) are also associated with PFS deterioration. Owing to the small event number, we could not conduct multivariable analysis for OS.

4. Discussion

In this study, we found no differences in PFS and OS between the L3 SMI sarcopenia and non-sarcopenia groups (*P*=0.415 and *P*=0.743, respectively). L3 sarcopenia was not a poor prognostic factor for PFS (aHR, 0.896; 95% CI, 0.504-1.591; *P*=0.707) and OS (aHR, 1.225; 95% CI, 0.416-3.604; *P*=0.712). However, the volumetric sarcopenia group showed significantly worse PFS (3-year survival rate, 78.3% vs. 88.7%; *P*=0.039) and OS (5-year survival rate, 90.0% vs. 97.6%; *P*=0.031), than did the volumetric non-sarcopenia group. In multivariable analysis adjusting for clinicopathologic factors, volumetric sarcopenia was identified as a poor prognostic factor for PFS (aHR, 1.922; 95% CI, 1.053-3.506; *P*=0.033), but not OS (aHR, 2.863; 95% CI, 0.965-8.496; *P*=0.058).

Sarcopenia, defined by L3 SMI, is a well-known prognostic factor for many malignancies despite the cut-off values varying among the studies. In patients with liver cancer, the presence of sarcopenia at the time of the initial treatment was associated with worse PFS and OS [25]. In colorectal cancer, baseline sarcopenia measured by CT was closely related to the risk of recurrence, postoperative complications, and long-term prognosis in older patients [26]. Consistent results have also been reported for other malignancies [36,37].

Only a few studies have investigated the prognostic role of sarcopenia in patients with cervical cancer. Matsuoka et al. reported that baseline sarcopenia was not a prognostic factor in patients with cervical cancer who received

primary CCRT or RT [29], similar to our results. However, the Japanese study differed from our study in terms of disease setting and primary treatment methods.

We consider that the analysis of a single cross-sectional CT image at the L3 level has limitations. Due to the displacement of the gastrointestinal tract, the abdominal muscle and fat may be measured inaccurately on abdominal CT images; the distribution of muscle and visceral fat may vary as high as twice the true value [29]. Therefore, we believe that volume measurement is more accurate and intuitive than a single areal measurement. It would be more reliable to analyze the prognostic factors of cancer by measuring volumetric sarcopenia.

In the current study, waist volumetric SMI was a new concept; it has not been studied in cancer research. Therefore, the appropriate cut-off value has not yet been determined. In general, a population-based study is needed to determine the cut-off value of sarcopenia. For example, many studies have referred to the two standard deviations of sex-specific, healthy young adults or the lower 20% of the sex-specific healthy aging adults [38,39]. In addition, the prevalence of sarcopenia is generally considered to be about 20% [40–43]. Using the Q1 value of the waist volumetric SMI, we found that the Q1 group was more differentiated from other groups in terms of PFS. Thus, we inferred that the Q1 group was suitable as a threshold for sarcopenia. Like our study, many previous studies of sarcopenia with L3 SMI or L3 psoas muscle used the Q1 as the cut-off value for sarcopenia [44–46].

There are many reasons for muscle loss, as there are for weight change,

during cancer treatment [47]. To date, studies on sarcopenia in cancer patients have been conducted in the context of cancer cachexia. Patients with advanced-stage cervical cancer are at a high risk for sarcopenia and cachexia. However, even among patients with early stage cervical cancer, some may already have cancer cachexia at the time of diagnosis. Patients with cancer cachexia, especially those with enlarging tumor masses, suffer metabolic dysfunction towards catabolism. Bowel obstruction during disease progression also causes anorexia and reduced food intake [48]. Adjuvant CCRT or RT further aggravates anorexia and loss of body weight [29]. Consequently, poor nutritional status and loss of muscle mass and strength are highly expected in patients with cancer cachexia. In addition to malnutrition, fatigue, physical inactivity, hormonal changes, and increased proinflammatory cytokines can also lead to muscle loss [49].

Current evidence suggests that excessive visceral fat accumulation, also known as visceral obesity, is associated with adverse metabolic consequences, systemic inflammation, and cancer development and progression [50]. However, in our study, the loss or gain of total fat volume and visceral fat volume during treatment did not affect the patients' PFS and OS. However, initially, the volumetric sarcopenia patients who gained total fat during treatment showed significantly worse PFS (P=0.023) than did the others. In multivariate analysis, initial volumetric sarcopenia with total fat gain during primary treatment was identified as an independent poor prognostic factor for PFS (P=0.026). Similar results were also observed in our previous study, which was investigated advanced high-grade serous ovarian cancer [51].

The coexistence of sarcopenia and fat gain seems to affect the survival outcome of patients, which is equal to or greater than the sum of the respective risks of obesity and sarcopenia [52]. A previous study reported that sarcopenia with fat gain increased the mortality of patients with colorectal cancer [53], which is similar to our results. Recent studies have shown that excessive intake, lack of exercise, inflammation, insulin resistance, and changes in the hormonal environment can lead to sarcopenia with fat gain [54].

In the era of precision medicine, identifying patients who have adverse body composition and who are, therefore, at a high risk of disease recurrence and mortality would be an important issue. Physicians may prescribe nutritional support or physical exercise for volumetric sarcopenia patients to prevent fat gain and maintain skeletal muscle mass, according to the recommendations from the study groups [55–57]. We may consider routine body composition analysis in patients with early stage cervical cancer to screen for sarcopenia.

This study had several limitations. First, the small sample size and possible selection bias due to the retrospective study design are problematic. Second, the relationship between sarcopenia and complications related to surgery, CCRT, or RT has not been studied. Third, we could not obtain BMI data after treatment or conduct further analysis based on the changes in BMI. Lastly, although muscle mass was successfully measured on CT scans, it was difficult to understand muscle quality using CT. It is well known that a decline in muscle quality is related to steatosis or fat infiltration (i.e., myosteatosis). Currently, MRI is the best method for evaluating muscle mass

and steatosis. In addition, MRI can also provide information on muscle inflammation, edema, fibrosis and atrophy [58]. However, because of its high cost, limited availability and long image acquisition time, MRI is not routinely performed during surveillance at our institution. Therefore, we could not conduct a longitudinal MRI analysis.

In this study, we used a commercially available artificial intelligence-based imaging analysis tool to measure the waist volume of each body component. Volume measurements seem to be more accurate in terms of body composition analysis. Furthermore, the artificial intelligence-based tool provided fast, labor-saving imaging analysis.

In conclusion, our study results demonstrate that volumetric sarcopenia might be a prognostic biomarker for early cervical cancer. In particular, initial sarcopenia patients who gained body fat during primary treatment were at a high risk of disease recurrence. To the best of our knowledge, this is the first study to use CT-based body composition measurement technology to determine the prognostic factors of Korean patients with early stage cervical cancer. Because CT scans are commonly performed in patients with cervical cancer before and after, it is feasible to measure the waist volume of each body component and evaluate its longitudinal changes as a potential prognostic biomarker for patients with cervical cancer.

Table 1. Clinicopathologic characteristics of study population

Characteristics	All (n=306, %)
Age, years	
Mean ± SD	51.5 ± 11.3
BMI, kg/m^2	
Median (IQR)	23.4 (21.2–25.9)
Underweight (<18.5)	12 (3.9)
Normal (18.5–22.9)	132 (43.1)
Overweight (23.0–24.9)	58 (19.0)
Obesity (≥25.0)	104 (34.0)
Diabetes	29 (9.5)
Surgical approach	
Open	143 (46.7)
Laparoscopy	131 (42.8)
Robot-assisted surgery	32 (10.5)
Conization	88 (28.8)
Histologic type	
Squamous cell carcinoma	227 (74.2)
Adenocarcinoma	66 (21.6)
Adenosquamous carcinoma	13 (4.2)
2009 FIGO stage	
IB1	196 (64.1)
IB2	49 (16.0)
IIA1	21 (6.9)
IIA2	40 (13.1)
Radicality of hysterectomy	
Type B	27 (8.8)
Type C	279 (91.2)
Para-aortic lymphadenectomy	
No	220 (71.9)
Sampling/Dissection	86 (28.1)
Clinical cervical tumor size*, mm	
Median (IQR)	26.5 (10.0–40.1)
Pathologic cervical tumor size†, mm	
Median (IQR)	34.0 (16.0–50.0)
<20	81 (26.5)
≥20 and <40	100 (32.7)
≥40	125 (40.8)
Pathologic risk factors	
Parametrial invasion	62 (20.3)
Lymph node metastasis	85 (27.8)
Resection margin involvement	30 (9.8)
LVSI	154 (50.3)
Deep one-third stromal invasion	161 (52.6)
Risk group	
Low-risk	119 (8.9)
Intermediate-risk	70 (22.9)
High-risk	117 (38.2)
Adjuvant treatment	
No	119 (38.9)
Radiation only	30 (9.8)

CCRT	157 (51.3)

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LVSI, lymphovascular space invasion; SD, standard deviation.

*Measured by either colposcopic examination or pre-treatment MRI.

†Measured on the uterine specimen.

Table 2. Baseline body composition of all patients.

Characteristics	All patients
L3 sectional body composition	
Measured	
Skeletal muscle area, cm^2	96.9 (84.2–110.5)
Calculated	
Skeletal muscle index, cm^2/m^2	39.4 (34.0–44.3)
Waist body composition	
Measured	
Skeletal muscle volume, cm^3	823.0 (681.2–935.1)
Total fat volume, cm^3	1888.3 (1254.0–2593.2)
Visceral fat volume, cm^3	580.6 (265.7–930.3)
Subcutaneous fat volume, cm^3	1265.7 (956.4–1699.3)
Calculated	
Skeletal muscle index, cm^3/m^3	206.5 (181.5–236.2)
Total fat index, cm^3/m^3	481.1 (320.3–675.8)
Visceral fat index, cm^3/m^3	145.4 (65.9–240.1)
Subcutaneous fat index, cm^3/m^3	327.0 (240.5–435.0)
Ratio	
Fat-to-muscle ratio	2.4 (1.7–3.1)
Visceral-to-subcutaneous fat ratio	0.4 (0.3–0.6)
Skeletal muscle-to-visceral fat ratio	1.4 (1.0–2.7)

Presented with median value with interquartile range.

Table 3. Clinicopathologic characteristics by L3 sarcopenia

Characteristics	Sarcopenia (n141, %)	Non-sarcopenia (n=165, %)	*P*
Age, years			
Mean ± SD	50.5 ± 11.1	52.2 ± 11.5	0.187
BMI, kg/m^2			
Median (IQR)	22.1 (20.3–24.3)	24.8 (22.2–27.0)	<0.001
Underweight (<18.5)	10 (7.1)	2 (1.2)	0.001
Normal (18.5–22.9)	77 (54.6)	55 (33.3)	
Overweight (23.0–24.9)	26 (18.4)	32 (19.4)	
Obesity (≥25.0)	28 (19.9)	76 (46.1)	
Surgical approach			0.456
Open	63 (44.7)	80 (48.5)	
Laparoscopy	60 (42.6)	71 (43.0)	
Robot-assisted surgery	18 (12.8)	14 (8.5)	
Conization	41 (29.1)	47 (28.5)	0.909
Histologic type			0.796
Squamous cell carcinoma	107 (75.9)	120 (72.7)	
Adenocarcinoma	28 (19.9)	38 (23.0)	
Adenosquamous carcinoma	6 (4.3)	7 (4.2)	
2009 FIGO stage			0.943
IB1	89 (63.1)	107 (64.8)	
IB2	23 (16.3)	26 (15.8)	
IIA1	9 (6.4)	12 (7.3)	
IIA2	20 (14.2)	20 (12.1)	
Radicality of hysterectomy			0.858
Type B	12 (8.5)	15 (9.1)	
Type C	189 (91.5)	150 (90.9)	
Para-aortic lymphadenectomy			0.678
No	103 (73.0)	117 (70.9)	
Sampling/Dissection	38 (27.0)	48 (29.1)	
Clinical cervical tumor size*, mm			
Median (IQR)	30.0 (10.0–41.0)	25.0 (10.0–40.0)	0.565
Pathologic risk factors			
Parametrial invasion	31 (22.0)	31 (18.8)	0.488
Lymph node metastasis	34 (24.1)	51 (30.9)	0.186
Resection margin	16 (11.3)	14 (8.5)	0.401
LVSI	73 (51.8)	81 (49.1)	0.640
Deep stromal invasion	74 (52.5)	87 (52.7)	0.966
Adjuvant treatment			0.678
No	55 (39.0)	64 (38.8)	
Radiation only	16 (11.3)	14 (8.5)	
CCRT	70 (49.6)	87 (52.7)	

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LVSI, lymphovascular space invasion; SD, standard deviation.

*Measured by either colposcopic examination or pre-treatment MRI.

†Measured on the uterine specimen.

Table 4. Factors associated with patients' progression-free survival

Characteristics		*Univariable analysis*			*Multivariable analysis*		
		HR	95% CI	*P*	aHR	95% CI	*P*
Age,years	≥ 50 vs. <50	1.159	0.662–2.027	0.606			
BMI, kg/m^2	≥ 23 vs. <23	0.995	0.554–1.788	0.987			
2009 FIGO stage	IIA vs. IB	1.418	0.764–2.632	0.268	0.687	0.337–1.399	0.301
Histologic type	Non-SCC vs. SCC	1.096	0.591–2.032	0.771	1.774	0.919–3.424	0.088
Tumor size, mm	≥ 40 vs. <40	2.253	1.292–3.930	0.004	1.793	0.977–3.292	0.060
Parametrial invasion	Yes vs. No	3.537	2.028–6.171	<0.001	3.058	1.556–6.011	0.001
Lymph node metastasis	Yes vs. No	3.999	2.276–7.027	<0.001	3.122	1.704–5.772	<0.001
Adjuvant treatment	Yes vs. No	3.934	1.769–8.745	0.001			
Surgical approach	MIS vs. Open surgery	1.005	0.575–1.758	0.985	1.693	0.920–3.114	0.091
L3 SMI	Sarcopenia vs. Non-sarcopenia	0.791	0.449–1.393	0.416	0.896	0.504–1.591	0.707

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

Table 5. Factors associated with patients' overall survival

Characteristics		*Univariable analysis*			*Multivariable analysis*		
		HR	95% CI	*P*	aHR	95% CI	*P*
Age,years	≥ 50 vs. <50	1.266	0.439–3.654	0.663			
BMI, kg/m^2	≥ 23 vs. <23	0.892	0.313–2.543	0.830			
2009 FIGO stage	IIA vs. IB	2.599	0.898–7.517	0.078	1.334	0.441–4.327	0.631
Histologic type	Non-SCC vs. SCC	1.084	0.339–3.462	0.892	2.059	0.594–7.139	0.255
Tumor size, mm	≥ 40 vs. <40	1.514	0.506–4.532	0.458			
Parametrial invasion	Yes vs. No	6.682	2.238–19.950	0.001	4.226	1.154–15.475	0.030
Lymph node metastasis	Yes vs. No	5.402	1.795–16.256	0.003	3.229	0.939–11.101	0.063
Adjuvant treatment	Yes vs. No	3.996	0.891–17.923	0.070			
Surgical approach	MIS vs. Open surgery	0.729	0.238–2.239	0.581			
L3 SMI	Sarcopenia vs. Non-sarcopenia	1.192	0.417–3.401	0.743	1.225	0.416–3.604	0.712

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

Table 6. Clinicopathologic characteristics of volumetric sarcopenia and non-sarcopenia groups

Characteristics	Sarcopenia (n=76, %)	Non-sarcopenia (n=230, %)	*P*
Age, years			
Mean ± SD	52.6 ± 11.0	51.1 ± 11.4	0.295
BMI, kg/m^2			
Median (IQR)	22.1 (20.2–24.7)	23.9 (21.7–26.4)	<0.001
Underweight (<18.5)	6 (7.9)	6 (2.6)	0.001
Normal (18.5–22.9)	42 (55.3)	90 (39.1)	
Overweight (23.0–24.9)	15 (19.7)	43 (18.7)	
Obesity (≥25.0)	13 (17.1)	91 (39.6)	
Diabetes	7 (9.2)	22 (9.6)	0.927
Surgical approach			0.914
Open	37 (48.7)	106 (46.1)	
Laparoscopy	31 (40.8))	100 (43.5)	
Robot-assisted surgery	8 (10.5)	24 (10.4)	
Conization	17 (22.4)	71 (30.9)	0.156
Histologic type			0.209
Squamous cell carcinoma	62 (81.6)	165 (71.7)	
Adenocarcinoma	11 (14.5)	55 (23.9)	
Adenosquamous carcinoma	3 (3.9)	10 (4.3)	
2009 FIGO stage			0.293
IB1	47 (61.8)	149 (64.8)	
IB2	9 (11.8)	40 (17.4)	
IIA1	8 (10.5)	13 (5.7)	
IIA2	12 (15.8)	28 (12.2)	
Radicality of hysterectomy			0.285
Type B	9 (11.8)	18 (7.8)	
Type C	67 (88.2)	212 (92.2)	
Para-aortic lymphadenectomy			0.916
No	55 (72.4)	165 (71.7)	
Sampling/Dissection	21 (27.6)	65 (28.3)	
Clinical cervical tumor size*, mm			
Median (IQR)	26.5 (13.5–26.5)	26.5 (10.0–40.0)	0.839
Pathologic cervical tumor size†, mm			
Median (IQR)	32.0 (20.0–55.0)	35.0 (15.0–48.5)	0.757
<20	18 (23.7)	63 (27.4)	0.761
≥20 and <40	27 (35.5)	73 (31.7)	
≥40	31 (40.8)	94 (40.9)	
Pathologic risk factors			
Parametrial invasion	18 (23.7)	44 (19.1)	0.392
Lymph node metastasis	21 (27.6)	64 (27.8)	0.974
Resection margin involvement	7 (9.2)	23 (10.0)	0.841
LVSI	36 (47.4)	118 (51.3)	0.552
Deep one-third stromal invasion	39 (51.3)	122 (53.0)	0.794
2018 FIGO stage			0.679
IB	41 (53.9)	135 (58.7)	

IIA	6 (7.9)	16 (7.0)	
IIB	8 (10.5)	15 (6.5)	
IIIC	21 (27.6)	64 (27.8)	
Risk group			0.735
Low-risk	30 (39.5)	89 (38.7)	
Intermediate-risk	15 (19.7)	55 (23.9)	
High-risk	31 (40.8)	86 (37.4)	
Adjuvant treatment			0.788
No	29 (38.2)	90 (39.1)	
Radiation only	9 (11.8)	21 (9.1)	
CCRT	38 (50.0)	119 (51.7)	

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LVSI, lymphovascular space invasion; SD, standard deviation.

*Measured by either colposcopic examination or pre-treatment MRI.

†Measured on the uterine specimen.

Table 7. Baseline body composition of volumetric sarcopenia and non-sarcopenia groups

Characteristics	Sarcopenia (n=76)	Non-sarcopenia (n=230)	*P*
L3 sectional body composition			
Measured			
Skeletal muscle area, cm^2	89.7 (79.9–104.5)	99.7 (85.9–113.1)	0.003
Calculated			
Skeletal muscle index, cm^2/m^2	36.4 (32.4–40.7)	40.3 (34.9–45.1)	0.002
Waist body composition			
Measured			
Skeletal muscle volume, cm^3	619.3 (534.2–679.0)	869.6 (771.1–980.4)	<0.001
Total fat volume, cm^3	1333.2 (959.0–1698.7)	2126.0 (1488.9–2812.7)	<0.001
Visceral fat volume, cm^3	387.3 (156.7–599.4)	670.7 (341.1–1034.3)	<0.001
Subcutaneous fat volume, cm^3	949.1 (687.5–1211.7)	1362.6 (1075.2–1810.3)	<0.001
Calculated			
Skeletal muscle index, cm^3/m^3	161.5 (145.4–172.5)	220.3 (201.5–250.6)	<0.001
Total fat index, cm^3/m^3	346.7 (232.8–452.0)	554.6 (386.6–722.5)	<0.001
Visceral fat index, cm^3/m^3	92.6 (37.2–145.8)	170.5 (83.5–262.3)	<0.001
Subcutaneous fat index, cm^3/m^3	243.2 (176.1–316.8)	352.2 (276.9–462.9)	<0.001
Ratio			
Fat-to-muscle ratio	2.175 (1.670–2.948)	2.395 (1.807–3.172)	0.127
Visceral-to-subcutaneous fat ratio	0.349 (0.196–0.562)	0.416 (0.282–0.615)	0.016
Skeletal muscle-to-visceral fat ratio	1.703 (1.050–3.469)	1.301 (0.852–2.468)	0.028

Presented with median value with interquartile range.

Table 8. Factors associated with patients' progression-free survival

Characteristics		*Univariable analysis*			*Multivariable analysis*		
		HR	95% CI	*P*	aHR	95% CI	*P*
Age,years	≥ 50 vs. <50	1.159	0.662–2.027	0.606			
BMI, kg/m^2	≥ 23 vs. <23	0.995	0.554–1.788	0.987			
2009 FIGO stage	IIA vs. IB	1.418	0.764–2.632	0.268	0.617	0.302–1.261	0.185
Histologic type	Non-SCC vs. SCC	1.096	0.591–2.032	0.771	2.001	1.020–3.926	0.044
Tumor size, mm	≥ 40 vs. <40	2.253	1.292–3.930	0.004	1.939	1.056–3.561	0.033
Parametrial invasion	Yes vs. No	3.537	2.028–6.171	<0.001	3.031	1.561–5.889	0.001
Lymph node metastasis	Yes vs. No	3.999	2.276–7.027	<0.001	3.223	1.770–5.869	<0.001
Adjuvant treatment	Yes vs. No	3.934	1.769–8.745	0.001			
Surgical approach	MIS vs. Open surgery	1.005	0.575–1.758	0.985	1.680	0.916–3.082	0.093
Volumetric SMI	Sarcopenia vs. Non-sarcopenia	1.823	1.023–3.248	0.042	1.922	1.053–3.506	0.033

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

Table 9. Factors associated with patients' overall survival

Characteristics		*Univariable analysis*			*Multivariable analysis*		
		HR	95% CI	*P*	aHR	95% CI	*P*
Age,years	≥ 50 vs. <50	1.266	0.439–3.654	0.663			
BMI, kg/m^2	≥ 23 vs. <23	0.892	0.313–2.543	0.830			
2009 FIGO stage	IIA vs. IB	2.599	0.898–7.517	0.078	1.066	0.320–3.551	0.917
Histologic type	Non-SCC vs. SCC	1.084	0.339–3.462	0.892	2.409	0.714–8.125	0.156
Tumor size, mm	≥ 40 vs. <40	1.514	0.506–4.532	0.458			
Parametrial invasion	Yes vs. No	6.682	2.238–19.950	0.001	4.323	1.186–15.749	0.026
Lymph node metastasis	Yes vs. No	5.402	1.795–16.256	0.003	3.352	0.993–11.322	0.051
Adjuvant treatment	Yes vs. No	3.996	0.891–17.923	0.070			
Surgical approach	MIS vs. Open surgery	0.729	0.238–2.239	0.581			
Volumetric SMI	Sarcopenia vs. Non-sarcopenia	3.004	1.052–8.574	0.040	2.863	0.965–8.496	0.058

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

Table 10. Changes in volumetric body composition

Characteristics	N	Δ Muscle (%)	*P*	Δ Total fat (%)	*P*	Δ Visceral fat (%)	*P*
All patients	192	-3.9 (-11.0–3.7)	<0.001	-5.3 (-17.6–8.0)	0.009	-3.1 (-19.7–16.5)	<0.001
2009 FIGO stage			0.296		0.002		0.134
IB1	116	-3.6 (-10.1–3.6)		-2.9 (-15.8–12.7)		-2.0 (-16.5–21.5)	
IB2	33	-4.0 (-10.2–6.3)		-5.8 (-18.3–7.0)		-3.0 (-20.7–14.3)	
IIA1	15	0.0 (-9.2–8.2)		-2.4 (-12.9–9.3)		-4.5 (-18.4–20.8)	
IIA2	28	-6.3 (-16.7–1.5)		-17.1 (-27.3–-7.2)		-21.0 (-34.4–10.5)	
Risk group			0.155		0.104		0.858
Low-risk	67	-2.5 (-8.8–3.1)		-2.5 (-10.6–9.0)		-2.5 (-13.5–12.3)	
Intermediate-risk	40	-6.6 (-13.7–0.9)		-11.1 (-19.0–5.6)		-5.2 (-23.3–12.2)	
High-risk	85	-4.2 (-11.6–5.3)		-7.4 (-19.7–9.0)		-4.8 (-23.6–26.7)	
Adjuvant treatment			0.168		0.099		0.835
No	66	-2.4 (-8.9–3.5)		-2.3 (-13.4–9.1)		-2.4 (-13.9–12.5)	
Radiation only	8	-0.0 (-10.4–17.1)		-5.0 (-21.5–17.3)		-9.1 (-23.6–25.4)	
CCRT	118	-4.8 (-12.4–3.2)		-8.7 (-19.3–6.9)		-3.8 (-23.5–22.8)	
Initial BMI, kg/m^2			0.454		0.742		0.448
Underweight-normal (<23.0)	86	-4.2 (-12.1–2.4)		-5.3 (-19.4–10.2)		0.1 (-25.8–27.6)	
Overweight (23.0–24.9)	34	-3.8 (-9.0–5.2)		-3.3 (-16.5–14.7)		-2.2 (-17.7–22.3)	
Obesity (≥25.0)	72	-4.8 (-10.1–6.0)		-5.8 (-17.9–5.2)		-6.6 (-18.4–8.8)	
Initial volumetric SMI			0.003		0.011		0.036
Sarcopenia	39	1.2 (-8.8–16.5)		6.0 (-16.1–17.2)		8.4 (-18.4–42.5)	
Non-sarcopenia	153	-4.5 (-11.3–2.2)		-6.7 (-18.3–4.1)		-5.3 (-21.6–13.0)	

Presented with median value with interquartile range.

Abbreviations: BMI, body mass index; SD, standard deviation.

Table 11. Clinicopathologic characteristics of total fat volume gain or loss

Characteristics	Total fat gain (n=74, %)	Total fat loss (n=118, %)	*P*
Age, years			
Mean ± SD	51.2 ± 11.3	51.4 ± 11.4	0.909
BMI, kg/m^2			
Median (IQR)	23.6 (21.2–26.4)	23.6 (21.2–26.0)	0.949
Underweight (<18.5)	3 (4.1)	4 (3.4)	0.950
Normal (18.5–22.9)	31 (41.9)	48 (40.7)	
Overweight (23.0–24.9)	14 (18.9)	20 (16.9)	
Obesity (≥25.0)	26 (35.1)	46 (39.0)	
Surgical approach			0.001
Open	25 (33.8)	70 (59.3)	
Laparoscopy	32 (43.2)	39 (33.1)	
Robot-assisted surgery	17 (23.0)	9 (7.6)	
Conization	23 (31.1)	30 (25.4)	0.393
Histologic type			0.206
Squamous cell carcinoma	60 (81.1)	87 (73.7)	
Adenocarcinoma	14 (18.9)	27 (22.9)	
Adenosquamous carcinoma	0	4 (3.4)	
2009 FIGO stage			0.087
IB1	50 (67.6)	66 (55.9)	
IB2	12 (16.2)	21 (17.8)	
IIA1	7 (9.5)	8 (6.8)	
IIA2	5 (6.8)	23 (19.5)	
Para-aortic lymphadenectomy			0.001
No	60 (81.1)	69 (58.5)	
Sampling/Dissection	14 (18.9)	49 (41.5)	
Clinical cervical tumor size*, mm			
Median (IQR)	25.0 (10–40.1)	31.5 (16.5–42.0)	0.112
Pathologic risk factors			
Parametrial invasion	14 (18.9)	31 (26.3)	0.242
Lymph node metastasis	23 (31.3)	39 (33.1)	0.776
Resection margin	4 (5.4)	17 (14.4)	0.052
LVSI	34 (45.9)	65 (55.1)	0.217
Deep one-third stromal	36 (48.6)	70 (59.3)	0.148
Adjuvant treatment			0.217
No	31 (41.9)	35 (29.7)	
Radiation only	3 (4.1)	5 (4.2)	
CCRT	40 (54.1)	78 (66.1)	

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LVSI, lymphovascular space invasion; SD, standard deviation.

*Measured by either colposcopic examination or pre-treatment MRI.

†Measured on the uterine specimen.

Table 12. Factors associated with patients' progression-free survival

Characteristics		*Univariable analysis*			*Multivariable analysis*		
		HR	95% CI	*P*	aHR	95% CI	*P*
Age,years	≥ 50 vs. <50	1.318	0.665–2.612	0.429			
BMI, kg/m^2	≥ 23 vs. <23	0.761	0.388–1.491	0.426			
2009 FIGO stage	IIA vs. IB	0.951	0.430–2.101	0.900			
Histologic type	Non-SCC vs. SCC	2.106	1.053–4.212	0.035	3.830	1.760–8.333	0.001
Tumor size, mm	≥ 40 vs. <40	1.656	0.841–3.259	0.144	1.986	0.945–4.175	0.070
Parametrial invasion	Yes vs. No	2.564	1.302–5.047	0.006	3.215	1.476–7.006	0.003
Lymph node metastasis	Yes vs. No	2.663	1.353–5.242	0.005	2.291	1.099–4.774	0.027
Adjuvant treatment	Yes vs. No	2.462	1.019–5.947	0.045			
Surgical approach	MIS vs. Open surgery	1.252	0.638–2.459	0.514	2.256	1.045–4.871	0.038
Total fat change	Gain vs. Loss	1.840	0.939–3.607	0.076	2.250	1.117–4.532	0.023

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

Table 13. Clinicopathologic characteristics of initially volumetric sarcopenia plus total fat volume gain group and others groups.

Characteristics	Others (n=170, %)	Vol sarcopenia plus fat gain (n=22, %)	*P*
Age, years			
Mean ± SD	51.2 ± 11.3	51.4 ± 11.4	0.330
BMI, kg/m^2			
Median (IQR)	23.6 (21.4–26.0)	23.5 (20.6–26.7)	0.750
Underweight (<18.5)	6 (3.5)	1 (4.5)	0.386
Normal (18.5–22.9)	68 (40.0)	11 (50.0)	
Overweight (23.0–24.9)	33 (19.4)	1 (4.5)	
Obesity (≥25.0)	63 (37.1)	9 (40.9)	
Surgical approach			0.787
Open	85 (50.0)	10 (45.5)	
Laparoscopy	63 (37.1)	8 (36.4)	
Robot-assisted surgery	22 (12.9)	4 (18.2)	
Conization	50 (29.4)	3 (13.6)	0.119
Histologic type			0.696
Squamous cell carcinoma	129 (75.9)	18 (81.8)	
Adenocarcinoma	37 (21.8)	4 (18.2)	
Adenosquamous carcinoma	4 (2.4)	0	
2009 FIGO stage			0.738
IB1	102 (60.0)	14 (36.6)	
IB2	31 (18.2)	2 (9.1)	
IIA1	13 (7.6)	2 (9.1)	
IIA2	24 (14.1)	4 (18.2)	
Para-aortic lymphadenectomy			0.120
No	111 (65.3)	18 (81.8)	
Sampling/Dissection	59 (34.7)	4 (18.2)	
Clinical cervical tumor size*, mm			
Median (IQR)	30.0 (12.0–41.3)	29.0 (18.3–41.3)	0.943
Pathologic risk factors			
Parametrial invasion	38 (22.4)	7 (31.8)	0.324
Lymph node metastasis	54 (31.8)	8 (36.4)	0.664
Resection margin	19 (11.2)	2 (9.1)	>0.999
LVSI	89 (52.4)	10 (45.5)	0.542
Deep one-third stromal	94 (55.3)	12 (54.5)	0.947
Adjuvant treatment			0.217
No	58 (34.1)	8 (36.4)	
Radiation only	7 (4.1)	1 (4.5)	
CCRT	105 (61.8)	13 (59.1)	

Abbreviations: BMI, body mass index; CCRT, concurrent chemoradiation therapy; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; LVSI, lymphovascular space invasion; SD, standard deviation.

*Measured by either colposcopic examination or pre-treatment MRI.

†Measured on the uterine specimen.

Table 14. Factors associated with patients' progression-free survival

Characteristics		*Univariable analysis*			*Multivariable analysis*		
		HR	95% CI	*P*	aHR	95% CI	*P*
Age,years	≥ 50 vs. <50	1.138	0.665–2.612	0.429			
BMI, kg/m^2	≥ 23 vs. <23	0.761	0.388–1.491	0.426			
2009 FIGO stage	IIA vs. IB	0.951	0.430–2.101	0.900			
Histologic type	Non-SCC vs. SCC	2.106	1.053–4.212	0.035	3.844	1.739–8.499	0.001
Tumor size, mm	≥ 40 vs. <40	1.656	0.841–3.259	0.144	1.923	0.913–4.050	0.085
Parametrial invasion	Yes vs. No	2.564	1.302–5.047	0.006	2.716	1.263–5.837	0.010
Lymph node metastasis	Yes vs. No	2.663	1.353–5.242	0.005	2.128	1.020–4.438	0.044
Adjuvant treatment	Yes vs. No	2.462	1.019–5.947	0.045			
Surgical approach	MIS vs. Open surgery	1.252	0.638–2.459	0.514	2.233	1.054–4.732	0.036
Sarcopenia and Δ total fat	Sarcopenia and fat gain vs. Others	2.613	1.182–5.776	0.018	2.565	1.118–5.885	0.026

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma; SMI, skeletal muscle index.

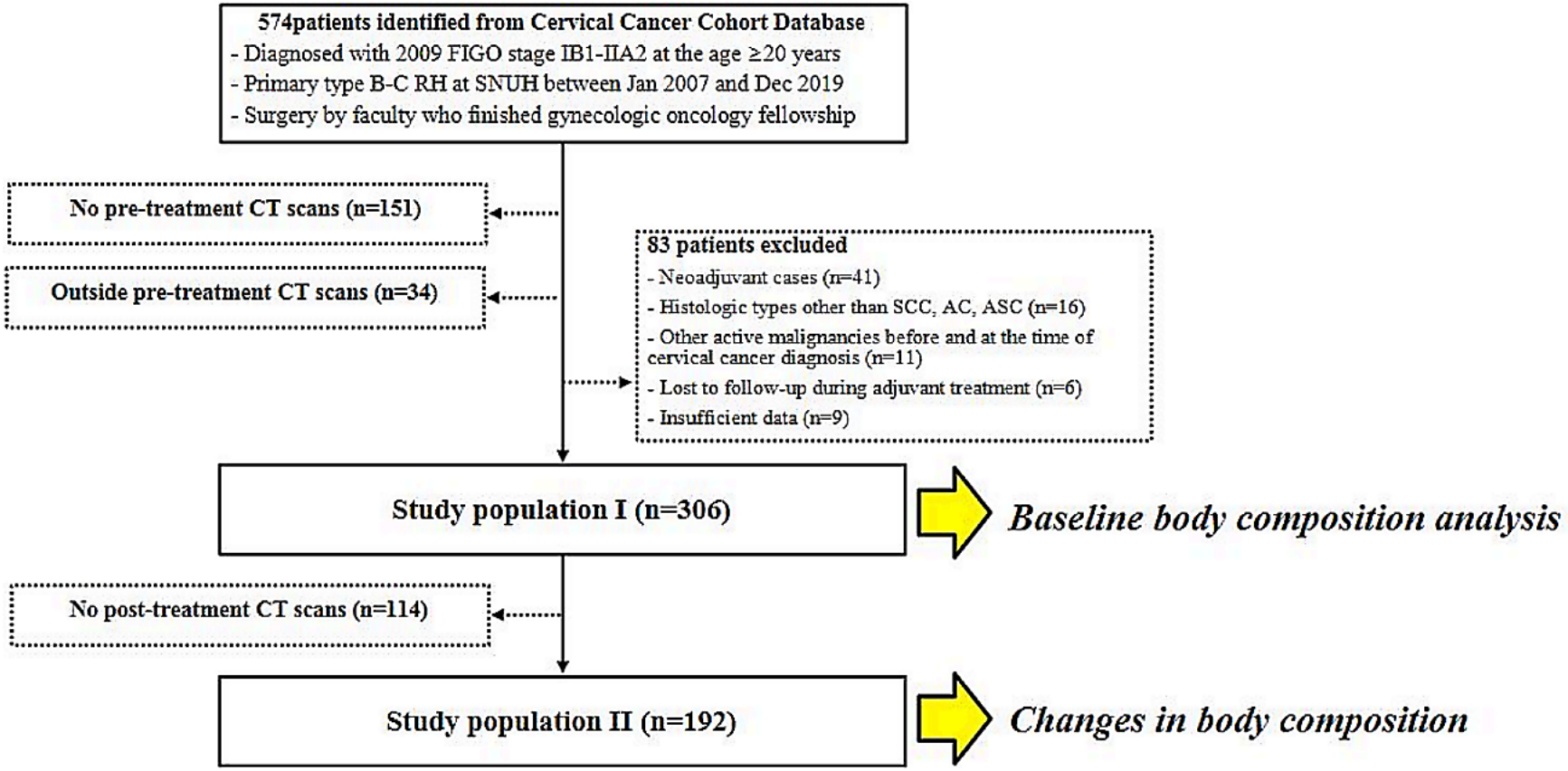


Figure 1. Selection of the study population

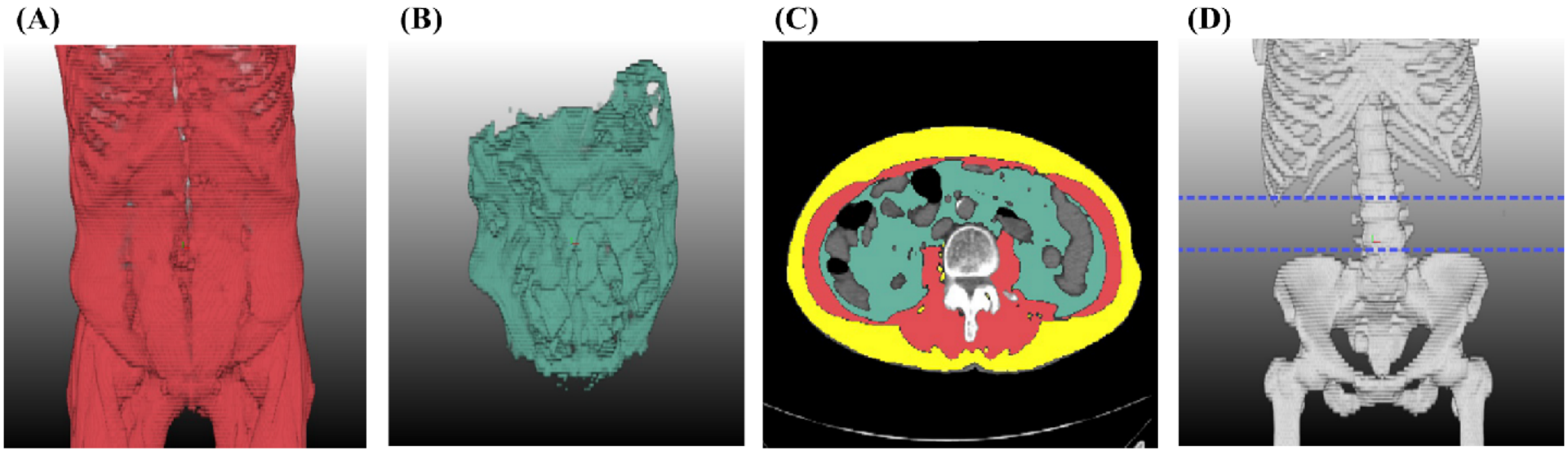


Figure 2. Evaluation of body composition using CT image. (A) Skeletal muscle; (B) Abdominal visceral fat; (C) L3 level cross sectional image; (D) Waist level.

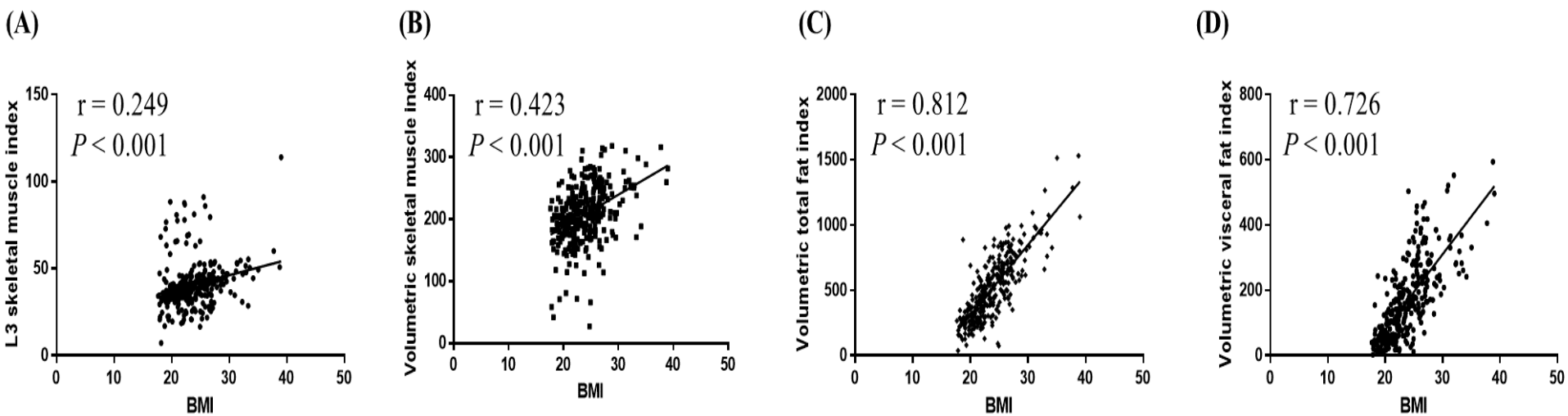
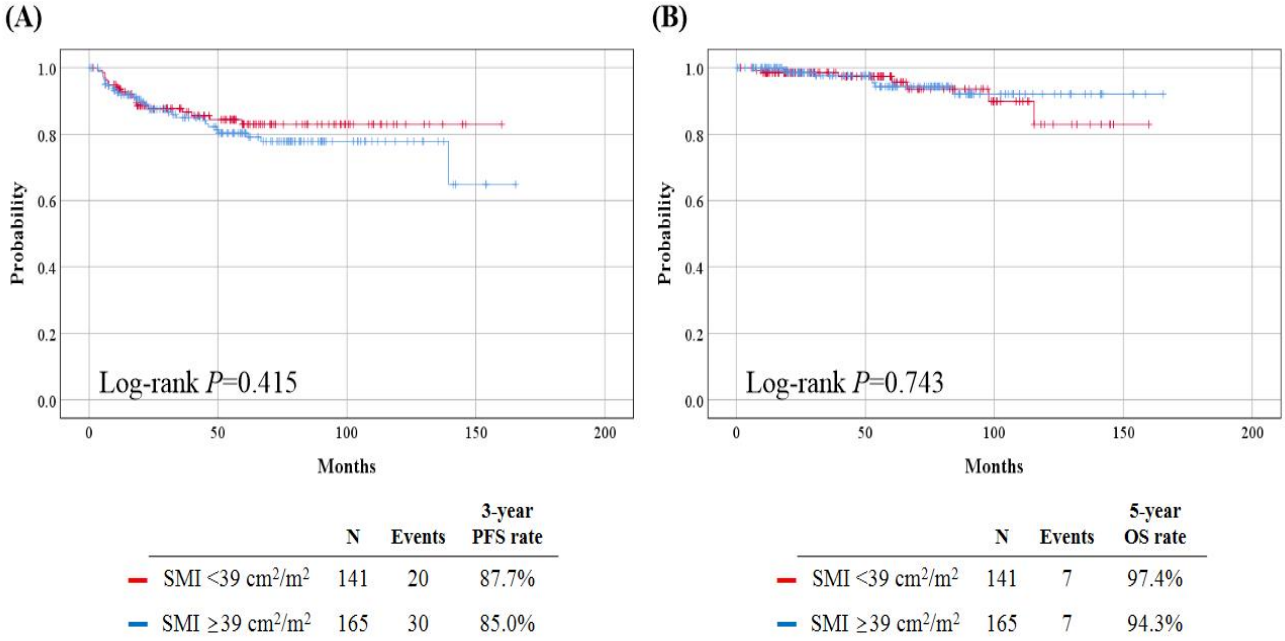


Figure 3. Correlations between body mass index and body composition indices. (A) L3 skeletal muscle index; (B) Volumetric skeletal muscle index; (C) Volumtic total fat index; (D) Volumetric fat index.

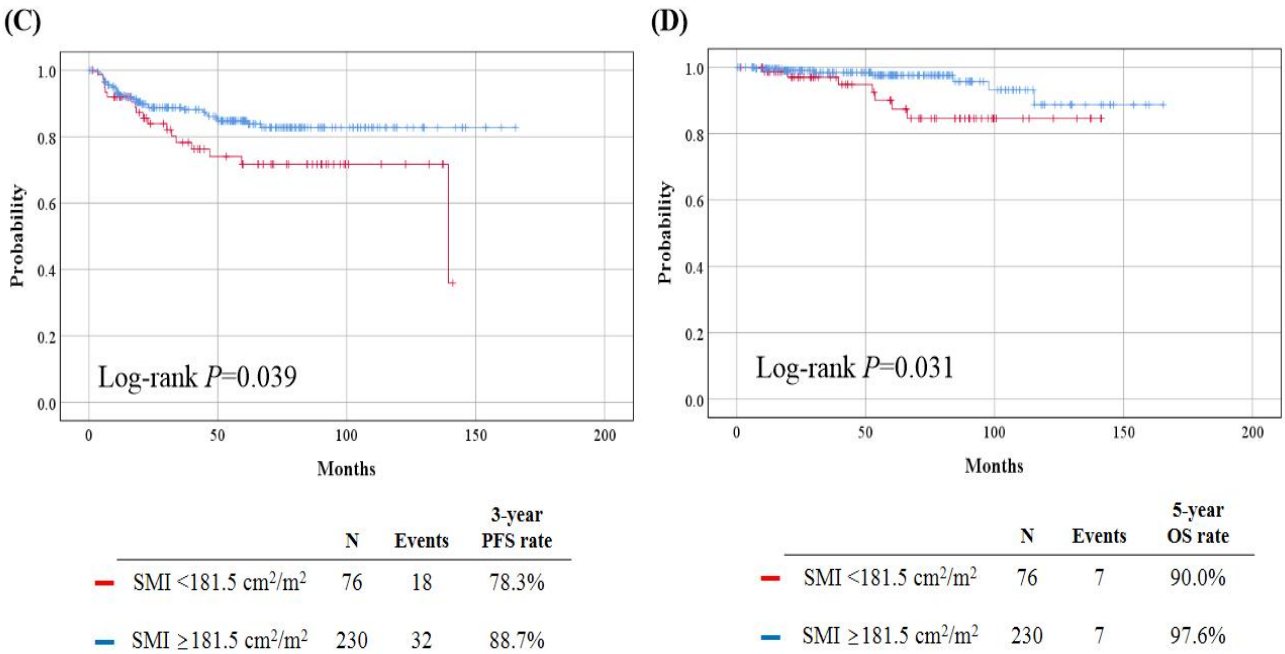
L3 skeletal muscle index



	N	Events	3-year PFS rate
SMI <39 cm²/m²	141	20	87.7%
SMI ≥39 cm²/m²	165	30	85.0%

	N	Events	5-year OS rate
SMI <39 cm²/m²	141	7	97.4%
SMI ≥39 cm²/m²	165	7	94.3%

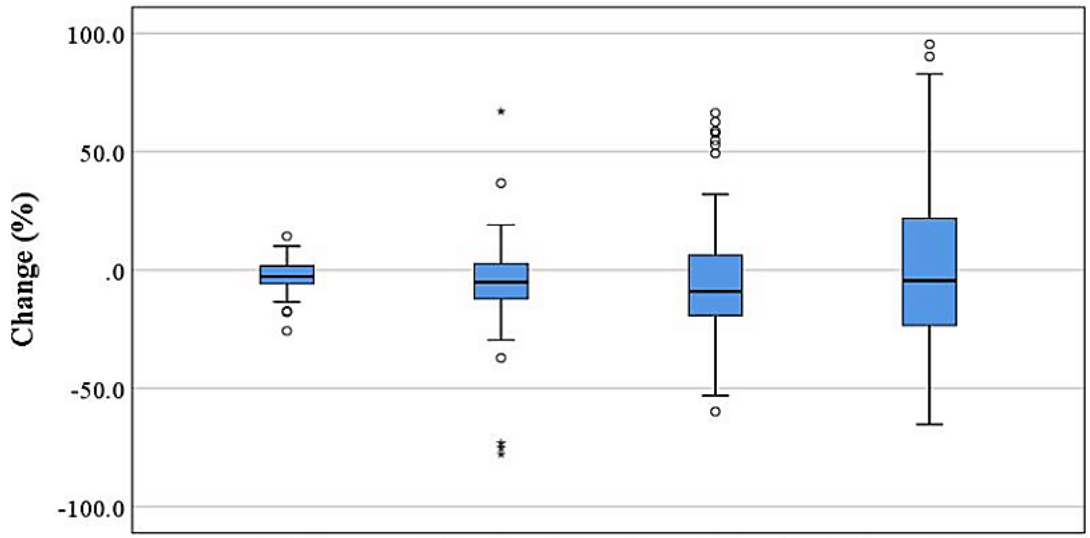
Volumetric skeletal muscle index



	N	Events	3-year PFS rate
SMI <181.5 cm²/m²	76	18	78.3%
SMI ≥181.5 cm²/m²	230	32	88.7%

	N	Events	5-year OS rate
SMI <181.5 cm²/m²	76	7	90.0%
SMI ≥181.5 cm²/m²	230	7	97.6%

Figure 4. Survival outcomes of patients by skeletal muscle index. (Upper) Calculated from L3 level cross sectional image; (Lower) Calculated from volumetric measurement of the waist. (A, C) Progression-free survival; (B, D) Overall survival.



	BMI	Muscle vol	Total fat vol	Visceral fat vol
Mean, %	-2.5	-5.8	-4.9	1.6
Median, %	-2.7	-5.2	-9.1	-4.5
IQR, %	-5.9, 1.8	-12.3, 2.8	-19.3, 6.5	-23.4, 22.8

Figure 5. Changes in body composition components of the patients who had BMI after treatment

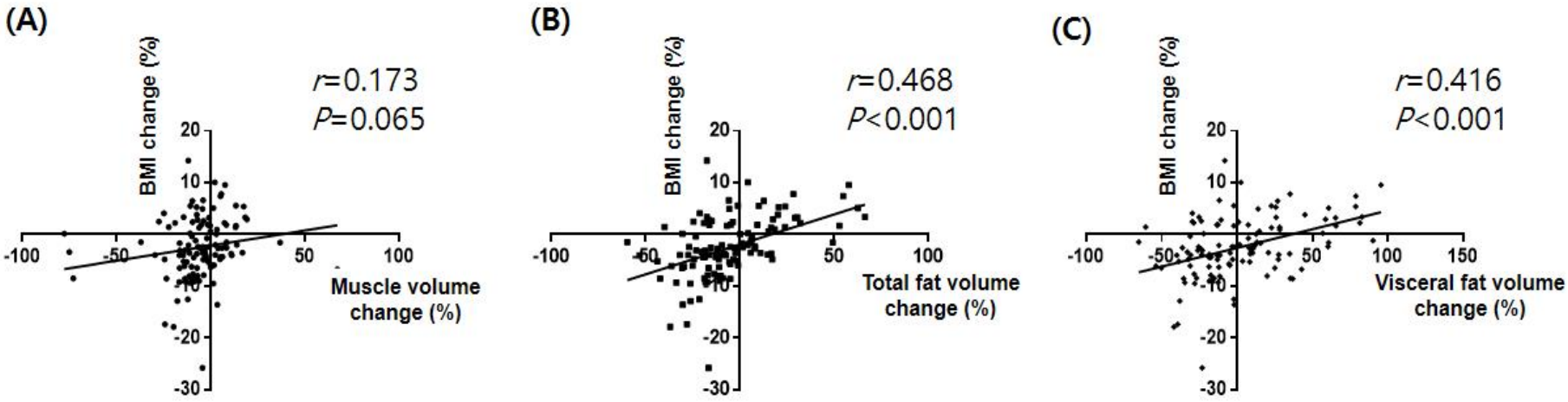
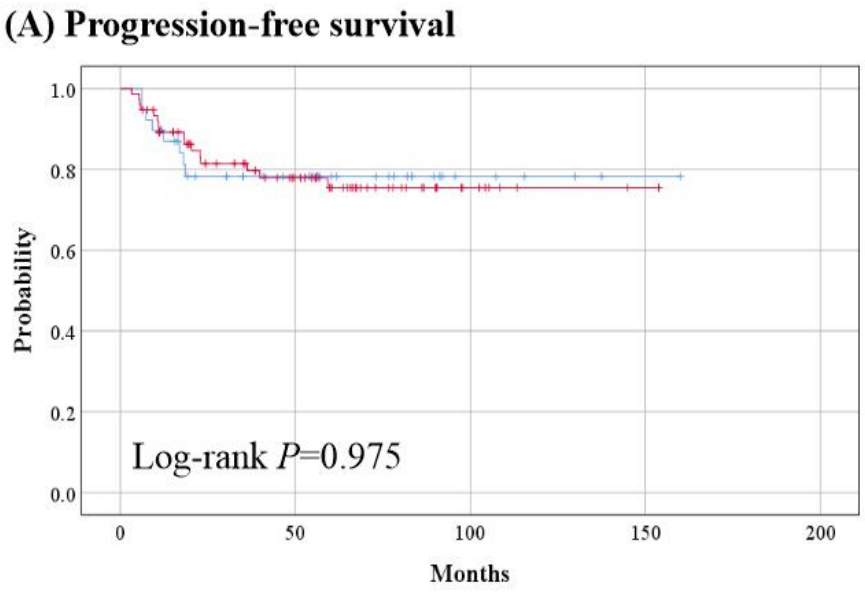
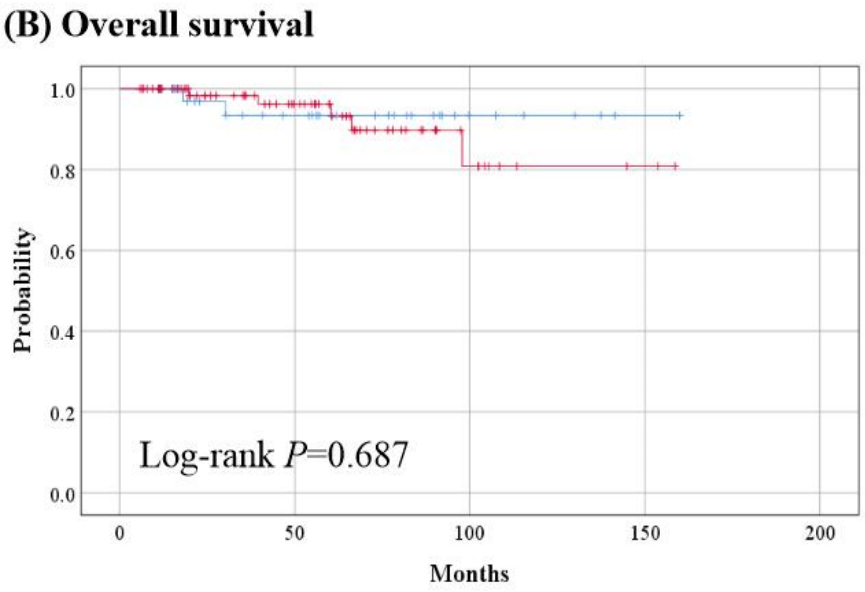


Figure 6. Correlation between BMI change with changes in body composition components. (A) Skeletal muscle volume; (B) Total fat volume; (C) Visceral fat volume.



	N	Events	3-year PFS rate
BMI loss	39	8	78.3%
BMI gain	76	16	81.5%



	N	Events	5-year OS rate
BMI loss	39	2	93.4%
BMI gain	76	5	96.2%

Figure 7. Survival outcomes of patients by BMI change.

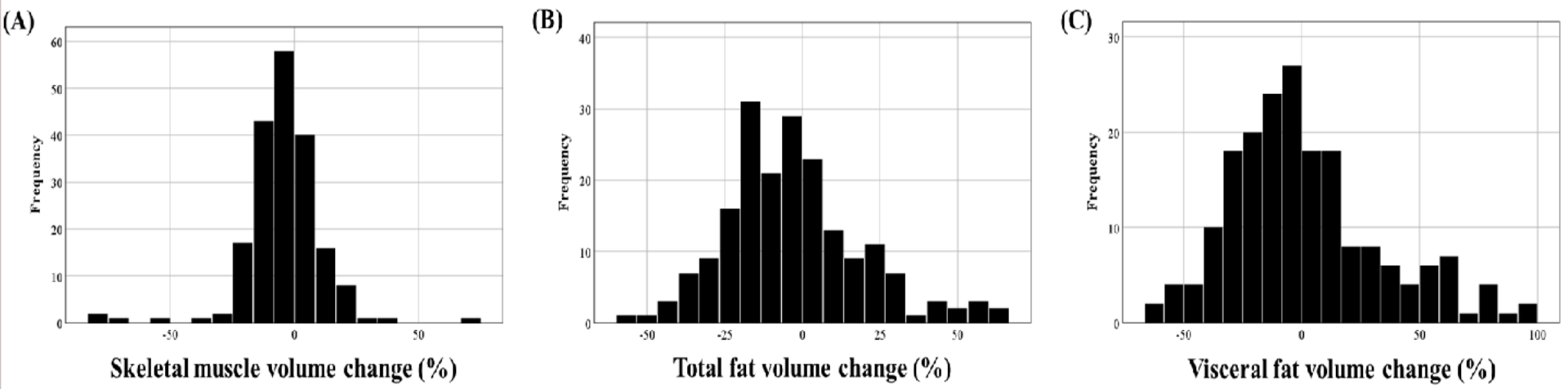


Figure 8. Distributions of the patients by extent of changes in body composition components. (A) Skeletal muscle volume; (B) Total fat volume; (C) Visceral fat volume.

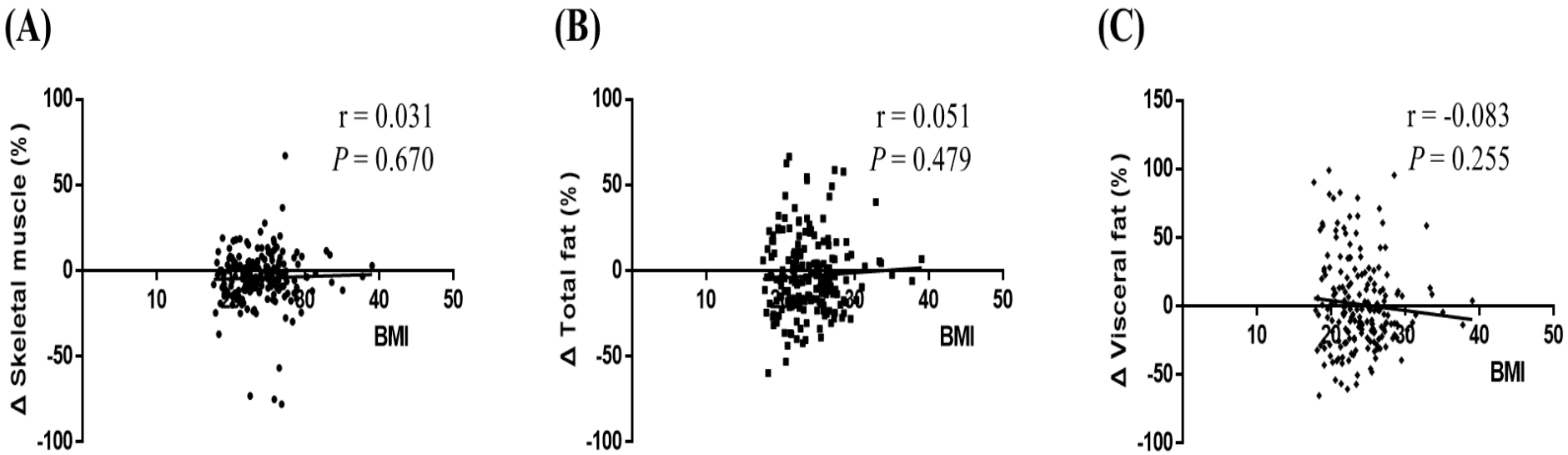


Figure 9. Distributions of the patients by baseline BMI and changes in body composition components. (A) Skeletal muscle volume; (B) Total fat volume; (C) Visceral fat volume.

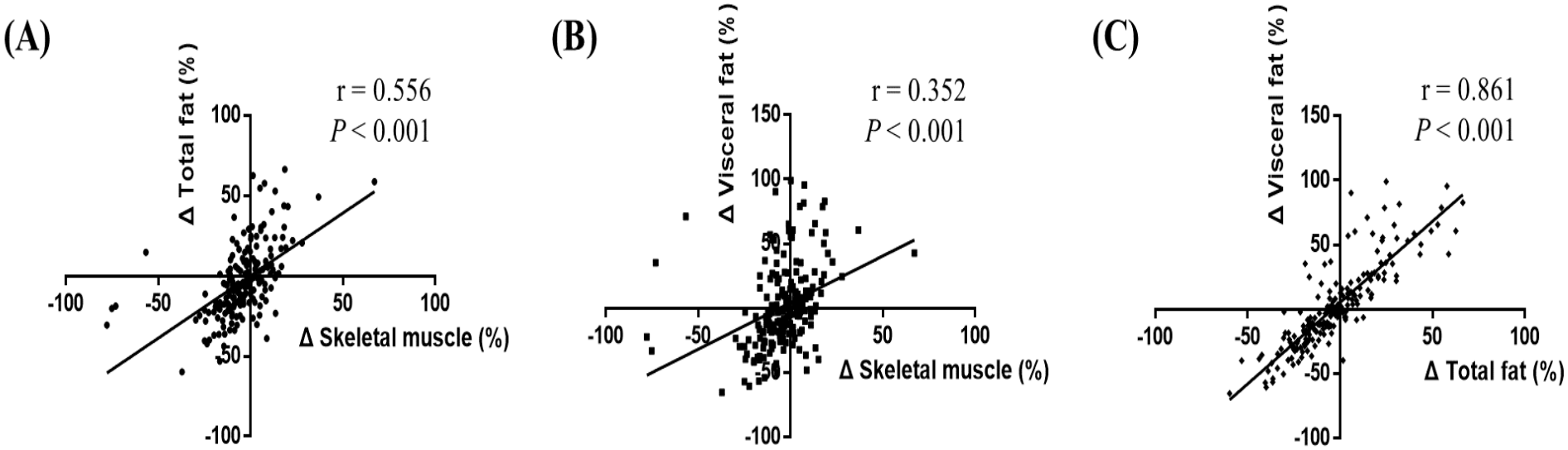


Figure 10. Correlation between changes in body composition components. (A) Skeletal muscle and total fat; (B) Skeletal muscle and visceral fat; (C) Total fat and visceral fat.

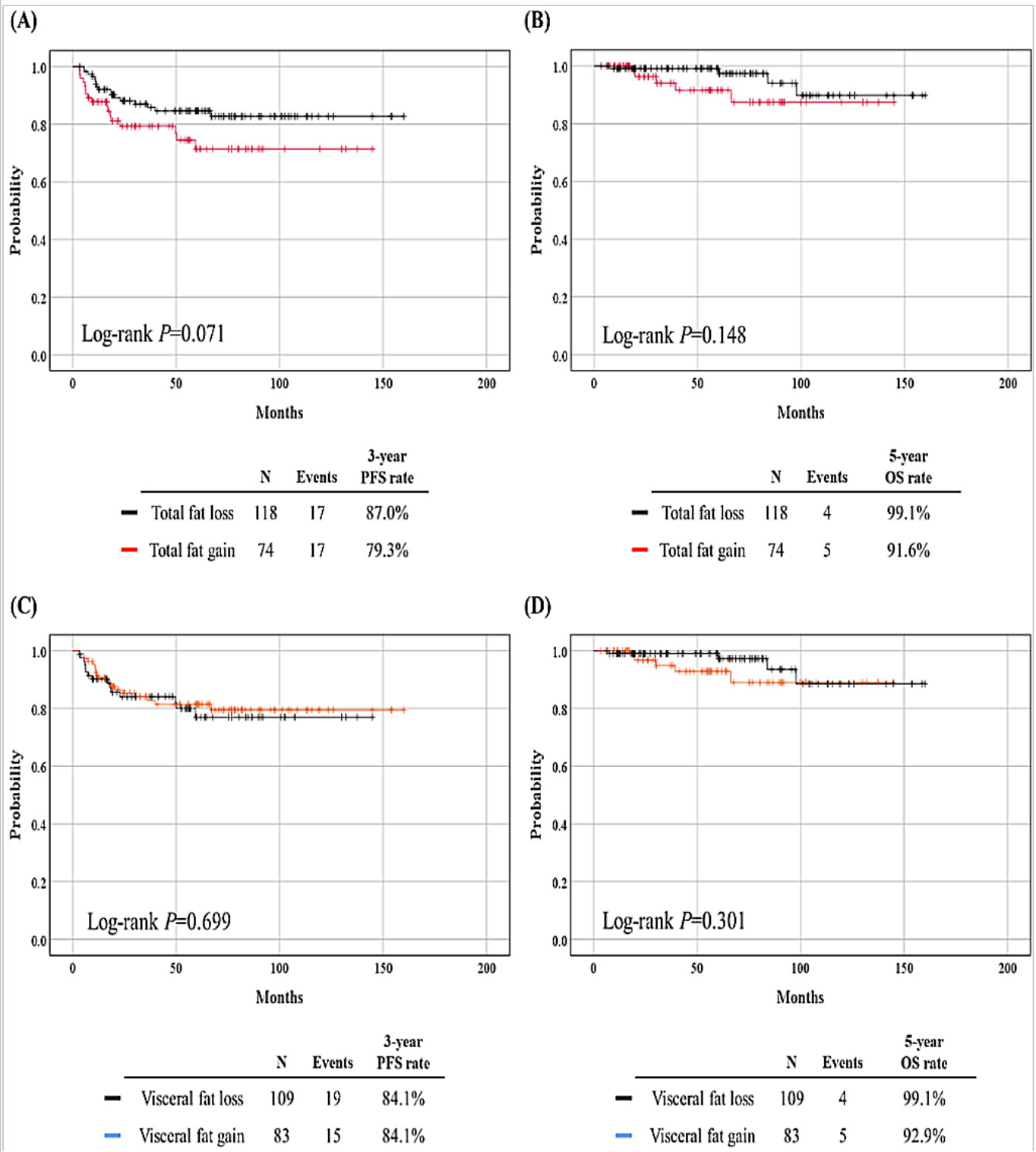
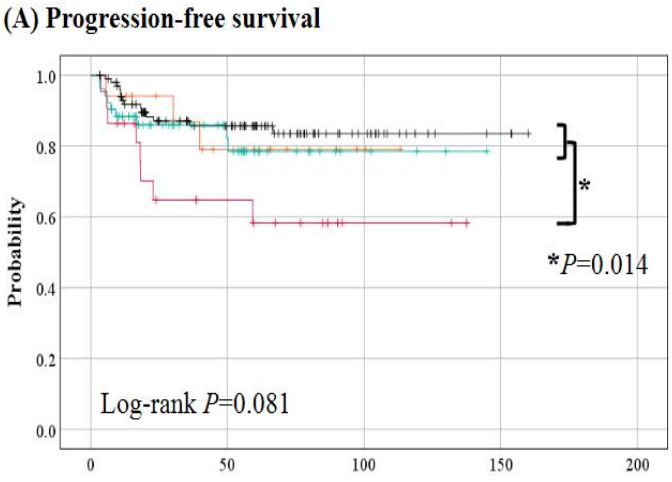
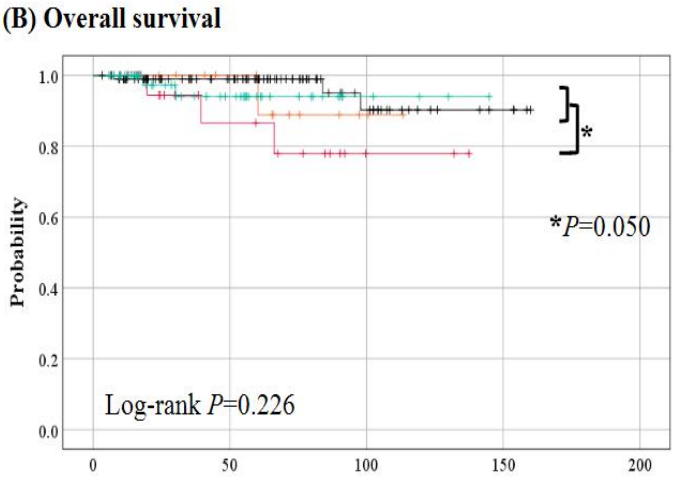


Figure 11. Comparisons of survival outcomes according to changes in total fat volume (Upper); and visceral fat volume (Middle). (A, C) Progression-free survival; (B, D) Overall survival.



Pre-treatment volumetric SMI	Total fat volume change	N	Events	3-year PFS rate
Non-sarcopenia	Loss	101	14	87.0%
Non-sarcopenia	Gain	52	9	86.0%
Sarcopenia	Loss	17	3	86.9%
Merge		170	26	86.6%
Sarcopenia	Gain	22	8	64.8%



Pre-treatment volumetric SMI	Total fat volume change	N	Events	5-year OS rate
Non-sarcopenia	Loss	101	3	99.0%
Non-sarcopenia	Gain	52	2	84.1%
Sarcopenia	Loss	17	1	100.0%
Merge		170	6	97.8%
Sarcopenia	Gain	22	3	86.6%

Figure 12. Comparisons of survival outcomes by combinations of initial sarcopenia and changes in total fat volume. (A) Progression-free survival; (B) Overall survival.

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FIGO: International Federation of Gynecology and Obstetrics

SNUH: Seoul National University Hospital

SMI: Skeletal muscle index

CT: computed tomography

L3: third lumbar vertebra

Q1: first quartile

PFS: progression-free survival

OS: overall survival

aHR: adjusted hazard ratio

CI: confidence interval

BMI: body mass index

WHO: World Health Organization

CCRT: concurrent chemoradiation therapy

RT: radiotherapy

MRI: magnetic resonance imaging

aHRs: adjusted hazard ratios

CIs: confidence intervals

국 문 초 록

인공 지능 기반으로 측정한 체성분 용적이 자궁경부암 환자 생존 예후에 미치는 영향

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본 연구는 한국의 초기 자궁경부암 환자 근 세포 감소와 신체 성분이 생존 결과에 미친 영향을 탐구 한다.

서울대학교병원에서 치료 받은 2009년 국제 산부인과 연합회 IB1-IIA2기 자궁경부암 환자를 회고적으로 분석 했다.

치료 전, 후 컴퓨터 단층 스캔에서 스캔한 익명 디지털 이미지는 인공 지능 기반 상업용 소프트웨어(DEEPCATCH v1.0.0.0; MEDICALIP Co. Ltd., Seoul, Korea). 이 소프트웨어는 신체 구성 요소의 자동 부피 분할을 제공 하며 가슴 늑골 하단과 장골 산마루 상단 사이에 복부 허리를 표시 하고 각 신체 구성 요소의 허리 부피를 측정 한다(cm^3). 골격 근, 복부 내장 지방과 피하 지방의 허리 부피를 계량화 하고 높이로 표준화 한다. 이 소프트웨어는 또 세번째 허리 척추(L3) 수준의 단일 횡단면 CT 영상에서 골격 근 면적(cm^2)을 자동 으로 측정 한다.골격 근 면적을 높이 단위로 분류 하여 L3 골격 근 지수를 얻을수 있다.

L3 근 세포 감소를 L3 SMI <39.0 cm^2/m^2로 정의 한다. 또 용적 SMI의 첫번째 4분 자리수(Q1) 값에 따라 용적 근 감소 증을 정의 했다. L3 근 세포 감소 증과 용적 근 세포 감소 증의 존재에 따라 환자의 임상 병리적 특성과 생존 결과를 비교해 봤다.

총 306명의 환자가 연구에 포함 되었다. L3 SMI, 근 감소 팀과 비 근 감소 팀 간의 무 진전 생존 율(PFS)과 총 생존 율(OS) 은 차이가 없었다(각각 *P*=0.415 와 *P*=0.743). L3 근육 감소 증(<39.0 cm^2/m^2) 팀은 비 근 세포 감소 증(≥39.0 cm^2/m^2) 팀에 비하면 체중 지수가 현저히 감소 (BMI) (22.1 vs. 24.8 kg/m^2; *P*<0.001), 체중 부족 비율이 비교적 높다(7.1% 대 1.2%;P = 0.001). 두 그룹의 환자 연령, 조직학 유형, 분기, 위험 그룹, 임상 자궁 경부 종양 크기 및 보조 치료가 비슷 했다. 다 변수 분석에서 L3 근 세포 감소는 환자의 PFS와 무관 하다(aHR, 0.896; 95% CI, 0.504-1.591; *P*=0.707) 와 OS (aHR, 1.225; 95% CI, 0.416-3.604; *P*=0.712).

이어 용적 SMI Q1 값에 따라 76명과 230명을 용적 근 감소 증(<181.5 cm^3/m^3)과 용적 비 근 감소 증(≥181.5 cm^3/m^3) 두 그룹으로 나누었다. 두 그룹의 환자 연령, 조직학 유형, 분기, 위험 그룹, 임상 자궁 경부 종양 크기, 병리 자궁 경부 종양 크기 및 보조 치료가 비슷 하다. 용적 근 감소 증 그룹의 PFS(3년 생존 율, 78.3% vs. 88.7%; *P*=0.039) 와 OS (5년 생존 율, 90.0% vs. 97.6%; *P*=0.031)는 용적 비 근 세포 감소 그룹보다 현저히 악화 했다. 임상 병리 요소를 교정 하는 다 변수 분석에서 용적 근 감소 증은 PFS(aHR, 1.922; 95% CI, 1.053-3.506; *P*=0.033)의 불량 예후 요인으로 여겨 진다. 그러나 OS(aHR, 2.863; 95% CI, 0.965-8.496; *P*=0.058)는 아니 였다.

이어서 우리는 치료 전, 후의 신체 성분(n=192)을 비교 했다. 첫 치료 기간에 총 지방을 증가 시키는 초기 용적 근 감소 증 환자의 PFS(3년 생존 율, 64.8% vs. 86.6%; *P*=0.014)가 다른 그룹 보다 현저히 떨어 졌다. OS(*P*=0.050)도 현저 하지는 않지만 차이는 있었다. 다 변수 분석에 따르면 첫 치료 기간의 초기 용적 근 감소와 총 지방

증가가 PFS(aHR, 2.565; 95% CI, 1.118-5.885; *P*=0.026) 악화와 관련 있다.

요약하면 한국 초기 자궁 경부 암 환자의 치료 전 용적 근육의 감소가 재발 율을 높였다. 또 첫 치료 기간에 근 용적이 감소 하고 총 지방이 증가 하는 환자가 재발 할 위험이 높다.

키워드: 자궁경부암, 체성분, 체중 지수, 내장 지방, 근육 질, 예후, 생존 율.

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