Muscle loss during primary debulking surgery and chemotherapy predicts poor survival in advanced-stage ovarian cancer

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Abstract

Background   Sarcopenia is commonly observed in patients with advanced-stage epithelial ovarian cancer (EOC). However, the effect of body composition changes—during primary debulking surgery (PDS) and adjuvant platinum-based chemotherapy—on outcomes of patients with advanced-stage EOC is unknown. This study aimed to evaluate the association between body composition changes and outcomes of patients with stage III EOC treated with PDS and adjuvant platinum-based chemotherapy.

Methods   Pre-treatment and post-treatment computed tomography (CT) images of 139 patients with stage III EOC were analysed. All CT images were contrast-enhanced scans and were acquired according to a standardized protocol. The skeletal muscle index (SMI), skeletal muscle radiodensity (SMD), and total adipose tissue index were measured using CT images obtained at the L3 vertebral level. Predictors of overall survival were identified using Cox regression models.

Results   The median follow-up was 37.9 months. The median duration between pre-treatment and post-treatment CT was 182 days (interquartile range: 161–225 days). Patients experienced an average SMI loss of 1.8%/180 days (95% confidence interval: −3.1 to −0.4; $P = 0.01$) and SMD loss of 1.7%/180 days (95% confidence interval: −3.3 to −0.03; $P = 0.046$). SMI and SMD changes were weakly correlated with body mass index changes (Spearman ρ for SMI, 0.15, $P = 0.07$; ρ for SMD, 0.02, $P = 0.82$). The modified Glasgow prognostic score was associated with SMI loss (odds ratio: 2.42, 95% confidence interval: 1.03–5.69; $P = 0.04$). The median time to disease recurrence was significantly shorter in patients with SMI loss ≥5% after treatment than in those with SMI loss <5% or gain (5.4 vs. 11.2 months, $P = 0.01$). Pre-treatment SMI (1 cm^2/m^2 decrease; hazard ratio: 1.08, 95% confidence interval: 1.03–1.11; $P = 0.002$) and SMI change (1%/180 days decrease; hazard ratio: 1.04, 95% confidence interval: 1.01–1.08; $P = 0.002$) were independently associated with poorer overall survival. SMD, body mass index, and total adipose tissue index at baseline and changes were not associated with overall survival.

Conclusions   Skeletal muscle index decreased significantly during treatment and was independently associated with poor overall survival in patients with stage III EOC treated with PDS and adjuvant platinum-based chemotherapy. The modified Glasgow prognostic score might be a predictor of SMI loss during treatment.

Keywords   Ovarian cancer; Sarcopenia; Computed tomography; Body composition; Cancer cachexia; Systemic inflammation

Introduction

Ovarian cancer is the most lethal gynaecologic malignancy, with approximately 295 414 new cases and 184 799 deaths worldwide in 2018.[1] Patients with advanced-stage epithelial ovarian cancer (EOC) often develop large tumours and ascites that can affect dietary intake and bowel function; therefore, patients often appear malnourished or have cachexia at the time of presentation.[2] Severe loss of muscle mass (i.e. sarcopenia) is a crucial component of cancer cachexia and was associated with poor outcomes in various malignancies.[3–10] Sarcopenia may also affect the outcomes of patients with advanced-stage EOC; however, previous studies showed inconsistent associations between pre-treatment sarcopenia and survival outcomes of patients with EOC.[11–17]

The mainstay of treatment for advanced-stage EOC is primary debulking surgery (PDS) and adjuvant platinum-based chemotherapy.[18] During the course of cancer therapy, body composition may change and influence outcomes of cancer patients.[5–10] Body composition changes could be associated with systemic inflammation, treatment-related toxicity, physical inactivity, malnutrition, cancer invasiveness, and cancer therapy.[19–25] Therefore, evaluating the body composition at a single specific time point may not help in predicting survival. A longitudinal study evaluating the changes in body composition during cancer therapy provides a more comprehensive understanding about the influence of body composition on the outcomes of EOC.[12] However, there is a paucity of data on the effect of body composition change during PDS and adjuvant chemotherapy on the outcomes of patients with advanced-stage EOC.

Systemic inflammation could play a role in EOC genesis, growth, and progression.[26–29] Patients with EOC may have systemic inflammation; systemic inflammation may also potentiate muscle wasting through anabolic and catabolic pathways responsible for skeletal muscle physiology.[19] Dolan *et al*. revealed that pre-treatment skeletal muscle mass and quality were significantly associated with systemic inflammatory markers in patients with colorectal cancer.[30] However, it is unclear whether systemic inflammation was associated with muscle loss during cancer therapy. Therefore, a longitudinal study would help evaluate the relationship between systemic inflammation and changes in skeletal muscle during cancer therapy.

Computed tomography (CT) images provide objective measures of the skeletal muscle and adipose tissue. The cross-sectional areas of the 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 adipose masses.[31,32] In addition, the use of contrast medium could influence the assessment of skeletal muscle radiodensity (SMD) and may affect the association with the outcomes.[33–36] Accordingly, evaluating the prognostic value of muscle measurement by using a standardized phase of contrast-enhanced CT images may provide more comparable or consistent results in body composition studies.[34]

We hypothesized that body composition change during PDS and adjuvant platinum-based chemotherapy would affect patient outcomes. Hence, the aims of this study were to assess the changes in body composition parameters using a standardized phase of contrast-enhanced CT images and to determine whether body composition measures were associated with survival outcomes of patients with stage III EOC undergoing PDS and adjuvant platinum-based chemotherapy.

Materials and methods

Patients

Our institutional review board approved this retrospective study and waived the need for informed consent from patients owing to the retrospective and observational nature of the study. Patients at our institution with International Federation of Gynecology and Obstetrics (FIGO) stage III EOC who had undergone PDS and adjuvant platinum-based chemotherapy between 2008 and 2017 were reviewed. The inclusion criteria were as follows: (i) routine abdominal CT performed before PDS and a second CT scan obtained after adjuvant chemotherapy and (ii) sufficient quality of CT scans for accurate measurements of the tissue area. Patients who received neoadjuvant chemotherapy or refused to continue chemotherapy after receiving one or two courses of adjuvant chemotherapy were not enrolled. Patients were also excluded if relevant clinical data could not be obtained from the patient's medical records.

All surgical procedures were performed by accredited gynaecological oncologists. The outcomes of PDS were categorized into complete (no macroscopic residual tumour), optimal (largest residual tumour ≤1 cm), or suboptimal (largest residual tumour >1 cm). Adjuvant platinum-based chemotherapy, every 3 weeks for 6 cycles, was recommended for all patients.[18] Adjuvant chemotherapy was started within 3 weeks after PDS. A routine pre-treatment CT image was obtained before PDS, and a post-treatment CT image was obtained within 6 months of adjuvant chemotherapy completion.

Computed tomography-based body composition analysis

The pre-treatment and post-treatment CT images were retrieved for analysis. Body weight and height were obtained from medical records within 2 weeks of the initial and follow-up CT scans. In our institution, routine abdominal and pelvic CT images were obtained for women after

intravenous administration of iohexol 300 (Omnipaque 300, GE Healthcare) or iopromide 300 (Ultravist 300, Bayer HealthCare) in a single uniphasic bolus dose of 80–100 mL via a power injector at 2 mL/s. The portal-venous phase was obtained with a fixed delay of 70 s after the administration of the contrast material, and a pitch between 1.0 and 1.5 before the contrast medium was excreted into the bladder. The following CT image parameters included the following information: contrast-enhanced, 5 mm slice thickness, 120 kVp, and approximately 290 mA.

Two consecutive transverse CT images extending from L3 to the iliac crest were analysed by using the Varian Eclipse software (Varian Medical Systems Inc., Palo Alto, CA, USA).[31,37] Predetermined Hounsfield unit (HU) thresholds were -29 to $+150$ HU for skeletal muscle, -50 to -150 HU for visceral adipose tissue, and -30 to -190 HU for subcutaneous and intermuscular adipose tissues.[31,32] The cross-sectional areas (cm^2) of the skeletal muscle (including the psoas, paraspinal, transversus abdominis, rectus abdominis, and internal and external oblique muscles) and adipose tissues were calculated. The mean radiation attenuation of the entire cross-sectional area of the skeletal muscle was the SMD. The total adipose tissue (TAT) area was calculated as the sum of the areas of the subcutaneous, intermuscular, and visceral adipose tissues. The mean tissue areas were calculated by using two consecutive images. One researcher, blinded to the patient information, measured the body composition parameters. The intraobserver coefficients of variation were 0.8%, 0.8%, and 1.0% for the skeletal muscle area, SMD, and TAT area, respectively, in a sample of 60 patients randomly selected from this cohort. The cross-sectional areas of the skeletal muscle and TAT were normalized based on the patients' height to determine the skeletal muscle index (SMI) and total adipose tissue index (TATI; cm^2/m^2).

As body composition varies greatly between regions, ethnicities, and cancer types,[38–41] we defined our own cut-off values for defining sarcopenia, myosteatosis, and low TATI on the basis of previous studies with similar population sizes [7–9,15]. Cut-off values were set at the lowest tertile for SMI and SMD and at the highest tertile for TATI. The post-treatment body composition change was the difference between the pre-treatment and post-treatment CT images. In this study, the median duration to complete PDS and adjuvant chemotherapy was 127 days [interquartile range (IQR): 120–140 days]. The median duration between pre-treatment and post-treatment CT scans was 182 days (IQR: 161–225 days). To account for variations in the scan interval duration, body composition changes were calculated as the change per 180 days for providing a standardized unit for comparisons between patients. Per the current definition of cachexia,[2] patients with a reduction in the weight, SMI, SMD, or TATI of $\geq$5% were classified as having 'loss';[6] patients with a reduction in the weight, SMI, SMD, or TATI of <5% or gain in the weight, SMI, SMD, or TATI were classified as having 'maintained'.

Markers of systemic inflammation

Differential blood cell counts and serum albumin were obtained prior to PDS. The neutrophil–lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count. The NLR was categorized using a cut-off value of 3 (i.e. $\leq$3 or >3).[42,43] The platelet–lymphocyte ratio (PLR) was defined as the absolute platelet count divided by the absolute lymphocyte count. The PLR was categorized using a cut-off value of 150 (i.e. $\leq$150 or >150).[42] Data of the serum C-reactive protein (CRP) level were available for a subset of 127 patients. The modified Glasgow prognostic score (mGPS) is a useful inflammatory index for assessing the status of cachexia. This score includes the CRP levels, to reflect the systemic inflammation status, and serum albumin levels, to reflect the nutritional status.[44] The mGPS was classified as follows: patients with both an elevated CRP level (>10 mg/L) and a reduced albumin level (<35 g/L) were given a score of 2; those with an elevated CRP level (>10 mg/L) and a non-decreased albumin level ($\geq$35 g/L) were given a score of 1; and those with a non-elevated CRP level ($\leq$10 mg/L), regardless of their albumin level, were given a score of 0.[42]

Statistical analysis

Continuous data were presented as the mean ± standard deviation or median and IQR, as applicable, while categorical data were presented as numbers and percentages. The distributions of patient characteristics were compared by using the chi-square test for categorical variables and independent *t*-test, Mann–Whitney *U* tests, or Kruskal–Wallis test for continuous variables as statistically appropriate. Paired *t*-tests and the Wilcoxon signed-rank test were used to assess body composition changes. The Spearman correlation coefficient was used to assess relationships between body composition parameters. Logistic regression models were used to test for associations between systemic inflammation markers and body composition parameters.

The primary endpoint was overall survival (OS), defined as the time from the date of surgery to the date of death from any cause; progression-free survival (PFS) was defined as the time from the date of surgery to the date of disease recurrence, progression, or death from any cause. Survival curves were constructed using the Kaplan–Meier method with log-rank tests. Cox proportional hazards models were used to estimate the hazard ratio and 95% confidence interval of body composition and risk of outcomes. All variables with a $P < 0.10$ on univariable analysis or with clinical relevance were added to the multivariable analysis. The data were analysed using IBM SPSS software (version 21.0; IBM Corp., Armonk, NY, USA). A $P < 0.05$ was considered statistically significant.

Results

A total of 139 patients met the inclusion criteria (*Figure* 1). The final analysis included 278 CT scans for the 139 patients. The baseline characteristics of the patients are presented in *Table* 1. The median duration between pre-treatment and post-treatment CT scans was 182 days (IQR: 161–225 days). The median duration between adjuvant chemotherapy completion and post-treatment CT scans was 44 days (IQR: 26–73 days).

Body composition at baseline and change after treatment

Table 2 summarizes the body composition characteristics at baseline and the changes after treatment. Overall, the body mass index (BMI) and TATI increased while SMI and SMD decreased after PDS and adjuvant chemotherapy. Eleven patients (7.9%) experienced weight loss of ≥5% while 48 patients (34.5%) each experienced SMI and SMD loss of ≥5%. SMI and SMD changes were not correlated with BMI change (Spearman ρ for SMI, 0.15; P = 0.07; ρ for SMD, 0.02; P = 0.82). TATI changes were moderately correlated with BMI change (Spearman ρ for TATI, 0.58; $P < 0.001$). SMI changes were weakly correlated with SMD change (Spearman ρ for SMD, 0.22; P = 0.01).

The cut-off values for sarcopenia, myosteatosis, and low TATI were SMI <39.2 cm^2/m^2, SMD <35.5 HU, and TATI <100.8 cm^2/m^2, respectively. Patient and tumour characteristics according to pre-treatment sarcopenia are summarized in Supporting Information, *Table S1*. There were marginally more patients with malignant ascites in the pre-treatment sarcopenia group than in the non-sarcopenia group (P = 0.051). The patient characteristics according to SMI change are presented in *Table* 1. The pre-treatment SMI was similar between the SMI-loss and SMI-maintained groups (P = 0.56); 14 (29.2%) and 33 (36.3%) patients in the SMI-loss and SMI-maintained groups, respectively, had pre-treatment sarcopenia (P = 0.40). However, 25 (52.1%) and 30 (33.0%) patients in the SMI-loss and SMI-maintained groups, respectively, had post-treatment sarcopenia (P = 0.03). The SMD decreased by a greater extent in patients in the SMI-loss group compared with those in the SMI-maintained group (P = 0.007); the TATI changes were not significantly different between the SMI-loss and SMI-maintained groups (P = 0.09). There were significantly more patients with residual disease after PDS or malignant ascites in the SMI-loss group than in the SMI-maintained group. Compared with patients treated with complete resection, patients with residual disease showed a greater decrease in the SMI (-2.9% vs. -0.7%; P = 0.03) and SMD (-2.5% vs. -1.0%; P = 0.37) during treatment. Patients with malignant ascites showed a greater decrease in SMI (-3.2% vs. 0.7%, respectively; P = 0.001) and SMD (-2.3% vs. -0.6%, respectively; P = 0.15) during treatment compared with patients with no ascites or non-malignant ascites.

Systemic inflammation markers and body composition

The systemic inflammation markers of the patients according to pre-treatment sarcopenia or SMI change are presented in

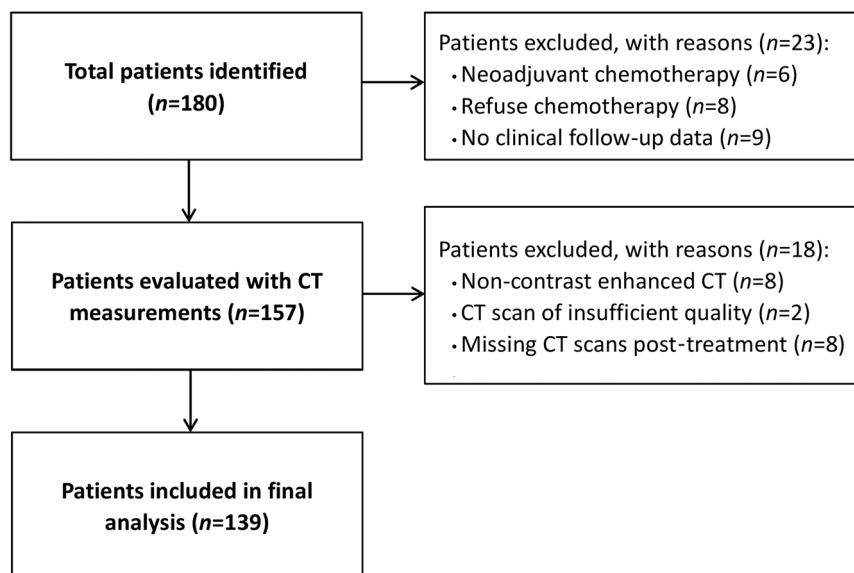**Figure 1** Flow chart for patient inclusion. CT, computed tomography.

Table 1 Patient and tumour characteristics

Characteristics	Overall (*n* = 139)	SMI loss (*n* = 48)	SMI maintained (*n* = 91)	*P*-value
Age (years)	54.4 ± 10.3	54.0 ± 8.7	54.6 ± 11.1	0.74
ECOG performance status				
0	130 (93.5)	44 (91.7)	86 (84.5)	0.50
1	9 (6.5)	4 (8.3)	5 (5.5)	
Pre-treatment BMI (kg/m^2)	22.3 ± 3.4	22.7 ± 3.4	22.0 ± 3.3	0.29
Weight loss ≥5%	11 (7.9)	6 (12.5)	5 (5.5)	0.19
Pre-treatment SMI (cm^2/m^2)	41.9 ± 7.0	42.4 ± 7.0	41.6 ± 7.1	0.56
Pre-treatment sarcopenia[a]	47 (33.8)	14 (29.2)	33 (36.3)	0.40
Post-treatment SMI (cm^2/m^2)	41.1 ± 7.5	38.4 ± 7.2	42.5 ± 7.2	**0.002**
Post-treatment sarcopenia[a]	55 (39.6)	25 (52.1)	30 (33.0)	**0.03**
Pre-treatment SMD (HU)	38.0 ± 7.3	36.8 ± 7.6	38.6 ± 7.0	0.17
Pre-treatment myosteatosis[a]	46 (33.1)	20 (41.7)	26 (28.6)	0.12
SMD change (%/180 days)	−1.7 ± 9.8	−4.8 ± 9.6	−0.1 ± 9.6	**0.007**
SMD maintained	91 (65.5)	25 (52.1)	66 (72.5)	**0.02**
SMD loss ≥5%	48 (34.5)	23 (47.9)	25 (27.5)	
Pre-treatment TATI (cm^2/m^2)	88.3 ± 44.8	93.3 ± 40.4	85.6 ± 47.0	0.34
Pre-treatment low TATI[a]	93 (66.9)	30 (62.5)	63 (69.2)	0.42
TATI change (%/180 days)	15.0 ± 34.7	8.2 ± 26.7	18.6 ± 38.0	0.09
FIGO stage				0.35
IIIA–IIIB	23 (16.5)	6 (12.5)	17 (18.7)	
IIIC	116 (83.5)	42 (87.5)	74 (81.3)	
Histological grade				0.15
Grade 1	7 (5.0)	1 (2.1)	6 (6.6)	
Grade 2	45 (32.4)	20 (41.7)	25 (27.5)	
Grade 3	87 (62.6)	27 (56.3)	60 (65.9)	
Residual disease after PDS				**0.03**
No macroscopic residual disease	73 (52.5)	18 (37.5)	55 (60.4)	
Residual disease ≤1 cm	48 (34.5)	21 (43.8)	27 (29.7)	
Residual disease >1 cm	18 (12.9)	9 (18.8)	9 (9.9)	
Ascites				**0.04**
No ascites	16 (11.5)	4 (8.3)	12 (13.2)	
Non-malignant ascites	35 (25.2)	7 (14.6)	28 (30.8)	
Malignant ascites	88 (63.3)	37 (77.1)	51 (56.0)	
Albumin (g/L)				0.14
≥35	95 (68.3)	29 (60.4)	66 (72.5)	
<35	44 (31.7)	19 (39.6)	25 (27.5)	
CRP (mg/L)				**0.004**
≤10	47 (33.8)	11 (22.9)	36 (39.6)	
>10	80 (57.6)	36 (75.0)	44 (48.4)	
Missing	12 (8.6)	1 (2.1)	11 (12.1)	
mGPS				**0.04**
0	47 (37.0)	11 (23.4)	36 (45.0)	
1	45 (35.4)	19 (40.4)	26 (32.5)	
2	35 (27.6)	17 (36.2)	18 (22.5)	
NLR				0.15
≤3	52 (37.4)	14 (29.2)	38 (41.8)	
>3	87 (62.6)	34 (70.8)	53 (58.2)	
PLR				0.25
≤150	31 (22.3)	8 (16.7)	23 (25.3)	
>150	108 (77.7)	40 (83.3)	68 (74.7)	
Median (IQR) duration between CT scans (days)	182 (161–225)	178 (159–224)	186 (164–226)	0.59

Data are mean ± standard error or number (%). Bolded *P*-values are those significant with a *P* < 0.05. BMI, body mass index; CRP, C-reactive protein; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HU, Hounsfield unit; IQR, interquartile range; mGPS, modified Glasgow prognostic score; NLR, neutrophil–lymphocyte ratio; PDS, primary debulking surgery; PLR, platelet–lymphocyte ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TATI, total adipose tissue index.
[a]SMI < 39.2 cm^2/m^2, SMD < 35.5 HU, and TATI < 100.8 cm^2/m^2 were defined as sarcopenia, myosteatosis, and low TATI, respectively.

Supporting Information, *Table S1* and *Table* 1, respectively. There were significantly more patients with higher mGPS in the pre-treatment sarcopenia group (*P* = 0.03) and SMI-loss group (*P* = 0.04). *Figure* 2 showed the association between mGPS and skeletal muscle parameters. Patients with a higher mGPS had a significantly lower pre-treatment SMD and a lower pre-treatment SMI, with marginal significance (*Figure* 2A and 2B). Patients with a higher mGPS lost significant more SMI during treatment, but the changes in SMD were not significant among the mGPS groups (*Figure* 2C and 2D). When adjusted for age and BMI, an elevated mGPS was independently associated with pre-treatment sarcopenia and myosteatosis (*Tables* 3 and 4). Because residual disease and malignant ascites were observed on PDS and were associated

Table 2 Change of body composition parameters during treatment

Variable	First CT scan Mean ± SD	Second CT scan Mean ± SD	Absolute change per 180 days			Relative change per 180 days (%)		
			Mean	95% CI	P-value	Mean	95% CI	P-value
BMI (kg/m^2)	22.3 ± 3.4	23.2 ± 3.3	0.8	0.6 to 1.1	**<0.001**	4.1	2.9 to 5.3	**<0.001**
SMI (cm^2/m^2)	41.9 ± 7.0	41.1 ± 7.5	−0.7	−1.3 to −0.2	**0.005**	−1.8	−3.1 to −0.4	**0.01**
SMD (HU)	38.0 ± 7.3	37.2 ± 7.3	−0.8	−1.4 to −0.2	**0.009**	−1.7	−3.3 to −0.03	**0.046**
TATI (cm^2/m^2)	88.3 ± 44.8	95.3 ± 43.6	6.7	3.2 to 10.2	**<0.001**	15.0	9.2 to 20.8	**<0.001**

Bolded P-values are those significant with a $P < 0.05$. BMI, body mass index; CI, confidence interval; CT, computed tomography; HU, Hounsfield unit; SD, standard deviation; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; TATI, total adipose tissue index.

with SMI loss during treatment (*Table 1*), these factors were also adjusted on logistic regression analysis of systemic inflammation markers and changes in body composition after PDS and adjuvant chemotherapy. An elevated mGPS was independently associated with SMI loss during treatment (*Table 3*); the mGPS was not associated with SMD loss (*Table 4*). The NLR and PLR were not associated with skeletal muscle parameters at baseline or changes after treatment (*Tables 3 and 4*). Systemic inflammatory markers were also not associated with TATI at baseline and changes after treatment (Supporting Information, *Table S2*).

Body composition at baseline and outcomes

The median follow-up duration was 37.9 months (IQR, 22.6–64.2 months). The 5 year OS and PFS rates for the entire cohort were 60.3% and 32.9%, respectively. The 5 year OS rate

was 54.7% in the sarcopenic group and 63.2% in the non-sarcopenic group ($P = 0.08$); the corresponding 5 year PFS rates were 22.3% and 38.5%, respectively ($P = 0.03$). The 5 year OS rate was 48.4% in the myosteatosis group and 65.7% in the non-myosteatosis group ($P = 0.02$); the corresponding 5 year PFS rates were 21.8% and 37.7%, respectively ($P = 0.24$). The 5 year OS rate was 57.5% in the low-TATI group and 68.7% in the high-TATI group ($P = 0.33$); the corresponding 5 year PFS rates were 29.1% and 34.4%, respectively ($P = 0.64$).

Body composition changes and outcomes

The median interval from post-treatment CT scans to disease recurrence was 5.4 months (IQR, 0.8–12.4 months) in the SMI-loss group and 11.2 months (IQR, 6.6–20.5 months) in the SMI-maintained group ($P = 0.01$); 7.6 months (IQR, 3.4–

Figure 2 Association of modified Glasgow prognostic score with (*A*) pre-treatment SMI, (*B*) pre-treatment SMD, (*C*) SMI changes, and (*D*) SMD changes. mGPS, modified Glasgow prognostic score; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.
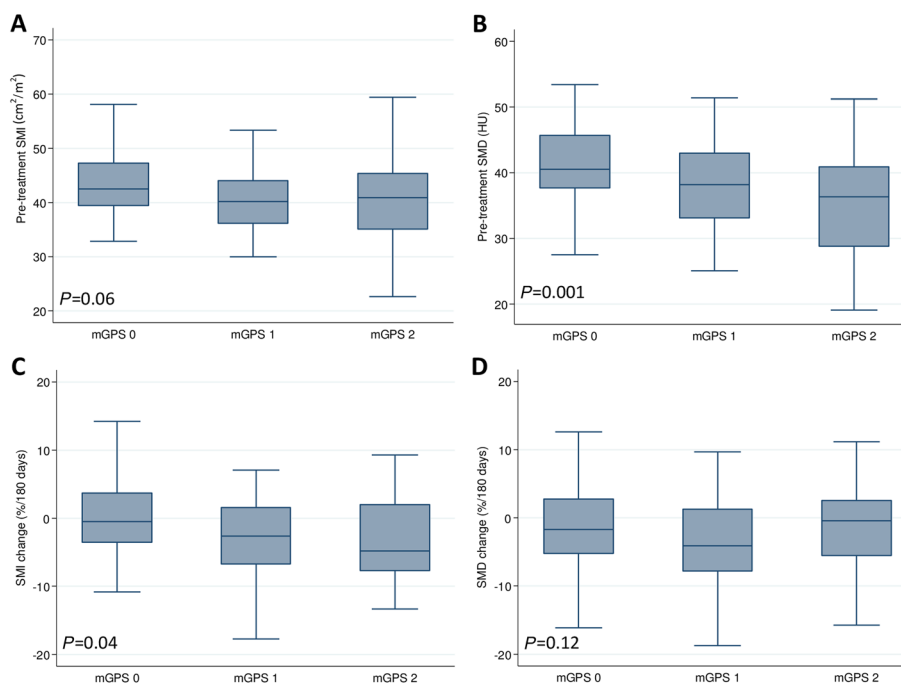
Table 3 Logistic regression analysis of systemic inflammation markers, pre-treatment sarcopenia, and skeletal muscle index loss

	Odds ratio (95% CI)	P-value
Pre-treatment sarcopenia[a]		
mGPS		
mGPS 0	Reference	
mGPS 1–2	2.37 (1.01–5.54)	**0.04**
NLR		
NLR ≤3	Reference	
NLR >3	0.81 (0.35–1.88)	0.63
PLR		
PLR ≤150	Reference	
PLR >150	1.60 (0.59–4.37)	0.36
SMI loss ≥5%[b]		
mGPS		
mGPS 0	Reference	
mGPS 1–2	2.42 (1.03–5.69)	**0.04**
NLR		
NLR ≤3	Reference	
NLR >3	1.66 (0.76–3.64)	0.21
PLR		
PLR ≤150	Reference	
PLR >150	1.57 (0.62–3.99)	0.35

Bolded *P*-values are those significant with a *P* < 0.05. CI, confidence interval; mGPS, modified Glasgow prognostic score; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; SMI, skeletal muscle index.
[a]Model adjusted for age and body mass index.
[b]Model adjusted for age, body mass index, residual disease after primary debulking surgery, and malignant ascites.

Table 4 Logistic regression analysis of systemic inflammation markers, pre-treatment myosteatosis, and skeletal muscle radiodensity loss

	Odds ratio (95% CI)	P-value
Pre-treatment myosteatosis[a]		
mGPS		
mGPS 0	Reference	
mGPS 1–2	3.47 (1.29–9.32)	**0.01**
NLR		
NLR ≤3	Reference	
NLR >3	1.37 (0.63–2.99)	0.43
PLR		
PLR ≤150	Reference	
PLR >150	2.01 (0.82–4.94)	0.13
SMD loss ≥5%[b]		
mGPS		
mGPS 0	Reference	
mGPS 1–2	1.26 (0.56–2.81)	0.58
NLR		
NLR ≤3	Reference	
NLR >3	1.65 (0.77–3.55)	0.20
PLR		
PLR ≤150	Reference	
PLR >150	2.13 (0.83–5.49)	0.12

Bolded *P*-values are those significant with a *P* < 0.05. CI, confidence interval; mGPS, modified Glasgow prognostic score; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; SMD, skeletal muscle radiodensity.
[a]Model adjusted for age and body mass index.
[b]Model adjusted for age, body mass index, residual disease after primary debulking surgery, and malignant ascites.

14.7 months) in the SMD-loss group and 10.3 months (IQR, 3.7–18.2 months) in the SMD-maintained group (*P* = 0.64); and 10.4 months (IQR, 3.0–18.8 months) in the TATI-loss group and 9.6 months (IQR, 3.7–15.8 months) in the TATI-maintained group (*P* = 0.94).

The 5 year OS rate was 44.4% in the SMI-loss group and 68.8% in the SMI-maintained group (*P* = 0.001); the corresponding 5 year PFS rates were 10.4% and 43.4%, respectively (*P* < 0.001; *Figure* 3A). The 5 year OS rate was 49.8% in the SMD-loss group and 67.2% in the SMD-maintained group (*P* = 0.10); the corresponding 5 year PFS rates were 21.8% and 38.5%, respectively (*P* = 0.02; *Figure* 3B). There were no significant differences in the OS and PFS rates between the groups based on weight or TATI change (Supporting Information, *Figure S1*). In a subgroup analysis, patients with SMI loss had significantly poorer OS and PFS rates in both the pre-treatment sarcopenia and non-sarcopenia groups (*Figure* 4).

On univariable analysis, pre-treatment SMI and SMD, SMI change, residual disease, and malignant ascites were predictors of OS and PFS (Supporting Information, *Table S3*). SMD change and FIGO stage were predictors of PFS, but not of OS. On multivariable analysis (*Table* 5), pre-treatment SMI and SMI change were independently associated with OS. Pre-treatment SMI and SMD as well as SMI change were independently associated with PFS. The baseline BMI and TATI and changes in BMI and TATI during treatment were not associated with OS or PFS.

Discussion

To the best of our knowledge, this is the first study that longitudinally assessed body composition changes by using a standardized phase of CT in patients with stage III EOC undergoing PDS and adjuvant platinum-based chemotherapy. We found that SMI and SMD decreased during treatment; the changes in SMI and SMD were not correlated with BMI change, suggesting that muscle loss was occult and occurred independent of BMI change. In addition, we found that the mGPS was associated with pre-treatment sarcopenia and myosteatosis as well as SMI loss during treatment. Patients with SMI loss experienced a significantly shorter time to disease recurrence. SMI at baseline and changes during treatment were independently associated with poor survival outcomes.

Previous studies have reported conflicting results regarding the effect of pre-treatment sarcopenia in patients with advanced-stage EOC.[11–17] These differences in the results might be attributed to the muscle changes that may occur during treatment, possibly influencing the outcomes.[12] Among patients with advanced-stage EOC treated with neoadjuvant chemotherapy and interval debulking surgery, SMI

Figure 3 Kaplan–Meier curve demonstrating overall survival and progression-free survival according to (*A*) SMI and (*B*) SMD change groups. OS, overall survival; PFS, progression-free survival; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.
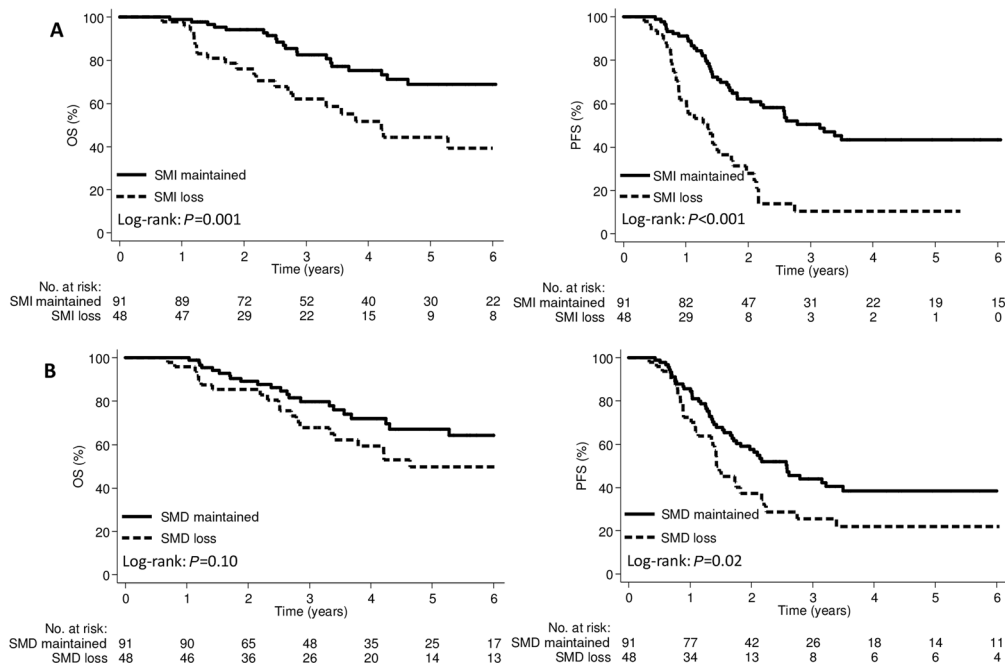
loss during neoadjuvant chemotherapy was associated with poorer OS, while low SMI at a specific time point was not.[12] In the present study, all patients were treated with PDS and adjuvant platinum-based chemotherapy.[18] We found that

SMI at baseline and changes during treatment were independently associated with poorer OS and PFS after adjusting for FIGO stage, PDS outcome, and malignant ascites. Complete resection is the goal of PDS and one of the most important

Figure 4 Kaplan–Meier curve demonstrating overall survival and progression-free survival according to SMI change groups for the pre-treatment (*A*) sarcopenia and (*B*) non-sarcopenia patients. OS, overall survival; PFS, progression-free survival; SMI, skeletal muscle index.
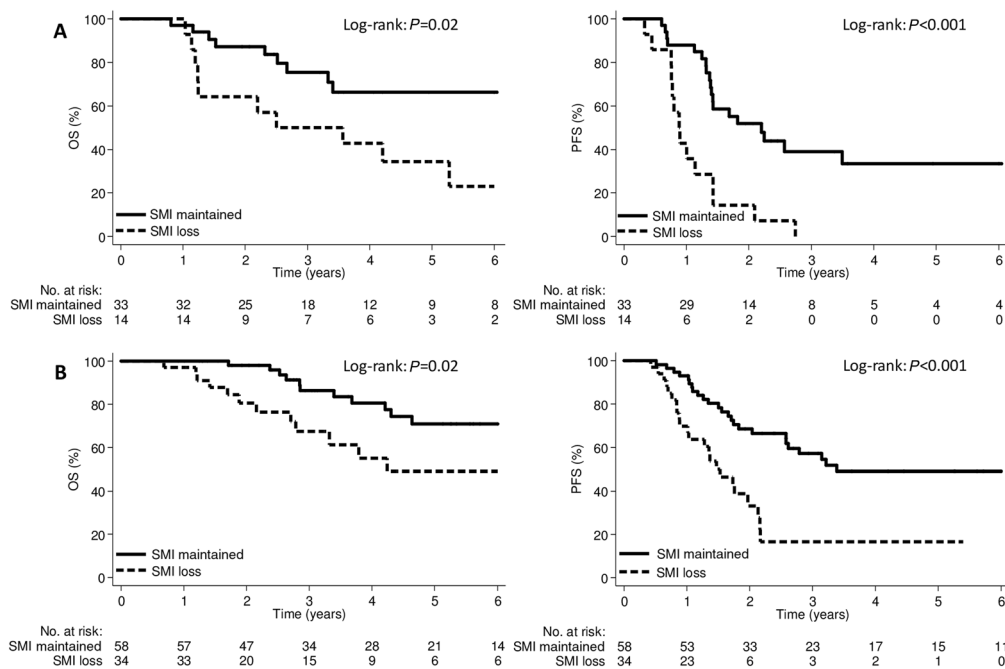
Table 5 Multivariable Cox proportional hazards model for overall survival and progression-free survival

Variable	OS		PFS	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age	1.01 (0.98–1.05)	0.51	1.02 (0.99–1.04)	0.17
Pre-treatment SMI (1 cm^2/m^2 decrease)	1.08 (1.03–1.11)	**0.002**	1.03 (1.01–1.06)	**0.04**
SMI change (per 1%/180 days decrease)	1.04 (1.01–1.08)	**0.002**	1.04 (1.01–1.06)	**0.003**
Pre-treatment SMD (1 HU decrease)	1.04 (0.99–1.10)	0.13	1.04 (1.01–1.09)	**0.03**
SMD change (per 1%/180 days decrease)	—	—	1.02 (0.99–1.04)	0.11
FIGO stage				
IIIA–B	Reference		Reference	
IIIC	1.47 (0.56–3.85)	0.43	1.23 (0.58–2.63)	0.59
Residual disease				
No macroscopic residual disease	Reference		Reference	
Residual disease >0 mm	1.70 (0.85–3.40)	0.14	1.51 (0.92–2.48)	0.10
Ascites				
No ascites or non-malignant ascites	Reference		Reference	
Malignant ascites	2.14 (0.93–4.93)	0.07	1.70 (0.98–2.95)	0.06

Bolded *P*-values are those significant with a *P* < 0.05. CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HU, Hounsfield unit; mGPS, modified Glasgow prognostic score; OS, overall survival; PFS, progression-free survival; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index.

prognostic factors for advanced-stage EOC.[45] The complete resection rate in the current study was 52.5%, similar to the rate obtained in previous large prospective randomized trials.[45–47]

It is of interest that the SMI at baseline was independently associated with PFS in this study. Previous studies also showed conflicting results of pre-treatment sarcopenia on PFS in EOC.[11,13] The possible reason for our findings might be cancer aggressiveness;[22] we found that there were marginally more patients with malignant ascites in the pre-treatment sarcopenia group than in the non-sarcopenia group. In addition, we found that there were more patients with a higher mGPS in the pre-treatment sarcopenia group. Systemic inflammation may also play a role in the processes associated with tumour progression [26]. Interleukin-6 plays an important role in the development of ascites as well as the spread of ovarian cancer through its induction of tumour angiogenesis, thus leading to rapid progression and short survival [22,26,29]. However, the measurement of interleukin-6 levels is not a part of current routine care for EOC [18]; accordingly, interleukin-6 levels could not be analysed in this retrospective study. Future studies are hence required to validate our findings.

The mechanism of how muscle loss results in poorer survival outcomes is not well understood. A possible explanation might be cancer-associated muscle loss [21–24]. In the current study, patients with residual disease after PDS or malignant ascites showed a significantly higher decrease in SMI compared with patients without these factors. Moreover, patients with SMI loss had a significantly shorter time to disease recurrence. Pin *et al.* evaluated the effect of intraperitoneal implantation of ES-2 human ovarian cancer cells on muscle wasting in an animal model. They implanted ES-2 cells intraperitoneally to simulate disseminated abdominal disease and malignant ascites formation and found progressive

muscle wasting via enhanced muscle protein catabolism, abnormal mitochondrial homoeostasis, and elevated tumour-derived interleukin-6 levels.[22] Therefore, our clinical findings may be explained by their results in the animal model. However, it is unknown if the body composition is causally related to the OS of patients with advanced-stage EOC. It is also unknown whether muscle deterioration can be reversed in cancer patients and if this reversal can affect prognosis. In patients with advanced-stage EOC, the performance status at baseline and at 3 months after adjuvant chemotherapy were associated OS, suggesting the relevance of optimal supportive care during cancer therapy.[48] Lifestyle therapy and pharmacotherapy may also offer benefits for the management of body composition in patients with EOC;[49–52] however, their effectiveness for advanced-stage EOC remains unclear. Hence, future studies are warranted to determine if the effects of body composition on survival outcomes are both causal and, more importantly, reversible through intervention for advanced-stage EOC.

Systemic inflammation was a risk factor for muscle loss and may be a useful marker of catabolic drive.[19,30] Dolan *et al.* reported that both pre-treatment low SMI and SMD were significantly associated with the systemic inflammatory response in patients with colorectal cancer.[30] Two previous longitudinal studies revealed that pre-treatment systemic inflammation was associated with muscle mass loss over time.[43,53] In the current study, we found that an elevated pre-treatment mGPS was associated with pre-treatment sarcopenia and myosteatosis, and SMI loss during treatment. However, we found that the SMD loss was not associated with systemic inflammatory markers including the mGPS, NLR, or PLR. SMD is a marker of lipid content in skeletal muscles and could be affected by physiological and pathological variations.[54] It is interesting that systemic inflammation may have different effects on SMI and SMD. Although the current

study evaluated the changes in SMI and SMD using contrast-enhanced CT scans with a standardized phase, the study included only a small number of patients, which may not be sufficient to draw a definite conclusion about the relationship between systemic inflammation and SMD loss. In addition, the food intake, lifestyle, or physical function could also confound the relationship between systemic inflammation and skeletal muscle; however, data about these factors were not comprehensively available for analysis given the retrospective nature of this study. It is also unknown whether moderation of the systemic inflammatory response could improve SMI and SMD during treatment.[19,30] Hence, we suggest further longitudinal studies with a larger number of patients to elucidate the relationship between systemic inflammation and skeletal muscle change during cancer therapy.

Sarcopenia has long been associated with ageing and is common in elderly people. Beyond the age of 50 years, loss of leg muscle mass (1–2% per year) and loss of strength (1.5–5% per year) have been reported.[55,56] In the current study, we found that age at diagnosis was not associated with pre-treatment sarcopenia or SMI loss during treatment. Age at diagnosis was also not associated with survival outcomes on the multivariable Cox model (Table 5). The possible explanation might be that we only evaluated body composition on pre-treatment and post-treatment CT images with a median duration of 182 days (IQR: 161–225 days). Data from more number of CT images during a longer follow-up might reveal the effect of age on muscle loss. However, in the current study, more number of CT images after post-treatment CT were not available for analysis because CT scans during follow-up were acquired only when clinically indicated. The small number of patients might also limit the statistical power to detect the effect of age on sarcopenia. Notably, cancer-associated muscle loss might be the major cause of muscle loss in this study; patients with SMI loss experienced a significantly shorter time to disease recurrence. Although age-associated muscle loss with time may potentially affect the Cox proportional hazards model, this effect could not be evaluated in the current study due to the short duration of CT images.

We used a standardized phase of contrast-enhanced CT images to assess body compositions in the current study. Contrast-enhanced CT images could confound the assessment of SMD, but their influence on the assessment of SMI may be clinically insignificant.[33–36] van Vugt et al. revealed that the mean SMI was significantly lower for the unenhanced phase (42.5 ± 9.9 cm^2/m^2) than for the arterial (42.8 ± 9.9 cm^2/m^2; $P = 0.021$) and portal-venous (43.6 ± 9.9 cm^2/m^2; $P < 0.001$) phases.[34] Paris et al. reported that the mean SMI increased in the arterial (54.9 ± 9.6 cm^2/m^2; $P = 0.007$) and 3 min phases (55.0 ± 9.6 cm^2/m^2; $P < 0.001$) than in the pre-contrast phase (54.3 ± 9.6 cm^2/m^2), with no differences between the arterial and 3 min phases.[35] Rollins

et al. revealed that the overall mean SMI was not significantly different between the different phases of the CT scans.[33] Although the difference in SMI measurements may not be clinically relevant, these studies still recommend the evaluation of skeletal muscle parameters with a standardized phase of contrast-enhanced CT scans because of the influence of contrast on SMD.[33–35] Moreover, documentation of the phase of CT analysed would assist in the interpretation of the effects of skeletal muscle on outcomes of patients with cancer.[33–35]

The current definition of cachexia is based on weight loss without considering body composition changes;[2] however, weight change might not be representative of muscle change.[5–8,57] Kays et al. reported that CT-based body composition analysis revealed muscle loss of >5% in 81% of patients, while the traditional definition of >5% weight loss was observed in 56.6%.[6] In the current study, 11 patients (7.9%) had weight loss of ≥5% while 48 (34.5%) patients had SMI loss of ≥5%. The BMI change was moderately correlated with TATI change but not with SMI or SMD changes. Overall, the BMI increased during treatment; the BMI increase was mainly attributed to TATI gain while muscle loss occurred. Moreover, weight loss was not associated with poorer survival outcomes while SMI was. Therefore, CT-based body composition could help define distinct cachexia phenotypes more precisely rather than using weight alone. Nevertheless, these findings should be validated in a large patient cohort.

The current study has several limitations. This study was a retrospective investigation involving a small number of patients, which possibly limited our statistical power to evaluate the relationship among the skeletal muscle parameters, systemic inflammation, and survival. Selection bias and residual and unmeasured confounding are potential limitations of this retrospective study. In addition, this study only analysed pre-treatment and post-treatment CT images acquired during routine cancer care. A longitudinal study with CT images of more time points may provide more comprehensive information; however, the CT images during the course of cancer therapy or follow-up would be acquired only when clinically indicated in real-world clinical practice.[18] Hence, more CT images at different time points could not be analysed in this study. The information regarding food intake, muscle strength (e.g. handgrip strength or chair stand test), or physical performance (e.g. timed-up-and-go test or gait speed) was not available in the present study. The revised definition of sarcopenia by EWGSOP2 indicates low muscle strength as a key characteristic of low muscle quality and requires the presence of low muscle quantity to confirm sarcopenia diagnosis. If a person also has functional impairment, confirmed with a physical performance measure, this is characterized as severe sarcopenia.[25,56] Moreover, our study included only Asian patients. Despite these limitations, the strength of our study is that patients received very similar treatments and consistently underwent pre-treatment and post-treatment CT with

a standardized protocol. The treatment outcomes were comparable with those obtained in previous studies,[11–16,46] and the follow-up period was adequate.

In conclusion, SMI loss occurred in patients with stage III EOC during PDS and adjuvant platinum-based chemotherapy; the mGPS might be a predictor of SMI loss during treatment. SMI at baseline and changes during treatment were independently associated with poor outcomes. Patients with SMI loss after treatment had a significantly shorter time to recurrence. Moreover, the changes in SMI were not correlated with changes in BMI, suggesting that body composition measurements using CT images acquired for routine cancer care should be incorporated into clinical practice, as they might help predict outcomes and potentially guide cancer therapy. Future studies are required to evaluate the value of cancer therapy and supportive care based on individual body composition phenotypes and systemic inflammatory markers; this would serve to improve the survival outcomes of patients with advanced-stage EOC.

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Conflict of interest

None declared.

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Authors contributions

Chueh-Yi Huang, Jie Lee, and Chih-Long Chang contributed to the conception and design of the study. All authors contributed to the acquisition, analysis, or interpretation of data. Ya-Ting Jan performed imaging data analysis. Chueh-Yi Huang and Jie Lee drafted the manuscript. All authors performed critical revision of the manuscript for important intellectual content. Jie Lee performed statistical analysis.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient and tumour characteristics according to pre-treatment sarcopenia groups (n = 139)
Table S2. Logistic regression of systemic inflammation markers and pre-treatment low TATI and TATI loss
Table S3. Univariable Cox proportional hazards model for overall survival and progression-free survival
Figure S1. Kaplan–Meier curve demonstrating overall survival and progression-free survival according to (A) weight and (B) TATI change groups. OS, overall survival; PFS, progression-free survival; TATI, total adipose tissue index.

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