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ORIGINAL ARTICLE

Male Health

Body composition changes following chemotherapy for testicular germ cell tumor: obesity is the long-term problem

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Metabolic syndrome is a long-term complication of systemic chemotherapy for testicular germ cell tumor (TGCT). It is believed to be caused by secondary hypogonadism or toxic medicines because of orchidectomy followed by systemic chemotherapy. In this study, changes in the body composition of patients over time were quantitatively analyzed up to 24 months after chemotherapy. This study retrospectively analyzed 44 patients with TGCT who underwent chemotherapy at our institution from January 2008 to December 2016. Subcutaneous and visceral fat areas and psoas and skeletal muscle areas were measured by computed tomography before and immediately after chemotherapy as well as 3 months, 6 months, 12 months, and 24 months after chemotherapy. The subcutaneous and visceral fat indices and psoas and skeletal muscle indices were calculated as each area divided by body height squared. The total fat area had already significantly increased 3 months after the initiation of chemotherapy ($P = 0.004$). However, it did not return to prechemotherapeutic levels even at 24 months after chemotherapy. The skeletal muscle area was significantly decreased at the end of chemotherapy ($P < 0.001$); however, the value returned to baseline within 12 months. In multivariable analysis, the prechemotherapeutic skeletal muscle index and number of chemotherapy cycles were independently associated with the reduction of skeletal muscle at the end of chemotherapy ($P = 0.001$ and $P = 0.027$, respectively). In patients with TGCT, skeletal muscle mass decreased during chemotherapy and recovered within 12 months, whereas fat mass progressively increased from the initiation of chemotherapy until 24 months after chemotherapy.

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Keywords: body composition; chemotherapy; obesity; sarcopenia; secondary hypogonadism; testicular cancer

INTRODUCTION

Testicular germ cell tumor (TGCT) is the most common malignant disease among young men, and it carries a favorable outcome as indicated by 10-year survival rates as high as 90%.[1] The improvement in survival was greatly influenced by the development of curative chemotherapeutic regimens. As survivors of TGCT treated with chemotherapy increase in number, long-term unfavorable health conditions, including cardiovascular disease, neurotoxicity, nephrotoxicity, cognitive impairment, and second malignancy, have become prominent problems.[2–5]

A large number of cancer survivors also encounter unfavorable changes in their body composition, including an increase in fat mass (obesity) and a decrease in skeletal muscle mass (sarcopenia).[6] The changes of body composition in cancer survivors are caused by various factors. Cancer treatments (surgery, chemotherapy, and radiotherapy) induce changes in hormonal homeostasis (growth hormone, thyroid hormone, and testosterone), metabolism, and sympathetic nervous activity, and these disorders may cause obesity or sarcopenia.[7] Lifestyle factors such as physical inactivity and dietary intake also cause body composition changes. It is known that most cancer survivors focus on the management of cancer itself, but they have low awareness of healthy lifestyles.[8] These changes in body composition are suggested to be one of the indicators of metabolic syndrome.[9,10] Recent studies revealed that metabolic syndrome is a common morbidity in cancer survivors.[11,12] Metabolic syndrome is associated with mortality from cardiovascular disease, diabetes mellitus, and chronic kidney disease and increased cancer risk.[13] Thus, obesity and sarcopenia can possibly lead to a decline in quality of life, a shortened survival, and a second malignancy resulting from metabolic syndrome, even after the successful treatment of primary cancer.

Among patients with advanced TGCT, several studies demonstrated that an increase in fat mass and a decrease in skeletal muscle mass occur along with androgen deficiency after chemotherapy, and these changes are associated with the development of metabolic syndrome over the long term.[6,14–16] However, regarding changes in body composition, only short-term data obtained within 12 months from the initiation of chemotherapy are available. This retrospective study assessed changes in body composition up to 24 months after the end of chemotherapy in patients with TGCT who underwent chemotherapy.

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PATIENTS AND METHODS

Patients

Forty-four consecutive patients with TGCT treated with chemotherapy from January 2008 to December 2016 at Yamagata University Hospital (Yamagata, Japan) were enrolled in this study. This retrospective observational study was approved by the Institutional Review Board of the Yamagata University Faculty of Medicine, Yamagata, Japan (Approval No. 2018-43). The opt-out method was used to obtain informed consent. The need for individual consent to participate in this study was waived by the same institutional review board, and the patients were given the opportunity to reject the usage of their data.

Measurement of fat and muscle components

The fat component was automatically analyzed, whereas the muscle component was manually analyzed using SYNAPSE VINCENT version 4 volume analyzer software (Fujifilm, Tokyo, Japan). The subcutaneous fat area, visceral fat area, and total fat area (the sum of the subcutaneous and visceral fat areas), were measured at the level of the umbilicus on axial computed tomography (CT) images. The muscle area was measured at the L3 spine level, and the psoas muscle area and skeletal muscle area which included the psoas muscle area, were also measured. These analyses were performed using CT images taken before and immediately after chemotherapy and 3 months, 6 months, 12 months, and 24 months after chemotherapy. The subcutaneous fat index (SFI), visceral fat index (VFI), and total fat index (TFI) were defined as subcutaneous fat area, visceral fat area, and total fat area divided by body height squared, respectively. Similarly, the psoas muscle index (PMI) and skeletal muscle index (SMI) were defined as the psoas muscle area and skeletal muscle area divided by body height squared, respectively.

Statistical analyses

All statistical analyses were performed using SPSS version 19 software (IBM Japan, Tokyo, Japan). Statistical analyses of sequential changes of all indices were conducted by analysis of variance (ANOVA). *Post hoc* analysis was conducted using Tukey's test. The Chi-squared test was used to compare the distribution of the patients stratified by TFI and SMI immediately and 12 months after the chemotherapy. Univariable and multivariable regression analyses were used to investigate the relative contribution of each variable to sarcopenia at the end of chemotherapy and to obesity at 12 months after chemotherapy. The following were included in the analyses as independent variables: pretreatment age, body mass index (BMI), SFI, VFI, TFI, SMI, PMI, retroperitoneal lymph node dissection, and the number of chemotherapy cycles. $P < 0.05$ indicated statistical significance.

RESULTS

The demographic and clinical data of the patients were obtained from medical records, and they are summarized in **Table 1**. For adjuvant chemotherapy, three cycles of etoposide plus cisplatin (EP), two cycles of bleomycin, etoposide, and cisplatin (BEP), and one or two cycles of carboplatin (AUC 7) were used in three, one, and six patients, respectively. The other 34 patients were treated with three or four cycles of EP, three or four cycles of BEP, and four or five cycles of vincristine, ifosfamide, and cisplatin as induction chemotherapy. Among these patients, 11 received subsequent salvage chemotherapy. The regimens are described in detail in **Table 1**.

Table 1: Demographics of patients

Clinical variable	*Patients (n=44)*
Age (year), median (range)	37 (19–80)
Pathological type, *n* (%)	
Seminoma	17 (38.6)
Nonseminoma	17 (38.6)
Mixed	10 (22.7)
TNM stage (UICC), *n* (%)	
I	10 (22.7)
II	9 (20.5)
III	18 (40.9)
Relapse	7 (15.9)
IGCCCG classification, *n* (%)	
Good	26 (59.1)
Intermediate	8 (18.2)
Poor	5 (11.4)
Unknown	5 (11.4)
Adjuvant chemotherapy, *n* (%)	
Carboplatin	6 (13.6)
BEP/EP	4 (9.1)
Induction chemotherapy, *n* (%)	
BEP/EP	32 (72.7)
VIP	2 (4.5)
Salvage chemotherapy, *n* (%)	
TIP	10 (22.7)
VeIP	3 (6.8)
GEMOX	2 (4.5)
TICE	1 (2.3)
Total cycles of chemotherapy (*n*), median (range)	4 (1–14)
Number of chemotherapy cycles, *n* (%)	
<4	20 (45.5)
4	14 (31.8)
>4	10 (22.7)
RPLND, *n* (%)	17 (38.6)
Follow-up period (month), median (range)	32 (2–112)
Alive patients, *n* (%)	41 (93.2)

TNM: tumor-node-metastasis; UICC: Union for International Cancer Control; IGCCCG: The International Germ Cell Cancer Collaborative Group; BEP: bleomycin, etoposide, and cisplatin; EP: etoposide plus cisplatin; VIP: vincristine, ifosfamide, and cisplatin; TIP: paclitaxel, ifosfamide, and cisplatin; VeIP: vinblastine, ifosfamide, and cisplatin; GEMOX: gemcitabine plus oxaliplatin; TICE: paclitaxel, ifosfamide, carboplatin, and etoposide; RPLND: retroperitoneal lymph node dissection

Changes in fat components

Pretreatment physical constitution and changes in fat and muscle components after chemotherapy are summarized in **Supplementary Table 1**. The total fat mass was significantly increased at 3 months after the initiation of chemotherapy ($P = 0.004$), and 34 patients (80.9%) displayed elevated fat mass at the end of chemotherapy. Fat mass progressively increased over time without returning to the baseline level between 6 months and 24 months after the completion of chemotherapy (**Figure 1a**). We also evaluated the changes in fat components among the 17 patients who underwent assessments at all time points from the initiation of chemotherapy to 24 months after the completion of chemotherapy. A similar continuous increase of fat mass was observed in this subgroup (**Supplementary Figure 1a**). The median total fat area was increased by 27.1% from 184.8 cm^2 at baseline to 234.9 cm^2 at 24 months after chemotherapy. There was no difference in the contribution of subcutaneous fat and visceral fat to the increase of the total fat area (**Supplementary Table 1**). The distribution of the TFI at the

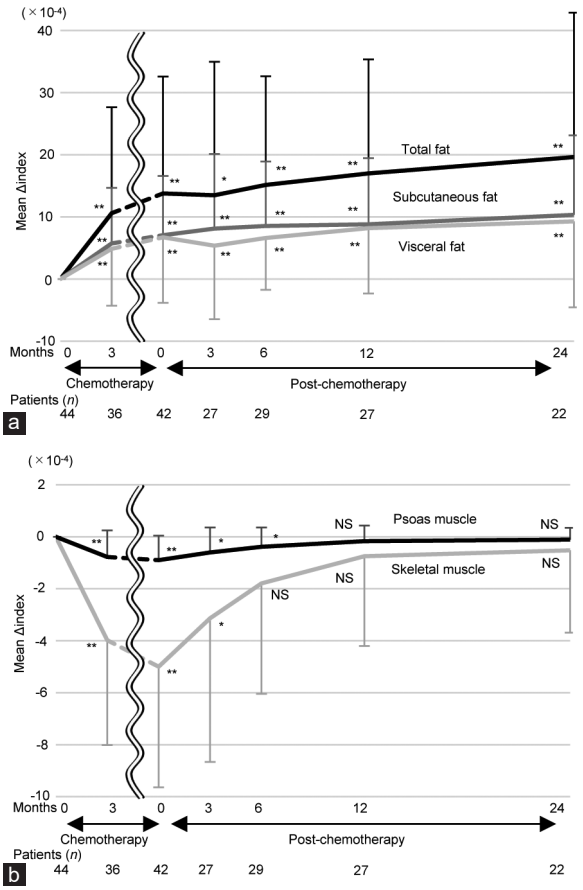

Figure 1: Changes in (**a**) fat and (**b**) muscle indices after the initiation of chemotherapy. Each value is presented as the mean change from baseline (mean Δindex). $^{*}P < 0.05$ (the indicated item *vs* prechemotherapy), $^{**}P < 0.001$ (the indicated item *vs* prechemotherapy). NS: not significant.

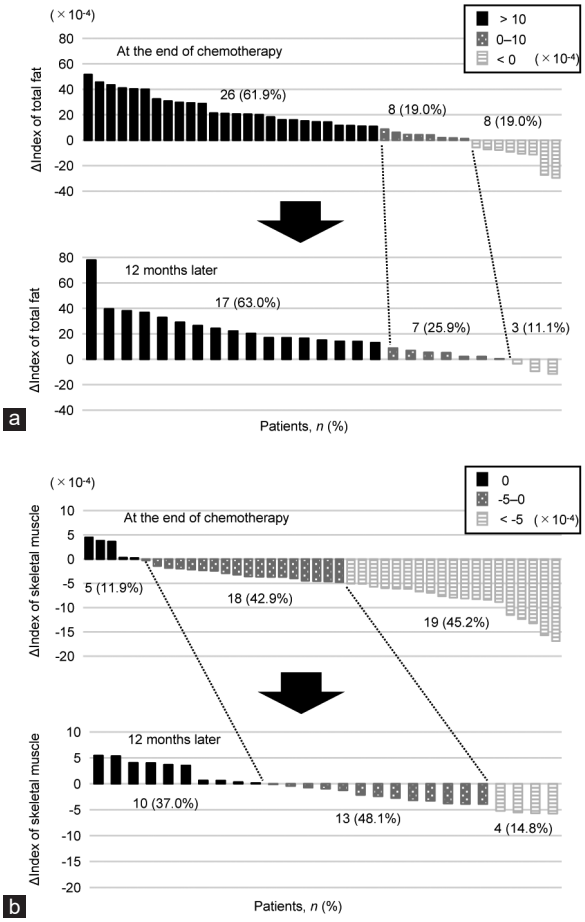

Figure 2: Changes in the (**a**) total fat index and (**b**) skeletal muscle index immediately and 12 months after the completion of chemotherapy. Each value is presented as the change from baseline (Δindex).

end of and 12 months after chemotherapy are presented in **Figure 2a**. The TFI ($\times 10^{-4}$) had increased by more than 10 and by 0–10 in 61.9% (26/42) and 19.0% (8/42) of patients, respectively, and decreased in 19.0% (8/42) of patients at the end of the chemotherapy. The distribution did not change even 12 months after chemotherapy ($P = 0.604$).

Changes in muscle components

The skeletal muscle area decreased within 3 months from the initiation of chemotherapy, reaching its lowest level at the end of chemotherapy ($P < 0.001$). Unlike fat mass, skeletal muscle mass recovered within 12 months after the end of chemotherapy (**Figure 1b**). In the 17 patients who underwent assessments at all time points, the course of the skeletal muscle mass change was similar to that among all patients (**Supplementary Figure 1b**). The median skeletal muscle area was decreased by 11.7% from 152.8 cm^2 at baseline to 134.9 cm^2 at the end of chemotherapy (**Supplementary Table 1**). The distributions of the SMI at the end of chemotherapy and 12 months after chemotherapy are presented in **Figure 2b**. The SMI ($\times 10^{-4}$) had decreased by more than 5 and by 0–5 in 45.2% (19/42) and 42.9% (18/42) of patients, respectively, and increased in 11.9% (5/42) of patients at the end of the chemotherapy. At 12 months after the completion of chemotherapy, the proportion of patients with a decrease of the SMI of more than 5 (4/27, 14.8%) was significantly reduced compared with the findings at the end of chemotherapy (45.2%; $P = 0.009$).

Factors affecting changes in body composition

Univariable regression analysis was performed to assess whether clinical factors affected the increase in the TFI at 12 months after the end of chemotherapy. Only the number of chemotherapy cycles was positively associated with the fat component ($P = 0.041$; **Table 2**). Next, we investigated factors affecting the decrease in the SMI at the end of chemotherapy, which reached its nadir during the follow-up period. In univariable analysis, BMI, the prechemotherapeutic TFI, the prechemotherapeutic SMI, and the number of chemotherapy cycles were negatively associated with the muscle component. Stepwise multivariable regression analysis illustrated that the prechemotherapeutic SMI and the number of chemotherapy cycles independently affected the reduction in skeletal muscle at the end of chemotherapy ($P = 0.001$ and $P = 0.027$, respectively; **Table 3**). The change of the SMI in patients who completed more than four cycles of chemotherapy was significantly larger than that in patients who received four or fewer cycles (−17.6% *vs* −2.6%, $P = 0.001$).

DISCUSSION

In this study, we retrospectively analyzed the long-term changes in body composition during and after chemotherapy in patients with

TGCT, and found that dynamic body composition changes occur even in relatively young patients. Although the loss of skeletal muscle was reversed within 12 months, the increase in body fat mass did not improve over time in the majority of patients. Previous studies demonstrated that visceral and subcutaneous fat and BMI were significantly increased within 1–12 months after the initiation of chemotherapy.[6,14] Our long-term observational data illustrated that once gained, the fat component was retained until at least 24 months after the completion of chemotherapy. Meanwhile, lean body mass reportedly continues to decrease until 1 year after the initiation of chemotherapy.[17] The detailed natural course of changes in muscle components after chemotherapy had not been previously reported. The present study first demonstrated that the muscle component, which was most strongly reduced at the time of chemotherapy completion, gradually recovered to baseline within 12 months after systemic chemotherapy.

There is cumulative evidence regarding the association of changes in the sex hormone milieu with obesity or metabolic syndrome following treatment for TGCT. In comparison with their siblings, TGCT survivors exhibited significantly higher levels of follicle-stimulating hormone and luteinizing hormone and significantly lower free and total testosterone levels during a median follow-up period of 12 years.[18] Similar hormonal changes were prominently observed in patients with TGCT treated with systemic chemotherapy compared with the findings in patients who underwent orchiectomy alone.[15,16] One study demonstrated that the total dose of cisplatin (>850 mg) is associated with a decline in serum testosterone levels during a 10-year follow-up period.[19] These results suggested that orchiectomy and subsequent chemotherapy affect sex hormone levels and that secondary hypogonadism appears to lead to the development of obesity and metabolic syndrome.[15–17,19,20]

Table 2: Factors affecting the increase of the total fat index at 12 months after chemotherapy

Factor	*Univariable regression analysis*	
	Partial regression coefficient (95% CI)	*P*
Age	0.086 (–0.528–0.699)	0.776
BMI	–0.014 (–1.776–1.748)	0.987
RPLND	5.462 (–9.294–20.218)	0.453
Pre-TFI	0.004 (–0.159–0.166)	0.965
Pre-SMI	–1.418 (–6.151–3.315)	0.543
Cycles of chemotherapy	2.799 (0.127–5.471)	0.041

BMI: body mass index; RPLND: retroperitoneal lymph node dissection; TFI: total fat index; SMI: skeletal muscle index; CI: confidence interval

It was revealed that reduced muscle mass is also associated with a decline in serum testosterone levels after chemotherapy.[17] However, our result that muscle mass was lowest at the end of chemotherapy and gradually recovered to baseline within 12 months suggests that factors other than serum testosterone may affect skeletal muscle mass. The direct effects of chemotherapeutic agents and reduced physical activity during treatment may cause the loss of skeletal mass.[21] A previous study demonstrated that three cycles of BEP significantly attenuated muscle fiber size and strength when no planned physical training was prescribed.[21] Our data identified the number of chemotherapy cycles as an independent predictor of the loss of skeletal mass. However, it is unclear whether the toxicity of chemotherapeutic agents or duration of treatment predominantly influences muscle loss.

Regarding the preventative effect of physical training on the loss of skeletal muscle during chemotherapy, several intervention trials have been conducted.[21,22] Unfortunately, these trials did not demonstrate a sufficient effect of physical training during chemotherapy on lean body mass and muscle fiber size compared with the effects of standard care.[22] The reason for this finding is that the adverse effects of chemotherapy, such as nausea and general malaise, likely lead to the discontinuation of exercise or reduction of its intensity. Our result demonstrated that patients with greater skeletal mass who completed more cycles of chemotherapy had a higher risk of muscle loss after chemotherapy, which suggests that men with higher pretreatment testosterone levels and physical activity are more susceptible to orchiectomy and subsequent chemotherapy. Meanwhile, in patients with advanced cancer undergoing standard care including chemotherapy, a 7-week testosterone injection course significantly improved lean mass as well as quality of life.[23] Testosterone replacement therapy may be an optional treatment for preventing these unfavorable health conditions in patients with TGCT and hypogonadism.[23,24]

This study had several limitations. First, because it was not designed as a prospective study, there were substantial amounts of missing or unavailable data. The loss of patients to follow-up could have created some selection bias. Second, this study included patients of various backgrounds who received different treatments. Differences in chemotherapy regimens and the number of cycles might have affected the results. Third, only changes in fat and muscle mass were analyzed, and the association of changes in body composition with biochemical and hormonal data was not assessed because these data were not systematically measured. Finally, this study lacked a control group. Even if patients with stage I TGCT served as a control group, it is unclear whether the direct effect of chemotherapy or reduction of physical activity is the primary component affecting body composition.

Table 3: Factors affecting the decrease of the skeletal muscle index at the end of chemotherapy

Factor	*Univariable regression analysis*		*Stepwise multivariable regression analysis*	
	Partial regression coefficient (95% CI)	*P*	*Partial regression coefficient (95% CI)*	*P*
Age	0.062 (–0.087–-0.212)	0.402		
BMI	–0.522 (–0.846–-0.199)	0.002		
RPLND	–0.576 (–3.553–-2.402)	0.698		
Prechemotherapy TFI	–0.035 (–0.069–-0.001)	0.047		
Prechemotherapy SMI	–0.268 (–0.417–-0.120)	0.001	–0.243 (–0.386–-0.068)	0.001
Cycles of chemotherapy	–0.691 (–1.242–-0.140)	0.015	–0.563 (–1.057–-0.068)	0.027

BMI: body mass index; RPLND: retroperitoneal lymph node dissection; TFI: total fat index; SMI: skeletal muscle index; CI: confidence interval

CONCLUSIONS

In patients with TGCT treated with systemic chemotherapy, skeletal muscle mass decreased during chemotherapy and recovered within 12 months, whereas fat mass progressively increased from the initiation of chemotherapy without returning to baseline over 24 months after the completion of chemotherapy. These data suggest that interventions targeting obesity rather than skeletal muscle loss are required in the long-term follow-up of patients with TGCT.

AUTHOR CONTRIBUTIONS

YT, NT, TK, and SN were involved in study design and data interpretation. HK and MY helped collect data. YT, NT, and SN were involved in the data analysis. AY, TS, HN, and TY critically revised the report, commented on drafts of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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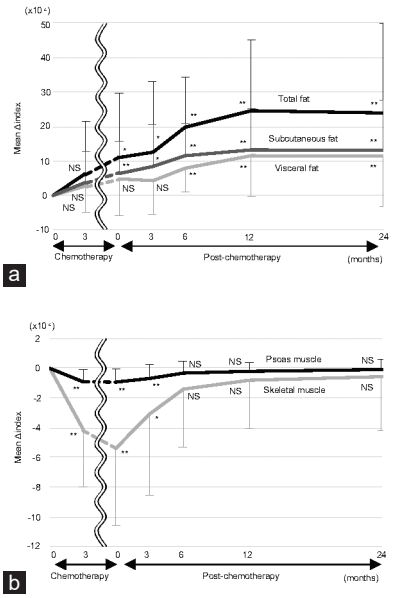
Supplementary Table 1: Pretreatment physical constitution and changes in fat and muscle mass after chemotherapy

	Pre-CTx	*3 months CTx*	*At the end of CTx*	*3-month follow-up*	*12-month follow-up*	*24-month follow-up*
Body height (m)	173.9 (149.5–1848.8)					
Body weight (kg)	67.9 (45.2–112.0)					
BMI (kg/m^2)	23.5 (16.8–35.3)					
Subcutaneous fat (cm^2)	114.3 (4.1–398.9)	118.7 (25.1–385.7)	108.2 (32.3–433.5)	119.7 (29.2–492.5)	128.5 (9.2–491.0)	131.4 (6.7–498.0)
SFI (×10^{-4})	37.8 (1.3–143.2)	40.1 (7.9–131.5)	39.1 (10.2–155.6)	41.2 (9.2–176.8)	44.4 (2.9–176.3)	45.4 (2.1–178.8)
Visceral fat (cm^2)	67.6 (10.3–201.8)	86.1 (11.9–199.3)	85.0 (18.9–223.8)	77.4 (22.4–175.0)	94.3 (13.9–320.5)	89.2 (7.6–337.2)
VFI (×10^{-4})	22.2 (3.2–69.1)	28.6 (3.8–58.4)	28.4 (6.0–73.8)	26.0 (7.2–60.1)	31.2 (4.4–115.2)	29.9 (2.4–121.2)
V/S ratio	0.69 (0.22–2.96)	0.68 (0.26–1.57)	0.75 (0.22–1.68)	0.65 (0.23–1.86)	0.86 (0.24–1.73)	0.72 (0.21–1.86)
Total fat (cm^2)	184.8 (16.4–585.4)	218.1 (37.0–554.3)	208.0 (51.2–575.4)	212.4 (52.2–633.5)	223.3 (23.0–609.4)	234.9 (14.3–623.8)
TFI (×10^{-4})	63.9 (5.2–186.0)	72.8 (11.7–170.5)	73.8 (16.2–206.6)	73.8 (16.5–227.4)	79.0 (7.3–218.8)	82.6 (4.5–223.9)
Psoas muscle (cm^2)	20.1 (9.8–34.6)	17.8 (10.1–31.8)	18.2 (9.4–26.5)	16.8 (10.8–28.0)	17.8 (11.9–26.6)	18.8 (11.2–28.8)
PMI (×10^{-4})	6.6 (3.1–11.3)	5.9 (3.3–9.5)	5.8 (2.9–8.5)	5.6 (3.4–9.2)	6.1 (3.7–9.3)	6.4 (4.3–10.1)
Skeletal muscle (cm^2)	152.8 (91.8–215.9)	134.9 (96.6–211.5)	134.9 (96.6–189.2)	130.6 (96.2–189.0)	141.3 (103.1–194.5)	150.7 (10.1–19.6)
SMI (×10^{-4})	51.6 (28.8–70.6)	46.0 (32.4–62.9)	45.6 (32.4–60.6)	44.1 (30.2–61.8)	48.7 (32.3–64.3)	49.9 (38.6–62.3)

Values are presented as the median (range). CTx: chemotherapy; SFI: subcutaneous fat index; VFI: visceral fat index; V/S ratio: visceral fat area/subcutaneous fat area ratio; TFI: total fat index; PMI: psoas muscle index; SMI: skeletal muscle index; BMI: body mass index



Supplementary Figure 1: Changes in (**a**) fat and (**b**) muscle indices among the patients who underwent assessments at all time points after the initiation of chemotherapy. Each value is presented as the mean change from baseline (mean Δindex). $^{*}P < 0.05$ (*vs* prechemotherapy), $^{**}P < 0.001$ (*vs* prechemotherapy), NS: not significant.