The Breast 66 (2022) 1–7

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Does neoadjuvant chemotherapy regimen affect sarcopenia status in patients with breast cancer?

Min Kyeong Jang [a,*], Seho Park [b], Chang Park [c], Ardith Z. Doorenbos [c,d], Jieon Go [b], Sue Kim [a]

[a] Mo-Im Kim Nursing Research Institute, Yonsei University College of Nursing, Seoul, South Korea
[b] Division of Breast Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, South Korea
[c] Department of Biobehavioral Nursing Science, University of Illinois Chicago College of Nursing, Chicago, IL, USA
[d] University of Illinois Cancer Center, Chicago, IL, USA

ARTICLE INFO

Keywords:
Body composition
Breast neoplasm
Muscle
Skeletal
Neoadjuvant chemotherapy
Sarcopenia

ABSTRACT

Background: Low muscle mass, or sarcopenia, predicts poorer treatment outcomes in breast cancer. Neoadjuvant chemotherapy is the main treatment to improve surgical outcomes for breast cancer, yet few studies have assessed the relationships between different chemotherapy regimens and sarcopenia. This study compared body composition change between two neoadjuvant chemotherapy regimens: AC-T (anthracyclines and cyclophosphamide followed by a taxane) and TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab).

Methods: This study included 298 patients with breast cancer who received neoadjuvant chemotherapy between 2017 and 2020 at one university hospital. Body composition was assessed by computed tomography. Multiple linear regression was performed to examine predictors of SMI change.

Results: Patients receiving TCHP showed a significant mean skeletal muscle index (SMI) decrease of 1.6 cm^2/m^2 (SD = 3.5, $p < .001$); patients receiving AC-T showed no significant change in mean SMI. The TCHP group also showed significantly decreased visceral and subcutaneous fat mass, while the AC-T group showed increases in both. The TCHP group had significantly more patients with newly diagnosed sarcopenia after neoadjuvant chemotherapy than the AC-T group (12% vs 1%, respectively). Chemotherapy regimen was the only significant predictor of muscle mass loss, and the TCHP group's mean SMI decrease was 3.124 greater than that of the AC-T group (p = .015).

Conclusions: Patients receiving TCHP have a higher risk of muscle mass loss than those receiving AC-T. Considering the severe SMI decline observed in the TCHP group, further prospective studies are called for to examine treatment-induced sarcopenia and its relationship to body composition.

1. Introduction

Sarcopenia, or low muscle mass, has been recognized as having a negative impact on chemotherapy toxicities and cancer survival, and thus has become a meaningful indicator of mortality in oncology. Specifically, sarcopenia in breast cancer patients is unfavorable to clinical outcomes: it has been associated with chemotherapy toxicities [1–4], faster tumor progression [5], and higher overall mortality [6]. For example, breast cancer patients with sarcopenia have been found to have a 71% greater risk of mortality compared to patients without sarcopenia [7]. Conversely, greater muscle mass in breast cancer patients has been related to decreases in hematologic toxic effects such as neutropenia, anemia, and thrombocytopenia [8]. This is compelling evidence which supports the relationship between low muscle mass and poor treatment outcomes.

Neoadjuvant chemotherapy is the mainstay of treatment for breast cancer, and it has been proven indispensable for eradicating cancer and preventing tumor recurrence. Different types of neoadjuvant chemotherapy involving combinations of two or more drugs (e.g., representative anthracyclines and cyclophosphamide followed by a taxane [AC-T] or docetaxel, carboplatin, trastuzumab, and pertuzumab [TCHP]) have been applied in clinical settings depending on patient clinical characteristics such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression and tumor histology, stage, and grade [9,10]. Research findings indicate that sarcopenia may be an essential indicator of poor tolerance of

* Corresponding author. Yonsei University College of Nursing, 50-1 Yonsei-ro, Seodaemun-gu, 03722 Seoul, South Korea.
E-mail address: mjang21@uic.edu (M.K. Jang).

https://doi.org/10.1016/j.breast.2022.08.009
Received 17 June 2022; Received in revised form 24 August 2022; Accepted 28 August 2022
Available online 29 August 2022

various types of chemotherapy as well as of increased mortality [11,12]. In a study of breast cancer patients undergoing taxane-based chemotherapy, patients with sarcopenia showed higher chemotherapy toxicity, more toxicity-related hospitalizations, and reduced time to treatment failure compared to patients without sarcopenia [3]. In a separate study of breast cancer patients who were undergoing neoadjuvant epirubicin plus cyclophosphamide therapy, those with sarcopenia showed significantly more laboratory adverse events than those without sarcopenia [13]. Furthermore, patients with metastatic breast cancer and sarcopenia who received capecitabine treatment showed higher chemotherapy toxicity and less time to tumor progression than patients without sarcopenia [5]. Considering that the mechanisms, cycles, effectiveness, and major toxicities related to different chemotherapy regimens vary, research is needed into how different types of regimens affect sarcopenia status post neoadjuvant chemotherapy.

Among patients with breast cancer, the prevalence of sarcopenia is known to be high—it has been estimated at about 39.8% [12], 43.2% [11], and 45.0% [7] in recent systematic reviews and meta-analyses. In the wake of such findings, it is crucial to assess breast cancer patients for sarcopenia before and after chemotherapy in order to optimize treatment efficacy and tolerance and minimize adverse side effects. Yet despite the significance of sarcopenia status to treatment outcomes, and the different mechanisms and toxicities associated with various chemotherapy regimens, little research attention has been given to actual muscle mass loss during neoadjuvant chemotherapy. There has been no prior research with a large sample of breast cancer patients to investigate the possibility that body composition changes during neoadjuvant chemotherapy might vary by treatment regimen. Consequently, the purpose of this study was to compare changes in body composition among two groups of breast cancer patients receiving neoadjuvant chemotherapy—one receiving an AC-T regimen and the other receiving a TCHP regimen—and to examine predictors of muscle mass loss in these groups.

2. Material and methods

2.1. Study design and setting

This was a retrospective cohort study of breast cancer patients who were treated in one university hospital in South Korea between January 2017 and November 2020. The institutional review board of the hospital of the Yonsei University Health System approved the study protocol (#4-2021-0452).

2.2. Study population

The hospital's big data team extracted patient data from the hospital's dataset based on ICD-10-CM Code C50 (malignant neoplasm of breast). Guided by our study's eligibility criteria, the team extracted data for patients with breast cancer who were women aged 20 years or older, had completed neoadjuvant chemotherapy, and had received at least two abdominal computed tomography (CT) scans which provided images of the third lumbar spine vertebra (L3) before and after neoadjuvant chemotherapy. We excluded patients who had stage IV cancer, did not receive the AC-T or TCHP chemotherapy regimen, or had inadequate CT images that did not allow analysis of body composition.

2.3. Data collection and measurement

As part of our comprehensive information collection effort, we reviewed participants' medical records for demographic and clinical data, including cancer- and chemotherapy-related information. In addition, we collected body composition data generated by the university's Convergence Medical Technology Center, which performed body composition analysis using Aquarius iNtuition viewer version 4.4.13. P6 software (TeraRecon, Durham, North Carolina). The Hounsfield unit (HU) values used for measurements ranged from −29HU to +150HU for skeletal tissue, −190HU to −30HU for subcutaneous fat, and −150HU to −50HU for visceral fat.

We assessed abdominal CT scans that provided images of L3 before and after neoadjuvant chemotherapy. The mean time until CT follow-up (from before to after neoadjuvant chemotherapy) was 6 months, with periods ranging from 3 to 9 months. The first CT was taken when patients visited the hospital to undergo biopsy, and the time interval between each patient's first neoadjuvant chemotherapy session and the first CT averaged 14 days (SD: 8.5). The second CT was taken after all neoadjuvant chemotherapy was completed (before surgery), and this time interval averaged 11 days (SD: 3.4). A single axial CT slice at the L3 level—a vertebral landmark previously validated in sarcopenia studies of cancer patients [14–18]—was selected for body composition analysis. We applied the sarcopenia cut-off value of 38.5 cm^2/m^2 for women [19]. We calculated the skeletal muscle index (SMI) as cm^2/m^2 by measuring the skeletal muscle mass cross-sectional area (in cm^2) at L3 and then normalizing the results for patient height in meters squared (m^2). Similar to the SMI, we calculated the subcutaneous fat index (SFI) and visceral fat index (VFI) by dividing each related cross-sectional area by height squared. Fig. 1 shows the change in body composition before and after neoadjuvant chemotherapy in one patient who received the TCHP regimen.

Finally, using the body mass index (BMI) classifications for Asia [20,21], we assigned four BMI categories: underweight (BMI <18.5), normal weight (BMI 18.5–22.9), overweight (BMI 23.0–24.9), and obese (BMI ≥25.0).

2.4. Statistical analysis

All statistical analyses were performed using STATA IC version 16. We employed chi-square tests to describe and compare the distributions of demographic and clinical data between a patient group receiving AC-T chemotherapy and a group receiving TCHP chemotherapy. A paired *t*-test was applied to examine body composition changes before and after the neoadjuvant chemotherapy regimens. Multiple linear regression was used to examine predictors of SMI change after neoadjuvant chemotherapy; *p* values lower than .05 were considered significant.

3. Results

3.1. Demographic and clinical characteristics

A total of 298 patients with breast cancer were included in this study. The demographic and clinical characteristics of the two participant groups (by AC-T or TCHP chemotherapy regimen) are shown in Table 1. The participants' mean age of approximately 53 years was similar in both groups, and most participants had stage II cancer ($n = 212$, 71.4%). In the AC-T group, mean BMI before chemotherapy was 23.7 ± 3.2 kg/m^2, with 56.6% of the participants categorized as overweight (BMI 23.0–24.9) or obese (BMI >25.0). For the TCHP group, the mean BMI before chemotherapy was 23.5 ± 3.3 kg/m^2, with 51.2% of participants categorized as overweight or obese. There was no significant heterogeneity between the groups except for the duration of neoadjuvant chemotherapy and the tumor subtype. For treatment period, the AC-T group had a median value of 161 days, and the TCHP group had a median value of 105 days ($p < .001$). With respect to tumor subtypes, all participants with triple-negative breast cancer received the AC-T regimen ($p < .001$).

3.2. Body composition and sarcopenia status before and after chemotherapy in AC-T and TCHP groups

Table 2 shows changes in body composition during neoadjuvant chemotherapy for the two treatment groups.

At the beginning of neoadjuvant chemotherapy, we observed no

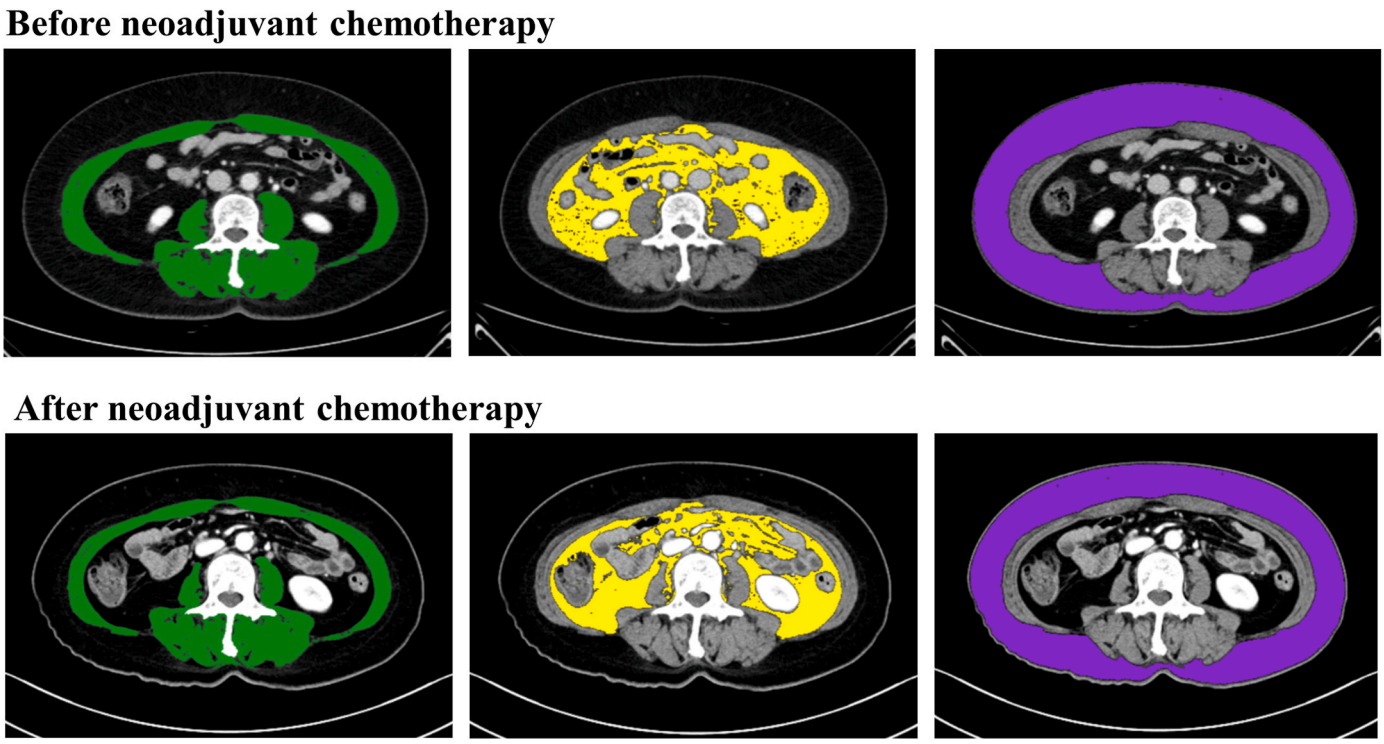

Fig. 1. Body composition evaluation via CT images for one 55-years-old woman before and after neoadjuvant TCHP. Axial CT images of the third lumbar vertebral region show the different proportions of skeletal muscle (green), visceral fat (yellow), and subcutaneous fat (purple) mass before and after TCHP (docetaxel, carboplatin, trastuzumab, and pertuzumab). This patient received six cycles of the TCHP regimen during neoadjuvant chemotherapy. Body mass index was 27.06 kg/m^2 (obese) before THCP and 24.56 kg/m^2 (overweight) after TCHP. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

significant heterogeneity in body composition parameters (SMI, VFI, SFI, BMI, and body surface area [BSA]) between the groups. However, there were significant between-group differences in body composition changes after chemotherapy. In the AC-T group ($n = 214$), the mean SMI was 42.4 cm^2/m^2 (SD = 5.4) before neoadjuvant chemotherapy and did not significantly change after chemotherapy (at 42.4 cm^2/m^2 [SD = 5.9]; t(213) = −0.22, $p = .830$). However, in the TCHP group, a significant difference in SMI was observed from before to after chemotherapy (t(83) = 4.00, $p = .0001$). In that group, the mean SMI was 42.6 cm^2/m^2 (SD = 5.8) before chemotherapy and decreased considerably (by almost 1.6 cm^2/m^2) to 41.0 cm^2/m^2 (SD = 5.6) after chemotherapy. In addition, based on a two-sample *t*-test between the AC-T and TCHP groups, we observed a significant difference in the groups' SMI changes during chemotherapy (t(296) = 3.41, $p = .0007$).

In addition, after neoadjuvant chemotherapy, the mean VFI in the AC-T group showed a significant increase of 2.554 cm^2/m^2, but the mean VFI in the TCHP group showed a significant decrease of 2.390 cm^2/m^2 (SD = 17.3). Similarly, the mean SFI in the AC-T group showed a significant increase of 1.745 cm^2/m^2 post chemotherapy, but the mean SFI in the TCHP group showed a significant decrease of 6.140 cm^2/m^2. Based on a paired *t*-test between the AC-T and TCHP groups, there were thus significant differences in both VFI and SFI changes during chemotherapy (t(296) = 4.26, $p = .0000$ and t(296) = 4.83, $p = .0000$, respectively).

3.3. Distributions of SMI change during chemotherapy in AC-T and TCHP groups

Fig. 2 presents the distribution of absolute SMI, VFI, and SFI changes during neoadjuvant chemotherapy between the AC-T and TCHP groups. This figure illustrates the different distribution characteristics of the two groups. The median value of SMI change in the TCHP group showed a considerably greater skeletal muscle mass loss than the median value in the AC-T regimen group (median: 1.6 vs. −0.05, respectively). In addition, the skewness of SMI change in the TCHP group was higher than that in the AC-T group (skewness: .191 vs. 0.055, respectively). Similarly, the median VFI and SFI changes in the TCHP group showed decreases during neoadjuvant chemotherapy, but the median VFI and SFI changes in the AC-T group showed increases. Accordingly, the distribution graph in Fig. 2 reveals a greater loss of skeletal muscle and fat in the TCHP group.

3.4. Sarcopenia prevalence during neoadjuvant chemotherapy

Fig. 3 presents the sarcopenia prevalence in the AC-T and TCHP groups before (at baseline) and at completion of neoadjuvant chemotherapy. Using the sarcopenia cut-off value for women [19], we observed no significant difference in sarcopenia prevalence between the groups before chemotherapy: both groups had a sarcopenia prevalence of about 25%. However, although only 1% of the AC-T group showed newly diagnosed sarcopenia after chemotherapy, the TCHP group showed a significant increase in newly diagnosed sarcopenia, of 12%. Thus, the group that received the TCHP regimen had a much higher proportion of patients experiencing sarcopenia status than the group that received the AC-T regimen (37% vs. 26%, respectively; $\chi^2(1) = 128.215$, $p < .001$).

3.5. Predictors of SMI change during neoadjuvant chemotherapy

Table 3 shows multiple linear regression results for SMI change during neoadjuvant chemotherapy. This regression included patient age, BMI at diagnosis, cancer stage, tumor subtype, chemotherapy regimen, and chemotherapy duration as independent predictors. The model fit statistics were significant (at $F(9,278) = 2.66$, $p < .01$), with 7% of the variance in SMI change explained with this model. Chemotherapy regimen was the only significant predictor of decreased SMI, and the

Table 1
Demographic and clinical characteristics of the AC-T and TCHP treatment groups (N = 298).

Characteristic		AC-T group (n = 214)	TCHP group (n = 84)	χ^2 or t (p value)
		Mean ± SD (range) or No. (%)	Mean ± SD (range) or No. (%)	
Age (years)		52.86 ± 10.54 (26–77)	53.06 ± 9.49 (35–82)	−0.1512 (.880)
Stage of tumor	I	3 (1.4)	2 (2.4)	0.358
	II	153 (71.5)	59 (70.2)	(.836)
	III	51 (23.8)	20 (23.8)	
Initial clinical T stage	1	21 (9.8)	9 (10.7)	5.483 (.241)
	2	148 (69.2)	50 (59.5)	
	3	19 (8.9)	12 (14.3)	
	4	18 (8.4)	9 (10.7)	
Initial clinical N stage	0	71 (33.2)	34 (40.5)	2.276 (.517)
	1	105 (49.1)	38 (45.2)	
	2	15 (7.0)	3 (3.6)	
	3	15 (7.0)	6 (7.1)	
Duration of neoadjuvant chemotherapy		160 ± 13.49	107 ± 5.84	34.485 (.000)
Tumor subtype	HR+/HER2-	100 (46.7)	3 (3.6)	202.099
	HR+/HER2+	12 (5.6)	36 (42.9)	(.000)
	HR-/HER2+	9 (4.2)	45 (53.6)	
	TNBC	93 (43.5)	0 (0.0)	
Ki-67	Low (<14%)	25 (11.7)	8 (9.5)	0.258
	High (≥14%)	181 (84.6)	72 (85.7)	(.612)
BMI at baseline	<18.5 (underweight)	5 (2.3)	4 (4.8)	2.650 (.449)
	18.5–22.9 (normal)	88 (41.1)	37 (44.0)	
	23.0–24.9 (overweight)	59 (27.6)	17 (20.2)	
	≥25.0 (obese)	62 (29.0)	26 (31.0)	

Notes. AC-T regimen = combination of an anthracycline and cyclophosphamide (AC) followed by a taxane; BMI = body mass index; HER2+/− = human epidermal growth factor receptor 2-positive/-negative; HR+/− = hormone receptor-positive/-negative; TCHP regimen = docetaxel, carboplatin, trastuzumab, and pertuzumab; TNBC = triple negative breast cancer.

mean SMI decrease in the TCHP group was 3.124 greater than in the AC-T group (β = −3.124 vs. β = 1.000, p = .015).

4. Discussion

Oncology research studies have shown increased interest in sarcopenia over the past decade, with the recognition that it has a negative impact on cancer treatment and survival. Sarcopenia has thus become a meaningful indicator for mortality in oncology. However, few studies have examined actual muscle mass loss during neoadjuvant chemotherapy, let alone the effects of different chemotherapy regimens on changes in body composition in a large cohort of patients with breast cancer. Our study contributes new insights in that the TCHP regimen was associated with a large increase in newly diagnosed sarcopenia during neoadjuvant chemotherapy as well as 3.124 greater loss of muscle mass than was seen with the AC-T regimen. These findings highlight the importance of closely monitoring muscle mass loss among breast cancer patients who receive the TCHP chemotherapy regimen.

Our study findings have several clinical implications. First, we found that the TCHP group showed greater loss of muscle mass during neoadjuvant chemotherapy than the AC-T group, even though they showed no significant SMI differences at baseline. A previous systematic review and meta-analysis reported an average SMI reduction of 2.7 cm^2/m^2 during chemotherapy (and/or radiotherapy) treatment for various cancer types [22]. Although cancer treatments such as chemotherapy, surgery, and radiotherapy are known to cause muscle mass loss, it is worrisome that we observed a mean SMI decrease of 1.6 cm^2/m^2 in just 3–4 months (6 cycles, median: 105 days) of TCHP neoadjuvant chemotherapy.

One previous study involving 119 patients with breast cancer in France reported a mean SMI of 42.3 cm^2/m^2 before chemotherapy [23], as measured by CT scan. That value is slightly lower than the mean baseline SMI of our TCHP group (42.6 cm^2/m^2). In another previous study, this one involving patients with metastatic breast cancer who received first-line taxane-based chemotherapy in the United States, the mean SMI measured by CT scan before chemotherapy was 41.2 cm^2/m^2 [3], which is lower than our TCHP group's mean SMI before chemotherapy but slightly higher than their mean SMI of 41.0 cm^2/m^2 after neoadjuvant chemotherapy. Also, another study involving 49 patients with metastatic breast cancer in France [24] found a mean SMI of 41.7 cm^2/m^2 before chemotherapy, as measured by CT scan. No previous breast cancer studies in South Korea have specified how much muscle mass was lost during neoadjuvant chemotherapy, but compared to studies performed in other countries, we observed a slightly higher SMI at baseline and a slightly lower SMI after chemotherapy, despite the fact that no metastatic cancer was present in our patients. As decreased SMI after neoadjuvant chemotherapy poses a threat to disease-free survival [25], decreased SMI should be given attention when determining the direction of clinical treatment and evaluating treatment effectiveness.

A second finding with clinical implications is that chemotherapy regimen was a significant predictor of SMI decrease. Compared to the AC-T group, the TCHP group showed 3.124 greater decrease in SMI. These findings indicate that muscle mass loss may differ depending on the chemotherapy regimen applied. As these two groups obviously differed in their tumor biology, such as ER, PR, and HER2, their differences in SMI change should be interpreted in light of the fact that chemotherapy regimens are selected according to the specific tumor biology present. A TCHP neoadjuvant regimen is generally used for patients with early or locally advanced breast cancer and with HER2-positive breast cancer to improve survival and achieve pathologically complete response; patients undergoing this regimen have reported experiencing adverse events such as mucositis, pain, diarrhea, fatigue, and anorexia [26,27]. A previous study involving patients with early

Table 2
Distributional difference in body composition in the AC-T and TCHP treatment groups.

Parameter	Group	Value distribution						
		Mean	Median	25th percentile	75th percentile	*Variance*	*Skewness*	*Kurtosis*
SMI (cm^2/m^2)	AC-T	0.054	−0.051	−2.097	2.242	13.528	.055	4.170
	TCHP	−1.545	−1.553	−3.492	0.110	12.526	.191	4.307
VFI (cm^2/m^2)	AC-T	2.554	2.119	−2.217	7.614	82.026	−.545	5.700
	TCHP	−2.390	−0.596	−7.110	1.953	79.249	−.459	4.419
SFI (cm^2/m^2)	AC-T	1.745	2.704	−6.266	9.236	165.056	−.309	3.740
	TCHP	−6.140	−5.863	−13.871	1.193	148.949	.337	5.121

Notes. AC-T = combination of an anthracycline and cyclophosphamide (AC) followed by a taxane; SFI = subcutaneous fat index; SMI = skeletal muscle mass index; TCHP = docetaxel, carboplatin, trastuzumab, and pertuzumab; VFI = visceral fat index.

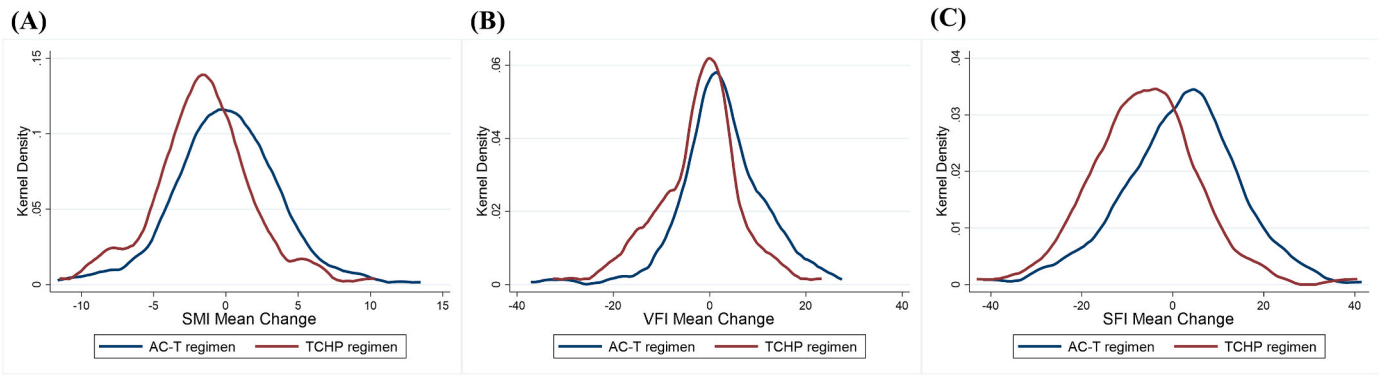

Fig. 2. Body composition changes during neoadjuvant chemotherapy in groups receiving AC-T versus TCHP neoadjuvant regimens. A value of 0 for SMI, VFI, and SFI indicates no changes during neoadjuvant chemotherapy. A higher negative mean change value for these parameters indicates a greater reduction during chemotherapy, and a higher positive mean change value indicates a greater increase during chemotherapy. AC-T = combination of an anthracycline and cyclophosphamide (AC) followed by a taxane; SFI = subcutaneous fat index; SMI = skeletal muscle index; THCP = docetaxel, carboplatin, trastuzumab, and pertuzumab; VFI = visceral fat index.

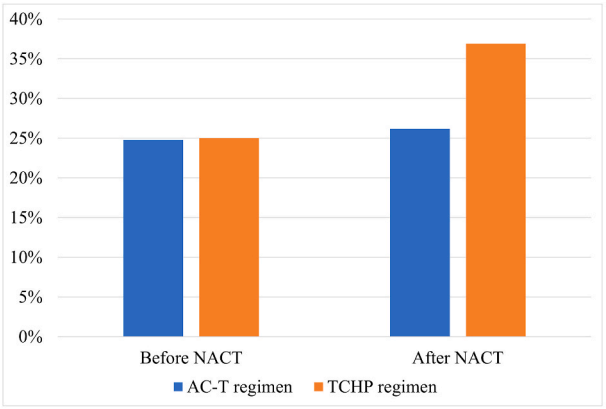

Fig. 3. Sarcopenia prevalence during neoadjuvant chemotherapy by group.
AC-T = combination of an anthracycline and cyclophosphamide (AC) followed by a taxane; NACT = neoadjuvant chemotherapy; TCHP = docetaxel, carboplatin, trastuzumab, and pertuzumab.

Fig. 3. Sarcopenia prevalence during neoadjuvant chemotherapy by group. AC-T = combination of an anthracycline and cyclophosphamide (AC) followed by a taxane; NACT = neoadjuvant chemotherapy; TCHP = docetaxel, carboplatin, trastuzumab, and pertuzumab.

Table 3
Multiple regression analyses to predict SMI change after neoadjuvant chemotherapy.

Variable		Coef	95% CI interval		*t*	*p* value
Chemotherapy regimen	AC-T	1.000				
	TCHP	−3.124	−5.646	−0.603	−2.44	.015
Tumor subtype	HR+/HER2-	1.000				
	HR+/HER2+	−0.440	−1.251	2.132	0.51	.609
	HR-/HER2+	−0.450	−2.505	1.604	−0.43	.666
	TNBC	−0.483	−1.566	0.600	−0.88	.381
Chemotherapy duration		−0.027	−0.060	0.006	−1.62	.107
Baseline BMI		−0.108	−0.257	0.041	−1.42	.156
Age at diagnosis (years)	<50	1.000				
	≥50	−0.270	−1.137	0.597	−0.61	.540
Stage	I	1.000				
	II	2.114	−2.962	7.191	0.82	.413
	III	1.281	−3.839	6.400	0.49	.623

Notes. BMI = body mass index; Coef = coefficient; CI = confidence interval; HR+/− = hormone receptor-positive/-negative; HER2+/− = human epidermal growth factor receptor 2-positive/-negative; TNBC = triple-negative breast cancer.
$F(9,278) = 2.66$, $p < .01$, pseudo r = 0.0717.

breast cancer has also reported that the proportion of patient-reported toxicities differed by chemotherapy regimen: a group receiving the AC-T regimen most frequently experienced fatigue over the entire course of chemotherapy, whereas a group receiving docetaxel/carboplatin with anti-HER2 therapy most frequently experienced diarrhea [28]. The fact that chemotherapy-related adverse events can vary by regimen due to the actions of the particular chemical combination involved could be indirectly or directly related to muscle mass loss. For example, the diarrhea and anorexia frequently associated with chemotherapy toxicities of the TCHP regimen could be related to loss of muscle or fat. Given the multiple causes of muscle loss in cancer patients—a combination of risk factors such as aging and cancer-related, and treatment-related factors [29]—further examination of the degree of muscle mass loss by chemotherapy regimen, in addition to other factors, is called for.

Another meaningful implication for the clinical oncology field is our finding that muscle, visceral fat, and subcutaneous fat all decreased during neoadjuvant chemotherapy in the TCHP group, whereas in the AC-T group, muscle did not significantly change but both visceral fat and subcutaneous fat increased. These findings argue that body composition during chemotherapy should be analyzed in detail, because assessing BMI alone can mask muscle decreases through fat increases (as was seen in the AC-T group). Particularly for patients with breast cancer, not only muscle mass loss but also increased body fat could be a crucial factor affecting treatment outcomes and patient survival. Furthermore, because different types of chemotherapy have different mechanisms, their effects on patients' changes in body composition may vary during treatment. In future studies of changes in body composition—ideally with larger samples of breast cancer patients, more specific chemotherapy regimens should be considered along with other pertinent factors such as use of hormone agents and steroids.

A prior study found greater visceral fat mass to be related to poor distant disease-free survival after neoadjuvant chemotherapy in patients with advanced breast cancer, especially those who are postmenopausal [30]. In patients with nonmetastatic breast cancer, those with high total adipose tissue have shown higher overall mortality [6]. To support understanding of the combination of low muscle mass and high fat mass, research in the oncology field has been turning to the concept of sarcopenic obesity. Our study findings suggest that different chemotherapy regimens may make different contributions to body composition

changes that lead to either sarcopenia or sarcopenic obesity. In terms of clinical relevance, our findings of the risk and severity of muscle mass loss in our TCHP group suggest a need for careful monitoring of body composition among breast cancer patients receiving this regimen.

This study has some limitations that should be recognized. First, our retrospective study collected all patient data from a single medical center. Accordingly, our results may have limited generalizability, and we could not determine cause-and-effect relationships. Second, we could not include skeletal muscle density as a variable due to the possibility that the use of CT contrast agents would produce inaccurate muscle density results. Third, although sarcopenia is generally associated with a negative prognosis, this does not directly apply to treatment-induced sarcopenia. Further prospective studies involving chemotherapy-related clinical outcomes should be performed to investigate the causes and clinical significance of treatment-induced sarcopenia. Furthermore, employing comprehensive datasets, future researchers should pursue a greater understanding of the relationships between sarcopenia and nutritional patterns, physical activity, toxicity differences by chemotherapy regimen, adverse effect grading, and use of steroid medication and hormone agents during chemotherapy. Finally, considering that skeletal muscle density has recently been found to be a major factor in characterizing sarcopenia and related variables, accurate measurement of skeletal muscle density should be ensured in future studies.

5. Conclusion

Our study of 298 breast cancer patients found that those receiving a neoadjuvant TCHP regimen experienced greater loss of muscle mass than those receiving a neoadjuvant AC-T regimen. This study's TCHP group lost both muscle and fat, whereas the AC-T group had no significant change in muscle but gained fat, which suggests that the type of chemotherapy regimen may be an important predictor of sarcopenia severity as well as of body composition changes in breast cancer patients undergoing neoadjuvant chemotherapy. Given the higher risk and the severity of SMI decline observed in our TCHP group, and the known relationships between sarcopenia and poor treatment outcomes, careful monitoring of body composition is necessary for breast cancer patients receiving a TCHP regimen.

Ethical approval

The institutional review board of the hospital of the Yonsei University Health System approved the study protocol (#4-2021-0452).

Funding

This work was supported by the National Research Foundation of Korea (NRF No. 2021R1C1C2004628) grant funded by the government of South Korea (Ministry of Science and ICT).

Declaration of competing interest

The authors have no conflict of interest to declare in relation to the work described in this article.

References

[1] Rossi F, Valdora F, Bignotti B, Torri L, Succio G, Tagliafico AS. Evaluation of body computed tomography-determined sarcopenia in breast cancer patients and clinical outcomes: a systematic review. Cancer Treat Res Commun 2019;21:100154. Jan 1.
[2] Mazzuca F, Onesti CE, Roberto M, Di Girolamo M, Botticelli A, Begini P, Strigari L, Marchetti P, Muscaritoli M. Lean body mass wasting and toxicity in early breast cancer patients receiving anthracyclines. Oncotarget 2018;9(39):25714. May 22.
[3] Shachar SS, Deal AM, Weinberg M, Nyrop KA, Williams GR, Nishijima TF, Benbow JM, Muss HB. Skeletal muscle measures as predictors of toxicity, hospitalization, and survival in patients with metastatic breast cancer receiving taxane-based chemotherapy. Clin Cancer Res 2017;23(3):658–65. Feb 1.
[4] Shachar SS, Deal AM, Weinberg M, Williams GR, Nyrop KA, Popuri K, Choi SK, Muss HB. Body composition as a predictor of toxicity in patients receiving anthracycline and taxane–based chemotherapy for early-stage breast cancer. Clin Cancer Res 2017;23(14):3537–43. Jul 15.
[5] Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, Mackey JR, Koski S, Pituskin E, Sawyer MB. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15(8):2920–6. Apr 15.
[6] Caan BJ, Feliciano EM, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, Quesenberry CP, Weltzien EK, Castillo AL, Olobatuyi TA, Chen WY. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. JAMA Oncol 2018;4(6):798–804. Jun 1.
[7] Zhang XM, Dou QL, Zeng Y, Yang Y, Cheng AS, Zhang WW. Sarcopenia as a predictor of mortality in women with breast cancer: a meta-analysis and systematic review. BMC Cancer 2020;20(1). Dec;, 1-1.
[8] Feliciano EM, Chen WY, Lee V, Albers KB, Prado CM, Alexeeff S, Xiao J, Shachar SS, Caan BJ. Body composition, adherence to anthracycline and taxane-based chemotherapy, and survival after nonmetastatic breast cancer. JAMA Oncol 2020;6(2):264–70. Feb 1.
[9] Korde LA, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, Khan SA, Loibl S, Morris EA, Perez A, Regan MM. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. J Clin Oncol 2021 May 1;39(13):1485–505. official journal of the American Society of Clinical Oncology.
[10] Tamirisa N, Hunt KK. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. Ann Surg Oncol 2022:1–4. Jan 6.
[11] Rossi F, Valdora F, Bignotti B, Torri L, Succio G, Tagliafico AS. Evaluation of body computed tomography-determined sarcopenia in breast cancer patients and clinical outcomes: a systematic review. Cancer Treat Res Commun 2019;21:100154. Jan 1.
[12] Aleixo GF, Williams GR, Nyrop KA, Muss HB, Shachar SS. Muscle composition and outcomes in patients with breast cancer: meta-analysis and systematic review. Breast Cancer Res Treat 2019;177(3):569–79. Oct.
[13] Ueno A, Yamaguchi K, Sudo M, Imai S. Sarcopenia as a risk factor of severe laboratory adverse events in breast cancer patients receiving perioperative epirubicin plus cyclophosphamide therapy. Support Care Cancer 2020;28(9):4249–54. Sep;.
[14] Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJ, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. Insights into imaging 2015;6(4):489–97. Aug.
[15] Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E. Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: a systematic review. Clin Nutr 2018;37(4):1101–13. Aug 1.
[16] Albano D, Messina C, Vitale J, Sconfienza LM. Imaging of sarcopenia: old evidence and new insights. Eur Radiol 2020;30(4):2199–208. Apr.
[17] Findlay M, White K, Lai M, Luo D, Bauer JD. The association between computed tomography–defined sarcopenia and outcomes in adult patients undergoing radiotherapy of curative intent for head and neck cancer: a systematic review. J Acad Nutr Diet 2020;120(8):1330–47. Aug 1.
[18] Su H, Ruan J, Chen T, Lin E, Shi L. CT-assessed sarcopenia is a predictive factor for both long-term and short-term outcomes in gastrointestinal oncology patients: a systematic review and meta-analysis. Cancer Imag 2019;19(1):1–5. Dec.
[19] Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008;9(7):629–35. Jul 1.
[20] Consultation WE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet (London, England) 2004;363(9403):157–63. Jan 10.
[21] Weir CB, Jan A. BMI classification percentile and cut off points.
[22] Jang MK, Park C, Hong S, Li H, Rhee E, Doorenbos AZ. Skeletal muscle mass change during chemotherapy: a systematic review and meta-analysis. Anticancer Res 2020;40(5):2409–18. May 1.
[23] Deluche E, Leobon S, Desport JC, Venat-Bouvet L, Usseglio J, Tubiana-Mathieu N. Impact of body composition on outcome in patients with early breast cancer. Support Care Cancer 2018;26(3):861–8. Mar.
[24] Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, Freyssenet D, Friedenreich C, Dufresne A, Bachelot T, Heudel PE. Sarcopenia and serum biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast cancer: results from the ABLE feasibility trial. Breast Cancer Res Treat 2021;188(3):601–13. Aug.
[25] Amitani M, Oba T, Kiyosawa N, Morikawa H, Chino T, Soma A, Shimizu T, Ohno K, Ono M, Ito T, Kanai T. Skeletal muscle loss during neoadjuvant chemotherapy predicts poor prognosis in patients with breast cancer. BMC Cancer 2022;22(327):1–11. Dec.
[26] Hussain N, Said AS, Khan Z. Safety assessment of neoadjuvant pertuzumab combined with trastuzumab in nonmetastatic HER2-positive breast cancer in postmenopausal elderly women of South Asia. Int J Breast Cancer 2018;2018:6106041. https://doi.org/10.1155/2018/6106041.
[27] Nyrop KA, Deal AM, Shachar SS, Basch E, Reeve BB, Choi SK, Lee JT, Wood WA, Anders CK, Carey LA, Dees EC. Patient-reported toxicities during chemotherapy regimens in current clinical practice for early breast cancer. Oncol 2019;24(6):762–71. Jun.

[28] Kim JY, Nam SJ, Lee JE, Yu J, Chae BJ, Lee SK, Ryu JM, Ahn JS, Im YH, Kim SW, Park YH. Real world evidence of neoadjuvant docetaxel/carboplatin/trastuzumab/pertuzumab (TCHP) in patients with HER2-positive early or locally advanced breast cancer: a single-institutional clinical experience. Cancer Research and Treatment; 2022. Jan 10.

[29] Williams GR, Rier HN, McDonald A, Shachar SS. Sarcopenia & aging in cancer. J Geriatr Oncol 2019;10(3):374–7. May 1.

[30] Iwase T, Sangai T, Nagashima T, Sakakibara M, Sakakibara J, Hayama S, Ishigami E, Masuda T, Miyazaki M. Impact of body fat distribution on neoadjuvant chemotherapy outcomes in advanced breast cancer patients. Cancer Med 2016;5(1):41–8. Jan.