Original Article

The Relationship of Pathological Response and Visceral Muscle and Fat Volume in Women With Breast Cancer Who Received Neoadjuvant Chemotherapy

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ABSTRACT

Objective: Differences in individual muscle/fat volumes may change the effectiveness of chemotherapy. In this study, the relationship between trunkal muscle and fat volume and body mass index (BMI) obtained before receiving neoadjuvant chemotherapy (NCT) in patients with breast cancer and complete pathological response (pCR) was investigated.

Materials and Methods: The volumes of psoas, abdominal and paraspinal muscles, and trunkal subcutaneous and visceral fat were calculated using CoreSlicer AI 2.0 opensource program from the F-18 fluorodeoxyglucose positron emission tomography/computed tomography (CT) and CT images before NCT and postoperative pCR rates to NCT were recorded. Muscle/fat volumes and BMI prior to NCT were compared in terms of pathological pCR rates. Patients were followed up regularly for recurrence and survival.

Results: Ninety-three patients were included with median (range) values for age, BMI, and body weights of 48 (28–72) years, 27 (16.8–51.6) kg/m², and 71.94 (43–137) kg, respectively. The median follow-up time was 18.6 (6.7–59.6) months. No significant correlation was found between total muscle or fat volumes of patients with and without pCR. BMI [26.2 (16.8–51.6) kg/m² *vs.* 24.6 (20.3–34.3) kg/m², $p = 0.03$] and pCR rates in patients with low right-psoas muscle volume [11.74 (7.03–18.51) *vs.* 10.2 (6.71–13.36), $p = 0.025$] were significantly greater. A significant relationship was found between right psoas muscle volume and disease-free survival (DFS) (11.74 cm³ (7.03–18.51) vs. 10.2 cm³ (6.71–13.36), $p = 0.025$). However, no significant relationship was detected between total muscle-fat volume, BMI and overall survival and DFS ($p>0.05$).

Conclusion: This is the first published study investigating the relationship between the pCR ratio and body muscle and fat volume measured by CoreSlicer AI 2.0 in patients with breast cancer who received NCT. No correlation was found between the pCR ratio and total muscle plus fat volume. However, these results need to be validated with larger patient series.

Keywords: Breast cancer; FDG-PET-CT; pCR; total muscle-fat volume; BMI; neoadjuvant chemotherapy

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Key Points

- This is the first published study in the to analyze the trunkal muscle/fat volumes from a single section obtained at a single level in computed tomography and to investigate the relationship between measurements and neoadjuvant chemotherapy (NCT).
- Muscle-Fat volume was measured by CoreSlicer AI 2.0 in patients with breast cancer who received NCT. In patients with pathological response (pCR), mean body mass index (BMI) and right psoas muscle volume was significantly less.
- Mean BMI and right psoas muscle volume were found to be significantly lower in patients with pCR. Total muscle volumes were higher in patients with pCR, but the difference was not statistically significant.
- Local/systemic recurrence occurred in 18 patients during the follow-up period, and no correlation was found between body muscle/fat volume and pCR in these patients.

Introduction

It is known that excess adipose tissue is a risk factor for the development of breast cancer (BC) by inducing insulin resistance, chronic inflammation, and hormonal changes (1). Obesity increases the risk of BC and decreases the effectiveness of neoadjuvant chemotherapy (NCT) (2, 3). Complete pathological response (pCR) and disease-free survival (DFS) rates after NCT are generally lower in obese patients (2, 4). Body mass index (BMI) is the most common measure for classifying weight and has been extensively studied to explore the relationship between obesity and survival in BC (5). A study that examined the effects of high visceral adipose tissue (VAT) on the survival of patients with BC showed that high VAT shortened DFS due to increased insulin levels, and increased insulin resistance (6). There is evidence that visceral fat plays a more significant role in the homeostasis of cancer cells than other adipose tissues. In addition, it has been reported that high visceral fat levels significantly affect chemosensitivity (7).

Sarcopenia and adiposity measurements obtained from abdominal computed tomography (CT) images in nonmetastatic BC patients provide more prognostic information than BMI and help to predict survival outcomes (5, 8). However, a low BMI can mask excessive fat while a high BMI can mask low muscle mass. It has also been shown that low muscle radiodensity increases the risk of mortality (5).

There is increasing interest in using body composition analysis to treat patients with BC (9, 10). CoreSlicer is the first open-source, web-based, medical image analysis software specifically designed and optimized for analytical morphometry, measuring specific biomarkers of body composition from CT images (11). The present study investigated the relationship between muscle/fat volume, BMI, and pCR using the CoreSlicer AI 2.0 program in patients who received NCT after diagnosis with BC.

Materials and Methods

Patients with a diagnosis of stage 2-3 BC in Istanbul Florence Nightingale Breast Health Center who received NCT (4 cycles of adriamycin/epirubicin + cyclophosphamide (AC/EC) + 4 cycles of taxane ± anti-Her-2 therapies) and whose data and follow-up were complete were included. The patient's demographic, clinical, pathological, and follow-up results were retrospectively evaluated (Graphic 1, Table 1). Patients younger than 18 years, receiving adjuvant chemotherapy, and metastatic patients with missing follow-up were excluded from the study. The pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy. The patients' body muscle and fat volumes were measured by a radiologist (K.Y.) with more than

10 years experience in abdomen imaging before NCT treatment using the CoreSlicer AI 2.0 (Figure 1) opensource software program (11). The volumes of the left and right psoas muscles, bilateral abdominal and paraspinal muscles, and subcutaneous and visceral fat were measured from the L3 v reference point.

Before the diagnosis, body weight and height measurements were made using SECA® (Medizinische Messsysteme und Waagen, Hamburg, Deutschland), BMI was calculated, and the results were evaluated according to the World Health Organization classification (12).

Statistical Analysis

SPSS for Windows, version 20.0 was used for statistical analysis (IBM Inc., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the distribution of variables, the Mann-Whitney U test for the comparison of non-normally distributed parameters (non-parametric), the chi-square test for the comparison of qualitative data, and two-way Pearson correlation test for determining the relationship between quantitative variables. The level of significance was set as $p < 0.05$ in all analyses.

Results

The median age, follow-up time, BMI, and weight values of all patients were 48 (28–72), 18.6 months (6.7–59.6), 27 kg/m² (16.8–51.6), and 71.94 kg (43–137), respectively (Graphic 1).

Of nineteen patients acheiving pCR, 2 (7.7%) were Luminal A, 7 (17.9%) were Luminal B, 6 (50%) were human epidermal growth factor receptor type 2 (HER2), and 4 (25%) were triple-negative breast cancer. The pCR rates were significantly lower in the luminal A and B groups ($p = 0.039$) (Table 1). Local/systemic recurrence was observed in 18 patients during follow-up and no correlation was found between body muscle-fat volume and pCR in these patients ($p > 0.05$).

In patients with pCR, median BMI and right psoas muscle volume were significantly lower than in patients not acheiving pCR (Table 1). Furthermore, total muscle [114.47 (43.54–155.82) *vs.* 106.65 (80.56–139.24), $p = 0.08$], and total fat [334.98 (21.77–878.58) *vs.* 309.22(111.32–595.51), $p = 0.36$] volumes tended to be lower in patients with pCR but were not sigficantly different.

Considering the effect of muscle-fat volumes on overall survival (OS) and DFS, a significant correlation was found between right psoas volume and DFS [11.74 cm³ (7.03–18.51) *vs.* 10.2 cm³ (6.71–13.36), $p = 0.025$]. It was calculated that each unit increase in right psoas volume increases the risk of recurrence or death by 1.2 times. No significant correlation was found between total muscle-fat volume, BMI, OS, and DFS ($p > 0.05$).

No significant difference was found when BMI and psoas, abdominal and paraspinal muscles, and subcutaneous and visceral fat volumes were examined in pre-and post-menopausal patients ($p>0.05$). In addition, no significant relationship was found between menopausal status and DFS vs. pCR ($p>0.05$).

Discussion and Conclusion

This is the first published study to calculate body muscle/fat volume by examining fluorodeoxyglucose- positron emission tomography (PET) CT images with CoreSlicer AI 2.0 open-source software web tool kit in patients with BC who received NCT and investigate the relationship

with pCR. CoreSlicer is the first open-source web-based medical imaging analysis designed and optimized for analytical morphometric assessment, designed to include artificial intelligence (11). Previous studies evaluated body compositions only as area, tissue, or mass (5, 13, 14). BMI, a more commonly used method, only measures the ratio between height and weight, and does not distinguish between muscle and adipose tissue, and cannot account for body fat distribution and type differences when used alone (5, 7). Thus, body composition-specific biomarkers obtained from CT images may be used instead of BMI in clinical evaluations (10, 15).

The relationships between BC and obesity, BMI, and body composition have been extensively studied (5, 6, 7, 9, 10, 16, 17-20). However, different results were obtained in studies investigating the relationship between muscle/fat tissue data obtained from CT images of these patients and BMI and survival (5, 13). Some studies have shown that body composition data obtained by BMI and CT are not associated with DFS (7, 10, 17). However, in a study by Iwase et al. (18) in 248 patients receiving NCT, decrease DFS was associated negatively with molecular subtypes, tumor stage, and high BMI. Some studies have shown muscle/fat volume measurements are more effective than BMI in determining survival. DFS is associated with visceral adiposity, insulin level, and insulin resistance (5, 6, 7, 9, 19, 20). In the present study, however, a significant relationship was found only between right psoas muscle volume and DFS, such that each unit increase in
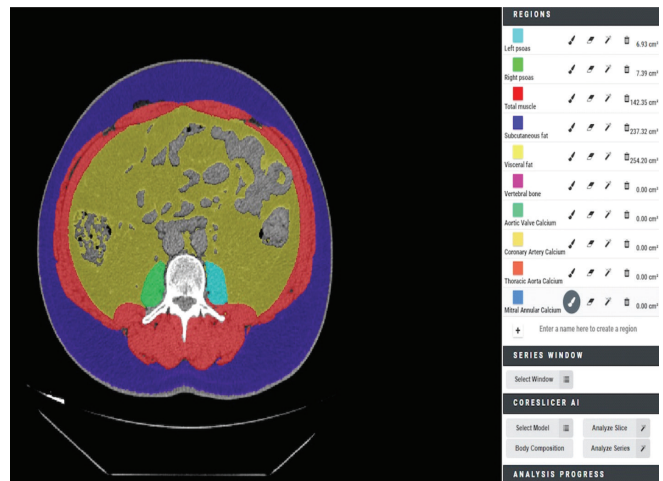
Table 1. The correlation between age, BMI, muscle and fat volumes, molecular subtypes, and pCR

	pCR (-) Median (min-max)	pCR (+) Median (min-max)	p
Age (years)	48 (29–72)	44 (28–67)	0.27[a]
BMI (kg/m²)	**26.2 (16.8–51.6)**	24.6 (20.3–34.3)	**0.03[a]**
Left-psoas volume (cm³)	11.69 (7.09–19.78)	11.53 (8.66–13.68)	0.3[a]
Right-psoas volume (cm³)	**11.74 (7.03–18.51)**	**10.2 (6.71–13.36)**	**0.025[a]**
Subcutaneous fat volume (cm³)	244.48 (10.88–703.55)	195.94 (91.11-382.61)	0.15[a]
Visceral fat volume (cm³)	84.38 (8.27–357.11)	81.5 (20.21–302.2)	0.74[a]
Abdominal muscle volume (cm³)	48.58 (10.88–75.24)	45.68 (35.18–65.6)	0.16[a]
Paraspinal muscle volume (cm³)	43.04 (10.88–56.75)	37.62 (27.18–53.36)	0.12[a]
TFV (cm³)	334.98 (21.77–878.58)	309.22 (111.32–595.51)	0.36[a]
TMV (cm³)	114.47 (43.54-155.82)	106.65 (80.56–139.24)	0.08[a]
Total fat/total muscle volume (cm³)	3.07 (0.5-7.1)	2.8 (1.1–4.8)	0.65[a]
Molecular Subtypes			
Luminal A (n = 26)	24 (92.3%)	2 (7.7%)	
Luminal B (n = 39)	32 (82.1%)	7 (17.9%)	0.039[b]*
HER2 (n = 12)	6 (50%)	6 (50%)	
TNBC (n = 17)	12 (75%)	4 (25%)	

[a]: Mann-Whitney U, [b]: Chi-square; pCR: Complete pathological response; BMI: Body mass index; TFV: Total fat volume; TMV: Total muscle volume; HER2: human epidermal growth factor receptor type 2; TNBC: Triple negative breast cancer

Figure 1. AI volume measurement image with coreslicer

Red: Total muscle, Yellow: Visceral fat, Purple: Subcutaneous fat, Green: Right psoas muscle, Turquoise: Left psoas muscle, AI: Artificial intelligence
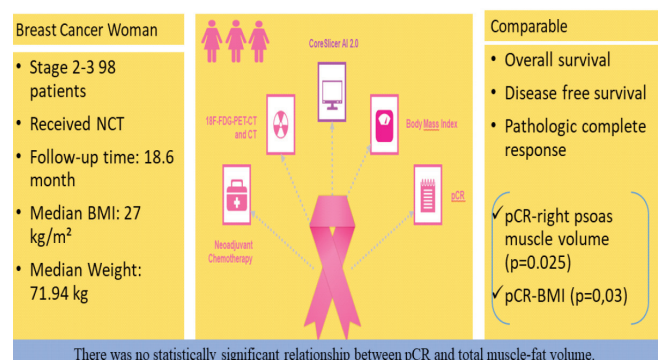
Graphic 1. The relationship of pathological response and visceral muscle and fat volume in women with breast cancer who received neoadjuvan chemotherapy

right psoas muscle volume increased the risk of recurrence or death by 1.2 times. However, no relationship was found between BMI and OS/DFS, which may be due to the low number of patients and low recurrence rate.

In patients with BC, body composition determines the dose, toxicity, and efficacy of NCT and is a determinant in improving the prognosis (7, 9, 20). A lower pCR rate and shorter progression-free survival times have been demonstrated in overweight patients treated with NCT (13). In another study, while no relationship could be found between pCR and BMI, it was found that high visceral fat volume and fatty liver were negative factors for acheiving pCR (7). A study by Trestini et al. (21) showed that body composition parameters did not affect pCR. Still, an increase of ≥10 % of VAT during NCT was associated with shorter DFS. In a study comparing body composition parameters measured using PET CT before NCT and response to NCT, no significant relationship was found between them. Still, a very weak correlation was found between superficial adipose tissue and pCR (22). In the present study, no significant relationship between muscle/fat volume and pCR was identified, but BMI was significantly lower in pCR-positive patients ($p = 0.03$).

There are significant changes in body fat distribution in the postmenopausal period (21). A study conducted with postmenopausal women with BC showed that these patients were more overweight and had a higher visceral fat area (VFA) and more fatty liver than premenopausal patients (7). In the present study, no significant relationship was found when postmenopausal status and BMI and CoreSlicer images were compared.

In a study examining menopausal status in patients with BC in detail, no relationship could be shown between body composition parameters and pCR. At the same time, distant DFS was found to be lower in the high VFA group ($p<0.05$) (20). In the present study, when BMI and CoreSlicer images were compared in pre-and postmenopausal patients, no significant difference was found between them. In addition, no significant relationship was found between menopausal status and DFS vs. pCR.

The fact that changes in body composition affect treatment outcomes differently in BCs with different molecular types is another matter for debate (23). In postmenopausal HER2+ and luminal BC patients, obesity increases mortality and morbidity (24). In addition, patients with Luminal type and BC with axillary lymph node metastases have been shown to have higher BMI and VAT levels (24). In the present study, pCR rates were significantly lower in patients in Luminal A and B groups, as expected. However, no significant correlation was observed between total muscle volume (TMV) and total fat volume and molecular subtypes.

Higher rates of pCR were obtained in patients in the present study with low total muscle volume, and this difference was close to significant ($p = 0.08$). Thus, it is possible that calculating TMV only using these volumetric techniques, independent of height and weight characteristics, may not be an objective criterion. Therefore, muscle volume distributions were calculated in proportion to the body surface area and BMIs of the patients and re-analyzed to examine whether there was a relationship between these ratios and the treatment response. Although the relationship between TMV/BMI and pCR was insignificant, it was found that there was a tendency close to numerical significance ($p = 0.065$). These results suggested that standardized

muscle volume analyses need to be further evaluated in studies with larger sample sizes.

Study Limitations

The strengths of the present study include being the first study in which body composition was calculated by a single radiologist with artificial intelligence-based volumetrically accurate and standardized measurements. The limitations include the small number of patients, the retrospective nature and the single-center design.

In conclusion, this is the first study to analyze the body muscle/fat volume from a single imaging section obtained at a single level in CT and to investigate the relationship between measurements and outcomes of NCT. There was no significant relationship between pCR and total muscle/fat volume. However, these results must be validated by prospective studies with more extensive patient series.

Authorship Contributions

Surgical and Medical Practices: S.İ., V.Ö.; Concept: T.K.T., F.Ç., K.Y., E.Ö., S.K., A.Ö., V.Ö.; Design: T.K.T., F.Ç., G.A., N.A., Ç.O., E.Ö., T.D., V.Ö.; Data Collection and/or Processing: T.K.T., K.Y., F.A., V.Ö.; Analysis and/or Interpretation: S.İ., G.S., N.A., Ç.Ü., Z.İ., V.Ö.; Literature Search: T.K.T.; Writing: T.K.T., F.Ç., G.S., E.Ö., V.Ö.

References

1. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. Cancer Epidemiol Biomarkers Prev 2009; 18: 2569-2578. (PMID: 19755644) **[Crossref]**

2. Lee K, Kruper L, Dieli-Conwright CM, Mortimer JE. The Impact of Obesity on Breast Cancer Diagnosis and Treatment. Curr Oncol Rep 2019; 21: 41. (PMID: 30919143) **[Crossref]**

3. Chan DS, Norat T. Obesity and breast cancer: not only a risk factor of the disease. Curr Treat Options Oncol 2015; 16: 22. (PMID: 25904412) **[Crossref]**

4. Lee JW, Kim SY, Lee HJ, Han SW, Lee JE, Lee SM. Prognostic Significance of CT-Attenuation of Tumor-Adjacent Breast Adipose Tissue in Breast Cancer Patients with Surgical Resection. Cancers (Basel) 2019; 11: 1135. (PMID: 31398863) **[Crossref]**

5. Caan BJ, Cespedes Feliciano EM, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, et al. Association of Muscle and Adiposity Measured by Computed Tomography With Survival in Patients With Nonmetastatic Breast Cancer. JAMA Oncol 2018; 4: 798-804. (PMID: 29621380) **[Crossref]**

6. Iwase T, Sangai T, Fujimoto H, Sawabe Y, Matsushita K, Nagashima K, et al. Quality and quantity of visceral fat tissue are associated with insulin resistance and survival outcomes after chemotherapy in patients with breast cancer. Breast Cancer Res Treat 2020; 179: 435-443. (PMID: 31620935) **[Crossref]**

7. Omarini C, Palumbo P, Pecchi A, Draisci S, Balduzzi S, Nasso C, et al. Predictive Role Of Body Composition Parameters In Operable Breast Cancer Patients Treated With Neoadjuvant Chemotherapy. Cancer Manag Res 2019; 11: 9563-9569. (PMID: 32009814) **[Crossref]**

8. Huh J, Park B, Lee H, An YS, Jung Y, Kim JY, et al. Prognostic Value of Skeletal Muscle Depletion Measured on Computed Tomography for Overall Survival in Patients with Non-Metastatic Breast Cancer. J Breast Cancer 2020; 23: 80-92. (PMID: 32140272) **[Crossref]**

9. Trestini I, Carbognin L, Monteverdi S, Zanelli S, De Toma A, Bonaiuto C, et al. Clinical implication of changes in body composition and weight in patients with early-stage and metastatic breast cancer. Crit Rev Oncol Hematol 2018; 129: 54-66. (PMID: 30097238) **[Crossref]**

10. 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: 861-868. (PMID: 28948392) **[Crossref]**

11. Mullie L, Afilalo J. CoreSlicer: a web toolkit for analytic morphomics. BMC Med Imaging 2019; 19: 15. (PMID: 30744586) **[Crossref]**

12. Global Health Observatory data repository. World Health Organization; [accessed 2023 Sep 5]. https://apps.who.int/gho/data/node.main. A904?lang=en **[Crossref]**

13. Del Fabbro E, Parsons H, Warneke CL, Pulivarthi K, Litton JK, Dev R, et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. Oncologist 2012; 17: 1240-1245. (PMID: 22903527) **[Crossref]**

14. Rossi F, Lambertini M, Brunetti N, De Giorgis S, Razeti MG, Calabrese M, et al. Muscle mass loss in breast cancer patients of reproductive age (≤45 years) undergoing neoadjuvant chemotherapy. Radiol Med 2023; 128: 49-57. (PMID: 36536266) **[Crossref]**

15. Pickhardt PJ, Summers RM, Garrett JW. Automated CT-Based Body Composition Analysis: A Golden Opportunity. Korean J Radiol 2021; 22: 1934-1937. (PMID: 34719894) **[Crossref]**

16. James FR, Wootton S, Jackson A, Wiseman M, Copson ER, Cutress RI. Obesity in breast cancer--what is the risk factor? Eur J Cancer 2015; 51: 705-720. (PMID: 25747851) **[Crossref]**

17. Fadelu T, Damuse R, Lormil J, Pecan E, Greenberg L, Dubuisson C, et al. Body Mass Index, Chemotherapy-Related Weight Changes, and Disease-Free Survival in Haitian Women With Nonmetastatic Breast Cancer. JCO Glob Oncol 2020; 6: 1656-1665. (PMID: 33151773) **[Crossref]**

18. Iwase T, Nakamura R, Yamamoto N, Yoshi A, Itami M, Miyazaki M. The effect of molecular subtype and body mass index on neo-adjuvant chemotherapy in breast cancer patients. Breast 2014; 23: 264-272. (PMID: 24530096) **[Crossref]**

19. Kim HJ, Kim D, Bae SJ, Ahn SG, Jeong J, Park WC, et al. 18F-FDG uptake of visceral adipose tissue on preoperative PET/CT as a predictive marker for breast cancer recurrence. Sci Rep 2022; 12: 21109. (PMID: 36473927) **[Crossref]**

20. Iwase T, Sangai T, Nagashima T, Sakakibara M, Sakakibara J, Hayama S, et al. Impact of body fat distribution on neoadjuvant chemotherapy outcomes in advanced breast cancer patients. Cancer Med 2016; 5: 41-48. (PMID: 26626021) **[Crossref]**

21. Trestini I, Caldart A, Cintoni M, Sperduti I, Drudi A, Aluffi G, et al. Predictive and prognostic effect of computed tomography-derived body composition analysis during neoadjuvant chemotherapy for operable and locally advanced breast cancer. Nutrition 2023; 105: 111858. (PMID: 36323147) **[Crossref]**

22. Kizildag Yirgin I, Has D, Arslan G, Aydin EC, Sari M, Onder S, et al. Comparison between body composition parameters and response to neoadjuvant chemotherapy by using pre-treatment PET CT in locally advanced breast cancer. Eur J Radiol Open 2020; 7: 100286. (PMID: 33294497) **[Crossref]**

23. Acevedo F, Walbaum B, Muñiz S, Petric M, Martínez R, Guerra C, et al. Obesity is associated with early recurrence on breast cancer patients that achieved pathological complete response to neoadjuvant chemotherapy. Sci Rep 2022; 12: 21145. (PMID: 36477462) **[Crossref]**

24. Pahk K, Joung C, Kim S. Visceral fat metabolic activity evaluated by preoperative 18F-FDG PET/CT significantly affects axillary lymph node metastasis in postmenopausal luminal breast cancer. Sci Rep 2020; 10: 1348. (PMID: 31992764) **[Crossref]**