

The Relationship Between Body Fat Distribution and Response to Primary Chemotherapy in Breast Cancer

Meme Kanseriinde Vücut Yağ Dağılımı ve Primer Kemoterapi Yanıtı İlişkisi

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Abstract

Objective: To examine how assessing body fat composition influences the prediction of neoadjuvant chemotherapy (NAC) response and overall survival cases of locally advanced breast cancer (LABC).

Methods: A total of 110 women with LABC, whose molecular subtypes were identified, who underwent pre-treatment abdominal computed tomography (CT) who received NAC and whose residual cancer burden (RCB) was calculated retrospectively between 2017 and 2021, were included. Total and visceral fat areas (VFAs) were quantified using semi-automated software, and the subcutaneous fat area was derived by subtracting the VFA from the total fat area.

Results: RCB scores showed a statistically significant association with VFA ($p=0.015$). A weak positive correlation was observed between VFA and RCB scores ($r=0.263$, $p=0.006$). Higher VFA was linked to an increased risk of death and was associated with a significant effect on overall survival ($p=0.011$).

Conclusion: Higher VFA was associated with elevated RCB scores, reflecting poorer treatment response and decreased overall survival. Quantification of body fat and muscle by CT, the gold-standard method may serve as a predictive criterion for treatment response and survival in LABC. Multidisciplinary supportive strategies might be considered to manage VFA during therapy.

Keywords: Breast neoplasms, intra-abdominal fat, tomography, neoadjuvant therapy, prognosis

Öz

Amaç: Lokal ileri evre meme kanseri (LİMK) olgularında vücut yağ kompozisyonu değerlendirmesinin neoadjuvan kemoterapi (NAK) yanıtı ve genel sağkalım tahminini nasıl etkilediğini incelemektir.

Yöntem: 2017-2021 yılları arasında, moleküler alt tipleri belirlenmiş, tedavi öncesi abdominal bilgisayar tomografisi (BT) çekilmiş, NAK almış ve rezidüel kanser yükü (RKY) retrospektif olarak hesaplanmış toplam 110 LİMK'li kadın çalışmaya dahil edildi. Toplam ve viseral yağ alanı (VYA) yarı otomatik bir yazılım kullanılarak ölçüldü ve deri altı yağ alanı, toplam yağ alanından VYA çıkarılarak elde edildi.



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Öz

Bulgular: RKY skorları, VYA ile istatistiksel olarak anlamlı bir ilişki gösterdi ($p=0,015$). VYA ve RKY skorları arasında zayıf pozitif bir korelasyon gözlemlendi ($r=0,263$, $p=0,006$). Daha yüksek VYA, artan ölüm riskiyle bağlantılıydı ve genel sağkalım üzerinde anlamlı bir etkiyle ilişkilendirildi ($p=0,011$).

Sonuç: Daha yüksek VYA, yüksek RKY skorları ile ilişkililiydi; bu da daha kötü tedavi yanıtını ve azalmış genel sağkalımı yansıtıyordu. Altın standart yöntem olan BT ile vücut yağ ve kas miktarının belirlenmesi, LİMK'de tedaviye yanıt ve hayatta kalma için öngörücü bir kriter olarak hizmet edebilir. Tedavi sırasında VYA'yı yönetmek için multidisipliner destekleyici stratejiler düşünülebilir.

Anahtar Kelimeler: Meme kanseri, karın içi yağ, tomografi, neoadjuvan terapi, prognoz

Introduction

According to the World Health Organization criteria, obesity is defined as a body mass index (BMI) above 30 kg/m^2 ⁽¹⁾. It represents a significant cause of death and disease-related complications, and is considered a public health issue⁽²⁾.

In the female population, breast cancer (BC) remains the most frequently occurring cancer and one of the leading causes of cancer-related death worldwide⁽³⁾. The prognosis of BC depends on several factors, including estrogen and progesterone receptor as well as the overexpression or amplification of human epidermal growth factor receptor 2 (HER2)⁽⁴⁾. A significant meta-analysis has shown an association between BMI and the risk of BC⁽⁵⁾. Another study reported that a high BMI is an important factor affecting survival outcomes in BC⁽⁶⁾. Additionally, higher BMI has been linked to the presence of advanced-stage BC at the point of diagnosis⁽⁷⁾.

Locally advanced breast cancer (LABC) refers to cases without distant organ metastases at the time of staging, for which systemic neoadjuvant chemotherapy (NAC) is recommended as the first-line treatment. NAC has become the standard of care for LABC, aiming to increase the likelihood of breast-conserving surgery⁽⁸⁾. Existing studies have yet to definitively ascertain the extent to which BMI influences the NAC response^(9,10).

BMI is a well-known and widely used metric for assessing body weight status, with individuals categorized as underweight (BMI $<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25\text{--}29.9 \text{ kg/m}^2$), or obese ($\geq 30 \text{ kg/m}^2$)⁽¹¹⁾. However, a fundamental limitation of BMI is that it cannot distinguish between adipose tissue and muscle tissue^(12,13). Recently, investigation of the effects of fat mass characteristics on disease prognosis and treatment response has received increasing attention. Numerous studies have demonstrated that these characteristics can significantly influence the prognosis of various diseases and affect treatment outcomes^(14–17). Various methods, including bioimpedance

analysis, dual-energy X-ray absorptiometry, computed tomography (CT), and magnetic resonance imaging, are commonly used to evaluate body fat composition⁽¹⁸⁾.

The residual cancer burden (RCB) is a histological scoring system that quantifies the amount of residual tumor after NAC in patients with LABC. The RCB score is calculated from surgical specimens based on five main parameters: the size of tumor, tumor cellularity (as percentage of the total area), percentage of *in situ* disease, count of positive lymph nodes, and diameter of largest metastasis⁽¹⁹⁾. RCB provides an objective measure of treatment response, offers prognostic information, and is one of widely accepted criteria in BC evaluation^(20–23). According to the RCB scoring system, RCB-0 indicates pathological complete response (complete response to treatment), RCB-1 indicates high response to treatment, RCB-2 indicates partial response, and RCB-3 indicates low response to treatment⁽²²⁾.

In this study, we conducted a retrospective analysis to assess how CT-based body fat composition measurements impact NAC response and overall survival (OS) in LABC patients. Furthermore, we analyzed the relationships among body fat composition, sarcopenia, and sarcopenic obesity.

Materials and Methods

Data Source and Patient Population

A total of 110 women diagnosed with LABC were retrospectively evaluated. Each had a defined molecular subtype, underwent abdominal CT scans prior to NAC, and received NAC during 2017–2021. Patients who did not meet the inclusion criteria and whose examinations were of insufficient quality were excluded. Data were gathered, including patient age, BMI, molecular subtype of BC, and RCB scores. Participants were categorized according to their molecular subtypes (luminal A, luminal B, HER2-positive and triple-negative) and further stratified based on RCB scores into groups (RCB-0, RCB-1, RCB-2, RCB-3)^(23,24).

The study protocol was formally evaluated and approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital's Ethics Committee prior to the commencement of the research (approval no: 2022/09-19, date: 15.09.2022). Analyzed retrospectively from patient medical records.



Figure 1. Subcutaneous fat (yellow) and visceral fat (purple) are highlighted. Cross-sectional abdominal computerized tomography image show measurements of subcutaneous fat area (yellow) and visceral fat area (purple)



Figure 2. Skeletal muscles (red) are delineated. Cross-sectional abdominal computerized tomography image at the level of the vertebral transverse processes of L3 with segmentation of skeletal muscles (red)

CT-based Parameter Measurement

Standard abdominal CT scans were acquired using a 128-slice CT scanner (Somatom Definition AS; Siemens, Munich, Germany). The acquisition protocol included 120 kV, automatic exposure control with variable mA and dose modulation, a soft-tissue reconstruction algorithm, a 512x512 matrix, a 30-635 cm field of view, and a reconstructed slice thickness of 5 mm.

Skeletal muscle area (SMA) measurements from the psoas, paraspinal muscles, and abdominal wall muscles were performed at level of L3 vertebra, where transverse prominences were clearly visible⁽²⁵⁻²⁷⁾. Total fat area (TFA) and visceral fat area (VFA) measurements were conducted at the same level as the SMA measurement. For tissue segmentation, attenuation thresholds were set at -29 to +150 HU for skeletal muscle and -190 to -30 HU for adipose tissue, encompassing both total and VFAs⁽²⁵⁾. Using these HU values, a semi-automated outline was generated with commercial software (AW Server 3.2 Ext 1.0; GE Healthcare, Chicago, United States) (Figures 1 and 2). The segmentation was visually verified by a radiologist and manually adjusted if necessary. After the operators gained sufficient experience, the measurement process took less than three minutes per patient. Two radiologists, with 5 and 20 years' experience, calculated the parameters by consensus. The skeletal muscle index (SMI) was obtained by dividing the SMA by height squared, while the subcutaneous fat area (SFA) was determined by subtracting the VFA from the TFA.

Sarcopenia was identified when the SMI was below 41 cm²/m² in underweight or normal-weight individuals, and below 53 cm²/m² in those classified as overweight or obese⁽²⁸⁾. Sarcopenic obesity was characterized by the presence of both sarcopenia and obesity⁽¹⁸⁾.

Statistical Analysis

Data normality was assessed by the Shapiro-Wilk test. Results were summarized as mean ± standard deviation. Student's t-test was used to compare continuous variables, while One-Way ANOVA with Tukey's post-hoc analysis was used to assess group differences in abdominal fat distribution. Relationships between fat distribution and muscle mass were evaluated using Pearson correlation, and survival analyses were conducted with Cox regression models. All data analyses were carried out using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA), with a significance threshold of p<0.05.

Results

One hundred ten women were enrolled in the study, and their mean age was 51.30 ± 11.35 years (range 29–75 years). The mean follow-up period was 36.3 ± 8.7 months, and the median follow-up was 39 months. Demographic characteristics, CT parameters, and RCB scores are presented in Table 1. The mean TFA, VFA, and SFA were 343.99 cm^2 , 126.87 cm^2 , and 217.13 cm^2 , respectively. Sarcopenia was identified in 47.3% of the patients, whereas sarcopenic obesity was observed in only 4.5%. The most common RCB score was RCB-2 (30.9%), while RCB-1 was the least common (18.2%) (Table 1).

The analysis revealed no significant association between the RCB scores and SFA or TFA, with $p=0.821$ and $p=0.326$. However, the results showed a statistically significant association between RCB scores and VFA ($p=0.015$) (Table 2).

Table 1. Demographical, clinical characteristics of the patients and computed tomography parameters

No of patients	110
Age (years), mean $\pm$ SD	51.3 ± 11.35
Total fat area (cm^2), mean $\pm$ SD	343.99 ± 118.55
Subcutaneous fat area (cm^2), mean $\pm$ SD	217.13 ± 9.62
Visceral fat area (cm^2), mean $\pm$ SD	126.87 ± 52.8
Sarcopenia	52 (47.3%)
Sarcopenic obesity	5 (4.5%)
Stage	
Stage 2A	30 (27.3%)
Stage 2B	33 (30%)
Stage 3A	40 (36.4%)
Stage 3B	6 (5.4%)
Stage 3C	1 (0.9%)
RCB score	
RCB 0	25 (22.5%)
RCB 1	20 (18.2%)
RCB 2	34 (30.9%)
RCB 3	31 (28.2%)
SD: Standard deviation, RCB: Residual cancer burden	

VFA was positively, though weakly, related to RCB scores ($r=0.263$, $p=0.006$). In contrast, no significant correlations were identified between RCB scores and SFA or TFA ($p=0.952$, $p=0.208$, respectively; Table 3).

Higher VFA levels were associated with increased mortality risk and significantly influenced OS ($p=0.011$). Neither TFA nor SFA showed a significant association with OS (p -values: 0.265 and 0.474) (Table 4).

RCB scores differed significantly across molecular subtypes ($p=0.007$; Table 5). While the luminal A and luminal B groups had lower RCB scores, the HER2-positive and triple-negative groups had higher scores.

Age was comparable between sarcopenic and non-sarcopenic patients ($p=0.402$). Mean SFA tended to be higher in the sarcopenic group, yet this trend was not statistically significant ($p=0.258$). Mean TFA and VFA were notably higher in sarcopenic than in non-sarcopenic individuals, with p -values of 0.024 and 0.001 (Table 6).

Discussion

Correlations among body fat composition parameters, RCB scores assessing treatment responses, and OS in patients with LABC were explored in the present study.

There are studies suggesting that BMI alone may not be a sufficient parameter for evaluating body composition^(12,13). The use of fat and muscle measurements to assess body composition has ained attention^(14–17). CT, which was used in our study to measure fat mass, was identified by Yip et al.⁽¹⁸⁾ as an important diagnostic tool. Iyengar et al.⁽²⁸⁾ demonstrated that body fat measurements obtained through CT were more strongly associated with the risk of invasive BC than BMI in postmenopausal women.

VFA revealed statistically significant variation in RCB scores ($p=0.015$). When the correlation between body fat distribution parameters and RCB scores was examined, VFA showed a positive, statistically significant relationship with RCB scores ($r=0.263$, $p=0.006$). In the study by Iwase et al.⁽²⁹⁾, no relationship

Table 2. Abdominal fat distribution of RCB scores

	RCB 0	RCB 1	RCB 2	RCB 3	p-value
Total fat area (cm^2), mean $\pm$ SD	336.52 ± 121.65	326.56 ± 121.32	329.43 ± 121.39	377.24 ± 109.83	0.326
Subcutaneous fat area (cm^2), mean $\pm$ SD	222.58 ± 82.21	213.27 ± 78.13	207.98 ± 78.86	225.25 ± 81.99	0.821
Visceral fat area (cm^2), mean $\pm$ SD	113.94 ± 48.89	113.30 ± 50.46	121.45 ± 53.48	151.99 ± 50.11	0.015
SD: Standard deviation, RCB: Residual cancer burden					

was found between body fat parameters and pathological complete remission (pCR, i.e., RCB-0). The discrepancy may be attributable to their study's focus on whether there was a complete NAC response. In our study, we classified RCB responses into 4 groups. This issue needs investigation with a larger sample size and in a multicenter setting. On the other hand, Kripa et al.'s⁽³⁰⁾ study showed that a good response to treatment was associated with higher VFA. In this study, cyclin-dependent kinase (CDK) 4/6 inhibitors were used as therapeutic agents, and VFA and the response to targeted therapy were compared. However, we can still conclude that VFA influences the response to different BC treatments.

Table 3. Correlation of abdominal fat distribution with RCB

	R-value	p-value
Total fat area	0.121	0.208
Subcutaneous fat area	0.006	0.952
Visceral fat area	0.263	0.006
RCB: Residual cancer burden		

Table 4. Prognostic impact of abdominal fat distribution on overall survival for LABC

	Overall survival		
	HR	95% CI	p-value
Total fat area	1.002	1.005-1.021	0.265
Subcutaneous fat area	0.998	0.994-1.003	0.474
Visceral fat area	1.009	1.002-1.017	0.011
LABC: Locally advanced breast cancer, CI: Confidence interval, HR: Hazard ratio			

Table 5. Molecular subtype of BC association with RCB

	Luminal A & luminal B	HER2-positive & triple-negative	p-value
RCB 0-1, mean ± SD	37±52.1	10±25.6	0.007
RCB 2-3, mean ± SD	34±47.9	29±74.4	
SD: Standard deviation, RCB: Residual cancer burden, HER2: Human epidermal growth factor receptor 2, BC: Breast cancer			

In another study, a significant association was found between pCR and BMI, whereas no correlation was observed with VFA⁽³¹⁾. The differences in findings may be attributed to variations in the agents, dosages, and durations of NAC protocols. While measurements in the referenced study were performed using an AI-assisted system, our study used a semi-automated method, which may also have contributed to the discrepancies.

In our study, VFA affected both NAC response and OS ($p=0.011$). In the current investigation by Iwase et al.⁽²⁹⁾, VFA showed a significant association with distant disease-free survival, which is indirectly consistent with our findings. Similarly, a significant relationship between VFA and distant progression-free survival was found, as observed in the present study⁽³²⁾.

In our study, VFA was found to be higher in sarcopenic patients. This finding aligns with previous research, which suggests a strong association between lipid metabolism and sarcopenia, highlighting the critical role of visceral fat in the progression of sarcopenia⁽³³⁾. Therefore, VFA may be elevated in sarcopenic patients, potentially indicating a poorer prognosis. As a result of a meta-analysis involving 5284 patients, a correlation between sarcopenia and negative outcomes was identified in BC patients⁽³⁴⁾.

Although we examined the effect of body fat composition on NAC response and OS in this study, we emphasize that the molecular subtypes of BC also affect NAC response. The HER2-positive and triple-negative types exhibit a poorer treatment response than the luminal types. The findings of a large cohort study also support with our results⁽³⁵⁾.

As reported by Isıklar et al.⁽³⁶⁾, the relationship between body muscle mass measured via positron emission tomography-CT and the NAC response in patients with LABC was evaluated. We could have included muscle measurements in our study to more comprehensively evaluate the effect of body composition on NAC response and OS.

Table 6. Abdominal fat distribution of the group with and without sarcopenia

	Sarcopenia	No sarcopenia	p-value
No of patients	52	58	
Age (years), mean $\pm$ SD	50.34 $\pm$ 12.10	52.17 $\pm$ 10.67	
Total fat area (cm ²), mean $\pm$ SD	370.90 $\pm$ 111.55	319.87 $\pm$ 120.37	0.024
Subcutaneous fat area (cm ²), mean $\pm$ SD	226.23 $\pm$ 79.61	208.96 $\pm$ 79.43	0.258
Visceral fat area (cm ²), mean $\pm$ SD	144.67 $\pm$ 51.70	110.91 $\pm$ 48.91	0.001
SD: Standard deviation			

In the study conducted by Cheng et al.⁽³⁷⁾, a composite overall risk score was developed using body composition parameters, and a significant association was found between this score and mortality risk. We believe that this risk score may be useful for both patients and clinicians in evaluating treatment response and prognosis. This study has served as an inspiration for our next research project.

Study Limitations

Despite its contributions, this study had several limitations, including its non-prospective design, one-institution setting, and relatively small sample size. The varying follow-up periods may have affected the assessment of recurrence. Nevertheless, automatic segmentation software for CT-based body composition measurements was advantageous. The chemotherapeutic agents used by the patients and their dosages could not be obtained due to a lack of documentation in the hospital information system.

Conclusion

Overall, our findings indicate that increased VFA corresponds to increased RCB scores, which reflect a poorer NAC response and reduced OS. Body fat and muscle measurements, for which CT is the gold standard, can be considered criteria for estimating NAC response and OS in patients with LABC.

Ethics

Ethics Committee Approval: The study protocol was formally evaluated and approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital's Ethics Committee prior to the commencement of the research (approval no: 2022/09-19, date: 15.09.2022).

Informed Consent: Analyzed retrospectively from patient medical records.

Footnotes

Authorship Contributions

Surgical and Medical Practises: H.Ç.T., G.Ç., H.E., C.K., E.E.P., Concept: E.A., Design: E.A., Data Collection or Processing: H.Ç.T., Ö.K., Analysis or Interpretation: Ş.Ş., Literature Search: E.G.V., Writing: E.G.V.

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