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Comparison between body composition parameters and response to neoadjuvant chemotherapy by using pre-treatment PET CT in locally advanced breast cancer

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HIGHLIGHTS

- Weight and the BMI are inadequate proxies for adiposity that do not distinguish between muscle and adipose tissue or different specific deposits of adipose tissue (visceral and subcutaneous), which have different physiological effects.
- Patients with the same BMI are likely to have different anatomical distribution of adipose and muscle tissue.
- To our knowledge, only few studies have investigated the association between fat and muscle tissue distribution of the body, and response to neoadjuvant chemotherapy.

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ABSTRACT

Purpose: To compare the adipose and muscle tissue areas in patients who responded differently to neoadjuvant chemotherapy.

Methods: One hundred and eighty six patients diagnosed with breast cancer who underwent neoadjuvant chemotherapy between January 2015- October 2019 and were operated after the treatment were retrospectively included in the study. Pathological results were divided into five groups using the Miller-Payne grading systems. Grade 1 indicating no significant reduction in malignant cells; Grade 2: a minor loss of malignant cells ($\leq$ 30 %); Grade 3: reduction in malignant cells between 30 % and 90 %; Grade 4: disappearance of malignant cells >90 %; Grade 5: no malignant cells identifiable. Pre-treatment PET CT scans were evaluated, and calculation of body composition parameters were performed on a single axial section passing through the L3 vertebrae. Spearman's

Abbreviations: ASP, Acylation-stimulating protein; BMI, Body mass index; CT, Computed tomography; DCIS, Ductal carcinoma in situ; ER, Estrogen receptor; HER-2, Human epidermal growth factor receptor-2; IHC, Immunohistochemistry; MT, Muscle tissue; MP, Miller -Payne; NAC, Neoadjuvant chemotheraphy; PAI-1, Plasminogen activator inhibitor-1; ypCR, Pathological complete response; PET, CT Positron-emission tomography-computed tomography; PR, Progesterone receptor; SAT, Subcutaneous adipose tissue; VAT, Visceral adipose tissue.

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correlation test was used to analyze the correlation between SAT, VAT, MT parameters and pathological responses.
Results: There was no strong correlation between the 5 groups separated according to neoadjuvant chemotherapy treatment response and tissue distributions. However, that there was a very low correlation found between superficial adipose tissue and pathological response (r=, 156).
Conclusion: In conclusion, our results have provided a very low correlation between SAT and more than 30 % response. More research is required to evaluate the role of the body fat and muscle parameters in response to neoadjuvant chemotherapy in larger patient populations.

1. Introduction

Adipose tissue is the loose connective tissue composing of adipocytes where the fat is deposited. Although its main reservoir is the subcutaneous adipose tissue (SAT), adipocytes can be found in different parts of the body. The second largest reservoir is the visceral adipose tissue (VAT) where adipocytes are located inside the abdominal cavity as intraperitoneal or retroperitoneal fat. Adipose tissue is regarded as one of the largest endocrine organ as it plays a major role in the production of sex steroids and peptide hormones such as leptin, cytokines, adipsin, acylation-stimulating protein (ASP), angiotensinogen, plasminogen activator inhibitor-1 (PAI-1), adiponectin, and resistin [1]. Androgens are converted to estrogens in the adipose tissue by the help of two enzymes. These enzymes are Cytochrome P450-dependent aromatase and 17βHSD which have different levels of expression in the SAT and VAT [2].

Obesity, the excess form of adipose tissue which is defined as the body mass index (BMI) over 25 kg/m2. It is a well-known risk factor for many types of cancers [3,4]. It is shown to increase the risk for breast cancer in the postmenopausal group, especially for the estrogen and progesterone positive breast cancers [5–7]. This has mostly been contributed to the increased levels of circulating pool of endogenous estrogens produced by the adipose tissue [8,9]. The Million Women Study involved 45,037 patients with breast cancer out of 1.2 million British women aged between 50–64 years [10]. This large population study revealed 30 % higher risk of developing postmenopausal breast cancer in obese patients [10]. Obesity is not only a strong risk factor for breast cancer, but it also affects the survival regardless of the menopausal status [11].

In addition, chemotherapy was shown to be less effective in obese patients [3,12]. Pathological complete response rates have been shown to be lower, and disease-free survival was shorter compared with the patients with normal BMI [12,13]. Litton et al. published a large study in 2008, which included 1169 breast cancer patients treated with neoadjuvant chemotheraphy (NAC). The study demonstrated that BMI was associated with the less probability of complete pathological response (pCR) [12]. However, BMI is not an adequate parameter to show the distribution of fat and muscle tissue (MT) in the body. Also, pre-treatment sarcopenia predicts chemotherapy toxicity, reduced response, increased disability, poor anti-tumor response, and survival [14].

If excess adipose tissue plays a role in the breast cancer survival, can we predict the response to neo adjuvant treatment by measuring the amount of adipose tissue of a patient?

To our knowledge, only few studies have investigated the association between the distribution of body fat and muscle tissue and response to NAC [15,16].

In this study, we aimed to find a correlation between the body adipose tissue (visceral and subcutaneous fat), muscle tissue (MT) and response to NAC for breast cancer.

2. Material and method

2.1. Patient selection

One hundred and eighty-six locally advanced breast cancer patients who underwent surgical resection after NAC in our hospital between January 2015 and October 2019 were included in the study. We included the patients from the hospital's database following the inclusion criteria: Patients with locally advanced breast cancer who had i) PET- CT scan performed for staging, ii) The clinico-pathological data including age, tumor characteristics and treatment with operation history in the medical records of our institution, iii) Core needle biopsy specimens obtained before NAC. The data including treatment history, imaging examination (positron emission tomography) and pathological assessment was retrospectively collected. The study protocol was approved by Oncology Institute of Istanbul University institutional ethics committee number with 70973125-604.01.01. Informed consent was waived due to the retrospective nature of the study.

2.2. Evaluation of the Body Fat, and muscle distribution

SAT is defined as the fat area superficial to the abdominal muscular wall; VAT is deep to the muscular wall, consisting of the mesenteric, subperitoneal and retroperitoneal component; MT is defined as 7 muscles as psoas, erector spinae, quadratus lumborum, transversus abdominis, and external oblique muscles. We examined the VAT, SAT and MT in one slice of a computed tomography (CT) level of L3 vertebrae using ImageJ software (National Institutes of Health, USA). ImageJ version 1.46 is a free downloadable public domain software programme developed by the National Institutes of Health for image processing, and analyzing (available from http://rsbweb.nih.gov/ij/download.html). The defined areas were manually drawn. A single radiologist was responsible for the measurement. The number of pixels in the drawn areas were calculated with this program (Fig. A1).

2.3. Pathological evaluation

All pathological evaluations were performed in Istanbul Faculty of Medicine by a ten year experienced pathologist. A pathological complete response (ypCR) after NAC was defined as the absence of invasive carcinoma in breast tissue of the resected specimen. Residual ductal carcinoma in situ (DCIS) was also included in the pCR group. Pathological responses to NAC were categorized using the Miller -Payne (MP) grading systems [17–21]. The system includes the following classification such as Grade 1: no change, no significant reduction in malignant cells; Grade 2: a minor loss of malignant cells ($\leq$ 30 %); Grade 3: reduction in malignant cells between 30 % and 90 %; Grade 4: disappearance of malignant cells $>$ 90 %; Grade 5: no malignant cells identifiable, DCIS may be present.

Prior to NAC, immunohistochemistry (IHC) analysis was performed on formalin-fixed, paraffin-embedded tissue sections using the standard procedures for breast tumor core needle biopsy specimens to evaluate the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2). The cut-off value for ER positivity and PR positivity was 10 % positive tumor cells with

nuclear staining. HER-2 was evaluated as 0, 1+, 2+ or 3+ using circumferential membrane bound staining and positivity (HER-2+) was considered as 3+ using IHC, whereas cases with 0 to 1+ were regarded negative (HER-2-). Suspected category was evaluated as 2 + . The cut-off value for Ki-67 level was 20 %.

2.4. Statistical methods

This study was designed as a retrospective patient control study. Study sample characteristics were described using the frequency, percentage, median, and minimum and maximum values. Spearman's correlation test was used to analyze the correlation between SAT, VAT, MT parameters and pathological responses and age. Mann-Whitney U and Wilcoxon test were used to analyze the correlation between SAT, VAT, MT parameters and hormon receptor status, HER-2 status, Ki-67 levels. All *p*-values were two tailed, and considered significant if $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 22, SPSS Company, Chicago, IL).

3. Results

3.1. Clinico-pathological characteristics

A total of 186 patients were included in this study. Pathological data are presented in Table A1. The median age was 49 years (range 21–73 years). One hundred and fifty six patients (78.8 %) had invasive ductal, 11 patients (5.6 %) had invasive lobular, 9 patients (4.5 %) had mixed, 4 patients (2 %) had micropapillary, 3 patients (1.5 %) had metaplastic and 3 patients (1.5 %) had mucinous histopathological subtypes. The subtypes were as follows: ER- positive (+) in 135 (68 %) patients, ER-negative (−) in 51 (25.8 %), PR-positive (+) in 104 (52.4 %) patients, PR-negative (−) in 82 (41.4 %) patients, HER2-negative (−) in 103(52 %) patients, HER2-positive (+) in 62 (31.3 %) patients, HER2 suspected category in 21(10.6 %) patients, triple negative (TN) in 50(25.3 %) patients, non-TN in 136(68.7 %) patients. Fifty (25.3 %) patients had low Ki-67 level, whereas133 (672%) patients had high Ki-67 level.

When the pathological responses of the patients were analyzed according to the Miller Payne classification system; 13 (6.6 %) patients were in Grade 1 group, 8 (4%) patients were in Grade 2 group, 78 (39.4 %) patients were in Grade 3 group, 34 (17.2 %) patients were in Grade 4 group and 53(26.8 %) patients were in Grade 5 group.

3.2. Evaluation of body fat and muscle distribution

The calculations (number of pixels) obtained by evaluating the axial CT sections passing through the L3 vertebra using PET-CT examinations taken for staging before neoadjuvant therapy levels were as follows. The median number of pixels of SAT were 35,101 (range 5921–126713), median number of pixels of VAT were 11,150 (range 237–719), median number of pixels of MT were 15,888 (range 3037–47236) (Table A2). We applied on a dedicated PET-CT scanner (Biograph True Point PET/CT Siemens Healthcare. Erlangen, Germany). An iodine-based oral contrast agent was administered to all patients. CT images were acquired in the caudocranial direction with 100 mA/s at 130 kV. All patients were scanned for whole body in two steps. CT acquisition was performed on a spiral CT scanner, with a slice thickness of 4 mm and a pitch of 1.

3.3. Results of correlation analysis

A statistically positive correlation was found between SAT and VAT (r=, 627; $p < 0.001$), SAT and MT (r=, 692; $p < 0.001$), VAT and MT (r=, 514; $p < 0.001$) using the Spearman's correlation test.

There was a statistically significant positive correlation between age and the SAT and VAT (r:186 $p < 0,05$, r: 470 $p < 001$ respectively) using the Spearman's correlation test. No statistically significant correlation was detected between age and MT (p:0,2).

Statistical analysis using the Mann-Whitney U and Wilcoxon test results between hormone receptor status, HER-2 status, Ki-67 levels and body tissue distributions were as follows: There was no statistically significant correlation between ER and PR status and SAT, VAT, MT (p:0,24, p:0,34, p:0,46 and p:0,18, p:0,29, p:0,42 respectively). Similarly, no correlation was found between triple negative status and SAT, VAT and MT (p:0,18, p:0,29, p:0,24). No correlation was detected between HER-2 status and Ki-67 levels with SAT, VAT and MT (p:0,29, p:0,72, p:0,37 and p:0,25, p:0,65, p:0,32).

There was no statistically significant correlation between pathological responses and SAT, VAT, MT using the Kruskal-Wallis H tests (p:0,19, p:0,45, p:0,83). In addition, no statistically significant correlation was found when 90 % response was taken as cut off value (p:0.29, p:0.96, p:0.25). No statistically significant correlation was found (p:0.82, p:0.36, p:0.46) in the analysis for those Grade-5 (ypCR) and others (non-ypCR). However, when a 30 % response was taken as a cut off value, a positive very low correlation was found between SAT and pathological response (r=, 156 ve $p < 0.05$), (Table A3). Additionally, no statistically significant correlation was found between VAT, MT and pathological responses (p:0.20, p:0.58).

4. Discussion

To our knowledge, this is the first study to evaluate the association between the body fat distribution and pathologic response to NAC using the Miller Payne classification among patients with operable non-metastatic breast cancer. In our study, SAT, VAT, MT were correlated with each other ($p < 0001$). We also found an increase in SAT and VAT as the age increased. Hormone receptor status, HER-2 status and Ki-67 levels showed no difference according to the body fat and muscle distribution. There was no correlation between 5 different groups separated in accordance with the NAC treatment response and tissue distributions. However, a weak positive correlation (r<.0,156) between SAT and response was achieved when 30 % response was taken as a cut-off value therefore Grade 1, 2, and Grade 3, 4, 5 were examined in two separate groups.

To date, an inverse relationship has been found between the BMI and breast cancer in most studies [5–7]. In addition, the BMI has been associated with poor prognosis [12,15]. Pathological complete response (pCR) is the most important criterion for demonstrating the efficacy of NAC treatment and many studies in recent years have shown that overall survival is longer in patients with pCR [21,22]. Following the increase in the number of patients receiving NAC therapy and the increase in the pCR rate, this issue has become the focus of attention. The effect of obesity on breast cancer treatment methods, especially on chemotherapy remains controversial. Litton et al. showed that patients with higher BMI were less likely to obtain pCR to NAC with a large study that included 1169 patients [12]. Similarly Chen et al. and Del Fabbro et al. have demonstrated that patients with higher BMI were less likely to achieve pCR [15,23]. In contrast, Fontanella et al. found no significant association between obesity and response to NAC in the meta-analysis of eight major clinical trials [24]. However all these studies only investigated the effect of BMI, not the distribution of adipose tissue in the body. Patients with the same BMI are likely to have different anatomical distribution of adipose and muscle tissue. In this study, we investigated the relationship between SAT, VAT, MT and chemotherapy response rather than investigating the relationship between the BMI and chemotherapy response. Although there are many studies comparing these parameters with patient prognosis, a few studies investigated the response to chemotherapy with some of these parameters [15,16,25]. Although Iwase et al. found that high VAT was associated with poor NAC outcomes in breast cancer patients especially in postmenopausal patients, they could not find any association between body composition parameters and pCR [25]. Similarly, we found no correlation between body composition parameters, and NAC when the patients were grouped as

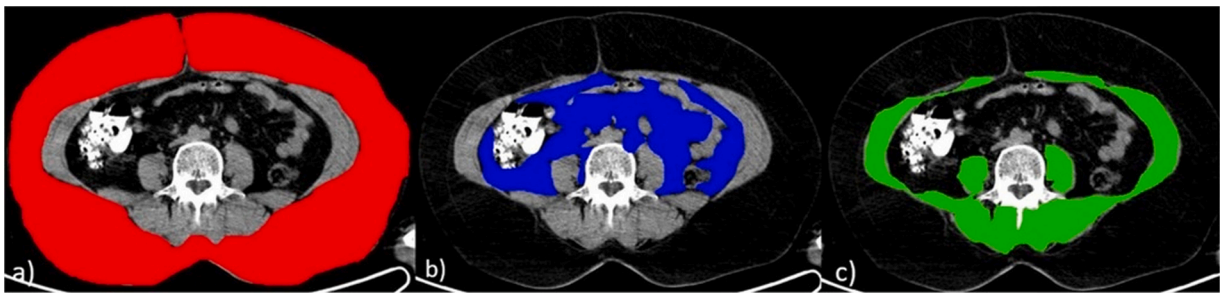

Fig. A1. A 50 year old female patient diagnosed with invasive ductal carcinoma. Reseptor status was as follows ER (+), PR (+), HER2(+), KI-67 level: %15. Pathological response categorized as in group-3 **a)** SAT (red area) calculated 106,803 pixels **b)** VAT (blue area) calculated 31,776 pixels **c)** MT (green area) calculated 31,920 pixels.

ypCR and non-ypCR. However, differently, we used MP grading system which revealed a positive correlation between SAT and more than 30 % response group. Although our patient numbers are similar, this difference may be due to different chemotherapy regimens and different distribution of patients among different receptor subtypes. Omarini et al. published a recent study, which suggested a negative predictive role of visceral fat in tumor response to NAC [16]. VAT seemed to be more biologically active and with more procancerous activity than SAT. We did not find any positive correlation between VAT and pathological response in our study. In another study, the correlation between BMI and sarcopenia and chemotherapy response was investigated by Del Fabbro et al. [15]. They found that the pCR rate was better in sarcopenic patients among patients with a normal BMI. The comparison of the muscle tissue measurement methods were the same with our study which both included the measurements of the same muscles at the level of the L3 vertebral axial section. The difference between our study and their study was that they used a cut off value for sarcopenia (L3 skeletal muscle index 38.5 cm^2/m^2 for women and 52.4 cm^2/m^2 for men) and they had a lower number of study sample with 68 patients. The studies in the literature about sarcopenia and breast cancer are mostly about survival analysis. Deluche et al. found negative correlation between disease-free survival, and overall survival and sarcopenia [26]. Sarcopenia was suggested as an independent prognostic factor of poorer survival ratesin obese patients with different cancers in many published studies [27–30].

Our study had some limitations which should be considered when interpreting the results. This is a retrospective study. Body fat, and muscle measurements calculated on cross-sectional CT images at the L3 vertebra might reflect the fat tissue in only a single anatomical area. There is a correlation between L3 vertebral level adipose tissue and total body adipose tissue ratio and researchers in many studies previously had used this method [31]. Calculations were made using PET-CT performed before the treatment, so adipose tissue changes during treatment were ignored. Also any chemotherapy dose changes or toxicities during treatment were not known. Another limitation was that most of the patients were in group 3.

In conclusion, our results have provided a very low correlation between SAT and more than 30 % response that can not be remarkable. Also our findings showed no correlation between body composition parameters and ypCR and non-ypCR groups. There is no enough strong evidence to include the evaluation of body composition, on CT scan analysis before breast cancer treatment with neoadjuvant chemotherapeutic agents. The results in the literature on this subject are controversial. More research is required to evaluate and clarify the role of the body fat and muscle parameters in response to NAC in a larger population of patients.

Ethical statement

The study protocol was approved by Oncology Institute of Istanbul University institutional ethics committee number with 70973125-604.01.01. Informed consent was waived due to the retrospective nature of the study.

Table A1
Number of patients are analyzed according to the Miller Payne classification.

	Number of patients	Percent (%)
Grade-1	13	6,6
Grade-2	8	4,0
Grade-3	78	394
Grade-4	34	172
Grade-5	53	268
Total	186	939

Grade 1: no change, no significant reduction in malignant cells; Grade 2: a minor loss of malignant cells ($\leq$ 30 %); Grade 3: reduction in malignant cells between 30 % and 90 %; Grade 4: disappearance of malignant cells $>$ 90 %; Grade 5: no malignant cells identifiable, DCIS may be present.

Table A2
Descriptive analysis of SAT, VAT, MT and age.

		Number of pixels	Std. Error
SAT	Mean	395,064,754	156,583,532
	Median	35,101,0000	
	Std. Deviation	2,118,222,760	
	Minimum	592,100	
	Maximum	126,713,00	
	Interquartile Range	2,061,200	
VAT	Mean	141,426,721	82,104,380
	Median	11,150,0000	
	Std. Deviation	1,110,687,461	
	Minimum	23,700	
	Maximum	7,190,000	
	Interquartile Range	1,073,000	
MT	Mean	171,410,601	49,425,218
	Median	15,888,0000	
	Std. Deviation	668,611,954	
	Minimum	303,700	
	Maximum	47,236,00	
	Interquartile Range	724,400	
AGE	Mean	489,126	,79,221
	Median	490,000	
	Std. Deviation	1,071,678	
	Minimum	2100	
	Maximum	7300	
	Interquartile Range	1500	
	Std. Deviation	,44,684	

SAT: subcutaneous adipose tissue, VAT: visceral adipose tissue, MT: muscle tissue.

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Table A3
Relationship between MT, SAT and VAT with> 30 % pathological response.

		>%30 RESPONSE	MT	SAT	VAT
>%30 RESPONSE	Correlation Coefficient	1000	,139	,156*	,093
	Sig. (2-tailed)	.	,058	,033	,209
	N	186	186	186	186
MT	Correlation Coefficient	,139	1000	,692**	,514**
	Sig. (2-tailed)	,058	.	,000	,000
	N	186	186	186	186
SAT	Correlation Coefficient	**,156***	,692**	1000	,627**
	Sig. (2-tailed)	,033	,000	.	,000
	N	186	186	186	186
VAT	Correlation Coefficient	,093	,514**	,627**	1000
	Sig. (2-tailed)	,209	,000	,000	.
	N	186	186	186	186

SAT: subcutaneous adipose tissue, VAT: visceral adipose tissue, MT: muscle tissue.

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

CRediT authorship contribution statement

Inci Kizildag Yirgin: Conceptualization, Methodology, Writing - original draft. **Duygu Has:** Visualization, Investigation. **Gozde Arslan:** Writing - original draft. **Esra Cureoglu Aydin:** Visualization, Investigation. **Murat Sari:** Formal analysis. **Semen Onder:** Data curation. **Yasemin Sanli:** Supervision, Writing - review & editing. **Neslihan Cabioglu:** Writing - review & editing. **Hasan Karanlik:** Data curation. **Mustafa Tukenmez:** Data curation. **Memduh Dursun:** Conceptualization, Methodology. **Mahmut Muslumanoglu:** Project administration. **Vahit Ozmen:** Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A

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