

The Effect of The Body Composition to Prognosis in Young Breast Cancer Patients

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Abstract

Background In cancer patients, the effect of the body composition on prognosis is a new clinical area of interest. In patients with class 2 or 3 obesity (BMI > 35), survival found to be worse control groups in a pooled analysis. BMI category is not truly representing body composition and hard to use to determine the true muscle and fat quantity. Computed tomography (CT) is a frequent method to determine body composition precisely.

Methods Axial CT images, including all abdominal muscles (psoas, erector spinae, quadratus lumborum) external and internal oblique and rectus abdominis) total skeletal muscle area (SMA), was calculated. Besides, axial CT images of the body fat subcutaneous adipose and visceral adipose tissue distribution (VAT, SAT) areas were calculated in cm² using threshold values of -30 to -190 for adipose tissue.

Results Eighty-four women included in the study. Most of the patients were normal or over-weighted. Invasive ductal carcinoma was the dominant histological subtypes, with 94% of the study population. The count of the sarcopenic and non-sarcopenic patients was 11 and 68 respectively. Although the median OS cannot be reached at the end of the follow-up period for both sarcopenic and non-sarcopenic patients, the difference between groups statistically insignificant. The median OS was not reached for both groups, the difference between low and high VAT groups was statistically significant.

Conclusion In this study, we demonstrate sarcopenia may be seen in patients with breast cancer under 40 years old, and it may not have a prognostic effect.

Background

In cancer patients, the effect of the body composition on prognosis is a new clinical area of interest.[1] Obesity is an increasing disease burden worldwide. In the USA, nearly 40% percent of the adult female population was categorized as obese.[2] The difference in body composition between sexes was observed in many studies. In both healthy subjects and cancer patients, males had higher muscularity while females had greater adipose tissue.[3–5]

Obesity considered to be related to both etiology, drug resistance, and decreased survival in breast cancer. In patients with high body mass index (BMI) who treated with neoadjuvant chemotherapy decreased complete responses and survival was observed when compared with normal population.[6–8] Although obesity has metabolic dysregulations and predisposition for many diseases, some obese or over-weight populations remain metabolically normal which is called the 'obesity paradox.'[9] In patients with decreased muscle volume which was masked due to an increase in BMI, 'sarcopenic obesity' term was defined.[10] BMI category is not truly representing body composition and hard to use to determine the true muscle and fat quantity.[11]

Cachexia is reported to be associated with increased mortality and morbidity in cancer patients.[12–14] The protein catabolism which constitutes the main structure of the skeletal muscle emphasized for

chronic conditions such as chronic obstructive disease and cancer.[15–17]

On the other hand, low BMI may cover the low muscularity and increased adiposity in some patients. For these limitations of the BMI, the studies investigating the effect of body composition to prognosis is increasing in breast cancer.[18–23]

One of the features of malnutrition was described as sarcopenia, which was defined by decreased muscle mass and quality.[24]

Computed tomography (CT) is a frequent method to determine body composition precisely. Body composition assessment with CT is a specific method for the calculation of muscle quality and adipose tissue.[25]

In this study, we try to evaluate the relationship between the sarcopenia and visceral adiposity with the clinical features and survival in women under 40 with breast cancer.

Methods

Study Participants

The archive records of patients between 2012 and 2019, diagnosed breast cancer at the Afyonkarahisar Health Sciences University Oncology Department were retrospectively analyzed. The patients who are under forty were included in the study. The patient characteristics, pathologic subtype, estrogen receptor (ER), Human epidermal growth factor receptor-2 (HER-2) status, stage of the disease, treatment modalities, disease recurrence, and last control or death dates were recorded. The exclusion criteria were lack of adequate cancer diagnosis, CT images, and follow-up.

Ethics

The study was approved by the ethics committee at Afyonkarahisar Health Sciences University Faculty of Medicine and carried out by the Declaration of Helsinki principles and all applicable regulations. An informed consent was not requested by ethic committee due to retrospective design of the study.

Statistical Analyze

The statistical analysis of the study performed with SPSS software (Statistical Package for the Social Sciences, version 22.0, SPSS Inc, Chicago, IL). Descriptive data are presented as either means or median for continuous variables, frequencies and percentages are reported for categorical variables. ROC analysis will be performed to determine the optimal cut-off value. Pearson χ^2 test is used to assessing the associations in categorical variables. Overall survival (OS) curves are estimated by the Kaplan-Meier product-limit method. Life tables established to determine the proportional survival analysis.

Body Composition Assessment and CT analyze

Axial CT images including all abdominal muscles (psoas, erector spinae, quadratus lumborum) external and internal oblique and rectus abdominis) total skeletal muscle area (SMA) was calculated. The total sarcopenia index (TSI) was calculated by dividing the square of the patient's height by the square meter (cm^2/m^2). Patients with a TSI lower than $38.9 \text{ cm}^2/\text{m}^2$ for female patients were considered to have decreased skeletal muscle mass.[14] Also, axial CT images of the body fat subcutaneous adipose and visceral adipose tissue distribution (VAT, SAT) areas were calculated in cm^2 using threshold values of -30 to -190 for adipose tissue. The total VAT (TVAT) cut-off value was calculated by ROC analysis and accepted as 134.3 cm^2

Results

Eighty-four women included in the study. Four patients' body weight or height data cannot be established. The mean age of the participants was 34.9 years. The mean weight, height, and BMI were 69.45 kg, 1.59 meters, and $27.13 \text{ kg}/\text{m}^2$ respectively. The BMI was categorized according to the cut-off values below 18.5, 18.6–25 and above $25.1 \text{ kg}/\text{m}^2$. The patient distribution due to the BMI cut-off values was 1, 39 and 40 respectively. Most of the patients were normal or over-weighted. Invasive ductal carcinoma was the dominant histological subtypes with 95% of the study population. Ninety-five percent of the patients were a non-smoker. The distribution of the patients due to stages 1 to 4 ordinaly at the diagnosis was 27, 29, 21 and 7 respectively. Eleven disease relapses were observed during follow-up which mostly occurred with bonny metastases. Most of the patients undergoing surgery with the nearly same frequency of both mastectomy (MRM) and breast-conserving surgery (BCS) (MRM/BCS:40/38). (Table-1) The mean values of the total, subcutaneous, intramuscular and visceral adipose tissue were 381.03 cm^2 , 272.1 cm^2 , 19.4 cm^2 , and 87.08 cm^2 respectively. The mean psoas and total muscle area were 16.14 and 113.3 cm^2 respectively.

When patients categorized according to the TSI, the count of the sarcopenic and non-sarcopenic patients were 11 and 68 respectively. Although the median OS cannot be reached at the end of the follow-up period for both sarcopenic and non-sarcopenic patients, the difference between groups statistically insignificant ($p = 0.12$). The percentage of patients who were still alive 4th year was 87% and 97% favoring non-sarcopenic group. The clinical factors smoking status, histologic subtype, ER status, HER-2 over-expression, type of the surgery, tumor size, metastatic disease at the diagnosis and disease recurrence were not significant when the groups compared. Only the nodal status at the time of diagnosis was different between groups ($p = 0.03$).

When patients were categorized by BMI as normal and over-weight, the median OS was not significantly different, although the follow-up period was not sufficient for both groups. ($p = 0.07$) The percentage of the patients were %92 and 100% favoring normal BMI group. The clinical factors among the over-weight and normal groups were similar.

Although the median OS was not reached for both groups, the difference between low and high TVAT groups was statistically significant. ($p = 0.047$) The four, five- and six-years survival percentage of

patients were 97% for low TVAT group while the high VAT group had 87%, 78%, and 64%, respectively. The clinical factors were similar between groups except for the type of surgery, which favored BCS among the low TVAT group. The TVAT remained to be an independent risk factor for OS with a borderline significance in multivariate analysis. ($p = 0.059$) The OS difference between groups was disappeared when de novo metastatic patients excluded. ($p = 0.14$)

Discussion

In our study, TVAT was confirmed to be a prognostic risk factor that reached statistical significance. Although the median OS not reached in non-sarcopenic and sarcopenic patients, the non-sarcopenic patients had a trend to better OS. BMI status of the patients was not different in terms of OS, although a non-significant trend was favoring normal weighed patients. In patients younger than 40 years, TVAT may be a better prognostic factor than TSI due to healthy muscle structure.

In chronic conditions, decreased muscle volume was shown to be related to poor prognosis rather than obesity and fat, especially in metabolic diseases. The role of the potential role of the muscle catabolism in disease physiopathology is still under investigation.[26, 27] Sarcopenia is a frequent phenomenon in cancer patients which is also related to poor survival.[28–31]

The frequently studied parameter in breast cancer patients is body mass index (BMI), which is calculated as weight in kilograms divided by height in squared meters. for. In patients with class 2 or 3 obesity (BMI > 35) survival found to be worse control groups in a pooled analysis. The lower levels of obesity had conflicting results in several studies.[32–34]

The literature was evaluating sarcopenia and TVAT in breast cancer mainly composed of metastatic and adjuvant studies. Although multiple studies designed to evaluate the prognostic value of body composition in breast cancer, to our knowledge, our study is the first for young breast cancer patients.

Bette et al. reported sarcopenia was a better prognostic indicator than visceral adiposity. Low muscle volume related to decreased survival and considered to be a better marker than BMI. Although this trial had the largest patient number, the age factor cut-off was determined as 55 years, which was inaccurate for young breast cancer. Also, the proportion of the young breast cancers was not specified.[35]

Five studies only reported the prognostic effect of sarcopenia in breast cancer. Three studies were designed in a metastatic patient group while two studies composed by non-metastatic patients.[18, 20–23] Only one of these studies demonstrated an increased risk of death in sarcopenic patients.[22] In another study, which reported sarcopenia to have a relation with over-all mortality in non-metastatic breast cancer patients, had a small number of events and evaluated TSI after chemotherapy.[23] Also, the composition of the muscle reported being an important factor in over-all mortality. Rier et al. found low muscle radiodensity was associated with increased overall mortality in the metastatic state.[21] This finding was speculated to be related to inflammatory conditions, and immune system were supported by more trials.[36–38]

One previous study reported a relationship between mortality and muscle density in metastatic patients in terms of very low mean cut-off value when compared with non-metastatic patients.[21, 35] The difference was hypothesized for the accumulation of fat tissue among muscles with the increased stage and disease burden, which also explained the difference in the cut-off value of muscle density in these populations.

Our study had compatible results with earlier studies in terms of visceral adiposity. Three previous studies reported decreased distant disease-free and overall survival in locally advanced breast cancer in patients with high visceral adiposity.[18, 19, 35] Even TVAT was found to be an independent risk factor in our study for young breast cancer patients, it may be more important in the de-novo metastatic population.

Although other studies had young patient populations, our study specifically designed to investigate the body composition of young breast cancer to avoid the change in time via life-style changes and co-morbidities. The effect of muscle tissue on prognosis may be lesser important than adipose tissue in young breast cancers.

Limitations

The cross-sectional design of the study had limitations to evaluate patient characteristics. All CT or PET-CT images gathered at the time of diagnosis, which may have a difference between de-novo metastatic and recurrent patients. Also, the small patient population does not allow subgroup analysis for recurrent or de-novo metastatic patients. Small numbers of recurrences do not allow disease-free survival analysis. The effect of lifestyle interventions, tolerance of adjuvant treatment, and toxicity profiles cannot be evaluated due to the retrospective design of the study.

Conclusion

In this study, we demonstrate sarcopenia may be seen in patients with breast cancer under 40 years old, and it may not have a prognostic effect. The visceral abdominal fat tissue may have a greater effect on survival in breast cancer in the early period of life span. Although both muscle and fat tissue can be modifiable risk factors for breast cancer, more prospective studies observing the effect of body composition before and during breast cancer may determine the role of these parameters more accurately.

List Of Abbreviations

BMI: Body mass index

CT: Computed tomography

SMA: Skeletal muscle area

VAT: Visceral adipose tissue

SAT: Subcutaneous adipose tissue

TVAT: Total visceral adipose tissue

MRM: Mastectomy

BCS: Breast conserving surgery

TSI: Total sarcopenia index

HER-2: Human epidermal growth factor receptor -2

OS: Overall survival

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee at Afyon Kocatepe University Faculty of Medicine and carried out in accordance with the Declaration of Helsinki principles and all applicable regulations.

Consent for publication

Not applicable

Availability of data and materials

Available if requested

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Main Idea: IB; Review of the literature and writing the article: HD, FK; Statistics: IB

All authors have read and approved the manuscript.

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Table 1

Table-1: Features of the patient population.

Features				
BMI	<18.5kg/m ²	18.6-25 kg/m ²	>25.1 kg/m ²	
Number (%)	1 (1.25%)	39 (38.75%)	40 (50%)	
Histology	Invasive Ductal Carcinoma	Other		
Number (%)	80 (95%)	4 (5%)		
Smoking Status	Smoker	Non-Smoker		
Number (%)	4 (5%)	80 (95%)		
Stage	I	II	III	IV
Number (%)	27 (33%)	29 (34%)	21 (25%)	7 (8%)
Surgery Type	Mastectomy	BCS	Not operated	
Number (%)	40 (47%)	38 (45%)	6 (7%)	
Oestrogen Receptor	Positive	Negative		
Number (%)	68 (80%)	16 (20%)		
HER-2	Positive	Negative		
Number (%)	20 (24%)	64 (76%)		
Adj. Chemotherapy	Received	Not-Received		
Number (%)	75 (89%)	9 (11%)		
Adj. Radiotherapy	Received	Not-Received		
Number (%)	63 (76%)	20 (24%)		
BMI: Body Mass Index, BCS: Breast-Conserving Surgery, HER-2: Human Epidermal Growth Factor Receptor-2, Adj.: Adjuvant				

Figures

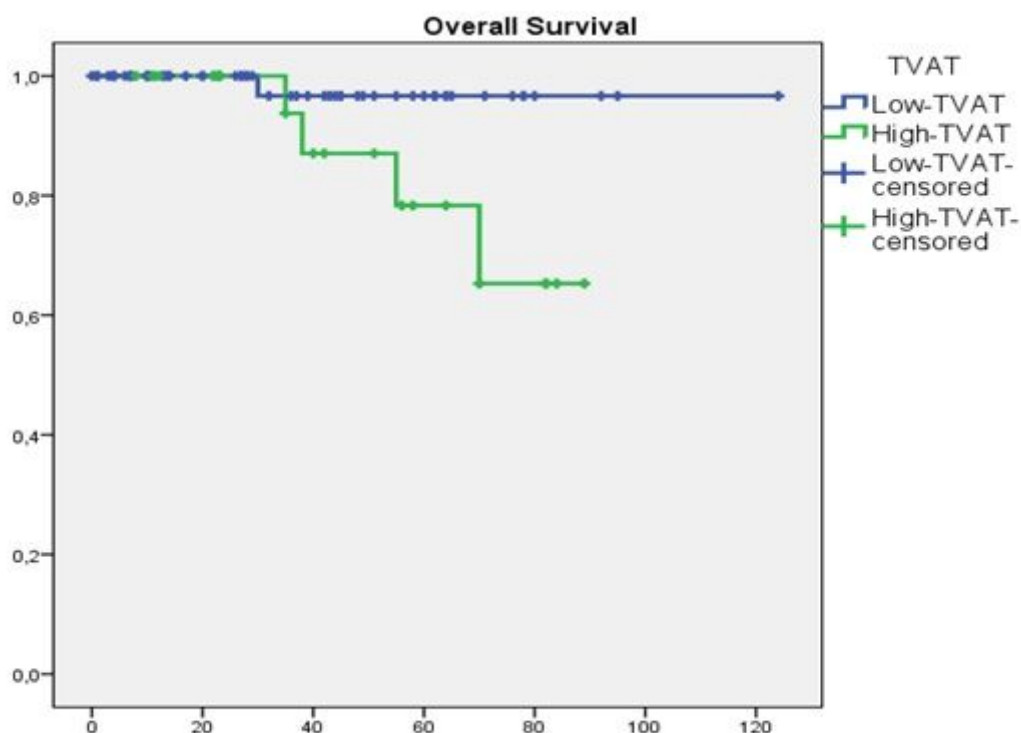


Figure 1

The OS curves of groups according to TVAT

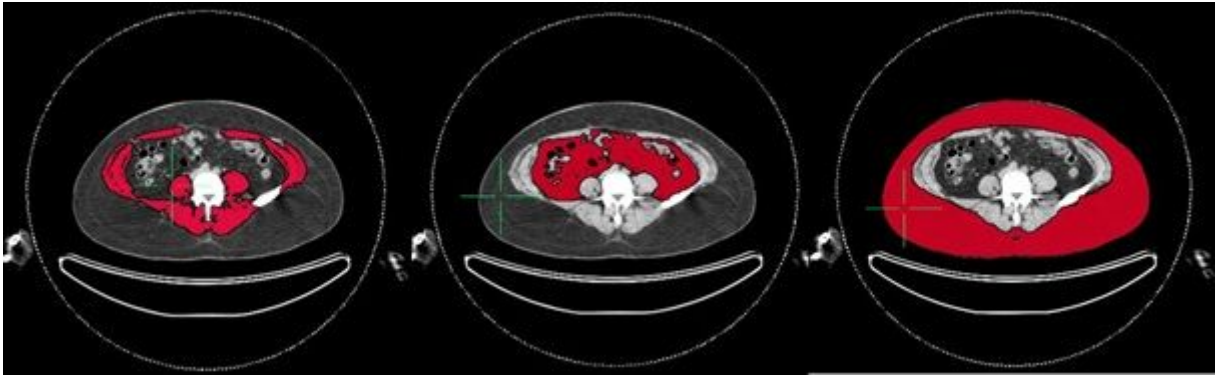


Figure 2

The calculation of total muscle tissue, visceral adipose tissue and subcutaneous adipose tissue area on computed tomography images