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GYNECOLOGIC ONCOLOGY

Muscle mass loss in patients with metastatic breast cancer

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Abstract

Purpose To assess the change of body mass index (BMI), muscle mass, visceral and subcutaneous fat in patients with metastatic breast cancer.

Methods In this retrospective chart analysis, patients with metastatic breast cancer as initial diagnosis between 2012 and 2016 were analyzed. Patients had received either chemotherapy (CTH) or endocrine therapy (ETH) according to the German S3 Guideline. BMI was calculated from the patients' weight and height. Change of muscle mass, visceral and subcutaneous fat was determined by comparing the surface area of these tissues on transverse CT images at the level of the third lumbar vertebrae (L3) at baseline and during treatment.

Results A total of 45 patients were included in the study, 29 on CTH and 16 on ETH. BMI, visceral and subcutaneous fat remained stable over time for both treatment groups. When taking both treatment groups together, muscle mass decreased significantly by 5.0 ± 2.5 cm^2 per year ($p < 0.05$).

Conclusion In patients with metastatic breast cancer, a slight reduction of muscle mass was observed, independent of therapy regimes.

Keywords Breast cancer · Body mass index · Muscle mass · Body fat · Gynecologic oncology

Introduction

As current data show, for women, breast cancer is the second most frequent cause of death from cancer globally [1] and the most fetal cancer in Germany [2].

Obese women show a higher incidence of breast cancer compared to women of moderate weight [3] and experience a higher recurrence rate and a shorter recurrence-free interval of breast cancer [4–7]. While obesity is a risk factor for breast cancer in general, patients with muscle loss and low muscle attenuation share a poor prognosis, regardless of overall body weight [4–7].

Current data shown, not overeating as a cause of weight gain among breast cancer patients is associated with problems, but sarcopenic obesity [8].

In early-stage non-metastatic breast cancer, sarcopenia even seems to be a predictor of disease-free survival and overall survival [9].

In metastatic breast cancer patients, even low muscle attenuation is a prognostic factor for the outcome of patients receiving first-line palliative chemotherapy [14].

Therefore, body weight and body composition measurement and modification should play a role of routine secondary cancer prevention and be part of integrative therapy of patients treated with cancer.

However, just determining body weight and body mass index (BMI) might be insufficient as a shift from muscle mass to subcutaneous/visceral fat might escape the treating physician's notice. This shift has been reported by Caan et al. [10] in non-metastatic breast cancer, by Tan et al. [11] and Rutten et al. [12] in patients with pancreatic cancer and ovarian cancer, respectively.

The aim of our study was to analyze the three major components of body weight, muscle mass, subcutaneous and

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visceral fat in a cohort of women with metastatic breast cancer during chemotherapy (CTH) or endocrine therapy (ETH).

Materials and methods

Study design and study population

For this retrospective chart analysis, we identified 77 patients with metastatic breast cancer at initial diagnosis between January 2012 and December 2016 presenting themselves at Saarland University Hospital, Germany, a tertiary referral center. Of these patients, 45 patients had a staging abdominal computed tomography (CT) at initial treatment and at least one additional examination later during the course of treatment. Depending on the hormone receptor status, patients received either chemotherapy (CTH) or endocrine therapy (ETH) according to the German S3 guideline [13] as stage-related and individually customized therapy.

Target parameters

Body mass index (BMI) was calculated using the patients' weight and height according to the formula BMI = mass (kg)/height^2 (m^2).

Muscle mass, visceral and subcutaneous fat were determined by retrospective analysis of at least two routine CT scans per patient, one from initial diagnosis and one or more later during treatment follow-up. Two transverse CT images (slice thickness 5 mm) at the level of the third lumbar vertebrae (L3) and L3 minus 5 mm on which both transverse processes were first clearly visible were assessed as proposed by Tan et al. [11]. Images were analyzed with OsiriX (Aycan Digital Systems, Version 2.04.000, Rochester, USA) which allowed tissue differentiation on the basis of Hounsfield units (HU) as follows: muscle (−29 to +150) [11], visceral fat (−150 to −50) [12] and subcutaneous fat (−190 to −30) [13]. Tissue boundaries were manually corrected, where the HU-based selection was inappropriate. Cross-sectional areas (cm^2) were computed automatically by summing tissue pixels and multiplying by pixel surface area. All CT images were analyzed by a trained reader.

Statistics

All available data were analyzed descriptively using absolute and relative frequencies for categorical variables, and mean and standard deviation for continuous variables. The influence of time on the target variables BMI, muscle mass, visceral fat, and subcutaneous fat was assessed by linear regression analysis. The influence of time and treatment on the target variables was assessed by analysis of covariance with factor treatment and co-variable time. As appropriate for exploratory analyses, a comparison-wise significance level α of 5% was used in this study. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The demographics of the study population are shown in Table 1.

Both therapy groups were not comparable as they remarkably differ with respect to age, baseline weight and disease staging. The CHT group is younger (55.7 years vs. 71.3 years), has lower body weight (73.6 kg vs. 76.1 kg), more bilateral disease and more invasive ductal carcinomas. In addition, more bone (22 vs. 16), lung (17 vs. 9), visceral (13 vs. 4), cutaneous (8 vs. 4) and craniocerebral (3 vs. 0) metastases were diagnosed in the CHT group.

BMI

The CTH group showed lower baseline BMI than the EHT group (27.4 ± 6.2 vs. 29.1 ± 6.2). However, for both groups, the BMI remained relatively stable over time. The time curves for both treatment groups are almost parallel (Fig. 1).

Muscle mass

The CHT group showed higher baseline muscle mass than the ETH group (94.6 ± 25.1 vs. 83.4 ± 11.9). Both groups together showed a statistically significant decrease over time by 5.0 ± 2.5 cm^2 per year ($p < 0.05$). This significance is not seen when the treatment groups are regarded separately (Fig. 2).

Visceral fat

The CTH group showed less visceral fat than the EHT group (119.7 ± 90.5 vs. 154.6 ± 84.7). However, visceral fat did not change significantly (+2.7 ± 9.5 cm^2 per year) during the treatment period (Fig. 3).

Subcutaneous fat

Similar to visceral fat, the CTH group showed less subcutaneous fat than the EHT group at baseline (237.9 ± 116.6 vs. 255.2 ± 93.8) and over time. There was no significant change (−4.1 ± 13.5 cm^2 per year) during treatment (Fig. 4).

Table 1 Demographics of the study population

	CHT ($n=29$)	ETH ($n=16$)
Demographics		
Age [years] mean (SD)	55.7 (14.1)	71.3 (9.8)
Weight [Kg] mean (SD)	73.6 (17.4)	76.1 (16.1)
Height [m] mean (SD)	1.6 (0.07)	1.6 (0.04)
BMI (kg/m^2)	27.4 (6.2)	29.1 (6.2)
Disease staging		
Unilateral *n* (%)	23 (79.3)	16 (100.0)
Bilateral *n* (%)	6 (20.7)	0 (0.0)
Tumor size		
T1 *n* (%)	1 (3.4)	1 (6.3)
T2 *n* (%)	11 (39.3)	7 (43.8)
T3 *n* (%)	4 (14.3)	2 (12.5)
T4 *n* (%)	12 (42.9)	6 (37.5)
Unknown *n* (%)	1	0
Nodal status		
N0 *n* (%)	5 (17.9)	2 (12.5)
N1 *n* (%)	11 (39.3)	7 (43.8)
N2 *n* (%)	8 (28.6)	4 (25.0)
N3 *n* (%)	4 (14.3)	3 (18.8)
Unknown *n* (%)	1	0
Metastases		
M0 *n* (%)	0 (0.0)	0 (0.0)
M1 *n* (%)	29 (100.0)	16 (100.0)
Tumor pathology		
Invasive ductal *n* (%)	25 (86.2)	9 (60.0)
Invasive lobular *n* (%)	2 (6.9)	4 (26.7)
Inflammatory	1 (3.5)	0 (0.0)
Mucinous *n* (%)	1 (3.5)	1 (6.7)
Tubulolobular *n* (%)	0 (0.0)	1 (6.7)
Other/unknown *n* (%)	0	1
Max grading		
G1 *n* (%)	1 (3.6)	0 (0.0)
G2 *n* (%)	16 (57.1)	11 (73.3)
G3 *n* (%)	11 (39.3)	4 (26.7)
Unknown *n* (%)	1	1
Receptor status		
ER+ *n* (%)	27 (93.1)	16 (100.0)
ER− *n* (%)	2 (6.9)	0 (0.0)
PR+ *n* (%)	16 (55.2)	8 (50.0)
PR− *n* (%)	10 (34.5)	4 (25)
PR uncertain (%)	3 (10.4)	4 (25)
Her2neu+ *n* (%)	12 (41.4)	0 (0.0)
Her2neu− *n* (%)	17 (58.6)	16 (100.0)
Ki67		
≤15% *n* (%)	9 (33.3)	6 (40.0)
>15–20% *n* (%)	5 (18.5)	5 (33.3)
>20% *n* (%)	13 (48.2)	4 (26.7)
Unknown	2	1

CHT Chemotherapy, *ETH* Endocrine therapy

Discussion

What did we do?

As far as apparent in the current literature, the study on hand is the first one examining body composition in two different therapy regimes in the metastatic situation.

It shows evidence for muscle mass loss in patients with metastatic breast cancer while almost no change in subcutaneous or visceral fat was measurable in two different therapy regimes.

This effect was independent of chosen therapy. These results are in accordance with the most recent literature in patients with non-metastatic and metastatic breast cancers treated with chemotherapy [3, 5, 10–12, 14–18].

What does the change in muscle mass mean?

A rough estimation suggests that this muscle mass loss is far above the physiological muscle mass loss due to aging, either caused by the disease or by the therapy or both [19]. Roland et al. estimated a physiological muscle mass loss of 1–2% per year [20]. In patients receiving CTH for ovarian cancer, muscle mass loss was correlated with reduced overall survival [12]. More recently, Deluche et al. [17] and Caan et al. [10] reported reduced overall survival in women with non-metastatic breast cancer. However, the role of therapy-induced muscle mass loss vs. disease induced is still in scientific debate.

In general, muscle mass loss triggers a reduction of daily physical activity causing reduced quality of life. A vicious circle starts: muscle mass loss–less physical activity–no stimulus of the immune system–aggravated fatigue syndrome–osteoporosis–fragility–accidents–(pathological) fractures (e.g., hip, spine, arms)–and further reduced physical activity [21–25].

What does this mean for patients?

Sarcopenia is associated with an increased risk of overall mortality in breast cancer patients and could be associated with breast cancer-specific mortality [14, 18].

The approach towards the problem and the development of possible interventions to maintain or even increase skeletal muscle mass to help to improve prognosis in breast cancer survivors could be possible integrative treatment options in the future [4, 5, 16, 26, 27].

To get the patients out of the vicious circle, an individually adapted medium-impact exercise program is suggested [16, 26], in particular as Ligibel et al. [5] and Veersteg

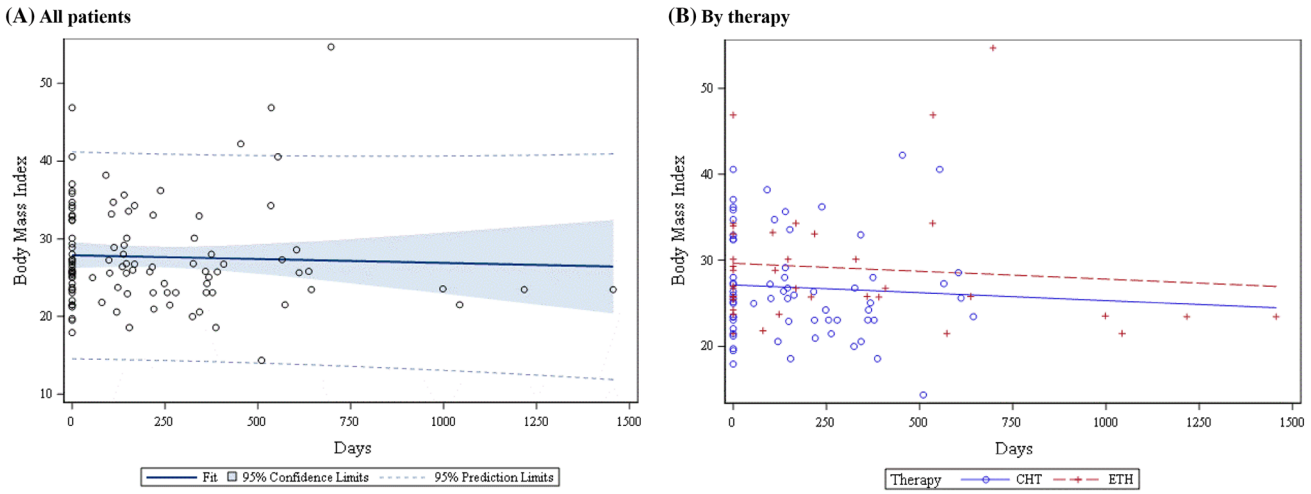

Fig. 1 Changes of BMI over time

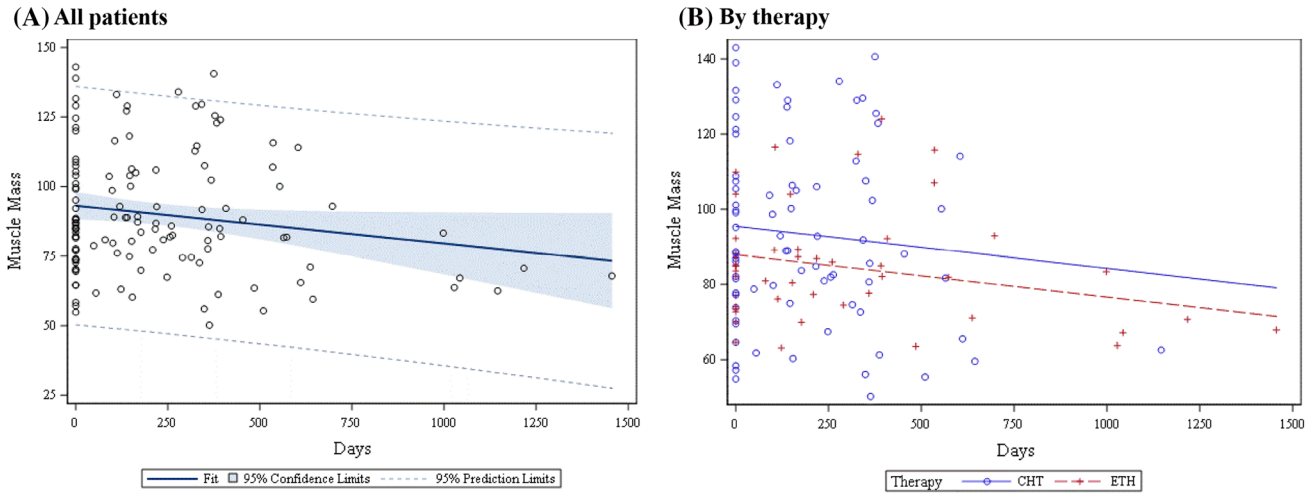

Fig. 2 Changes of muscle mass over time

et al. [27] reported reduced recurrence rates and increased overall survival rates due to physical activity.

This is also true for women with metastatic disease [14, 24, 25]. Increased muscle mass also prevents patients from falling and its deleterious sequelae [28]. Several researchers analyzed different exercise programs for patients with breast cancer and their benefits for the patients [24, 25, 29].

Limitations

Finally, two limitations need to be addressed: CT scans are not routinely performed in breast cancer patients. Therefore, observation time points differed and the sample size was relatively small, which might explain the missing statistical significance for the two fat parameters. Second, the retrospective study design and the group comparison approach limit the quality of the data. The missing difference between patients undergoing chemotherapy and endocrine therapy might be liable to little patient data on hand. A prospective study in a larger cohort is needed for confirmation of these findings.

Conclusion

In conclusion, there is initial evidence that patients with metastatic breast cancer treated with CHT and ETH experience a reduction of muscle mass. For this reason, assessing body composition could be an approach to individualize patient treatment during therapy, even in a metastatic situation.

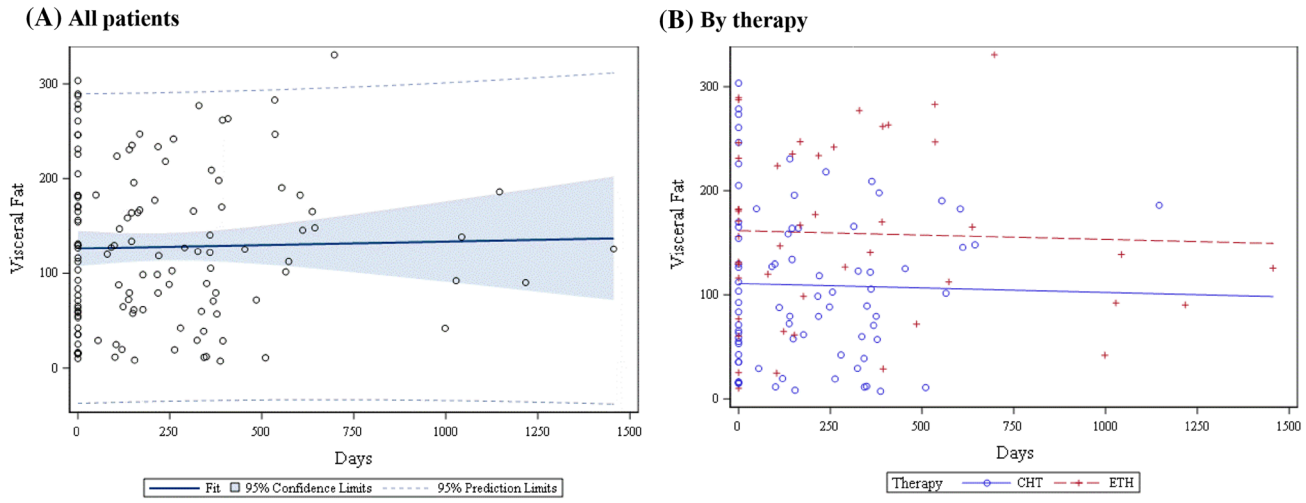

Fig. 3 Changes of visceral fat over time

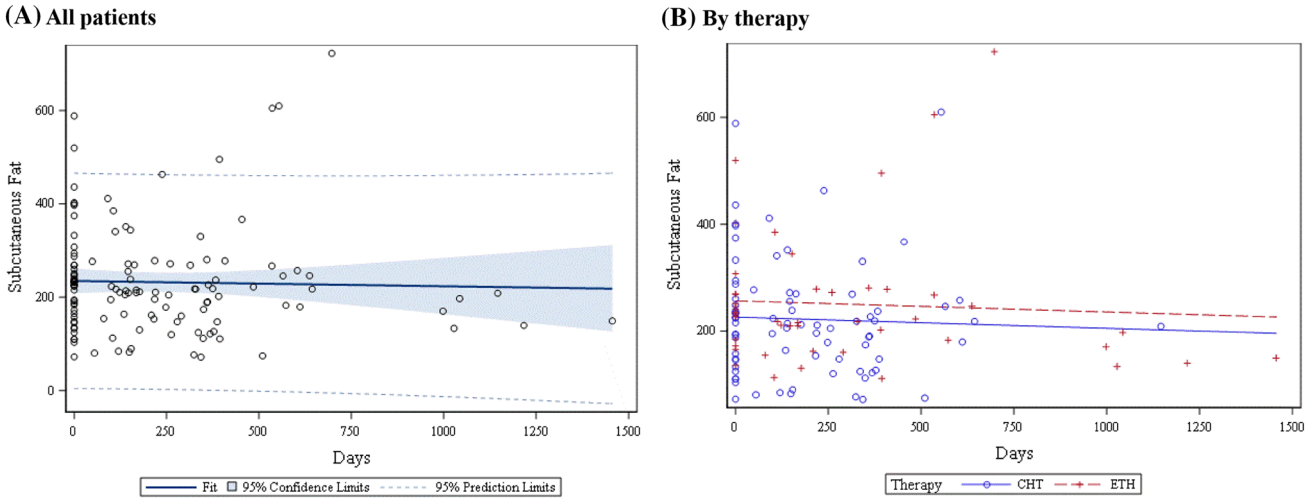

Fig. 4 Changes of subcutaneous fat over time

Author contributions EFS, EMB, JCR, JE and CG designed the study and drafted the manuscript. EMB, JSMZ and JS performed the measurements. JSMZ and JS helped draft the manuscript. In addition, each author has read and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval As this was exclusively a retrospective review of patient records, no formal ethical approval was required after the regulations of Saarland University and Saarland ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal participant rights statement This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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