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ORIGINAL ARTICLE

The effect of obesity on recurrence pattern in early breast cancer patients

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Summary

Purpose: *Obesity is a well known risk factor for breast cancer recurrence and poor prognosis. We studied the effect of body mass index (BMI) on recurrence pattern in early breast cancer patients.*

Methods: *This retrospective cross-sectional study analyzed the data of 2731 early stage breast cancer patients. Patients who had metastatic disease at the time of diagnosis and with unknown BMI values were excluded from study (N=276). Patients were classified into three BMI categories: normal body weight, overweight, and obese. The recurrent/metastatic sites of patients were grouped in 8 categories: local, contralateral, lymph node, bone, lung, liver, brain and others. The association between first relapse site of early breast cancer patients and BMI categories were evaluated.*

Results: *The median patient age was 48 years (range 18-92). The median follow up time was 40 months (range 1-284). During follow-up, 469 (17.1%) patients developed recurrence and/or metastasis. Of 2455 total patients, 853 (34.6%) were classified as having normal weight, 898 (36.2%) were overweighted and 704 (29.2%) were obese. In the whole patient group no relation between metastatic sites and BMI groups was noticed. The first primary metastatic sites were also not associated with BMI groups in pre and postmenopausal subpopulations. In obese patients, disease free survival (DFS) was shorter compared to normal weighted patients, but the difference was not significant. There was no significant difference between site-specific DFS in relation to BMI categorization. Obese and overweighted patients had significantly shorter overall survival (OS) compared to the normal-weight group (p=0.003).*

Conclusion: *Although obesity had no effect on recurrence pattern of early breast cancer patients, obese early breast cancer patients had shorter OS compared to their normal-weight counterparts.*

Key words: *breast cancer, body mass index, obesity, recurrence*

Introduction

Obesity is a well known risk factor for breast cancer recurrence and poor prognosis. In a study including 2298 breast cancer patients, the effect of BMI on recurrence and survival was evaluated. Obese patients had lower recurrence-free, breast cancer-specific and OS (82 vs 77%, p<0.01; 87 vs 85%, p=0.046; 81 vs 77%, p=0.02, respectively) [1]. Obesity is associated with poor prognosis of breast cancer. A review of 26 studies involved 29 460 women and showed that increased BMI was associated with adverse prognosis of breast cancer [2]. In a meta-analysis, it was reported that in patients with increased BMI, the recurrence risk was 1.91(95% CI, 1.52-2.40) at 5 years and death risk was 1.6 (95% CI, 1.38-1.76) at 10 years. These results showed that obese women have increased

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risk of relapse and death [3]. In a prospective cohort study including 512 women with early stage breast cancer (T1 -T3, N0-N1, and M0) , increased BMI was strongly associated with poor DFS and OS [4]. In many large cohort studies inverse association between increased BMI and breast cancer mortality was verified [5-8]. A population-based large study, which included 2863 invasive breast cancer patients, tested the relationship between obesity and stage of breast cancer. This study reported that increased BMI was associated with non-localized breast cancer [9]. The adverse effect of obesity on breast cancer prognosis was detected both in pre and postmenopausal women [10,11]. However, there were controversial results regarding the association of obesity and survival in premenopausal women. In many studies there was inverse association between breast cancer risk and premenopausal women [12,13].

Several mechanisms are suggested to explain the association between obesity and poor prognosis of breast cancer. The effect of obesity on the hormonal status of women and tumor characteristics are the most widely discussed mechanisms. However, there has been no study showing an exact underlying pathophysiological mechanism. Also, no data are available about the relationship of first metastasis and obesity in early breast cancer patients. Therefore, in this study we aimed to assess the effect of BMI on recurrence pattern and survival in early stage breast cancer patients.

Methods

This retrospective cross-sectional study analyzed the data of 2731 early stage breast cancer patients who were admitted at Hacettepe University Cancer Institute, Department of Medical Oncology of Ankara Numune Education and Research Hospital between January 2002 and October 2013. Patients who had BMI values at the time of diagnosis were included into the study. We were not able to obtain the BMI values of 276 patients at the time of diagnosis and therefore these patients were excluded. The patients who had metastatic disease at the time of diagnosis were also excluded from study. BMI was calculated as weight (kg)/height^2 (m^2), and patients were classified into three categories: normal body weight (BMI:18.5-24.9 kg/m^2); overweight (BMI:25-29.9 kg/m^2) and obese (BMI ≥30.0 kg/m^2). The first recurrent/metastatic sites were grouped in 8 categories: local, contralateral, lymph node, bone, lung, liver, brain and others. In all patient groups and also in pre and postmenopausal patient subpopulations, we evaluated the effect of BMI on first relapse pattern. The site-specific DFS was calculated and evaluated for each previously defined metastatic site and compared according to BMI groups.

Statistics

The x^2 test and Fisher's exact test were used to evaluate the associations between BMI subgroups and menopausal status, tumor lymphovascular and perineural invasion, tumor grade, tumor size, tumor hormone receptors and chemotherapy containing regimens. Kruskal-Wallis test was used to evaluate the associations with age. ANOVA and Kruskal-Wallis tests were used to evaluate the relationship between metastatic site categories and BMI groups. Kaplan-Meier method was used to estimate survival and log rank test was used to evaluate the differences in survival of BMI groups. A p value <0.05 was considered as significant. All data were analyzed using the Statistical Package for Social Sciences version 18.0 (SPSS, Inc, Chicago, Ill, USA).

Results

A total of 2455 patients with early stage breast cancer patients was evaluated. The median follow up of patients was 40 months (range 1-284). According to BMI groups 853 (34.6%) patients had normal weight, 898 (36.2%) were overweighted and 704 (29.2%) were in the obese group. The median patient age was 48 years (range 18-92). During follow-up, 469 (17.1%) patients developed recurrence and/or metastasis. At the time of diagnosis, the median BMI was 27 kg/m^2 (range 15-55). One hundred and eighty (7.3%) patients died. Clinical and pathological characteristics according to BMI groups are shown in Table 1. Normally weighted patients were significantly younger than obese patients (p<0.01). The ratio of premenopausal women in normally weighted patients was significantly higher compared to the obese patient group (66.8 and 33.1%, respectively, p<0.01). According to BMI groups the menopausal status difference was statistically significant (with increasing BMI the ratio of postmenopausal women was also increased; p<0.01). In all BMI groups, the most frequently detected histology was ductal carcinoma, equally dispersed among BMI groups. Most of the patients had grade 2 or 3 disease in the 3 BMI groups. Perineural and lymphovascular invasion ratios of patients were similar among groups (p=0.77 and p=0.85, respectively). Tumors larger than 2 cm were commonly observed among obese patients, followed by overweighted patients, but the difference was not significant (p=0.07). Normally weighted patients had received more chemotherapy compared to over-

Table 1. Patient and tumor characteristics according to body mass index subtypes

Characteristics	*Normal weight (BMI < 25)*		*Overweight (BMI ≥ 25 and < 30)*		*Obese (BMI ≥ 30)*		*p value*
	N	%	*N*	%	*N*	%	
Patient age at diagnosis (years)							
< 50	631	74.1	494	55	293	41.7	<0.01
> 50	221	25.9	404	45	410	58.3	
Menopausal status							<0.01
Pre	569	66.8	407	45.4	233	33.1	
Peri	49	5.6	67	7.2	52	7.3	
Post	235	27.6	424	47.4	419	59.6	
Right-left breast							0.02
Right	437	50.8	404	44.5	324	46.1	
Left	416	49.2	494	54.5	380	53.9	
Histological type							0.30
Ductal	609	71.9	625	70	505	71.9	
Lobular	40	4.5	48	5.2	29	4	
Mixed	116	13.4	122	13.4	95	13.4	
Other	88	10.2	103	11.4	75	10.7	
Histologic grade							0.50
I	125	14.7	109	12.1	84	11.9	
II	379	44.6	411	45.8	315	44.8	
III	349	40.7	378	42.1	304	43.3	
Lymphovascular invasion							0.85
Yes	320	37.4	379	42.3	140	19.8	
No	533	62.5	518	57.6	563	80.2	
Perineural invasion							0.77
Yes	275	32.3	90	10.2	131	18.7	
No	571	67.7	255	28.5	571	81.2	
Estrogen receptor							0.17
Positive	654	76.7	662	73.8	508	72.2	
Negative	198	23.3	236	26.2	196	26.4	
Progesterone receptor							0.21
Positive	625	73.3	634	70.6	484	68.7	
Negative	228	26.7	264	29.4	220	31.3	
HER-2 receptor							<0.01
Positive	140	16.4	201	22.4	136	19.3	
Negative	713	83.6	697	77.6	568	80.7	
Tumor size, cm							0.07
0-2	332	38.9	321	35.7	232	33	
> 2	521	61.1	577	64.3	472	67	
Chemotherapy							0.32
Yes	640	75	646	72	500	71	
No	208	25	251	28	204	29	

BMI: body mass index

Table 2. Relationship of metastatic site according to body mass index groups in whole patient cohort

Recurrence site	*Normal weight (BMI < 25)*		*Overweight (BMI ≥ 25 and < 30)*		*Obese (BMI ≥ 30)*		*p value*
	N	*%*	*N*	*%*	*N*	*%*	
Local	24	2.8	22	2.4	16	2.3	0.78
Contralateral	12	1.4	15	1.7	8	1.1	0.66
Lymph node	28	3.3	21	2.3	20	2.8	0.48
Bone	55	6.4	46	5.1	46	6.5	0.38
Lung	25	2.9	27	3	23	3.3	0.95
Liver	22	2.6	24	2.7	20	2.8	0.95
CNS	10	1.2	10	1.1	5	0.7	0.62
Other	9	1.1	13	1.4	4	0.6	0.23

BMI: body mass index, CNS: central nervous system

Table 3. Relationship of metastatic site according to body mass index groups in premenopausal patients

Recurrence site	*Normal weight (BMI < 25)*		*Overweight (BMI ≥ 25 and < 30)*		*Obese (BMI ≥ 30)*		*p value*
	N	*%*	*N*	*%*	*N*	*%*	
Local	17	3	11	2.7	9	3.9	0.71
Contralateral	10	1.8	7	1.7	1	0.4	0.33
Lymph node	20	3.5	14	3.5	7	3.0	0.93
Bone	36	6.3	26	6.5	20	8.6	0.47
Lung	21	3.7	14	3.5	12	5.2	0.53
Liver	20	3.5	14	3.5	6	2.6	0.78
CNS	7	1.2	6	1.5	3	1.3	0.94
Other	6	1.1	6	1.5	2	0.9	0.74

BMI: body mass index, CNS: central nervous system

Table 4. Relationship of metastatic site according to body mass index groups in postmenopausal patients

Recurrence site	*Normal weight (BMI < 25)*		*Overweight (BMI ≥ 25 and < 30)*		*Obese (BMI ≥ 30)*		*p value*
	N	*%*	*N*	*%*	*N*	*%*	
Local	7	3	11	2.6	7	1.7	0.50
Contralateral	2	0.9	8	1.9	6	1.4	0.54
Lymph node	7	3	5	1.2	10	2.4	0.24
Bone	15	6.4	17	4	24	5.8	0.35
Lung	3	1.3	12	2.9	11	2.6	0.42
Liver	2	0.9	8	1.9	12	2.9	0.2
CNS	1	0.4	4	1	2	0.5	0.62
Other	3	1.3	6	1.4	2	0.5	0.32

BMI: body mass index, CNS: central nervous system

weighted and obese patients, but the difference was not significant (p=0.32). Estrogen and progesterone receptor status was not different among BMI groups. However, HER-2 receptor-positive tumors were significantly more frequent in the overweighted and obese patients, compared to the normally weighted group (p<0.01).

In the whole patient group we did not notice any relation between metastatic sites and BMI groups (Table 2). Also, we did not observe any significant relationship between metastatic sites and BMI groups in pre and postmenopausal patients (Tables 3 and 4).

In obese patients, DFS was shorter compared

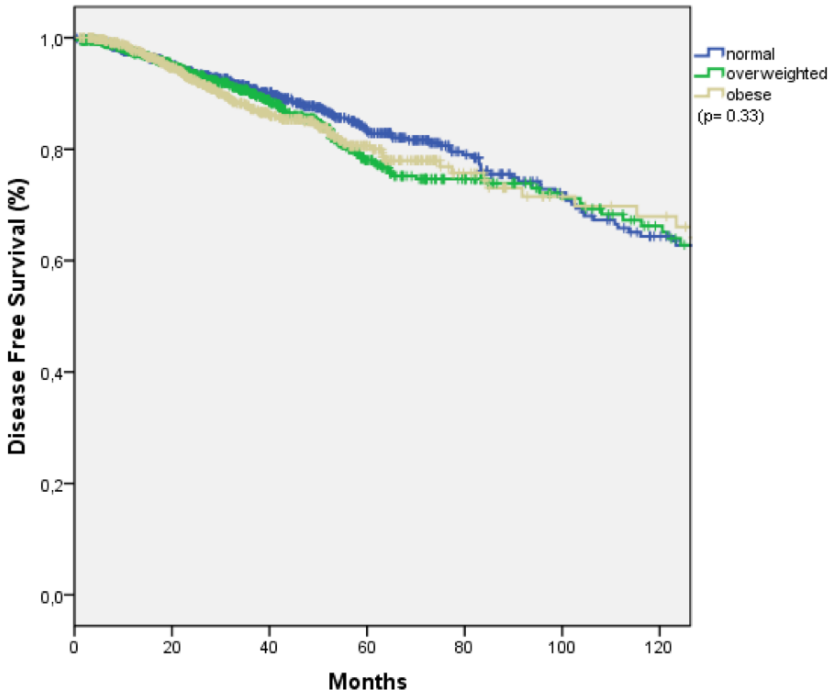

Figure 1. Kaplan-Meier estimates of disease-free survival according to body mass index groups.

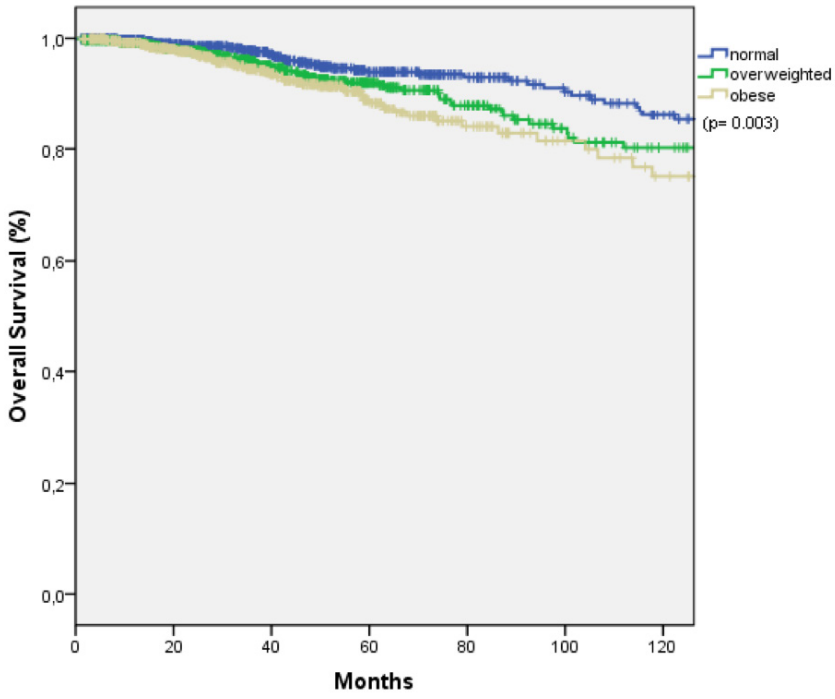

Figure 2. A: Kaplan-Meier estimates of overall survival according to body mass index groups.

to normally weighted patients, but the difference was not significant (Figure 1). In premenopausal patients, the DFS in obese patients was shorter compared to normally weighted patients but the difference was not significant. However, normally weighted postmenopausal patients had a tendency for shorter DFS compared to obese patients, but the difference was not significant. No significant difference between site-specific DFS was registered according to BMI groups. Obese and overweighted patients had significantly shorter OS compared to the normal-weight group (Figure 2a,

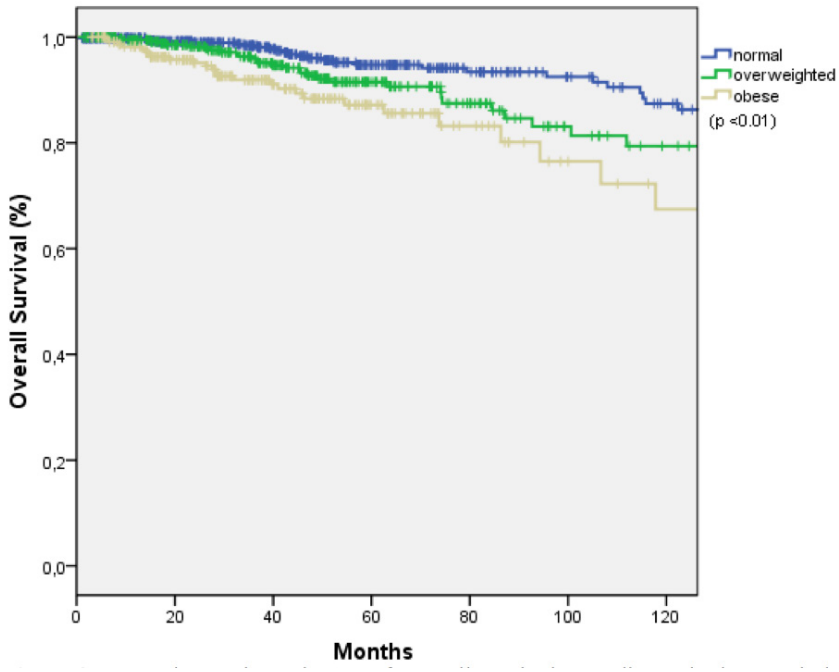

Figure 2. B: Kaplan-Meier estimates of overall survival according to body mass index groups in premenopausal patients.

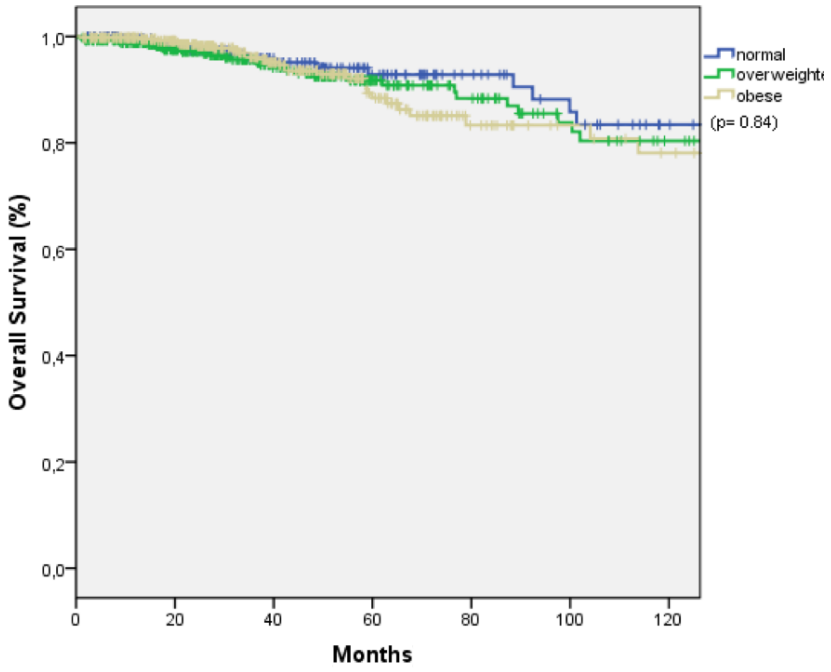

Figure 2. C: Kaplan-Meier estimates of overall survival according to body mass index groups in postmenopausal patients.

p=0.003). In the subpopulation of premenopausal patients, obese patients had significantly shorter OS compared to over- and normal-weight group (Figure 2b, p<0.01). In the subpopulation of postmenopausal patients, normally weighted patients had shorter OS compared to overweight and obese group, the difference being not significant (Figure 2c).

Discussion

In the current study, we showed that obese,

early breast cancer patients had shorter OS compared to normally weighted patients. In postmenopausal women, we did not notice unfavorable effect of obesity on OS. No significant difference between DFS according to BMI groups was registered. According to BMI groups, site-specific DFS of metastatic regions was not different. Obesity had no effect on the recurrence pattern of early breast cancer patients.

In a meta-analysis of 43 studies, non-obese breast cancer patients had more favorable survival compared to obese breast cancer patients, which was the same for OS (HR=1.33; 95% CI: 1.21-1.47) and breast cancer-specific survival (HR=1.33; 95% CI: 1.19-1.50). In a study, obesity caused 33% increment in the rate of death among breast cancer patients [14]. A meta-analysis involving 29,460 women showed that obese breast cancer patients had worse prognosis compared to non obese patients [2]. In a randomized study, the effect of BMI on breast cancer prognosis was searched. In this study, 636 breast cancer patients were enrolled and the authors reported that increased BMI was associated with decreased recurrence free survival and OS [8]. In a trial, the prognostic effect of BMI was evaluated in 602 patients with locally advanced breast cancer. It was reported that obese and overweighted patients had worse OS and DFS (p=0.001) and visceral recurrence compared to normally weighted patients [15]. A meta-analysis searching the association between body weight and breast cancer demonstrated that obese patients had 1.78-fold greater risk of recurrence (95% CI, 1.50-2.11) and the risk of death was 1.36-fold greater at 10-year follow-up (95% CI, 1.19-1.55) [5]. These data provide the most powerful evidence linking obesity to breast cancer mortality. In these studies, obesity was associated with adverse outcomes both in pre and postmenopausal breast cancer patients. Similarly, in the present study we demonstrated that obese and overweighted patients had shorter OS compared to normally weighted patients. As already known, the hormonal statuses of women differ in the pre and postmenopausal periods. We evaluated the OS in pre and postmenopausal patients and, although we detected significantly poor OS difference in overweighted and obese premenopausal patients compared to normally weighted patients, we were not able to show the same effect for postmenopausal patients. Also, according to BMI groups, no significant difference in DFS in the whole patient group and in pre and postmenopausal subpopulations was demonstrated.

The poor survival of obese breast cancer patients might be explained by many possible mechanisms. These possible mechanisms can be divided into three subclasses: host-related, tumor-related and treatment-related. One of the topics included in host-related factors is the hormonal status of obese women. Higher concentrations of estrogen and testosterone levels may contribute to poor prognosis in postmenopausal obese breast cancer patients . In a study, obese breast cancer patients had higher levels of estrogen and estradiols compared to non-obese patients [17]. Although some studies showed that obesity and poor survival relationship did not differ by menopausal status, most of the studies demonstrated poor OS associated with obesity in postmenopausal patients [13,14,18]. However, there were controversial results regarding the association of obesity and survival in premenopausal women [12,13]. In 2 studies which evaluated the role of obesity on tamoxifen treatment, obesity did not appear to be independent prognostic factor in breast cancer patients. According to these 2 studies estrogens were not responsible for the adverse effect of obesity on the survival of breast cancer patients [19,20]. Our results are consistent with these 2 studies as we also did not show poor OS in postmenopausal obese women. Based on our results, we think that estrogen-dependent mechanism did not explain the poor OS in breast cancer patients. The other reason might be the effect of second and further line therapies in postmenopausal patient groups. We did not evaluate the second and further line regimens according to BMI groups. The next point that might explain the different OS results in postmenopausal subpopulation was comorbid diseases. As expected, postmenopausal patients were older and had more comorbid diseases compared to premenopausal women. In this context, in the postmenopausal patient group multiple comorbid diseases might effect the OS. Comorbidities might be different in BMI groups. In our study, we did not consider the comorbidities of patient population and calculate the breast cancer-specific survival. Therefore, this might explain the insignificant OS difference in BMI groups in postmenopausal patients.

The evidence is still insufficient to define any exact mechanism. According to the difference in tumor characteristics in different BMI groups we hypothesized that BMI might effect the survival via effecting the relapse pattern of early breast

cancer patients. However, we did not demonstrate statistically significant difference between metastatic sites according to BMI groups. Controversial evidence suggests that high estrogens might explain the link between obesity and poor prognosis of breast cancer. Due to different hormone status in pre and postmenopausal periods, obesity might have different effects on the relapse pattern. Therefore, we reevaluated the relationship of BMI to first relapse sites of pre and postmenopausal patients with breast cancer and we did not demonstrate significant relationship between BMI groups and metastatic sites in pre and postmenopausal subpopulations.

Although host-related factors can explain the association of obesity and poor survival up to a certain point, tumor-related factors might play significant role. Tumor size, pathological features and lymph node metastasis status are tumor-related factors [21,22]. In a study that included 698 postmenopausal patients with breast cancer, obese patients had higher probability of having tumors larger than 2 cm in size and with metastatic disease compared to normally weighted patients [22,23]. In a single center experience 2,298 breast cancer patients were reviewed. Among them, 417 obese patients had larger breast tumor on average compared to non obese patients (median 2.3 vs 2.1 cm, p<0.01). In this report increasing BMI was associated with worse prognosis of breast cancer [1]. In a large cohort including 1177 younger women with breast carcinoma, obese patients had high histological grade (OR, 1.7; 95% CI, 1.0-2.9), high mitotic cell count (OR, 2.0; 95% CI, 1.2-3.1), and large tumor size (2-5 cm: OR, 2.3; 95% CI, 1.5-3.1; or ≥5 cm: OR, 2.7; 95% CI, 1.5-4.8) compared to the tumors of non obese women [24]. After adjusted for age and tumor size, it was noticed that obese women had 2-fold increased risk of axillary involvement compared to their non obese counterparts [25,26]. These results showed that obese women with breast cancer might have more aggressive malignant phenotype. In a study, tumor characteristics leading to poor OS in obese breast cancer patients were defined as advanced clinical stage, more regional lymph node involvement and increased tumor size [27]. In contrast to this data, we did not demonstrate any relationship between tumor characteristics and obesity. However, our study showed that with increasing BMI, tumor size was also increasing, and the difference was close to significance (p=0.07). This might be an explanation for poor OS in obese patients.

In the current study, obese and overweighted patients had more frequent HER-2 positive tumors compared to normally weighted group, which might speak for the aggressiveness of these tumors. This might be another tumor-related explanation for poor OS in the obese group in our study. It should be noted that some of our patients did not receive anti-HER-2 therapy because they were diagnosed and followed before the routine recommendation of anti-HER-2 treatment in metastatic breast cancer. Therefore, some of the overweighted and obese patients had no anti-HER-2 treatment that might be one of the reasons for the poor OS in this patient group.

Another suggested mechanism is connected with the tendency of clinicians to reduce in everyday practice the doses of chemotherapy in obese patients to avoid possible side effects. In obese patients, if the actual body surface area exceeds 2 m^2, empiric dose reductions are frequently applied and, therefore, these patients are treated with lower doses of chemotherapy [28]. Although the chemotherapy administration rate was similar among BMI groups, we did not calculate the dose intensities. Therefore, the obese group might have lower-dose chemotherapy that might effect the survival of the obese group.

There are some limitations in our study. We did not differentiate the study population according to pathological subgroups. We retrospectively designed the study. We did not consider second and further lines of chemotherapy according to BMI groups. Especially in postmenopausal patients, comorbidities might effect the OS of BMI groups. Also, we did not consider comorbid diseases of the patients.

Our results showed that obese early breast cancer patients had shorter OS compared to normally weighted patients. There was no association between first metastatic sites and obesity. Hormone-dependent mechanisms do not explain the poor OS in obese patients. Obesity might cause more aggressive tumor features. Further randomized trials investigating the possible mechanisms of the relationship between obesity and breast cancer survival are needed.

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