RESEARCH ARTICLE

Relationship of Body Mass Index with Prognosis in Breast Cancer Patients Treated with Adjuvant Radiotherapy and Chemotherapy

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Abstract

Background: The aim of this study was to investigate the relationship of body mass index with overall and progression-free survival as well as other prognostic factors of breast cancer in patients with non-metastatic breast cancer. Materials and Methods: We retrospectively reviewed 456 patients diagnosed with breast cancer in the Radiation Oncology department of Kayseri Teaching Hospital between 2005 and 2013. We investigated relationship of body mass index with prognosis and other prognostic factors. Results: The study included 456 patients (447 women and 9 men). Mean age at presentation was 55.6 years. Of the cases, 96.9% underwent modified radical mastectomy and 95.0% received chemotherapy, while 82.4% received radiotherapy and 60.0% were given hormone therapy. Body mass index was >25 mg/kg^2 in 343 cases. Five- and 10-years overall survival rates were 77% and 58% whereas progression-free survival rates were 65% and 49%, respectively. In univariate analyses, factors including stage (p=0.046), tumor diameter (p=0.001), lymph node metastasis (p=0.006) and body mass index (p=0.030) were found to be significantly associated with overall survival, while perinodal involvement was found to be significantly associated with progression-free survival (p=0.018). In multivariate analysis, stage (p=0.032; OR: 3.8; 95% CI: 1.1-13), tumor diameter (p<0.000; OR: 0.0; 95% CI: 0.0-0.3), lymph node metastasis (p=0.005; OR: 0.0; 95% CI: 0.0-0.5) and BMI (p=0.027; OR: 0.02; 95% CI: 0.0-0.8) remained as significantly associated with OS. Conclusions: In our study, it was seen that overall survival time was shorter in underweight and obese patients when compared to normal weight patients.

Keywords: Breast cancer - body mass index - prognosis

Asian Pac J Cancer Prev, **15 (10)**, 4233-4238

Introduction

Breast cancer is the most common malignant disease among women and second leading cause of cancer-related deaths (Siegel et al., 2012; Wu et al., 2014). American Cancer Society (ACS) estimates that 29% of all newly diagnosed malignant disease will be breast cancer and it will be cause in 16% of the deaths (Parekh et al., 2012; Siegel et al., 2012; Taghavi et al., 2012). Increased number of survivors after diagnosis of breast cancer suggests that modifiable risk factors that can improve remission, survival and quality of life should have to be investigated (Malcolm et al., 2009; Klimant et al., 2011). It has been thought that obesity may be one of the independent risk factors in patients with breast cancer. In recent studies, a negative correlation was identified between body mass index (BMI) and progression-free and overall survival times in patients with early breast cancer. However, it hasn't been clarified whether obesity affects patients with breast cancer independently (Ryu et al., 2001; Protani et al., 2010; Alegre et al., 2013; Suleeporn et al., 2013; Ladoire et al., 2014).

The aim of this study was to investigate whether BMI at diagnosis have prognostic value in breast cancer patients who underwent surgery.

Materials and Methods

Patient group and demographic characteristics

We retrospectively reviewed operated breast cancer patients who were followed in Radiation Oncology department of Kayseri Teaching Hospital between 2005 and 2013. Patients with missing data and those lost in follow-up were excluded from analysis. The study was planned in accordance to local ethics regulations and Helsinki Declaration. We reviewed age, gender, menopausal status, family history of breast cancer, height, weight, BMI, tumor localization, tumor stage, surgery type, histopathological findings, data regarding chemotherapy and radiotherapy, and survival times. In the histopathological diagnosis, tumor type, tumor localization, tumor diameter, lymphatic metastasis, number of lymph nodes excised, number of lymph nodes with metastatic infiltration, level of estrogen and progesterone receptors, cerb-B2 status, grade, and

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lymphovascular and perineural invasion status were recorded.

Weight and height measurements were performed to determine body mass index. BMI categories were defined according to World Health Organization criteria as follows: BMI<18.5 kg/m^2 as underweight; 18.5-24.9 kg/m^2 as normal weight; 25.0-29.9 kg/m^2 as grade 1 obesity; 30.0-39.9 kg/m^2 as grade 2; and ≥40 kg/m^2 as grade 3 obesity.

Treatments

Surgery: all patients underwent abdominal sonography, mammography, complete blood count, biochemical evaluations and posterioanterior chest radiography before surgery. Fine-needle aspiration biopsy or excisional biopsy was performed to mass. After biopsy, modified radical mastectomy (MRM) and breast-conserving surgery (BCS) were performed as surgical therapy. After surgery, staging was performed based on histopathology results by using American Joint Committee on Cancer (AJCC) 2002 staging system.

Adjuvant chemotherapy: decision regarding postoperative chemotherapy and/or hormone therapy was made by considering performance status, biological age, and comorbid diseases. Chemotherapy was given to patients with tumor diameter >1 cm or axillary lymph node ≥1-positive, those with ECOG (Eastern Cooperative Oncology Group) performance status 0-2, those having no severe cardiac problem, and those with normal renal and bone marrow functions. Chemotherapy schedules included one of the following: CMF (Cyclophosphamide, Methotrexate, 5-Flurouracyl), CAF (Cyclophosphamide, Doxorubicin, 5-Flurouracyl), CEF (Cyclophosphamide, Epirubicin, 5-Flurouracyl), AC (doxorubicin, cyclophosphamide) or docetaxel.

Adjuvant radiotherapy: radiotherapy was given to the patients with tumor diameter >5 cm, insufficient lymph node dissection, axillary lymph node positivity ≥3, and those underwent BCS. Total dose was 50-60 Gy in patients underwent MRM, while 60-66 Gy in those underwent BCS. Firstly, radiotherapy was delivered to whole breast and/or peripheral lymphatics with a dose of 46-50 Gy in all patients underwent BCS. Then, additional electron doses of 10-16 Gy with appropriate energy levels were delivered to metallic clips, incision scar and excision pouch detected by sonography with a margin of 1 cm. For patients with MRM, additional doses of 10 Gy were given to cases with skin invasion and extra-capsular invasion.

Adjuvant hormone therapy: hormone therapy was given to the patients with positive estrogen and/or progesterone receptors. Tamoxifen and/or LHRH analogs were given to premenopausal patients while tamoxifen or aromatase inhibitors were given to postmenopausal patients for 5 years.

Follow-up

Follow-up visits were scheduled by 3-months interval within first year; biannually until end of year 5; and annually thereafter. Complete blood count, biochemical parameters, and Ca 15-3 and CEA levels were measured biannually, while chest radiographs, mammography, abdominal sonography and bone scintigrapy were obtained annually.

Statistical analysis

Statistical analysis was performed by using SPSS for Windows 13.0 (Statistical Package for the Social Sciences, Chicago, IL). Descriptive statistics including minimum-maximum, mean, standard deviation and percentages were used in data analysis. In comparative studies, One-Sample Kolmogorov-Smirnov test was used to evaluate normal distribution. In groups, t test was used to assess quantitative data with normal distribution while Mann Whitney U test was used to assess quantitative data with skewed distribution. Progression-free survival was defied as the time from surgery to local or distant relapse. Overall survival was defined as time from surgery to death in non-survivors and time from surgery to last control in survivors. Five- and 10-years survival rates were calculated by using survival tables. In univariate analysis, Kaplan-Meier curves were compared by using Log-Rank method. $p<0.05$ was considered as statistically significant.

Results

Overall, 43 patients were excluded from analysis due to missing data (n=30), a second primary breast cancer (n=7; 1.5%) and a secondary malignancy (n=6; 1.2%). Thus, overall 456 patients (447 women, 9 men) were included to the analysis. Mean age at presentation was 55.6 years (range: 26-88). There was family history of breast cancer in 40 (8.8%) of the cases. Of the cases, 254 (55.7%) were postmenopausal; 355 (77.6%) were younger than 65 years; 248 (54.4%) had breast cancer at the left; 205 (45.0%) had stage II disease; 92.1% had invasive ductal carcinoma; 57.4% had T2 tumor; 46.7% had grade II tumor; 58.7% were ER positive; 53.5% were PR positive; 26.5% were HER2 positive; 64.9% had perinodal invasion; and 65.4% had lymphovascular invasion. Lymph node was found to be negative in 163 (44%), while number of positive lymph nodes was 1-3 in 123 (27.7%); 4-9 in 95 (21.4%) and ≥10 in 63 (13.8%) of the patients. Mean number of lymph nodes excised was 17, while mean number of metastatic lymph nodes was 3.8. MRM was performed in 442 cases (96.9%). Of the cases, 433 (95.0%) received chemotherapy and 376 (82.4%) received radiotherapy, while 301 (60.0%) received hormone therapy. The most commonly used chemotherapy protocol was FEC (Cyclophosphamide, Epirobucin, 5-Fluorouracil) in 117 cases; followed by AC (Doxorubicin, Cyclophosphamide) in 96 cases and CAF (Cyclophosphamide, Doxorubicin, 5-Fluorouracil) in 25 cases. According to WHO body mass index classification, mean BMI was calculated as 29.0 kg/m^2 at presentation.

In cases with breast cancer, the relationship between BMI and other prognostic factors were investigated by using Pearson chi-square test. BMI was between 30.0-39.9 kg/m^2 in 192 patients, 18.5-24.9 kg/m^2 in 112 patients, and 25.0-29.9 kg/m^2 in 112 patients. BMI was higher than 25.0 kg/m^2 in 343 of 456 patients. Significant correlations were detected between BMI and menopausal status ($p=0.029$), histological type ($p<0.000$), chemotherapy

(p=0.003) and hormone therapy (p=0.014). Follow-up was ranging from 4.8 and 195 months. During follow-up, 48 patients died due to disease (n=22) or non-related causes (n=26; cardiovascular disease, senility, renal tumor, cerebrovascular disease etc.) Local recurrence or distant metastasis was detected in 72 cases. There was multiple-organ metastasis in 26 cases, bone metastasis in 24 cases, pulmonary metastasis in 10 cases and other organ metastasis in 12 cases.

Table 1 presents mean OS and PFS rates and factors affecting OS and PFS. Mean OS was 125.8 months and 5- and 10-years OS rates were calculated as 77% and 58%, respectively. Factors associated with OS were found as T size (p=0.004), lymph node metastasis (p=0.003) and BMI (p=0.008). When OS was assessed according to BMI, it was found that mean OS was 95.2 months in cases with BMI<18.5 kg/m^2, 168.8 months in cases with BMI of 18.5-24.9 kg/m^2, and <89 months in cases with BMI ≥25.0 kg/m^2. It was found that OS was worse in both underweight and obese patients (Figure 1). Mean PFS was 108.8 months and 5- and 10-years PFS rates were 65% and 49%. Univariate analysis of factors affecting PFS was

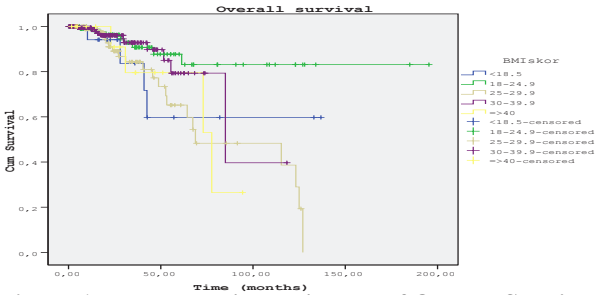

Figure 1. Kaplan-meier Estimates of Overall Survival for Obese Versus Non-obese Patients

Table 1. Results of Univariate Analyses

Variable		No. of patients	Mean OS (95% CI)		p value	Mean PFS (95% CI)		p value
Gender	Male	9	98.7	(56.7-140.7)	0.361	60.9	(22.1-99.6)	0.066
	Female	446	130.5	(112.3-125.0)		113.8	(97.5-130.0)	
Age (years)	<65	355	127.2	(106.9-147.5)	0.906	89.3	(78.2-100.5)	0.34
	≥65	101	116.6	(87.3-146.0)		101.5	(74.2-128.2)	
Menopausal status	Premenopausal	192	92.5	(76.9-108.2)	0.408	80.9	(66.1-95.7)	0.096
	Postmenopausa	254	131.6	(109.4-127)		115.0	(95.0-134.9)	
Family history of breast cancer	No	415	121.8	(103.1-140.4)	0.16	107.5	(90.8-124.2)	0.541
	Yes	40	118.8	(94.1-143.5)		95.0	(65.6-124.3)	
Tumor localization	Right	208	122.4	(99.2-145.6)	0.459	111.8	(91.6-104.8)	0.095
	Left	248	126.8	(102.4-151.2)		93.3	(81.9-104.2)	
AJCC stage	I	62	131.5	(126.8-136.2)	0.054	106.7	(85.4-128.1)	0.668
	II	205	121.9	(94.9-148.9)		84.4	(71.9-96.9)	
	III	189	111.5	(88.6-134.4)		107.9	(84.9-130.9)	
Histology type	Invasive ductal	420	126.6	(108.6-144.6)	0.354	113.2	(96.6-129.8)	0.033
	The other	36	121.3	(106.2-136.5)		77.6	(52.6-102.6)	
Tumor size	I	97	145.2	(116.0-175.7)	0.004	107.5	(92.6-122.5)	0.4
	II	257	113.6	(91.8-135.3)		105.3	(86.6-124.1)	
	III	67	105.7	(94.8-116.5)		87.4	(63.9-110.9)	
	IV	27	67.5	(36.1-98.9)		88.8	(45.9-131.7)	
Lymph node status	0	163	136.1	(104.9-167.3)	0.003	88.8	(71.6-105.1)	0.381
	I	123	112.8	(99.6-126.1)		83.4	(68.9-97.9)	
	II	95	115.3	(86.4-144.3)		117.4	(86.5-148.2)	
	III	63	72.7	(50.8-94.7)		99.5	(76.1-122.8)	
Histologic grade	I	94	135.7	(106.2-165.3)	0.224	125.2	(95.3-155.0)	0.204
	II	213	108.3	(95.1-121.4)		94.4	(80.5-108.3)	
	III	112	90.4	(72.0-108.7)		73.7	(57.1-90.3)	
	Unknown	37	77.4	(56.2-98.7)		78.2	(58.1-98.2)	
ER status	Positive	267	125.8	(101.2-150.3)	0.228	100.5	(88.5-112.6)	0.064
	Negative	176	115.6	(92.0-139.2)		98.5	(77.2-119.9)	
PR status	Negative	193	117.7	(91.0-144.5)	0.944	88.2	(75.9-100.4)	0.209
	Positive	244	127.8	(104.7-150.8)		88.5	(76.1-100.6)	
HER2	Negative	311	123.4	(104.9-142.0)	0.503	108.9	(91.1-126.7)	0.721
	Positive	121	117.5	(80.2-154.9)		80.1	(68.3-91.9)	
Perinodal involvement	No	151	139.1	(114.3-163.8)	0.218	106.4	(85.4-127.4)	0.92
	Yes	296	111.9	(90.5-133.3)		93.6	(79.9-107.3)	
Lymphovascular invasion	No	150	121.7	(85.5-157.9)	0.392	126.5	(97.7-155.3)	0.167
	Yes	298	120.7	(100.2-141.2)		86.1	(76.1-96.2)	
Surgery	Mastectomy	442	125.0	(106.8-143.2)	0.343	107.9	(92.0-123.9)	0.697
	Lumpectomy	14	101.8	(68.3-135.3)		64.0	(50.5-77.5)	
Chemotherapy	Yes	433	126.2	(107.4-145.0)	0.286	105.0	(88.7-121.4)	0.059
	No	23	102.7	(67.4-138.0)		122.7	(97.4-147.9)	
Radiotherapy	Yes	375	115.5	(98.2-132.8)	0.146	104.3	(87.5-121.1)	0.201
	No	80	156.1	(118.8-193.5)		106.6	(87.8-125.4)	
Hormon replacement therapy	Yes	301	128.1	(104.0-152.2)	0.99	115.0	(92.9-137.1)	0.079
	No	137	95.5	(81.5-109.6)		78.6	(64.7-92.5)	
BMI	<18.5	21	95.2	(67.7-127.8)	0.008	98.1	(69.1-127.1)	0.197
	18.5-24.9	112	168.8	(150.4-187.2)		128.0	(103.8-152.2)	
	25-29.9	112	83.7	(68.5-98.9)		69.7	(55.8-83.6)	
	30-39.9	192	89.0	(68.9-109.2)		91.7	(80.7-102.7)	
	≥40	19	70.5	(54.4-86.6)		68.9	(48.7-89.1)	

Table 2. Hazard Ratios of Baseline Characteristics for OS and DFS among the Breast Cancer Patients (univariate analysis)

Risk factors		Overall survival univariate analysis		Disease-free survival univariate analyis	
		OR (95% CI)	p value	OR (95% CI)	p value
Gender	Male	Ref		Ref	
	Female	0.5 (0.1-2.1)	0.369	0.4 (0.1-1.1)	0.076
Age	<65	Ref		Ref	
(years)	≥65	0.9 (0.5-1.9)	0.906	0.7 (0.4-1.3)	0.343
Menopausal status					
Premenopausal		Ref		Ref	
Postmenopausal		0.4 (0.1-1.6)	0.244	0.4 (0.1-1.1)	0.109
Family history of breast cancer					
No		Ref		Ref	
Yes		2.6 (0.6-10.9)	0.177	0.5 (0.5-3.2)	0.544
Height (cm)		0.0 (0.0-0.9)	0.048	0.4 (0.0-8.1)	0.567
Weight (kg)		0.9 (0.9-1.0)	0.853	1.0 (0.9-1.0)	0.587
Tumor localization					
Right		Ref		Ref	
Left		1.2 (0.7-2.2)	0.46	0.6 (0.4-1.0)	0.098
AJCC stage					
I		Ref		Ref	
II		0.1 (0.0-0.9)	0.046	0.7 (0.3-1.7)	0.466
III		0.7 (0.4-1.3)	0.317	1.0 (0.6-1.7)	0.777
Histology type					
Invasive ductal		Ref		Ref	
The other		1.1 (0.2-4.6)	0.875	0.6 (0.2-1.5)	0.273
Tumor size					
I		Ref		Ref	
II		0.1 (0.0-0.4)	0.001	0.5 (0.2-1.7)	0.294
III		0.3 (0.1-0.7)	0.012	0.9 (0.3-2.6)	0.903
IV		0.3 (0.0-1.0)	0.062	0.8 (0.2-2.6)	0.688
Lymph node status					
0		Ref		Ref	
I		0.3 (0.1-0.7)	0.006	0.9 (0.4-2.3)	0.986
II		0.2 (0.0-0.5)	0.002	1.5 (0.6-3.5)	0.287
III		0.4 (0.2-1.0)	0.057	1.0 (0.4-2.6)	0.84
Number of lymph nodes excised		0.9 (0.9-1.0)	0.526	1.0 (0.9-1.0)	0.537
Metastatic lymph nodes		1.0 (0.9-1.0)	0.863	1.0 (0.9-1.0)	0.577
Histologic grade					
I		Ref		Ref	
II		0.6 (0.2-1.8)	0.123	0.7 (0.2-2.1)	0.586
III		0.4 (0.1-1.2)	0.793	0.9 (0.3-3.8)	0.882
ER status	Positive	Ref		Ref	
	Negative	1.2 (0.3-3.2)	0.388	1.6 (0.2-3.9)	0.916
PR status	Negative	Ref		Ref	
	Positive	1.5 (0.4-5.2)	0.488	3.3 (0.7-14.2)	0.103
HER2	Negative	Ref		Ref	
	Positive	2.0 (0.4-9.0)	0.347	1.5 (0.4-5.3)	0.476
Perinodal involvement					
No		Ref		Ref	
Yes		0.6 (0.3-1.2)	0.22	1.9 (1.1-3.4)	0.018
Lymphovascular invasion					
No		Ref		Ref	
Yes		0.5 (0.0-4.3)	0.608	0.6 (0.0-4.8)	0.662
Surgery					
Mastectomy		Ref		Ref	
Lumpectomy		2.5 (0.3-18.3)	0.36	1.3 (0.3-5.4)	0.698
Chemotherapy	Yes	Ref		Ref	
	No	0.9 (0.3-2.5)	0.886	5.4 (0.7-39.0)	0.094
Radiotherapy	Yes	Ref		Ref	
	No	0.1 (0.1-1.3)	0.155	0.6 (0.2-1.3)	0.604
Hormonotherapy	Yes	Ref		Ref	
	No	0.9 (0.5-1.8)	0.99	0.6 (0.4-1.0)	0.081
Body mass index (kg/m^2)					
<18.5		Ref		Ref	
18.5-24.9		0.7 (0.1-2.6)	0.553	1.0 (0.2-3.8)	0.99
25-29.9		0.2 (0.0-0.8)	0.03	0.6 (0.2-1.8)	0.417
30-39.9		0.9 (0.3-2.8)	0.967	1.2 (0.4-3.4)	0.725
≥40		0.4 (0.1-1.3)	0.157	0.6 (0.2-1.9)	0.48
BMI (kg/m^2)		1.0 (0.9-1.0)	0.259	1.0 (0.9-1.0)	0.368

Table 3. Overall Survival Multivariate Analysis

Risk factors		Overall survival multivariate analysis	
		OR (95% CI)	p value
AJCC stage	I	Ref	
	II	0.8 (0.0-9.5)	0.871
	III	3.8 (1.1-13.0)	0.032
Tumor size	I	Ref	
	II	0.0 (0.0-0.3)	0.000
	III	0.0 (0.0-0.3)	0.000
	IV	0.0 (0.0-0.3)	0.000
Lymph node status	0	Ref	
	I	0.1 (0.0-0.5)	0.005
	II	0.0 (0.0-0.2)	0.000
	III	0.0 (0.3-0.8)	0.016
Body mass index (kg/m^2)	<18.5	Ref	
	18.5-24.9	0.4 (0.0-2.7)	0.388
	25-29.9	0.2 (0.0-0.8)	0.027
	30-39.9	1.1 (0.3-3.8)	0.878
	≥40	0.4 (0.0-1.3)	0.135

performed by using Kaplan-Meier Log-Rank methods. Prognostic factor associated with PFS was histological type (p=0.033). Both OS and PFS were found to be better in female patients, postmenopausal patients, those without family history of breast cancer, those with early disease, those with invasive ductal carcinoma, those without lymph node metastasis, those with smaller tumor diameter, those with grade 1 disease, those with positive ER, those without perinodal and lymphovascular invasion, those receiving chemotherapy and hormone therapy, but the difference didn't reach statistical significance.

Table 2 and 3 present results of univariate and multivariate analysis for OS and PFS according to risk factors. In univariate analysis, factors including height (p=0.048), stage (p=0.046), tumor diameter (p=0.001), lymph node metastasis (p=0.006) and BMI (p=0.030) were found to be significantly associated with OS. In multivariate analysis, stage (p=0.032; OR: 3.8; 95% CI: 1.1-13), tumor diameter (p<0.000; OR: 0.0; 95% CI: 0.0-0.3), lymph node metastasis (p=0.005; OR: 0.0; 95% CI: 0.0-0.5) and BMI (p=0.027; OR: 0.02; 95% CI: 0.0-0.8) remained to be significantly associated with OS. In univariate and multivariate analysis, perinodal involvement was the only factor that was significantly associated with PFS (p=0.018).

Discussion

Up to date, although many studies have been conducted about relationship between breast cancer and obesity, and many proposals have been made, it has been failed to establish that obesity plays a role as a primary etiological factor. However, some suggestive evidence has been revealed as a result of these intensive investigations. Although an increased risk by increasing body weight has been reported in preliminary studies investigating relationship between body weight and breast cancer, it was emphasized that further comprehensive studies are needed to draw conclusion about this finding in the recent studies. In terms of breast cancer, it was shown that low body weight increases risk during premenopausal period, while increased body weight increases risk during postmenopausal period. As a result, investigators began to evaluate prognostic value of obesity in breast cancer,

since available studies suggested a small but significant relationship between obesity and risk for breast cancer. (Petrelli et al., 2002; Sestak et al., 2010; Klimant et al., 2011; Suleeporn et al. 2013).

In our study, significant correlations were detected between BMI and menopausal status, histological type, chemotherapy and hormone therapy. It has been thought that many metabolic and hormonal pathways are involved in the relationship between obesity and prognosis. In premenopausal women, the estradiol is the predominant estrogen, while, in postmenopausal women, estrone is main estrogen source, which is produced from androstenedion through aromatization in the presence of aromatase enzyme in fat tissue. It is thought that increased serum estrogen play role in induction and progression of breast cancer by increasing frequency of DNA mutations via stimulation of cell division and triggering growth of estrogen-dependent tumors. In addition, levels of sex-hormone binding globulin are also decreased in these patients. Given that obesity may be a component of metabolic syndrome causing insulin resistance, hyperinsulinemia developed in obesity may lead poorer prognosis in patients with breast cancer through insulin-like growth factor-1 (IGF-1) (Petrelli et al., 2002; Protani et al., 2010; Goodwin 2013; Suleeporn et al. 2013). In recent studies, a negative correlation was detected between obesity and survival in patients diagnosed as early stage breast cancer. There is substantial evidence suggesting that higher BMI (>25 kg/m^2) is associated with worse outcome in patients with breast cancer. This is also true for specific subgroups including women with locally advanced breast cancer and postmenopausal women. Although there is controversy in literature, it was reported that hormone therapy was less effective in women with higher BMI. There are several randomized studies comparing AIs and tamoxifen in adjuvant treatment of breast cancer effects of BMI on relative effectiveness of AI and tamoxifen were reported in four of these studies (ATAC, BIG 1-98 and TEAM in the postmenopausal setting and ABCSG-12 in the premenopausal setting). ATAC and BIG 1-98 but not TEAM study confirmed obesity as a negative prognostic factor; in addition, obesity was associated with poor outcomes in anastrozole arm in ABSCG-12 study (Sestak et al., 2010; Ewertz et al., 2011; Goodwin 2013). In a study on 4996 patients with node-positive breast cancer, Ladoire et al. reported that endocrine treatment didn't modified effect of obesity on tumor prognosis (Ladoire et al., 2014). In a study by Griggs et al., it was reported that obese patients were more likely to receive reduced doses of chemotherapy compared to normal weight women, which was associated with poor prognosis (Griggs et al., 2005). In the study by Ladoire et al., it was reported that obesity remained to be associated with poorer baseline tumor characteristics but had no effect on the prognosis when modern adjuvant chemotherapy was delivered at appropriate doses (Ladoire et al., 2014).

In our study, 343 of 456 patients were in obesity group with a BMI >25 kg/m^2. It was found that OS was significantly higher in the group with normal BMI when compared to those in the underweight and obese patient groups. It was found that the factors significantly associated with OS were stage, tumor diameter, lymph node metastasis and BMI. In many studies, there are strong evidence suggesting that disease-free and overall survival times were significantly decreased by increasing BMI. These findings were attempted to be explained by different risk factors (de Azambuja et al., 2010; Protani et al., 2010; Ewertz et al., 2011; Alegre et al., 2013; Ladoire et al., 2014). In the study, de Azambuja et al. (2010) retrospectively evaluated 2887 patients with node-positive breast cancer who were enrolled to Breast International Group (BIG) 02-98 study. Authors reported that obesity is a negative prognostic factor affecting both PFS and OS (de Azambuja et al., 2010). Again, in the study by Petrelli et al., it was reported that mortality was higher in morbid obese postmenopausal women with breast cancer compared to those with normal BMI. In a study on 605 patients with breast cancer, disease-free and overall survivals were found to be shorter in underweight patients when compared to other groups (Petrelli et al., 2002). In a meta-analysis by Ryu et al., it was found that obesity at diagnosis was associated with poorer prognosis (Ryu et al., 2001). In contrast, some studies suggested that BMI had no effect of DFS but it had significant negative effect on OS. In a study on 6972 patients with early stage breast cancer, Berclaz et al. investigated effect of BMI on survival. Authors combined normal and underweight groups because of smaller sample size. In conclusion, they reported that OS was found to be higher in patients with normal BMI when compared to overweight or obese patients (p=0.03), whereas BMI had no effect on PFS (Berclaz et al., 2004). In a study on 418 patients with triple-negative breast cancer, Ademuyiwa et al. reported that BMI had no effect on either OS or PFS (Ademuyiwa et al., 2011). Our results were in agreement with those of Marret et al., Berclaz et al., and Petrelli et al. regarding overall survival. In our study, smaller sample size, genetic characteristics of patient population and potential body weight changes during follow-up can explain our results regarding PFS. In future, interactions of BMI with other prognostic factors such as blood parameters, clinical factors and receptor levels need to be established (Elgin et al., 2013; Olmez et al., 2013; Tanriverdi et al., 2014).

In conclusion, in our study, it was found that overall survival was shorter in patients with BMI<18.5 kg/m^2 or >25.0 kg/m^2 when compared to other patient groups. In addition, it was also found that progression-free survival was shorter but the difference didn't reach statistical significance. We think that this finding could be due to small sample size. These findings should be further tested in comprehensive studies.

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