The Role of Body Mass Index in Triple Negative Breast Cancer

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Introduction

With the aid of new molecular techniques, breast cancer is now been classified into 4 major molecular subtypes based on the expression of receptors for estrogen (ER), progesterone (PR), and human epidermal growth factor (HER-2) and ki-67 staining. Among these subtypes, triple-negative breast cancer (TNBC) refers to a subgroup of patients with no expression of ER, PR or HER-2, and accounts for 10–20% of all newly diagnosed breast cancer cases [1]. TNBC differs from the other subgroups on that it lacks a well-defined therapeutic target, and the primary therapy therefore consists of systemic chemotherapy.

Strategies aimed at defining the risk factors in breast cancer suggested a role for obesity in breast cancer development. Follow-up studies also indicated a negative impact of obesity on breast cancer survival [2, 3]. Higher body mass index (BMI) was shown to be a negative prognostic feature in early breast cancer patients [4], node-positive patients [5] and also among younger women [6, 7].

Although obesity and lack of hormone receptors are known as distinctive unfavorable prognostic factors in breast cancer, there are only limited data on how obesity interacts with prognosis of non-luminal tumors [8, 9]. TNBC is an aggressive subtype of breast cancer with higher local and distant recurrence rates and shorter survival, and, in this study, we evaluated the impact of obesity on clinical outcomes of patients with this form of cancer.

Materials and Methods

We reviewed the clinicopathological data from medical records of 2,900 breast cancer patients who were admitted to Ege University Medical Oncology Clinic between December 2005 and December 2010. The clinicopathological features of tumors (size, histopathological subtype, axillary lymph node in-
volvement, immunohistochemical analysis of ER, PR and HER-2, Ki-67 index and p53 status) as well as socio-demographic data of patients were recorded. Surrogate definitions suggested by the 2013 St Gallen International Consensus Conference and European Society of Medical Oncology guidelines were used to determine TNBC subtype [10].

Female TNBC patients who had completed an adjuvant chemotherapy schedule and follow-up at Ege University Medical Oncology were included in the study. TNBC patients who were referred for a second opinion, and had completed a chemotherapy schedule outside our clinic, were excluded from the study. We enrolled 112 TNBC patients. Weight at the time of the diagnosis and height of these patients were recorded, and BMIs were calculated using the formula: weight (kg)/(height (m))^2. The patients were classified into 1 of 3 groups according to their BMI value: < 25 (normal/underweight); 25.0–29.9 (overweight); or ≥ 30 (obese).

Menopausal status at the time of diagnosis was also recorded; 8 perimenopausal patients were classified into the postmenopausal group. 14 patients had an unknown menopausal status, 4 of whom were older than 50 years and were classified as postmenopausal.

Overall survival (OS) was defined as the time from pathological diagnosis to death or to the last follow-up, and was calculated for all patients (n = 112). Patients were diagnosed between November 2004 and December 2009. Disease-free survival (DFS) was defined as the time from pathological diagnosis to the first recurrence or metastasis and was evaluated for 109 patients. 3 patients had metastasis at initial diagnosis and were excluded from the DFS analysis. The last follow-up controls were performed between June 2011 and February 2012, either during their routine clinic visit or by the telephone.

### Statistical Analysis

Statistical analyses were performed using PASW Statistics. A 2-sided p value below 0.05 was considered significant. Mean values are expressed as mean ± standard deviation. The categorical variables of the BMI groups were compared using the χ² test. The mean ages of 3 subgroups were compared using a 1-way ANOVA, and the mean tumor size, Ki-67 and p53 were compared using a Kruskal-Wallis test. Spearman and Pearson coefficients were calculated to evaluate correlations between various numeric parameters. Survivals were analyzed using the Kaplan-Meier method. A log rank (Mantel-Cox) test was applied to evaluate differences in survival between the BMI groups. As menopausal status significantly differed among the groups, a Cox proportional hazard model was applied to adjust for a possible confounding by menopausal status. The Kaplan-Meier estimated mean OS and DFS are presented with their 95% confidence intervals (CIs).

### Results

Among the 2,900 assessed patients, 112 (3.9%) were diagnosed with TNBC based on ER, PR and HER2 status. Of these, 30 (26.8%) were normal/underweight, 30 (26.8%) were overweight and 52 (46.4%) were obese at the time of diagnosis. The distribution of patient characteristics overall, and according to BMI categories are shown in table 1.
The mean age of patients was 50.4 ± 10.6 years; patients in the obese group were older than the others (p = 0.015). At the baseline, 59 patients (60.8%) were at the postmenopausal stage. 44 patients (39.28%) had received breast-conserving surgery, and 62 (55.35%) had modified radical mastectomy. 8 patients (7.14%) had received neoadjuvant, and 102 (91.0%) adjuvant chemotherapy. No treatment data was recorded for the remaining 2 patients. Adjuvant radiotherapy was performed in 66 patients (58.9%) for local control. There were no statistically significant differences in tumor size, histopathological subtype, Ki-67 index, p53 status and axillary lymph node involvement between the 3 subgroups (normal, overweight and obese). The mean BMI of premenopausal patients was significantly lower than that of the postmenopausal women (27.1 ± 5.6 vs. 30.3 ± 6.1, p = 0.014). The mean follow-up period was 29.4 ± 17.4 months. Only 2 patients (1.78%) had metastasis at the time of initial diagnosis. During the follow-up, 12 recurrences (10.71%) and 6 deaths (5.35%) were recorded. The mean OS for all patients was estimated as 72.4 (95% CI 67.9–76.9) months. The mean DFS of the 109 initially metastasis-free patients was estimated as 68.0 (95% CI 62.8–73.1) months. In the survival analysis for all patients, no significant differences were determined in OS or DFS between the 3 BMI groups (figs. 1 and 2) (log rank p = 0.304 and 0.160, respectively). When DFS analysis was adjusted for menopausal status, the p value of the overall Cox model was 0.486, and the survival curves are presented in figure 3.

Discussion

Obesity is known to increase the risk of breast cancer [11–13] and affects the prognosis unfavorably. The precise mechanism of the effect of obesity in breast cancer has not yet been clearly elucidated. The most well-known hypothesis was defined for postmenopausal hormone receptor-positive breast cancer, and involves an increased peripheral aromatization of androgens to estrogen in peripheral fat tissue due to obesity [14]. This leads to higher free estradiol levels in the circulation, and production of growth-enhancing factors in cancer cells. However, this hypothesis does not explain the role of obesity in the premenopausal state and hormone receptor-negative tumors.

A number of studies evaluating the role of obesity in breast cancer survival demonstrated that obese patients were more likely to be older and also, they tended to have larger tumors with more
advanced stages of disease with higher frequency of lymph node involvement, when compared with non-obese patients regardless of the hormonal status [4, 5, 7, 15]. The majority of these analyses did not evaluate the receptor status in these patient groups.

One of the largest study with ER- and lymph node-negative breast cancer patients was the NSABP-14 trial [9], and confirmed that the risk of contralateral breast cancer and overall mortality (although not necessarily breast cancer-related mortality) were increased in the obese patients. In addition, the subgroup analysis of the BIG 02–98 trial also showed that obese patients appeared to have worse outcomes if they had at least 1 hormone receptor negativity [5]. Both the study and the meta-analysis data performed by Protani et al. [16] had insufficient information about HER2 status to draw conclusions for the TNBC status.

Only limited data are available for evaluating the role of obesity in TNBC patients [17, 18]. Dawood et al. [17] investigated the impact of obesity in 2,311 TNBC patients and were not able to determine any relationship between BMI and survival. However, in a pooled analysis of neoadjuvant trials, it was determined that a higher BMI was associated with lower pathological complete response (pCR), and that there was a detrimental effect on the survival with shorter DFS in obese TNBC patients compared to their non-obese counterparts [19].

In our study, no statistically significant survival difference was detected between the BMI subgroups. To rule out the effects of other prognostic factors on the survival analyses, we compared tumor size, lymph node involvement, and Ki-67 index in the 3 subgroups, and showed that there was no difference regarding these factors. Women with a BMI of 30 were more likely to be older (p = 0.015), and this was also consistent with the previous studies [8, 17]. When the models were stratified by menopausal status, similar results were obtained and these results were consistent with a previous study [17].

The main limitation of our study is that our study group is rather small for accurately defining an impact of BMI on TNBC, but it may help to illuminate this topic to some extent. As we had only 2 (1.78%) patients with metastases at diagnosis, we could not perform any further analysis in advanced stage disease. Moreover, TNBC patients could not be further separated into other subgroups due to lack of basal markers.

In conclusion, we believe that obesity does not have a prognostic role in TNBC. The present data are inadequate for determining the role of obesity in TNBC, although there is clearer proof for hormone receptor-positive tumors. Until larger studies are performed to clarify the role of obesity in breast cancer development, it would be appropriate to advise patients to maintain a healthy weight to minimize any negative impacts of obesity on their disease control.

Disclosure Statement

The authors declare that they have no conflict of interest.

References
