Morbid Obesity Does Not Disadvantage Patients with *In Situ* or Early-stage Carcinoma Undergoing Breast-conserving Surgery

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Abstract. *Aim: To determine whether morbidly obese (MO) patients with early-stage breast cancer (BCa) benefit from standard-of-care interventions. Patients and Methods: Between 1992 and 2005, 100 patients underwent breast-conserving surgery and postoperative whole-breast irradiation of 50 Gy for minimally invasive BCa with tumor-free surgical margins. Twenty-seven MO women were compared to 73 non-morbidly obese (NMO) patients. Results: At 10 years, the cumulative disease-free survival rate for the NMO patients was 91% compared to the non-statistically significant lower rate of 89% in the MO women (p=0.66). Patients who were excessively obese were not at an increased risk for local (p=0.99) or regional disease recurrence (p=0.29). Conclusion: The results suggest that patients with minimally invasive BCa and excessively large body habitus should not be disqualified from receiving breast-conserving therapy.*

Obese women with breast cancer (BCa) have a poorer survival than women with BCa who are not obese (1). The poorer prognosis in obese patients with BCa has been attributed to more advanced stage of disease, larger tumors, and often nodal metastatic involvement, at diagnosis (2). Obese patients with large fatty breasts and early-stage BCa are thought to be more appropriately managed by breast-conserving treatment (BCT) because a unilateral mastectomy can cause an unacceptable degree of asymmetry that will make prosthesis fitting very difficult, and could result in a substantial imbalance, adversely affecting the quality of life (3). The oncological outcomes of morbidly obese (MO) women with early BCa have not been clearly described in the literature. We hypothesized that these individuals have a worse prognosis after BCT for pre-invasive or early-stage BCa than their non-morbidly obese (NMO) counterparts.

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Patients and Methods

Between October 1992 and October 2005, 100 patients met the inclusion criteria for the retrospective study because they had a documented diagnosis of carcinoma in situ or early-stage BCa with tumor-free surgical margins; they were treated by breast- conserving surgery and irradiation, and had available post-treatment follow-up information. Exclusion criteria included: individuals with stage III or IV BCa, who were lost to follow-up, were treated elsewhere, or did not complete the prescribed radiotherapy course.

After obtaining approval from the Institutional Review Board (#H11-078), demographic and tumor-specific data; height and weight; age at diagnosis; estrogen, progesterone, human epidermal growth factor receptor-2/*neu*/*c-erb-2* receptor status; grade of BCa; and the presence or absence of significant coexisting illness were collected and reviewed. Morbid obesity was defined as a body mass index (BMI) of ≥35 kg/m^2 (4). Twenty-seven MO women were compared against a cohort of 73 NMO patients with a BMI of <35 kg/m^2.

Following breast-conserving surgery, fractionated whole-breast irradiation (WBI) to a total dose of 50 Gy given in 25 fractions was administered using two tangential megavoltage 6 MV photon beams (5); the computer-generated treatment plan was designed to deliver a homogenous dose to the breast with ≤15% maximum variation in dose. Adjuvant chemotherapy (primarily four cycles of doxorubicin and cyclophosphamide with or without four cycles of paclitaxel) was administered to 53 patients prior to WBI. Chemotherapy dosage was calculated based on actual body surface area without dosage adjustment for obesity. All 36 patients with estrogen- and/or progesterone receptor-positive tumors began adjuvant hormone manipulation therapy after irradiation.

All analyses were performed using SAS software for statistical computing (SAS version 9.2, SAS Institute Inc., Cary, NC, USA). Cohort outcomes were in terms of local and regional recurrence rates, as well as overall and disease-free survival rates. Survival rates were estimated using the Kaplan Meier method and compared by the log-rank test. Statistical significance was defined as a value of $p \leq 0.05$. Cox proportional hazards regression analysis was used to examine factors that impact on overall and disease-free survival.

Variables included in the model were age, tumor differentiation and receptor status, the presence of comorbidity, and the application of chemotherapy/hormonal therapy. BMI was analyzed as a continuous variable in the Cox model.

Results

The mean age at the time of diagnosis was 58.5 years (range=28-80 years). Twenty-four patients were 45 years old or younger, and 76 women were older than 45 years. Breast cancer histologies, aside from intraductal carcinoma (88 patients), included invasive lobular carcinoma (three patients); medullary, micropapillary, mucinous or tubular carcinoma (seven patients) and invasive intraductal mixed with lobular invasive carcinoma (two patients). Stratification by age, tumor receptor status (estrogen, progesterone and *HER-2* neu) and grade, as well as the presence of comorbidity showed no distinct dissimilarities between the compared groups (Table I). The median follow-up was 96 months (range=17-215 months). The local and regional recurrence rates were comparable between the MO and NMO groups (p=0.99 and p=0.29 respectively). Although the overall survival rates favored the NMO patients over the MO women (p=0.02), there was no meaningful difference in disease-free survival rates between the groups (p=0.66). Stepwise selection into the Cox model failed to reveal a single predominant factor predictive of prognosis. Because of limited information, acute toxicity, complications, and cosmesis were not evaluated.

Table I. *Distribution of patient characteristics and oncologic outcomes according to Body Mass Index (BMI).*

Feature	BMI ≥35 kg/m^2 (n=27)	BMI <35 kg/m^2 (n=73)	p-Value
Elderly (≥65 years patients)	(24)* 89%	(52) 71%	0.07
Tumor receptors			
Estrogen-positive	(14) 56%	(30) 48%	0.052
Progesterone-positive	(13) 52%	(29) 47%	0.66
HER-2 neu-positive	(8) 40%	(11) 22%	0.14
High grade tumor**	(8) 40%	(19) 30%	0.47
Comorbidity present***	(20) 74%	(49) 67%	0.50
Local recurrence rate	4%	4%	0.99
Regional recurrence rate	8%	3%	0.29
10-Year overall survival rate	79%	95%	0.02
10-Year disease-free survival rate	89%	91%	0.66

*Evaluable patients; **high-grade/grade 3 tumor according to the Scarff-Bloom-Richardson system; ***coronary artery disease, hypertension, congestive heart failure, diabetes mellitus, non-Hodgkin's lymphoma, vulvar cancer, multiple sclerosis, myasthenia gravis or hypothyroidism.

Discussion

In our study of over a period of 13 years, we found that MO women did not experience a greater incidence of locoregional tumor recurrence nor poorer long-term survival when compared to their NMO counterparts.

To date, there are limited information about the oncological adequacy of BCT with long-term follow-up in MO patients with early BCa. In order to better understand the association of body weight and death from the disease, Enger and colleagues observed that women who were heavier had a 2.5-fold increased risk of dying from BCa compared to the less heavy patients; their investigation involved body weight (not BMI), 1,555 women with stage I and IIA disease, and a median follow-up of 6.8 years (6). Since an apparent poorer prognosis in obese individuals with BCa has been ascribed to the presence of more advanced neoplastic disease, Dignam *et al*. specifically examined 432 MO patients out of 4,677 patients with node-negative BCa – a clinical situation with a lesser effect of disease stage (4). The analyzed findings were: A 30% greater mortality hazard for the MO group compared to the women with normal weight (p=0.004); although deaths followed the appearance of tumor relapse in most cases, a greater BMI was not generally related to an increased risk of recurrent tumor. Ewertz *et al*., with their objective of characterizing the impact of obesity on the risk of BCa recurrence and death from the disease and other causes, retrospectively studied 18,967 Danish female participants in the adjunctive treatment trials for early-stage BCa with BMIs of <25 kg/m^2, 25-29 kg/m^2 and ≥30 kg/m^2 (2). Observations from the investigation included: The lack of association between BMI and the 10-year cumulative risk of locoregional recurrence; after adjusting the data for disease characteristics, the risk of developing distant metastasis after 30 years was significantly increased by 46% and also the risk of dying from BCa significantly increased by 38% for patients with a BMI of ≥30 kg/m^2. Certainly with the preceding considerations, it is not altogether possible to carry out meaningful comparisons of the published data to our observations about MO and NMO with pre-invasive and early-stage BCa.

It is true that our retrospective study, with its sample size, restricts generalization of the findings; other shortcomings of this study are the non-identification of other potential prognostic confounding factors and incompleteness of the case notes in some cases. Nonetheless, we believe that morbid obesity cannot be used to predict an ominous outcome.

In conclusion, we focused on the outcome after BCT for a subset of MO women with early BCa, and failed to demonstrate a distinctly adverse prognosis in this select patient group. Based on this study, morbid obesity should not be a contraindication for breast-conserving surgery and irradiation in these particular patients.

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