



The impact of obesity on treatment choices and outcomes in operable breast cancer



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ABSTRACT

Introduction: Obesity has been associated with negative oncologic outcomes in breast cancer.

Methods: Retrospective review of patients with operable breast cancer at a single institution from 2009 to 2012. Patients with carcinoma in situ or metastatic disease were excluded. Variables included utilization of MRI, surgical treatment, perioperative, and long-term oncologic outcomes. Primary outcome was rate of breast conserving surgery. Secondary outcomes included MRI utilization, contralateral prophylactic mastectomy, and perioperative outcomes.

Results: There were 1566 patients included for the study, 596 (38%) of whom were obese. MRI was utilized less in obese patients (62.4% vs 51.2%, $p < 0.001$). Breast conserving surgery was more common in obese patients (53.1% vs 59.7%, $p 0.010$). There was no difference in performance of contralateral prophylactic mastectomy or post-mastectomy reconstruction. Perioperative outcomes were inferior in obese patients including increased surgical site infections (5.7% vs 11.7%, $p < 0.001$), return to the emergency department (2.5% vs 5.2%, $p 0.004$), and hospital readmissions (1.8% vs 3.7%, $p 0.017$). No difference in survival was observed.

Conclusion: Obese patients with operable breast cancer receive different treatment than non-obese patients, however survival and recurrence outcomes were similar among the two groups.

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Background

Breast cancer is the most common cancer in the United States with approximately 12.4% of US women being diagnosed during their lifetime.¹ Obesity has been linked to an increased risk of developing hormone-receptor positive breast tumors with some studies demonstrating up to a 52% increase in the risk of developing hormone receptor positive breast cancers in post-menopausal women with obesity. The increased risk in post-menopausal obese women is thought to be due to increased levels of aromatase in adipose tissue leading to higher circulating estradiol levels.²

In addition to increasing the risk of developing breast cancer, a meta-analysis looking at more than 80 studies demonstrated that obesity has been linked to an increased risk of all-cause mortality

and breast cancer-specific mortality. The increased risk was similar in both pre- and post-menopausal women in this analysis.³ However, obesity has been most consistently linked to an inferior disease-free survival rate and overall survival rate in patients with hormone receptor positive, HER-2 Neu negative disease.⁴

Obesity is linked to higher rates of complications after surgical treatment of breast cancer and elective breast surgery. Higher rates of surgical site infections, lymphedema, seroma and increased length of stay are a few of these complications.⁵ One study looking at the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database for patients undergoing unilateral mastectomy without reconstruction found that increasing BMI through the three classes of obesity (Class I with BMI 30–34.9, Class II with BMI 35–39.9 and Class III > 40) had an increased risk of both minor and major complications which progressively increased with each level of obesity.⁵ In another study utilizing the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database for patients

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undergoing breast reconstruction with either autologous or implant-based reconstruction, patients with obesity were shown to have a significantly increased rate of wound complications, medical complications, and higher rate of graft or flap loss when compared to normal weight patients⁶

Given these findings of increased risks of both the development of breast cancer in obese women as well as the impact of obesity on survival and post-operative complications, our goal was to determine if treatment choices varied between normal weight and obese women. We secondarily examined perioperative and long-term oncologic outcomes in our patient population to evaluate if there was any correlation with obesity.

Materials and methods

The study was conducted as a retrospective review of consecutive patients with invasive breast cancer diagnosed between 2009 and 2012. This was conducted within a single institution, Spectrum Health, at the Butterworth and Blodgett Campuses. The study obtained approval from the Institutional Review Board with a waiver of informed consent.

Identification of patients

Patients were identified from a query of the medical record based on ICD-9 diagnosis codes for breast cancer. All patients received surgical therapy at our institution. Charts were reviewed to ensure patients had operable disease, and those with metastatic disease were excluded. Patients with ductal carcinoma in situ were also excluded.

Data collection and variable definitions

Patient data were gathered from chart review starting from time of diagnosis to death or date of last follow-up. Co-morbid conditions of interest included hypertension, diabetes mellitus (DM), hyperlipidemia, and hypothyroidism. Body mass index (BMI) was calculated by the equation $BMI = kg/m^2$ using height and weight measurements at the time of surgical consultation. Obesity was defined as a BMI greater than or equal to $30 kg/m^2$. Utilization of magnetic resonance imaging (MRI) was recorded if performed within 90 days of the start of breast cancer treatment. Surgical procedures were defined by the intention-to-treat principle with the first surgical approach being listed as the treatment of record. Patients who underwent mastectomy were divided into unilateral and bilateral groups. For patients who underwent bilateral mastectomy the reason for contralateral surgery was recorded including for synchronous cancer or prophylaxis. Those who received bilateral mastectomy for synchronous cancer were excluded from analyses of contralateral prophylactic mastectomy. Pathologic data were gathered including margin width with a “close” margin defined as $<2 mm$ from ink. Estrogen and progesterone receptor positivity was defined as expression $\geq 2\%$. The American Joint Committee on Cancer Staging Manual, 7th ed, was used for staging purposes. Postoperative outcomes including surgical site infection, hematoma, readmission, and return to the emergency department were all limited to 30 days from the date of surgery.

Statistical analysis

The primary outcome of interest was the rate of breast conserving surgery. Secondary outcomes included rate of MRI utilization, contralateral prophylactic mastectomy, postoperative

morbidity and readmission, and overall/recurrence-free survival. Patients were analyzed in two groups as obese and non-obese. Univariate comparisons were made using the Mann-Whitney *U* test for continuous data and chi-square or Fisher's exact test for categorical data, as appropriate based on distributions. Multivariate analysis of surgical complications was performed using a model consisting of age, co-morbid conditions, and BMI. A multivariate analysis was performed to analyze survival by creating a Cox Proportional Hazards model which included age, race, grade, estrogen receptor expression, HER2/neu staining, AJCC stage, and BMI. Statistical analysis was completed using SPSS v21.0.0.0 (Armonk, NY).

Results

Demographics

There were 1566 patients included for study, of which 596 (38%) were obese. The groups were equivalent for nulliparity, tumor histology, grade, nodal disease, lymphovascular invasion, and hormone receptor status. Obese patients were older with a higher incidence of comorbidities including hypertension, DM, hyperlipidemia and hypothyroidism. Obese patients were also more likely to present with stage II breast cancer. Please see [Table 1](#) for further information on demographics and tumor characteristics.

Obesity and clinical management

MRI was utilized less frequently in obese patients, with 62% of normal weight and only 51% of obese patients receiving MRI as part of their pre-operative work-up ($p < 0.001$). Breast conserving surgery was performed more frequently in obese patients with 60% of obese patients undergoing lumpectomy in comparison to only 53% of normal weight patients ($p = 0.010$). This observation was maintained across T stage groups including T1 (69% vs 61%, $p = 0.014$) and T2 tumors (47% vs 36%, $p = 0.038$). For patients undergoing mastectomy, 415 (60%) received reconstruction. Of these patients, 372 (90%) received immediate reconstruction while 43 (10%) had reconstruction performed in delayed fashion. There was no significant difference in the rate of post-mastectomy reconstruction between groups (57% obese vs 61% non-obese, $p = 0.305$). The rate of contralateral prophylactic mastectomy for those without bilateral breast cancer was 39% and also did not differ between groups (36% obese vs 41% non-obese, $p = 0.219$).

Obesity and postoperative outcomes

Obese patients were less likely to close or positive margins after resection ($p = 0.002$). There was a trend toward decrease rate of margin re-excision for obese patients who underwent lumpectomy (25% vs 30%, $p = 0.139$). Obese patients had a higher incidence of surgical site infections (12% vs 6%, $p < 0.001$). This observation was noted for both lumpectomy (9% vs 3%, $p < 0.001$) and mastectomy patients (16% vs 9%, $p = 0.005$). The rate of return to the emergency department after discharge (5% vs 3%, $p = 0.004$), and increased hospital readmission within 30 days of surgery (4% vs 2%, $p = 0.017$) was noted for obese patients. On multivariate analysis obesity remained an independent predictor of SSI (OR 2.1, 95% CI 1.4–3.0), return to the ED after discharge (OR 2.2, 95% CI 1.3–3.7), and hospital readmission (OR 2.1, 95% CI 1.1–4.0).

Obesity and oncologic outcomes

The median follow-up for the entire cohort was 84 months. The 5-year overall and recurrence-free survival were 88% and 90% for

Table 1
Demographics, major co-morbidities, tumor characteristics, and complication rates among non-obese and obese women in our study population.

Variables		Normal weight (n = 970)	Obese (n = 596)	P value
Age (median:IQR)		60 (22)	62 (16)	0.017
Race				0.016
	Asian-PI	7 (0.7%)	0 (0%)	
	Black	31 (3.2%)	35 (5.9%)	
	Hispanic	15 (1.5%)	13 (2.2%)	
	White	911 (93.9%)	546 (91.6%)	
	Other	6 (0.7%)	2 (0.4%)	
Family history of breast cancer		395 (41.4%)	238 (41.0%)	0.900
HTN		365 (37.7%)	352 (59.2%)	<0.001
Diabetes mellitus		78 (8.1%)	132 (22.2%)	<0.001
Hyperlipidemia		283 (29.2%)	247 (41.5%)	<0.001
Hypothyroidism		131 (13.5%)	112 (18.8%)	0.005
Nulliparous		99 (10.5%)	51 (8.7%)	0.260
MRI		605 (62.4%)	305 (51.2%)	<0.001
Surgery type				0.010
	Lumpectomy	515 (53.1%)	356 (59.7%)	
	Mastectomy	455 (46.9%)	240 (40.3%)	
CPM		178/433 (41.1%)	81/224 (36.2%)	0.219
Reconstruction		278/455 (61.1%)	137/240 (57.1%)	0.305
Tumor size (median:IQR)		1.5 ¹	1.5 ²	0.052
SLN positive		221/835 (26.5%)	142/506 (28.1%)	0.524
Histology				0.288
	Ductal	816 (84.1%)	489 (82.0%)	
	Lobular	100 (10.3%)	62 (10.4%)	
	Other	54 (5.6%)	45 (7.6%)	
Margin status				0.002
	Negative	676 (70.3%)	441 (75.6%)	
	Close (<2 mm)	180 (18.7%)	70 (12.0%)	
	Positive	105 (10.9%)	72 (12.3%)	
Grade				0.056
	1	305 (31.8%)	165 (28.0%)	
	2	410 (42.7%)	242 (41.1%)	
	3	245 (25.5%)	182 (30.9%)	
Lymphovascular invasion		207 (21.7%)	125 (21.4%)	0.897
ER positive		774 (81.4%)	481 (81.0%)	0.840
PR positive		695 (73.2%)	429 (72.3%)	0.702
HER2 positive		122 (13.0%)	69 (11.7%)	0.472
AJCC stage				0.036
	1	594 (61.7%)	328 (55.1%)	
	2	278 (28.9%)	202 (33.9%)	
	3	90 (9.4%)	65 (10.9%)	
SSI		55 (5.7%)	70 (11.7%)	<0.001
Hematoma		26 (2.7%)	13 (2.2%)	0.538
Readmission		17 (1.8%)	22 (3.7%)	0.017
Return to ED		24 (2.5%)	31 (5.2%)	0.004

both groups ($p = 0.297$) (Fig. 1). The 10-year overall and recurrence-free survival were 78% and 76%, and 87% and 84% for obese and non-obese patients, respectively. Obesity was not a significant contributor to survival on multivariate analysis. Independent predictors of mortality included age (HR 1.05, 95% CI 1.04–1.06), ER-negative tumors (HR 1.84, 95% CI 1.39–2.45), and AJCC stage 2 (HR 2.13, 95% CI 1.61–2.81) or stage 3 (HR 3.33, 95% CI 2.35–4.71).

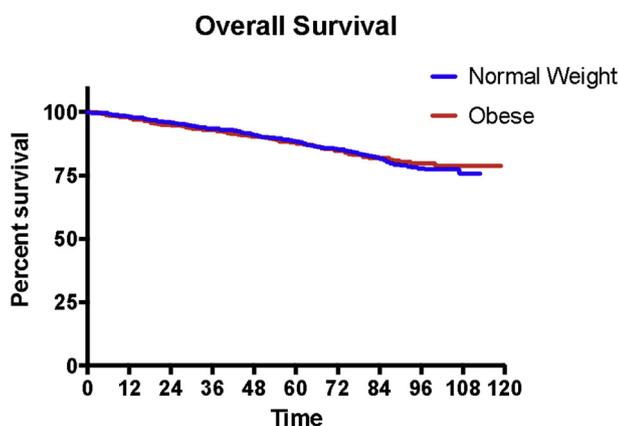


Fig. 1. Overall survival curve for non-obese and obese women over the course of 120 month follow up period. There was no statistically significant difference in overall survival among the two groups.

Discussion

The rate of obesity in the United States has been steadily increasing over the past several decades. In the wake of this epidemic, it is important to understand the impact of obesity on the treatment and outcomes of other diseases. We sought to examine the impact of obesity on a large consecutive cohort of patients with invasive breast cancer.

Obese patients in our study were more likely to undergo breast conserving surgery than non-obese patients. This is important as mastectomy rates increase nationally. Presumably obese patients would more commonly present with a more favorable breast size:tumor size ratio to encourage breast conserving surgery, however, the differences between groups were seen for even T1 tumors. Somewhat alarmingly, mastectomy rates were nearly 40% for T1 tumors and greater than 60% for T2 tumors in non-obese patients.

Similar to previous studies examining patients undergoing breast surgery either with or without reconstruction^{5,6} our study found that the rate of surgical site infections was increased in patients with obesity. Rates of SSI were highest in obese patients who underwent mastectomy (16%). Obese patients were also more likely to return to the ED or be readmitted to the hospital after surgery. These data should inform appropriate risk stratification to include obesity when considering bundled payment models. Further study could also examine the impact of these complications on timing of

adjuvant chemotherapy or radiotherapy.

An interesting finding in our study was that the rate of MRI utilization was lower in obese patients with newly diagnosed breast cancer. Currently, the NCCN guidelines for the use of MRI in breast cancer state that it can be used for pre-operative staging evaluation to define the extent of cancer or the presence of multifocal or multicentric cancer in the ipsilateral breast, screening the contralateral breast for disease at diagnosis, evaluation before and after systemic therapy to define extent of disease and response to therapy, and identification of occult tumor in patients with axillary nodal metastasis or Paget's disease with the primary tumor not identified on other imaging modalities.⁷ At our institution at the time of this study, it was left up to the discretion of the physicians involved in the patient's care whether MRI was obtained as a part of initial work-up in a new diagnosis of breast cancer. For some obese patients, it may be possible that they cannot obtain an MRI due to their physical size and the weight and positioning limitations for obtaining the breast MRI. One other potential factor is that obese patients have been shown to have lower breast density on mammography. After controlling for both age and menopausal status, a study looking at the breast tissue density and BMI found that patients with elevated BMI (>25) had significantly lower breast density scores and lower amounts of fibroglandular tissue on breast MRI.⁸ Due to the lower density of breast tissue on mammography in obese patients, the clinicians (radiologist and breast surgeon) may feel that the images are adequate from the mammogram and the enhanced imaging of the MRI is not necessary for pre-operative evaluation and surgical planning.

One finding in our patient population that differed from previous literature on the subject was that there was no difference in survival between the patients with obesity and those with a BMI <30. Previous literature has suggested that there is a significant increase in both all-cause mortality and breast cancer specific mortality in patients with obesity, especially in post-menopausal patients with hormone receptor positive tumors.^{3,4} We did not perform a subgroup analysis on pre-vs post-menopausal women with breast cancer, therefore it is unclear based on our current findings whether this survival difference would be present in our population, however, there were no trends identified to suggest any potential survival differences.

Our study is limited by its retrospective nature and single institution which could lead to bias in treatment patterns. There were also no criteria in place for physicians at our institution on obtaining MRI for procedural planning during the time of the study,

though protocols have since been adopted. Our current institutional protocol for obtaining an MRI as a part of the pre-operative work-up includes patients with invasive lobular carcinoma and women with extremely dense breasts on mammography. As far as demographics, the majority of our patient population was white, which will limit the generalizability of our results to other patient populations with a larger proportion of minority patients. Despite these limitations, our study does include a large consecutive cohort of patients with long-term follow-up.

In conclusion, we investigated a consecutive cohort of breast cancer patients and found that obese patients receive different pre-operative care, surgical treatment of the primary tumor, and have inferior postoperative outcomes compared with their non-obese counterparts but similar survival rates among the two groups. With increasing focus on costs of care, these data identify a high-risk population who are likely to increase utilization of healthcare resources. Further study into methods for mitigating these costs is warranted.

Conflict of interest disclosures

The authors have no disclosures.

References

1. SEER Stat Fact Sheets: Female Breast Cancer. National Cancer Institute (<https://seer.cancer.gov/statfacts/html/breast.html>), Accessed June 10, 2018.
2. Key TJ, Appleby P, Barnes I, et al. Endogenous sex hormones and breast cancer in the postmenopausal women: reanalysis of nine prospective studies. *J Natl Cancer Inst.* 2002 April 17;94(8):606–616.
3. Chan DSM, Vieira AR, Aune D, et al. Body mass index and survival in women with breast cancer—systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol.* 1 October 2014;25(10):1901–1914.
4. Sparano JA, Wang M, Zhao F, et al. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. *Cancer.* 2012 December 1;5937–5946.
5. Garland M, Hsu F, Clark C, et al. The impact of obesity on outcomes for patients undergoing mastectomy using the ACS-NSQIP data set. *Breast Canc. Res. Treat.* 2018;168:723–726.
6. Fischer JP, Nelson JA, Kovach SJ, et al. Impact of obesity on outcomes in breast reconstruction: analysis of 15,937 patients from the ACS-NSQIP datasets. *J. Am. Coll. Surg.* 3 March 2013;217(4):656–664.
7. National comprehensive cancer network clinical practice guidelines in oncology. Breast Canc (Version 1.2018) https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf. Accessed July 15, 2018.
8. Gillman J, Chun J, Schwartz S, et al. The relationship of obesity, mammographic breast density, and magnetic resonance imaging in patients with breast cancer. *Clin Imag.* 2016 May 26;40(1):1167–1172.