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Impact of BMI on clinical axillary nodal assessment in breast cancer patients

Damian McCartan, MD¹, Michelle Stempel, MPH¹, Anne Eaton, MS², Monica Morrow, MD¹, and Melissa Pilewskie, MD¹

¹Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

²Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background—Over one-third of American adults are obese, and an elevated body mass index (BMI) has been postulated to reduce the sensitivity of the clinical evaluation of the axilla. Clinical nodal exam is important in allocating breast cancer patients to appropriate axillary management. We sought to determine whether BMI influences the rate of nodal positivity in women designated clinically node negative (cN0) by physical examination.

Methods—Breast cancer patients deemed cN0 who underwent sentinel lymph node biopsy (SLNB) from 2/2006–12/2011 were identified from a prospectively maintained database. Clinicopathologic features including BMI and axillary surgery results were recorded and compared among pathologically node-negative and node-positive patients.

Results—Overall, 5142 cN0 patients underwent 5262 SLNB procedures during the study period. Nearly one-third (28%) of patients were obese (BMI>30kg/m²). A positive SLN was identified in 25% of patients; 84% proceeded to axillary lymph node dissection. Predictors of SLN positivity included younger age, larger tumor size, high nuclear grade, multifocality, and lymphovascular invasion. An increased BMI did not correlate with a higher likelihood of SLN positivity (p=0.6). The likelihood of cN0 patients having a high burden of axillary metastases (>3 positive nodes) was 4% overall and, similarly, did not differ according to BMI (p=0.4).

Conclusion—Elevated BMI was not associated with a higher likelihood of SLN positivity or heavy nodal disease burden among women staged as cN0 by physical exam. These findings indicate that physical examination is appropriate and sufficient for preoperative axillary evaluation in women undergoing initial surgery regardless of patient BMI.

Keywords

breast cancer; body mass index; BMI; sentinel lymph node biopsy

Corresponding author: Melissa Pilewskie, MD, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, (T) 646 888 4590, (F) 646 888 4920, pilewskm@mskcc.org.

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Introduction

The prognostic significance of axillary lymph node metastases in patients with breast cancer has been recognized since the 1970s.¹ However, the surgical management of the axilla has changed substantially since that time. Evaluation of the axilla with sentinel lymph node biopsy (SLNB) has expanded considerably, with SLNB alone now the standard staging procedure among all clinically node-negative (cN0) breast cancer patients.^{2,3} In addition, SLNB is increasingly the sole axillary surgical procedure among select patients with low-volume axillary metastases.⁴⁻⁷

The stratification of a breast cancer patient as clinically node positive or node negative is an important factor when treatment options are being considered.⁸ Patients with palpable adenopathy at presentation are at risk for harboring heavier nodal disease burden, have confirmation of nodal metastasis by needle biopsy, and are managed with either upfront axillary lymph node dissection (ALND) or, increasingly, neoadjuvant chemotherapy.⁹ In contrast, cN0 patients comprised the study populations that established the safety of SLNB alone for micro- and macro-metastatic axillary disease^{2,5,9-11}, and are frequently spared the morbidity of ALND.¹² Therefore, the accuracy of the surgeons' nodal exam at presentation is paramount in allocating patients to the appropriate axillary treatment.

Little is known about the accuracy of axillary clinical exam with varying patient body mass indices (BMI). This is a relevant topic to address as over one-third of adults in the United States are obese, defined as a BMI of $>30\text{kg/m}^2$.¹³ An elevated BMI has been thought to reduce the sensitivity for certain clinical examinations¹⁴, and increasing BMI has been identified as a risk factor for failure of sentinel node mapping^{15,16}, but differences in the accuracy of axillary physical exam based on patient BMI are unknown. One might postulate that physical exam is less sensitive in obese patients who would therefore be at higher risk for having axillary nodal metastasis on SLNB even with a benign axillary exam. Here we sought to compare the likelihood of SLN metastasis among obese and non-obese cN0 breast cancer patients to determine if the ability to clinically identify nodal positivity and heavy nodal disease burden differs by patient BMI.

Methods

After receipt of Memorial Sloan Kettering Cancer Center (MSKCC) institutional review board approval, consecutive patients who underwent SLNB from 02/01/2006 to 12/30/2011 were identified from a prospective institutional database. Patients eligible for inclusion were those with biopsy-proven invasive breast cancer who were deemed cN0 on the basis of preoperative physical examination. Patients undergoing neoadjuvant chemotherapy and patients with palpable adenopathy were excluded. While some patients had axillary ultrasound performed prior to presentation at MSKCC, axillary ultrasound was not a routine part of the diagnostic work-up for cN0 patients with de novo breast cancer. A random sample of 10% of the patient population ($n = 530$) was reviewed to assess axillary ultrasound use. Overall, 25% of women underwent axillary ultrasound, 67% of which were performed at an outside institution prior to presentation at MSKCC. There was no significant variation of ultrasound use by patient BMI.

Patient characteristics, including height and weight at the time of surgical treatment, were available for all identified cases. Details of breast and axillary surgery were obtained from procedure reports (failure of SLNB, SLNB alone, SLNB, and ALND). Pathology records were reviewed, and total number of SLNs removed, number of positive SLNs, ALND total and positive lymph node yield, and final N stage were identified. Lymph nodes were designated as positive for the presence of either micro- or macro-metastases. Isolated tumor cells were classified as node negative. Completion ALND during this time period was routinely performed for all pathologically node positive (pN+) patients. Subsequent to the publication of the American College of Surgical Oncology Group (ACOSOG) Z0011 study in 2010⁵, patients who met the Z0011 eligibility criteria underwent completion ALND for 3 positive SLNs or gross extracapsular extension. SLNB was performed using dual modality mapping with technetium-99 m and isosulfan blue dye or with the use of isosulfan blue dye alone, based on surgeon's preference.

BMI was assessed both as a continuous variable and as a categorical variable based on the World Health Organization classification of BMI¹⁷ of < 18.5 as underweight, 18.5–24.9 normal weight, 25.0–29.9 overweight/pre-obese, and ≥ 30.0 as obese. Statistical analysis was performed using R 3.1.1 (R Foundation, Vienna, Austria). Associations between outcomes of interest and categorical variables were assessed using Chi-squared test and between outcomes of interest and continuous variables were assessed using Wilcoxon rank-sum test. A p-value of less than 0.05 was considered statistically significant.

Results

Between February 2006 and December 2011, 5142 patients underwent 5262 SLNB procedures for axillary staging for invasive breast cancer that was designated as cN0 pre-operatively. The median patient age was 58 years (range 21–92), and the median BMI was 26.2kg/m² (range 16–61). Nearly one-third (28%) of patients were classified as obese with a BMI > 30kg/m², and a further 31% of patients were overweight (BMI > 25kg/m²) (Figure 1). Table 1 outlines the clinicopathologic features for the entire cohort and by pathologic nodal status.

The sentinel lymph node contained metastases in 25% of cases (n = 1314); 6% (n = 318) of the population had micrometastases and 19% (n = 996) had macrometastases. Among the 1314 patients with a positive SLN, 76% (n = 996) had 1 or 2 positive nodes, 8% (n = 102) had 3 positive nodes, and 16% (n = 216) had 4 or more positive nodes. Only 318 cases (6.2%) of the overall cohort had > 2 positive lymph nodes. An increased BMI did not correlate with a higher likelihood of SLN positivity when evaluated as either a continuous (p = 0.31) or categorical variable (p = 0.58). The rate of macrometastatic nodal disease alone (pN1) did not vary according to patient BMI (p = 0.5) (Table 2) and, similarly, the likelihood of cN0 patients having a high burden of axillary metastases (pN2 disease) did not differ according to BMI (p = 0.47) (Figure 2). Known clinicopathologic factors predicted nodal positivity, including younger age, larger primary tumor size, high nuclear grade, and tumor multifocality as well as the presence of lymphovascular invasion (p < 0.001)(Table 1).

The average number of SLNs removed was 2 for the entire cohort (Table 2). Among pN+ patients, 994 (76%) underwent a completion ALND. A further 224 pN+ patients who had undergone breast-conserving surgery and met Z0011 criteria underwent SLNB alone for axillary metastases in 2 SLNs.

A sentinel lymph node was identified in 99.1% of cases. While the rate of failed sentinel lymph node mapping was higher in obese versus non-obese patients (1.6% versus 0.5%, $p = 0.003$), among the obese cohort, an SLN was identified in over 98% of cases (Table 3). In patients with class I obesity (BMI 30–35 kg/m²) the rate of failure of identification of the SLN was 1.1%, rising to 1.7% in those with class II obesity (BMI 35–40 kg/m²) and 3.3% in patients with class III obesity (BMI ≥ 40 kg/m²) ($p < 0.001$). Overweight and obese patients were more likely to have been treated with breast-conserving surgery than those with a BMI < 25 kg/m². In addition, overweight and obese patients were significantly older than non-obese patients (61 and 62 years compared to 51 years of age, respectively, $p > 0.001$).

Discussion

Evidence from randomized clinical trials over the last 2 decades has heralded practice-changing advances in the surgical management of the axilla in breast cancer patients.¹⁸ Here we demonstrate, in a cohort of over 5200 patients, that rates of SLN positivity did not differ among cN0 women with varying BMI classifications, suggesting similar accuracy of axillary physical exam among obese and non-obese patients.

Despite advances in estimating prognosis and predicting response to adjuvant therapy, axillary lymph node status remains a critical component in surgical decision making and in determining therapeutic strategies. The finding of palpable adenopathy, when corroborated by a positive axillary ultrasound and needle biopsy, is used to allocate patients to either neoadjuvant chemotherapy or upfront ALND. In comparison, SLNB is the standard for axillary staging among cN0 patients. The success of SLNB is predicated on the basis of a high technical success rate, low false-negative rate and a reduction of postoperative morbidity when compared to ALND.^{7,19}

Landmark trials such as ACOSOG Z0011⁵ and AMAROS¹⁰ that included patients with macro-metastatic nodal disease, identified patients with positive SLNs in whom further axillary surgery can be omitted without compromise of regional or overall disease-free survival. Our findings have demonstrated that in cN0 patients, only 6% will have a final pathological nodal yield of more than 2 positive nodes and that this risk of clinically occult heavy nodal burden is not increased in patients with an elevated BMI. These findings support the value of SLNB, without additional preoperative axillary imaging, for axillary staging among all cN0 patients, regardless of body habitus.

The technical success of SLNB mapping did differ among women in different BMI categories, even among a group of experienced breast specialists. Obese patients had a higher rate of failed SLNB mapping, with failure rates ranging from 0.5% in normal/underweight patients to 3.3% in class III obese patients. Previous studies have implicated both obesity and increased age as patient factors that reduce the success of SLNB.^{15,16,20}

However, the absolute difference of < 3% in SLN identification among the extremes of BMI classifications is likely not clinically meaningful, considering that among all obese patients, > 98% had successful SLN mapping.

In addition to physical examination, some advocate the use of axillary ultrasound to identify patients with nodal metastases preoperatively to obviate the need for SLNB. A meta-analysis has shown that preoperative staging axillary ultrasound coupled with FNA or core biopsy of suspicious or abnormal nodes will correctly identify approximately 50% of node-positive patients.²¹ However, the role of axillary imaging in cN0 patients meeting ACOSOG Z0011 criteria has been questioned. We have previously demonstrated that the identification of abnormal nodes on preoperative imaging²² or even a positive needle biopsy²³ does not reliably identify a group of patients who require ALND when ACOSOG Z0011 eligibility criteria are otherwise met. While BMI has been not been shown to impact the sensitivity of axillary ultrasound²⁴⁻²⁶, our data suggest that obesity itself is not an indication for additional axillary evaluation.

This is a retrospective review with the associated limitations. Although the majority of patients at our institution are designated as cN0 by physical exam alone, approximately one-quarter of women in this cohort underwent axillary ultrasound. The SLN positivity rate of 25% seen here is similar to the 29% seen in NSABP-B32² and the 25% in the ALMANAC trial¹⁶, two multi-center trials that randomized cN0 patients without the use of axillary ultrasound. Therefore it is unlikely that there exists a large cohort of patients who were deemed cN0 by physical exam, but who, on the basis of positive findings on axillary ultrasound, were excluded from upfront SLNB. Furthermore, it is our practice to stage clinically node-negative patients with a SLNB who meet ACOSOG Z0011 criteria regardless of axillary ultrasound findings. The strengths of this study include a large patient cohort with available patient and pathologic data. Our results replicate a number of known risk factors for nodal metastases among cN0 patients, including age, tumor size, grade, lymphovascular invasion, and multifocality, but, importantly, did not show a difference in overall node positivity or heavy nodal disease burden based on patient BMI.

Elevated BMI is not associated with a higher likelihood of SLN positivity or heavy nodal disease burden among women staged as cN0 by physical exam. Clinical assessment of axillary status in newly diagnosed breast cancer patients with physical exam appears equivalent in non-obese and obese patients, and remains an appropriate evaluation for axillary treatment allocation regardless of patient BMI.

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Synopsis

This study examines the influence of BMI on the accuracy of designating a patient as clinically node negative. We find that the rate of nodal positivity and heavy nodal disease burden does not differ with increasing BMI.

Fig. 1. Histogram of body mass index category frequencies in clinically node-negative patients

Fig. 2. Final pathological nodal stage of clinically node-negative patients stratified according to body mass index

Table 1
Clinicopathologic features of entire cohort and by pathologic nodal status

	Overall (n = 5262)	pN+ (n = 1314)	pN0 (n = 3948)	p-value
Age, median (range)	58 (21–92)	54 (22–92)	59 (21–92)	< 0.001
BMI, median (range)	26.2 (16–61)	26.0 (17–60)	26.2 (16–61)	0.31
BMI category				
Normal/Underweight (< 25kg/m ²)	2165 (41%)	556 (42%)	1609 (41%)	0.58
Overweight (25.0–29.9kg/m ²)	1606 (31%)	389 (30%)	1217 (31%)	
Obese (≥ 30kg/m ²)	1491 (28%)	369 (28%)	1122 (28%)	
Tumor size, cm, median (range)	1.3 (0.1–12.4)	1.8 (0.1–12.4)	1.2 (0.1–9)	< 0.001
Postmenopausal ultrasound (n = 5168)	3363 (65%)	763 (59%)	2600 (67%)	< 0.001
Nuclear grade (n = 3977)				
High	1492 (38%)	466 (47%)	1026 (34%)	< 0.001
Intermediate	2266 (57%)	500 (51%)	1766 (59%)	
Low	219 (6%)	18 (2%)	201 (7%)	
LVI present (n = 4992)	1460 (29%)	719 (57%)	741 (19%)	< 0.001
Multifocal tumor (n = 5219)	1312 (25%)	482 (37%)	830 (21%)	< 0.001
ER positive (n = 5221)	4443 (85%)	1131 (86%)	3312 (85%)	0.16
PR positive (n = 5220)	3846 (74%)	982 (75%)	2864 (73%)	0.23
HER2/neu overexpressing (n = 5186)	559 (11%)	157 (12%)	402 (10%)	0.10

BMI, body mass index; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor

Table 2
Results of axillary surgery stratified according to BMI in clinically node-negative patients

	Overall n = 5262	Normal/Underweight n = 2165	Overweight n = 1606	Obese n = 1491	p-value
Nodal Yield					
Median SLNs Removed	2	3	2	2	<0.001
Median Positive SLNs	0	0	0	0	0.7
Completion ALND	1146 (22%)	489 (23%)	334 (21%)	323 (22%)	0.4
Final Pathologic N Stage					
pN0	3948 (75%)	1609 (74%)	1217 (76%)	1122 (75%)	0.6
pN1mi	318 (6%)	138 (6%)	97 (6%)	83 (6%)	
pN1	780 (15%)	338 (16%)	218 (14%)	224 (15%)	
pN2	145 (2.8%)	56 (2.6%)	48 (3.0%)	41 (2.7%)	
pN3	71 (1.3%)	24 (1.1%)	26 (1.6%)	21 (1.4%)	

SLNs, sentinel lymph nodes; ALND, axillary lymph node dissection

Table 3

Breast and axillary operative interventions

Breast and Axillary Procedures	Overall n = 5262	Normal/Underweight n = 2165	Overweight n = 1606	Obese n = 1491	p-value
Mastectomy	1909 (36%)	937 (43%)	532 (33%)	440 (30%)	< 0.001
Breast-Conserving Therapy	3353 (64%)	1228 (57%)	1074 (67%)	1051 (70%)	
Failed SLNB converted to ALND	46 (0.9%)	10 (0.5%)	12 (0.7%)	24 (1.6%)	0.003
SLNB only	4111 (78%)	1676 (77%)	1269 (79%)	1166 (78%)	
SLNB with completion ALND	1105 (21%)	479 (22%)	325 (20%)	301 (20%)	

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection