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False Negative Rate of Sentinel Lymph Node Biopsy in Multicentric and Multifocal Breast Cancers May be Higher in Cases with Large Additive Tumor Burden

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Abstract

We aimed to evaluate the feasibility of sentinel lymph node biopsy (SLNB) in multicentric/multifocal breast cancer. In this prospective study, 23 women with multicentric/multifocal breast cancer underwent SLNB at our institution from April 2002 to February 2006. Presence of preoperative axillary metastases was confirmed by FNA. Patients underwent sub-areolar radiopharmaceutical injection $\pm$ isosulfan blue to perform SLNB, then completion ALND. The false-negative (FN) rate of SLNB was determined based upon final pathology. Twenty women with multicentric and three with multifocal invasive carcinoma were enrolled. The SLN identification rate was 100%. The overall FN rate of SLNB was 15% (95% CI 0.0466, 0.4281). Both cases with FN SLNB had multicentric disease, pathologic stage III breast cancer and a larger tumor burden compared with the study population. SLNB using sub-areolar injection is feasible for patients with multicentric/multifocal breast cancer yet may be associated with a higher FN rate in patients with large additive tumor burden.

Keywords

lymphoscintigraphy; multicentric breast cancer; multifocal breast cancer; sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB), when applied to clinically node-negative breast cancers, has demonstrated sufficient accuracy to be recommended as an alternative to axillary lymph node dissection (ALND). Current contraindications to SLNB include locally advanced invasive breast cancers (T3 and T4), inflammatory breast cancer, previous nononcologic breast or axillary surgery, or where suspicious palpable lymph nodes are encountered; limited evidence exists supporting the use of SLNB in cases of previous diagnostic or excisional breast biopsy or multicentric (MC)/multifocal (MF) breast cancers (1). Most investigators have thus excluded patients with MCMF lesions from SLNB out of

concern that tumors located in separate quadrants of the breast do not drain to the same sentinel lymph node, thus possibly leading to an unacceptably high false-negative rate. Likewise, a large additive tumor burden is often difficult to identify by preoperative imaging and biopsy, as only final pathologic analysis reveals the true extent of the multicentric disease process. Elucidation of those features that may be predictive of false-negative SLNB in MCMF breast cancers is essential to spare some patients the morbidities of ALND as well as to identify those who may not be good candidates for SLNB. The aims of our study were to evaluate the feasibility and false-negative rate of SLNB in patients with MCMF breast cancer in conjunction with other clinicopathologic features.

METHODS

Following approval from the Institutional Review Board, we enrolled women with MF or MC invasive breast cancer, confirmed by final histopathologic examination, in this prospective study. All patients underwent SLNB and completion ALND at our institution between April 2002 and February 2006. Multicentric disease was defined as the presence of two or more invasive tumors ≥ 5 cm apart or in distinct quadrants of the breast on clinical exam, mammography, or ultrasonography and confirmed by biopsy. Multifocal disease was defined as two or more invasive tumors <5 cm apart or within the same quadrant of the breast. Presence of axillary metastases at time of initial diagnosis was documented by ultrasound and confirmed by fine-needle aspiration biopsy (FNA). These patients were defined as clinically node positive. All other patients with indeterminate axillary ultrasound findings and FNA-negative lymph nodes, negative axillary ultrasound, or no palpable adenopathy on physical examination were considered clinically node negative. All patients, regardless of nodal status, were entered on the protocol. The sole exclusion criteria for our study were patients who did not undergo completion ALND after SLNB.

All patients underwent injection of 2.5–3.0 mCi of technetium-labeled filtered sulfur colloid the day before surgery and/or 0.5 mCi on the day of surgery in the sub-areolar location, prior to incision. Preoperative lymphoscintigraphy following sub-areolar injection was performed at the surgeons' discretion. Blue dye (5 cc of 1% isosulfan blue) was also injected in the subareolar location to facilitate intraoperative SLN identification at the surgeons' discretion. Intraoperatively, a hand-held gamma counter was used to identify the SLN. All lymph nodes with a radioactivity count higher than 10% above the highest ex vivo count of the sentinel lymph node and all blue nodes were removed and treated as SLNs. Axillary SLNs were serially sectioned at 2–3 mm intervals along the short axis of the node, embedded in paraffin blocks, and then serially sectioned at 5 μ m. Hematoxylin and eosin (H&E) staining was performed; negative results were subjected to immunohistochemical staining for cytokeratin. All patients underwent completion level I and II ALND and those nodes were evaluated by routine H&E staining following sectioning. Patient and tumor characteristics were described using simple descriptive statistics. Analyses were conducted using SAS for Windows (release 9.1; SAS Institute, Cary, NC). The false-negative rate and corresponding exact 95% confidence intervals were calculated for SLN biopsy in predicting axillary nodal status based upon permanent pathologic results, with the false-negative rate defined as the number of false-negative cases divided by the sum of true positive and false-negative cases.

RESULTS

Twenty patients with multicentric and three patients with multifocal invasive breast carcinoma fulfilled our study criteria. At the time of surgery, patients ranged from 34 to 87 years of age with a mean age of 53 years (SD = 12.5 years). Clinically, the majority (66%) of patients in this study had stage I (26%) or stage IIA (39%) breast cancer. Seven patients had undergone prior surgery to the breast. Six patients were clinically node positive at presentation, and four of those patients had received neo-adjuvant chemotherapy. Table 1 further describes the characteristics of the study population.

Preoperative lymphoscintigraphy following radiopharmaceutical injection in the sub-areolar location was performed for 16 (70%) of the 23 patients and demonstrated axillary drainage in all cases, with two cases demonstrating concomitant supraclavicular and internal mammary nodal drainage. Biopsy of extra- axillary sentinel lymph nodes was not performed.

The intraoperative SLN identification rate was 100% and all sentinel nodes biopsied contained radioactive tracer; no sentinel lymph nodes contained blue dye alone. There was no significant difference in the number of SLNs removed in patients with multicentric versus multifocal disease ($p = 0.7961$). The overall incidence of sentinel lymph node metastasis was 48% (11/23 patients). Six patients (26%) demonstrated axillary lymph node metastases by H&E on ALND, yet SLNB detected only four of these cases. The over-all false-negative rate for our patient population was 15% (95% CI 0.0466, 0.4281). In comparison, the false-negative rate for patients who underwent neo- adjuvant chemotherapy was 25%. The false-negative rate for each patient subset is outlined in Table 2.

There were two false-negative cases among the clinically node-negative patients. Interestingly, both patients did have indeterminate axillary nodes seen by ultrasound but were cytologically confirmed negative by FNA. Both patients harbored multicentric disease and two discrete invasive lesions in separate breast quadrants. The sum of the tumor load for these patients measured 80 mm and 62 mm, with final pathology indicating these patients to have stage IIIA (T3pN1M0) and stage IIIC (T2pN3M0) breast cancer, respectively. One of these patients had received neo-adjuvant chemotherapy, which consisted of anthracycline and taxol-based therapy, while the other did not; the latter patient had undergone a prior excisional biopsy to the ipsilateral breast. Table 3 further describes the characteristics of the two false-negative cases.

DISCUSSION

Early sentinel node validation studies were performed on patients with unifocal disease. Several groups have since attempted to establish the feasibility and accuracy of SLNB in MC/MF breast cancer yet have excluded patients with a history of receiving neo- adjuvant chemotherapy, prior ipsilateral breast surgery and/or advanced pathologic cancer stage (2–11). Our study is unique in that we did not exclude patients with pretreatment axillary metastases nor those who had received neo-adjuvant chemotherapy, as all patients were committed to undergo ALND.

Limited data suggests that previous excisional breast biopsy does not affect the success of SLN identification, and current ASCO guidelines conclude that previous excisional or diagnostic biopsy are not contraindications to SLNB (1). Thus, the fact that one of our false-negative cases had undergone a previous excisional biopsy does not in itself explain the false-negative result.

While the SLN identification rate in MC/MF disease ranges from 92–100% in the literature, the reported false-negative rate has been variable, ranging from 0–11% (2–6,10,11). In our study, we removed but did not count clinically suspicious axillary nodes (nodes with no uptake of radiopharmaceutical or blue dye, yet palpated intraoperatively) as sentinel lymph nodes. This factor may have contributed to our 14% false-negative rate, as in both of our FN cases, blue dye and radiopharmaceutical tracer failed to identify the axillary metastases. Our results thus support the recommendation from several studies that clinically suspicious nodes should also be evaluated intraoperatively at the time of SLNB to avoid missing metastatic disease not detected by radioactive tracer or blue dye (1,2,4,11).

There is some speculation that lymphatic mapping may not be accurate following neo-adjuvant chemotherapy for patients with unifocal breast cancers. In our study, we observed a higher FN rate of 25% among patients receiving neo-adjuvant chemotherapy. The higher false-negative rate observed among patients with unifocal tumors and pretreatment nodal metastases who undergo SLNB following neo-adjuvant chemotherapy has been previously documented by our group, with our 2007 study citing a similar 25% FN rate (7). Taking this into account, in this patient subset, the presence of MC/MF disease does not appear to increase the FN rate beyond that seen with neo-adjuvant treatment alone.

Apart from the fact that patients with advanced cancer stage often do receive neo-adjuvant chemotherapy, other reasons for the observed increase in the false-negative rate may rest in the finding that meta-static LN involvement has been shown to be significantly higher in MC breast cancers as compared with unifocal tumors (8). Multicentricity may not necessarily in itself be an independent risk factor for nodal metastases. Rather, the sum of the dimensions of all tumor foci provides a more accurate estimate of the total tumor burden and cancer stage with a corresponding increase in associated nodal positivity (9). ASCO guidelines do not recommend SLNB in cases of T3 and T4 disease, yet total tumor burden is often difficult to quantitate preoperatively in MC disease and may be underestimated. Both of our false-negative cases demonstrated a pathologic dominant tumor size and total tumor burden above the observed mean of the study population. As supported by other studies, the observed higher false-negative rate may not be due to the MC nature of the lesion, but rather it may reflect presence of more advanced disease, as evidenced by those patients' final pathologic stages (2,4,5,10,11).

CONCLUSION

In conclusion, SLNB may be considered in MC/MF breast cancer, as it has demonstrated an axillary SLN identification rate comparable to that observed with unifocal tumors following sub-areolar injection. Though currently deemed acceptable for cases of MC/MF disease by ASCO guidelines, SLNB should be employed cautiously in patients with large tumor

burdens due to the higher false-negative rate observed. Our study also stresses the importance of performing intraoperative assessment of not only sentinel lymph nodes, but all clinically suspicious lymph nodes, to avoid missing axillary metastases. Further studies are warranted in patients with MCMF disease and large additive tumor burdens.

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Table 1Characteristics of the study population ($n = 23$)

Characteristics	Number patients(%)
Age (years)	
Mean	53
Range	34–57
BMI (kg/m ²)	
Median	26
Range	20–53
Menopausal status	
Pre	9 (39)
Post	14 (61)
MF	3 (13)
MC	20 (87)
Number of lesions	
2	14 (61)
3	7 (30)
4	2 (9)
Clinically node positive	6 (26)
Final Pathologic stage	
I	6 (26)
II	12 (52)
III	5 (22)
Surgery performed	
Mastectomy	22 (96)
Segmental mastectomy	1 (4)
Pathologic size dominant tumor (mm)	
Mean	22
Range	6–50
Sum of tumor load (mm)	
Mean	54
Range	7–80
Tumor Histology	
IDC	20 (87)
IDC + ILC	3 (13)
Neo-adjuvant chemotherapy	8 (35)
Prior ipsilateral breast surgery	7 (30)
Follow-up (months)	
Median	28
Range	4–52
Alive, free of disease	22 (96)
Deceased from disease	1 (4)

MC, multicentric; MF, multifocal; BMI, body mass index; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.

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Table 2

Pathologic status of SLN and ALN for study patients

	ALN(+)	ALN(–)	Total Patients
A. Overall group (FN rate = 15%)			
SLN (+)	4	7	11
SLN (–)	2	10	12
Total	6	17	23
B. Group receiving neo-adjuvant chemotherapy (FN rate = 25%)			
SLN (+)	2	1	3
SLN (–)	1	4	5
Total	3	5	8

FN, false-negative rate; SLN, sentinel lymph node pathology; ALN, axillary lymph node pathology.

Table 3

Features of false-negative cases

Characteristics	False Negative A	False Negative B
Age (years)	71	58
BMI (kg/m ²)	26.0	34.6
Disease distribution	MC	MC
Pathology	IDC	IDC
Clinical stage at presentation	IIB (T2N1M0)	IIA (T2N0M0)
Final pathologic stage	IIIA (T3pN1M0)	IIIC (T2pN3M0)
Number of lesions	2	2
Pathologic size dominant tumor (mm)	50	22
Sum tumor load (mm)	80	62
No of SLNs removed	2	1
Total no of ALNs positive/no removed	1/12	17/19
Neo-adjuvant chemotherapy	yes	no
Prior ipsilateral breast surgery	no	yes

MC, multicentric; BMI, body mass index; IDC, invasive ductal carcinoma; SLN, sentinel lymph node; ALN, axillary lymph node.