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SENTINEL LYMPH NODE BIOPSY IN PATIENTS WITH MULTICENTRIC/MULTIFOCAL BREAST CANCER: LOW FALSE NEGATIVE RATE AND LACK OF AXILLARY RECURRENCE

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Abstract

Background—Accuracy of sentinel lymph node biopsy (SLNB) and rate of axillary recurrence in multicentric (MC)/multifocal (MF) breast cancer are reported.

Methods—From 1999–2006, 93 patients with MC/MF breast cancer underwent SLNB; 41 had axillary lymph node dissection (ALND) regardless of SLN pathology (group 1) and 52 had ALND only if a SLN was positive (group 2). Patient demographics, SLN techniques, and pathology were recorded.

Results—There were no differences between the two groups with respect to patient age, tumor size, grade, stage, histology, or method of SLN detection. The incidence of axillary metastasis was greater in group 1 patients (68%) compared to group 2 patients (12%) ($p < 0.01$). In group 1, the sensitivity and specificity of SLNB were 93% and 100%, with a false negative rate of 7%. None of the 52 patients in group 2 experienced an axillary recurrence (median follow-up 4.8 years).

Conclusions—The accuracy of SLNB in MC/MF breast cancer is comparable to that observed in unifocal breast cancer. Despite a lower rate of SLN positivity in those undergoing SLNB only, axillary recurrence is not observed.

Keywords

Breast Cancer; Multicentric (MC); Multifocal (MF); Sentinel Lymph Node Biopsy (SLNB)

INTRODUCTION

Sentinel lymph node biopsy (SLNB) has emerged as the standard method of axillary staging in breast cancer patients with clinically negative axillas (1–3). The goal of SLNB is to minimize morbidity while maintaining high sensitivity and a low false negative rate, such that axillary staging is similar to the standard provided by axillary lymph node dissection (ALND) pathology. Absolute and relative contraindications for the use of SLNB have been

proposed, including prior mastectomy, prior axillary surgery or previous SLNB, palpable lymphadenopathy, prior excisional breast biopsy, T3 and T4 tumors, male breast cancer, neoadjuvant chemotherapy, and multicentric/multifocal (MC/MF) breast cancers (1–9). However, as surgeon experience with SLNB has progressed, the previously described contraindications for SLNB have been challenged.

MC breast cancer is defined as two or more tumors arising in different quadrants of the breast, while MF breast cancer is used to describe two or more foci of invasive breast cancer within the same quadrant (4). The diagnosis of MC/MF breast cancer has been a relative contraindication to SLNB secondary to concerns that there may be multiple dominant lymphatics draining from each individual tumor to the axilla (9). The lymphatics may drain to a different SLN for each tumor present such that SLN mapping may only identify the drainage of one tumor and miss the SLN associated with the other tumors present (3–9). However, this is inconsistent with reports that a single, retroareolar injection of tracer and/or blue dye is comparable to a peri-tumoral injection in reliably identifying the SLN for patients with unifocal breast cancer (4–10). An additional concern regarding the use of SLNB for patients with MC/MF invasive breast cancer is that the identification of all involved SLN(s) may be less likely, leading to higher axillary recurrence rates.

The aim of the current study was to examine the accuracy of SLNB in MC/MF breast cancer and the rate of axillary recurrence.

PATIENTS AND METHODS

Institutional review board approval was obtained prior to the commencement of this retrospective study. Written informed consent of patients was not required. The prospectively maintained surgical database at Washington University/Barnes Jewish Hospital was queried from January 1, 1999 to December 31, 2006 to identify all patients with a diagnosis of biopsy-proven MC/MF invasive breast cancer who underwent SLNB with or without concurrent ALND (n=93). Patients who underwent ALND without SLNB were excluded from the analysis (n=17). All patients required mastectomy for local control. For statistical comparisons, patients were divided into two groups: 1) patients who had completion axillary lymph node dissection (ALND) regardless of SLN pathology (n=41); and 2) patients who had ALND only for a positive SLNB (n=52).

All SLNB procedures were performed under general anesthesia. Standard SLNB techniques using radiocolloid and/or blue dye injection were used for all patients. ^{99m}Technetium radiocolloid was injected peri-tumorally in all patients by the nuclear medicine department at least 2 hours prior to the planned SLNB procedure. Five milliliters of blue dye was injected either peri-tumorally or subareolar by the operating surgeon 5 minutes prior to the planned SLNB procedure. All SLN(s) were identified with the gamma probe and/or by identifying the blue-stained lymphatic.

Pathological analysis of SLN(s) included hematoxylin and eosin staining and immunohistochemistry with a monoclonal cytokeratin antibody mix. Analysis of non-SLN(s) removed during ALND included hematoxylin and eosin staining of bivalved lymph

node sections only. Patient demographics, method of SLN localization, injection site, and final lymph node pathology were recorded. Axillary recurrence was used as a surrogate for the true status of the axilla for group 2 patients. All data were transferred to a single spreadsheet (Excel; Microsoft, Redmond, WA). Statistical calculations were performed using software (StatView; Abacus Concepts, Berkeley, CA). For all analyses, results were considered statistically significant if the *P* value was 0.05 or less.

RESULTS

Ninety-three patients were identified with clinically node-negative MC/MF invasive breast cancer during the study period. Of the 93 patients, 41 had an ALND regardless of SLN pathology (group 1) and 52 had an ALND only if the SLN was positive on final pathology (group 2). From the retrospective review, this difference in approach appeared to be attributed to surgeon discretion; there were no identifiable clinical factors accounting for this finding. A comparison of the demographic and histopathologic characteristics of the two groups is presented in Table 1. There were no differences between the two groups with respect to patient age, tumor size, tumor grade, stage, histology, estrogen receptor (ER) status, progesterone receptor (PR) status, or Her-2-neu status ($p > 0.05$ for all). Method of SLN detection (70% blue dye only, 3% radiocolloid only, and 27% blue dye + radiocolloid) and site of injection of blue dye (71% peri-tumoral, 29% retroareolar) and radiocolloid (100% peri-tumoral) was also similar between the two groups. Lymphovascular invasion was present in 35.7% of patients in group 2 compared to only 19.6% of patients in group 1, but this difference was not statistically significant. The rate of post-mastectomy radiation was high for both groups (58.8% in group 1 and 71.1% in group 2) and was not significantly different. We were unable to determine retrospectively which patients had axillary field radiation as part of their post-mastectomy radiation treatment. There were no statistically significant differences in the rates of systemic chemotherapy and/or endocrine therapy use between the two groups.

The incidence of axillary metastasis was greater in those patients who had a planned ALND regardless of the SLN results (group 1; 28 of 41, 68%) compared to those who only had an ALND if the SLN was positive (group 2; 6 of 52, 12%) ($p < 0.01$). Of the 93 patients, 14 (15%) underwent neoadjuvant therapy (group 1: 5 of 41, 12%; group 2: 9 of 52, 17%). Of the 14 patients who had neoadjuvant therapy, 12 underwent axillary staging prior to neoadjuvant therapy initiation (all 5 Group 1 patients and 7 Group 2 patients). The 2 patients who did not have pre-therapy axillary staging were also in Group 2 and were enrolled in neoadjuvant endocrine therapy trials; one of them had a positive SLN following therapy and one had a negative SLN following therapy.

For patients in group 1, the sensitivity and specificity of SLNB were 93% and 100%, respectively, with a false negative rate of 7%. The SLN was the only metastatic node in 43% of group 1 patients. Six of the 52 patients in group 2 had a positive SLN and underwent completion ALND; none of the patients within this group experienced an axillary recurrence at follow-up (median 4.8 years).

DISCUSSION

SLNB has been validated in unicentric, clinically node negative breast cancer and has become the standard of care for axillary staging in this patient population (1–3). The NSABP B-32 trial was designed to demonstrate whether SLNB could achieve the same diagnostic accuracy as the gold standard, ALND, while significantly decreasing morbidity (11). In over 5600 patients enrolled in NSABP B-32, the SLN was identified successfully in 97.2% of patients, with an overall accuracy of 97.1% and a false negative rate of 9.8% (11).

Patients with MC/MF invasive breast cancers have traditionally been considered to be poor candidates for SLNB for accurate axillary staging. The main concern is regarding the possibility of multiple dominant lymphatics draining to more than one SLN, which may lead to a high false negative rate. Therefore, surgical therapy for patients with MC/MF invasive breast cancer has traditionally included a modified radical mastectomy. Despite these concerns, several studies have demonstrated the validity of SLNB in patients with MC/MF breast cancers (4–9). Concerns of disparate lymphatic drainage from MC/MF breast cancers have been challenged by reports that the breast drains to common SLN(s) through a small number of common lymphatic channels regardless of the location of the primary tumor (10). Furthermore, there appears to be little effect of mapping agent injection site on SLN identification rate, and studies have failed to show that any one site of injection is superior to another (4–10). Our data are consistent with these findings, where the overall SLN identification rate was 100%, despite widely varying methods of SLN mapping (blue dye +/- radiocolloid, retroareolar vs. peri-tumoral injection).

Previous reports support the use of SLNB in patients with MC/MF invasive breast cancers (4–9). Tousimis et al. (4) reported their experience in 70 patients with MC/MF invasive breast cancer and clinically negative axillas who required total mastectomy for local control. All 70 patients underwent SLNB followed by planned ALND regardless of SLN pathology, and the overall accuracy of SLNB was 96%, with 93% sensitivity and a false-negative rate of 8%. Similarly, Kumar et al. (5) retrospectively analyzed data from 48 patients with MF/MC breast cancer undergoing SLNB followed by ALND; they were able to identify the SLN in 93.5% of cases, with 100% sensitivity and a false negative rate of 6%. In the current study, patients who underwent planned ALND despite SLN pathology (group 1) had a successful SLNB with 93% sensitivity and a 7% false negative rate which is comparable to that observed in unicentric cancers (11).

In our study, we observed that patients who underwent a planned ALND following SLNB (group 1) had a significantly higher rate of node-positive disease than patients who only underwent ALND if the SLNB was positive (group 2). The reasons for this finding are unclear. It is possible that the group 1 patients were selected to undergo a planned ALND because of some clinical factor predisposing to increased risk for lymph node metastasis, though the two patient groups did not differ significantly with regards to patient and tumor characteristics. An alternative explanation is that the false negative rate of SLNB in the group 2 patients is higher than that demonstrated in the group 1 patients and we are simply unable to identify this rate because the group 2 patients did not have routine ALND performed following the SLNB. Though we cannot measure this directly, using clinical

axillary recurrence as a surrogate marker for residual axillary disease, there were no axillary recurrences in the 52 patients in group 2 during the follow-up period. Further, axillary recurrence was not observed despite a relatively high rate of lymphovascular invasion in group 2 patients (35.7%). The impact of neoadjuvant therapy also did not appear to significantly alter this rate of node positivity. Axillary radiation and systemic therapies could account for this lack of local recurrence, in part, but there was no difference in the use of post-mastectomy radiation therapy or systemic treatment modalities between the two groups. Our findings are consistent with studies of SLNB in unifocal breast cancer where the axillary recurrence rate is very low. It is unclear whether this is due to the accuracy of the technique or the effectiveness of adjuvant therapies and will only be answered by randomized clinical trials.

Despite these limitations, the current study demonstrates that SLNB in MC/MF clinically node-negative breast cancer is feasible, with high sensitivity and specificity and low false negative rates that are similar to those observed in unicentric breast cancers. Further, the SLN identification rate is independent of the site of mapping agent injection. There were no axillary recurrences observed in our patient population. Our data support the routine use of SLNB for axillary staging in patients with clinically node negative MC/MF invasive breast cancer.

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Table 1

Patient and Tumor Characteristics in 93 Patients with Multicentric/Multifocal Invasive Breast Cancer Undergoing Sentinel Lymph Node Biopsy

Variable	Planned ALND (n = 41)	ALND only for positive SLN (n = 52)	P value
Mean Age (years)	54	59	NS
Tumor size			NS
T1	28(68%)	43(83%)	
T2	9(22%)	8(15%)	
T3	2(5%)	0	
T4	2(5%)	1(2%)	
Stage			NS
I	11(27%)	36(69%)	
II	21(51%)	14(27%)	
III	9(22%)	2(4%)	
IV	0	0	
Tumor grade			NS
I	3(7%)	11(21%)	
II	17(42%)	31(60%)	
III	21(51%)	10(19%)	
Histology			NS
IDC	33(80%)	40(77%)	
ILC	4(10%)	8(15%)	
Mixed	4(10%)	4(8%)	
LVI	10(20%)	15(36%)	NS
ER status			NS
ER positive	34(83%)	38(73%)	
ER negative	6(15%)	13(25%)	
Unknown	1(2%)	1(2%)	
PR status			NS
PR positive	27(66%)	30(58%)	
PR negative	12(29%)	20(38%)	
Unknown	2(5%)	2(4%)	
Her-2-neu status			NS
Amplified	8(19%)	9(17%)	
Non-amplified	31(74%)	38(73%)	
Unknown	3(7%)	5(10%)	
Method of SLN injection			NS
Blue dye	27(66%)	37(71%)	
Radiocolloid	2(4%)	1(2%)	
Both	12(30%)	14(27%)	
Site of injection			NS
Blue dye			

Variable	Planned ALND (n = 41)	ALND only for positive SLN (n = 52)	P value
Retroareolar	8(16%)	17(33%)	
Peri-tumoral	42(84%)	34(67%)	
Radiocolloid			
Peri-tumoral	14(100%)	15(100%)	
XRT	30(58.8%)	27(71.1%)	NS
Systemic chemotherapy			NS
Yes	31(76%)	42(81%)	
No	10(24%)	10(19%)	
Endocrine therapy			NS
Yes	27(66%)	31(59%)	
No	14(34%)	21(41%)	
Axillary Metastasis	28(61%)	6(12%)	<0.01

ALND = axillary lymph node dissection; SLN = sentinel lymph node; IDC = invasive ductal cancer; ILC = invasive lobular cancer; LVI = lymphovascular invasion; ER = estrogen receptor; PR = progesterone receptor; XRT=radiation therapy