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Axillary Recurrence Rate Following Negative Sentinel Node Biopsy for Invasive Breast Cancer: Long-Term Follow-Up

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ABSTRACT

Objective. Sentinel lymph node (SLN) biopsy has replaced axillary lymph node dissection (ALND) as the definitive nodal staging procedure for breast cancer. SLN biopsy has been proven to cause less morbidity and be more cost effective than complete ALND. Short-term follow-up has shown that lymphatic mapping and SLN have a low false-negative rate, but there is limited data demonstrating long-term outcomes within a large consecutive series of patients.

Methods. Retrospective review of a prospective database of breast cancer patients at our institution was performed. The initial mapping of 1,530 patients with invasive breast cancer who demonstrated a negative sentinel node biopsy and no axillary dissection between January 1995 and June 2003 were collated and reviewed to achieve a long-term follow-up. These 1,530 patients were reviewed for follow-up time, local recurrences, distant metastases, and survival.

Results. 1,530 consecutively mapped invasive breast cancer patients had a negative SLN biopsy and no ALND. The mean invasive tumor size was 1.40 cm. Of 1,530 patients, 73% (1,121) underwent lumpectomy and 27% (409) underwent mastectomy. Mean follow-up was 4.92 years (range 0–12.0 years). There have been 4 (0.26%) patients presenting with local axillary recurrences, 54 (3.53%) patients presenting with local recurrences in the ipsilateral breast/chest wall, and 24 (1.57%) presenting with distant metastases.

Conclusion. These data confirm that SLN biopsy is an effective and safe alternative to ALND for detection of nodal metastases in patients with invasive breast cancer and should be used as the standard tool for nodal staging.

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The status of the axillary nodal basin is one of the most important prognostic indicators for recurrence and survival in patients with breast cancer.[1,2] Until the introduction of sentinel node mapping in the early 1990s, the standard operation of staging the axilla involved a level I and II axillary nodal dissection. This operation provided maximum local control of cancer while providing valuable staging information that guided additional treatment choices and provided prognostic information for patients and clinicians alike. Unfortunately, the advantages of an axillary dissection did not come without significant morbidity. Acute and chronic lymphedema, paresthesia and pain from intercostal and intercostal-brachial nerve injury, and seromas from axillary dissections made the ramifications of the surgery some of the most significant complaints of breast cancer treatment.[3]

As screening mammography and breast cancer awareness increased, the percentage of patients with positive lymph nodes decreased to approximately 30%.[4] As a result, 70% of patients with breast cancer were taking on morbidity of an axillary dissection while receiving minimal benefit. The advent of lymphatic mapping which removed the first few nodes that drained the breast provided a solution to this problem that minimized morbidity from axillary surgery while improving the ability to stage the axilla accurately.[5,6]

Initially, sentinel node biopsies were validated with mandatory completion axillary nodal dissections following removal of the sentinel node to ensure a low rate of false-

negative nodes being missed. Multiple published trials produced false-negative rates of 5–10%, which was deemed acceptable to avoid an axillary dissection with a negative sentinel node.[7–9] Further studies demonstrated that this false-negative rate could be lowered to less than 5% with immunohistochemical staining of the sentinel node and increased surgeon experience.[8] As a result, the accuracy of a sentinel node improved the detection of locating axillary metastases where the single node could be thoroughly sectioned, immunohistochemically (IHC) stained, and reviewed pathologically versus the prior cursory review of hematoxylin and eosin (H&E) stains of single sections of all bivalved harvested nodes.[10]

While these initial studies were promising, long-term data have been limited. While diagnostic accuracy may have improved with sentinel node biopsy, local recurrence should be improved. The aim of this study is to demonstrate the accuracy of sentinel node biopsy alone without combined axillary dissection as an effective tool for axillary staging and concomitant local control by demonstrating a low axillary recurrence rate on long-term follow-up.

MATERIALS AND METHODS

An Institutional Review Board (IRB)-approved Health Insurance Portability and Accountability Act (HIPPA)-compliant breast cancer database and electronic health record (IRB# 102554) prospectively accrued 3,682 patients undergoing 4,186 sentinel node biopsies between January 1995 and June 2003. Under separate IRB approval (IRB# 105928), this database was queried for invasive breast cancer patients with pathology reports showing no metastatic disease N0 (i-) IHC negative on sentinel node biopsy and no axillary further axillary dissection.

A total of 1,530 patients were identified that fulfilled this requirement. The sentinel nodes were identified using a combination technique of technetium sulfur colloid and isosulfan blue dye.[11] Routine pathologic evaluation included intraoperative imprint cytology of nodes, followed by sectioning of the node into 2-mm sections and sequential placement in cassettes for paraffin embedding, which were then faced, cut, and stained with H&E, followed by cuts at 50 and 100 μm stained for CK-IHC (CAM 5.2; Becton Dickinson) and, as a control for the IHC stains, counterstained with hematoxylin.

Follow-up data was obtained from IRB-approved (IRB #102554) breast cancer database and chart review. To improve the accuracy of survival data for all patients, data was checked against the Social Security Death Index online database (http://ssdi.rootsweb.com).

RESULTS

Between January 1995 and June 2003, 1,530 patients with invasive breast cancer were found to have a sentinel node negative for malignancy and did not receive an axillary dissection. The mean age at time of surgery was 59.7 years (range 24.6–91.0 years). The histology of the invasive tumor was as follows: invasive ductal (78.0%), invasive lobular (9.0%), mixed (5.2%), tubular (3.4%), mucinous (1.7%), and other (2.8%). The mean size of the invasive tumor was 1.40 cm.

The mean number of SLNs excised per axilla was 2.45 (range 0–9). The mean number of nonsentinel nodes excised was 0.98 (range 0–9). All sentinel nodes removed were negative for malignancy by hematoxylin and eosin as well as immunohistochemistry. All nonsentinel nodes were negative for hematoxylin and eosin only. Of 1,530 patients, 1,121 (73%) had their primary breast cancer resected with a lumpectomy, whereas 409 (27%) underwent mastectomy. Adjuvant chemotherapy was delivered to 392 (25.6%) patients, whereas 775 (51.0%) patients received hormonal therapy following their operation for breast cancer.

The average time of follow-up for the 1,530 patients was 4.92 years (range 0–12 years). Four patients (0.26%) have presented with local axillary recurrences, at an average of 5.76 years after their initial sentinel node operation. One of these four patients developed an axillary recurrence at the same time that an ipsilateral breast recurrence was identified. Twenty-four patients (1.57%) presented with distant metastatic disease, at an average of 3.69 years after the sentinel node operation. Table 1 compares these groups by site of recurrence. There have been 157 patients (10.3%) who have died, at an average of 4.23 years following the surgery.

DISCUSSION

As surgeon experience with sentinel node biopsies has improved and mandatory axillary dissections have been abandoned, the efficacy of negative sentinel node biopsy needs long-term validation. Not only does the sentinel node need to stage the patient's cancer accurately; it must also provide local control of disease comparable to that of axillary dissection. There is little argument over the accuracy of staging with a sentinel node; however, the risk of axillary recurrence after a sentinel node alone is slowly emerging.

The universal convention of the reporting of sentinel node false-negative (FN) rates throughout the world's literature and the methods of calculating the FN rates have lead to great confusion. The following example illustrates the point: 1 FN case out of 173 patients mapped with 120

TABLE 1 Patient characteristics by site of recurrence

Number of patients	Recurrence site	%	Average age (years)	Follow-up time (years)	SLN excised	Non-SLN excise	Size invasive tumor (cm)	Time to recurrence (years)	Deaths
1,429	No evidence of disease	93.40%	59.86	4.85	2.45	0.97	1.38	n/a	125
4	Ipsilateral axilla	0.26%	66.03	6.60	3.00	0.25	1.65	5.76	3
54	Ipsilateral breast/chest wall	3.53%	52.61	6.10	2.43	1.17	1.55	4.08	10
19	Contralateral breast	1.24%	67.45	5.71	1.63	1.32	1.44	2.91	3
24	Metastatic disease	1.57%	57.52	5.10	2.63	1.25	2.05	3.69	16
1,530	Total		59.68	4.92	2.45	0.98	1.40		157

negative sentinel nodes and 53 positive sentinel nodes constitutes our original data for all having a sentinel node biopsy followed by axillary dissection.[12] The method that has been universally reported in sentinel node papers for the calculation of the false-negative rate is FN/(true positives + FN) [1/(53 + 1) = 1.9%], which defines how many of the positive cases would be missed by a sentinel node mapping.[7–9] This should be compared with FN/(true negatives + FN) [1/(119 + 1) = 0.83%], which was not held as the convention but defines how many of the node-negative patients would have a positive lymph node following axillary dissection. Interestingly, the later calculation is the one that most closely parallels the actual long-term follow-up data (0.26% ipsilateral recurrence rate) and that is the more clinically relevant. Despite all of these concerns that have led to an overreporting of false negatives for SLN mapping throughout the literature, the observed rate of recurrence in patients with a negative sentinel node remains lower than any calculated risk, validating its efficacy in staging and local control.

A review article and meta-analysis that assessed the existing published data on this subject through the beginning of 2007 was recently published.[13] Forty-eight papers were identified, with an average follow-up of 34 months. An axillary recurrence rate after a negative sentinel node of 0.3% was identified, involving 14,959 patients and with most recurrences occurring within 20 months of the negative sentinel node biopsy. The largest study included in the meta-analysis was Memorial Sloan–Kettering's 2005 evaluation of 2,340 patients with 31-month follow-up, demonstrating a 0.13% recurrence rate.[14] Since this review article was published, The Swedish Multicenter Cohort Study has reported a 1.2% recurrence rate based on 2,246 patients with mean follow-up of 37 months.[15] Table 2 summarizes the recurrence rates of publications with at least 500 patients.[14–22]

An interesting note should be made of the meta-analysis in that only one paper had follow-up longer than 5 years (65 months).[23] The recurrence rate in this group was higher than in the majority of the papers published in the past (2.68%). In the evaluation of our local axillary recurrences, the mean time to axillary recurrence was 5.76 years (23, 46, 102, and 110 months), which is longer than any published data mean follow-up.

Although our data and multiple other publications support an acceptable rate (0.1–0.3%) of local axillary recurrences with short-term follow-up, we caution that this rate may increase as the length of follow-up extends past 5 years, as half of our local recurrences occurred after this period of time. However, in response to questioning of the local control of a negative sentinel node, we doubt that the rate of axillary recurrences would rise to levels greater than

TABLE 2 Publications on axillary recurrence rates following a negative sentinel node biopsy with at least 500 patients

First author	Year	Number of patients	Mean follow-up (months)	Axillary recurrences	Rate of axillary recurrence (%)
Naik[14]	2004	2,340	31	3	0.13
Bergkvist[15]	2008	2,246	37	27	1.20
Kiluk	2009	1,530	59.9	4	0.26
Takei[16]	2007	1,062	34	4	0.38
Veronesi[17]	2005	953	38	3	0.31
Poletti[18]	2008	804	38.8	6	0.75
Blanchard[19]	2003	685	29	1	0.15
Jeruss[20]	2005	592	27	1	0.17
Swenson[21]	2005	580	33	3	0.52
Carcoforo[22]	2006	566	26	3	0.53

the historical values of recurrence following axillary dissection. As Naik et al. reviewed among clinical node-negative patients who underwent axillary dissection, axillary recurrence rates are less than 2% with follow-up greater than 5 years.[14,24–27] Furthermore, recurrence rates with either a sentinel node biopsy or axillary dissection compare favorably with axillary recurrence rates without axillary treatment. For T1c and T2 lesions, local axillary recurrence rates have been found to be 10% and 18%, respectively, with 5 years of follow-up when the axilla is not addressed by either axillary dissection, sentinel node or axillary radiation.[28]

As surgeons, it must be clearly stated that the surgical role in the treatment of breast cancer is twofold: *accurate staging* and *local control*. The status of the axilla in breast cancer plays an important role in determining prognosis as well as maximizing local axillary control. While not the focus of this paper, the improved accuracy for breast cancer staging of sentinel node mapping achieves the primary surgical objective. This study demonstrates that the surgical role of local control with a mean of 5 years of follow-up in over 1,000 patients is not compromised by avoiding an axillary dissection in a patient who has a negative sentinel lymph node.

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