Original Study

Characteristics of Breast Carcinoma Cases With False-Negative Sentinel Lymph Nodes

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Abstract

A false negative sentinel lymph node is defined histologically as devoid of metastases but found to be positive on additional axillary nodes. We characterized the clinicopathologic features of these cases by identifying and studying 63 cases over 12 years. False negative sentinel lymph nodes were found to be associated with lobular or poorly differentiated histology and or partial/complete replacement of nodes.

Background: In the past decade, sentinel lymph node biopsy (SLNB) has become standard for patients with early-stage clinically node-negative breast carcinoma (BC). Despite high overall surgical identification success rates with introduction of the dual-tracer techniques (dye and radiolabeled probe), false-negative rates remained unchanged in most recent meta-analyses. **Patients and Methods:** We analyzed cases with false-negative SLN biopsy results over a 12-year period in a single institution to evaluate their clinicopathologic characteristics. Sixty-three false-negative cases (3.1%) were found in 2043 successful SLN mapping procedures, all of which were followed by varying amounts of additional axillary sampling. **Results:** There was a higher proportion of invasive lobular carcinomas (ILCs; 23 cases [37%]) when compared with this lesion's overall reported frequency (5%-15%). The majority of invasive ductal carcinoma (IDC) cases (31 of 40) were poorly differentiated. In 80% of the ductal-type cases, 1 or more nonsentinel nodes (NSLNs) were completely or partially replaced by tumor, as opposed to less than half of such cases of the lobular type. Twenty-two cases had multiple positive NSLN metastases, which were significantly associated with larger tumor size ($\geq$ 1.0 cm) and tumor replacement of NSLNs. Eighty-two percent of the cases with known hormone receptor status were positive for estrogen or progesterone receptors, or both. **Conclusion:** False-negative SLN biopsy results were more often associated with a primary BC characterized by a lobular or poorly differentiated ductal histologic type or partial to complete replacement of NSLNs with tumor, or both.

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Introduction

When used properly, sentinel lymph node biopsy (SLNB) is a minimally invasive procedure that accurately assesses axillary lymph node (ALN) status, with significant reduction in morbidity.[1-3] Strictly defined, the SLN is the first lymph node (or group of nodes) in a lymphatic basin that receives drainage from a region or primary tumor occurring in that region, or both, and is identified by blue dye or radiotracer, or both. For the purpose of our study, we used only this definition rather than including cases that were clinically suspicious intraoperatively; lymph nodes were classified by the surgeons as "sentinel" only when they were blue or "hot," or both blue and hot. Given that breast carcinoma (BC) is the most common cancer and the second cause of cancer deaths in women today, it is in BC that SLNB has had its greatest impact overall. A standard level I and level II ALN dissection (ALND) has been reserved only for patients with positive or unsatisfactory SLNB results (failure to identify the SLN). However in light of recent results of the ACOSOG Z11 trial[4] in patients with T1-2 carcinomas treated by lumpectomy, SLNB, irradiation, and systemic therapy, ALND may be unnecessary. The results indicate that the additional information conferred by ALND did not change therapy or prognosis. However, if ALND is to be avoided, the pathologic accuracy of the SLN status should be maximized and the incidence of false-negative SLNB results should be minimized.

From the pathologist's point of view, rather than performing histologic examination of multiple ALNs, it is easier to focus on

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the few SLNs that most likely contain metastasis, thereby increasing the likelihood of finding micrometastases or isolated tumor cells. Although the definition of an SLN has been reasonably well established, breast surgeons have given false-negative SLNs multiple different definitions, of which the most accepted is one in which an SLN is disease free on initial pathologic evaluation, but metastasis is identified in additional ALNs any time thereafter.[5] Conversely, despite their pivotal clinical role, the pathologic handling of SLNs remains variable, and there is no consensus.[6] The incidence of false-negative SLN biopsy results, albeit rare in experienced hands, must be minimized if the procedure is to be used as a substitute for ALND. However, a large body of literature has focused on minimizing surgical identification failures, and little has been written regarding the histopathologic aspects of false-negative SLN cases. Thus, the goal of this study was to evaluate the characteristics of BC cases with false-negative SLNs using a large single-institution population of patients whose SLNs were handled pathologically in a uniform manner.

Patients and Methods

Over a 12-year period (February 1998-August 2009), 2811 consecutive unselected SLN localization procedures were performed on patients with newly diagnosed breast cancer at Mount Sinai Hospital (New York, NY), 106 procedures of which failed to identify an SLN. Among the remaining successful SLN biopsy procedures, 2043 cases had varying amounts of additional ALND in addition to SLNB, nearly all of which were performed at the same time. As a standard surgical practice, additional ALND was performed in patients with any suspicious nodes intraoperatively, other than those identified by blue dye or radiotracer. Histologic features of the primary tumor identified on core biopsy that were predictive of a positive SLN—such as high grade of tumor, lymphatic invasion, and a micropapillary histologic type—also influenced the surgeon's decision to remove additional lymph nodes. Finally additional ALND was performed routinely in the earliest years of the study population at a time when surgeons were still familiarizing themselves with the SLNB procedure. Reoperative SLN cases were excluded.

All SLNs removed in our institution were bisected, entirely embedded, and sectioned by a routine protocol of 5 additional levels stained with hematoxylin and eosin followed by 2 immunohistochemical (IHC) stains for keratins (CAM 5.2 and AE1/AE3), as previously described.[7] The presence of completely negative SLNs with one or more positive non-SLNs (NSLNs) was defined as a false-negative SLN. Although we currently use the American Joint Committee on Cancer, 7th edition staging manual, for the purposes of this study, cases of single or multiple SLNs containing only individual tumor cells—ie, N0(i+)—were excluded from consideration as being potentially false negative. We reviewed the clinical and microscopic features of all the primary BCs and SLNs, including IHC results. We used the Bloom-Richardson grading system for grading the primary BCs, assessing the degree of tumor tubule formation, mitotic activity, and nuclear grade. IHC analysis for estrogen receptor (ER; clone SP1), progesterone receptor (PR; clone 1E2), and human epidermal growth factor receptor 2 (HER2) (mAb 4B5) was performed and reviewed on paraffin sections of the BC, and creatine kinase IHC analysis was performed for SLNs using a protocol previously described.[8]

Table 1 Clinicopathologic Characteristics of False-Negative Sentinel Lymph Nodes

Variable	IDC	ILC	Overall
Number of Cases	40	23	63
Average Age (years)	55 (25-85)	58 (26-80)	56 (25-85)
Average Tumor Size (cm)[a]	1.8 (0.1-3.8)	1.7 (0.5-5.0)[b]	1.8 (0.1-5.0)
Multifocality	6	4	10
Histologic Variants	5 micropapillary[c] 3 anaplastic	7 tubulolobular[d] 8 pleomorphic[d]	
Tumor Grade			
Well differentiated	1		
Moderately differentiated	8		
Poorly differentiated	31		
Lymphatic Invasion	21	12	33
NSLN Replacement by Tumor	32[e]	11	43
Multiple Positive NSLNs	15	7	22[f,g]
Extranodal Extension	6	5	11[h]
ER/PR/HER2 Status			
ER+ and/or PR+	29	18	47
ER-/PR-/HER2+	3	0	3
ER-/PR-/HER2-	5	2	7
Unknown	3	3	6

Abbreviations: ER^+ = estrogen receptor positive; ER^- = estrogen receptor negative; $HER2^+$ = human epidermal growth factor receptor positive; $HER2^-$ = human epidermal growth factor receptor negative; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; NSLN = nonsentinel lymph node; PR^+ = progesterone positive; PR^- = progesterone negative.
[a]The largest sizes were used in case of multifocality.
[b]n = 22 (one consultation case was reportedly multifocal and the size could not be assessed on a single slide).
[c]Significantly associated with lymphatic invasion ($P = .025$).
[d]Tubulolobular carcinomas were less likely, and pleomorphic lobular carcinomas were more likely, to have NSLN tumor replacement, but not to the extent of statistical significance ($P = .069$ and .089, respectively).
[e]Significantly associated with NSLN tumor replacement ($P = .012$).
[f]Significantly associated with tumor size $\geq$ 1.0 cm ($P = .009$).
[g]Significantly associated with replacement by tumor ($P = .0006$).
[h]Significantly associated with lymphatic invasion ($P = .046$) and NSLN replacement by tumor ($P = .028$).

We also noted the identity of the particular surgeon performing SLNB in each case.

The data obtained were statistically evaluated using either the χ^2 test or the Fisher exact test, as appropriate. $P = .05$ was considered statistically significant.

Results

Characteristics of cases with false-negative SLNs are summarized in Table 1. SLNs were falsely negative in 63 of 2043 cases (3.1%). The false-negative rate did not vary between individual surgeons. The patients' ages ranged from 25 to 85 years, with an average of 56 years. The invasive tumor size ranged from 0.1 to 5.0 cm (average, 1.8 cm), of which 10 cases were multifocal.

In reviewing the BC in these cases, 40 (63%) were invasive ductal carcinomas (IDCs), 10 (16%) were invasive lobular carcinomas (ILCs), and 13 (21%) were mixed ductal and lobular, predominantly lobular. There were no significant differences in patient age or tumor size between different tumor types.