ANNALS OF SURGERY
Vol. 229, No. 4, 536–541

Do All Patients With Sentinel Node Metastasis From Breast Carcinoma Need Complete Axillary Node Dissection?

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Objective

To determine the likelihood of nonsentinel axillary metastasis in the presence of sentinel node metastasis from a primary breast carcinoma.

Summary Background Data

Sentinel lymphadenectomy is a highly accurate technique for identifying axillary metastasis from a primary breast carcinoma. Our group has shown that nonsentinel axillary lymph nodes are unlikely to contain tumor cells if the axillary sentinel node is tumor-free, but as yet no study has examined the risk of nonsentinel nodal involvement when the sentinel node contains tumor cells.

Methods

Between 1991 and 1997, axillary lymphadenectomy was performed in 157 women with a tumor-involved sentinel node. Fifty-three axillae (33.5%) had at least one tumor-involved nonsentinel node. The authors analyzed the incidence of nonsentinel node involvement according to clinical and tumor characteristics.

Results

Only two variables had a significant impact on the likelihood of nonsentinel node metastasis: the size of the sentinel node metastasis and the size of the primary tumor. The rate of nonsentinel node involvement was 7% when the sentinel node had a micrometastasis (≤2 mm), compared with 55% when the sentinel node had a macrometastasis (>2 mm). In addition, the rate of nonsentinel node tumor involvement increased with the size of the primary tumor.

Conclusions

If a primary breast tumor is small and if sentinel node involvement is micrometastatic, then tumor cells are unlikely to be found in other axillary lymph nodes. This suggests that axillary lymph node dissection may not be necessary in patients with sentinel node micrometastases from T1/T2 lesions, or in patients with sentinel node metastases from T1a lesions.

Although surgical management of a primary breast cancer has evolved from radical mastectomy to breast-conserving techniques, surgical management of the axilla has changed little. The tumor status of lymph nodes excised during axillary lymph node dissection (ALND) is the best predictor of survival for patients with invasive breast cancer: as the number of lymph node metastases increases, survival decreases.[1,2] The presence of metastases often determines the need for adjuvant therapy, especially in patients with small primary tumors, and the number of metastases may influence the type of adjuvant therapy. However, the role of ALND as a therapeutic procedure is not clear. Several studies have suggested that it is without therapeutic benefit, even in patients with tumor-involved axillary lymph nodes.[3] Others assert that routine use of ALND can improve survival by ensuring regional control.[2]

The increased use of screening mammography has resulted in the earlier detection and the smaller size of inva-

Presented at the 51st Annual Cancer Symposium of the Society of Surgical Oncology, March 26–29, 1998, San Diego, CA.

Supported by funding from the Ben B. and Joyce E. Eisenberg Foundation (Los Angeles, CA), the Fashion Footwear Association of New York, and the Associates for Breast Cancer Research.

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Accepted for publication October 12, 1998.

sive breast cancers, thereby decreasing the incidence of axillary metastases.[3] This decrease intensifies the question of whether ALND is needed in all patients with invasive cancer. The incidence of axillary metastases is low in patients with T1a lesions,[4–7] but still arguably high enough to consider routine ALND.[8,9] An accurate means of identifying patients at low risk for axillary metastases would eliminate routine ALND in this group.[10]

Sentinel lymphadenectomy (SLND) is a highly accurate technique for identifying axillary metastases from an invasive breast carcinoma.[11–14] The sentinel node is defined as the first lymph node draining a specific breast cancer. It may be identified using a vital blue dye alone or in combination with a radioactive colloid.[2,14] If histopathologic examination shows that the sentinel node is free of metastasis, then other nodes in the same axilla are highly unlikely (1% to 2%) to contain tumor cells,[13,14] and the patient is unlikely to benefit from ALND. If the sentinel node contains tumor cells, however, the status of the remaining nonsentinel nodes in the axilla is unclear. This study examined tumor-related and patient-related factors that might be correlated with nonsentinel node metastasis in patients with a tumor-involved sentinel node.

PATIENTS AND METHODS

Patients and Operative Procedure

Intraoperative lymphatic mapping and SLND for patients with potentially curable breast cancer was initiated at our institution in 1991. From September 1991 through September 1995, SLND was undertaken in all patients scheduled for ALND, including those with locally advanced disease, large primary tumors, and/or palpable axillary lymph nodes. SLND was followed immediately by a completion ALND that removed all nodes in levels 1 and 2 and occasionally some nodes from level 3. From October 1995 through July 1997, SLND was undertaken only in patients with no clinical evidence of axillary involvement, and was not followed immediately by completion ALND unless frozen section examination of the sentinel node revealed tumor cells.

Of the 422 axillae in which a sentinel node was identified, 163 (38.6%) had a tumor-involved sentinel node. Five patients refused completion ALND, and therefore our study group consisted of 157 patients, including one case of bilateral synchronous breast cancer, for a total of 158 axillae. All 158 operations were performed by the same senior surgeon (AEG) after informed consent had been obtained.

Our technique of dye-directed SLND for patients with invasive breast cancer has been previously described.[11,13] Briefly, 3 to 5 cc of isosulfan blue dye (Lymphazurin 1%, Hirsch Industries, Inc., Richmond, VA) is injected into the breast parenchyma surrounding the primary tumor or biopsy cavity. Care is taken not to inject the dye into the biopsy cavity. After 5 to 7 minutes an axillary incision is made and a blue lymphatic tract is identified. This tract is dissected both proximally and distally until a blue-stained lymph node (sentinel node) is identified. The sentinel node is excised and sent for frozen section analysis.

During the assessment period (1991 to 1994) of the SLND technique, some patients underwent sentinel node localization using radiocolloid in addition to dye. Before surgery, 0.25 to 1.0 mC of a technetium-labeled radiopharmaceutical (Tc-99m albumin colloid, DuPont de Nemours, Billerica, MA; or Tc-99m sulfur colloid, CisUS, Bedford, MA) was injected into the breast parenchyma surrounding the primary tumor, or into the wall of the cavity created by the previous biopsy. For nonpalpable lesions, a needle left in the breast parenchyma after either mammographic or ultrasonographic localization was used as a guide to instill radioisotope in the area of primary tumor. Care was taken not to contaminate the skin with the radiopharmaceutical. Blue dye was also injected as described above. After the induction of general anesthesia or heavy intravenous sedation, a hand-held gamma counter (C-Trak, Carewise Medical, Palo Alto, CA; or Neoprobe 1000, Neoprobe Corp., Dublin, OH) covered with a sterile plastic sheath was used to localize the sentinel node. The lymphatic drainage pattern was mapped in the operating room, and a transverse axillary incision was made in the skin overlying the area with the greatest radioactivity. Blunt dissection was then carefully performed with the tips of a curved hemostat until the signal intensified; the lymph node with the greatest radioactivity and/or a blue stain was identified as the sentinel node. This node was excised and sent for pathologic review. The residual radioactivity in the axilla was then measured; if the basin remained hot, an attempt was made to find a second sentinel node.

When completion ALND was performed immediately after SLND, the ALND specimen was submitted separately for histopathologic examination. All patients underwent either segmental mastectomy or mastectomy after SLND. In patients seen after September 1995, completion ALND was performed as a second procedure if examination of permanent sections of sentinel node identified tumor cells not found during frozen section examination.

All patients were prospectively followed, and both clinical and tumor characteristics were entered into the database. Clinical characteristics included age, mode of tumor detection, and lymph node status; tumor characteristics included histologic type, grade, and size. The size of the primary tumor was determined from histopathologic sections by measuring the invasive component, and was used to classify the tumor according to the guidelines of the American Joint Committee on Cancer.[15] The size (maximum diameter) of sentinel node metastases, the number of tumor-positive sentinel nodes, and the mode of tumor detection (hematoxylin and eosin or immunohistochemistry) were also entered prospectively. Sentinel node tumor foci were defined as micrometastases ($\leq$2 mm) or macrometastases ($>$2 mm) using hematoxylin and eosin staining. A sentinel node metastasis detected only by immunohistochemistry

was identified as an immunohistochemistry metastasis. Estrogen receptor status, progesterone receptor status, HER-2/neu expression, DNA ploidy, and S-phase were evaluated as tumor-associated indicators of prognosis.

Histologic Examination of Axillary Lymph Nodes

All sentinel nodes and nonsentinel nodes were examined by multiple pathologists at our institution. Sentinel nodes were evaluated independently of nonsentinel nodes. For this study, all sentinel nodes were reviewed by pathologists to determine the size of metastases and method of detection. Each sentinel node removed during SLND was bisected and a frozen section was obtained to look for metastatic cells. The sentinel node was then processed routinely for permanent section with hematoxylin and eosin. Each node was blocked individually, with preparation of two permanent-section levels per paraffin block. If hematoxylin and eosin staining was negative for tumor cells, the sentinel node was examined with immunohistochemistry using an antibody cocktail (MAK-6, Ciba-Corning, Alameda, CA) directed against low- and intermediate-molecular-weight cytokeratin. Approximately six to eight histologic sections (including the frozen section) of each sentinel node were examined.

The ALND specimens were examined using standard pathologic techniques. Lymph nodes were identified visually or with manual palpation; no lymph node clearing solution was employed. Lymph nodes greater than 3 to 4 mm were grossly sectioned and all nodal tissue was embedded in paraffin; one or two histologic sections, stained with hematoxylin and eosin, were prepared for diagnostic evaluation. Cytokeratin immunohistochemical stains were not routinely used.

Statistical Analysis

All data were reviewed and analyzed by the biostatistical unit at our institution. The Pearson chi square test was used to assess the relation between nonsentinel node metastasis and each of the following potential predictors: age, histologic type, tumor grade, hormone receptors, S-phase fraction, DNA ploidy, HER-2/neu expression, angiolymphatic invasion, tumor location, tumor size, palpable primary tumor, palpable axillary nodal disease, size of sentinel node metastasis, number of tumor-involved sentinel nodes, and the mode of sentinel node micrometastasis detection. Multivariate analysis was carried out using logistic regression, and a stepwise procedure was employed for covariate selection.

RESULTS

The median age of the 157 patients was 52.5 years (range 28 to 91). Sixty-eight patients were premenopausal and 89 were postmenopausal. The median size of the primary tumor was 2.0 cm (range 0.1 to 11 cm). The mean number of sentinel nodes identified was 1.8 (range 1 to 7), and the mean number of tumor-involved sentinel nodes was 1.3 (range 1 to 5). The mean number of nonsentinel nodes identified was 17.8 (range 5 to 60), and the mean number of tumor-involved nonsentinel nodes was 1.5. The majority of patients (79%) underwent segmental mastectomy; 33 patients (21%) underwent mastectomy. The sentinel node was the only positive lymph node in 105 of 158 axillae (66.5%). The remaining 53 (33.5%) axillae had at least one tumor-involved nonsentinel node (range 1 to 31; Table 1).

Table 1. NUMBER OF TUMOR-INVOLVED NONSENTINEL NODES IN PATIENTS WITH A TUMOR-INVOLVED SENTINEL NODE

No. of Tumor-Involved Nonsentinel Nodes	Number of Axillae (%)
0	105 (66.5)
≥1	53 (33.5)
1	16 (30.2)
2	13 (24.5)
3	6 (11.3)
4	4 (7.5)
5	1 (1.9)
6	3 (5.7)
7	2 (3.8)
10	2 (3.8)
12	1 (1.9)
14	1 (1.9)
16	2 (3.8)
20	1 (1.9)
31	1 (1.9)

By univariate analysis, four factors were significant predictors of nonsentinel node metastasis: size of sentinel node metastasis (Fig. 1), size of primary tumor (Fig. 2), clinical status of the axilla (Fig. 3), and number of tumor-positive sentinel nodes (see Fig. 3). The mode of sentinel node tumor detection was also significant in patients with sentinel node micrometastasis (Table 2); if the sentinel node metastasis was detected by immunohistochemical staining only, none of the nonsentinel nodes demonstrated metastasis (see Fig. 3). Among the other risk factors examined, only tumor grade and angiolymphatic invasion approached statistical significance (see Table 2).

Multivariate analysis using logistic regression and a stepwise procedure defined only two covariates: size of primary tumor and size of sentinel node metastasis (see Table 2). The clinical status of the axilla (palpable *vs.* nonpalpable) and the number of tumor-positive sentinel nodes dropped out because of their significant correlation with primary tumor size and the size of sentinel node metastasis.

Primary tumor size was then correlated with sentinel node macrometastasis and sentinel node micrometastasis independently to demonstrate the different rates of nonsentinel node metastasis. In patients with T1 and T2 lesions, the incidence of nonsentinel node involvement was 50% with

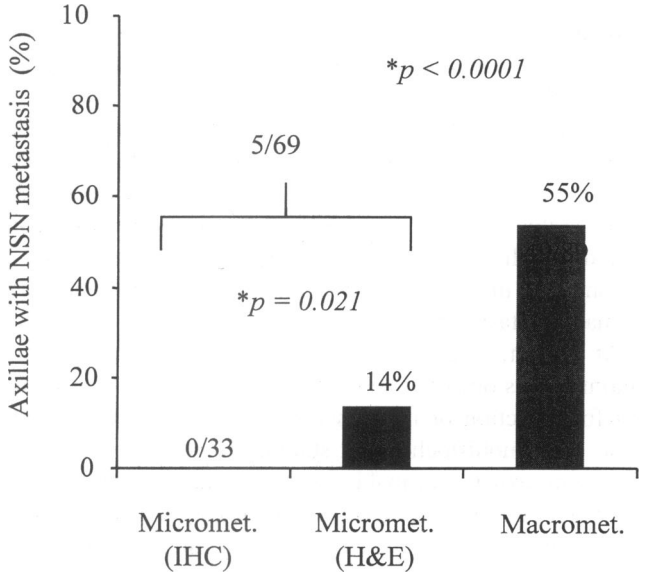

Figure 1. Rate of nonsentinel node metastasis according to the size of the sentinel node metastasis. Macrometastasis (macromet.) is defined as a tumor deposit >2 mm in maximum diameter; micrometastásis (micromet.) is a tumor deposit ≤2 mm in maximum diameter. H&E = hematoxylin and eosin stain; IHC = immunohistochemistry. The ratios inside the bars indicate the number of tumor-involved axillae with respect to the total number of axillae having the same number of tumor-involved sentinel nodes. *Analysis performed using the Pearson chi square test.

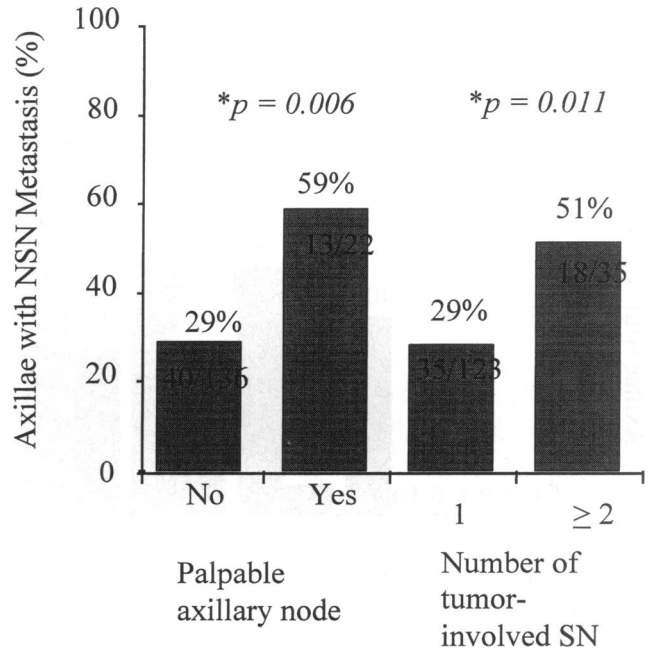

Figure 3. Rate of nonsentinel node metastasis according to the clinical status of the axilla and the number of tumor-involved sentinel nodes. The ratios inside the bars indicate the number of tumor-involved axillae with respect to the total number of axillae. *Analysis performed using the Pearson chi square test.

sentinel node macrometastases but only 6% with sentinel node micrometastases (Fig. 4). Of the five patients with T1a lesions, four had sentinel node micrometastases, one had sentinel node macrometastases, and none had nonsentinel node metastases. Among patients with T1b lesions, none of the 10 patients with sentinel node micrometastases had nonsentinel node involvement, whereas 2 of 5 (40%) with

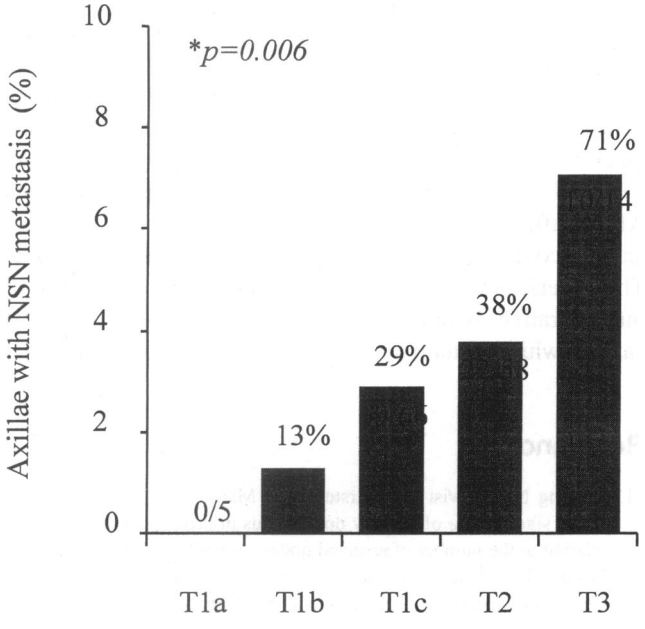

Figure 2. Rate of nonsentinel node metastasis according to the size of the primary tumor (T stage). The ratios inside the bars indicate the number of tumor-involved axillae with respect to the total number of axillae for each primary tumor size. *Analysis performed using the Pearson chi square test.

Table 2. LIKELIHOOD OF NONSENTINEL NODE METASTASIS: UNIVARIATE AND MULTIVARIATE ANALYSIS

Clinicopathologic Factors	p Value	
	Univariate	Multivariate
Size of sentinel node metastasis	<0.0001	0.0001
Size of primary tumor	0.006	0.014
Palpable axillary node	0.006	—
Number of tumor-positive sentinel nodes	0.011	—
Mode of detecting micrometastasis*	0.021	—
Tumor grade	0.051	—
Angiolymphatic invasion	0.073	—
DNA ploidy	0.145	—
Age	0.187	—
Estrogen receptor	0.207	—
S-phase fraction	0.216	—
Palpability	0.349	—
HER-2/neu expression	0.444	—
Progesterone receptor	0.714	—
Tumor location	0.722	—
Histology	1.000	—

Hematoxylin and eosin *vs.* immunohistochemistry.

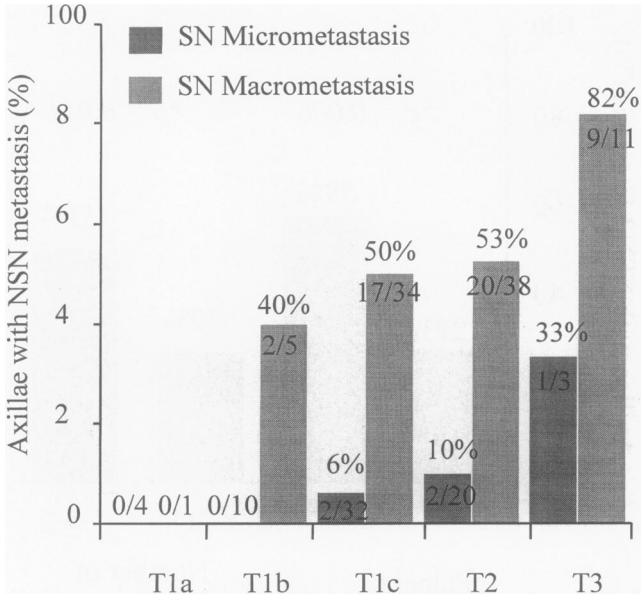

Figure 4. Rate of nonsentinel node metastasis according to the size of the primary tumor and the size of the sentinel node metastasis. The ratios inside the bars indicate the number of tumor-involved axillae with respect to the total number of axillae for each primary tumor size.

sentinel node macrometastases had nonsentinel node metastases. The incidence of nonsentinel node metastasis increased with the size of the primary tumor in patients with sentinel node macrometastases or micrometastases.

DISCUSSION

Sentinel lymph node dissection is emerging as a highly sensitive sampling technique for identifying axillary metastases from an invasive breast carcinoma.[13,16] If hematoxylin and eosin plus immunohistochemical staining of multiple sections of a sentinel node reveals no tumor cells, then nonsentinel axillary nodes are very unlikely to contain tumor. If the sentinel node contains tumor cells, the incidence of nonsentinel node metastasis increases but may still be very low in certain patients. In this study, we were able to identify these patients based on the size of the primary tumor and the size of the sentinel node metastasis. Consistent with many studies,[17–21] we found that the incidence of nonsentinel node metastases increased as the primary tumor increased in size. Even more important was the size of sentinel node metastases: the incidence of nonsentinel node involvement was 6% in patients with sentinel node micrometastases, regardless of the primary tumor size. However, if the sentinel node contained a macrometastasis, the incidence of nonsentinel node metastases increased to 47.5%, even in patients with T1 lesions. Thus, patients with T1 or T2 tumors and sentinel node micrometastases had a low incidence of nonsentinel node metastases (see Fig. 4).

The incidence of axillary metastases from T1 breast carcinomas approached 25% in our previous study and other reports.[9,13] This rate may be too high to abandon examination of axillary lymph nodes. Sentinel lymphadenectomy can identify patients with axillary involvement from a T1 tumor with a very low morbidity rate. Of the five patients in our study with T1a lesions, one patient had sentinel node macrometastasis, four patients had sentinel node micrometastases, and none had nonsentinel node metastasis. We propose that completion ALND might not be beneficial in patients with sentinel node micrometastases from T1/T2 lesions, and in patients with sentinel node micrometastases or macrometastases from T1a lesions.

At present, surgical management of invasive breast carcinoma relies on conventional hematoxylin and eosin staining for detection of micrometastases in an excised lymph node. Immunohistochemical staining is more sensitive but also more expensive, making it impractical for routine use in nonsentinel node specimens. Moreover, although immunohistochemical staining would likely increase the incidence of nonsentinel node micrometastases, the clinical significance of tumor deposits detected by immunohistochemistry is unclear. Several studies[22,23] suggest that occult metastases may affect overall survival, whereas others do not come to this conclusion.[3,24] Further studies are needed to determine the significance of micrometastases.

In summary, SLND with focused sentinel node pathologic examination is predictive of metastases in the rest of the axillary nodes, not only when the sentinel node is tumor-free but also when it is involved with tumor. Interestingly, we found that the size of the sentinel node metastasis was more significant than the size of the primary tumor in predicting tumor involvement of nonsentinel nodes. These two independent predictors can be used together to identify a subgroup of patients in whom ALND is unlikely to remove residual disease detected by hematoxylin and eosin, and who thus may not benefit from completion ALND. These patients have T1 or T2 lesions and sentinel node micrometastasis, or T1a lesions and sentinel node macrometastasis or micrometastasis. A prospective randomized trial now is indicated to determine whether completion ALND after SLND has any significant impact on the clinical outcome of patients with invasive breast carcinoma. The American College of Surgeons will soon begin a trial of intraoperative lymphatic mapping and SLND for breast cancer, which potentially could answer this question.

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