Axillary Dissection Is Not Required for All Patients With Breast Cancer and Positive Sentinel Nodes

J. Michael Guenther, MD; Nora M. Hansen, MD; L. Andrew DiFronzo, MD; Armando E. Giuliano, MD; J. Craig Collins, MD; Baiba L. Grube, MD; Theodore X. O’Connell, MD

Hypothesis: Sentinel node (SN) biopsy for breast cancer enhances staging sensitivity, often demonstrating only micrometastases (<2 mm) or isolated, keratin-positive cells. When SN metastasis is present, the value of additional axillary dissection is unclear and not all patients benefit from axillary lymph node dissection (ALND).

Design: Prospective cohort study, median 32-month follow-up.

Setting: Multidisciplinary breast cancer centers.

Patients: Forty-six women having SN metastases diagnosed between May 1, 1996, and September 1, 2001, who refused ALND or were recommended to omit ALND owing to serious comorbid conditions.

Interventions: Isosulfan blue dye–directed SN biopsy. Axillary lymph node dissection was not performed. Standard breast irradiation was given. Adjuvant systemic therapy was provided as determined by an oncologist. Interval clinical evaluation was performed.

Main Outcome Measure: Axillary and systemic failure rates.

Results: Mean patient age was 61.6 years (age range, 36-92 years). Mean tumor size was 1.65 cm (range, 0.4-5.5 cm). Thirty-five (76%) of 46 tumors were ductal carcinomas and 39 (87%) of 45 were estrogen receptor–positive. A mean of 2.6 SNs were identified (median, 2; range, 1-7). Thirty-nine patients (85%) had a single positive SN; the remaining 7 patients (15%) had 2 positive SNs. Seven patients (15%) had macrometastases (>2 mm); 16 (35%) had micrometastases (<2 mm); and 23 (50%) had cellular metastases. Only 16 positive SNs (35%) were seen on hematoxylin-eosin staining, while 30 SNs (65%) had positive immunohistochemical staining. There have been no axillary recurrences. One patient (2%) developed distant metastases during follow-up (range, 4-61 months).

Conclusions: Patients with SN metastases who did not have ALND had a low incidence of regional failure. To confirm this observation, we suggest that patients with SN metastases are ideal candidates for trials evaluating the necessity of ALND.

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THE APPLICATION of Cabanas’ concept of the “sentinel node” (SN) to malignant melanoma by Morton et al in 1992 greatly increased the sensitivity of surgical staging and provided a basis for omitting routine lymphadenectomies when the SN is tumor free. This practice substantially reduces the number of patients undergoing complete lymph node dissections, which avoids the possible complication of lymphedema. Use of isosulfan blue dye and, later, radioisotopes for audiovisual identification of the node(s) most likely to contain metastatic disease has revolutionized the treatment of melanoma. In a similar fashion, the adaptation of lymphatic mapping and SN biopsy for breast cancer staging by Giuliano et al and Krag et al has been one of the most significant surgical innovations of the last decade and has revolutionized the approach to treatment of breast cancer. Sentinel node biopsy for breast cancer has repeatedly and reproducibly been proven to increase the sensitivity of surgical staging through the discovery of microscopic or even cellular metastases missed on routine pathologic review.

Although increased staging accuracy is desirable, the main benefit for patients with SNs negative for disease is the negligible incidence of arm lymphedema. Most (60%-80%, depending on tumor size) patients undergoing this more refined method of surgical staging have tumor-free SNs; thus, the benefit most

From the Kaiser Los Angeles Medical Center, Los Angeles, Calif (Drs Guenther, DiFronzo, Collins, and O’Connell), and the Joyce Eisenberg Keefer Breast Center at St John’s Hospital, Santa Monica, Calif (Drs Hansen, Giuliano, and Grube).
women receive is a result of avoiding axillary lymph node dissection (ALND).

For patients with lymph node metastases, ALND has long been the standard of care. The standard levels 1 and 2 ALNDs obtain excellent regional control, provide prognostic information to patients and physicians, and have the potential to alter the extent or type of adjuvant therapy. A survival benefit of ALND has not been demonstrated, nor has it been conclusively disproved. As a result, important questions remain, namely, what is the role of ALND for patients whose SN contains metastatic disease? Is ALND a therapeutic procedure that is essential for regional and/or systemic control or merely a radical staging procedure with little other benefit? What is the axillary recurrence rate if no further axillary surgery beyond SN dissection is performed? We hypothesize that a significant percentage of patients with SN metastases, particularly those with small, estrogen receptor (ER)–positive cancers and SN micrometastases, have low regional recurrence rates and may safely avoid ALND and its complications.

### METHODS

From May 1, 1996, to September 1, 2001, 46 women with invasive breast cancer and SN metastases were identified and underwent no further axillary surgery after definitive breast surgery. Either these patients were given a recommendation to omit ALND or they refused ALND despite recommendations to the contrary.

A recommendation to avoid ALND was made based on any of several factors: advanced age, the presence of significant medical comorbidity, inability to tolerate general anesthesia, a high likelihood of lymphedema after ALND, the combination of small primary tumors with SN micrometastases, and the lack of effect of further nodal pathologic abnormality on adjuvant therapy decisions.

Patients refusing ALND cited various reasons, including alteration of body image and inability to tolerate any significant lymphedema (careers based on upper extremity function—athletes, sculptors, musicians, and others). Another reason given was the lack of proven therapeutic benefit from ALND. None of the study group underwent ALND.

### OPERATIVE TECHNIQUE

Lymphatic mapping was performed using isosulfan blue dye injected into peritumoral breast tissue or the biopsy cavity wall if a previous excisional biopsy had been performed. In most circumstances, 5 mL of isosulfan blue dye was injected, but the amount varied with the distance of the primary tumor from the axilla; 6 to 7 mL was injected around tumors remote from the axilla; and 3 to 4 mL was injected around tumors high in the upper outer quadrant of the breast. Similarly, breast compression and percussion was performed for about 5 minutes after injection of the dye. The duration also varied with the distance of the tumor from the axilla. Radioisotopes were not used.

After an appropriate amount of breast compression and percussion, a 3- to 4-cm transverse incision was made beneath the hair-bearing portion of the axilla. Gentle dissection with attention to hemostasis was performed until an isosulfan blue–stained channel or node was identified. A node was considered an SN if it directly received a blue lymphatic channel or if the node itself was blue. Once an SN was identified, it was dissected proximally into the tail of the breast to assure the primacy of the node identified. The afferent channel was ligated and additional blue nodes were sought in the axilla. After all isosulfan blue–stained nodes were removed, the remainder of the axilla was inspected and palpated to exclude suspicious non-SNs or extensive, matted disease (<1% of all patients undergoing an SN biopsy). Definitive breast surgery (segmentectomy or total mastectomy) was performed at the same setting, but after lymphatic mapping and the SN biopsy were complete.

### PATHOLOGIC ANALYSIS

Sentinel nodes were routinely sent for intraoperative frozen section when a same-anesthetic axillary dissection was contemplated. Sentinel nodes negative for disease by frozen section underwent serial sectioning and staining with hematoxylin-eosin. Nodes found to be tumor free by routine analysis were stained for cytokeratin immunohistochemistry (IHC). Tumor-positive SNs were grouped according to the amount of tumor present in the node—macrometastases (>2 mm, hematoxylin-eosin–positive), micrometastases (<2 mm, hematoxylin-eosin–positive and/or IHC-positive), and cellular metastases (IHC-positive only).

### POSTOPERATIVE TREATMENT AND FOLLOW-UP ASSESSMENT

All patients were treated and followed up prospectively in either the Breast Cancer Clinic at Kaiser Los Angeles Medical Center, Los Angeles, Calif, or the Joyce Eisenberg Keefer Breast Center at St John’s Hospital, Santa Monica, Calif. Patients with SNs positive for disease received adjuvant therapy and breast irradiation after consultation with appropriate specialists. Axillary, internal mammary, and supraclavicular radiation fields were not used with the exception of a single patient who received irradiation to an additional supraclavicular field. Postoperatively, surgeons examined patients semiannually; medical oncology and radiation oncology specialists examined patients at similar intervals.

### RESULTS

All patients were women with a mean age of 61.6 years (age range, 36-92 years). Mean tumor size was 1.65 cm (range, 0.4-5.5 cm) (Figure 1). Thirty-five (76%) of the

![Figure 1. Primary tumor distribution according to tumor size.](image-url)
Developing metastases.

She is alive with disease 30 months after systemic metastases to the liver, lung, and bones 18 months later. She refused ALND and underwent adjuvant cyclophosphamide-methotrexate-fluorouracil therapy. In addition, patients with 4 or more positive nodes may be recommended to undergo postmastectomy radiation therapy.

Advocates of ALND have stated that the clinical significance of a precise count of tumor-involved nodes justifies the morbidity and cost of the procedure, since the disease severity is directly related to the number of positive nodes. This prognostic information, they argue, is important for the patient and family as well as for adjuvant therapy deliberations. Until recently, patients with 10 or more positive nodes often were treated with high-dose chemotherapy and stem cell transplantation. In addition, patients with 4 or more positive nodes may be recommended to undergo postmastectomy radiation therapy.

Much of the prognosis treatment selection argument becomes moot, however, in the context of current medical oncology practices. Many premenopausal patients with positive lymph nodes are being treated with a combination of doxorubicin hydrochloride–cyclophosphamide followed by a taxane, regardless of the number of positive nodes. In fact, many patients who are node-negative receive combination therapy of doxorubicin hydrochloride–cyclophosphamide with or without taxotere based simply on their age and the histopathologic features of the primary tumor. High-dose chemotherapy with stem cell rescue has not been proven to prolong survival and is only being done investigentially. Conversely, elderly patients who have ER-positive tumors and positive nodes are often treated effectively with tamoxifen citrate or aromatase inhibitors, regardless of the number of positive nodes. Many of these patients simply are not candidates for aggressive chemotherapy. In summary, the current patterns of delivery of adjuvant therapy have reduced greatly the necessity for quantitating axillary disease.

In addition, a significant percentage of positive SNs reveal only keratin-positive cells not seen on routine hematoxylin-eosin stains. The clinical significance of these cells remains to be determined by large, prospective studies such as the American College of Surgeons’ Oncology Group (ACOSOG) study Z0010. Hansen et al12 in a study of 683 patients demonstrated that patients with IHC-only positive SNs had the same overall survival as did patients with negative SNs. Most physicians do not recommend making treatment decisions based solely on IHC-only positive SNs.

Data from validation studies combining sentinel lymphadenectomy and ALND have shown that most of the time the SN is the only positive node. Chu et al13 used multivariate analysis of various demographic and histopathologic characteristics of 157 women undergoing SN biopsy with concomitant ALND to identify risk factors for non-SN involvement. They found that only the size of the primary tumor and the size of the SN metastasis were independent variables. In particular, T1a and T1b primary tumors had non-SN metastatic rates of 0% and 13%, respectively. All 33 patients with IHC-only positive SNs had hematoxylin-eosin–negative non-SNs, while only 14% of patients with SN micrometastases had non-SN metastases. It is, thus, possible to identify prospectively subsets of patients such as those with small primary tumors and micrometastatic deposits in the SN who are at very low risk for additional axillary disease. In fact, most patients with 1 or 2 positive SNs undergo an ALND that has no abnormality.

46 cancers were ductal carcinomas; the remaining 11 (24%) were invasive lobular cancers. The vast majority (39/45 [87%]) of cancers were positive for the ER or progesterone receptor. A single patient with a microinvasive (T1a) primary tumor did not have enough tissue to determine receptor status.

A mean of 2.6 SNs per patient was identified (median, 2 SNs; range, 1-7 SNs). Thirty-nine patients (85%) had a single positive SN; the remaining 7 (15%) had 2 positive SNs.

The amount of tumor present in an SN was measured by microscopic assessment. Seven patients (15%) had SN macrometastases. Sixteen patients (35%) had micrometastases smaller than 2 mm. Half the patients in the study had clustered or scattered cellular metastases seen only with keratin antibody IHC stains (Figure 2). Sixteen patients’ (35%) SN metastases were seen using routine hematoxylin-eosin staining; the majority (30 [65%]) was only visible using IHC. Twenty-three patients (50%) received adjuvant chemotherapy postoperatively.

There have been no axillary recurrences during the mean follow-up interval of 32 months (range, 4-61 months). One patient with an ER-progesterone receptor-negative T1c primary tumor and 2 SN micrometastases who refused ALND and underwent adjuvant cyclophosphamide-methotrexate-fluorouracil therapy developed systemic metastases to the liver, lung, and bones 18 months later. She is alive with disease 30 months after developing metastases.

**COMMENT**

Halsted’s concept of an orderly pattern of metastasis from a primary tumor to regional lymph nodes and then to the systemic circulation has influenced breast cancer surgery since the late 19th century. Until recently, ALND combined with either segmentectomy or total mastectomy has been the standard criterion for regional control while providing prognostic information and helping to determine appropriate systemic therapy.
patients, SN lymphadenectomy provides regional control without lymphedema.

It is clear, however, that some patients with SN metastases will have non-SN disease. Most surgeons, our own institutions included, would recommend that patients with bulky axillary disease be treated with a standard axillary dissection. Fortunately, this is usually not the case. Even if there is a reasonable chance that additional positive non-SNs are present in the axilla, additional nonsurgical treatment modalities are available. It is certainly possible, even likely, that breast radiation therapy, chemotherapy, and hormonal therapy will be effective in treating regional disease. Whole breast radiation therapy applied in opposing tangents treats low axillary nodes with the tail of the breast and may control any residual disease in low, level I lymph nodes. It is clear that present-day chemotherapy applied as a neoadjuvant can downstage the extent of axillary metastases and in some cases even obliterate it. Doxorubicin and cyclophosphamide administered as a preoperative neoadjuvant have been shown to increase the incidence of pathologically negative axillary nodes by 37%.16 It is likely that such agents, perhaps given with a taxane in the post-SN biopsy setting, will have a similar effect.

Similarly, tamoxifen therapy consistently confers a statistically significant improvement in survival and relapse-free survival regardless of ER, nodal, or menopausal status.17 Hughes et al11 have reported that women aged 70 years and older with clinical stage I, ER-positive tumors randomized to either tamoxifen and breast radiation therapy or tamoxifen alone had an axillary failure rate of 2 (0.3%) of 636 with 28 months’ median follow-up. Our study includes wider patient demographics and some more significant tumor histopathologic features without an axillary failure. The only patient in our study who failed systemically had an ER-/progesterone-receptor-negative primary tumor. For this reason, it seems to us that patients with ER-/progesterone-receptor-positive tumors are better candidates for axillary observation than those with more aggressive disease.

The axillary recurrence rate in patients who undergo no axillary surgery has been reported to be 2% to 18%, depending on the size of the primary tumor.18 For patients with positive nodes, ALND is a proven method of regional control, with regional recurrence rates of 1% to 2%.19 This regional failure rate is similar to our regional failure rate without ALND. Fisher et al20 in NSABP B-04 (National Surgical Breast and Bowel Adjuvant Project B-04) reported that the mean (SD) time to axillary recurrence was 14 (8) months, with a range of 2 to 49 months and a median of 12 months and nearly all axillary recurrences were within 24 months of total mastectomy. To date we have not noted a single axillary recurrence in this study cohort, with a median follow-up of 32 months. The lack of axillary recurrence and the duration of follow-up support our hypothesis that completion ALND may not be necessary for selected patients with positive SNs.

A therapeutic benefit of ALND has long been hypothesized but has never been proven conclusively. Controversy abounds regarding the effect of locoregional failure on overall survival. There are large studies that show no significant effect of locoregional control on survival; however, protocol violations and a lack of statistical power make some of them vulnerable to criticism.20,21 Conversely, some studies purported to show a locoregional effect on survival were weakened by retrospective,22 disproportional randomization,23 nonstandard axillary surgery,9,24 and suboptimal radiation therapy.25 A definitive resolution of the therapeutic effect of ALND is beyond the scope of our study, but further information is likely to be gained by data from the ACOSOG study Z0011. This open study randomizes patients with positive SNs to either ALND or observation of the axilla, and prohibits additional axillary, internal mammary, or supraclavicular radiation therapy. The excellent regional control rates for the patients in our cohort treated without ALND supports the randomized enrollment of large numbers of patients in the ACOSOG study Z0011.

Much of our discussion has focused on offering counterpoints to the rationale for traditional ALND. It is apparent that there are patient and tumor characteristics that are harbingers of favorable outcomes, regional and systemic included. Our data attest to the safety of avoiding ALND for patients with small, ER-positive primary tumors and limited disease in the SN(s). In particular, we suggest that such patients with IHC-only positive nodes are ideal candidates for axillary surveillance. The natural history of true micrometastases also remains to be determined, but we have not seen an axillary recurrence in this subset of patients. We cannot yet recommend routine observation of the axilla for patients with SN macrometastases as the number of these patients’ is too low to be conclusive. In the absence of controlled data examining the effectiveness of nonsurgical regional therapies for patients with positive SNs, the question remains—do all patients with positive SNs require ALND? Our study supports entry into definitive clinical trials to answer this question.

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Corresponding author and reprints: J. Michael Guenther, MD, Cranley Surgical Associates, 3747 W Fork Rd, Cincinnati, OH 45247.

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