The Time Has Come to Change the Algorithm for the Surgical Management of Early Breast Cancer

Nora M. Hansen, MD; Baiba J. Grube, MD; Armando E. Giuliano, MD

Hypothesis: If the sentinel lymph nodes (SNs) draining a primary invasive breast cancer are free of tumor, then axillary lymph node dissection is not necessary for management of disease.

Design and Intervention: In July 2000, we reported our initial experience of a small cohort of patients who underwent axillary lymph node dissection only if their SNs were involved with metastases. We now report outcome data for all patients who underwent breast conservation and sentinel lymph node dissection without completion axillary lymph node dissection between October 1, 1995, and April 30, 1999.

Setting: Tertiary breast referral center.

Patients: Two hundred thirty-eight patients whose SN staining results were negative for tumor by both hematoxylin-eosin and immunohistochemical stains. Median age was 58.4 years. Most patients (85%) had a T1 tumor; 15% had a T2 tumor. Most (86%) had infiltrating ductal carcinoma with or without extensive ductal carcinoma in situ; 10% had invasive lobular cancer.

Results: At a median follow-up of 38.9 months (range, 6-69 months), we found no axillary recurrences, and 98.3% of patients are alive without evidence of disease. Three patients have died of causes not related to breast cancer. Four patients are alive with metastatic disease but have not developed axillary recurrences.

Conclusions: Sentinel lymph node dissection is a safe and efficacious treatment option for patients with early breast cancer. It provides excellent regional control and is associated with excellent survival. A multicenter trial such as the American College of Surgeons Oncology Group Z0010 is needed to corroborate findings of this single-institution study.

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During the past 100 years, new and less invasive methods to detect, diagnose, and treat early-stage breast cancer in women at risk for death due to the disease have been introduced. Large randomized trials have proved that breast conservation treatment saves the breast and results in long-term survival rates equivalent to those after modified radical mastectomy.1-7 Because clinicians have been unable to identify axillary metastases accurately using noninvasive methods,8-14 axillary lymph node dissection (ALND) has continued to be an integral part of breast cancer staging and regional control.15 However, numerous trials have demonstrated no improvement in overall survival after ALND vs observation for patients with clinically negative nodes.1,16-18 Moreover, because recommendations for adjuvant systemic therapy are often based primarily on characteristics of the primary tumor,19,20 ALND may no longer be necessary for this purpose.

A new method of axillary assessment, sentinel lymph node dissection (SLND), has changed the field of surgical oncology. As first described by our group in a study of patients with cutaneous melanoma,21 the sentinel node (SN) concept is based on the fact that the afferent lymphatic channel draining the primary tumor courses to the first (sentinel) lymph node in that specific regional lymphatic basin.22 In 1991, we adapted dye-directed intraoperative lymphatic mapping to identify the axillary SNs in patients with early-stage breast cancer.21,24 A variety of mapping techniques have been successfully developed,25-32 resulting in the rapid emergence of intraoperative lymphatic mapping and SLND as a less invasive and highly accurate procedure for the staging of breast cancer.

The documented staging accuracy of SLND mandates reconsideration of the extent of axillary surgery in a patient with a...
histopathologically negative SN. Is further axillary dissection necessary? Several compelling reasons indicate that it may not be. First is the changing epidemiology of breast cancer: increased use of screening mammography has led to the identification of smaller tumors.33 Second, the smaller tumors are associated with a lower incidence of nodal metastasis.31-35 Third, the use of postoperative local radiation may be therapeutic because tangents to the breast after segmental resection cover the lower axilla.36-39 Fourth, recommendations for chemotherapy and tamoxifen citrate are based primarily on the size and characteristics of the primary tumor19,20; lymph node metastases predict systemic disease but may not govern systemic manifestations.40 Fifth, overall survival may not be affected by immediate vs delayed ALND for regional recurrence in clinically node-negative early-stage breast cancer.30,41-43 Finally, preliminary data from 2 single-institution trials demonstrated no adverse outcome after SLND alone in patients with tumor-free SNs.44,45 These 2 studies suggest that if metastases are not found in an SN, observation of the axilla does not have an adverse outcome. No local recurrences were found during early follow-up in either study.

As a diagnostic, prognostic, and therapeutic modality, ALND is undergoing reevaluation in terms of cost, morbidity, and overall benefit.61 We herein report our experience with SLND followed by observation for early-stage breast cancer.

PATIENTS AND METHODS

From October 1, 1995, through April 30, 1999, patients with invasive breast cancer and clinically negative axillary lymph node findings were enrolled in a prospective study examining SLND without ALND and in conjunction with breast conservation surgery. In May 1999, we began enrolling patients into the American College of Surgeons Oncology Group (ACOSOG) SN trials. None of these patients are included in this report. All patients signed an informed consent form in accordance with the ethical standards of the institutional review board of the John Wayne Cancer Institute at St John’s Health Center, Santa Monica, Calif. The study also complied with the Helsinki Declaration. We excluded patients with primary tumors greater than 5 cm as detected on results of examination or mammography, multicentric tumors, locally advanced disease, ductal carcinoma in situ, or stage IV disease at presentation and patients enrolled in ACSOG trials.

Intraoperative lymphatic mapping was performed using a 1% solution of vital blue dye (Lymphazurin; US Surgical, Norwalk, Conn). In selected cases, technetium Tc 99m filtered sulfur colloid was also used as a mapping agent. We injected 3 to 5 mL of dye into the breast parenchyma surrounding the primary tumor or into the wall of the biopsy cavity. If the tumor was not palpable, a localization procedure was performed operatively, and the dye was injected around the localizing wire. After manual compression of the breast for 3 to 7 minutes, an incision was made approximately 1 cm below the hair-bearing region of the axilla. The incision was continued through the axillary fascia using blunt dissection, and all blue-stained lymphatic tracts were identified and traced proximally and distally to each blue-stained SN. After all SNs or suspicious nodes were identified and excised, a breast-conserving procedure was performed.

Evaluation of the primary tumor was performed by the pathology department at St John’s Health Center, and all original biopsy slides were reviewed. The SNs were examined at 2 step-section levels of each paraffin block, each separated by 40 µm and stained at each level with hematoxylin-eosin (H-E). If metastases were not identified, the SN was examined with cytokeratin immunohistochemistry (IHC) using a monoclonal anticytokeratin antibody cocktail (Zymed Laboratories, Inc, San Francisco, Calif). In the early part of this study, frozen-section analyses were performed at the time of surgery to confirm the presence of nodal tissue and metastases, but this practice was eventually abandoned.

Decisions regarding adjuvant systemic therapy were made by a team consisting of the surgeon, the medical oncologist, and the radiation oncologist. External-beam radiation therapy was offered to all patients. Therapy consisted of 4000 to 5000 rad (40 to 50 Gy) of radiation to the whole breast as tangential fields with a boost to the tumor bed to a total of at least 6000 rad (60 Gy). An axillary or supraclavicular radiation port was not used in any of these patients.

Patients were followed up and examined at 1 and 4 weeks postoperatively and then every 6 months for 2 years or as frequently as needed. Mammography was performed biannually for the first 2 years and annually thereafter.

RESULTS

We enrolled 238 patients in the study. Approximately half (53.8%) of the patients underwent lymphatic mapping with dye alone; the remaining patients underwent mapping with a combination of radioactive colloid and dye. An SN was identified in all cases. The median number of SNs removed was 1.9 (range, 1-8). Results of H-E and IHC staining for all SNs were negative for tumor.

Median patient age was 58.4 years (range, 29-89 years). Approximately half (51.7%) of the patients had nonpalpable lesions identified on results of mammography and/or ultrasonography; the remaining patients had palpable tumors identified on results of a physical examination. Definitive diagnosis of invasive carcinoma was made by means of fine-needle aspiration biopsy in 12% of patients, core biopsy in 24% of patients, and excisional breast biopsy in 64% of patients. Twenty-one percent of patients were premenopausal, and 79% of patients were perimenopausal or postmenopausal. Perimenopausal was defined as having a menstrual cycle within the past year. Menopausal status was determined by means of patient history; confirmatory blood tests were not performed.

The complication rate of SLND was low (3.3%), and no complication required operative intervention or hospitalization. Four patients had axillary seromas that required aspiration and, in 1 case, temporary placement of a Penrose drain. One patient had a supraclavicular seroma that required aspiration; another patient developed cellulitis that was resolved with oral antibiotic therapy. An elderly patient experienced a temporary decrease in range of motion that completely resolved with physical therapy. An elderly patient experienced a temporary decrease in range of motion that completely resolved with physical therapy. An elderly patient experienced a temporary decrease in range of motion that completely resolved with physical therapy. An elderly patient experienced a temporary decrease in range of motion that completely resolved with physical therapy. An elderly patient experienced a temporary decrease in range of motion that completely resolved with physical therapy.
Based on the American Joint Committee on Cancer staging guidelines, 85% of patients had stage I cancer and 15% had stage II A cancer. The median tumor size was 1.3 cm (range, 1 mm to 4.5 cm). Eighty-five percent of tumors were no larger than 2 cm (Figure). Findings in 184 tumors were positive for estrogen receptors; 146, for progesterone receptors; and 27, for Her-2 neu (a genetic marker on cancer cells that connotes a worse survival). Most tumors were infiltrating ductal carcinomas (85.7%); of these, 9.8% were associated with extensive ductal carcinoma in situ. Of all the tumors, 10.1% of tumors were invasive lobular, and 1.3% had features of ductal and lobular cancer. Two mucinous tumors and 5 tubular cancers were found.

Systemic adjuvant therapy was used in 66.4% of patients. Overall, 11% of patients were treated with chemotherapy alone; 42%, with tamoxifen alone; and 13.6%, with a combination of chemotherapy and tamoxifen. The remaining 33% of patients did not receive adjuvant systemic therapy. All patients were advised to undergo adjuvant radiation therapy and 19 refused.

At a median follow-up of 38.9 months (range, 6-69 months), no axillary recurrences have been detected, and 98.3% of patients are alive with no evidence of disease. Metastatic disease developed in 4 patients (1.7%), all of whom are alive with disease. Three patients died, all of causes unrelated to breast cancer. An ipsilateral breast recurrence developed in 4 patients (1.7%), a new contralateral primary breast cancer in 4 (1.7%), and a new ipsilateral breast cancer in 1 (0.4%). Seven patients were diagnosed as having new nonbreast cancers, including lung cancer, colon cancer, hepatoma, and angiosarcoma.

**COMMENT**

For the past century, ALND has been the standard of care for patients with invasive breast cancer. It has been considered an important factor in staging, regional control, and survival. Lymph node metastasis is the most important prognostic indicator for patients with invasive breast cancer, and it is an important component of the American Joint Committee on Cancer staging system. The National Institutes of Health Consensus Conference in 1991 recommended levels I and II ALND for staging and regional control of early breast cancer.15 However, the stage is determined by the presence but not necessarily the number of tumor-involved regional lymph nodes. Therefore, the more limited but still highly sensitive surgical technique of SLND is challenging the role of ALND in the management of invasive breast cancer. Many studies of SLND followed routinely by completion ALND have demonstrated the staging accuracy of SLND.2,3,12-44,46 Reported rates of SN identification using vital blue dye and/or radioactive colloid range from 82% to 98%, and the reported accuracy of the SN as a predictor of the tumor status of axillary nodes ranges from 95% to 100%. Most experienced centers now have SN identification rates of at least 98% and rates of false-negative findings of about 1%.46

The importance of ALND in patients with breast cancer was first challenged by Fisher et al,1 who demonstrated that treatment of the axilla did not affect survival after mastectomy. The National Surgical Adjuvant Breast and Bowel Program B04 study randomized patients to modified radical mastectomy, mastectomy with axillary radiation therapy, or mastectomy with no axillary treatment. In the group of patients who underwent a modified radical mastectomy, 38% had tumor-involved lymph nodes. Because this was a randomized study, it was assumed that the other 2 groups had a similar axillary tumor burden. The 10-year axillary recurrence rate after total mastectomy without radiation therapy was 18%, and an axillary recurrence developed in more than 75% of these patients within the first 2 years. These patients received delayed ALND. No statistically significant effect of locoregional control on survival was found when all 3 study arms were compared. That study established the natural progression of breast cancer in the axilla of patients who did not receive direct axillary therapy, and it provided the most compelling support for those who believe that ALND offers no survival advantage. Critics of that trial contend that it was too small to detect a small advantage of axillary dissection.

Our decision to abandon ALND in patients with no evidence of disease in the SN was based on several factors. In a prospective study by our group that used the mature technique for SLND (ie, the technique we used after completing our learning phase), 107 patients underwent SLND followed by ALND. The SN was identified in 93% of cases and it was 100% predictive of axillary nodal status.49 Our group also demonstrated the accuracy of SLND and the biological validity of the SN concept by means of complete examination of all non-SNs in a cohort of 60 patients whose SNs had no evidence of tumor; results of histopathologic evaluation of 1087 non-SNs identified only 1 tumor-positive node when 4000 nodal sections were stained with H-E and IHC.50 These findings validated the SN concept and led us to initiate the current study, since it is highly unlikely that removal of tumor-free nodes improves survival when numerous studies including patients with tumor-involved nodes fail to show an improvement in survival after axillary therapy.

In July 2000, our group published our initial data on a cohort of 67 patients who underwent SLND from October 1, 1995, through July 31, 1997, but who did not undergo completion ALND because their SNs were tumor-free.44 No axillary recurrences were detected at a me-
dian follow-up of 39 months, which has increased to nearly 5 years. The expanded findings of the current report, which includes patients undergoing SLND through April 1999, support the hypothesis that ALND can be safely abandoned in patients with no evidence of disease in the SN. The absence of axillary recurrences at a median follow-up of 38.9 months suggests that these patients did not have metastatic deposits in non-SNs. In the National Surgical Adjuvant Breast and Bowel Program B-04 study, most axillary recurrences occurred in the first 2 years. The use of local, regional, and systemic adjuvant therapy in our study might have reduced the risk for axillary recurrence, but since this was not a randomized study designed to evaluate adjuvant therapy, it is impossible to determine the impact of adjuvant therapy.

The surgeon who performs SLND must document a high rate of SN identification and a low rate of false-negative findings before abandoning ALND as a staging procedure. Several investigators have examined the minimal number of cases required for technical proficiency. Cox et al51 reported that failure to identify an SN dramatically decreased after approximately 20 cases, and that success rates reached 90% and 95% after an average of 23 and 33 cases, respectively. Cody et al52 found that most of the false-negative findings at Memorial Sloan-Kettering Cancer Center, New York, NY, occurred in the surgeon’s first 15 cases; as more cases were performed, the false-negative rate ranged from 2% to 5% but never reached 0. Because intraoperative lymphatic mapping and examination of the SN constitute a multidisciplinary undertaking, success depends on the surgeon, the pathologist, and the nuclear medicine physician. This conclusion underlines the importance of a learning phase during which the team’s success is assessed by routine use of completion ALND.

The wide range of complications associated with ALND has not received much attention because this procedure has been considered a necessary component of breast cancer therapy. However, with the emergence of SLND, the emphasis on complications becomes more important. A major benefit of SLND is a lower complication rate. In the present study, only 3.3% of patients had minor complications. In general, most patients undergoing SLND have minimal postoperative discomfort and can resume normal activities and return to work within 1 to 2 days. Patients undergoing ALND may experience significant postoperative pain and limitation in arm movement and may delay resumption of normal activities.35,36 Another anticipated advantage of SLND is reduced cost, because this procedure requires less operative time and can be performed on an outpatient basis.

In the present study, the decision for or against adjuvant systemic therapy in patients with node-negative findings was primarily based on age and on the features of the primary tumor. Although no patient had evidence of nodal metastasis, most received adjuvant systemic therapy. Identification of SN metastases may alter recommendations for adjuvant systemic therapy; however, this study was not designed to address the indications for adjuvant therapy.

En bloc resection of the breast and lymph nodes was originally assumed to improve survival by complete removal of local and regional tumor (halstedian concept). However, many studies have invalidated the halstedian concept and questioned the impact of axillary surgery on survival. Thus, it is difficult to understand the benefit of ALND in the patient with a tumor-free SN. In this group, ALND is unlikely to affect survival. Metastatic disease may still develop in these patients, because tumor-free regional nodes do not preclude systemic spread of breast cancer. However, metastatic disease developed in only 4 (1.7%) of our patients, and all are alive with disease at this time. We have concluded from previous studies comparing SLND with ALND in the same patient that SLND accurately stages breast cancer. These studies in which SLND and ALND were performed on the same patient use the best study design to test the diagnostic accuracy of SLND. The present report shows that in patients with SN-negative disease, SLND provides excellent regional control with minimal complications. We believe that once SLND has been validated by the multidisciplinary team at an institution, this technique can be safely offered to patients with clinically negative axillary node findings and used as the sole axillary staging procedure when the results of histopathologic examination of the SN are negative. The ACSOG Z0010 study will examine this hypothesis in a large, multi-institutional trial.

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Corresponding author and reprints: Nora M. Hansen, MD, John Wayne Cancer Institute, 2200 Santa Monica Blvd, Santa Monica, CA 90404 (e-mail: HansenN@jwci.org).

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