Completion Axillary Lymph Node Dissection Not Required for Regional Control in Patients With Breast Cancer Who Have Micrometastases in a Sentinel Node

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Hypothesis: Completion axillary lymph node dissection (ALND) is not required for regional control in patients with metastases in the sentinel lymph node (SLN).

Design: Prospective cohort study.

Setting: Urban teaching hospital.

Patients: Fifty patients with breast cancer who underwent breast-conserving surgery, had an SLN positive for metastasis, and did not undergo completion ALND.

Interventions: Breast-conserving surgery with SLN biopsy, breast irradiation, and systemic therapy.

Main Outcome Measures: Locoregional and distant recurrence and survival.

Results: The mean patient age was 57 years (range, 29-83 years). The mean tumor size was 1.9 cm (range, 0.4-5 cm). The mean number of positive nodes was 1.3 (median, 1; range, 1-2). Fourteen patients (30%) had macrometastases (>2 mm), and 33 patients (71%) had micrometastases. The mean duration of follow-up was 82 months (median, 79 months; range, 6-142 months). One patient with an SLN micrometastasis (1 of 33; 3%) and 1 patient with an SLN macrometastasis (1 of 14; 7%) developed an axillary recurrence with distant metastasis at 84 months and 28 months, respectively. There was 1 death (2%) not related to breast cancer.

Conclusions: Patients with SLN metastases who do not undergo ALND have a low incidence of regional recurrence. Axillary lymph node dissection is not necessary for regional control in patients with micrometastatic disease.

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Sentinel lymph node biopsy (SLNB) has revolutionized the treatment of a number of solid tumors. It is a widely accepted and safe technique that increases the accuracy of axillary staging in breast cancer and avoids axillary lymph node dissection (ALND) when the sentinel lymph node (SLN) is negative. It has decreased morbidity compared with ALND, including a lower rate of lymphedema, cellulitis, seroma, sensory changes, and psychological morbidity and its use has been advocated in the American Joint Committee on Cancer staging handbook. Since it has been shown that as many as 48.3% of patients with a positive SLN have additional nodal disease on ALND, a completion ALND is generally recommended for patients with a positive SLN detected on routine histopathologic examination. The role of completion ALND is less clear in the setting of SLN micrometastases, which are defined as lymph node metastases larger than 0.2 mm but not larger than 2 mm as detected with hematoxylin-eosin staining or immunohistochemical analysis with antibodies to cytokeratin. The American Society of Clinical Oncology guidelines recommend completion ALND for patients with micrometastases found on SLNB, regardless of the method of detection. However, there are insufficient data as to the clinical relevance of micrometastases, and studies available on this topic are of a retrospective nature with short follow-up and small numbers of patients.

In addition to increased morbidity, there are a number of hypothetical reasons for omitting a completion ALND. These include the potential ability of adjuvant therapies in achieving locoregional in addition to systemic control and no clear survival advantage in performing an ALND.

We hypothesized that the incidence of axillary recurrence is low in patients with a positive SLN who do not undergo a completion ALND, and therefore, comple-
clinical studies were excluded from this analysis. Patient and/or clinician preference. Patients enrolled in the American College of Surgeons Oncology Group Z0010 or Z0011 clinical studies were excluded from this analysis.

RESULTS

Between January 1997 and September 2004, 50 patients underwent breast-conserving surgery and SLNB for invasive cancer and did not undergo completion ALND for a positive SLN. Three patients were lost to follow-up and were excluded from the analysis. The mean patient age was 57 years (range, 29-83 years). Mean tumor size was 1.9 cm (range, 0.4-5 cm). The majority of patients had invasive ductal carcinoma (33 of 47; 70%), and most tumors were Bloom-Richardson grade II (25 of 47; 53%). The most common tumor stage was T1c (22 of 47, 47%). The majority of tumors were ER positive (43 of 47; 91%) and lymphovascular invasion was present in 20 of 47 tumors (43%) (Table 1).

A mean of 3 SLNs was identified per patient (range, 1-9). Most tumor-positive SLNs consisted of micrometastases (23; 49%); the most common method of detection was hematoxylin-eosin staining with serial sectioning (Table 2).

All patients underwent segmental mastectomy and all received breast irradiation without dedicated axillary irradiation. Forty-three patients (92%) received systemic chemotherapy, and 36 patients (76%) received endocrine therapy.

The mean follow-up was 82 months (median, 79 months; range, 6-142 months). With respect to outcomes, there was 1 death unrelated to breast cancer. Two patients (2 of 47; 4.3%) had a local recurrence in the ipsilateral breast. Two patients (2 of 47; 4.3%) developed an axillary recurrence, one with a macrometastasis and another with a micrometastasis. Thus, 32 of 33 patients (97%) with micrometastases did not develop an axillary recurrence, and 13 of 14 patients (93%) with macrometastatic tumor in an SLN did not develop an axillary recurrence. No patient with isolated tumor cells only developed an axillary recurrence.

To approximate the risk of having tumor-positive non-SLNs in our study cohort, the individual tumor and SLN characteristics were applied to the additional nodal metastases nomogram developed by Van Zee and colleagues at Memorial Sloan-Kettering Cancer Center. Using this model, the calculated median risk for having positive non-SLNs in our overall patient population was 11.5% (range, 2%-26%) (Table 3). There was no significant difference between the estimated risk of having a positive non-SLN in either the micrometastases or macrometastases group (10% vs 12%).

With respect to the 2 individual patients who developed axillary recurrences, the first patient was diagnosed with right breast cancer at age 29 years. She had a 1.5-cm invasive ductal carcinoma with lymphovascular invasion and was found to have a 4-mm metastasis in 1 of 2 SLNs. She declined completion ALND, citing an intolerance of any chance of lymphedema. She received adjuvant chemotherapy, followed by whole-breast irradiation and endocrine therapy. She had a clinical axillary recurrence 28 months after initial diagnosis. Axillary lymph node dissection was performed and 13 of 21 nodes were involved by metastatic tumor. She also developed synchronous distant metastases to

PATHOLOGIC EVALUATION

Sentinel lymph nodes were sent for intraoperative frozen section when immediate axillary dissection was contemplated. Sentinel lymph nodes that were negative for metastases on frozen section underwent routine hematoxylin-eosin staining and immunohistochemical analysis. Positive SLNs were grouped into 2 categories: macrometastases, which were defined as any metastatic deposit of carcinoma 2 mm or more; and micrometastases, which were defined as any metastasis less than 2 mm, including isolated tumor cells (immunohistochemical positive only).

Primary tumors were evaluated for size of invasive component, nuclear grade, histologic type, presence of lymphovascular invasion, and receptor status (estrogen receptor [ER], progesterone receptor, human epidermal growth factor receptor 2).

ADJUVANT THERAPY

Adjuvant chemotherapy was generally offered to patients with primary tumors 1 cm or greater with lymph node-negative disease and for patients with lymph node involvement by tumor. No study patient underwent neoadjuvant chemotherapy. All patients had whole-breast irradiation without dedicated axillary irradiation, and patients with hormone receptor-positive tumors received hormonal therapy.

PATIENT FOLLOW-UP

Patients were followed up prospectively in the Breast Cancer Clinic at Kaiser Los Angeles Medical Center, Los Angeles, California. Postoperative follow-up included annual mammograms and semiannual examination by surgeons, as well as medical and radiation oncologists, for at least the first 5 years after definitive breast surgery.

METHODS

After obtaining institutional review board approval, the records of patients with breast cancer who underwent breast-conserving surgery and SLNB, and in whom SLN metastases were present but a completion ALND was omitted, were reviewed. The decision to omit completion ALND was owing to patient and/or clinician preference. Patients enrolled in the American College of Surgeons Oncology Group Z0010 or Z0011 clinical studies were excluded from this analysis.

TECHNIQUE OF SLNB

Our technique of SLNB has been described elsewhere. Briefly, on the day of surgery, 5 to 7 mL of 1% isosulfan blue dye (Lymphazurin; US Surgical, Norwalk, Connecticut) was injected into the breast in a peritumoral fashion and the breast was compressed intermittently for 5 to 7 minutes. A small axillary incision was made, and dissection with electrocautery was performed until blue-stained lymph nodes were identified. Any lymph node with uptake of blue dye or with a blue-stained lymphatic channel leading to it was considered an SLN and was removed. After all blue-stained nodes were excised, the axilla was examined for palpable lymph nodes. These were removed and labeled as additional nonsentinel nodes. Radioisotopes were not routinely used.

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the pleura and bone and a contralateral breast cancer 5 years after her first diagnosis. She has since undergone bilateral mastectomy and currently has stable metastatic disease.

The second patient was diagnosed with a right invasive mammary carcinoma with lobular and ductal features in 2001 at age 58 years. She had a 2.5-cm ER-positive tumor with lymphovascular invasion, and 1 of 2 SLNs was positive for a micrometastasis. She elected axillary observation and was treated with whole-breast irradiation and systemic chemotherapy, and tamoxifen combination for initial evaluation of regional nodal metastatic disease. For decades, ALND was the standard approach for obtaining regional control and providing prognostic information in patients with invasive breast cancer. Sentinel lymph node biopsy has essentially replaced ALND as the initial method of axillary staging in breast cancer, as it clearly confers less morbidity and improves the accuracy of staging. Currently, SLNB is the accepted practice for initial evaluation of regional nodal metastatic disease; however, the role of completion ALND after SLNB remains controversial.

In most practice settings, ALND is omitted when the SLN is found to be tumor-free by routine histopathologic examination. This is advised because metastases are found in non-SLNs in approximately 10% of patients with isolated tumor cells in the SLN, the primary tumor size, and the presence of lymphovascular invasion.14-18 Despite the presence of data that could be valuable in identifying patients who have a low risk for non-SLN metastasis,

Table 1. Patient and Tumor Characteristics

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<tr>
<th>Patient age, y, mean (range)</th>
<th>56.8 (29-83)</th>
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<td>Follow up, mo, mean (range)</td>
<td>82.3 (6-142)</td>
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Table 2. Sentinel Node Characteristics

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<th>No. (%)</th>
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<td>Overall (n=47)</td>
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Table 3. Risk of Having Tumor-Positive Nonsentinel Nodes Based on MSKCC Nomogram Compared With Actual Clinical Axillary Recurrence

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<th>%</th>
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<td>Overall (n=47)</td>
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Abbreviation: SLN, sentinel lymph node.

Abbreviation: MSKCC, Memorial Sloan-Kettering Cancer Center.
the current most common practice pattern is to perform ALND when the SLN is positive for tumor.

There are several compelling reasons to avoid completion ALND. These include the morbidity conferred by the operation; the infrequent alteration of therapy that results from the additional information obtained from knowledge of the status of non-SLN; the potential efficacy of systemic therapy and irradiation in achieving locoregional control; and the observation that a survival benefit from performing ALND has never been demonstrated.

In our study, 2 axillary recurrences (4.5%) were observed with a median follow-up of 79 months. In both cases, despite a full complement of adjuvant therapy (chemotherapy, irradiation, and endocrine therapy), the patient relapsed with synchronous axillary recurrence and distant metastases. In both cases, the results obtained from SLNB provided adequate information to guide therapy. However, therapy in both patients failed, with distant recurrence, and both patients had extensive axillary involvement despite appropriate systemic therapy.

The extensive nodal metastases in the 2 patients is noteworthy and highlights the question of the potential value of ALND in patients with a tumor-positive sentinel node. In these 2 cases, the Halsted concept of an orderly pattern of metastasis from a primary tumor to regional lymph nodes and then to the systemic circulation would seem to suggest that the extensive tumor burden is a missed opportunity to control the development of metastatic disease. However, it is more likely that the presence of both synchronous distant metastases and extensive axillary nodal disease, despite adequate systemic therapy, is reflective of the aggressive biology of the tumor and the likely simultaneous hematogenous and lymphatic pattern of metastatic spread. Omitting completion ALND did not appear to have a clear impact on outcome or survival in these patients.

Our analysis included patients with both micrometastases and macrometastases. We elected to analyze all available data to observe axillary recurrence as a whole and to detect any significant difference between the study groups. Additionally, although the number of patients with macrometastases is clearly very small (n = 14), the axillary recurrence is still low in this group (7%), and knowledge of this relatively low recurrence rate may be of benefit, either to promote further study or possibly even for making recommendations in clinical practice.

To assist clinicians and patients to determine the potential need for a completion ALND, Van Zee et al12 created a multivariate model that predicts the likelihood of additional non-SLN metastases in the presence of SLN metastasis. This additional nodal metastasis nomogram incorporates 9 variables based on data from 702 patients who had a positive SLN and completion ALND and was prospectively validated on a population of 373 patients. These variables are primary tumor size, presence of lymphovascular invasion, size of SLN metastases, number of positive SLNs, number of SLNs harvested, ER status, method of detection of metastatic disease, presence of multicentric disease, and whether intraoperative frozen section was performed.

When applied to our study population, this nomogram predicted the risk of having tumor-positive non-SLNs in our patient population to be a median of 11.5% (range, 2%-26%). Importantly, in our study, 32 of 33 patients (97%) with micrometastases in the SLN did not develop an axillary recurrence. Thirteen of 14 patients (93%) with macrometastatic tumor in an SLN did not develop an axillary recurrence at a mean follow-up of more than 6 years. Thus, the number of patients who developed a clinical axillary recurrence was considerably lower than that predicted by the Van Zee et al nomogram.

Multiple other studies with shorter follow-up have identified similar findings. Hwang et al10 reviewed 196 patients with a tumor-positive SLN who did not undergo completion ALND. No axillary recurrence was observed with a median follow-up of 30 months. However, at least 20% of patients received some form of axillary irradiation. In a previous study from our institution combined with data from John Wayne Cancer Institute, Guenther et al10 reported no axillary recurrence in 46 patients with 32-month mean follow-up. With median follow-up of 42 months, Langer et al11 reported recurrence in 27 patients with micrometastases, and with a mean follow-up of 30 months, Fant et al12 observed no axillary recurrence in 31 patients. Even in the setting of routine ALND the incidence of a clinical axillary recurrence is not zero; numerous studies have previously demonstrated a local failure rate of 0% to 2.1% after ALND, with a follow-up ranging from 40 to 180 months.19-28 This is similar to our axillary recurrence rate of 3% in patients with micrometastases in the SLN.

Another factor to consider in omitting routine completion ALND for SLN metastases is the potential ability of adjuvant therapy in achieving locoregional control. Several studies have shown that patients who undergo neo-adjuvant chemotherapy are less likely to have nodal disease at the time of operation.29-32 In addition, data from National Surgical Adjuvant Breast and Bowel Project B-18 has shown that 36% of patients with clinically node-positive disease did not have metastatic nodal disease on final pathology examination following ALND.31 Multiple studies have also addressed the effect of radiotherapy in achieving local control of the axilla. Sarvi et al32 reported 1 axillary recurrence in 63 patients with a positive SLN who did not undergo ALND and were treated with breast and axillary irradiation with a median follow-up of 31.2 months. Pejavar et al33 reported no recurrence with a median follow-up of 13 years in 16 patients with positive SLN who received irradiation therapy without completion ALND. Gadd et al34 reported 1 axillary recurrence in 73 patients (with median follow-up of 32 months) with positive SLN without completion ALND and with axillary irradiation therapy.

Finally, it is unclear if ALND confers any survival advantage in patients who have axillary metastases from breast cancer. A number of studies have failed to show a survival benefit to ALND, and several landmark studies, including National Surgical Adjuvant Breast and Bowel Project B-04, have demonstrated that a delayed ALND performed after patients developed a clinical axillary recurrence results in no compromise in overall survival. Studies specifically examining the effect of micrometastasis on survival have been inconclusive. Some studies
have demonstrated that micrometastases have an adverse effect on survival, while others have shown no effect on survival. The American College of Surgeons Oncology Group Z0011 clinical trial was designed to definitively answer the question of the benefit of ALND in patients with axillary metastases. Patients with a positive SLN were randomized into 2 groups: completion ALND or axillary observation. Unfortunately, the study closed prematurely secondary to poor accrual, and it is unlikely that the number of subjects enrolled successfully in the study will provide adequate power to show a survival difference, if it exists.

Unless new randomized controlled trials are designed and conducted, it will be necessary to rely on the results of retrospective studies, coupled with patient preference and the statistical likelihood of having non-SLN metastases, to select patients who can avoid completion ALND. With more than 6 years’ median follow-up, 97% of patients with micrometastases in an SLN in our study group have not developed an axillary recurrence. Based on these results, omitting completion ALND in patients with micrometastatic disease is reasonable and unlikely to have an adverse impact on survival and control of locoregional disease. Additional data regarding the outcome of patients with macrometastases in an SLN and who do not undergo completion ALND will be needed to determine if ALND can be safely omitted in this group as well.

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