Background: Current American Society of Clinical Oncology guidelines for management of sentinel node micrometastases (SNMM) in breast cancer recommend axillary lymph node dissection (ALND) for all patients.

Objective: To assess nationwide use of ALND for SNMM.

Design: Population-based retrospective observational study.

Setting: The National Cancer Institute’s Surveillance, Epidemiology, and End Results database (1998-2005).

Patients: Five thousand three hundred fifty-three patients with SNMM.

Main Outcome Measure: Use of ALND after identification of SNMM.

Results: The prevalence of SNMM increased from 2.5% in 1998 to 17.7% in 2005. Of 5353 patients with SNMM, 2160 (40.4%) had no further nodal surgery and 3193 (59.6%) underwent ALND. In the latter group, histopathologic examination of nonsentinel nodes upstaged 18.6% of cases to N1, 2.2% to N2, and 0.1% to N3 disease. Multivariate analysis using logistic regression showed that age younger than 66 years (odds ratio [OR], 1.79; 95% confidence interval [CI], 1.56-2.04), high tumor grade (OR, 1.22; 95% CI, 1.07-1.40), and tumor size larger than 2 cm (OR, 1.16; 95% CI, 1.01-1.32) were predictive of ALND. Predictors of upstaging were infiltrating lobular histology (OR, 1.23; 95% CI, 1.00-1.51), T2 stage (OR, 1.38; 95% CI, 1.14-1.67), T3 stage (OR, 3.66; 95% CI, 1.70-7.90), and number of nodes examined (OR, 1.04; 95% CI, 1.03-1.05).

Conclusions: Only 60% of patients with SNMM from breast cancer are treated according to American Society of Clinical Oncology guidelines. Nodal staging based only on sentinel node biopsy may underestimate the extent of nodal disease in 20.9% of cases. Surgical management of SNMM should be standardized.

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The most important predictor for decreased survival and recurrence in patients with early breast cancer is the presence of axillary lymph node metastases. Traditionally, axillary lymph node dissection (ALND) was used to stage the axilla and was performed routinely. However, the application of the sentinel lymph node biopsy (SLNB) technique to breast cancer dramatically altered treatment of these patients. The sentinel lymph node is defined as the first node that receives lymphatic drainage from the cancer and hence is the most likely to harbor metastases. Sentinel lymph node biopsy is as effective as axillary dissection in staging a clinically negative axilla, and it has less morbidity.

Fewer lymph nodes are removed with SLNB, allowing for more focused histopathological analysis, including multiple sectioning with traditional hematoxylin-eosin staining supplemented with immunohistochemical staining. More intense examination has led to increased identification of micrometastases in the lymph nodes. To reflect these changes, the amount of tumor burden in the nodes as well as the number of positive nodes have been incorporated into the sixth edition of the American Joint Committee on Cancer staging for breast cancer. Tumor deposits in lymph nodes are now classified by size: macrometastases (≥2.0 mm), micrometastases (>0.2 mm to <2.0 mm), and isolated tumor cells (≤0.2 mm). The corresponding node stages are N1 for macrometastases, N1mi for micrometastases, and NO(i+) for isolated tumor cells.

The clinical significance of micrometastases is uncertain, leading to potential variability in regional and systemic management. In an effort to standardize the role of SLNB in early breast cancer and the treatment of patients with node-positive disease, the American Society of Clinical Oncology (ASCO) convened an expert...
ence to the guidelines. This led us to suspect underuse by only 23% of surgeons, 23% of medical oncologists, and 15% of radiation oncologists, suggesting a lack of adherence. This treatment recommendation is based on the association of sentinel node micrometastases (SNMM) with macrometastases in nonsentinel nodes. Although micrometastases may have a questionable prognostic impact, macrometastases remain the most important predictor of recurrence and decreased survival in breast cancer.

Despite these recommendations, in a recent survey of ASCO members from different specialties on the management of SNMM, ALND for N1mi was recommended by only 23% of surgeons, 23% of medical oncologists, and 15% of radiation oncologists, suggesting a lack of adherence to the guidelines. This led us to suspect underuse of completion ALND for SNMM and hence inadequate clearance of potential macrometastases in nonsentinel nodes. To test our hypothesis, we used a population-based cancer registry to investigate the management of SNMM in patients with breast cancer.

**METHODS**

**SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS DATABASE**

The National Cancer Institute–sponsored Surveillance, Epidemiology, and End Results (SEER) tumor registry database was used for this study. The SEER database contains more than 3 million cases from 17 geographic sites, covering approximately 26% of the US population. The database was designed to reflect the overall characteristics of the US population and is regarded as a model population-based tumor registry. The SEER program registries routinely collect data on patient demographics (eg, age and sex), primary tumor characteristics (size, extent, grade, and hormone-receptor status), nodal staging (sentinel node biopsy, number of nodes examined, number of positive nodes, and size of metastases), operation performed (partial mastectomy vs mastectomy), vital status, and survival. Although information on radiation therapy is recorded, no information on hormonal or chemotherapy is reported. Furthermore, information on the method of detection of sentinel lymph node metastases (eg, hematoxylin-eosin vs immunohistochemical staining) is available only for 2003 to 2005. The November 2007 update was used for this study, providing information from 1971 to 2005. Because it was a population-based study with no patient identifiers, this study was exempt from institutional research board review.

**CASE SELECTION**

Patients in the study were treated from 1998 to 2005. We chose 1998 as a cutoff because even though SLNB was introduced in the early 1990s, it was not widely used until later and detection of micrometastases may have required a learning curve. Using the *International Statistical Classification of Diseases, 10th Revision*, histology codes 8500 and 8520, we identified all patients with a diagnosis of infiltrating ductal carcinoma and infiltrating lobular carcinoma of the breast. Further selection was done by including patients who had an ALND performed. Using the SEER extent of disease code for lymph node involvement, patients were then selected for SNMM and if breast conservation surgery was performed. Patients who did not undergo breast conservation were excluded, as axillary lymph nodes are routinely removed as part of the specimen in a mastectomy. Also excluded were patients with evidence of distant metastases, with male breast cancer, no histological confirmation of the diagnosis, and cases identified from autopsy reports only. Cases of macrometastases identified (≥2 mm) following ALND were considered to be upstaged from N1mi to N1, N2, or N3 disease according to American Joint Committee on Cancer staging.

**STATISTICAL ANALYSIS**

For analysis purposes, the study population was divided into patients undergoing an SLNB only (SLNB group) and those undergoing an SLNB and an ALND (SLNB + ALND group). Categorical variables were compared using χ² analysis. Differences between continuous variables were determined by using the *t* test. We identified predictors of having an ALND performed following SLNB with multivariate analysis, using logistic regression and including the following variables in our model: age older than 66 years, tumor size larger than 2 cm, estrogen receptor status of primary tumor, and tumor grade. The age cutoff used was median age and the tumor size cutoff of 2 cm was based on the current American Joint Committee on Cancer staging for breast cancer. In patients who were found to have involvement of nonsentinel lymph nodes by macrometastases after ALND (ie, upstaged), logistic regression analysis was used to identify predictors of additional nodal disease with the following variables in the model: histology, tumor stage, tumor grade, and number of nodes examined. Variables were selected for regression models if they were significant on univariate analysis. Survival analysis was performed using Kaplan-Meier curves and log-rank tests to identify differences in survival. All statistical analyses were performed using SPSS, version 16.0 (SPSS Inc, Chicago, Illinois), or SAS (SAS Institute, Cary, North Carolina) and conducted with the assistance of the John Wayne Cancer Institute Department of Biostatistics. Significance levels were set at *P* < .05. All tests were 2-sided.

**RESULTS**

Our study population consisted of 5353 patients with SNMM. Following SLNB, only 3193 (59.6%) underwent ALND, as recommended by ASCO guidelines. The remaining 2160 (40.4%) had SLNB only. The prevalence of SNMM increased from 2.5% in 1998 to 17.7% in 2005 (Figure 1).
DEMOGRAPHICS, TUMOR, AND TREATMENT CHARACTERISTICS

Demographic characteristics of the SLNB and the SLNB + ALND groups are outlined in Table 1. The mean age of patients in the SLNB + ALND group was significantly younger than the SLNB group (56.6 vs 60.2 years, \( P < .001 \)). Variation between the SEER regions was seen in the use of ALND for SLNB micrometastases (Figure 2), with the highest rate seen in New Mexico (75%) and the lowest in Louisiana (47%). Patients in the SLNB + ALND group were more likely to have larger tumors (mean, 1.8 vs 1.7 cm, \( P = .002 \)) and higher tumor grade (33% vs 28%, \( P < .001 \)) and less likely to be estrogen receptor–positive (85% vs 88%, \( P = .003 \)) than the SLNB group. There were no significant differences between the 2 groups with regard to tumor location, laterality, histology, progesterone receptor status, or radiation therapy.

UPSTAGING

Of the 3193 (59.6% of total) cases of ALND following SLNB, 668 (20.9%) were upstaged from N1mi disease. Histopathologic examination of the nonsentinel nodes upstaged 18.6% to N1, 2.2% to N2, and 0.1% to N3 disease. Demographic and tumor characteristics within the SNB + ALND group were compared according to presence or absence of upstaging (Table 2). Cases upstaged by ALND following SLNB were more likely to have infiltrating lobular histology (24% vs 20%, \( P = .03 \)), higher tumor grade (\( P = .02 \)), higher T stage (\( P < .001 \)), and more nonsentinel nodes examined (median, 12 vs 10, \( P < .001 \)) than cases that were not upstaged. No differences were seen between the 2 groups with regard to age, tumor location, laterality, or estrogen or progesterone receptor status. Upstaging increased with increasing T stage: T1, 18.9%; T2, 25.4%; and T3, 48.1%. We could not identify a subset of patients in whom upstaging did not occur after ALND.

REGRESSION ANALYSIS

Predictors of ALND following SLNB were age younger than 66 years, tumor size larger than 2 cm, and high tumor grade (Table 3). In patients whose cancers were upstaged by ALND following an SLNB with micrometastases, predictors of upstaging were infiltrating lobular histology, stage T2 or T3, and number of nodes examined.

SURVIVAL ANALYSIS

With a median follow-up of 36 months, there was no significant difference in 5-year overall survival between pa-
patients undergoing SLNB only and those undergoing SLNB + ALND (89% vs 90%, P = .98), despite the 20.6% of patients with additional involved nonsentinel nodes on ALND.

This study used a population-based database to investigate adherence to current ASCO guidelines on the use of ALND following an SLNB revealing micrometastases. Only 59.6% of patients with SNMM from breast cancer undergo a completion ALND. Nodal staging based on SLNB only may underestimate the extent of nodal disease in 20.9% of patients. We confirm our hypothesis that ALND is underused in these patients.

Table 2. Primary Tumor Characteristics of Patients Treated With SLNB and ALND

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Treated With SLNB and ALND, %</th>
<th>Cancer Upstaged, % (n=668)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), median, y</td>
<td>56.8 (11.8), 56</td>
<td>56.1 (12), 55</td>
<td>.76</td>
</tr>
<tr>
<td>Location of tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOQ</td>
<td>42.4</td>
<td>42.5</td>
<td>.36</td>
</tr>
<tr>
<td>LOQ</td>
<td>7.5</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>UIQ</td>
<td>10.2</td>
<td>9.3</td>
<td></td>
</tr>
<tr>
<td>LIQ</td>
<td>6.0</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Central</td>
<td>5.8</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Overlapping</td>
<td>20.3</td>
<td>19.8</td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td>7.8</td>
<td>8.5</td>
<td></td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>50.3</td>
<td>51.2</td>
<td>.68</td>
</tr>
<tr>
<td>Left</td>
<td>49.7</td>
<td>48.8</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal carcinoma</td>
<td>79.8</td>
<td>76.0</td>
<td>.03</td>
</tr>
<tr>
<td>Infiltrating lobular carcinoma</td>
<td>20.2</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>72.7</td>
<td>63.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T2</td>
<td>25.7</td>
<td>32.9</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>0.6</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>ER positive</td>
<td>84.9</td>
<td>85.5</td>
<td>.69</td>
</tr>
<tr>
<td>PR positive</td>
<td>74.7</td>
<td>75.9</td>
<td>.55</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>20.1</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>45.7</td>
<td>44.5</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>29.6</td>
<td>33.4</td>
<td>.02</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>1.3</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>No. of nodes examined, mean (SD)</td>
<td>11 (6.8), 10</td>
<td>13 (7.1), 12</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval; OR, odds ratio.

As a continuous variable.

Table 3. Regression Analysis to Identify Predictors of ALND and Upstaging

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors of ALND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;66 y</td>
<td>0.56 (0.49-0.64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Tumor size &gt;2 cm</td>
<td>1.16 (1.01-1.32)</td>
<td>.04</td>
</tr>
<tr>
<td>High tumor grade</td>
<td>1.22 (1.07-1.40)</td>
<td>.003</td>
</tr>
<tr>
<td>Predictors of upstaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating lobular histology</td>
<td>1.23 (1.00-1.51)</td>
<td>.048</td>
</tr>
<tr>
<td>T2 stage</td>
<td>1.38 (1.14-1.67)</td>
<td>.001</td>
</tr>
<tr>
<td>T3 stage</td>
<td>3.66 (1.70-7.90)</td>
<td>.001</td>
</tr>
<tr>
<td>No. of nodes examineda</td>
<td>1.04 (1.03-1.05)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ALND, axillary lymph node biopsy; ER, estrogen receptor; LIQ, lower inner quadrant; LOQ, lower outer quadrant; NOS, not otherwise specified; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; UIQ, upper inner quadrant; UOQ, upper outer quadrant.

Figure 2. Variation in frequency of sentinel lymph node biopsy (SLNB) followed by complete axillary lymph node dissection (ALND) across Surveillance, Epidemiology, and End Results database regions.
would not alter treatment, it is possible that the decision to forgo ALND was a conscious one. It has been previously shown that there is selective application of ALND by surgeons in elderly women with early-stage breast cancer. However, when we performed a subset analysis of patients younger than 66 years, there were still 36.8% who underwent an SLNB only, suggesting that comorbidity may not explain all of the discrepancy seen. Similarly, the argument has been made that in patients with SNMM and T1a tumors, the likelihood of finding additional disease (0%-8%) is too low to justify routine ALND. This is not borne out by our study, in which 16.1% of cases with tumors smaller than 0.5 cm (T1a) were upstaged from N1mi.

We show that additional nodal metastases are identified in 20.9% of patients who undergo a completion ALND following an SLNB in which micrometastases were identified. This is consistent with the 13% to 26% range reported by the largest series in the literature on nonsentinel node involvement with SNMM. A meta-analysis by Cserni et al on the subject showed a 20% incidence of nonsentinel node metastases after low-volume (N1mi or isolated tumor cells) involvement of the sentinel node. Even if the higher-quality studies alone were considered, this number is unlikely to be less than 15%. Most of these studies concluded that a completion ALND should be carried out following identification of SNMM, in concordance with recommendations of the ASCO expert panel.

We identify infiltrating lobular histology, T2/T3 stage, and number of nodes examined as predictors of nonsentinel node involvement and potential upstaging. Tumor size is a well-known predictor of nonsentinel node involvement and has been reported by many groups. A meta-analysis of the clinicopathologic characteristics of the primary tumor that predict nonsentinel node metastases identified, among other factors, tumor size greater than 2 cm as predictive of lymph node metastases. The association between infiltrating lobular histology and nonsentinel node involvement has not been as well reported and this may be due to limitations in sample size in the published series. Owing to the “shotgun” pattern and small cell size of tumors with infiltrating lobular histology, immunohistochemical staining is often used to evaluate the sentinel lymph nodes. In patients with infiltrating lobular cancer, metastases detected by immunohistochemical staining only were associated with nonsentinel metastases in 24% of cases, a rate higher than generally reported for infiltrating ductal cancer. In our study, 24% of infiltrating lobular cancers were upstaged following ALND compared with 20.2% with infiltrating ductal cancers. The association of upstaging with total number of nodes examined is less surprising. It is possible that there were tumor and patient characteristics (eg, larger tumor size, higher grade, and younger age) that prompted more extensive dissection by surgeons and more thorough retrieval and examination by pathologists. With ALND, the more lymph nodes retrieved, the greater the chances of finding additional disease. Current recommendations from the National Comprehensive Cancer Network are to remove at least 10 nodes for optimal staging of the axilla in breast cancer. In our patient population, a subset analysis of patients who had 10 or more lymph nodes removed on ALND (n = 1764) revealed that 25.2% of cases were upstaged, compared with 20.9% in the study group as a whole, and only 15.7% for cases with fewer than 10 lymph nodes retrieved.

The use of population-based data has several inherent limitations. Although the database is checked regularly for discrepancy and is reported to have 95% accuracy, the possibility of coding errors remains. In many cases, it is possible that the decision to omit an ALND is tempered by the fact that the patient will receive either hormonal therapy or chemotherapy following surgery. No information on either treatment is provided in the database, so we could not study this further. Similarly, although information on radiation treatment is available, patients were selected only if they had breast conservation therapy and the majority received radiation therapy after. Detailed information on the fields of radiation and whether these fields were used to radiate the axilla in patients with positive sentinel nodes is not available. It is possible in some cases that the choice was made to radiate the entire axilla and not to perform an ALND. We are also not able to identify the method used to detect micrometastases (ie, hematoxylin-eosin vs immunohistochemical staining) for most of the patients. Finally, we cannot account for variability in pathology protocols used to identify micrometastases across the different SEER regions or for interobserver variability among pathologists.

To conclude, we used a population-based database to show that current ASCO guidelines recommending routine ALND following identification of micrometastases in the sentinel lymph node are being followed in only 60% of cases. We also show that the use of SLNB alone for staging of the axilla in these cases may lead to underestimation of the extent of nodal disease in 20% of cases. Currently, omission of ALND in patients with SNMM should only be for medical reasons or in the setting of a clinical trial, as we have yet to reliably identify a subset of patients in which this can be safely done.

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Author Contributions: Dr Wasif had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wasif, Maggard, Ko, and Giuliano. Acquisition of data: Wasif and Giuliano. Analysis and interpretation of data: Wasif, Maggard, Ko, and Giuliano. Drafting of the manuscript: Wasif. Critical revision of the manuscript for important intellectual content: Wasif, Maggard, Ko, and Giuliano. Statistical analysis: Wasif and Maggard. Study supervision: Ko and Giuliano.

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REFERENCES


