Therapeutic Effect of Sentinel Lymphadenectomy in T1 Breast Cancer

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Objective: To evaluate whether the tumor status of the sentinel lymph node (SN) would alter the systemic adjuvant therapy administered to patients with T1 breast cancer.

Design and Patients: Consecutive breast cancer patients (tumors ≤ 2 cm) who underwent successful sentinel lymphadenectomy.

Main Outcome Measures: Metastatic tumor in the SN, primary tumor size, recommendations for systemic adjuvant therapy before and after histopathologic evaluation of the SN, and actual systemic adjuvant therapy received by the patient.

Results: Of 142 total patients, 14 had T1a tumors; 35, T1b; and 93, T1c. Recommendations for systemic adjuvant therapy were initially determined solely by primary tumor characteristics and menopausal status. These recommendations were compared with recommendations for systemic adjuvant therapy based on tumor characteristics, menopausal status, and SN status; and then were compared with actual systemic adjuvant therapy received by the patient. Among the 118 patients with T1a, T1b, and favorable (positive estrogen or progesterone receptors and a low S-phase percentage with respect to DNA content) T1c tumors, 15 (37.5%) of 40 premenopausal patients and 20 (25.6%) of 78 postmenopausal patients became candidates for chemotherapy when examination of the SN revealed axillary metastasis; chemotherapy was actually administered to all 15 premenopausal patients but to only 6 postmenopausal patients. In the remaining 24 patients with unfavorable T1c tumors, SN status did not change the recommendation for chemotherapy but may have altered the choice of specific chemotherapeutic agents.

Conclusions: Identification of tumor-involved SN may alter systemic adjuvant therapy in patients with T1a, T1b, and favorable T1c tumors and may potentially change the type or dose of chemotherapeutic agents given to patients with unfavorable T1c tumors. Surgical axillary staging of the axilla remains an essential part of breast cancer management and should not be abandoned.

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Following surgical management of primary breast cancer, systemic adjuvant therapy is indicated for patients with axillary metastases but also is increasingly recommended for those without histological evidence of axillary node involvement. Because of this trend to use systemic adjuvant therapy regardless of lymph node status and because of the direct relationship between the incidence of axillary metastasis and the size of the primary tumor, recent reports have questioned the benefit of routine level I and II axillary lymph node dissection (ALND) in patients with T1 primary breast cancers, particularly T1a and T1b lesions.

The National Institutes of Health Consensus Development Conference on the treatment of early-stage breast cancer recommended levels I and II ALND for the prevention of axillary recurrence and for accurate staging. Axillary lymph node dissection improves regional control in patients with palpable or nonpalpable tumors involved nodes, but its effect on survival remains controversial. It may prolong survival by removing metastatic disease or because more patients with lymph node metastases receive systemic adjuvant therapy. However, patients without histologically involved nodes clearly do not derive a therapeutic benefit from ALND and must deal with the associated potential morbidity of the procedure.

Because routine ALND for all patients with T1 breast cancer is associated with potential morbidity and no realized therapeutic benefit in those without tumor-involved lymph nodes, nonsurgical staging alternatives have been explored.
PATIENTS AND METHODS

Candidates for this study were patients undergoing operative management of potentially curable breast cancer at the John Wayne Cancer Institute from October 1, 1991, through October 3, 1995. Only clinically node-negative patients with histopathologically confirmed American Joint Committee on Cancer T1 breast cancer were included. After signing informed consent forms, all patients underwent intraoperative lymphatic mapping with SLND, followed immediately by level I and II ALND. Patients who did not have a successful SLND were excluded.

Our technique of intraoperative mapping and SLND for breast cancer has been described previously.20-22 Each SN was examined by frozen and permanent section with hematoxylin-eosin staining. If no tumor was identified using hematoxylin-eosin, then a cytoketarin immunohistochemical stain was performed using an antibody cocktail (MAK-6, Ciba-Corning, Alameda, Calif) that binds to cytoketarins. The nonsentinel axillary lymph nodes were processed by routine surgical pathologic techniques for isolation of lymph nodes, and were examined only with hematoxylin-eosin.

All patients were seen in consultation by at least 1 surgical oncologist (A.E.G.) and 1 medical oncologist. If a patient was ineligible or declined to participate in an adjuvant therapy trial, recommendations for systemic adjuvant therapy were made by the treating oncologist following the definitive breast cancer operation.

For this study, we constructed an algorithm for determining systemic adjuvant therapy based solely on the patient’s menopausal status and primary tumor characteristics.

Following American Joint Committee on Cancer guidelines,24 the distribution of tumors was 14 of type T1a (<0.5 cm); 35, T1b (0.5 cm but <1.0 cm); and 93, T1c (1.0 cm but <2.0 cm). The histological status, hormone receptor status, and flow cytometry results for the primary tumor are summarized in Table 1. Patients who had insufficient or inadequate tumor tissue for receptor assays or flow cytometry were considered to have favorable tumors. The mean number of SNs examined per patient was 1.8 (range, 1-7) (Table 2); the mean number of non-SNs examined was 17.3 (range, 4-44). The use of both staining techniques identified 43 patients (30.3%) with SN metastases.

Table 3 shows how recommendations for systemic adjuvant therapy changed with the identification of SN metastases. All 6 premenopausal women with T1a or T1b tumors and SN metastases became candidates for and received systemic chemotherapy. All 9 premenopausal women with favorable T1c lesions (positive for estrogen or progesterone receptors and a low S-phase percentage for DNA content) and SN metastases became candidates for and received systemic chemotherapy. Thus, 15 (37.5%) of the 40 premenopausal women with T1a, T1b, or favorable T1c tumors received a treatment they would not have received based only on primary tumor characteristics. Tumor involvement of the SN did not alter recommendation of chemotherapy as the adjuvant mo-

RESULTS

The median age of the 142 patients eligible for study was 56.4 years (range, 31.8-90 years). The size of the primary tumor as measured on histopathologic sectioning ranged from microinvasive (arbitrarily defined as <0.1 cm) to 2 cm in the greatest dimension (median, 1.15 cm).
Primary tumor–based systemic adjuvant treatment algorithm. According to this algorithm, patients with T1a and T1b tumors would not receive systemic chemotherapy or hormonal therapy. Premenopausal women with favorable T1c lesions (estrogen receptor–positive or progesterone receptor–positive, low S-phase percentage with respect to DNA content) would receive tamoxifen therapy, and premenopausal women with unfavorable T1c tumors (estrogen receptor–negative and progesterone receptor–negative, high S-phase with respect to DNA content) would receive systemic adjuvant chemotherapy. Postmenopausal women with favorable T1c cancers would receive tamoxifen therapy, whereas patients with unfavorable T1c tumors would receive chemotherapy. Asterisk indicates “if no prohibitive medical comorbidity exists.”

Table 1. Primary Tumor Characteristics*

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>T1a</th>
<th>T1b</th>
<th>T1c</th>
<th>Total T1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median size, cm</td>
<td>0.35</td>
<td>0.81</td>
<td>1.57</td>
<td>1.15</td>
</tr>
<tr>
<td>Histological finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal</td>
<td>10</td>
<td>30</td>
<td>84</td>
<td>124 (87.3)</td>
</tr>
<tr>
<td>Invasive lobular</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>13 (9.2)</td>
</tr>
<tr>
<td>Special subtypes</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>5 (3.5)</td>
</tr>
<tr>
<td>Receptor status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7</td>
<td>28</td>
<td>76</td>
<td>111 (78.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>6</td>
<td>5</td>
<td>16</td>
<td>27 (19.0)</td>
</tr>
<tr>
<td>Insufficient material</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Progesterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>9</td>
<td>23</td>
<td>61</td>
<td>93 (65.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>10</td>
<td>29</td>
<td>43 (30.3)</td>
</tr>
<tr>
<td>Insufficient material</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6 (4.2)</td>
</tr>
<tr>
<td>DNA content</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diploid</td>
<td>5</td>
<td>22</td>
<td>42</td>
<td>69 (48.6)</td>
</tr>
<tr>
<td>Aneuploid</td>
<td>4</td>
<td>7</td>
<td>47</td>
<td>58 (40.9)</td>
</tr>
<tr>
<td>Insufficient material</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>15 (10.6)</td>
</tr>
<tr>
<td>Proliferative index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>7</td>
<td>21</td>
<td>53</td>
<td>81 (57.0)</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>3</td>
<td>27</td>
<td>31 (21.8)</td>
</tr>
<tr>
<td>Insufficient material</td>
<td>6</td>
<td>11</td>
<td>13</td>
<td>30 (21.1)</td>
</tr>
</tbody>
</table>

*Values are expressed as number of tumors with each characteristic, unless otherwise specified.

Table 2. Results of Sentinel Lymphadenectomy*

<table>
<thead>
<tr>
<th>Stage of Cancer</th>
<th>T1a (n = 14)</th>
<th>T1b (n = 35)</th>
<th>T1c (n = 93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean No. SNs examined (range)</td>
<td>1.6 (1-3)</td>
<td>1.7 (1-5)</td>
<td>1.8 (1-7)</td>
</tr>
<tr>
<td>Tumor-positive SNs</td>
<td>2</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>HE stain, No. of tumors detected</td>
<td>0</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Macrometastasis</td>
<td>2</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Micrometastasis</td>
<td>0</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

*SN indicates sentinel node; HE, hematoxylin-eosin; IHC, cytokeratin immunohistochemical.

COMMENT

Cady et al report a 13% incidence of axillary metastasis in patients with T1a and T1b primary tumors and suggest that no axillary dissection is needed in patients with mammographically detected T1a or T1b tumors. Silverstein et al report only a 3% incidence of axillary metastases in T1a tumors and recommend no axillary dissection for patients with T1a tumors that demonstrate good prognostic features. However, review of the Surveillance, Epidemiology, and End Results (SEER) Program Registry of more than 8000 T1 tumors shows a higher incidence of axillary metastasis: 19.6% for T1a tumors; 20.6%, T1b; and 33.1%, T1c. Similarly, we previously reported a 15%, 15%, and 33% incidence of axillary metastases in T1a, T1b, and T1c tumors, respectively. The SEER data and our own institutional data indicate that nonsurgical evaluation of the axilla would understage 15% to 20% of the patients with T1a or T1b tumors.

In the present study, tumor involvement of the SN had a significant effect on the recommendations for systemic adjuvant therapy administered to premenopausal patients with T1 breast cancers, compared with recommendations for systemic adjuvant therapy based on the primary tumor. Prior to SN examination, 40 patients (28.2%) would have received no systemic adjuvant treatment (for T1a or T1b tumors) or adjuvant tamoxifen alone (for favorable T1c tumors); detection of SN metastasis changed the recommendations for systemic adjuvant therapy in 15 (37.5%) of these patients. The potential benefit of systemic adjuvant chemotherapy is highest in premenopausal women with axillary metastases, and accurate axillary staging is essential to avoid overtreatment (if the axilla is assumed to harbor metastasis) or undertreatment (if the nodes are assumed to be free of tumor).
In our group of postmenopausal patients, 20 (25.6%) of 78 women with T1a, T1b, or favorable T1c tumors were candidates for systemic adjuvant chemotherapy based on metastatic tumor in the SN. The fact that only 6 (30.0%) of the 20 actually received chemotherapy underlines the tendency to avoid more aggressive systemic adjuvant therapy in postmenopausal women due to preexisting medical comorbidities, advanced chronologic and physiologic age, and/or oncologist preference. In our postmenopausal patients, controversy over the significance of axillary micrometastasis detected by cytokeratin immunohistochemical staining may have discouraged more frequent use of adjuvant systemic chemotherapy.

Patients with unfavorable T1c tumors have a poorer prognosis than those with favorable T1c tumors. The standard recommendation is systemic adjuvant chemotherapy regardless of lymph node status, providing there is no prohibitive medical comorbidity. The tumor status of the SN did not change recommendations for systemic adjuvant chemotherapy in this group of patients but it may have altered the selection of chemotherapeutic agents, particularly if completion ALND revealed multiple tumor-involved nodes. Some medical oncologists might even consider high-dose chemotherapy with peripheral stem-cell support for patients with more than 10 involved nodes, and some high-dose chemotherapy protocols are accepting patients with as few as 4 tumor-involved nodes. Thus, even patients with unfavorable T1c tumors potentially could receive a different chemotherapy regimen based on identification of axillary metastasis.

The clinical significance of axillary micrometastasis remains controversial, but the medical oncologists in our community consider micrometastatic SN involvement to be node-positive breast cancer. Thus, if the SN harbors tumor cells, all patients with T1a, T1b, and favorable T1c breast cancers potentially could receive an alternate systemic adjuvant therapy, whereas patients with unfavorable T1c lesions might receive an alternate chemotherapeutic regimen. We recommend SLND to provide an axillary specimen for focused histopathologic examination. Except among those investigators who have demonstrated a high degree of accuracy with this technique, SLND should routinely be followed by completion level I and II ALND to ensure accurate axillary staging and effective regional control. Surgical staging of the axilla remains essential in the management of breast cancer and should not be abandoned.

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### REFERENCES