Risk Factors for Lymph Node Metastases in Breast Ductal Carcinoma In Situ With Minimal Invasive Component

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Hypothesis: Clinical and pathological variables may be predictors of axillary dissemination in T1mic and T1a breast carcinoma.

Design: Retrospective medical chart review.

Setting: University-affiliated tertiary referral center.

Patients: All patients diagnosed as having ductal carcinoma in situ (DCIS) with microinvasion between January 1, 1988, and December 30, 1998.

Main Outcome Measures: Pathology slides were reviewed according to the 1997 Cancer Staging Manual put forth by the American Joint Committee on Cancer. The number of involved ducts was noted. Patients with no invasive component or invasive components larger than 5 mm were excluded. Pathological and clinical variables were analyzed for their effect on axillary lymph node metastases.

Results: The study group included 57 women aged 37 to 71 years (median, 60 years), 37 with T1mic disease and 20 with T1a. Modified radical mastectomy was performed in 29 patients (18 with T1mic and 11 with T1a) and breast-preserving surgery in 28 (19 with T1mic and 9 with T1a). Forty-three patients (28 with T1mic and 15 with T1a) underwent axillary lymph node dissection. Axillary involvement was detected in 3 patients in each group. Forty-seven patients received adjuvant therapy (radiotherapy alone, or with hormones or chemotherapy). Follow-up was 3 to 120 months (median, 40 months). One patient was unavailable for follow-up, another died of disseminated disease, and a third developed contralateral primary carcinoma. Comedo DCIS (P<.03) and the number of DCIS-involved ducts (P<.002) in the T1mic group, and nuclear grade 3 (P<.001) in both groups, were independent significant predictors of axillary metastases.

Conclusions: The significant rate of axillary metastases in T1a and T1mic breast tumors makes axillary staging a must. High nuclear grade, comedo DCIS, and high number of DCIS-involved ducts may predict axillary metastasis and should be considered when axillary dissection is done selectively.

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DUCTAL CARCINOMA IN SITU (DCIS) accounts for 12% to 15% of all newly diagnosed cases of breast cancer annually. Ductal carcinoma in situ with a microinvasive component accounts for fewer than 1% of all breast cancers, and 13.5% of all DCISs have a microinvasive component. Microinvasion were defined by Rosner et al as microscopic stromal invasions below the basement membrane, limited to less than 10% of the examined section surface, and by Schuh et al as foci of stromal invasions. Some researchers believe the number of invasive foci is prognostically significant, whereas others stress the size of the invasive component. In 1997, the American Joint Committee on Cancer defined microinvasive breast carcinoma (T1mic) as "the extension of cancer cells beyond the basement membrane into the adjacent tissues, with no single focus larger than 1 mm in greatest dimension." When the invasive component is 1 to 5 mm in its greatest dimension, the tumor is classified as T1a. This system refers only to the largest invasive component and ignores the size of the DCIS and the number of invasive foci. This diversity in the histopathological definition may explain the 0% to 22% range of reported rates of axillary lymph node metastasis in microinvasive breast carcinoma. Axillary lymph node metastasis is one of the most important prognostic factors in breast cancer, serving as an indication for systemic adjuvant therapy. Risks of nodal involvement increase with an increase in tumor size, pa-
tient age, and tumor grade. Other characteristics of the primary tumor, such as S-shape fraction, p53, HER-2/neu, lymphatic invasion, vascular invasion, and hormonal status, may also be important.10,11 The role of axillary lymph node dissection (ALND) for the staging and treatment of invasive breast carcinoma is well established. It is considered the standard of care, although it is being replaced, in part, by minimally invasive axillary samplings. A few authors have recommended that ALND should not be used to treat minimally invasive breast cancers, because no trial has proven a real survival advantage and because the anticipated rate of axillary dissemination is low anyway. Other studies, however, have reported higher rates of axillary metastases in association with small breast tumors, suggesting that this patient group should be offered the standard surgical treatment.

In general, ALND is not recommended for DCIS, and its role in DCIS with microinvasion has always been challenged, although solid data on the subject are scarce. The objective of the present series was to examine the rate of axillary lymph node metastases in T1mic and T1a breast cancer to identify patients at higher risk of dissemination to the axillary nodal basin.

### RESULTS

Fifty-seven women (median age, 60 years; range, 37-71 years) were included in the study (Table 1). Thirty-seven had T1mic disease (<1 mm) and 20 had T1a (1-5 mm). Mean ± SEM age was similar in the 2 groups (53.5 ± 4.2 and 52.9 ± 3.7 years, respectively). All patients had undergone preoperative mammography. Calcification was the most frequent presentation (42 patients), followed by a palpable mass in 11 patients and nipple discharge in 4. These presenting signs had no correlation with the size of the invasive component or the presence or absence of axillary metastases.

Twenty-nine patients (18 with T1mic and 11 with T1a) underwent modified radical mastectomy, and 28 (19 with T1mic and 9 with T1a) had a breast-preserving procedure (Table 1). Fourteen patients with unknown axillary status were excluded from the statistical analyses. Twelve of these received local irradiation. Median follow-up for the group without ALND was 47.7 months (range, 30-101 months). Axillary lymph node dissection was performed in 43 patients (75% of the whole sample), including 28 of the 37 patients with T1mic lesions and 15 of the 20 with T1a lesions. Six of them had lymph node metastases, 3 in the T1mic group and 3 in the T1a group. The mean ± SEM number of excised lymph nodes was 17.9 ± 9.

Seventeen (40%) of the 43 patients treated with ALND had comedo DCIS; these included all 6 patients with axillary metastases. Comedo DCIS had a significant statistical correlation with axillary lymph node metastases in the T1mic group (P < .03). The extent of DCIS was evaluated by counting the total number of ducts with malignant involvement. When a biopsy or lumpectomy was complemented with a mastectomy or wide local excision because of unclear margins, the sum of all the involved ducts in the primary and the complemented specimens was calculated. In the T1mic group, a statistically significant correlation was noted between high number of involved ducts and the presence of axillary lymph node metastases (P < .002) (Table 2). This was not true in the T1a group. Both groups showed a significant correlation between high nuclear grade and axillary involve-

### METHODS

The computerized archives (January 1, 1988, to December 30, 1998) of the Department of Pathology, Rabin Medical Center, Beilinson Campus, were surveyed for diagnosis of DCIS. Patients with DCIS as a part of infiltrating duct carcinoma were excluded. All slides corresponding to the pathology reports of DCIS or of DCIS with microinvasion were reviewed by a single pathologist (S.M.), who reclassified them according to the 1997 Cancer Staging Manual put forth by the American Joint Committee on Cancer. All patients identified on this review as having DCIS with no invasive component or invasive components larger than 5 mm were excluded. The remaining patients with DCIS and microinvasive components were divided into T1mic and T1a groups. All specimens were then reexamined pathologically for exact size of the tumor and of the invasive and the noninvasive components. The highest observed nuclear grade was recorded, in addition to the histological subtype (comedo or noncomedo). The number of involved ducts was recounted, and the presence or absence of lymphatic and vascular invasion was reevaluated. All available axillary specimens were reviewed for the presence or absence of metastatic lymph nodes. Slides were reviewed for estrogen and progesterone receptor status.

Clinical data were obtained from review of the patients’ medical charts. Attention was directed to patient age, preoperative mammographic findings, anatomic tumor site, and extent of the definitive surgical procedure. (Margins were considered clean if the distance to the inked margin exceeded 2 mm.) Follow-up information was obtained from the medical files of the outpatient oncology clinic, starting from the day of the definitive surgical procedure and ending with the most recent follow-up visit or death. The follow-up data included postoperative adjuvant treatment and state of health at the end point.

The association between variables was assessed by contingency tables and evaluated with Fisher exact test, χ² test, or t test, where applicable. Statistical significance was defined as P < .05. Patients who did not undergo axillary dissection were excluded from the statistical analysis because their axillary status was unknown.

### Table 1. Characteristics of Patients and Surgical and Adjuvant Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1mic (n = 37)</th>
<th>T1a (n = 20)</th>
<th>Total (N = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SEM age, y</td>
<td>53.5 ± 4.2</td>
<td>52.9 ± 3.7</td>
<td>53.1 ± 3.1</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>18 (48.6)</td>
<td>11 (55.0)</td>
<td>29 (50.9)</td>
</tr>
<tr>
<td>Breast preservation</td>
<td>19 (51.4)</td>
<td>9 (45.0)</td>
<td>28 (49.1)</td>
</tr>
<tr>
<td>Axillary lymph node dissection</td>
<td>28 (75.7)</td>
<td>15 (75.0)</td>
<td>43 (75.4)</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>16 (43.2)</td>
<td>8 (40.0)</td>
<td>24 (42.1)</td>
</tr>
<tr>
<td>Radiotherapy and tamoxifen</td>
<td>13 (35.1)</td>
<td>10 (50.0)</td>
<td>23 (40.4)</td>
</tr>
<tr>
<td>Citrate or chemotherapy</td>
<td>8 (21.6)</td>
<td>2 (10.0)</td>
<td>10 (17.5)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated.
mation (P<.001 and P<.009, respectively). No other statistically significant differences were found within or between the groups for any of the other variables tested (Table 2).

Forty-seven patients received adjuvant therapy: 24 had radiotherapy alone and 23 had radiotherapy with tamoxifen citrate or chemotherapy. Median follow-up was 40 months (range, 3-120 months). One patient who had had no axillary metastases was unavailable for follow-up, and 4 patients died of unrelated causes during follow-up. One patient who did not undergo ALND but received adjuvant regional radiotherapy died of metastatic disease 1 year after diagnosis. None of the other patients without axillary dissection experienced axillary relapse during follow-up. Another patient developed a contralateral second primary carcinoma with a synchronous ipsilateral recurrent DCIS focus 94 months after the first event. She is now free of disease 21 months after her second surgery. The remaining patients were alive and free of disease at the time of the last follow-up.

**COMMENT**

The present study is based on the 1997 American Joint Committee on Cancer’s staging classification for breast carcinoma. Pathological reclassification was performed to include patients who met the criteria of the updated T1mic and T1a categories.

Axillary dissection is considered the gold standard for the staging and treatment of invasive breast carcinoma. Advocates of ALND for small (<1 cm) tumors base their recommendation on the high rates of axillary relapses reported in patients treated by tumor excision alone. White et al followed up 1000 patients with T1a and T1b breast cancer treated without ALND and noted significantly decreased disease-free survival and decreased breast cancer–specific survival. In a study of 247 patients with small breast carcinomas and a 10% to 15% rate of axillary metastases, Mann et al found that after 6 years, nodal status was the most significant factor predicting distant disease-free survival. The 1990 International (Ludwig) Breast Cancer Study Group emphasized the added value of detailed histological evaluation of the axillary lymph nodes. A significantly poorer outcome was associated with micrometastases discovered by serial sectioning and immunohistochemistry. Mustafa and Bland stressed that it is because of the small amount of tissue available for further biological analysis in these small tumors that this group of patients would benefit from ALND for disease staging and adjuvant treatment planning.

However, ALND is associated with significant postoperative morbidity, and others have found that it does not improve long-term survival in patients with small breast tumors. Chontos et al reported a 4.5% rate of axillary lymph node metastases associated with 66 T1a breast tumors. They concluded that routine ALND should not be performed in this patient group. In a recent study by Greco et al, 401 patients with T1 and T2 disease were treated without axillary dissection. After 5 years, nodal relapse was noted in 2% of T1a tumors and 1.7% of T1b tumors. These authors emphasized the negligible effect of axillary dissection on outcome, suggesting that adjuvant treatment be given on the basis of biological markers of the primary tumor. They claimed that with close follow-up, all patients with axillary relapse can be salvaged surgically. Another study by 28 of 240 patients demonstrated that axillary nodal status affected the decision for adjuvant therapy in only 5% of node-negative patients. Silver and Tavassoli reported a 0% incidence of axillary metastases in 38 patients with DCIS and microinvasion who underwent mastectomy. After a mean follow-up of 7.5 years, only 1 patient had a recurrence, in the contralateral breast.

Diagnostic and therapeutic intraoperative lymph node mapping and sentinel node biopsy have also been used in patients with breast cancer. The prediction rate of the axillary nodal basin status by sentinel node sampling has ranged from 95% to 100%, with false-negative rates ranging from 1% to 3%. Axillary irradiation may also serve as an alternative to ALND for clinically node-negative patients, with similar recurrence rates reported for both modes and up to a 50% reduction in ALND-related morbidity with axillary irradiation. However, axillary irradiation does not provide nodal status information. The European Organization for Research and Treatment of Cancer is conducting a prospective study comparing axillary dissection with irradiation following sentinel node biopsy. Data are not yet available.

**Table 2. Pathological Determinants of the Primary Lesion and Axillary Lymph Nodes***

<table>
<thead>
<tr>
<th>Axillary Status</th>
<th>Positive (n = 3)</th>
<th>Negative (n = 25)</th>
<th>P Value</th>
<th>Positive (n = 3)</th>
<th>Negative (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comedo DCIS</td>
<td>3</td>
<td>6</td>
<td>&lt;.03</td>
<td>3</td>
<td>5</td>
<td>.20</td>
</tr>
<tr>
<td>Mean ± SEM No. DCIS-involved ducts</td>
<td>655.7 ± 29.4</td>
<td>274.3 ± 62.6</td>
<td>&lt;.002</td>
<td>210 ± 3.6</td>
<td>238 ± 78.2</td>
<td>.13</td>
</tr>
<tr>
<td>Nuclear grade 3</td>
<td>3</td>
<td>2</td>
<td>&lt;.001</td>
<td>3</td>
<td>1</td>
<td>&lt;.009</td>
</tr>
<tr>
<td>DCIS multifocality</td>
<td>1</td>
<td>7</td>
<td>&gt;.99</td>
<td>3</td>
<td>5</td>
<td>.20</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>1</td>
<td>1</td>
<td>&gt;.99</td>
<td>1</td>
<td>5</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Estrogen receptors</td>
<td>1</td>
<td>10</td>
<td>&gt;.99</td>
<td>1</td>
<td>5</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Progesterone receptors</td>
<td>1</td>
<td>15</td>
<td>.56</td>
<td>0</td>
<td>4</td>
<td>.51</td>
</tr>
<tr>
<td>Mammographic calcification</td>
<td>3</td>
<td>15</td>
<td>.53</td>
<td>2</td>
<td>3</td>
<td>.24</td>
</tr>
<tr>
<td>Mean ± SEM tumor size, mm</td>
<td>16.6 ± 3.3</td>
<td>19.2 ± 1.2</td>
<td>.16</td>
<td>16.5 ± 3.4</td>
<td>17.5 ± 1.7</td>
<td>.15</td>
</tr>
</tbody>
</table>

*Data are given as number of patients unless otherwise indicated. DCIS indicates ductal carcinoma in situ; NA, not applicable.
In the present study, the incidence of axillary involvement was 14% (6/43, 3 in the T1mic group and 3 in the T1a group). In view of this rate, we cannot support the wholesale abandonment of ALND in all patients with DCIS with microinvasion. After a median follow-up of 40 months, our series showed an excellent survival rate, with a single patient who relapsed and died 12 months after diagnosis. A second patient who relapsed 94 months after diagnosis is now free of disease after a second operation. Fourteen patients had no ALND. Twelve patients in this group received only local irradiation. All 14 patients were excluded from the statistical analysis because their axillary status was unknown. Nevertheless, except for 1 patient in this group who died from disseminated disease, none of the patients had an axillary recurrence during follow-up.

Factors predicting axillary lymph node metastases in small breast tumors have been investigated. Among predictive variables, Rivadeneira et al listed high tumor grade, lymphovascular invasion, increased tumor size, poor histological grade, and younger age. In the study by Shoup et al of 23 T1a tumors, 55 T1b tumors, and 126 T1c tumors, lymphovascular invasion, grade 3 pleomorphism, and increased tumor size were predictors of nodal involvement. The method of determination of tumor size varies among investigators, with some including the DCIS component and others not. We used the noninvasive and invasive components, and size was not a significant predictor of axillary metastases (Table 2). Significant predictors were nuclear grade 3 in the T1a and T1mic groups (P < .009 and P < .001, respectively) and for comedo DCIS (P < .03) in the T1mic group. Comedo DCIS was reported in 82% of the cases associated with microinvasion in the study by Silver and Tavassoli and in 67% of the cases in the study by Simpson et al. It was the dominant histological finding in 14 (38%) of the 37 T1mic tumors in our study and correlated significantly with positive nodal status (P < .03). Comedo morphologic structure was also associated with an increased number of DCIS-involved ducts, indicating a higher degree of invasiveness. A high number of ducts involved with DCIS was significantly correlated with lymph node metastases in the T1mic group (P < .002).

In conclusion, we report a significant rate of axillary metastases in patients with T1mic and T1a disease. Axillary lymph node dissection or selective axillary node dissection has a place in the surgical approach to DCIS with a microinvasive component. It should be particularly considered when the primary tumor characteristics include T1mic disease with a dominant comedo DCIS, which is not an unequivocal indication for adjuvant chemotherapy.

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REFERENCES