Management and Outcomes of Isolated Axillary Node Recurrence in Breast Cancer

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Hypothesis: Management strategies affect the outcome of axillary recurrence in breast cancer.

Design: Population-based analysis.

Setting: Cancer agency breast cancer database.

Patients: Two hundred twenty women diagnosed with stage 0 through III breast cancer between 1989 and 2003 who subsequently developed an isolated axillary relapse.

Main Outcome Measures: Overall survival rate and disease-free survival rate according to treatment strategy of the axillary recurrence.

Results: Among 19,789 women diagnosed with stage 0 through III breast cancer during the study era, 220 had an isolated axillary recurrence (Kaplan-Meier 5-year isolated axillary relapse rate, 1.0%). The median interval between primary breast cancer diagnosis and axillary recurrence was 2.2 years (range, 1.8 months to 11.9 years). Median follow-up time after axillary recurrence was 5.4 years. Treatment for the axillary recurrence included lymph node biopsy (47.3%), complete axillary dissection (25.9%), axillary radiation (65.0%), chemotherapy (24.1%), and hormonal therapy (68.2%). The 5-year Kaplan-Meier overall survival rate estimate after axillary recurrence was 49.3% (95% confidence interval, 42.0-56.3). Median survival time from the isolated axillary recurrence was 4.9 years (range, 2.0 months to 15.1 years). Overall (P<.001) and disease-free (P=.006) survival times were highest in those treated with a combination of surgery and radiation. Other factors associated with improved overall survival rate were an interval from diagnosis to relapse greater than 2.5 years (P=.003), no initial axillary radiation (P=.001), asymptomatic presentation of the recurrence (P=.05), and subsequent systemic treatment (P=.02).

Conclusions: The 5-year isolated axillary recurrence rate of women treated for breast cancer was 1.0%. Multimodality management at the time of recurrence, including axillary surgery, radiation, and systemic therapy, significantly improved overall and disease-free survival.

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HE AXILLARY NODES RECEIVE 97% OF THE LYMPHATIC DRAINAGE FROM THE BREAST.1 AXILLARY LYMPH NODE DISSECTION IMPROVES REGIONAL CONTROL, MAY IMPROVE SURVIVAL, AND PROVIDES IMPORTANT PROGNOSTIC INFORMATION.2,3 AFTER AN ADEQUATE AXILLARY LYMPH NODE DISSECTION, ISOLATED AXILLARY NODE FAILURE IS RELATIVELY RARE,4-9 OCCURRING IN 1% TO 3% OF PATIENTS BETWEEN 19 AND 27 MONTHS AFTER INITIAL TREATMENT. THE 5-YEAR OVERALL SURVIVAL FOR PATIENTS WITH AN ISOLATED AXILLARY RELAPSE HAS BEEN REPORTED TO BE 27% TO 49%.9,10

Because of the relatively rare occurrence of isolated axillary node failure, most studies examining this topic have small sample sizes and limited follow-up.5-11 There are limited data about the optimal management of these patients.3,9 This is a report of a population-based analysis to evaluate localized axillary recurrence in breast cancer with respect to frequency, management, outcomes, and possible prognostic indicators for recurrence and survival.

METHODS

Ethical approval for this study was obtained from the University of British Columbia and the British Columbia Cancer Agency (BCCA) research ethics board. Subjects were identified from the Breast Cancer Outcomes Unit database of the BCCA. This database contains detailed demographic, staging, treatment, and outcome information for patients diagnosed with breast cancer and referred to the BCCA since January 1, 1989. Approximately 75% of patients with breast cancer in the province were referred to the BCCA.
BCCA during the study interval. Included in the current study were all women with a new diagnosis of stage 0 through III breast cancer between 1989 and 2003 who had treatment with curative intent and subsequently developed an isolated axillary recurrence. Excluded were men, those patients with initial diagnoses of M1 or N3 disease, and those patients with synchronous or previous breast cancer even after preoperative therapy with chemotherapy and/or radiotherapy. Patients were also excluded if they had developed systemic recurrence before the diagnosis of axillary recurrence or developed a local or systemic recurrence within 4 months of the axillary recurrence or if there were multiple sites of local or regional recurrence (eg, concurrent internal mammary, supraclavicular, infraclavicular, breast, or chest wall recurrent disease).

Patient demographics, primary breast cancer characteristics and treatment, and patient outcomes were obtained from the Breast Cancer Outcomes Unit database. Details on presentation and management of the axillary recurrence were obtained from BCCA hospital records. Primary end points were axillary relapse rate, time interval between primary breast cancer diagnosis and axillary recurrence, and median survival time after recurrence. Secondary end points were overall survival and disease-free survival according to strategy of treatment of the axillary recurrence.

Statistical analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, Ill). Survival data were analyzed using the Kaplan-Meier method and comparisons made using the log-rank test (2-tailed). Kaplan-Meier survival analyses were calculated from diagnosis of the first axillary recurrence.

RESULTS

There were 19 789 women diagnosed with breast cancer in British Columbia between January 1, 1989, and December 31, 2003, who were referred to the BCCA and who met the criteria for inclusion in this study. Of these, 220 were found to have an isolated axillary recurrence for a 5-year Kaplan-Meier recurrence rate of 1.0%. Median follow-up time for surviving patients after the axillary recurrence was 5.4 years (range, 0.9-15.1 years).

PRIMARY BREAST CANCER CHARACTERISTICS AND INITIAL MANAGEMENT

The characteristics of the primary breast cancer diagnoses are listed in Table 1. The mean age at initial diagnosis was 59.5 years. The majority of patients had a T1 or T2 tumor and an N stage of 0. Forty-eight percent (n=105) had breast-conserving therapy. One hundred seventy-eight patients (80.9%) had an axillary lymph node dissection as part of their initial management; 82 (46.1%) had axillary node metastases and, of these, 22 (26.8%) had extranodal extension. The mean number of nodes removed during the axillary lymph node dissection was 8.2 (median, 7.0). Thirty-three patients (15.0%) had regional lymph node radiation. Sixty percent of patients received initial hormonal therapy, chemotherapy, or both.

PRESENTATION OF ISOLATED AXILLARY RECURRENCE

The median interval between primary breast cancer diagnosis and axillary recurrence was 2.2 years (range, 1.8 months to 11.9 years). Half of the patients (50.9%) palpated the axillary recurrence on their own. Twenty-nine percent of the recurrences were discovered on follow-up by a physician; only 3% were discovered by follow-up imaging; and in 6% of patients, the mode of presentation was unknown. Eleven percent of patients experienced symptoms as a result of their recurrence as defined by pain, numbness, weakness, or edema of the arm. The remainder experienced no documented symptoms beyond palpable disease as a result of their recurrence.

TREATMENT OF ISOLATED AXILLARY RECURRENCE

Treatment strategies for the axillary recurrence are listed in Table 2. The majority of patients had axillary surgery (73.2%). This included complete axillary dissection and isolated axillary lymph node removal. The mean number of lymph nodes removed was 5.9 (median, 4.0). Regional nodal radiation therapy was given in almost all of the cases when it had not been part of the initial treatment (97.9%). Almost half of patients (48.6%) received

Table 1. Characteristics of the Primary Breast Cancer in 220 Patients Who Developed an Isolated Axillary Recurrence

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis, y</td>
<td>59.5</td>
</tr>
<tr>
<td>T stage at diagnosis (pathologic or clinical if pathologic unknown), No. (%)*</td>
<td>71 (46.8)</td>
</tr>
<tr>
<td>T1</td>
<td>94 (42.7)</td>
</tr>
<tr>
<td>T2</td>
<td>80 (36.4)</td>
</tr>
<tr>
<td>T3 or T4</td>
<td>15 (6.8)</td>
</tr>
<tr>
<td>Tis</td>
<td>12 (5.5)</td>
</tr>
<tr>
<td>Unknown T stage</td>
<td>19 (8.6)</td>
</tr>
<tr>
<td>Mean tumor size, cm</td>
<td>2.5</td>
</tr>
<tr>
<td>N stage at diagnosis (pathologic or clinical if pathologic unknown), No. (%)*</td>
<td>119 (59.0)</td>
</tr>
<tr>
<td>N0</td>
<td>112 (50.9)</td>
</tr>
<tr>
<td>N1</td>
<td>75 (34.1)</td>
</tr>
<tr>
<td>N2</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Unknown N stage</td>
<td>26 (11.8)</td>
</tr>
<tr>
<td>ER positive, No. (%)</td>
<td>120 (54.5)</td>
</tr>
<tr>
<td>ER negative, No. (%)</td>
<td>66 (30.0)</td>
</tr>
<tr>
<td>ER unknown, No. (%)</td>
<td>34 (15.5)</td>
</tr>
<tr>
<td>Extranodal extension, No. (%)</td>
<td>22 (26.8)</td>
</tr>
<tr>
<td>Initial surgery, No. (%)</td>
<td>25 (11.4)</td>
</tr>
<tr>
<td>With ALND</td>
<td>178 (80.9)</td>
</tr>
<tr>
<td>Without ALND</td>
<td>42 (19.1)</td>
</tr>
<tr>
<td>Radiation to axilla, No. (%)</td>
<td>111 (50.5)</td>
</tr>
<tr>
<td>Initial chemotherapy, No. (%)</td>
<td>95 (43.2)</td>
</tr>
<tr>
<td>Initial hormonal therapy, No. (%)</td>
<td>85 (38.6)</td>
</tr>
</tbody>
</table>

Abbreviations: ALND, axillary lymph node dissection; ER, estrogen receptor.
*T and N stage definitions from the fifth edition of the Cancer Staging Manual from the American Joint Committee on Cancer.
both axillary surgery and radiation. Seventy-nine percent of patients received some sort of systemic treatment with the majority being hormonal therapy.

OUTCOMES OF ISOLATED AXILLARY RECURRENCE

Forty-six percent of patients eventually developed distant metastases on follow-up. The 5-year overall survival rate following isolated axillary recurrence was 49.3% (95% confidence interval, 42.0-56.3). Median survival time from the axillary recurrence was 4.9 years (range, 2.0 months to 15.1 years). Overall and disease-free survival rate estimates, according to clinical characteristics and treatment strategies, are presented in Table 3. Patients with initial T1 stage disease had an improved 5-year disease-free survival rate (P = .01), but this was not associated with an overall survival benefit (P = .19). Patients with initial N0 stage disease had improved overall and disease-free survival rates compared with patients with initial stage N1 or N2 disease (P < .001). Initial axillary lymph node dissection did not correlate with an improved disease-free or overall survival rates after axillary recurrence. Factors correlating with improved disease-free and overall survival rates included time to axillary recurrence greater than 2.5 years, no initial axillary radiation, asymptomatic presentation of recurrence, and the use of subsequent axillary radiation and systemic treatment. There was no difference in overall (P = .26) or disease-free survival rates (P = .72) when comparing isolated axillary node removal with an axillary dissection. A multimodal approach (surgery plus radiation) was associated with an improved overall survival rate (Figure).

In Table 4, patient and treatment characteristics are compared according to treatment received for the axillary recurrence: surgery alone, radiation therapy alone, or both surgery and radiation. Overall, patient age and initial disease variables were equally distributed with a trend to more favorable prognostic variables in the surgery-plus-radiation group. Initial treatment was not equally distributed. Patients treated with both radiation and surgery for the recurrence were more likely to have not received chemotherapy or axillary radiation at initial diagnosis and more likely to have received systemic therapy for their axillary recurrence.

This was a population-based assessment of axillary recurrence using referrals to the BCCA with a median follow-up time of 5.4 years after the axillary recurrence. Surgical treatment for breast cancer in British Columbia was performed in multiple hospitals, but all patients requiring a radiation oncology opinion, and the majority of those requiring a medical oncology opinion, were referred to the BCCA.

Axillary recurrence is a rare event after treatment for breast cancer. We found a 5-year Kaplan-Meier isolated axillary recurrence rate of 1.0%, which is slightly lower than that in previous studies. This may be due in part to our conservative definition of an “isolated” axillary recurrence. To be included as an isolated recurrence, there had to have been no other breast cancer event (local recurrence, other regional recurrences, distant metastases, contralateral new breast primary, or breast cancer death) prior to or within 4 months of the axillary recurrence. Although considerable effort is made to ensure complete reporting of recurrence events in the Breast Cancer Outcomes Unit database, it is possible that some patients with recurrence could have been missed. There were no prescribed guidelines for completeness of staging at relapse, so the extent to which these were truly isolated relapses is difficult to assess. Our 5-year overall survival rate after axillary recurrence was 49.3%, which is similar to that in the published literature. Even with treatment, patients who develop axillary recurrence have a high rate of subsequent distant metastases.

PRIMARY BREAST CANCER CHARACTERISTICS AND INITIAL TREATMENT

This study focused on the management of the axillary recurrence and its impact on survival rate. We did not specifically look at risk factors for axillary recurrence. Others have identified age younger than 40 years, larger tumor size, the number and proportion of involved axillary nodes, and higher histologic grade at diagnosis to increase a woman’s risk for axillary recurrence. In the current study, primary breast cancer characteristics associated with a worse outcome after recurrence were T3/T4 tumors and node-positive disease at diagnosis.

Axillary dissection for the primary breast cancer was performed in 81% of patients. Whether a patient initially had an axillary dissection or not did not correlate with survival rate after recurrence. Patients who underwent sentinel node biopsy were excluded from our analysis; however, the increasing use of these techniques may have an important impact on axillary recurrence. There

### Table 2. Management Strategies for 220 Patients With an Isolated Axillary Recurrence

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical management</td>
<td></td>
</tr>
<tr>
<td>Yes, No. (%)</td>
<td>161 (73.2)</td>
</tr>
<tr>
<td>Isolated lymph node removal, No. (%)</td>
<td>104 (47.3)</td>
</tr>
<tr>
<td>Axillary lymph node dissection, No. (%)</td>
<td>57 (25.9)</td>
</tr>
<tr>
<td>ALND with no previous ALND, No.</td>
<td>26/57</td>
</tr>
<tr>
<td>ALND with previous ALND, No.</td>
<td>31/57</td>
</tr>
<tr>
<td>No, No. (%)</td>
<td>59 (26.8)</td>
</tr>
<tr>
<td>Regional nodal radiation</td>
<td></td>
</tr>
<tr>
<td>Yes, No. (%)</td>
<td>143 (65.0)</td>
</tr>
<tr>
<td>Yes; axilla previously radiated, No.</td>
<td>3/143</td>
</tr>
<tr>
<td>Yes; axilla not previously radiated, No.</td>
<td>140/143</td>
</tr>
<tr>
<td>No, No. (%)</td>
<td>77 (35.0)</td>
</tr>
<tr>
<td>No; axilla previously radiated, No.</td>
<td>50/77</td>
</tr>
<tr>
<td>No; axilla not previously radiated, No.</td>
<td>47/77</td>
</tr>
<tr>
<td>Chemotherapy after recurrence, No. (%)</td>
<td>53 (24.1)</td>
</tr>
<tr>
<td>Hormone therapy after recurrence, No. (%)</td>
<td>150 (68.2)</td>
</tr>
</tbody>
</table>

Abbreviation: ALND, axillary lymph node dissection.
is an anticipated 5% to 20% false-negative rate associated with sentinel node biopsy.\textsuperscript{14-18} This understaging may result in undertreatment of some women with breast cancer. Because of the small number of patients and the retrospective nature of the analysis, our results do not inform the issue of whether the extent of axillary surgery or the omission of axillary surgery affects survival rate or regional control.

Only 33 patients (15.0\%) had radiation to the regional lymph nodes as part of the treatment of their primary breast cancer. Regional nodal radiation is used selectively in British Columbia for patients deemed to be at higher risk of regional recurrence on the basis of the extent of primary tumor or nodal disease.\textsuperscript{19} Patients who had received initial regional radiation therapy had worse disease-free and overall survival rates after an axillary recurrence. This is likely a result of a selection bias. It may also indicate that breast cancer that recurs within a previously irradiated field is more aggressive biologically, 

<table>
<thead>
<tr>
<th>Characteristic or Strategy</th>
<th>No.</th>
<th>5-Year Disease-Free Survival Estimate (CI)</th>
<th>P Value</th>
<th>5-Year Overall Survival Estimate (CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage at initial diagnosis (pathologic or clinical if pathologic unknown)\textsuperscript{*}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T1</td>
<td>94</td>
<td>45.0 (33.8-55.6)</td>
<td>.01</td>
<td>53.9 (42.5-63.9)</td>
<td>.19</td>
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<tr>
<td>T2</td>
<td>80</td>
<td>27.3 (16.9-39.6)</td>
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<td>T3 and T4</td>
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<td>24.0 (6.3-47.9)</td>
<td></td>
<td>37.5 (14.1-61.2)</td>
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<tr>
<td>N stage at initial diagnosis (pathologic or clinical if pathologic unknown)\textsuperscript{†}</td>
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<tr>
<td>N0</td>
<td>112</td>
<td>50.8 (40.1-60.4)</td>
<td>&lt;.001</td>
<td>61.7 (51.1-70.7)</td>
<td>&lt;.001</td>
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<tr>
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<td>75</td>
<td>22.2 (13.0-32.8)</td>
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<td>33.7 (22.9-44.9)</td>
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<tr>
<td>N2</td>
<td>7</td>
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<td></td>
<td>14.3 (0.7-46.5)</td>
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<td>Initial axillary lymph node dissection</td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>42</td>
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<td>.08</td>
<td>48.6 (30.0-64.9)</td>
<td>.75</td>
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<td>Yes</td>
<td>178</td>
<td>36.1 (28.6-43.7)</td>
<td></td>
<td>49.4 (41.3-56.9)</td>
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<td>Initial axillary radiation</td>
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<td>No</td>
<td>187</td>
<td>44.7 (36.7-52.3)</td>
<td>&lt;.001</td>
<td>54.9 (46.6-62.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>6.9 (1.2-19.7)</td>
<td></td>
<td>22.3 (9.9-37.8)</td>
<td></td>
</tr>
<tr>
<td>Interval of diagnosis to recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Within 2.5 y</td>
<td>124</td>
<td>31.9 (23.3-40.8)</td>
<td>.02</td>
<td>42.1 (32.9-51.0)</td>
<td>.003</td>
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<tr>
<td>After 2.5 y</td>
<td>96</td>
<td>47.8 (36.1-58.6)</td>
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<td>60.1 (48.2-70.1)</td>
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<td>Presentation of axillary recurrence\textsuperscript{†}</td>
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<td>Asymptomatic</td>
<td>184</td>
<td>42.6 (34.6-50.4)</td>
<td>.003</td>
<td>51.6 (43.5-59.2)</td>
<td>.05</td>
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<td>Symptomatic</td>
<td>24</td>
<td>21.1 (7.2-39.7)</td>
<td></td>
<td>30.8 (11.9-51.9)</td>
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<tr>
<td>Size of axillary recurrence\textsuperscript{†}</td>
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<tr>
<td>≤2.0 cm</td>
<td>71</td>
<td>41.9 (29.4-54.0)</td>
<td>.42</td>
<td>65.5 (52.3-75.8)</td>
<td>.07</td>
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<tr>
<td>&gt;2.0 cm</td>
<td>86</td>
<td>41.1 (29.3-52.5)</td>
<td></td>
<td>45.2 (33.2-56.3)</td>
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<td>Axillary surgery for recurrence</td>
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<td>59</td>
<td>35.6 (22.7-48.8)</td>
<td>.19</td>
<td>35.8 (23.1-48.8)</td>
<td>.007</td>
</tr>
<tr>
<td>Yes</td>
<td>161</td>
<td>39.8 (31.4-48.0)</td>
<td></td>
<td>54.4 (45.7-62.4)</td>
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<td>Extent of axillary surgery for recurrence</td>
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<td>Complete ALND</td>
<td>57</td>
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<td>.72</td>
<td>45.5 (30.9-59.1)</td>
<td>.26</td>
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<tr>
<td>Isolated axillary lymph node removal</td>
<td>104</td>
<td>41.3 (31.0-51.3)</td>
<td></td>
<td>59.2 (48.3-68.7)</td>
<td></td>
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<tr>
<td>Axillary radiation for recurrence</td>
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<td></td>
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<tr>
<td>No</td>
<td>77</td>
<td>25.7 (15.3-37.5)</td>
<td>.001</td>
<td>37.7 (26.3-49.1)</td>
<td>&lt;.001</td>
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<tr>
<td>Yes</td>
<td>143</td>
<td>44.8 (35.8-53.4)</td>
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<td>55.8 (46.5-64.2)</td>
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<td>Systemic treatment for recurrence</td>
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<td>No</td>
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<td>.008</td>
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<td>.02</td>
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<td>174</td>
<td>41.9 (33.8-49.9)</td>
<td></td>
<td>53.2 (44.8-60.9)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALND, axillary lymph node dissection; CI, confidence interval.
\textsuperscript{*}Tis and TX excluded from Kaplan-Meier analyses.
\textsuperscript{†}Unknown cases excluded from Kaplan-Meier analyses.

Figure. Overall survival rate by treatment for axillary recurrence.

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more likely to be associated with future systemic relapse, and less amenable to curative treatment.

PRESENTATION

The median time interval from diagnosis of primary breast cancer to the axillary recurrence was 2.2 years. This is similar to that in other studies. Half the patients detected the axillary recurrence themselves and only one third of recurrences were detected by a physician or follow-up imaging. The detection of the axillary recurrence may be improved by increasing the frequency of examinations by physicians. However, it was only the patients with symptoms (pain, edema, weakness) who had a worse prognosis. This is expected because the disease was likely more aggressive or extensive to interfere with the nerves and lymphatics of the axilla.

TREATMENT OF AXILLARY RECURRENCE

The relative rarity of axillary recurrence does not allow for randomized clinical trials, and therefore, the ideal management remains unanswered. The best evidence available is from retrospective analyses like the current study. Approximately 75% of patients were treated with surgery to the axilla. Of the procedures performed, 65% were isolated lymph node removal compared with 35% who had more extensive lymph node dissection. Interestingly, more extensive surgery did not correlate with improved survival rate. This may be because axillary recurrence is an indicator of systemic disease rather than a truly isolated event. Nevertheless, nearly half of the patients treated for the axillary recurrence did not die from breast cancer. The small numbers in our series made it difficult to statistically exclude a meaningful clinical benefit of complete surgery at the time of recurrence.

Patients who had a combination of surgery and radiation for their axillary recurrence had the best prognosis (Figure 1). Five-year overall survival rate from the time of axillary recurrence was 63% for patients treated with surgery plus radiation compared with 34.8% to 38.3% if treated by surgery or radiation alone or neither (P<.001). Therefore, our data suggest that a multimodal approach with surgery and radiation results in an improved outcome. Analysis of the 3 treatment groups revealed that there were significantly more patients who had not received initial axillary radiation in the multimodality group rather than the surgery- or radiation-only groups. Because patients who did not undergo initial radiation had an improved survival rate, this could explain the results. It is possible that patients with lower bulk disease may have had tumors that were easier to resect. However, this does not explain why patients treated with surgery alone also did less well than those treated with surgery plus radiation. Alternatively, patients whose cases were managed with surgery alone at relapse often received radiotherapy as part of their initial treatment, limiting its further use, and may suggest more biologically aggressive disease in this subgroup. The majority of patients who had not received regional nodal radiation as part of their primary treatment had radiation for the axillary recurrence.

The addition of systemic therapy (chemotherapy or hormonal therapy) was associated with improved survival rate (P=.02) and was given to approximately 80% of patients. However, our numbers were too small to confidently recommend chemotherapy for the treatment of axillary recurrence. Because of the retrospective nature of the analysis, we were unable to make any meaningful comments on adverse effects of therapy, such as lymphedema.

IMPLICATIONS

This is the largest reported series of patients with isolated axillary recurrences after primary treatment of
breast cancer. Our results confirm the observations of others. The rate of isolated axillary relapse was low in an era of level 1 and 2 axillary dissections. The use of both surgery and radiation was associated with better outcomes than either modality alone. Interestingly, the extent of surgery to the axilla (ie, biopsy vs full dissection) did not impact survival rate. Patients who had systemic therapy (chemotherapy and hormonal therapy) did show an enhanced survival rate in our series, but low numbers caution us in recommending this as standard treatment. Whether the risk of axillary recurrence after limited approaches to the axillary lymph nodes, such as sentinel node biopsy alone, will be equivalent to rates after complete axillary dissection remains to be proven. Any change in practice that leads to an increase in the rate of axillary relapse could be associated with decreased overall survival.

CONCLUSIONS

Axillary recurrence is a rare but significant event after breast cancer treatment and is associated with a median survival time of 5 years. Factors correlating with improved disease-free and overall survival rates were a time to recurrence greater than 2.5 years, no initial axillary radiation, and asymptomatic presentation of the recurrence. In univariate analysis, treatment of isolated axillary recurrence with axillary radiation and systemic treatment were also associated with improved outcome. Our data support the multimodality management of isolated axillary recurrence of breast cancer and suggest that resectable disease be surgically excised followed by radiation therapy if not delivered as adjuvant therapy. Hormonal therapy is frequently used and seems justified. While the benefit of chemotherapy is the subject of current clinical trials, the risks and benefits should be considered given the high risk of future systemic recurrence. The description of risk estimates and outcomes in the current study are useful when considering all of these therapies in the care of women with isolated axillary recurrence of breast cancer.

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REFERENCES


John T. Vetto, MD, Portland, Ore: A decade after the end of World War II, Dr Michael Shimkin, associate director of the NCI, received a report from the town of Rockford, Ill. It seems that in that town during the war a curious thing happened: all the general surgeons, but none of the general practitioners, were drafted. (I trust this was only a chance occurrence and noth- ing more!) As a result, for 4 years, breast cancer there was treated with only total mastectomy without axillary dissection as the GP's were not comfortable performing Halsted radical mastec- tomies, the surgical standard of care at the time. A review of the cases by the medical board showed no decrease in survival compared to previous survival rates. Intrigued, Shimkin rec- ommended that clinical trials be conducted to test the hypothes- is that axillary dissection does not alter survival in breast cancer. The result, the B-04 study demonstrated that although 40% of the radical mastectomy specimens showed positive nodes, axillary recurrence in the total mastectomy arm was only 15% and that after salvage dissection for axillary recurrence, there was no difference in disease-free or overall survival between the 2 groups.

The paper we have just heard from the BC Cancer Agency uses registry-based data to more closely examine the determinants and outcomes of isolated axillary recurrence. From this
large group of patients, 81% of whom underwent initial axillary dissection, the authors culled out 220 (approximately 1%) with an axillary recurrence.

Comparing this result to the B-04, one might conclude that 2 level node dissection (compared to no dissection) decreases axillary recurrence from 13% to 1%. The issue is more complicated; the patients in the present study received multiple adjuvant therapies, and the recently published International Breast Cancer Study Group (IBCSG) 10-93 trial demonstrated that among older women with ER+ breast cancer receiving tamoxifen, the addition of an axillary dissection reduced recurrence only from 3 to 1%. Similarly, in a CALGB trial in which older women were treated with lumpectomy and tamoxifen, only 2 axillary recurrences were seen in the entire study. These and other recent trials suggest that isolated axillary recurrence may be most likely in ER− disease (a factor not analyzed in the present study) and may be most impacted on by adjuvant therapy, not local control.

Regarding outcomes after recurrence, despite their excellent stringent definitions of isolated axillary recurrence (a major strength of the paper), the authors noted a 5-year overall survival of only 49%, suggesting a poorer outcome. This must not be construed to mean that axillary dissection improves survival; this has not been found in any of the randomized trials I have quoted, and it may simply mean that isolated axillary recurrence in modern series can be a predictor of aggressive tumor biology. Indeed, the authors found that worse survival after isolated axillary recurrence correlated with a short disease-free interval and symptomatic recurrences, surrogates of more aggressive disease. Similarly, the authors’ finding that salvage axillary operation and radiation for isolated axillary recurrence yielded the best survival may have been a result of selection of better patients for these treatments; some patients survived as little as 2 months after axillary recurrence, selecting themselves out of getting any local therapy.

In short, the authors may be describing 2 types of axillary recurrence: recurrence in good prognosis patients in whom the recurrence represented a technical failure (with resulting good outcomes after local therapy) and recurrence in poor prognosis patients in whom the recurrence represented aggressive tumor biology.

I have 3 questions for the authors. (1) Could the axillary recurrences in the better-prognosis patients have been the result of inadequate initial local therapy? I note that the axillary dissections performed on these patients recovered a mean of only 8 nodes. (2) The authors allude to the potential future impact of sentinel lymph node biopsy (SLNB) on isolated axillary recurrence. Given that SLNB false-negative rates are as high as 14% in prospective trials, do the authors believe we will see an increase in isolated axillary recurrences, or will the rate stay low due to increased use of neoadjuvant and targeted therapies? (3) First detection of the axillary recurrences were by patients in over half of the cases and by providers and imaging in only 29% and 3%, respectively. Can the authors suggest better ways of detecting such recurrences in the future?

I congratulate the authors for reporting the largest series of isolated axillary recurrences to date and for using strict definitions to define this entity.

Nathalie M. Johnson, MD, Portland: I would like to ask just a few more questions. In terms of where the axillary recurrences were, could you delineate this a little better? Were these level 3 nodes that weren’t removed with the initial axillary dissection, or where were they located? I would also like to challenge the authors to go back and give us more details on the characteristics of the tumor (i.e., were they ER/PR negative, HER-2-neu positive?) as that would help us better define the biology of these recurrences.

Philip I. Haigh, MD, Los Angeles, Calif: This question relates to the practice patterns of surgeons in British Columbia. I must say that I am Canadian, and whenever I only get 10 lymph nodes from an ALND, my colleagues always joke with me and say, “Well, you’re from Canada and you guys don’t know how to do ALNDs because the British Columbia study shows a mean of only 8 nodes.” Since most of your provincial data are from rural community hospitals, I imagine that the node count would be similar from a hospital in Yreka, Calif, for example. But I would like to ask if the completion ALNDs in your study are done in specialized centers? Are recurrences generally sent to the specialized centers for multidisciplinary management? How many lymph nodes are removed in the completion ALNDs compared to the first time around? Were there any cases of completion ALNDs performed in a specialized urban center that have more nodes harvested than the original operation? Are the rural surgeons doing the hasty picking compared to the specialized centers?

Howard Silverman, MD, Los Angeles: I draw completely different inferences than Dr Vetto did from this paper. It seems to me that the term “recurrence” is not correct here. You are really describing residual or persistent disease because, as you reported, none of these patients had a complete axillary dissection. Further, I think the fact that the residual disease in the axilla carried a 30% mortality and yet was not associated with any evidence of disseminated disease speaks on behalf of the controversies on metastases can metastasize. In contrast to Dr Vetto’s comments, the British Columbia and Danish randomized, controlled trials demonstrated that in stage II disease axillary radiation, a surrogate for axillary dissection, does in fact improve survival. So I think the data reported here could argue for a return to Halstedian complete axillary dissections. The fear that such 3-level dissections would substantially increase the lymphedema rate is not borne out by prospective data.

Frederick M. Dirbas, MD, Stanford, Calif: Perhaps I missed this, but were these all confirmed nodal recurrences, or were any of these soft tissue recurrences in the axilla?

Armando E. Giuliano, MD, Los Angeles: I think there is confusion between the value of an initial axillary dissection and whether that has therapeutic or survival impact and the management of a recurrence in the axilla. These are 2 very different situations. These authors show very nicely what the natural history is of axillary recurrence. They have not convinced me that axillary surgery, the resection of these recurrences, improves survival. But I personally try to resect every one of them, if possible, because these patients who do not have disseminated disease will have tremendous local problems. I think it is a nice paper with a lot of data. I am not sure that the conclusion that axillary surgery improves survival is warranted.

Irene L. Wapnir, MD, Stanford: This is a very large series of isolated axillary recurrences, and I do think their data are suggestive of a role for systemic therapy improving survival. I would like to mention that there is now an international trial cosponsored by the IBCSG and the NSABP to look at the long-term outcome of such patients after randomization to chemotherapy vs no chemotherapy. So I think this is an important topic, and your study is valuable in terms of turning our attention to this problem.

Noelle Lee Davis, MD, Vancouver, British Columbia: This paper actually predates the use of widespread sentinel lymph node mapping in the province of British Columbia, and I believe it serves as a baseline from which trends in axillary recurrences can be monitored. We have demonstrated an acceptable level of axillary recurrence, which is 1% or less. A number of discussants commented about adequacy of surgery. Basically in this series, the operations were undertaken in the 100 or more different hospitals within the province of British Columbia. In some cases, those hospitals and surgeons...
are doing fewer than 10 cases per annum. Similarly, pathology analysis in some of the smaller centers can be challenging. I do believe that there is a reasonable standard of care, and this is because there is a low rate of axillary recurrence. The impact of breast cancer surgery regionalization on survival and local recurrence could be reviewed; however, our data reflects standard of care in most communities and regions.

Unfortunately, we did not specifically look at some of the patient characteristics relative to number of nodes retrieved, so I really can’t answer Dr Vetto’s first question, which was could axillary recurrences in better prognosis patients have been a result of inadequate initial local therapy. I think this is a very important question, and identifying patients in whom surgery has a greater impact than other modalities in locoregional control would be an important question to address.

Dr Vetto’s second question asked if, given a high false-negative rate, will use of sentinel node biopsy increase local recurrences in the axilla? I believe that we will see increasing recurrences locally, but I doubt if this will impact survival of breast cancer patients for the reasons alluded to.

Dr Vetto’s final question was if there was any better way of detecting recurrences other than physical examination or patient observation. Most of our patients are followed with annual mammography, and this is supplemented by ultrasonography in some patients. Only 3% of recurrences were detected on imaging studies. We do not have widespread use of PET scans or MRIs, so I basically don’t think at this point in time there is any better way of detecting recurrence other than instructing patients.

Dr Johnson asked where the axillary recurrences were located, and because these nodes were palpable, they were all basically level 1 recurrences. We have not specifically looked at characteristics of the tumor biology but are planning to regionalize pathology reporting, especially with respect to HER-2-neu protein receptor. I believe this will help identify patients in whom indolent disease can be identified.

Dr Haigh talked again about completion of axillary lymph node dissection in regionalized centers, and, no, the surgery is done throughout the province of British Columbia.

Dr Silberman stated that he felt that we were looking at persistent and not recurrent disease. I suspect most recurrences in fact are persistent and did arise from the primary at some point. The question is just have we done a good enough job biologically of sorting out which patients are more apt to recur and which requires surgical as opposed to other therapies.

Dr Dirbas asked if this was soft tissue vs nodal recurrence. We do believe it was nodal recurrence. This was confirmed pathologically when cases were reviewed.

There was a comment about the use of chemotherapy as part of management of local recurrences, and in our study, patients who had chemotherapy following the recurrent disease had an improved survival. This would again speak to the need for prospective, randomized studies.