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Routine completion axillary lymph node dissection for positive sentinel nodes in patients undergoing mastectomy is not associated with improved local control

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KEYWORDS:
Axillary lymph node dissection; Mastectomy; Sentinel lymph node biopsy

Abstract

BACKGROUND: The current practice of completion axillary lymph node dissection (ALND) for patients with a positive sentinel lymph node (SLN) is being questioned. This led us to examine the outcomes of patients with positive SLNs undergoing mastectomy who underwent ALND compared with those who did not.

METHODS: A retrospective review of cancer registry data identified 561 women with stages 1 to 3 breast cancer with positive SLNs who underwent mastectomy between 2000 and 2010. Four hundred twenty-six women underwent formal ALND and 135 were managed expectantly. Recurrence-free survival was defined as no locoregional or distant metastases.

RESULTS: Mean time to recurrence was 29.9 months. Mean follow-up for patients without recurrence was 40.3 months. Survival curves showed no significant difference in recurrence-free survival between the 2 groups ( \( P = .23 \)).

CONCLUSIONS: In our experience, there is no significant difference in recurrence-free survival in patients with positive SLNs undergoing mastectomy when completion ALND was not performed, suggesting that a closer look at the indications for ALND in early breast cancer be further explored.

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The presence of axillary lymph node metastasis in early breast cancer continues to be an important prognostic predictor.1,2 Evaluation of axillary node status remains a mainstay in the care of newly diagnosed patients with breast cancer. The traditional axillary lymph node dissection (ALND) carries significant morbidity, including lymphedema, neuralgia, and seroma.3 Sentinel lymph node biopsy (SLNB) was developed to identify the first nodes receiving lymphatic drainage from the affected breast, which are most likely to harbor metastases—a less invasive method of evaluating the axilla. This technique accurately stages the axilla,4 with only a 10% false-negative rate in most series. In addition it causes significantly less morbidity compared with ALND.5,6,7

The development of SLNB introduced a paradigm shift in the management of early breast cancer. ALND was no
longer necessary to stage the axilla but was still believed to
add to local control. The SLNB technique allows surgeons to
selectively perform ALND for patients with positive nodes.
The American College of Surgeons Oncology Group chal-
lenged the concept that completion axillary dissection was
necessary in the setting of a positive sentinel node. The
innovative Z0011 randomized multicenter trial demonstrated
that SLNB alone was not inferior to ALND for patients with a
positive SLNB result.7 The Z0011 trial studied only patients
undergoing lumpectomy with adjuvant radiation therapy. No
study has yet evaluated if the findings from the Z0011 trial
also hold true for patients undergoing mastectomy without ra-
diation therapy. Currently, the standard of care for this group
is completion axillary dissection. For various reasons, how-
ever, not all patients found to have a positive SLN are returned
to the operating room for completion dissection after mastec-
tomy. We did a retrospective review of our node-positive pop-
ulation to compare outcomes between those who had a
completion dissection and those who did not.

Methods

Retrospective review of cancer registry data from 2
community-based health systems was performed on all
women with node-positive disease treated with mastectomy
between 2000 and 2010. All patients underwent preoper-
ative lymphatic mapping by injection of technetium-99m
and intraoperative subdermal injection of blue dye into the
periareolar and peritumoral area. SLNs containing meta-
static breast cancer were identified by frozen section, touch
preparation, hematoxylin-eosin staining on permanent sec-
tion, or a combination of these techniques. Male patients
and those with stage 4 metastatic disease were excluded
from this study.

Review identified 561 women with breast cancer and a
positive SLN at the time of total mastectomy who met
inclusion criteria. Formal ALND was undertaken in 426
patients and 135 were managed expectantly. The primary end
point was recurrence-free survival defined from the time of
definitive surgical treatment of invasive breast cancer to
recurrence. Recurrence was classified as either locoregional
recurrence (breast, axilla, ipsilateral supraclavicular, subcla-
vicular, or internal mammary nodes) or distant metastatic
disease (eg, bone, brain, lung). Date of last oncologic follow-
up was used to calculate median length of follow-up for those
patients without recurrence.

Micrometastasis was defined as any nodal metastasis
measuring 2 mm or less. Macrometastasis was defined as
greater than 2 mm. This multicenter retrospective review
was approved by the institutional review boards of the
participating centers.

Statistical analysis

The 2 groups were compared using $P$ values calculated
from both linear regression models in which the variable is
continuous and binomial regression in which the variable is
either present or not present. For primary tumor size and
size of metastasis, the log of these values were used because
the data was skewed to the right as a result of some very large
tumors or metastatic lymph node sizes before running the lin-
ear regression. Chi-squared analysis was used to calculate
the $P$ value of the categorical data to compare the T stage be-
tween the 2 groups. A Cox proportional hazards model was
used to evaluate for recurrence-free survival. A $P$ value of
less than .05 was considered statistically significant.

Results

The 2 groups, ALND vs no ALND, are compared in
Table 1. A total of 426 patients underwent completion
ALND and 135 patients were managed without ALND.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ALND (n = 426)</th>
<th>No ALND (n = 135)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>55.7 (12.6)</td>
<td>58.8 (13.5)</td>
<td>.015</td>
</tr>
<tr>
<td>Primary tumor size (cm)</td>
<td>3.2 (2.6)</td>
<td>2.5 (1.7)</td>
<td>.003</td>
</tr>
<tr>
<td>Stage T1</td>
<td>21.8%</td>
<td>32.6%</td>
<td>.011</td>
</tr>
<tr>
<td>Stage T2</td>
<td>37.6%</td>
<td>34.8%</td>
<td>.406</td>
</tr>
<tr>
<td>Stage T3</td>
<td>13.1%</td>
<td>6.7%</td>
<td>.030</td>
</tr>
<tr>
<td>ER$^+$</td>
<td>83.5%</td>
<td>83.0%</td>
<td>.886</td>
</tr>
<tr>
<td>PR$^+$</td>
<td>76.4%</td>
<td>78.5%</td>
<td>.614</td>
</tr>
<tr>
<td>HER2$^+$</td>
<td>34.4%</td>
<td>21.8%</td>
<td>.007</td>
</tr>
<tr>
<td>No. nodes removed</td>
<td>14.0 (6.5)</td>
<td>6.6 (4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. positive nodes</td>
<td>3.8 (4.9)</td>
<td>1.7 (1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Size of node metastasis (mm)</td>
<td>6.4 (6.3)</td>
<td>2.6 (1.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Micrometastases</td>
<td>15.5%</td>
<td>47.4%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Extranodal extension</td>
<td>36.0%</td>
<td>15.5%</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Values are means (standard deviation) or percentages.
ALND = axillary lymph node dissection; ER$^+$ = estrogen receptor–positive; HER2$^+$ = human epidermal growth factor receptor 2–positive; PR$^+$ = progesterone receptor–positive.
Those managed expectantly had a negative SLN evaluation result intraoperatively and were found to have positive nodes on permanent sections. They were not returned for completion dissection. There was a difference between the 2 groups in age at diagnosis, with the no ALND group being older and having a lower American Joint Committee on Cancer stage and smaller primary tumor size. The mean total number of lymph nodes removed and the mean total number of histologically confirmed tumor-positive nodes was lower in the no ALND group. However, there is a wide standard deviation (SD), and the mode number of nodes removed during the SLN is 4. The presence of extranodal extension and human epidermal growth factor receptor 2–positive (HER2⁺) status was higher in the ALND group, whereas micrometastases were significantly higher in the no ALND group. The groups were very similar with regard to estrogen receptor and progesterone receptor status and were also closely matched in the use of adjuvant chemotherapy and adjuvant chest wall radiation therapy (Table 2).

In the no ALND group, there were 7 of 135 (5.2%) recurrences; 6 (4.4%) were distant and 1 (0.7%) was locoregional. In the ALND group, there were 43 of 426 (10.1%) recurrences; 37 (8.7%) were distant and 6 (14.0%) were locoregional.

Follow-up for all patients with an identified breast cancer recurrence was 29.9 months (SD, 25.5; range, 0.1 to 105.2). Follow-up for patients without recurrence was 40.3 months (SD, 30.7; range, 0.03 to 144.1). The Cox proportional hazards model showed no significant difference between the 2 groups in recurrence-free survival (P = .233) (Fig. 1).

Comments

We have moved into an era of attempting to be less invasive with our surgical procedures and to lower the long-term morbidity associated with our interventions so that we improve the quality of life for cancer survivors. Yet, in the midst of this movement, we cannot lose sight of the ultimate goal—cure and control of cancer. The advent of SLNB has helped us to decrease the morbidity of the axillary dissection, but is SLNB alone good enough in the setting of metastatic nodal disease or is the axillary dissection still required to improve cancer-related outcomes? The American College of Surgeons Oncology Group completed the Z0011 randomized multicenter trial showing that SLNB alone was not inferior compared with ALND for patients with a positive SLNB result.⁷ All patients in this study had breast conservation and whole breast irradiation. Unfortunately, this trial did not meet its accrual goal, which has led many to question its findings. At last follow-up it confirmed noninferiority for positive SLNs without nodal dissection and hence strengthened the premise that completion dissection may not be required in all clinical settings.

The idea that axillary dissection does not improve survival and is therefore not therapeutic was based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial in which patients were randomized to total mastectomy with or without axillary dissection as well as with or without radiation therapy. Patients who did not initially have an axillary dissection did have higher local recurrences; however, those who had salvage axillary dissection did not have improved overall cancer-specific outcomes.⁵ Of course this study was performed before the general use of adjuvant therapies, as is current clinical practice. Nonetheless, this begs the question that in today’s world of improved adjuvant therapy how relevant is completion ALND? For example, adjuvant therapy is now often predicated on multigene recurrence and prognostic factors rather than on node positivity.

The inherent weaknesses of retrospective studies are of course applicable to this study. The study groups were not randomized, and it is clear that there was selection bias in the group that did not return to the operating room. Sample size is also a limiting factor. It is apparent that patients who underwent ALND had more aggressive tumor pathologic processes and biological features based on tumor size, a higher proportion of HER2⁺ tumors, and increased burden of disease in the lymph nodes. These patients also tended to be younger at the age of diagnosis. Approximately 15% to 20% of breast cancers are HER2⁺. This study selects a subpopulation of women with positive SLNs. Because patients who are HER2⁺ have more aggressive disease, it is not surprising that the percentage of HER2⁺ tumors is higher in both groups. In addition, the average number of sentinel nodes harvested in our review is higher than in most published studies on sentinel nodes, which may presume a lower false-negative rate than in most SLN series. The mode was 4, which is in accordance with many other studies on

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Table 2  Neoadjuvant and adjuvant therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ALND</th>
<th>No ALND</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 426)</td>
<td>(n = 135)</td>
</tr>
<tr>
<td>Adjuvant radiation</td>
<td>18.1% (77)</td>
<td>13.3% (18)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>91.8% (391)</td>
<td>94.1% (127)</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>3.05% (12)</td>
<td>1.5% (2)</td>
</tr>
</tbody>
</table>

ALND = axillary lymph node dissection.
SLNs. Based on the NSABP B-32 trial, we can presume an average false-negative rate of 11%, and the axillary failure rate reported in most series is less than 2%. These observations of low overall reported axillary recurrence even with an approximate 11% false-negative SLNB result rate would still validate this study’s findings.

Our data suggest that there is a subset of patients who will do well without ALND even without added regional radiation therapy. There was clearly a bias toward smaller tumors, micrometastasis, and older age in the no ALND group, and this is the cohort that will likely benefit most from this management approach. Although studies are being done to reduce the morbidity of ALND, eg, reverse lymphatic mapping, it is time for us to proactively design studies to discern which patients will derive a therapeutic benefit from ALND and obviate its morbidity in others. Designing neoadjuvant therapy trials to study patients with positive nodal disease after neoadjuvant therapy may ultimately identify a subgroup that will derive therapeutic benefit from completion ALND.

Acknowledgments

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References


Discussion

Maryam Parviz, M.D., Spokane, WA: I applaud the authors for tackling a topic that is generally on the mind of every breast surgeon these days—should I go back to do a completion axillary lymph node dissection (ALND) or not? It has long been established, thanks to the NSABP B-04 trial, that axillary dissection does not affect overall survival but that its purpose has been locoregional control and to guide the use of adjuvant therapy. The American College of Surgeons Oncology Group Z0011 trial then further elucidated whether ALND is really necessary for locoregional control. In patients with early-stage breast cancer and limited involvement of sentinel lymph nodes (SLNs), undergoing breast conservation therapy, omission of ALND did not adversely impact locoregional control. Thus, it seems very appropriate to ask whether this same shift in practice can be applied to patients undergoing mastectomy.

The authors completed a retrospective analysis of 561 patients with breast cancer and positive SLNs who underwent mastectomy, comparing recurrence-free survival between those who had ALND and those who did not. Their data show no significant difference in recurrence-free survival between the 2 groups.

The study population includes an extremely diverse group of patients and tumor characteristics, with tumors ranging from T1 to T4, but the exact breakdown of patients in each group by T stage is not provided. Additionally, more than 47% of the no ALND group had only micrometastatic disease in the SLNs compared with 15.5% of the ALND group. The American Joint Committee on Cancer places patients with stage T1 micrometastatic nodal disease in a separate stage because they have a significantly better prognosis than do other patients with stage T1N1 disease. It is unclear what percentage of the no ALND study group had stage T1N1mic disease and whether inclusion of that group is improving the survival curve of the no ALND group. Also surprising was the high average number of SLNs (6.6) removed in the no ALND group. Could this be viewed as a “mini–axillary dissection”? Other potentially important statistically significant differences between the 2 groups include younger age, larger tumor size, and greater percentage of HER2+ tumors in the ALND group. Both groups seemed to have similar use of adjuvant treatments with chemotherapy and radiation therapy.

It is to be expected that a retrospective study would inherently have selection bias. However, the drastic differences in the 2 study groups in terms of patient demographics and tumor characteristics raise some doubt as to the validity of this comparison. Nevertheless, this will not be the last that we hear of this topic. Studies such as this one that have pushed the envelope and asked intriguing questions and challenged the status quo form the foundation of larger randomized and prospective trials. I thank Dr Crawford, Dr Johnson, and their team for presenting these results and creating a framework that we can continue to build on to provide our patients not only with improved oncologic outcomes but also with improved quality of life.

Do you intend to reanalyze your data looking at better matched or similarly staged patients?