Axillary Node Interventions in Breast Cancer
A Systematic Review

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IMPORTANCE Recent data from clinical trials have challenged traditional thinking about axillary surgery in patients with breast cancer.

OBJECTIVES To summarize evidence regarding the role of axillary interventions (surgical and nonsurgical) in breast cancer treatment and to review the association of these axillary interventions with recurrence of axillary node metastases, mortality, and morbidity outcomes in patients with breast cancer.

EVIDENCE REVIEW Ovid MEDLINE (1946–July 2013), Cochrane Database of Systematic Reviews (2005–July 2013), Cochrane Database of Abstracts of Reviews of Effects (1994–July 2013), and Cochrane Central Register of Controlled Trials (1989–July 2013) were searched for publications on axillary interventions in breast cancer. Clinical trials, observational studies, and meta-analyses with at least 2-year follow-up were included. A total of 1070 publications were reviewed, 17 of which met final inclusion criteria.

FINDINGS Partial mastectomy followed by whole breast radiation is breast-conserving therapy. For women with no suspicious, palpable axillary nodes who undergo breast-conserving therapy, there is little evidence of benefit from surgical complete axillary node dissection compared with sentinel node biopsy alone. Complete axillary node dissection in patients with no palpable lymph nodes, compared with sentinel node biopsy, provides no survival benefit and is associated with a 1% to 3% reduction in recurrence of axillary lymph node metastases, but is associated with a 14% risk of lymphedema. Surgical axillary staging via sentinel node biopsy in patients with benign axillary nodes on radiological and clinical examination helps to inform decisions regarding adjuvant systemic and radiation therapy. Patients and physicians should tailor axillary lymph node interventions to maximize regional disease control and minimize morbidity. Complete axillary lymph node dissection is indicated in patients who present with palpable or needle biopsy–proven axillary metastases, patients with positive sentinel nodes undergoing mastectomy (who do not, as a standard, receive adjuvant radiation), patients with more than 3 positive sentinel nodes undergoing breast-conserving therapy, and patients not meeting eligibility criteria for recent trials establishing the safety of sentinel node biopsy alone in patients with breast cancer and metastases in their sentinel nodes.

CONCLUSION AND RELEVANCE Available evidence suggests that axillary node dissection is associated with more harm than benefit in women undergoing breast-conserving therapy who do not have palpable, suspicious lymph nodes, who have tumors 3.0 cm or smaller, and who have 3 or fewer positive nodes on sentinel node biopsy.
In the United States, nearly 230,000 breast cancers are diagnosed annually.1 Over the past 20 years, the average tumor size at initial presentation has decreased by 10% every 5 years2 and is currently 1.8 cm.3 The majority of patients now have the option of choosing breast-conserving therapy (BCT), which requires partial mastectomy (removal of the tumor with a margin of surrounding normal tissue) followed by radiation therapy, or total mastectomy (removal of the entire breast) alone. Breast-conserving therapy is supported by randomized prospective trials4,5 and provides equivalent survival compared with total mastectomy. Because of effective systemic therapies and population screening, 5-year breast cancer survival in the United States has now reached 90%.1

The second major component of a breast cancer operation is axillary lymph node surgery. A complete axillary node dissection for patients with breast cancer was introduced in the 1800s, both for staging and to achieve regional disease control.6,7 If breast cancer has spread to the lymph nodes, patients require more aggressive systemic therapies (such as chemotherapy) and, in some cases, axillary/chest wall radiation to improve survival and decrease recurrence.8 Complete axillary node dissection involves removal of all tissue between the anatomical landmarks (Figure 1) of the axillary vein (superiorly), the thoracodorsal bundle (laterally), and the long thoracic nerve (medially); 10 to 40 nodes are removed, and this is referred to as a level 1 and 2 node dissection. Level 1 and 2 lymph node dissection surgery is associated with an increased risk of adverse outcomes, including lymphedema (14%), limited shoulder/arm motion (28%), and neuropathic pain (31%).9 A desire to minimize morbidity led to the development of the sentinel lymph node (SLN) biopsy technique.

With improvements in breast cancer screening,10 more patients now present without palpable or sonographically evident nodal metastases.11 First described in 1994,12 breast SLN biopsy takes advantage of the orderly pattern of lymphatic drainage. Radioactive technetium Tc 99m and/or blue dye (isosulfan or methylene blue), are injected directly into the breast or into the skin of the breast. The first 1 to 4 nodes that take up Tc 99m and/or blue dye are subsequently removed and evaluated for metastases because these nodes are presumed to be those to which metastatic disease would first spread. If there is no evidence of metastases in the sentinel nodes, there is less than a 10% chance that the axilla harbors any nodal metastases,13,14 obviating the need for further surgery. With the introduction and validation of SLN biopsy, complete axillary node dissection as the initial axillary intervention is no longer an acceptable option for patients in the United States who have no palpable or ultrasound evidence of axillary metastases.13,15-17

Prior to 2011, however, clinical practice guidelines18 advised completion axillary node dissection (complete axillary node dissection after SLN biopsy reveals metastases) for patients undergoing...
BCT to achieve regional disease control and obtain staging information. In 1999, the American College of Surgeons Oncology Group (ACOSOG) initiated the Z11 trial to determine whether completion axillary node dissection improves outcomes in patients with sentinel node metastases undergoing BCT.\textsuperscript{19,20} The results of this randomized trial have substantially changed surgical practice.\textsuperscript{21}

Therefore, herein we review the risks and benefits of SLN biopsy compared with complete axillary node dissection and compared with nonsurgical axillary interventions (ie, axillary radiation) in women with breast cancer who do not have palpable lymph nodes or ultrasound evidence of axillary lymph node metastases. The rate of recurrence of axillary node metastases, mortality, and morbidity associated with each intervention are reviewed.

Methods

We searched the following online databases: Ovid MEDLINE (1946–July 2013), Cochrane Database of Systematic Reviews (2005–July 2013), Cochrane Database of Abstracts of Reviews of Effects (1994–July 2013), and Cochrane Central Register of Controlled Trials (1989–July 2013). Medical Subject Headings used were axilla, axillary lymph node excision, lymph node excision, lymph node biopsy, and key-word searches were performed for axillary node clearance/dissection/excision, lymph node biopsy, and breast cancer. Non–English-language studies and case reports were excluded. Retrieval for this review was limited to meta-analyses, randomized clinical trials, and cohort, longitudinal, or prospective studies that reported on oncologic outcomes after axillary surgery or radiation in patients with breast cancer. The resulting 1070 publications were reviewed. Randomized trials were included if they met the eligibility criteria of at least 2 years of follow-up. Nonrandomized studies were included if the patients enrolled in the studies had a diagnosis of breast cancer and underwent surgery and the studies had at least 2 years of postoperative follow-up in at least 50% of patients undergoing treatment for breast cancer that included surgery or radiation of the axillary nodes (eFigure in the Supplement). End points reviewed were isolated recurrence of axillary lymph node metastases, complication rates, and survival with the different surgical techniques and interventions. All abstracts were reviewed by 2 authors (R.R. and D.E.). The 17 studies meeting final inclusion criteria were fully reviewed and summarized by 3 authors (R.R., D.E., and C.B.). Most studies were excluded because of their retrospective review design. The American College of Cardiology/American Heart Association\textsuperscript{22} level of evidence classification system was used to rate the evidence.

Results

Recurrence of Axillary Lymph Node Metastases

In cancer operations, the risk of recurrence must be weighed against the benefits of new, less invasive surgical strategies.

Axillary Lymph Node Dissection vs No Directed Treatment

Complete axillary lymph node dissection involves removal of level 1 and 2 nodes. The risk of local regional recurrence with and without axillary node dissection is primarily dependent on the absolute number of lymph nodes with metastases and the size of the metastatic disease in the node (axillary tumor burden),\textsuperscript{23,24} with lymphatic spread in invasive cancers being associated with larger tumor size,\textsuperscript{25,26} higher tumor grade,\textsuperscript{26,27} younger age at diagnosis,\textsuperscript{25} and lymphovascular invasion.\textsuperscript{27} The initial National Surgical Adjuvant Bowel and Breast Project (NSABP) B-04\textsuperscript{28} trial was started in 1971 (Table 1). Patients without evidence of suspicious, palpable axillary metastases were randomized to receive radical mastectomy (removal of the entire breast, level 1 and 2 axillary nodes, and pectoral major and minor muscles; n = 362), total mastectomy (removal of all breast tissue with preservation of pectoral muscles and axillary nodes) with axillary radiation (n = 352), or total mastectomy alone (n = 365). In the 2 groups without axillary node dissection, the risk of developing axillary node metastases was 18.6%. If palpable axillary node metastases developed, patients underwent subsequent complete axillary node dissection. Overall survival at 25 years was not significantly different (P = .68) between groups. The NSABP B-04 trial supported the adoption of combining surgery with radiation as a multimodal approach to breast cancer. The trial suggested that patients with breast cancer may benefit from less radical surgical interventions, but it may have been underpowered to detect small differences in survival.\textsuperscript{33}

Greco et al\textsuperscript{29} omitted axillary surgery altogether in 401 patients who primarily underwent partial mastectomy followed by whole breast radiation therapy (Table 1). All tumors were 3.0 cm or smaller and patients were primarily (81%) postmenopausal and had no evidence of suspicious, palpable axillary metastases. Axillary lymph node metastatic recurrence was 1.7% to 10% among subsets of T1 tumors and 18% in T2 tumors. Martelli et al\textsuperscript{30} reported a 1.8% recurrence rate of axillary lymph node metastases for 110 women aged 65 years or older with T1 tumors treated with BCT and postoperative adjuvant tamoxifen but no axillary surgery (Table 1). There were no axillary lymph node metastatic recurrences among the 109 controls who underwent BCT with complete axillary lymph node dissection.

A second subset in the NSABP B-04 trial examined outcomes for patients with palpable, suspicious nodes who were randomized to receive radical mastectomy (n = 292) or total mastectomy with radiation therapy and no lymph node dissection (n = 294) (Table 1). The risk of recurrence of axillary node metastases was slightly higher in the group receiving radiation to the axilla alone (8%) vs the radical mastectomy group (1%; P = .40). As a result, patients presenting with palpable, suspicious axillary nodes are offered complete axillary lymph node dissection after pathologic confirmation of nodal metastases. Pathologic confirmation of palpable nodes can be obtained via percutaneous fine needle aspiration or core needle biopsy.\textsuperscript{35,36} In general, complete axillary lymph node dissection provides excellent regional control, with reported recurrence of axillary lymph node metastases of 0% to 3.5%\textsuperscript{14,32,34,37,44} in patients with and without suspicious, palpable axillary nodes.

Complete Axillary Lymph Node Dissection vs Radiation Therapy

Prior to establishing the efficacy of SLN biopsy, there was an interest in axillary radiation as an alternative to complete axillary lymph node dissection for patients with breast cancer. Axillary radiation trials focused on patients without palpable, suspicious nodes and T1 to T2 breast cancers (Table 2). In a large clinical trial, Louis-Sylvestre et al\textsuperscript{38} randomized 658 patients younger than 70 years to either partial mastectomy with complete axillary node dissection or partial mastec-
Table 1. Trials of Axillary Lymph Node Dissection vs No Directed Axillary Therapy (Level A Evidence)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Period</th>
<th>Participant Age</th>
<th>Axillary Status</th>
<th>Tumor Size</th>
<th>Follow-up</th>
<th>Study Interventions</th>
<th>Sample Size</th>
<th>Recurrence, No. (%)</th>
<th>Survival, % (SE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al,4 2002</td>
<td>1971-1974</td>
<td>Any age (70% &gt;50 y)</td>
<td>No palpable, suspi. nodes on examination</td>
<td>Mean, 3.7 (SD, 2) cm</td>
<td>Mean, 20 y</td>
<td>Radical mastectomy</td>
<td>292</td>
<td>22 (8)*</td>
<td>11 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mastectomy + radiation</td>
<td>294</td>
<td>33 (11)*</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Fisher et al,4 2002</td>
<td>1971-1974</td>
<td>Any age (70% &gt;50 y)</td>
<td>No palpable, suspi. nodes on examination</td>
<td>Mean, 3.7 (SD, 2) cm</td>
<td>Mean, 20 y</td>
<td>Radical mastectomy</td>
<td>362</td>
<td>15 (4)</td>
<td>19 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mastectomy + radiation</td>
<td>352</td>
<td>15 (4)</td>
<td>13 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total mastectomy</td>
<td>365</td>
<td>23 (6)*</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Greco et al,29 2000</td>
<td>1986-1994</td>
<td>Any age (85% &gt;50 y)</td>
<td>No palpable, suspi. nodes on examination</td>
<td>All tumors &lt;3.0 cm on examination</td>
<td>Median, 5.1 y</td>
<td>Partial mastectomy or mastectomy with no axillary lymph node dissection + radiation if age &lt;70 y</td>
<td>401</td>
<td>19 (5)*</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Martelli et al,30 2010</td>
<td>1996-2000</td>
<td>Median, 76 y</td>
<td>No palpable, suspi. nodes on examination</td>
<td>Any tumor size (93% T1/T2)</td>
<td>Median, 15 y</td>
<td>BCT + axillary lymph node dissection</td>
<td>109</td>
<td>0</td>
<td>96</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCT alone</td>
<td>110</td>
<td>2 (1.8)</td>
<td>94</td>
</tr>
<tr>
<td>Hughes et al,41 2004</td>
<td>1994-1999</td>
<td>&gt;70 y</td>
<td>No palpable, suspi. nodes on examination</td>
<td>All tumors &lt;2.0 cm on examination</td>
<td>Median, 5 y</td>
<td>BCT + tamoxifen</td>
<td>200</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial mastectomy + tamoxifen</td>
<td>204</td>
<td>2 (1)</td>
<td>86</td>
</tr>
<tr>
<td>Rudenstam et al,42 2006</td>
<td>1993-2002</td>
<td>Median, 74 y</td>
<td>No palpable, suspi. nodes on examination</td>
<td>Any tumor size (56% &lt;2 cm)</td>
<td>Median, 6.6 y</td>
<td>Mastectomy or BCT + axillary lymph node dissection</td>
<td>234</td>
<td>2 (1)</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mastectomy or BCT with no axillary surgery</td>
<td>239</td>
<td>6 (3)</td>
<td>73</td>
</tr>
</tbody>
</table>

Abbreviation: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation).

* No statistically significant difference in survival among groups.

Table 2. Trials of Axillary Lymph Node Dissection vs Axillary Radiation (Level A Evidence)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Period</th>
<th>Participant Age</th>
<th>Axillary Status</th>
<th>Tumor Size</th>
<th>Follow-up</th>
<th>Study Interventions</th>
<th>Sample Size</th>
<th>Recurrence, No. (%)</th>
<th>Survival, % (SE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansen et al,45,46 1990</td>
<td>1951-1957</td>
<td>Any age (70% ≥50 y)</td>
<td>Palpable, suspicious nodes ±2.5 cm or no palpable, suspicious nodes on examination</td>
<td>Any tumor size (50 y)</td>
<td>Mean, 50 y</td>
<td>Total mastectomy + radiation</td>
<td>219</td>
<td>Not reported</td>
<td>1% (65% breast cancer-specific deaths)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Extended radical mastectomyb</td>
<td>206</td>
<td>Not reported</td>
<td>2% (64% breast cancer-specific deaths)</td>
</tr>
<tr>
<td>Louis-Sylvestre et al,48 2004</td>
<td>1982-1987</td>
<td>Mean, 50 y/ Mean, 52 y</td>
<td>No palpable, suspicious nodes on examination</td>
<td>All tumors &lt;3.0 cm on examination</td>
<td>Median, 5 y</td>
<td>BCT + axillary node dissectionc</td>
<td>326</td>
<td>2 (0.6)*</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCT + radiation to axilla</td>
<td>332</td>
<td>6 (1.8)*</td>
<td>74</td>
</tr>
<tr>
<td>Hoebers et al,37 2000</td>
<td>1983-1997</td>
<td>Mean, 64 y</td>
<td>No palpable, suspicious nodes on examination</td>
<td>Median size on examination, 2.0 cm</td>
<td>Median, 3.4 y</td>
<td>BCT + radiation to axilla and supraclavicular nodes</td>
<td>105</td>
<td>2 (2)</td>
<td>83</td>
</tr>
<tr>
<td>Veronesi et al,47 2005</td>
<td>1995-1998</td>
<td>Median, 57 y</td>
<td>No palpable, suspicious nodes on examination</td>
<td>All tumors &lt;1.5 cm on intraoperative examination</td>
<td>Median, 5.2 y</td>
<td>BCT alone (no axillary intervention)</td>
<td>214</td>
<td>3 (1.5)</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCT + axillary radiation</td>
<td>221</td>
<td>1 (0.5)</td>
<td>97</td>
</tr>
</tbody>
</table>

Abbreviation: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation).

* No statistically significant difference in survival among groups.

b Extended radical mastectomy: radical mastectomy with supraclavicular and internal mammary node dissection.

c Radiation to supraclavicular nodes if node metastases identified on pathology.

P = .04 for comparison between the 2 groups.
radiation is not commonly used in patients without evidence of axillary node metastases, resulting in overtreatment. Consequently, primary axillary radiation, all patients with breast cancer would have to receive axillary radiation, however, cannot provide the staging information afforded by SLN biopsy. Patients without sentinel node metastases do not require axillary radiation, however, without this pathologic information, all patients with breast cancer would have to receive axillary radiation, resulting in overtreatment. Consequently, primary axillary radiation is not commonly used in patients without evidence of axillary node dissection and accurately reflecting the pathologic status of the entire axilla (Table 3). The largest of these studies was the NSABP B-32 trial, conducted at 80 centers in the United States and Canada. The NSABP B-32 trial included patients with a diagnosis of invasive ductal or lobular breast cancer without palpable, suspicious lymph node metastases (Table 3). A total of 2807 women were randomized to receive SLN biopsy followed by complete axillary node dissection and 2804 women were randomized to receive SLN biopsy followed by lymph node dissection if the SLN biopsy result was negative (n = 2011) or completion axillary node dissection if the SLN biopsy result was positive (n = 806). The mean time in the study for patients with a negative SLN biopsy result was 95.6 months. Recurrence of axillary node metastases was seen in 8 patients (0.4%) who underwent SLN biopsy followed by complete axillary node dissection and in 14 (0.7%) of patients who underwent SLN biopsy and completion axillary node dissection only for nodal metastases.

Auxillary Lymph Node Dissection vs SLN Biopsy
Sentence node biopsy allows selective removal of the first few nodes that drain the breast. These nodes are analyzed with serial sectioning to obtain staging information. Early investigations validated SLN biopsy and confirmed its sensitivity for identifying axillary metastases and accurately reflecting the pathologic status of the entire axilla (Table 3). The largest of these studies was the NSABP B-32 trial, conducted at 80 centers in the United States and Canada. The NSABP B-32 trial included patients with a diagnosis of invasive ductal or lobular breast cancer without palpable, suspicious lymph node metastases (Table 3). A total of 2807 women were randomized to receive SLN biopsy followed by complete axillary node dissection and 2804 women were randomized to receive SLN biopsy followed by lymph node dissection if the SLN biopsy result was negative (n = 2011) or completion axillary node dissection if the SLN biopsy result was positive (n = 806). The mean time in the study for patients with a negative SLN biopsy result was 95.6 months. Recurrence of axillary node metastases was seen in 8 patients (0.4%) who underwent SLN biopsy followed by complete axillary node dissection and in 14 (0.7%) of patients who underwent SLN biopsy and completion axillary node dissection only for nodal metastases.

Table 3. Trials of Axillary Lymph Node Dissection vs SLN Biopsy (Level A Evidence)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Period</th>
<th>Participant Age</th>
<th>Axillary Status</th>
<th>Tumor Size</th>
<th>Follow-up</th>
<th>Study Interventions</th>
<th>Sample Size</th>
<th>Recurrence, No. (%)</th>
<th>Survival, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veronesi et al,14,40 2010</td>
<td>1998-1999 Mean, 56 y for complete axillary node dissection Median, 55 y for sentinel node only</td>
<td>No palpable, suspicious nodes on examination All tumors ≤2.0 cm on final pathology</td>
<td>Mean, 7.9 y</td>
<td>BCT + negative SLN biopsy result BCT + SLN biopsy and completion axillary lymph node dissection BCT + SLN biopsy and complete axillary lymph node dissection</td>
<td>167</td>
<td>2 (1.2)</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canavese et al,13 2009</td>
<td>1998-2001 Mean, 58 y</td>
<td>No palpable, suspicious nodes on examination All tumors &lt;5.0 cm on final pathology</td>
<td>Median, 5.5 y</td>
<td>BCT or mastectomy + negative SLN biopsy result BCT or mastectomy + completion axillary lymph node dissection BCT or mastectomy + completion axillary lymph node dissection</td>
<td>115</td>
<td>1 (0.9)</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mansel et al,43 2006b</td>
<td>1999-2003 Mean, 57 y</td>
<td>No palpable, suspicious nodes on examination Any tumor size (74% &lt;2.0 cm)</td>
<td>Mean, 1 y</td>
<td>BCT or mastectomy + negative SLN biopsy result BCT or total mastectomy + complete axillary node dissection BCT or total mastectomy + SLN biopsy + completion axillary lymph node dissection BCT or total mastectomy + SLN biopsy + axillary radiation if positive SLN biopsy result</td>
<td>368</td>
<td>1 (0.8)</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zavagno et al,44 2008</td>
<td>1999-2004 Mean, 57 y</td>
<td>No palpable, suspicious nodes on examination All tumors ≤3.0 cm on examination</td>
<td>Median, 4.6 y</td>
<td>BCT or mastectomy + negative SLN biopsy result BCT or total mastectomy + SLN biopsy + completion axillary node dissection BCT or total mastectomy + SLN biopsy + completion axillary node dissection BCT or total mastectomy + SLN biopsy + complete axillary node dissection</td>
<td>218</td>
<td>1 (0.4)</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krag et al,13 2010</td>
<td>1999-2004 Any age (75% ≥50 y)</td>
<td>No palpable, suspicious nodes on examination Any tumor size (98% ≤4.0 cm)</td>
<td>Mean, 7.9 y</td>
<td>BCT or mastectomy + negative SLN biopsy result BCT or mastectomy + negative SLN biopsy result and complete axillary node dissection BCT or mastectomy + negative SLN biopsy result and complete axillary node dissection</td>
<td>1978</td>
<td>8 (0.4)</td>
<td>83</td>
<td>2011</td>
<td>14 (0.7)</td>
</tr>
</tbody>
</table>

Abbreviations: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation); SLN, sentinel lymph node.

a No statistically significant difference in survival among groups.

b Completion axillary node dissection only for nodal metastases after SLN biopsy reveals metastatic disease.

c Complete axillary lymph node dissection = performed regardless of result of SLN biopsy.

d Study closed early because of benefits of SLN biopsy alone group; results are for intention to treat analysis. Also included are 123 patients who underwent “4 node axillary sampling”; 1 recurrence was in this group.
There was no significant difference in survival between groups. Similarly designed international studies as well as a meta-analysis have yielded the same results (Table 3). The meta-analysis revealed no difference in overall survival, disease-free survival, or regional lymph node recurrence for SLN biopsy vs complete axillary node dissection in patients without palpable, suspicious lymph nodes and negative SLN biopsy result. Available evidence suggests that compared with complete axillary lymph node dissection, SLN biopsy identifies axillary node metastasis 90% to 99% of the time that nodal metastases are present. The techniques sensitivity improves with greater surgeon experience with the procedure. A false-negative rate of 1% to 10% raises the concern for recurrence due to residual metastases, but, in practice, this has not been observed, with rates of axillary node metastatic recurrences of only 0% to 10%.

### Table 4. Axillary Lymph Node Dissection or Not for Positive SLN Biopsy Result (Level B Evidence)

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Period</th>
<th>Participant Age</th>
<th>Axillary Status</th>
<th>Tumor Size</th>
<th>Follow-up</th>
<th>Study Interventions</th>
<th>Sample Size</th>
<th>Recurrence, %</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giuliano et al, 2011</td>
<td>1999-2004</td>
<td>Median, 56 y</td>
<td>No palpable, suspicious nodes on examination</td>
<td>Tumors ≤3.0 cm on examination</td>
<td>Median, 6.3 y</td>
<td>BCT + positive SLN biopsy result + completion axillary node dissection</td>
<td>388</td>
<td>2 (0.5)</td>
<td>88.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCT + positive SLN biopsy result</td>
<td>425</td>
<td>4 (0.9)</td>
<td>89.9</td>
</tr>
<tr>
<td>Straver et al, 2010</td>
<td>2001-2005</td>
<td>Median, 57 y</td>
<td>Tumors ≤3.0 cm on examination</td>
<td>NA</td>
<td></td>
<td>BCT or mastectomy + negative SLN biopsy result</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td></td>
<td></td>
<td></td>
<td>BCT or mastectomy + SLN biopsy + completion axillary lymph node dissection</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCT or mastectomy + positive SLN biopsy result + axillary radiation</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Galimberti et al, 2013</td>
<td>2001-2010</td>
<td>Median, 54 y</td>
<td>Tumors ≤5.0 cm on intraoperative gross measurement</td>
<td>Median, 5 y</td>
<td></td>
<td>BCT or mastectomy + positive SLN biopsy result + completion axillary node dissection</td>
<td>464</td>
<td>1 (0.2)</td>
<td>87.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BCT or mastectomy + positive SLN biopsy result alone</td>
<td>467</td>
<td>4 (0.8)</td>
<td>84.4</td>
</tr>
</tbody>
</table>

Abbreviations: BCT, breast-conserving therapy (partial mastectomy followed by whole breast radiation); NA, data not available; SLN, sentinel lymph node.

*No statistically significant difference in survival among groups.

P = .22. The above cited trials showed the benefits of multimodal approaches to breast cancer treatment with less need for surgery. Studies also showed that nonsurgical treatments such as radiation or systemic chemotherapy effectively treated nodal metastases. These observations called into question the need for completion axillary node dissection even when metastases were demonstrated by SLN biopsy. To examine this question, the ACOSOG Z11 trial was initiated (Table 4). Patients had clinical T1 to T2 (0.1-5 cm) N0M0 cancers and were undergoing partial mastectomy with SLN biopsy. Key exclusion criteria were receipt of partial breast radiation, T3/T4 (>5 cm or chest wall/skin invasion) tumors, presentation with palpable/matted lymph nodes, and 3 or more metastatic lymph nodes on SLN biopsy. Patients found to have SLN metastases were randomized to either observation or receipt of completion axillary node dissection. All patients received adjuvant whole breast radiation, and, although not specified in the protocol, 97% received adjuvant systemic therapy per local institutional treatment paradigms. Study end points were survival and recurrence. The trial was terminated before complete accrual because of an unexpected low event rate in both groups. Eight hundred ninety-one patients were randomized, with a median follow-up of 6.3 years. Analysis was performed on the treatment received. 32 patients in the axillary node dissection group did not receive axillary lymph node dissection and 11 patients in the SLN biopsy alone group underwent axillary lymph node dissection. Two of 420 patients with axillary node dissection (0.5%) had a recurrence of axillary lymph node metastases vs 4 (0.9%) of 436 in the SLN biopsy alone group (P = .45). Results supporting ACOSOG Z11 were recently published from the International Breast Cancer Study Group Trial 23-013 (Table 4). The results of the similarly designed After Mapping the Axilla: Radiotherapy or Surgery (AMAROS) trial are pending (Table 4). For patients with tumors 5 cm or smaller and no suspicious axillary lymph nodes on clinical examination who are undergoing BCT and systemic therapy, omitting completion axillary node dissection in the setting of 3 or fewer metastatic lymph nodes on SLN biopsy does not increase the risk of recurrence of axillary lymph node metastases.

### Survival

As described above, the NSABP B-04 trial randomized 1079 patients with breast cancer who had no palpable, suspicious axillary nodes to receive radical mastectomy, total mastectomy with axillary radiation, or total mastectomy alone (Table 1). With a mean follow-up of 20 years, there were no differences in disease-free, distant disease-free, or overall survival. Rudenstam et al randomized 473 women aged 60 years or older with breast cancer and no palpable, suspicious axillary nodes to receive complete axillary node dissection (Table 2). There was no statistically significant difference in survival compared with the group randomized to observation. Similar to the NSABP B-04 trial, this trial found no differences in survival (Table 2). Therefore, completion axillary node dissection in this patient population is unnecessary. The NSABP B-04 trial included patients with tumors 5 cm or smaller and no suspicious axillary lymph nodes, which is a high-risk population. Further studies are needed to examine the risk of recurrence in this patient population.
dissection or no axillary treatment (Table 1). With a median follow-up of 6.6 years, disease-free and overall survival were nearly identical. Similarly, Martelli et al’s randomized 219 women with breast cancer and no palpable, suspicious axillary nodes to complete axillary dissection or no axillary treatment (Table 1). After 5 years of follow-up, there was no difference in disease-free or overall survival. Several randomized trials have compared axillary dissection with SLN biopsy in patients with no suspicious, palpable axillary nodes (Table 3). None reported a difference in disease-free or overall survival. All studies demonstrated that in patients without suspicious, palpable nodes, complete axillary node dissection does not affect survival compared with SLN biopsy. No trials exist assessing survival in women with suspicious palpable nodes randomized to a no-axillary-intervention group.

**Adverse Outcomes With Axillary Surgery**

Both axillary surgery and axillary radiation therapy can cause shoulder and arm symptoms including lymphedema, pain or numbness, and reduced range of motion (Table 5). The incidence of complications is dependent on the approach used to ascertain symptoms and on the period between axillary treatment and assessment. Patient factors such as obesity and higher tumor stage can increase morbidity. Shoulder and arm morbidity was carefully assessed at multiple time points following axillary surgery in the ALMANAC trial. Axillary node dissection was associated with significant reductions in shoulder flexion and abduction at 1 month but range of motion had returned to near baseline by 12 months. Similarly, 62% of women reported arm pain or numbness at 1 month and 31% still reported these symptoms at 12 months. Clinicians rated these symptoms as severe in only 1% at 12 months. Women may develop measurable arm swelling after axillary surgery without symptoms; consequently, lymphedema rates are generally higher for studies that measure arm volumes or circumferences than for studies that rely on patient-reported symptoms. Unlike other shoulder and arm symptoms, the prevalence of lymphedema generally increases over time. Subjective lymphedema is reported by 14% of patients following axillary dissection, and 5% to 7% of patients following SLN biopsy. Randomized prospective clinical trials consistently report reduced rates of shoulder and arm morbidity for SLN biopsy compared with axillary dissection.

**Risk of Additional Axillary Metastases**

One factor to consider when determining whether completion axillary node dissection is required is the risk of additional nodal metastases beyond the sentinel nodes removed. Various nomograms have been developed for this. One of the most widely validated is the Memorial Sloan-Kettering nomogram. This nomogram was developed using retrospective data on 702 patients and then validated in a 373-patient prospective cohort. The nomogram is available online and uses tumor and nodal metastatic characteristics to predict the risk of additional nodal metastases. While helpful, the nomogram is a guide, and each patient must weigh the risk of finding additional nodal metastases vs the risk of clinically significant lymphedema.

**Risk of Developing Symptomatic Axillary Recurrence**

Although the majority of studies reveal a low rate of recurrence, even in the setting of presumed residual nodal metastases, recurrence of axillary lymph node metastases can negatively affect quality of life. In particular, axillary metastatic disease that involves the chest wall, brachial plexus, or pectoralis musculature may not be amenable to surgery and has the potential to result in significant pain and disability. An increased risk of recurrence of axillary lymph node metastases is seen in patients who have diagnoses at a younger age, have higher-grade tumors, have estrogen/progesterone receptor-negative tumors, and have not had radiation. For patients with high-risk disease who would not meet ACOSOG Z11 inclusion criteria, completion axillary node dissection is indicated to prevent potential development of symptomatic recurrence of axillary lymph node metastases. Scenarios in which complete axillary node dissection is still supported by data include patients (1) with palpable, suspicious axillary nodes (even if there is a good response to neoadjuvant chemotherapy); (2) undergoing mastectomy with a positive SLN biopsy result; (3) with a positive SLN biopsy result who cannot get radiation therapy; (4) with a positive SLN biopsy result who will not get adjuvant systemic therapy; and (5) who would not meet inclusion criteria for the ACOSOG Z11 trial.

**Adjuvant Therapy Decisions**

In the past, axillary nodal status was a critical factor considered in adjuvant systemic therapy decisions. With the validation of SLN biopsy, the same staging information is obtained with less morbidity. Now, in the era of personalized therapy, decisions regarding adjuvant treatments are often guided by molecular tumor profiling, making it necessary to continue assessing the value of surgical axillary staging. These commercially available genomic assays along with traditional pathologic tumor markers, often drive decisions regarding adjuvant chemotherapy, sometimes irrespective of nodal status. One of the genomic assays is able to provide information regarding recurrence risk in estrogen receptor–positive tumors based on 16 cancer genes. It was developed specifically to determine what benefit may be obtained from adding chemotherapy to a treatment regimen. There remain, however, clinical scenarios in which additional

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**Table 5. Long-term Rates of Adverse Outcomes Associated With Axillary Operations**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Axillary Lymph Node Dissection, %</th>
<th>Sentinel Node Biopsy Alone, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphedema</td>
<td>10-20</td>
<td>5-7</td>
</tr>
<tr>
<td>Quality-of-life reduction</td>
<td>35-9</td>
<td>23-9</td>
</tr>
<tr>
<td>Arm pain/numbness</td>
<td>31-54</td>
<td>11-43</td>
</tr>
</tbody>
</table>
nodal metastases may influence decisions on systemic therapy; for these patients, a tailored approach with completion axillary node dissection is appropriate.

**Conclusion**

Among patients with breast cancer but no palpable lymph nodes, completion axillary node dissection provides no survival benefit compared with SLN biopsy but reduces the risk of recurrence of axillary node metastases by 1% to 3%. However, complete axillary node dissection is associated with a 14% risk of lymphedema compared with only 5% to 7% in patients undergoing SLN biopsy. In the future, multimodal treatment will be dependent on primary tumor features, including molecular markers, potentially rendering the staging information obtained via axillary lymph node dissection inconsequential.

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**ARTICLE INFORMATION**

**Author Contributions:** Dr Rao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Rao, Euhus, Balch. Acquisition of data: Rao, Mayo. Analysis and interpretation of data: Rao, Euhus. Drafting of the manuscript: Rao, Euhus, Mayo, Balch. Critical revision of the manuscript for important intellectual content: Rao, Euhus, Mayo, Balch. Administrative, technical, or material support: Rao, Mayo. Study supervision: Rao, Euhus, Balch.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Euhus reports payment from PER Group for speaking at CME conferences. Dr Balch reports consultancy for Amgen and payment for lectures/speakers bureaus from Merck. No other disclosures were reported.

**Submissions:** We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

**REFERENCES**


