TO: Surgery Residents, Surgery Faculty at Altru, Sanford, & VA Medical Center and Medical students
FROM: Geralyn Lunski, Conference Coordinator - 777-2589
DATE: March 12, 2015

Meeting Information
Date: Tuesday, March 17, 2015
Time: 6:00 PM
Location: Sanford Clinic, Fargo, North Dakota
          Altru Hospital, Grand Forks, North Dakota
Room: Clinic B2, Sanford Health
       SurgSimLab, Altru Hospital
Topic: Breast Cancer
Moderator: BreAnn Neiger, MD

ARTICLES: Attached.

Dinner will be provided by Cubist
Clinical Investigation: Breast Cancer

Society of Surgical Oncology—American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

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Summary

Changes in the management of breast cancer over time have led to decreased rates of ipsilateral breast tumor recurrence (IBTR). The 2013 SSO/ASTRO guidelines on margins in breast-conserving surgery for invasive cancer are available at www.redjournal.org.

Purpose: To convene a multidisciplinary panel of breast experts to examine the relationship between margin width and ipsilateral breast tumor recurrence (IBTR) and develop a guideline for defining adequate margins in the setting of breast conserving surgery and adjuvant radiation therapy.

Methods and Materials: A multidisciplinary consensus panel used a meta-analysis of margin width and IBTR from a systematic review of 33 studies including 28,162 patients as the primary evidence base for consensus.

Results: Positive margins (ink on invasive carcinoma or ductal carcinoma in situ) are associated with a 2-fold increase in the risk of IBTR compared with negative margins. This increased risk is not mitigated by favorable biology, endocrine therapy, or a radiation boost. More widely clear margins than no ink on tumor do not significantly decrease the rate of IBTR compared with no ink on tumor. There is no evidence that more widely clear margins reduce IBTR for young patients or for patients with high-grade tumors.

Acknowledgments—The authors thank David Euhus, MD (Society of Surgical Oncology [SSO]), Beryl McCormick, MD (American Society for Radiation Oncology [ASTRO]), Benjamin Smith, MD (ASTRO), Kimberly Van Zee, MD (SSO), and Lee Wilkie, MD (SSO) for critical review of the manuscript, and Shan-san Wu for editorial assistance.

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Supplementary material for this article can be found at www.redjournal.org.
Introduction

Multiple randomized, phase III trials with mature follow-up have conclusively demonstrated that survival after breast-conserving therapy (BCT), defined as surgical excision of the primary tumor and a margin of surrounding normal tissue followed by whole-breast radiation therapy (WBRT), is equivalent to mastectomy for the treatment of stages I and II invasive breast cancer (BC) (1, 2). Of these trials, only one, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B06, required a microscopically clear margin, defined as no ink on tumor (2); all others required complete gross removal of the tumor but did not specify a microscopic margin width. Although BCT has been standard practice for more than 20 years, there is still no consensus on what constitutes an optimal negative margin width (3, 4). As a consequence, approximately 1 in 4 women undergoing BCT undergo a re-excision, and nearly half of these procedures are performed with the rationale of obtaining more widely clear margins in women whose margins are negative, as defined by no ink on tumor (5, 6). These additional surgical procedures have the potential for added discomfort, surgical complications, compromise in cosmetic outcome, unnecessary additional emotional stress for patients and families, and increased health care costs, and have been associated with patient preference for conversion to bilateral mastectomy (7). In the past 30 years since the randomized trials that established the equivalence of BCT and mastectomy, the landscape of BC management has changed dramatically. Breast imaging has improved, and adjuvant systemic therapy is now commonly used, even for small, node-negative BCs, resulting in a decline in rates of ipsilateral breast tumor recurrence (IBTR) (8).

In view of these changes, the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) convened a multidisciplinary expert panel (ie, Margins Panel [MP]) in 2013 for the purpose of examining the relationship between margin width and IBTR. The primary clinical question was: What margin width minimizes the risk of IBTR? Specific clinical circumstances that might have an impact on this question, such as tumor histology, patient age, use of systemic therapy, and technique of radiation delivery, were also examined. The guideline developed from this consensus panel is intended to assist treating physicians and patients in the clinical decision-making process. As with any guideline, the monitoring of outcomes at the institutional level is encouraged. The key findings of the guideline are summarized in Table 1.

Methods and Materials

The Margins Panel (MP) comprised a multidisciplinary group of experts designated by their respective organizations, an expert methodologist who led the evidence review, and a patient representative (Table 2). The process for development of this guideline followed, to the extent possible, the standards of the Institute of Medicine (IOM) (9). The panel commissioned a systematic review and meta-analysis of the literature as the primary evidence base for the guideline. Additional literature reviews for specific clinical questions that could not be addressed in the meta-analysis were performed by designated panel members. The panelists met in July 2013, and all of the recommendations in this guideline were unanimously adopted. The guideline manuscript was approved by all panel members and sent to external reviewers for feedback, which was incorporated into the final document. The content of the manuscript was approved by the SSO Executive Council and ASTRO Board of Directors. Patient-related information regarding the guideline and a question–answer sounding board will be made available for patients on the Susan G. Komen Web site.

Literature review and meta-analysis

The systematic review methods were adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations, IOM standards for systematic reviews and meta-analyses, and previously published methods (10-12). A comprehensive literature search of MEDLINE and evidence-based medicine was conducted of articles published from 1965 to January 2013, and was combined with data from a previously published systematic review that included 21 studies from 1965 to 2010 (12). These new analyses are referred to as the margins meta-analysis and are part of the work led by Houssami et al (13), published in full elsewhere. All studies eligible for inclusion in the margins meta-analysis were reviewed and underwent data extraction by 2 independent investigators as previously described (12). A study-level analysis was conducted, and was adjusted for study-specific median follow-up time (to account for the inherent increased risk of IBTR with longer follow-up) as well as co-variates.

Inclusion/exclusion criteria

Studies eligible for inclusion had to allow for calculation of the proportion of IBTR in relation to margin widths and had to meet the following criteria: (1) patients had to have early-stage invasive BC (stages I and II); patients treated with neoadjuvant chemotherapy or with pure ductal carcinoma in situ were not included; (2) treatment consisted of BCT (all patients receiving adjuvant WBRT); (3) microscopic margins had to be reported quantitatively with defined threshold distances/widths; (4) age data had to be present; and (5) a minimum median/mean follow-up time of 4 years was required. Details of the data collected can be found in the complete publication of the meta-analysis (13) and are included in Supplementary Appendix A (available online).
Study quality and limitations of the literature

All publications that met the inclusion criteria were retrospective in nature, with the exception of 2 studies (14, 15). Therefore, the majority of studies included in the meta-analysis provided observational-level data, and the analysis was conducted at the study level because of a lack of patient-level data from the retrospective studies. The characteristics and quality assessment of the studies included in the meta-analysis are reported elsewhere (13).

Management of conflicts of interest for the MP

At the time of the initial telephone planning conference, the MP candidates declared and discussed their potential conflicts. Written disclosures were subsequently obtained at the consensus meeting. The co-chairs reviewed each conflict of interest (COI) form and determined that there were no individuals on the panel for whom a COI could influence the development or process of specific recommendations for this guideline.

Results

The margins meta-analysis was based on 33 eligible studies published between 1965 and 2013. The analysis included 28,162 patients, of whom 1506 had an IBTR. The median follow-up was 79.2 months, and the median prevalence of IBTR was 5.3% (interquartile range, 2.3-7.6%). Patients with unknown margin status were not included in the analysis. Table 3 summarizes the

<table>
<thead>
<tr>
<th>Table 1 Summary of clinical practice guideline recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical question</td>
</tr>
<tr>
<td>What is the absolute increase in risk of IBTR with a positive margin? Can the use of radiation boost, systemic therapy, or favorable tumor biology mitigate this increased risk?</td>
</tr>
<tr>
<td>Do margin widths wider than no ink on tumor cells reduce the risk of IBTR?</td>
</tr>
<tr>
<td>What are the effects of endocrine or biologically targeted therapy or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths?</td>
</tr>
<tr>
<td>Should unfavorable biologic subtypes (such as triple-negative breast cancers) require wider margins (than no ink on tumor)?</td>
</tr>
<tr>
<td>Should margin width be taken into consideration when determining WBRT delivery techniques?</td>
</tr>
<tr>
<td>Is the presence of LCIS at the margin an indication for re-excision? Do invasive lobular carcinomas require a wider margin (than no ink on tumor)? What is the significance of pleomorphic LCIS at the margin?</td>
</tr>
<tr>
<td>Should increased margin widths (wider than no ink on tumor) be considered for patients of young age (&lt;40 years)?</td>
</tr>
<tr>
<td>What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?</td>
</tr>
</tbody>
</table>

Abbreviations: BCT = breast-conserving therapy; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; IBTR = ipsilateral breast tumor recurrence; LCIS = lobular carcinoma in situ; WBRT = whole breast radiation therapy.
characteristics of the studies, and the patient, tumor, and treatment variables included in this analysis. Houssami et al (13) provide additional details of the included studies and full results of the meta-analysis. A synoptic overview of the results is shown in Table 4. In model 1 (all studies), margin status was fitted as a dichotomous variable (negative vs close/positive). Close and positive margins were combined because the data reported in some studies did not allow separation of these 2 categories. In model 2, only those studies that provided information on specific margin widths were included; margin status was fitted as 3 categories (positive, close, negative), and margin distance was analyzed as a categorical variable. All models were adjusted for length of follow-up. For the 19 studies of 13,081 patients with sufficient detail to separate negative, close, and positive margins, the OR for positive versus negative margins after adjustment for study-specific follow-up and for the covariates of endocrine therapy or use of a boost was 2.44 (95% CI, 1.97-3.03) (13). Other published literature supports the observation that the risk of IBTR with a positive margin is at least 2-fold greater than that seen with negative margins (16, 17). Although various other treatment modalities, including use of a boost dose of radiation and adjuvant systemic therapy with endocrine therapy, chemotherapy, or biologically targeted agents, have all demonstrated a favorable impact on IBTR (see below), adjustment for the covariates of endocrine therapy or use of a boost dose of radiation did not nullify the increased risk of IBTR seen with a positive margin in the meta-analysis. In the 18 studies reporting information about the use of a boost, the risk of IBTR in patients with positive margins remained elevated (OR, 2.45; P < .001) after adjustment for study-specific follow-up and for the proportion of patients who had a boost. Other studies support this finding. For example, a European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrated that an additional boost dose of 16 Gy targeting the tumor bed after microscopically complete removal of the tumor and WBRT significantly reduced the rate of IBTR. The overall cumulative incidence of IBTR at 10 years was 10.2% (95% CI, 8.7-11.8%) without a boost and 6.2% (95% CI, 4.9-7.5%) with a boost (P < .001) (18). In the small subset of 251 patients who had positive margins and received a boost, the cumulative incidence of IBTR at 10 years was 17.5% (95% CI, 10.4-24.6%) with 10 Gy and 10.8% (95% CI, 5.2-16.4%) with 26 Gy (P > .10) (19). These data suggest that, although a boost provides a degree of reduction in IBTR when margins are microscopically positive, the absolute benefit is not sufficient to reduce the rate of IBTR to that seen with negative margins and the use of a boost.

Guideline recommendations

1. Positive margins

A positive margin, defined as ink on invasive cancer or ductal carcinoma in situ (DCIS), is associated with at least a 2-fold increase in IBTR. This increased risk in IBTR is not nullified by:

a) Delivery of a boost dose of radiation

b) Delivery of systemic therapy (endocrine therapy, chemotherapy, or biologic therapy), or

c) Favorable biology

A positive margin is defined as the presence of ink at the surface of the surgical specimen on either invasive tumor cells or DCIS, and implies a potentially incomplete resection that is associated with a significantly higher risk of IBTR. There is no debate regarding this concept. As shown in Table 4, the margins meta-analysis of 33 studies including 28,162 patients with a median follow-up of 6.6 years reported an odds ratio (OR) for IBTR of 1.96 (95% confidence interval [CI], 1.72-2.24) for close or positive margins compared with negative margins after adjustment for length of follow-up. For the 19 studies of 13,081 patients with sufficient detail to separate negative, close, and positive margins, the OR for positive versus negative margins was 2.44 (95% CI, 1.97-3.03) (13). Other published literature supports the observation that the risk of IBTR with a positive margin is at least 2-fold greater than that seen with negative margins (16, 17). Although various other treatment modalities, including use of a boost dose of radiation and adjuvant systemic therapy with endocrine therapy, chemotherapy, or biologically targeted agents, have all demonstrated a favorable impact on IBTR (see below), adjustment for the covariates of endocrine therapy or use of a boost dose of radiation did not nullify the increased risk of IBTR seen with a positive margin in the meta-analysis. In the 18 studies reporting information about the use of a boost, the risk of IBTR in patients with positive margins remained elevated (OR, 2.45; P < .001) after adjustment for study-specific follow-up and for the proportion of patients who had a boost. Other studies support this finding. For example, a European Organisation for Research and Treatment of Cancer (EORTC) trial demonstrated that an additional boost dose of 16 Gy targeting the tumor bed after microscopically complete removal of the tumor and WBRT significantly reduced the rate of IBTR. The overall cumulative incidence of IBTR at 10 years was 10.2% (95% CI, 8.7-11.8%) without a boost and 6.2% (95% CI, 4.9-7.5%) with a boost (P < .001) (18). In the small subset of 251 patients who had positive margins and received a boost, the cumulative incidence of IBTR at 10 years was 17.5% (95% CI, 10.4-24.6%) with 10 Gy and 10.8% (95% CI, 5.2-16.4%) with 26 Gy (P > .10) (19). These data suggest that, although a boost provides a degree of reduction in IBTR when margins are microscopically positive, the absolute benefit is not sufficient to reduce the rate of IBTR to that seen with negative margins and the use of a boost.

Similarly, despite the well-recognized benefit of systemic therapy in reducing IBTR, as discussed in detail below (20), the effects of a positive margin do not appear to be negated by the use of either adjuvant endocrine therapy or chemotherapy. In a
subanalysis of 16 studies within the margins meta-analysis that allowed adjustment for the proportion of patients who received endocrine therapy (and adjusted for follow-up), the adjusted OR for positive margins (vs negative) remained significantly higher at 2.53 (P<.001).

Finally, based on the results of the margins meta-analysis (13) and other retrospective series, the panel concluded that patients with positive margins who have favorable tumor biology, such as those with tumors that are strongly estrogen receptor (ER) positive, remain at higher risk for IBTR than similar patients with negative margins, despite good biologic features. From the model of 19 studies reporting margin widths in the meta-analysis, adjusted analysis of 15 studies that included detailed information on ER status found that the adjusted OR for IBTR among patients with ER-positive tumors with positive (vs negative) margins remained significantly elevated at 2.66 (P<.001). The impact of a boost dose of radiation, the use of systemic therapy, and biologic subtype on margin width is discussed further below.

Table 3 Summary of study characteristics

<table>
<thead>
<tr>
<th>Study characteristics</th>
<th>No. of studies</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients per study</td>
<td>33</td>
<td>701 (79-3899)</td>
</tr>
<tr>
<td>Prevalence of IBTR (%)</td>
<td>33</td>
<td>5.3 (2.3-7.6)</td>
</tr>
<tr>
<td>Follow-up time (mo)</td>
<td>33</td>
<td>79.2 (48.0-160)</td>
</tr>
<tr>
<td>Time to IBTR (mo)</td>
<td>14</td>
<td>53.5 (47.0-60.0)</td>
</tr>
<tr>
<td>Patient and tumor characteristics</td>
<td>No. of studies</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>32</td>
<td>53.4 (45.0-60.6)</td>
</tr>
<tr>
<td>Stage distribution (%)</td>
<td>11</td>
<td>0 (0-1.4)</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>55.0 (52.5-56.9)</td>
</tr>
<tr>
<td>II</td>
<td>44.4 (39.4-45.9)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0 (0-0.9)</td>
<td></td>
</tr>
<tr>
<td>Nodal status (%)</td>
<td>30</td>
<td>25.8 (17.9-28.8)</td>
</tr>
<tr>
<td>Positive</td>
<td>70.5 (65.5-74.2)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.6 (1.5-2.1)</td>
<td></td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td>8</td>
<td>28.3 (20.6-30.6)</td>
</tr>
<tr>
<td>High-grade (III) (%)</td>
<td>17</td>
<td>2.9 (0.8-21.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>45.5 (38.4-45.6)</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor status (%)</td>
<td>24</td>
<td>20.5 (16.6-26.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>28.4 (14.2-42.0)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>40.6 (33.5-47.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>22.0 (19.4-28.0)</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor status (%)</td>
<td>10</td>
<td>38.4 (23.8-44.7)</td>
</tr>
<tr>
<td>Positive</td>
<td>9.6 (7.5-15.7)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>30.1 (10.0-46.7)</td>
<td></td>
</tr>
<tr>
<td>EIC present (%)</td>
<td>16</td>
<td>47.2 (45.0-50.0)</td>
</tr>
<tr>
<td>LVI present (%)</td>
<td>16</td>
<td>12.0 (12.0-30.3)</td>
</tr>
<tr>
<td>Treatment characteristics</td>
<td>No. of studies</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Receipt of chemotherapy (%)</td>
<td>26</td>
<td>25.6 (18.3-38.0)</td>
</tr>
<tr>
<td>Receipt of endocrine therapy (%)</td>
<td>27</td>
<td>38.0 (19.3-36.9)</td>
</tr>
<tr>
<td>Receipt of WBRT (%)</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Receipt of radiation boost (%)</td>
<td>30</td>
<td>96 (73.1-100)</td>
</tr>
<tr>
<td>WBRT dose (Gy)</td>
<td>26</td>
<td>47.2 (45.0-50.0)</td>
</tr>
<tr>
<td>Radiation boost dose (Gy)</td>
<td>12</td>
<td>10.5 (10.0-13.1)</td>
</tr>
</tbody>
</table>

Abbreviations: EIC = extensive intraductal component; IBTR = ipsilateral breast tumor recurrence; IQR = interquartile range; LVI = lymphovascular invasion; WBRT = whole-breast radiation therapy.
* Including patient, tumor, and treatment variables included in the margins meta-analysis (13).
† Denotes median (of the median or mean values across studies).
‡ Inclusion criteria for meta-analysis required WBRT.

2. Negative margin widths

Negative margins (no ink on tumor) minimize the risk of IBTR. Wider margins do not significantly lower this risk. The routine practice to obtain negative margin widths wider than no ink on tumor is not indicated.

As discussed above, negative margins, defined as no ink on invasive carcinoma or DCIS, substantially reduce the risk of local recurrence compared with positive margins. However, the amount of normal breast tissue around the tumor that constitutes an optimal negative margin is controversial. To address this question, the MP considered what is known about the microscopic distribution of tumor in the breast in clinically and mammographically unicentric BC, whether the standardization and reproducibility of pathologic processing of lumpectomy specimens allow meaningful differentiation of margin widths of 1 or 2 mm, and the impact of changes in BC management on the relevance of older studies examining margin width to practice today.

Holland et al (21), in a meticulous study of mastectomy specimens, demonstrated that clinically unicentric T1–T2 BCs are frequently associated with subclinical foci of invasive cancer and/or DCIS in the surrounding breast tissue that may be present at large distances from the primary tumor site. Although the cases examined in this study preceded the mammographic era, the frequency of additional foci was independent of tumor size. For example, even among T1 lesions, 42%, 17%, and 10% of patients had additional foci of invasive cancer and/or DCIS >2 cm, >3 cm, and >4 cm from the index tumor, respectively. The frequent presence of foci of invasive carcinoma and DCIS at considerable distances from the index lesion may at least partially explain why increasing the width of lumpectomy margins in 1-mm intervals has no significant impact on the risk of local recurrence after breast-conserving surgery or WBRT.

There are also technical limitations to lumpectomy margin evaluation that confound the interpretation of data relating margin width to risk of local recurrence. Once a lumpectomy specimen is removed from the breast, there is flattening because of lack of support from the surrounding tissue. This is further exaggerated by compression in specimens submitted for specimen radiography. These factors result in artifactually narrower margins than existed in vivo (22). Furthermore, ink applied to the surface of the specimen often tracks into deeper portions of the specimen, which, in turn, can pose significant challenges for the pathologist to microscopically determine the location of the true margin. In addition, there is no standard method for margin evaluation, and this process is highly prone to sampling error. The two major options for lumpectomy margin evaluation include sectioning the specimen perpendicular to the inked margin (in which case, the precise distance to the margin can be determined) and shaving the specimen margins and examining them en face (in which case, any residual tumor in the shaved specimen is considered a positive margin). Some surgeons submit separate margins obtained by shaving the specimen margins and examining them en face (in which case, the precise distance to the margin can be determined) and shaving the specimen margins and examining them en face (in which case, any residual tumor in the shaved specimen is considered a positive margin). Some surgeons submit separate margins obtained from the walls of the biopsy cavity after the lumpectomy specimen is removed; these can be examined by either the inked or the shaved method. Although the shaved margin method permits examination of a greater surface area of the specimen margin than can be examined by the inked method, the use of shaved margins results in the categorization of many margins as positive that are, in fact, negative by

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the inked margin method—this, in turn, may result in unnecessary re-
excision or even mastectomy (23). Sampling of lumpectomy speci-
mens is also highly variable and ranges from submission of a limited
number of sections to total sequential embedding of the entire
specimen. However, even the process of total sequential embedding
results in the examination of only a very small proportion (<1%)
of lumpectomy specimen margins (24). Finally, the presence of tumor at
a certain distance from the inked margin on any single slide may not
represent the true state of that margin 3-dimensionally; a margin that
appears adequate on one given section may actually be positive if
additional sections are examined and even if deeper sections are cut
from the same tissue block. As a group, these studies indicate that
there is a great degree of variability in margin assessment and that,
regardless of the technique of margin evaluation used, a negative
margin does not guarantee the absence of residual tumor in the breast.

Despite the variability in margin assessment discussed above,
great attention has been paid to achieving specific negative margin
widths in the belief that this reduces the risk of IBTR, and re-
excision is frequently performed for margins in which there is no
ink on tumor (5). To address the question of the importance of margin width, we evaluated the results of the model of the meta-
analysis in which the relationship between specific margin widths
(1 mm, 2 mm, 5 mm) and IBTR was evaluated, as shown in
Table 4 (19 studies; 13,081 patients; 753 IBTRs; 8.7 years median
follow-up). After adjustment for study-specific length of follow-
up, there was no statistically significant evidence that the odds of IBTR
were associated with margin distance (P = .90), nor was
there statistical evidence for a trend that the odds of IBTR
decreased as the distance for declaring negative margins increased
(P = .58 for trend). Adjusting for covariates, including age, me-
dian year of study recruitment, use of endocrine therapy, use of a
radiation boost, use of re-excision, ER status, and type of IBTR
(first vs any), did not change these results. Although an analysis of
these data using study-specified margin definitions of negative, close,
and positive did reveal a significant increase in the odds of IBTR with close (OR, 1.74; 95% CI, 1.42-2.15) or positive (OR,
2.44; 95% CI, 1.97-3.03) margins compared with negative margins
(P < .001), the panel believed that the analysis of specific
margin widths superseded this finding because of the heteroge-
neity among studies in the definitions of “close” and “positive”;
margins defined as positive in one study could be classified as
close or even negative in other studies included in this analysis. In
addition, the panel recognized that there have been significant
changes in BC management that are not reflected in the relatively

**Table 4** Summary of selected results of margins meta-analysis (13)

<table>
<thead>
<tr>
<th>Relationship between IBTR and margin status</th>
<th>No. of Studies</th>
<th>No. of participants</th>
<th>Adjusted OR of IBTR*</th>
<th>95% CI</th>
<th>P (association)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin category (model 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close/positive</td>
<td>33</td>
<td>6178</td>
<td>1.96</td>
<td>1.72-2.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Negative</td>
<td>33</td>
<td>21,984</td>
<td>1.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Margin category (model 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19</td>
<td>1641</td>
<td>2.44</td>
<td>1.97-3.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Close</td>
<td>19</td>
<td>2407</td>
<td>1.74</td>
<td>1.42-2.15</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>19</td>
<td>9033</td>
<td>1.0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Threshold distance (model 2)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.90</td>
</tr>
<tr>
<td>1 mm</td>
<td>6</td>
<td>2376</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 mm</td>
<td>10</td>
<td>8350</td>
<td>0.91</td>
<td>0.46-1.80</td>
<td>-</td>
</tr>
<tr>
<td>5 mm</td>
<td>3</td>
<td>2355</td>
<td>0.77</td>
<td>0.32-1.87</td>
<td>-</td>
</tr>
</tbody>
</table>

Impact of margin width on IBTR adjusted for individual covariates and follow-up†

<table>
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<tr>
<th>Covariate</th>
<th>No. of studies</th>
<th>1 mm</th>
<th>2 mm</th>
<th>5 mm</th>
<th>P (association)</th>
</tr>
</thead>
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<tr>
<td>Age</td>
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<td>1.0</td>
<td>0.53</td>
<td>0.77</td>
<td>.53</td>
</tr>
<tr>
<td>Endocrine therapy</td>
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<td>0.95</td>
<td>0.90</td>
<td>.95</td>
</tr>
<tr>
<td>Radiation boost</td>
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<td>1.0</td>
<td>0.86</td>
<td>0.92</td>
<td>.86</td>
</tr>
</tbody>
</table>

† Threshold distance was also tested for significance for trend (reflects whether there was statistical evidence of a decrease in the odds of IBTR as the
threshold margin distance increased from 1 mm, 2 mm, and 5 mm). P (trend) = .58.

* Adjusted for study-specific median length of follow-up.

**Fig. 1.** Scatter plot of unadjusted rates of ipsilateral breast
tumor recurrence, by median year of study recruitment.
older studies included in this meta-analysis comparing negative versus close versus positive margins. Only 26% and 38% of patients included in the entire meta-analysis received chemotherapy and endocrine therapy, respectively, despite a median tumor size of 1.6 cm and a 26% incidence of nodal positivity. Because the incidence of local recurrence increases with time, a median follow-up of at least 4 years was one of the criteria for inclusion in the meta-analysis, and inclusion of studies with a longer follow-up period was believed to be important for an accurate assessment of the risk of local recurrence. As noted in Fig. 1, the crude incidence of IBTR declined over time, and although this was observed for all margin widths, the decline appeared more pronounced in those with margins <5 mm. As discussed in detail below, the benefits of adjuvant systemic therapy in reducing IBTR are well documented (20). The widespread use of systemic therapy today, even for patients with small, node-negative BC, increased the confidence of the MP that wider margins were unlikely to enhance local control in a clinically significant way in the current era. In addition, although the median year of study recruitment of studies included in the meta-analysis was 1990, the median prevalence of IBTR in all studies in the meta-analysis was only 5.3%. Although the ORs in Table 4 numerically suggest that 5-mm margins offer an advantage compared with margins of 1 to 2 mm, these differences lack statistical significance despite the use of 2 different statistical tests and robust sample sizes, making it unlikely that the meta-analysis lacks the power to detect clinically meaningful differences in IBTR based on margin width. Furthermore, with the overall rate of IBTR of 5.3%, the absolute benefit in possible decreases IBTR with an OR of 0.77 is on the order of 1% to 2%. More importantly, adjustments for covariates, such as the use of endocrine therapy and the use of a boost dose of radiation, which are a standard part of practice today, virtually eliminate the numeric differences in the ORs (Table 4). Thus, although larger margin widths may have resulted in small reductions in local recurrence in the past, there is no evidence that they are important in the setting of current multimodality treatment. It was not possible to compare rates of IBTR between margins of no ink on tumor and margins of ≥1 mm in model 2 (Table 4), because only a small number of studies with these margin definitions were available for review. The MP considered the long-term results of the NSABP B06 randomized trial (2), which defined a negative margin as no ink on tumor, began accrual in 1976, and reported a 5% rate of IBTR after 12 years of follow-up in patients receiving systemic therapy. In addition, the variability in margin assessment discussed above, the lack of evidence of a significant difference in rates of IBTR among margins of 1 mm, 2 mm, and 5 mm, and the benefits of a boost dose of radiation on local control as discussed below led the MP to believe that the totality of evidence did not support a distinction between margins of no ink on tumor and margins of 1 mm.

The use of systemic therapy in the treatment of early-stage BC has changed dramatically over the past 30 years; throughout this period, consistent evidence has accumulated that successful systemic therapy improves local control. In the NSABP B06 trial, only those women with node-positive disease received chemotherapy (melphalan and fluorouracil [FU]). Within the cohort that underwent irradiation, node-positive patients demonstrated roughly half the rate of IBTR compared with node-negative patients (5% vs 12%) (2) at 12 years, an advantage attributable to the use of chemotherapy. This positive impact of systemic treatment on local control has continued with improvements in systemic therapy. As illustrated in subsequent analyses of NSABP trials of systemic therapy, each improvement that led to improved survival was accompanied by a decline in IBTR. In NSABP B14 (tamoxifen vs no tamoxifen for ER-positive, node-negative disease), the rate of IBTR was 11.6% in the control group compared with 5.0% in the tamoxifen group (P<.001) (8); in NSABP B13 (chemotherapy vs not for node-negative disease), IBTR rate was 15.3% in the control and 5.4% in the treated patients (P<.001) (8); in NSABP B19 (methotrexate and FU vs cyclophosphamide, methotrexate, and FU in ER-negative, node-negative patients), the IBTR rates were 8.2% and 4.8% (P<.03) (25). The 1990s saw the introduction of taxanes into adjuvant and neoadjuvant regimens, and pooled data from NSABP trials B18 (anthracycline-based chemotherapy) and B27 (inclusion of docetaxel) demonstrated that women who did not achieve a pathologic complete response (pCR) in the breast had an increased hazard ratio (HR) for local-regional recurrence (HR, 1.55; 95% CI, 1.01-2.59) compared with those who did (26). Thus, achieving a pCR—which heralds a much-reduced risk of distant disease and breast cancer death—also results in a significantly reduced risk of IBTR.

The adjuvant systemic therapy of today is substantially improved over that of 20 years ago and is likely to continue to improve, with better targeting of specific BC subtypes. For women with ER-positive BC undergoing BCT, the 10-year rates of IBTR in the Early Breast Cancer Trialists’ Group overview were 18.6% when tamoxifen was not used and 8.7% when tamoxifen was used (1). The introduction of aromatase inhibitor therapy instead of, or in addition to, tamoxifen in postmenopausal women has led to a consistent reduction in the rates of IBTR across essentially all trials, with an average reduction in the HR of approximately 0.67 (27). The addition of taxanes to anthracycline-based regimens is also accompanied by a relative reduction in the rate of IBTR (20). Finally, the addition of trastuzumab to cytotoxic regimens for patients with human epidermal growth factor receptor 2 (HER2)—positive BC leads to a further reduction in the crude hazard of IBTR, with HRs of 0.47 and 0.66 in the pooled U.S. trials and European Herceptin Adjuvant (HERA) trial (28, 29). These data from large randomized clinical trials establish the principle that systemic therapy advances that lead to improved survival and decreased risk of distant disease also contribute to improved local control and suggest that, as systemic therapy continues to improve, so will its impact on diminishing IBTR.

The panel agreed that the evidence indicates clearly that systemic therapy, used for the vast majority of patients with BC today, reduces the overall risk of IBTR. It also strengthened the confidence of the MP that 1-mm increments in margin widths are unlikely to affect IBTR once a margin of no ink on tumor cells has been obtained. Although the evidence base was less robust, the panel agreed that, in the rare circumstance in which a patient does...
not receive any form of systemic treatment, there is no evidence to suggest that obtaining margins wider than no ink on tumor would result in any further reduction of IBTR.

### 4. Biologic subtypes

Margins wider than no ink on tumor are not indicated based on biologic subtype.

An improved understanding of biologic subtypes of BC has led to great improvements in systemic therapy that have, in turn, decreased IBTR. Several large studies have examined IBTR rates with BCT in relation to molecular markers. In one of the largest studies, Arvold et al (30) reviewed the cases of 1434 patients who underwent BCT and found that those patients with triple-negative BC (TNBC) and HER2-positive tumors had a significantly higher risk of IBTR compared with patients with other subtypes. However, the study did not include treatment with adjuvant trastuzumab, which lowers IBTR for the HER2-positive group. Another large study, by Voduc et al (31), of nearly 3,000 patients with a median follow-up of 12 years, also found increased IBTR among those patients with HER2-enriched and basal tumors. Interestingly, the investigators found no increased IBTR among TNBCs with nonbasal tumor markers (31). Mazouni et al (32) reported on 1194 patients and found no statistically significant differences in IBTR on the basis of subtype. They did, however, note that mastectomy was more commonly performed for HER2-positive disease and TNBC than for luminal A and luminal B tumors, suggesting that surgeons were less comfortable with BCT for more aggressive tumor subtypes, despite a lack of data. Haftty et al (33), as well as Freedman et al (34), also found no significant differences in IBTR among patients treated with BCT when comparing TNBC with non-TNBC. A recent study by Gangi et al (35) examined outcome among 1851 consecutive patients treated between 2000 and 2012, during which trastuzumab was routinely used for HER2-positive patients. There was no significant difference in IBTR among patients with TNBC compared with other subtypes of tumors.

Intuitively, it might be thought that wider margins are necessary to control the more aggressive tumor types. However, there is no reason to believe that HER2-positive disease and TNBC are more difficult to resect. Pilewskie et al (36) examined the impact of margin width on local recurrence in 535 patients with TNBC. At 60 months, the incidence of IBTR did not differ significantly between patients with margins ≤2 mm and those with margins >2 mm (7.3% vs 5.1%). Alternatively, local failure occurs as a marker of aggressive biology, as is seen after mastectomy. Three retrospective studies have examined the incidence of local failure in TNBC after BCT or mastectomy, and have found no difference based on surgical procedure, suggesting that these local recurrences are more likely a result of aggressive biology, not residual tumor at the surgical site, which could be improved with wider lumpectomy margins (29, 37-39). This theory is supported by the approximately 40% decline in IBTR seen in patients with HER2-positive tumors receiving adjuvant systemic trastuzumab and other HER2-targeted agents (29). In summary, the MP concluded that, although there is evidence that the risk of IBTR varies by subtype based on the results of many studies, patients with aggressive tumors remain at equally increased risk for local failure irrespective of treatment with mastectomy or BCT, indicating that there is no justification for more widely clear margins over no ink on tumor for any BC subtype.

### 5. Radiation therapy delivery

The choice of WBRT delivery technique, fractionation, and boost dose should not be dependent on margin width.

WBRT options have expanded significantly in the last decade. Delivery techniques such as prone positioning and intensity-modulated radiation therapy have been designed to limit treatment-related toxicity by decreasing heart/lung volumes and improving homogeneity across the whole-breast radiation field, respectively (40-43). In addition, attempts have been made to decrease the burden of the protracted treatments inherent to conventionally fractionated WBRT through the use of accelerated, hypofractionated, whole-breast schemas. Two large randomized trials have now reported comparable long-term efficacy and toxicity data with these shorter fractionation schedules, establishing it as an acceptable alternative (44, 45). In general, the studies evaluating these approaches did not specify particular surgical margin widths, and required only complete microscopic excision of tumor (40-43, 45). The large United Kingdom Standardization of Breast Radiotherapy (START) trial did mandate a ≥1-mm margin, but comparable long-term results were reported in the similar Canadian hypofractionation trial that excluded only those with involved margins (45-47). Although neither of these trials was designed to address a possible interaction between margin width and the specifics of radiation delivery, there is no evidence to suggest that margin width should dictate patient selection for these therapies.

As discussed earlier, a radiation boost to the tumor bed after WBRT has been shown to significantly reduce the risk of IBTR at a cost of increased, although acceptable, rates of late radiation toxicity (18, 48, 49). In the randomized trials establishing the benefit of a boost, negative surgical margins were largely defined as no ink on tumor.

Further tailoring of the boost dose has been explored in several single-institution series (50-52). In each of these studies, margin width was used as an indicator of potential residual tumor burden, and boost doses were increased with decreasing margin width. The MP believed that interpretation of these and other retrospective data evaluating both radiation dose and surgical margins was complicated by the heterogeneity of total radiation doses and techniques and by a lack of control cohorts with comparable margin widths and uniform doses. Therefore, the panel concluded that there was no clear reduction in IBTR as a result of escalating the radiation dose when margin widths were smaller. In one report, an increased rate of IBTR was noted in patients with close or positive margins despite the dose-escalation strategy (51). The other studies simply noted the lack of a clear relationship between local control and margin width or radiation dose (50, 52).

In summary, margin width should not be used to determine the delivery technique or fractionation for WBRT or vice versa.
Furthermore, in patients with negative margins (no ink on tumor), the use and dose of a tumor bed boost should be based on a priori estimation of local failure risk and should not be determined, in isolation, by the width of the surgical margin.

ILCs comprise 5% to 15% of all BCs. Several large retrospective studies have demonstrated that when negative margins were obtained, the risk of IBTR was not significantly different between ILC and invasive ductal carcinoma (53-55). Wider margins do not yield lower IBTR rates. In a retrospective study of 382 patients comparing margins > 1 cm with smaller margins, no differences in local recurrence rates were observed (56). In addition, most classical ILCs have a luminal A phenotype and are ER positive, so the benefits of endocrine therapy on local control, as discussed previously, will be seen in this population. Thus, the MP concluded that the general recommendations regarding margin width should not be altered for invasive lobular histology.

In contrast to clear evidence demonstrating that DCIS at the margin increases IBTR, the presence of LCIS at the margin does not affect IBTR. In a retrospective study, the 10-year cumulative incidence rate of IBTR in patients with BC was not significantly different in patients with or without LCIS unless tamoxifen was withheld (57). In other large studies, the presence of LCIS within the specimen or at the resection margin did not appear to affect the risk of local recurrence (58, 59). There is concern that the pleomorphic variant of LCIS, which has some features more akin to high-grade DCIS than to classical LCIS, may carry an increased risk of recurrence when at the margin. Given the limitation of only small retrospective studies with a very limited number of events available to address this question (60), the MP did not believe that a recommendation regarding pleomorphic LCIS at the margin could be made at this time.

6. Invasive lobular carcinoma and lobular carcinoma in situ

Wider negative margins than no ink on tumor are not indicated for invasive lobular carcinoma (ILC). Classic lobular carcinoma in situ (LCIS) at the margin is not an indication for re-excision. The significance of pleomorphic LCIS at the margin is uncertain.

7. Young age

Young patient age, usually defined as < 40 years, has been associated with an increased risk of IBTR after BCT compared with that in older women. In the Early Breast Cancer Trialists’ Collaborative Group meta-analysis of breast-conserving surgery with and without radiation therapy, the rate of any first recurrence by age was 5.9% per year for age < 40 years, 2.7% per year for age 40 to 49 years, and 1% to 1.9% per year for ≥ 50 years in the node-negative subgroup (1). Corresponding rates in the node-positive subgroup were 8.3% per year for age < 40 years, 6.5% per year for age 40 to 49 years, and 4.8% to 6.5% per year for age ≥ 50 years, respectively. An increased risk for BC mortality was also seen in the subgroup of women aged < 40 years. Other studies have confirmed a higher risk of distant recurrence as well as IBTR in young women (61, 62).

Young patient age is not associated with an improved outcome with mastectomy. The risk for locoregional recurrence after mastectomy without radiation is also significantly higher in young women compared with their older counterparts (63), and the increased risk of both recurrence and BC death is not improved with mastectomy compared with BCT (62, 64). The increased IBTR rates in young women likely result from the greater frequency of adverse biologic and pathologic features in this group compared with older women. Young women have more aggressive tumor characteristics, such as high histologic grade, lymphovascular invasion, hormone receptor—negative BC, BRCA1, and BRCA2 mutation—associated cancers, and BCs associated with adverse gene expression profiles (65, 66) compared with their older counterparts. In 1 study, very young patients with tumors classified as luminal B, HER2, and triple-negative subtypes were at increased risk for IBTR when compared with older patients, but no significant effect of age was seen in the subgroup with the most favorable luminal A subtype (66). Young age may be a less important factor for IBTR when controlling for adverse gene-expression profile (30, 67) or may not be important at all in predicting recurrence and survival in an era of modern systemic therapy and anti-HER2—directed therapy, as suggested in 1 recent study of young women with HER2-overexpressing cancers (68).

There was no evidence in the margins meta-analysis that, once a negative margin has been achieved, young patients benefit from a greater negative margin width than no ink on tumor. In 18 studies in the meta-analysis, the adjusted OR for IBTR with age as a covariate did not differ significantly when negative margin widths were defined as 1 mm, 2 mm, or 5 mm (P for association, .86; P for trend, .58). This is consistent with the finding that mastectomy, which theoretically should provide the largest margin width that can be obtained, is also associated with an increased risk of local recurrence in younger compared with older women. In addition, there are data demonstrating equivalent risks for recurrence and BC death in young women irrespective of treatment with BCT or mastectomy (62, 64).

Thus, the MP concluded that although the adverse pathologic and biologic factors associated with young age are mitigated to some extent by excision to negative margins, use of systemic therapies, use of a radiation boost, and possible exclusion of young BRCA mutation carriers from a BCT approach, there is no evidence of an association between increased risk of IBTR and EIC when margins are negative.

8. Lobular carcinoma in situ

A lobular carcinoma in situ (EIC) identifies patients who may have a large residual DCIS burden after lumpectomy. There is no evidence of an association between increased risk of IBTR and EIC when margins are negative.
evidence supporting obtaining wider negative margins beyond no ink on tumor solely on the basis of young patient age.

EIC is a pathologic description of invasive ductal carcinoma that has a prominent intraductal component within the tumor and adjacent normal tissue. The basis of the definition of EIC was the observation in the 1970s at the Harvard Joint Center for Radiation Therapy, at a time when margins of resection were not routinely assessed, that a high rate of IBTR was observed in patients undergoing BCT when a prominent DCIS burden was noted within the confines of the invasive cancer (approximately 25%) and within breast tissue beyond the edges of the invasive cancer (69). These EIC-positive cancers often recurred within or at the edge of the boost volume and were more commonly seen in young patients (<35 years of age). Furthermore, IBTR was more common in young EIC-positive patients than in older EIC-positive patients.

In subsequent years, when margins of resection were inked, and re-excisions were performed for positive or close margins, patients with EIC-positive cancers (but not EIC-negative cancers) were frequently found to have considerable residual DCIS in the re-excision specimens (70). Pathologic examination of a cohort of mastectomy specimens revealed that 33% of EIC-positive cancers with EIC-positive cancers were re-excisions performed for positive or close margins, patients with EIC-positive cancers (but not EIC-negative cancers) were more commonly seen in young patients (≤35 years of age). Furthermore, IBTR was more common in young EIC-positive patients than in older EIC-positive patients.

In subsequent years, when margins of resection were inked, and re-excisions were performed for positive or close margins, patients with EIC-positive cancers (but not EIC-negative cancers) were frequently found to have considerable residual DCIS in the re-excision specimens (70). Pathologic examination of a cohort of mastectomy specimens revealed that 33% of EIC-positive cancers had prominent DCIS (>6 low-power fields of DCIS) at ≥2 cm from the edge of the index cancer compared with only 2% of EIC-negative cancers (71). In aggregate, these studies indicated that an EIC denotes a cancer that may have extensive multifocal DCIS involvement and an increased rate of IBTR if not adequately resected.

Later, additional studies revealed that patients with EIC-positive tumors did not have an increase in IBTR unless tumor cells were present at the inked margin (72). In a cohort of EIC-positive patients, IBTR was 0% at 5 years when there were no tumor cells at the inked margin or when the margin was defined as close, but it was 50% when there was more than focal positivity (72). On the basis of this information, the MP did not believe that the available evidence supports the routine use of margins wider than no ink on tumor. However, in view of the potential for substantial residual DCIS in EIC-positive patients, consideration should be given to obtaining postoperative mammographic imaging to assist in identifying residual tumor bed calcifications warranting re-excision. In addition, when an EIC is present, young age and multiple close margins are associated with an increased risk of IBTR and can be used to select patients who might benefit from re-excision (69, 72). Postexcision mammography is a useful adjunct to margin status to assess the completeness of excision of lesions with calcifications even when an EIC is not present.

References


TWENTY-YEAR FOLLOW-UP OF A RANDOMIZED TRIAL COMPARING TOTAL MASTECTOMY, LUMPECTOMY, AND LUMPECTOMY PLUS IRRADIATION FOR THE TREATMENT OF INVASIVE BREAST CANCER

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ABSTRACT

Background In 1976, we initiated a randomized trial to determine whether lumpectomy with or without radiation therapy was as effective as total mastectomy for the treatment of invasive breast cancer.

Methods A total of 1851 women for whom follow-up data were available and nodal status was known underwent randomly assigned treatment consisting of total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation. Kaplan–Meier and cumulative-incidence estimates of the outcome were obtained.

Results The cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3 percent in the women who underwent lumpectomy and breast irradiation, as compared with 39.2 percent in the women who underwent lumpectomy without irradiation (P<0.001). No significant differences were observed among the three groups of women with respect to disease-free survival, distant-disease–free survival, or overall survival. The hazard ratio for death among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P=0.51). The hazard ratio for death among the women who underwent lumpectomy followed by breast irradiation, as compared with those who underwent total mastectomy, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P=0.74). Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the hazard ratio for death among the women who underwent postoperative breast irradiation, as compared with those who did not, was 0.91 (96 percent confidence interval, 0.77 to 1.06; P=0.23). Radiation therapy was associated with a marginally significant decrease in deaths due to breast cancer. This decrease was partially offset by an increase in deaths from other causes.

Conclusions Lumpectomy followed by breast irradiation continues to be appropriate therapy for women with breast cancer, provided that the margins of resected specimens are free of tumor and an acceptable cosmetic result can be obtained. (N Engl J Med 2002;347:1233-41.)

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I

N 1971, the National Surgical Adjuvant Breast and Bowel Project (NSABP) initiated the B-04 study, a randomized clinical trial conducted to resolve controversy over the surgical management of breast cancer. The 25-year findings from that study showed that there was no significant difference in survival between women treated with the Halsted radical mastectomy and those treated with less extensive surgery. In 1973, we began to design a second randomized trial, B-06, to evaluate the efficacy of breast-conserving surgery in women with stage I or II breast tumors that were 4 cm or less in diameter. Patients were treated with lumpectomy, an operation that involved removal of enough normal breast tissue to ensure that the margins of the resected specimen were free of tumor. The outcome for women who were treated with lumpectomy alone or with lumpectomy and postoperative breast irradiation was compared with that for similar women who were treated with total mastectomy. Previous analyses showed no significant differences in survival among the women in the three treatment groups and demonstrated a significant decrease in the rate of recurrent cancer in the ipsilateral breast after lumpectomy plus irradiation. We now report the 20-year findings.

METHODS

Study Design

Between August 8, 1976, and January 27, 1984, a total of 2163 women with invasive breast tumors that were 4 cm or less in their largest diameter and with either negative or positive axillary lymph nodes (stage I or II breast cancer) were randomly assigned to one of three treatments: total mastectomy, lumpectomy (which we initially called segmental mastectomy), or lumpectomy followed by breast irradiation. Axillary nodes were removed regardless of the tumors have been described previously.

The women treated with lumpectomy underwent tumor resection, with removal of sufficient normal breast tissue to ensure both tumor-free specimen margins and a satisfactory cosmetic result. Only the lower two levels of the axillary nodes were removed, whereas in the women who underwent total mastectomy, the ax---

illary nodes were removed en bloc with the tumor. The protocol specified that 10 Gy of radiation be administered to the breast but not the axilla, in women who underwent lumpectomy and had irradiation. Neither external-beam nor interstitial irradiation was used as a supplemental boost. All women with one or more positive axillary nodes received adjuvant systemic therapy with melphalan and fluorouracil.4 Lumpectomy-treated women whose resected-specimen margins were found on histologic examination to contain tumor underwent total mastectomy but continued to be followed for subsequent events.

**Statistical Analysis**

Two cohorts were considered for the analysis of end points. One cohort included all the women with follow-up information who had originally consented to participate in the study (2105 women); the other included eligible women with follow-up information who accepted the assigned treatment, and whose nodal status was known (1851 women). Analysis of the two cohorts yielded similar results. To facilitate comparison of the current findings with those presented in prior reports, only the results of the analysis of the latter cohort are reported here.

The end points for overall treatment comparisons were disease-free survival, distant-disease-free survival, and overall survival. The times to these end points were calculated from the date of surgery. The events included in our analysis of disease-free survival were the first recurrence of disease at a local, regional, or distant site; the diagnosis of a second cancer; and death without evidence of cancer. A first recurrence of a tumor in the chest wall or in the operative scar, but not in the ipsilateral breast, was classified as a local recurrence. The protocol specified that the occurrence of a tumor in the ipsilateral breast after lumpectomy would not be considered an event in the analysis of disease-free survival because women who underwent total mastectomy as the assigned treatment were not at risk for such an event. Instead, the occurrence of a tumor in the ipsilateral breast after lumpectomy was considered to be a cosmetic failure. Recurrences in the internal mammary, supraclavicular, or ipsilateral axillary nodes were classified as regional occurrences. Recurrences at other locations were classified as distant recurrences. For the analysis of distant-disease-free survival, events included distant metastases as first recurrences, distant metastases after a local or regional recurrence, and all second cancers, including tumors in the contralateral breast. The analysis of overall survival included all deaths. The Kaplan–Meier method was used to estimate disease-free survival, distant-disease-free survival, and overall survival for each treatment group.5 Estimates are reported with their standard errors. Treatments were compared with the use of log-rank tests for all available observation times.6 Tests of heterogeneity were used for two-way and three-way comparisons of end points. Comparisons of the two lumpectomy groups included only the 1137 women whose surgical specimens had tumor-free margins. Cox proportional-hazards models were used to estimate hazard ratios.7 A hazard ratio greater than 1 indicates a better outcome, on average, for women in the reference group, whereas a value of less than 1 indicates a worse outcome for women in that group. If the total-mastectomy group was included in a comparison, it was designated as the reference group. In comparisons involving only the lumpectomy groups, the group of women who underwent lumpectomy without irradiation was designated as the reference group.

In the lumpectomy groups, hazard rates for a recurrence in the ipsilateral breast as a first event were compared with the use of the log-rank test. A nonparametric method8 was used to estimate the cumulative-incidence curves for recurrence in the ipsilateral breast as a first event, and Gray’s K-sample test statistic9 was used to determine whether the difference in cumulative incidence between the lumpectomy-treated groups was significant.

Differences among the treatment groups with respect to death causes other than breast cancer were determined with the use of the log-rank statistic, with all follow-up data censored after a first recurrence or a diagnosis of cancer in the contralateral breast. The method of log-rank subtraction10 was then used to determine differences with respect to deaths related to breast cancer. This approach obviates the difficulty of having to precisely determine causes of death after recurrence but does require an assumption of independence between causes of death related to breast cancer and other causes of death, conditional on treatment. We also estimated cumulative-incidence curves for deaths that occurred without evidence of a recurrence or a diagnosis of cancer in the contralateral breast and for deaths that followed a recurrence or the development of disease in the contralateral breast. We compared these cumulative-incidence curves among the three treatment groups, using Gray’s K-sample test.

All reported P values are based on two-sided tests. P values less than 0.05 were considered to be statistically significant. The current analysis was based on follow-up information through December 31, 2001, that was received at the NSABP Biostatistical Center as of March 31, 2002. Sixty-nine percent of all the women included in the analysis either were followed for at least 20 years or were known to have died during the follow-up period. The percentage of women who were followed for less than 20 years was similar among the treatment groups.

**RESULTS**

The distribution of women among the three treatment groups is shown in Table 1. For 58 of the 2163 women who were enrolled, follow-up information was not available.4 Of the remaining 2105 patients, 81 were ineligible; 36 of these women had noninvasive tumors. Of the 2024 eligible patients with follow-up data, 165 refused the assigned treatment, and 8 had unknown nodal status. Thus, 1851 patients were included in the primary analysis.

The distribution of the women among the treatment groups according to age, tumor size, and nodal status was similar.2 About 60 percent of the women were 50 years of age or older. Women with small tumors (≤2.0 cm in diameter) and women with large tumors (2.1 to 4.0 cm in diameter) were uniformly distributed among the treatment groups. Slightly more than 50 percent of the women had small tumors, and slightly less than 50 percent had large tumors. Sixty-two percent of the women had negative nodes, 26 percent had one to three positive nodes, and 12 percent had four or more positive nodes. Although determination of the estrogen-receptor status of the tumor was not a study requirement, the status was determined for about 75 percent of the tumors in each of the treatment groups; 36 percent were negative for estrogen receptor and 64 percent were positive. Tumor was found in the margins of specimens removed from 64 of the 634 women assigned to lumpectomy and from 61 of the 628 assigned to lumpectomy and irradiation.

**Recurrence in the Ipsilateral Breast after Lumpectomy**

Breast irradiation decreased the likelihood of a recurrence in the ipsilateral breast in the group of 1137 lumpectomy-treated women whose surgical specimens...
had tumor-free margins. The cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery was 14.3 percent among the women who underwent irradiation after lumpectomy and 39.2 percent among those who underwent lumpectomy without irradiation (P<0.001) (Fig. 1). The benefit of radiation therapy was independent of the nodal status. Among the women with negative nodes, 36.2 percent of those who did not receive radiation therapy and 17.0 percent of those who did had a recurrence in the ipsilateral breast within 20 years (P<0.001). Among the women with positive nodes, 44.2 percent of those who did not undergo irradiation and 8.8 percent of those who did had a recurrence in the ipsilateral breast (P<0.001). In the group of women treated with lumpectomy alone, 73.2 percent of these events occurred within the first 5 years after surgery, 18.2 percent occurred 5 to 10 years after surgery, and 8.6 percent occurred more than 10 years after surgery. In the group of women treated with lumpectomy followed by breast irradiation, 39.7 percent of recurrences in the ipsilateral breast were detected within the first 5 years, 29.5 percent at 5 to 10 years, and 30.8 percent after 10 years.

Disease-free Survival and Distant-Disease–free Survival

Of the 1851 women in the current analysis, 36.8 percent were alive and free of cancer (Table 2). The most frequent first events were distant recurrences (in 24.5 percent of the women). With the exception of the rate of local recurrence, which was lower in the group treated with lumpectomy followed by breast irradiation than in the other two groups, the distribution of all first events was fairly similar among the three groups of women.

Table 1. Distribution of Patients and Duration of Follow-up among the Treatment Groups.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TOTAL MASTECTOMY</th>
<th>LUMPECTOMY ALONE</th>
<th>LUMPECTOMY PLUS IRRADIATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled (no.)</td>
<td>713</td>
<td>719</td>
<td>731</td>
</tr>
<tr>
<td>No follow-up data</td>
<td>21</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>Excluded (no.)</td>
<td>103</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>Refused assigned treatment</td>
<td>76</td>
<td>34</td>
<td>55</td>
</tr>
<tr>
<td>Ineligible</td>
<td>26</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Unknown nodal status</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Included in analysis of total mastectomy vs. lumpectomy with or without irradiation (no.)</td>
<td>589</td>
<td>634</td>
<td>628</td>
</tr>
<tr>
<td>Included in analysis of lumpectomy alone vs. lumpectomy plus irradiation (no.)</td>
<td>—</td>
<td>570</td>
<td>567</td>
</tr>
<tr>
<td>Time in study (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.8</td>
<td>20.6</td>
<td>20.7</td>
</tr>
<tr>
<td>Range</td>
<td>17.9–25.6</td>
<td>17.9–25.6</td>
<td>17.9–25.7</td>
</tr>
</tbody>
</table>

*Of the 1262 women who underwent lumpectomy with or without irradiation, 125 were not included because of the presence of tumor at the margins of the resected specimen.
There were no significant differences in disease-free survival among the three treatment groups (P = 0.26) (Fig. 2A). The hazard ratio for a first event (diagnosis of recurrent disease or a second cancer or death without evidence of cancer) among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95 percent confidence interval, 0.92 to 1.21; P = 0.47), and the hazard ratio for the women who underwent lumpectomy and breast irradiation, as compared with those who underwent total mastectomy, was 0.94 (95 percent confidence interval, 0.82 to 1.09; P = 0.41). At 20 years, disease-free survival was 36±2 percent for the women who underwent total mastectomy, 35±2 percent for those who underwent lumpectomy alone, and 35±2 percent for those who underwent lumpectomy and breast irradiation. There was a nearly significant increase in disease-free survival for women who underwent lumpectomy and irradiation, as compared with those who underwent lumpectomy alone (hazard ratio, 0.87; 95 percent confidence interval, 0.75 to 1.01; P = 0.07). At 20 years, disease-free survival was 35±2 percent for the women treated with lumpectomy alone and 36±2 percent for those treated with lumpectomy and postoperative irradiation. There was no significant difference in distant-disease–free survival among the three treatment groups (P = 0.34) (Fig. 2B). The hazard ratio for an event (diagnosis of distant disease or a second cancer) among women in the lumpectomy-alone group, as compared with the total-mastectomy group, was 1.11 (95 percent confidence interval, 0.94 to 1.30; P = 0.21); the hazard ratio for the group treated with lumpectomy and irradiation, as compared with the total-mastectomy group, was 1.01 (95 percent confidence interval, 0.86 to 1.18; P = 0.95). At 20 years, distant-disease–free survival was 49±2 percent for the women treated with total mastectomy, 45±2 percent for those treated with lumpectomy alone, and 46±2 percent for those treated with lumpectomy plus irradiation. There was no significant difference in distant-disease–free survival between the women in the two lumpectomy groups who had specimens with tumor-free margins (hazard ratio, 0.89; 95 percent confidence interval, 0.75 to 1.04; P = 0.15). At 20 years, distant-disease–free survival was 46±2 percent for the women treated with lumpectomy alone and 47±2 percent for those who received radiation therapy after lumpectomy.

Of the 702 first recurrences, 69 percent were detected within the first 5 years after surgery, and 11 percent after 10 years; 9 percent of local recurrences, 7 percent of regional recurrences, and 13 percent of distant recurrences were detected after 10 years (Table 3). Of the 165 tumors in the contralateral breast, 38 percent were detected within 5 years after surgery and 32 percent after 10 years.

**Overall Survival**

There was no significant difference in overall survival among the treatment groups (P = 0.57) (Fig. 2C). The hazard ratio for death among the women treated with lumpectomy alone, as compared with those treated with total mastectomy, was 1.05 (95 percent confidence interval, 0.90 to 1.23; P = 0.51); the hazard ratio for the women treated with lumpectomy plus breast irradiation, as compared with those treated with total mastectomy, was 0.97 (95 percent confidence interval, 0.83 to 1.14; P = 0.74). At 20 years,
Figure 2. Disease-free Survival (Panel A), Distant-Disease–free Survival (Panel B), and Overall Survival (Panel C) among 589 Women Treated with Total Mastectomy, 634 Treated with Lumpectomy Alone, and 628 Treated with Lumpectomy plus Irradiation.

In each panel, the P value above the curves is for the three-way comparison among the treatment groups; the P values below the curves are for the two-way comparisons between lumpectomy alone or with irradiation and total mastectomy.

### Table 3. First Breast-Cancer–Related Events According to Treatment Group and Time of Occurrence.

<table>
<thead>
<tr>
<th>Event and Years of Follow-up</th>
<th>Total Mastectomy</th>
<th>Lumpectomy Alone</th>
<th>Lumpectomy plus Irradiation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any first recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 yr</td>
<td>161 (74)</td>
<td>187 (70)</td>
<td>133 (62)</td>
<td>481 (69)</td>
</tr>
<tr>
<td>&gt;5 and ≤10 yr</td>
<td>38 (17)</td>
<td>55 (20)</td>
<td>49 (23)</td>
<td>142 (20)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>20 (9)</td>
<td>27 (10)</td>
<td>32 (15)</td>
<td>79 (11)</td>
</tr>
<tr>
<td>Local</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 yr</td>
<td>47 (78)</td>
<td>43 (77)</td>
<td>5 (29)</td>
<td>95 (71)</td>
</tr>
<tr>
<td>&gt;5 and ≤10 yr</td>
<td>9 (15)</td>
<td>10 (18)</td>
<td>7 (41)</td>
<td>26 (20)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>4 (7)</td>
<td>3 (5)</td>
<td>5 (29)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Regional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 yr</td>
<td>24 (89)</td>
<td>44 (80)</td>
<td>26 (76)</td>
<td>94 (81)</td>
</tr>
<tr>
<td>&gt;5 and ≤10 yr</td>
<td>2 (7)</td>
<td>8 (15)</td>
<td>4 (12)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>1 (4)</td>
<td>3 (5)</td>
<td>4 (12)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Distant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 yr</td>
<td>90 (68)</td>
<td>100 (63)</td>
<td>102 (63)</td>
<td>292 (64)</td>
</tr>
<tr>
<td>&gt;5 and ≤10 yr</td>
<td>27 (20)</td>
<td>37 (23)</td>
<td>38 (23)</td>
<td>102 (23)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>15 (11)</td>
<td>21 (13)</td>
<td>23 (14)</td>
<td>59 (13)</td>
</tr>
<tr>
<td>Cancer in contralateral breast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 yr</td>
<td>19 (38)</td>
<td>25 (45)</td>
<td>19 (32)</td>
<td>63 (38)</td>
</tr>
<tr>
<td>&gt;5 and ≤10 yr</td>
<td>11 (22)</td>
<td>17 (30)</td>
<td>21 (36)</td>
<td>49 (30)</td>
</tr>
<tr>
<td>&gt;10 yr</td>
<td>20 (40)</td>
<td>14 (25)</td>
<td>19 (32)</td>
<td>53 (32)</td>
</tr>
</tbody>
</table>
survival was 47±2 percent among the women treated with total mastectomy, 46±2 percent among those treated with lumpectomy alone, and 46±2 percent among those treated with lumpectomy followed by breast irradiation. There was also no significant difference in survival between the two groups of lumpectomy-treated women who had specimens with tumor-free margins (hazard ratio for death among the women who underwent irradiation as compared with those who did not, 0.91; 95 percent confidence interval, 0.77 to 1.06; \( P=0.23 \)). At 20 years, survival was 46±2 percent for the lumpectomy-alone group and 47±2 percent for the lumpectomy-plus-radiation group.

Figure 3 shows cumulative-incidence curves for all deaths regardless of the cause, for deaths that followed a recurrence or the development of cancer in the contralateral breast, and for deaths that occurred in the absence of any evidence of breast cancer among the women who underwent lumpectomy alone or lumpectomy followed by irradiation. As noted above, the cumulative incidence of deaths from all causes did not differ significantly between the two lumpectomy groups. However, on the basis of an analysis with the use of log-rank subtraction, lumpectomy followed by breast irradiation, as compared with lumpectomy alone, was associated with a marginally significant decrease in deaths due to breast cancer (hazard ratio, 0.82; 95 percent confidence interval, 0.68 to 0.99; \( P=0.04 \)). This survival advantage was partially offset by an increase in deaths from other causes (hazard ratio, 1.23; 95 percent confidence interval, 0.89 to 1.71; \( P=0.21 \)). Other pairwise comparisons showed no significant differences in deaths due to breast cancer or other causes.

The cumulative incidence of death from any cause among the 1851 women was 53.5 percent at 20 years (Fig. 4A); 40.4 percent of the women died after a recurrence or a diagnosis of cancer in the contralateral breast, and 13.2 percent died without evidence of breast cancer. Among the women with negative nodes, the cumulative incidence of death from any cause was 47.7 percent (Fig. 4B); 32.0 percent of the women died after a treatment failure or a diagnosis of cancer in the contralateral breast, and 15.6 percent died in the absence of such an event. Among the women with positive nodes, the cumulative incidence of death was 63.3 percent (Fig. 4C); 54.2 percent of the women died after a breast-cancer–related event, and 9.1 percent died in the absence of such an event.

DISCUSSION

After 20 years of follow-up, we found no significant difference in overall survival among women who underwent mastectomy and those who underwent lumpectomy with or without postoperative breast irradiation. The results of other studies support our finding that there was no decrease in overall survival after mastectomy compared with lumpectomy with or without postoperative breast irradiation.
breast-conserving surgery.\textsuperscript{13,17} The 1995 meta-analysis reported by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG),\textsuperscript{12} which included trials of breast conservation and axillary dissection with and without radiation therapy and trials that compared mastectomy with breast-conserving surgery plus radiotherapy, found no significant difference in overall mortality at 10 years. The results were similar regardless of whether data from the NSABP B-06 trial were included. A more recent meta-analysis by the EBCTCG,\textsuperscript{18} which estimated the proportional effects of radiation therapy on cause-specific mortality among women treated with breast-conserving surgery and axillary dissection, showed a marginally significant reduction in the risk of death due to breast cancer after lumpectomy and irradiation ($P=0.04$). This reduction was offset by an increase in the risk of death from causes other than breast cancer ($P=0.05$). With regard to cause-specific mortality, our results are in accordance with those of the recent meta-analysis.\textsuperscript{18} There has been concern that postoperative breast irradiation may increase the risk of cancer in the contralateral breast. Such an increase was not observed in our trial or in a recent retrospective study.\textsuperscript{19}

Although breast-conserving surgery has generally been accepted as a treatment for invasive breast cancer, there is less agreement about whether lumpectomy as performed by our group or quadrantectomy as performed by the Milan group\textsuperscript{13} is preferable. The two operations are different in both magnitude and biologic concept. We used a short, curvilinear or transverse incision to remove the tumor and sufficient normal tissue to ensure that the inked margins of the resected specimen were free of tumor.\textsuperscript{20} An en bloc dissection was not carried out, not even for tumors in the upper outer quadrant of the breast, and no skin, pectoral fascia, or muscle was removed. Nodal dissection was limited to the lower two levels of the axilla. The procedure was performed in women with tumors that were 4 cm or less in diameter. In subsequent studies, women with tumors up to 5 cm in diameter were candidates for the procedure. Women of any age and with negative or positive axillary nodes were candidates, regardless of the location of the tumor in the breast and of the particular characteristics of the tumor.

A quadrantectomy, as initially described,\textsuperscript{21} was used for tumors that were 2 cm or less in diameter. With this procedure, a long radial incision was made, and the tumor was removed with a 2-to-3-cm cuff of normal breast tissue. Skin, pectoral fascia, and the pectoralis minor muscle were also removed. An en bloc dissection was used to remove lesions in the upper outer quadrant, and a total axillary dissection was performed. Because of the extent of the surgery, it is often not possible to obtain a satisfactory cosmetic result. Thus, although the quadrantectomy is a breast-conserving procedure, like the modified radical or simple mastectomy, it retains features of the Halsted approach. Lumpectomy, however, represents a complete departure from the Halsted procedure and the biologic principles regarding its use.\textsuperscript{22}

It would be inappropriate to choose a breast-conserving operation on the basis of a comparison of the

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Cumulative Incidence of Death from Any Cause, Death Following a Recurrence or a Diagnosis of Contralateral Breast Cancer, and Death in the Absence of a Recurrence or Contralateral Breast Cancer among All 1851 Women (Panel A), 1156 Women with Negative Axillary Nodes (Panel B), and 695 Women with Positive Axillary Nodes (Panel C).}
\end{figure}
recurrence rates in the current NSABP and in the study by Veronesi et al., reported elsewhere in this issue of the journal, because differences in the patient populations in the two trials, rather than in the extent of the operative procedure, might account for any difference in recurrence rates. In the quadrantectomy trial, all the women had tumors that were 2 cm or less in diameter, and more than 70 percent of the women had negative nodes, whereas in our trial, 45 percent of the women had tumors that were more than 2 cm in diameter, and nearly 40 percent had positive nodes.

Our findings at 20 years still show that lumpectomy and breast irradiation, as compared with lumpectomy alone, significantly decrease the incidence of a recurrence in the ipsilateral breast. Nevertheless, it has been argued that, if a wider margin of normal breast tissue surrounding the tumors had been removed, there would have been fewer ipsilateral recurrences. However, systemic therapy is now administered after lumpectomy, regardless of nodal status, to reduce the risk of distant metastases, and such therapy also reduces the rate of recurrent cancer in the ipsilateral breast. In the B-06 trial, only women with positive nodes received chemotherapy, and the regimen was less effective than current regimens. Thus, the incidence of recurrence is lower with current approaches. In NSABP trials conducted after B-06, the incidence of recurrent cancer in the ipsilateral breast among women with negative nodes who received systemic therapy in addition to radiation therapy was about 6 percent after more than 10 years of follow-up.

A substantial proportion of events in our study occurred after five years of follow-up. This finding supports the need for long-term follow-up. Our findings also indicate the need for information about the cause of death in clinical trials with long-term follow-up, particularly among women with negative nodes. Cumulative mortality at 20 years was nearly four times that at 5 years among the women with negative nodes in our study. That difference was related more to an increase in mortality from causes other than breast cancer than to an increase in mortality from breast cancer. Thus, with increasing follow-up, overall mortality becomes less indicative of mortality related to breast cancer.

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We are indebted to Carol Redmond, Sc.D., and her associates, who were responsible for all biostatistical aspects of this study until 1994; to Linda Gilarski for data management; to Cheryl Butch, R.N., for the review of medical records; to Tanya Sperock for editorial assistance; and to Mary Hof for assistance in the preparation of the manuscript.

APPENDIX

The following institutions and principal investigators participating in the National Surgical Adjuvant Breast and Bowel Project contributed to this study: Albany Regional Cancer Center, New York — T.J. Cunningham; Albert Einstein College of Medicine, New York — H. Volk; Baptist Medical Center, Oklahoma City — K.K. Boatman; Baylor University Medical Center, Waco, Tex. — L. Dragon; Billings Interhospital Oncology Project, Billings, Mont. — D.B. Myers; Boston University, Boston — P. Deckers; Bryn Mawr Hospital, Bryn Mawr, Pa. — T.G. Fraizer; Community Clinical Oncology Program, Billings Interhospital Project, Billings, Mont. — N. Hammond; Community Clinical Oncology Program, Central New York, Syracuse — K. Gale; Community Clinical Oncology Program, Midwest, Kansas City, Mo. — H.S. Hanson; City of Faith Medical and Research Center, Tulsa, Okla. — A.F. Hoge; City of Hope Medical Center, Duarte, Calif. — J. Terz; Cross Cancer Institute, Edmonton, Alta., Canada — S. 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REFERENCES

2. Fisher B, Bauer M, Margoles R, et al. Five-year results of a randomized...

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JOURNAL INDEX

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Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis
A Randomized Clinical Trial

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Context Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Interventions All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician.

Main Outcome Measures Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point.

Results Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy.

Conclusion Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Trial Registration clinicaltrials.gov Identifier: NCT00003855

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sentinel lymph nodes (SLNs) are histologically free of tumor, while ALND remains the standard of care for patients whose SLNs contain metastases.11

Cancer biology is much better understood now than it was when ALND was introduced. Biological factors may affect the predilection of some malignant cells to selectively invade lymph nodes rather than visceral organs, just as certain tumor types metastasize to certain organs and not others.12 Recognition of the complexity of tumor biology has changed cancer treatment, with more liberal use of systemic therapy to treat occult cancer cells wherever they may be in the body. Consequently, the decision to administer systemic therapy is influenced by a variety of patient- and tumor-related factors, with lymph node tumor status influencing13,14 but not necessarily dictating the use of chemotherapy.15-18 Other factors, such as early cancer detection by screening mammography, have led to earlier intervention in breast cancer, reducing the incidence of nodal metastases and even the number of tumor-involved lymph nodes.19

These evolving concepts have called into question the need for ALND.20,21 A variety of algorithms have been developed to help clinicians decide which patients would benefit from ALND.22-24 Review of Surveillance, Epidemiology, and End Results data has shown that the use of ALND for SLN metastases has decreased in recent years.25 No study has conclusively demonstrated a survival benefit or detriment for omitting ALND when metastatic breast cancer is identified by SLND. In the late 1990s, the American College of Surgeons Oncology Group designed and began the multicenter Z0011 trial. The primary aim of this study was to determine the effects of ALND on overall survival in patients with SLN metastases treated in the contemporary era with lumpectomy, adjuvant systemic therapy, and tangential-field radiation therapy.

METHODS
Patient Characteristics
This multicenter, randomized phase 3 trial was registered with the National Cancer Institute and approved by the institutional review boards of participating centers. All patients provided written informed consent. Adult women with histologically confirmed invasive breast carcinoma clinically 5 cm or less, no palpable adenopathy, and an SLN containing metastatic breast cancer documented by frozen section, touch preparation, or hematoxylin-eosin staining on permanent section were eligible for participation. Patients with metastases identified initially or solely with immunohistochemical staining were ineligible. Treatment with lumpectomy to negative margins (no tumor at ink) was required. Women were ineligible if they had 3 or more positive SLNs, matted nodes, or gross extranodal disease, or if they had received neoadjuvant hormonal therapy or chemotherapy.

Study Design and Treatment
Before randomization, all women underwent SLND and were stratified according to age (≤50 and >50 years), estrogen-receptor status, and tumor size (≤1 cm, >1 cm and ≤2 cm, or >2 cm). Eligible women were randomly assigned to ALND or no further axillary-specific intervention—specifically, no third-field nodal irradiation. ALND was defined as an anatomical level I and II dissection including at least 10 nodes. All women were to receive whole-breast opposing tangential-field radiation therapy. The use of adjuvant systemic therapy was determined by the treating physician and was not specified in the protocol.

Patients most commonly entered the study post-SLND following identification of metastases on final pathology report. However, of the 891 registered patients, 287 were registered pre-SLND and assigned to treatment after intraoperative documentation of SLN metastases. Patients in this group subsequently found to have 3 or more tumor-involved lymph nodes were included in the analysis. Patients were assessed for disease recurrence according to standard clinical practice. History and physical examination were performed every 6 months for the first 36 months and yearly thereafter. Annual mammography was required; other testing was based on symptoms and investigator preference.

Study End Points
The primary end point was overall survival, defined as the time from randomization until death from any cause. A short-term primary end point was occurrence of surgical morbidities. The study plan was to report surgical morbidities following the completion of accrual and prior to overall survival reporting after receiving permission from the data and safety monitoring committee. These morbidities have been reported.10

A secondary end point was disease-free survival, defined as the time from...
randomization to death or first documented recurrence of breast cancer. Breast cancer recurrence was categorized as locoregional disease (tumor in the breast or ipsilateral supraclavicular, subclavicular, internal mammary, or axillary nodes) or distant metastases. Disease-free survival and its components (locoregional disease and distant metastases) are reported instead of the protocol-specified secondary end point (eg, distant disease-free survival) to facilitate comparison with other studies.

**Statistical Analysis**
The primary end point was overall survival as a measure of noninferiority of no further axillary specified interventions (SLND-alone group) compared with the ALND group. Based on the literature at the time of study design, we hypothesized that overall survival was 80% at 5 years for optimally treated women with positive nodes.25-28 Clinical noninferiority was defined as the SLND-alone group having a 5-year survival of not less than 75% of that observed in the ALND group. Noninferiority of the SLND-alone treatment was also considered if the hazard ratio (HR) for mortality was less than 1.3 when compared with ALND. An estimated 500 deaths were needed for the study to have 90% power to confirm noninferiority of SLND alone compared with ALND, with the use of a 2-sided 90% confidence interval (CI) for the HR from a Cox regression model.29 Specifically, if the 90% CI for the HR was below 1.3, this would indicate that patients undergoing SLND alone do not have an acceptably worse overall survival than patients undergoing SLND plus ALND.

The use of a 2-sided 90% CI corresponds to a 1-sided significance level of .05. The enrollment of 1900 patients in 4 years with a minimum follow-up period of 5 years was initially planned. Four formal interim analyses and 1 final analysis were planned for overall survival, and the O’Brien-Flemming α-spending strategy was used to generate stopping boundaries for each planned analysis. The overall study significance was maintained at .05. However, none of the planned interim analyses were performed before the study was closed based on the recommendation of the data and safety monitoring committee. Because of this, a single terminal hypothesis test with an α of .05 is applied to the data, which makes it consistent with the planned overall significance level of .05 in the original study plan.

Ineligible patients were retained in all analyses (ie, both the intent-to-treat analyses and the treatment-received analyses). Kaplan-Meier survival curves for overall survival were compared by log-rank test. The unadjusted HR (and 90% CI) was calculated using a Cox regression analysis, and noninferiority P values are reported. As a secondary analysis, known prognostic factors including adjuvant treatment were included in the Cox regression model to generate an adjusted HR for overall survival (with a 90% CI and noninferiority P values). Disease-free survival was analyzed using Kaplan-Meier curves and univariable and multivariable Cox regression analyses with 95% CIs. The fact that there were only 94 deaths limited the number of variables that could be used in a multivariable model without affecting model stability. We created a base model that included the treatment group (SLND alone vs ALND), age (<50 vs >50 years), and whether the patient received adjuvant therapy (yes vs no) and added prognostic variables to this model individually. Only variables obtained on 90% or more of the patients were included in the multivariable analysis. Locoregional recurrence rates were compared with the Fisher exact test. Each analysis, other than analysis for the primary end point of overall survival, was performed with 2-sided P values, 5% significance, and a 95% CI; all analyses were performed using SAS release 9.1 (SAS Institute Inc, Cary, North Carolina).

**RESULTS**

**Patient Characteristics**
The first patient was enrolled in May 1999, and accrual closed in December 2004 based on a recommendation of the independent data and safety monitoring committee because of concerns regarding the extremely low mortality rate. Even if the trial had accrued the targeted 1900 patients, it would have taken more than 20 years of follow-up to observe 500 deaths at the realized event rate. At the time of the decision to terminate the study there had been no formal analysis comparing the survival experience between the 2 groups; the decision was based solely on the ob-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ALND (n = 420)</th>
<th>SLND Alone (n = 436)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), y</td>
<td>59 (24-92)</td>
<td>54 (25-90)</td>
</tr>
<tr>
<td>Clinical T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>284 (67.9)</td>
<td>303 (70.6)</td>
</tr>
<tr>
<td>T2</td>
<td>134 (32.1)</td>
<td>126 (29.4)</td>
</tr>
<tr>
<td>Tumor size, median (range), cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7 (0.4-7.0)</td>
<td>1.6 (0.0-5.0)</td>
<td></td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>129 (40.6)</td>
<td>113 (26.2)</td>
</tr>
<tr>
<td>No</td>
<td>189 (59.4)</td>
<td>208 (73.8)</td>
</tr>
<tr>
<td>Modified Bloom-Richardson score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>71 (22.0)</td>
<td>81 (25.6)</td>
</tr>
<tr>
<td>2</td>
<td>158 (46.9)</td>
<td>148 (46.8)</td>
</tr>
<tr>
<td>3</td>
<td>94 (29.1)</td>
<td>87 (27.5)</td>
</tr>
<tr>
<td>Tumor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal</td>
<td>344 (82.7)</td>
<td>356 (84.0)</td>
</tr>
<tr>
<td>Other</td>
<td>27 (6.5)</td>
<td>36 (8.5)</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4 (1.2)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>1</td>
<td>199 (52.0)</td>
<td>266 (59.1)</td>
</tr>
<tr>
<td>2</td>
<td>68 (19.8)</td>
<td>76 (18.3)</td>
</tr>
<tr>
<td>3</td>
<td>25 (7.3)</td>
<td>11 (2.7)</td>
</tr>
<tr>
<td>≥4</td>
<td>47 (13.7)</td>
<td>4 (1.0)</td>
</tr>
</tbody>
</table>

**Abbreviations**: ALND, axillary lymph node dissection; ER, estrogen receptor; LVI, lymphovascular invasion; PR, progesterone receptor; SLND, sentinel lymph node dissection.
ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Figure 2. Survival of the ALND Group Compared With SLND-Alone Group

<table>
<thead>
<tr>
<th>Years</th>
<th>ALND</th>
<th>SLND alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>420</td>
<td>436</td>
</tr>
<tr>
<td>1</td>
<td>408</td>
<td>421</td>
</tr>
<tr>
<td>2</td>
<td>398</td>
<td>411</td>
</tr>
<tr>
<td>3</td>
<td>391</td>
<td>403</td>
</tr>
<tr>
<td>4</td>
<td>378</td>
<td>387</td>
</tr>
<tr>
<td>5</td>
<td>313</td>
<td>326</td>
</tr>
<tr>
<td>6</td>
<td>222</td>
<td>226</td>
</tr>
<tr>
<td>7</td>
<td>141</td>
<td>142</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>74</td>
</tr>
</tbody>
</table>

No. at risk
ALND 420 408 398 391 378 313 222 141 74
SLND alone 436 421 411 403 387 326 226 142 74

Log-rank P = .25

Table 1

<table>
<thead>
<tr>
<th>ALND</th>
<th>SLND alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>137</td>
<td>365</td>
</tr>
<tr>
<td>37.5%</td>
<td>35.7%</td>
</tr>
</tbody>
</table>

The 5-year disease-free survival was 92.5% (95% CI, 90.0%-95.1%) in the ALND group and 91.8% (95% CI, 89.1%-94.5%) in the ALND group. This was substantially greater than the 80% anticipated at protocol design. The HR for overall survival adjusting for adjuvant therapy (chemotherapy, endocrine therapy, and/or radiation therapy) and age for the SLND-alone group compared with the ALND group was 0.87 (95% CI, 0.62-1.23). The adjusted HRs comparing the SLND-alone group with the ALND group in the other multivariable models ranged from 0.86 to 0.92 (TABLE 2), all similar to the unadjusted rate of 0.79. An exploratory analysis revealed that treatment with ALND vs SLND alone produced no statistically significant difference in outcome among patients grouped by receptor status of the primary tumor (ER+/PR+ or ER-/PR-).

**Disease-Free Survival**

Disease-free survival (Figure 2) did not differ significantly between treatment groups. The 5-year disease-free survival was 83.9% (95% CI, 80.2%-87.9%) for the SLND-alone group and 82.2% (95% CI, 78.3%-86.3%) for the ALND group (P = .14). The unadjusted HR comparing the SLND-alone group with the ALND group was 0.82 (95% CI, 0.58-1.17), and the HR adjusted for adjuvant treatment and age was 0.88 (95% CI, 0.62-1.25) (TABLE 3). The adjusted HRs comparing the SLND-alone group with the ALND group in the other multivariable models ranged from 0.86 to 0.92 (TABLE 4), all similar to the unadjusted rate of 0.79. An exploratory analysis revealed that treatment with ALND vs SLND alone produced no statistically significant difference in outcome among patients grouped by receptor status of the primary tumor (ER+/PR+ or ER-/PR-).
able models ranged from 0.84 to 0.89 (Table 3), all similar to the unadjusted rate of 0.82. Locoregional recurrence and its correlates have been previously reported. The 5-year rates of local recurrence were 1.6% (95% CI, 0.7%-3.3%) in the SLND-alone group and 3.1% (95% CI, 1.7%-5.2%) in the ALND group (P=.11). Locoregional recurrence-free survival at 5 years was 96.7% (95% CI, 94.7%-98.6%) in the SLND-alone group and 95.7% (95% CI, 93.6%-97.9%) in the ALND group (P=.28).

**Surgical Morbidities**

Paresthesias, shoulder pain, weakness, lymphedema, and axillary web syndrome are recognized morbidities of ALND. As previously reported, the rate of wound infections, axillary seromas, and paresthesias among patients in the Z0011 trial was higher for the ALND group than for the SLND-alone group (70% vs 25%, P<.001). Lymphedema in the ALND group was significantly more common by subjective report (P<.001) and also tended to be higher by objective assessment of arm circumference. These findings are in accordance with other randomized comparisons of SLND with vs without ALND.

**COMMENT**

In the American College of Surgeons Oncology Group Z0011 randomized trial, ALND did not significantly affect overall or disease-free survival of patients with clinical T1-T2 breast cancer and a positive SLN who were treated with lumpectomy, adjuvant systemic therapy, and tangential-field whole-breast radiation therapy. These survival findings are consistent with those of the National Surgical Adjuvant Breast and Bowel Project B04 trial, in which women with clinically negative nodes were randomized to treatment by radical mastectomy, total mastectomy plus nodal irradiation, or total mastectomy with delayed ALND if nodal recurrence was observed. Initially and at each interim analysis for up to 25 years of follow-up, no statistically significant survival differences were observed between any of the groups. For patients treated in the modern era, the relevance of the B04 study, which included patients with larger tumors undergoing mastectomy without adjuvant systemic therapy, is uncertain, because an axillary recurrence after SLND in patients with a lower risk of death from distant disease might negatively affect survival. The findings from Z0011 document the high rate of locoregional control achieved with modern multimodality therapy, even without ALND.

In contrast to B04, in which about 40% of patients in the radical mastectomy group were node-positive and the same number in the total mastectomy group were assumed to be node-positive and 5-year overall survival was only about 60%, 100% of patients in Z0011 had nodal involvement; yet the 5-year over-

![Figure 3. Hazard Ratios Comparing Overall Survival Between the ALND and SLND-Alone Groups](image)

Blue dashed line at hazard ratio=1.3 indicates non-inferiority margin, blue-tinted region to the left of hazard ratio=1.3 indicates values for which SLND alone would be considered noninferior to SLND plus ALND. ALND indicates axillary lymph node dissection; CI, confidence interval; SLND, sentinel lymph node dissection.

### Table 2. Adjusted Hazard Ratios for Overall Survival Comparing SLND-Alone vs ALND Groups

<table>
<thead>
<tr>
<th>Model Variables</th>
<th>No.</th>
<th>Adjusted HR (90% CI)</th>
<th>Noninferiority P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (SLND alone vs ALND), age (≤50 vs &gt;50 y), adjuvantly treated (yes vs no)</td>
<td>839 92</td>
<td>0.87 (0.62-1.23)</td>
<td>.03</td>
</tr>
<tr>
<td>Variables in row 1 + primary tumor size (per 1 cm, continuous)</td>
<td>818 92</td>
<td>0.89 (0.62-1.25)</td>
<td>.03</td>
</tr>
<tr>
<td>Variables in row 1 + estrogen receptor status (negative vs positive)</td>
<td>778 87</td>
<td>0.92 (0.64-1.30)</td>
<td>.05</td>
</tr>
<tr>
<td>Variables in row 1 + modified Bloom-Richardson score (1 vs 2 vs 3)</td>
<td>839 92</td>
<td>0.86 (0.61-1.21)</td>
<td>.02</td>
</tr>
<tr>
<td>Variables in row 1 + tumor type (ductal vs lobular vs other)</td>
<td>839 92</td>
<td>0.88 (0.63-1.25)</td>
<td>.03</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLND, sentinel lymph node dissection.

### Table 3. Adjusted Hazard Ratios for Disease-Free Survival Comparing SLND-Alone vs ALND Groups

<table>
<thead>
<tr>
<th>Model Variables</th>
<th>No.</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group (SLND alone vs ALND), age (≤50 vs &gt;50 y), adjuvantly treated (yes vs no)</td>
<td>839 127</td>
<td>0.88 (0.62-1.25)</td>
<td>.47</td>
</tr>
<tr>
<td>Variables in row 1 + primary tumor size (per 1 cm, continuous)</td>
<td>818 125</td>
<td>0.86 (0.60-1.22)</td>
<td>.40</td>
</tr>
<tr>
<td>Variables in row 1 + estrogen receptor status (negative vs positive)</td>
<td>778 117</td>
<td>0.84 (0.58-1.20)</td>
<td>.33</td>
</tr>
<tr>
<td>Variables in row 1 + modified Bloom-Richardson score (1 vs 2 vs 3)</td>
<td>839 127</td>
<td>0.87 (0.61-1.23)</td>
<td>.43</td>
</tr>
<tr>
<td>Variables in row 1 + tumor type (ductal vs lobular vs other)</td>
<td>839 127</td>
<td>0.89 (0.62-1.27)</td>
<td>.52</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALND, axillary lymph node dissection; CI, confidence interval; HR, hazard ratio; SLND, sentinel lymph node dissection.

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all survival was more than 90%. Furthermore, a 19% rate of axillary first failure was observed in B04, whereas the axillary nodal recurrence rate was only 0.9% in the SLND-alone group in Z0011. The excellent local and distant outcomes in this study highlight the effects of multiple changes in breast cancer management during the interval between the 2 studies. These changes, which include improved imaging, more detailed pathological evaluation, improved planning of surgical and radiation approaches, and more effective systemic therapy, emphasize the need for ongoing reevaluation of “standard” local therapy.

The well-documented morbidity from ALND has led other investigators to explore alternative methods of axillary treatment in patients with clinically negative nodes, including radiation, systemic therapy, and axillary observation. These have consistently demonstrated low axillary failure rates, with no significant differences in survival.35,36 The International Breast Cancer Study Group trial of ALND vs observation is noteworthy because more than half of the patients did not receive breast or axillary radiotherapy. In women 60 years and older receiving adjuvant tamoxifen but no axillary treatment, the rate of axillary recurrence was only 3%, and overall survival was 73% at a median follow-up of 6.6 years.30

The low rates of locoregional recurrence at 5 years and the nearly identical overall and disease-free survival between treatment groups in Z0011 would suggest that differences in survival between study groups are unlikely to emerge with longer follow-up, because ALND would only affect survival by virtue of improved locoregional control. In the Early Breast Cancer Trialists’ Collaborative Group overview, statistically significant survival differences between treatments at 15 years were seen only when differences in locoregional recurrence between treatments were greater than 10% at 5 years.37 Axillary recurrence is usually an early event, occurring at a median of 14.8 months in B04; in that trial, only 7 of 68 axillary recurrences occurred more than 5 years after study entry.38 Greco et al37 reported that median time to axillary recurrence was 30.6 months for 401 patients who underwent breast-conserving procedures and radiation therapy with no axillary surgery. Recent reports of long-term follow-up in randomized trials confirm these findings.38,39 Because the total locoregional recurrence rate in the Z0011 SLND-alone group at 5 years is only 2.5% compared with 3.6% in the ALND group, it is unlikely that further follow-up would result in enough additional recurrences to generate a clinically meaningful survival difference between groups. The absolute difference in 5-year overall survival between the treatment groups in Z0011 is 0.7%, numerically favoring the SLND-alone group. The HR for overall survival comparing the SLND-alone group with the ALND group was 0.79 (90% CI, 0.56-1.10). The worst HR (1.10) is less than 1.3, which was hypothesized as the inferiority margin threshold. In essence, this means that the 5-year overall survival for the SLND-alone group might be as low as 90.3% if the true 5-year overall survival for the ALND group was 91.8% and the HR as high as 1.10. Most importantly, there is no suggestion that rates of locoregional recurrence, the mechanism by which variations in local therapy result in survival differences, differ between groups to the extent needed to produce survival differences or are likely to do so in the future. Taken together, this suggests that contemporary women may sustain the morbidity of ALND without any meaningful improvement in survival rates. Limitations of the study, such as failure to achieve target accrual and possible randomization imbalance favoring the SLND-alone group, must be considered. However, even in high-risk women (ER−/PR−) in Z0011, preliminary analysis suggests no effect of elimination of ALND on survival.

Despite limitations of the Z0011 trial, its findings could have important implications for clinical practice. Examination of the regional nodes with SLND can identify hematoxylin–eosin–detected metastases that would indicate a higher risk for systemic disease and the need for systemic therapy to reduce that risk. Results from Z0011 indicate that women with a positive SLN and clinical T1-T2 tumors undergoing lumpectomy with radiation therapy followed by systemic therapy do not benefit from the addition of ALND in terms of local control, disease-free survival, or overall survival. The only additional information gained from ALND is the number of nodes containing metastases. This prognostic information is unlikely to change systemic therapy decisions and is obtained at the cost of a significant increase in morbidity.10 The only rationale for ALND in these patients would be if the finding of additional nodal metastases would result in changes in systemic therapy. Because current guidelines do not support differences in adjuvant systemic therapy based on the number of positive lymph nodes, except in some uncommon select subgroups,40 ALND does not appear to be warranted in this patient population.

The Z0011 trial did not include patients undergoing mastectomy, those undergoing lumpectomy without radiotherapy, those treated with partial-breast irradiation, those receiving neoadjuvant therapy, and those receiving whole-breast irradiation in the prone position, in which the low axilla is not treated. In those patients, ALND remains standard practice when SLND identifies a positive SLN. However, ALND may no longer be justified for women who have clinical T1-T2 breast cancer and hematoxylin–eosin–detected metastasis in the SLN and who are treated with breast-conserving surgery, whole-breast irradiation, and adjuvant systemic therapy. Implementation of this practice change would improve clinical outcomes in thousands of women each year by reducing the complications associated with ALND and improving quality of life with no diminution in survival.

Author Contributions: Dr Giuliano 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: Giuliano.
SENTINEL NODE DISSECTION IN INVASIVE BREAST CANCER

Acquisition of data: Giuliano, Beitsch, Whitworth, Blumencranz, Leitch, Saha, Morrow
Analysis and interpretation of data: Giuliano, Hunt, Ballman, Whitworth, Leitch, McColl, Morrow
Drafting of the manuscript: Giuliano, Ballman, Beitsch, Whitworth, Morrow
Critical revision of the manuscript for important intellectual content: Giuliano, Hunt, Ballman, Beitsch, Whitworth, Blumencranz, Leitch, Saha, Morrow
Statistical analysis: Ballman, McColl
Administrative, technical, or material support: Giuliano, Hunt, Whitworth, Leitch
Study supervision: Giuliano, Whitworth
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This study was supported by National Cancer Institute grant U10 CA 76001 to the American College of Surgeons Oncology Group (ACOSOG).

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REFERENCES

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