Effect of Margin Status on Local Recurrence After Breast Conservation and Radiation Therapy for Ductal Carcinoma In Situ

Clive Dunne, John P. Burke, Monica Morrow, and Malcolm R. Kell

ABSTRACT

Purpose
There is no consensus on what constitutes an adequate surgical margin in patients receiving breast-conserving surgery (BCS) and postoperative radiation therapy (RT) for ductal carcinoma in situ (DCIS). Inadequate margins may result in high local recurrence, and excessively large resections may lead to poor cosmetic outcome without oncologic benefit.

Methods
A comprehensive search for published trials that examined outcomes after adjuvant RT after BCS for DCIS was performed using MEDLINE and cross referencing available data. Reviews of each study were conducted, and data were extracted. Primary outcome was ipsilateral breast tumor recurrence (IBTR) related to surgical margins.

Results
A total of 4,660 patients were identified from trials examining BCS and RT for DCIS. Patients with negative margins were significantly less likely to experience recurrence than patients with positive margins after RT (odds ratio [OR] = 0.36; 95% CI, 0.27 to 0.47). A negative margin significantly reduced the risk of IBTR when compared with a close (OR = 0.59; 95% CI, 0.42 to 0.83) or unknown margin (OR = 0.56; 95% CI, 0.36 to 0.87). When specific margin thresholds were examined, a 2-mm margin was superior to a margin less than 2 mm (OR = 0.53; 95% CI, 0.26 to 0.96); however, we saw no significant difference in the rate of IBTR with margins between 2 mm and more than 5 mm (OR = 1.51; 95% CI, 0.51 to 5.0; \( P > 0.05 \)).

Conclusion
Surgical margins negative for DCIS should be obtained after BCS for DCIS. A margin threshold of 2 mm seems to be as good as a larger margin when BCS for DCIS is combined with RT.

J Clin Oncol 27:1615-1620. © 2009 by American Society of Clinical Oncology

INTRODUCTION

As a consequence of population-based screening and the increased use of surveillance mammography, ductal carcinoma in situ (DCIS) now accounts for 20% of newly diagnosed breast cancers.1 Multiple studies have examined the role of breast-conserving surgery (BCS) combined with radiation therapy (RT) in the setting of DCIS2-19 and have documented high rates of local control and low rates of disease-specific mortality. BCS with RT is now considered a standard treatment option in women with localized DCIS.20

It has become apparent that DCIS is primarily a unifocal disease,20 with only 8% of DCIS patients having a multifocal growth pattern with gaps more than 10 mm21 between foci of DCIS. However, even in patients who receive excision to negative margins, there is inevitably residual low-volume disease left in the breast, and the role of RT treatment after BCS is to sterilize this residual occult disease and thus reduce local recurrence. Recurrence rates for DCIS have been associated with the degree of tumor differentiation, histologic type, young patient age, and symptomatic presentation of DCIS,15,22-24 but the width of the tumor-free margin is considered the most important predictor of local recurrence in DCIS.25,26

The principles of BCS for DCIS dictate surgical margins free of disease, but margin status or an exact margin threshold is impossible to accurately assess intraoperatively. The absolute threshold width of disease-free margin required for local control remains a contentious issue,25 and the excision of large amounts of normal breast tissue is known to increase the likelihood of deformity of the breast and a poor cosmetic outcome.28
No prospective randomized data exist examining the optimum margin for BCS in DCIS. The intensity of the surgical debate on margins and local recurrence in DCIS has resulted in great confusion among patients about treatment choices and may cause patients to choose mastectomies and suffer morbidity as a result of unnecessarily radical surgery. To address this issue, we performed a meta-analysis of clinical trials that examined BCS with RT for the treatment of DCIS. In addition, we identified studies where BCS was performed and in which data on margin width were available to examine the impact of specific margin widths in an attempt to define the optimum width of disease-free margin.

**Identification of Studies**

We searched MEDLINE and EMBASE by entering the following in the searching algorithm: ductal carcinoma in situ AND (surgery OR radiation OR therapy OR DCIS) AND (clinical trial OR randomized controlled trial OR double-blind OR single-blind OR random OR randomized OR placebo). We also searched the Cochrane Central Register of Controlled Trials for randomized trials that compared RT with surgery alone for DCIS. We set English as a language restriction. The latest search was performed on January 31, 2007. Two authors (C.D. and M.R.K.) independently examined the title and abstract of citations, and the full texts of potentially eligible trials were obtained; disagreements were resolved by discussion.

**Eligibility Criteria**

Randomized and nonrandomized trials and prospective and retrospective series were examined on both screened and symptomatically presenting patients with DCIS. Only reports on patients with a primary diagnosis of DCIS who were treated with BCS and RT were included, and patients with a prior personal history of breast cancer were excluded. All studies in which a standardized surgery was performed were considered eligible regardless of margin threshold or RT dose. We included trials regardless of the exact RT schedule, as long as the schedule was standardized to the treatment arm. The primary end point of this meta-analysis was margin status as a risk factor for ipsilateral breast tumor recurrence (IBTR), not the effect of specific RT regimens. When results for the same group of patients were reported more than once, we included only the report with the longest follow-up (largest number of events) to avoid duplication of information. When two studies reported on a group of patients at the same institution within an overlapping time period, the study with the shortest follow-up period was excluded. Studies where the margin threshold was not stated were excluded; likewise, studies where the data could not be accurately extracted were excluded.

**Data Extraction and Outcomes**

We recorded the following information regarding each eligible trial: authors’ names, journal, year of publication, and study design items (including whether there was a description of the mode of random assignment, allocation concealment, number of withdrawals per arm, and blinding). We recorded the following information from both arms of each eligible trial: the number of patients randomly assigned to treatment and analyzed per arm, median age, following information from both arms of each eligible trial: the number of patients at the same institution within an overlapping time period, the study to avoid duplication of information. When two studies reported on a group of patients were reported more than once, we included only the report with the longest follow-up (largest number of events) to avoid duplication of information. When two studies reported on a group of patients at the same institution within an overlapping time period, the study with the shortest follow-up period was excluded. Studies where the margin threshold was not stated were excluded; likewise, studies where the data could not be accurately extracted were excluded.

**Statistical Analysis**

For IBTR in each study, we estimated the odds ratio (OR) of the simple proportions of events, with its variance and 95% CI. In studies that did not provide explicit accounting of the numbers of events for each arm, this was

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Study Duration</th>
<th>Country</th>
<th>Median Age (years)</th>
<th>Median Follow-Up Time (months)</th>
<th>No. of Patients Analyzed</th>
<th>Radiotherapy</th>
<th>Radiotherapy Boost</th>
<th>Boost Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bornstein et al^4^</td>
<td>1991</td>
<td>1976-1985</td>
<td>US</td>
<td>49</td>
<td>80.4</td>
<td>38</td>
<td>46</td>
<td>100</td>
<td>18</td>
</tr>
<tr>
<td>Cutuli et al^5^</td>
<td>1992</td>
<td>1975-1987</td>
<td>France</td>
<td>49</td>
<td>55.2</td>
<td>34</td>
<td>46-54</td>
<td>94</td>
<td>8</td>
</tr>
<tr>
<td>Catalotti et al^5^</td>
<td>1992</td>
<td>1968-1990</td>
<td>Italy</td>
<td>54</td>
<td>94</td>
<td>36</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kuske et al^7^</td>
<td>1993</td>
<td>1979-1987</td>
<td>US</td>
<td>55</td>
<td>48</td>
<td>75</td>
<td>50</td>
<td>75</td>
<td>6-8</td>
</tr>
<tr>
<td>Fisher et al^10^</td>
<td>1995</td>
<td>1985-1990</td>
<td>NSABP B-17</td>
<td>Grouped</td>
<td>60</td>
<td>299</td>
<td>50</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Solin et al^15^</td>
<td>1996</td>
<td>1967-1985</td>
<td>Multi-institution EU and US</td>
<td>50</td>
<td>123.6</td>
<td>270</td>
<td>50</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>Boyages et al^11^</td>
<td>1999</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kestin et al^13^</td>
<td>2000</td>
<td>1980-1993</td>
<td>US</td>
<td>Grouped</td>
<td>86.4</td>
<td>132</td>
<td>50</td>
<td>93</td>
<td>10.4</td>
</tr>
<tr>
<td>Cutuli et al^14^</td>
<td>2001</td>
<td>1985-1992</td>
<td>France</td>
<td>53.2</td>
<td>91</td>
<td>255</td>
<td>50</td>
<td>90</td>
<td>8-14</td>
</tr>
<tr>
<td>Solin et al^2^</td>
<td>2001</td>
<td>1973-1990</td>
<td>Multi-institution EU and US</td>
<td>51</td>
<td>112.8</td>
<td>422</td>
<td>50</td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>Vicini et al^22^</td>
<td>2001</td>
<td>1980-1993</td>
<td>US</td>
<td>Grouped</td>
<td>86.4</td>
<td>106</td>
<td>45</td>
<td>95</td>
<td>15.4</td>
</tr>
<tr>
<td>Cutuli et al^15^</td>
<td>2002</td>
<td>1985-1995</td>
<td>France</td>
<td>53.7</td>
<td>84</td>
<td>515</td>
<td>45</td>
<td>80</td>
<td>10-20</td>
</tr>
<tr>
<td>Solin et al^17^</td>
<td>2005</td>
<td>1973-1995</td>
<td>Multi-institution EU and US</td>
<td>53</td>
<td>102</td>
<td>1,003</td>
<td>50</td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>Sahoo et al^18^</td>
<td>2005</td>
<td>1986-2000</td>
<td>US</td>
<td>Grouped</td>
<td>63</td>
<td>103</td>
<td>46</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>Bijker et al^23^</td>
<td>2006</td>
<td>1986-1996</td>
<td>EORTC</td>
<td>57</td>
<td>126</td>
<td>507</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: US, United States; NA, not available; NSABP, National Surgical Adjuvant Breast and Bowel Project; EU, European Union; EORTC, European Organisation for Research and Treatment of Cancer.
Heterogeneity between the ORs for the same outcome between studies was assessed by use of the χ²-based Q statistic. Data were then combined across studies by the use of general variance methods with fixed and random effects models. To assess specific margin thresholds, data were pooled from combined randomized and nonrandomized studies of treatment arms when a specific margin could be identified in relation to IBTR. These were then divided into groups according to individual margin widths, and the OR was calculated from percentages at study end point for IBTR or from other information available in the publication.

Analyses were conducted using Statadirect version 2.5.6 (Statadirect Ltd, Chesire, United Kingdom) and SPSS version 12.0 (SPSS, Inc, Chicago, IL). All statistical tests were two tailed.

### RESULTS

#### Eligible Studies

We identified 49 potentially eligible studies that examined BCS with RT for DCIS; 27 studies were excluded from the meta-analysis (Fig 1). Three additional ongoing trials for which no peer-reviewed reports have been published were also excluded, resulting in 22 eligible trials, as shown in Table 1.2-14,16-19,29-33 All 22 trials enrolled patients between 1967 and 2003, and seven of the 22 trials were multicenter trials.2,9,14,16,17,30,33

A total of 4,660 patients for whom outcome data were measured were identified; 806 of these patients were identified from randomized controlled trials. The mean patient age in the studies examined ranged between 48 years and 57 years, and all trials included both premenopausal and postmenopausal patients.

#### Margin Status

The median time to IBTR was 60 months (interquartile range, 47.5 to 78 months). In the initial meta-analysis, we examined the available data on IBTR for differing margin status when compared with a negative margin. The definition of a negative margin used in each trial was used, with negative margins ranging from tumor not touching the ink to 10 mm. We used a random effects analysis to investigate differences in the primary outcome of IBTR. We found a 64% reduction in the risk of recurrence in patients with a negative margin after BCS compared with patients with positive margins (OR = 0.36; 95% CI, 0.27 to 0.47; Fig 2A).

---

**Fig 1.** Improving the quality of reports of meta-analyses of randomized controlled trials; the Quality of Reporting of Meta-Analyses (QUOROM) statement flow diagram.

**Fig 2.** Meta-analysis for the primary outcome of ipsilateral breast tumor recurrence after breast-conserving surgery followed by radiation therapy for ductal carcinoma in situ. In each panel, each study is shown by the point estimate of the odds ratio (OR; square proportional to the weight of each study) and 95% CI for the OR (extending lines); the combined ORs and 95% CIs by random effects calculations are shown by diamonds. (A) Negative versus positive margins (n = 2,682; P < .01; test for heterogeneity, Q = 20.7; df = 12; P = .064; I² = 42.2%). Arrow indicates that 95% CI extends beyond the depicted range.
We then examined the trial data set for differences in IBTR between patients with negative and close margins (close margin was defined as between the study margin threshold and positive and ranged from < 1 to < 5 mm); the risk of recurrence was reduced with a negative compared with a close margin (OR = 0.59; 95% CI, 0.42 to 0.83; Fig 2B). In addition, a negative margin significantly reduced the risk of IBTR compared with an unknown margin (OR = 0.56; 95% CI, 0.36 to 0.87; Fig 2C).

**Specific Margin Thresholds**

In further analysis, we compared the rate of IBTR in patients with close and positive margins. A close margin significantly reduced the risk of IBTR compared with a positive margin (OR = 0.43; 95% CI, 0.24 to 0.77; Fig 3). To help define an optimum margin threshold, we extracted data on IBTR for separate margin widths. Rates of IBTR ranged from 3.9% in patients with margins of 5 mm to greater than 9.4% in patients with tumor not touching ink. Compared with a margin of 5 mm or greater, no cells on the ink (OR = 2.56; 95% CI, 1.1 to 7.3; P < .05) and margins of 1 mm (OR = 2.89; 95% CI, 1.26 to 8.1; P < .05) were associated with a significantly higher risk of IBTR. However, when a 5-mm or greater margin was compared with a margin of 2 mm, no significant difference in the risk of IBTR was observed (OR = 1.51; 95% CI, 0.51 to 5.04; P > .05; Table 2). When specific margin thresholds were examined, a 2-mm margin was found to be superior to a margin less than 2 mm (OR = 0.53; 95% CI, 0.26 to 0.96; P < .05).

**Potential Bias**

The populations were evenly distributed by age, method of detection, and receptor status. Patient selection criteria for BCS and RT as opposed to mastectomy were poorly defined beyond localized DCIS and may have differed between centers and time periods. Even in the randomized trials, the extent of margin sampling to declare a margin negative was not clearly defined, and some studies did not define how the margin was measured. Finally, there was variation in the RT treatments used in terms of both dose and the use of a boost. It is possible that the impact of margin status on the risk of IBTR varies with the dose of RT used, and this could not be assessed in our analysis. In addition, it is possible that inclusion of the six trials for which data could not be extracted may have changed the results.

**Table 2. Optimum Margin Threshold for DCIS Resection (n = 2,514)**

<table>
<thead>
<tr>
<th>Margin Width</th>
<th>No. of Patients</th>
<th>% of Patients With IBTR</th>
<th>Relapse v &gt; 5 mm</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cells on ink</td>
<td>914</td>
<td>9.4</td>
<td>2.56</td>
<td>1.1 to 7.3</td>
<td>&lt; .05</td>
<td></td>
</tr>
<tr>
<td>1-mm margin</td>
<td>1,239</td>
<td>10.4</td>
<td>2.89</td>
<td>1.3 to 8.1</td>
<td>&lt; .05</td>
<td></td>
</tr>
<tr>
<td>2-mm margin</td>
<td>207</td>
<td>5.8</td>
<td>1.51</td>
<td>0.51 to 5.0</td>
<td>&gt; .05</td>
<td></td>
</tr>
<tr>
<td>≥ 5-mm margin</td>
<td>154</td>
<td>3.9</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DCIS, ductal carcinoma in situ; IBTR, ipsilateral breast tumor recurrence; OR, odds ratio.

We found a significant difference in the rate of IBTR between patients who had a negative versus a positive margin after BCS and RT for DCIS in a meta-analysis including 4,660 patients. Higher rates of IBTR were observed with margins less than 2 mm compared with larger negative margins. However, a further decrease in local recurrence was not observed when margins of 2 mm or more were compared with margins of 5 mm or greater.

Wide local excision with a negative margin has been accepted as the standard of care in women with unifocal DCIS, but there is no consensus on what constitutes a negative margin. In a recent survey of 1,137 RT oncologists, 45.9% of North American respondents and 27.6% of Europeans defined a negative margin as tumor cells not touching an inked surface. In almost all studies, positive margins are associated with an increased risk of local recurrence, although the magnitude of the increase is variable. Beyond the definition of tumor touching an inked surface as a positive margin, there is little consensus on the precise margin width necessary to maintain local control.

However, the retrospective studies from the Silverstein group demonstrate a strong relationship between margin width and local control. In a group of 260 patients treated with excision and RT, after a median follow-up time of 105 months, local recurrence was observed in 30% of patients with margins of 1 mm or less, 17% of patients with margins of 1 to 9 mm, and only 2% of patients with margins of 10 mm or greater. In contrast, in 418 patients treated at multiple institutions and observed for a median of 9.4 years, Solin et al observed a 10-year rate of local recurrence rate of 7% for patients with close margins (defined as within 1 to 3 mm) compared with 9% for patients with negative margins. These results are similar to what is seen in invasive cancer, where a linear relationship between margin width and local control is observed. There is no standard method of margin processing, so variability in sampling may account for some of the observed differences between studies. In addition, most studies have not considered the amount of DCIS in proximity to a margin. It is likely that
large amounts of DCIS approaching the margin surface are predictive of a heavier tumor burden in the remaining breast tissue than low-volume DCIS near the margin, a finding that has been observed in invasive carcinoma.48

Postexcision mammography was used in some but not all of the studies included in this meta-analysis, potentially biasing the results. Patients shown to have residual calcifications on postexcision mammmograms generally undergo re-excision for close margins, reducing the likelihood of local failure in patients with close margins not found to have residual calcifications. In addition, local recurrence is multifactorial in its etiology. Younger age is strongly correlated with an increased risk of local recurrence in both randomized9,39 and non-randomized studies.9 Retrospective studies suggest that more widely negative margins may mitigate some of this difference.90 Differences in the age distribution of patients among the studies included in this meta-analysis may have masked the benefits of a more widely negative margin. Similarly, lack of a uniform policy regarding a boost dose of RT across studies may have masked the benefits of a wider excision.

Despite these differences among studies, this meta-analysis clearly indicates that there is no rationale for the routine use of margins of 1 cm or more in patients treated with excision and RT. Large resections are clearly associated with a worsening of cosmetic outcome.41,42 The primary impetus for wide margins of resection in DCIS has been the potential to avoid RT in these patients. This approach has been primarily based on retrospective work by Silverstein et al25 suggesting that no benefit for RT is seen in patients excised to margins of 1 cm or greater independent of other characteristics of the DCIS. The validity of this hypothesis must be questioned because of failure to confirm low recurrence rates with this approach in two prospective studies,45,46 and this approach certainly should not be routinely applied to patients who will receive postoperative RT.

Our meta-analysis has some limitations. We found some evidence that small trials gave different results from larger trials, and publication bias cannot be totally excluded. The meta-analysis is based on available published results, and the use of updated individual patient data may further enhance the accuracy and reduce the uncertainty of the estimates.45,46 Another potential limitation is that the results of recently launched randomized studies were not available to include in the meta-analysis, and data from some published studies could not be extracted. However, given the accumulated evidence to date, the overall summary estimates for the primary outcomes that we include in the meta-analysis, and data from some published studies may further enhance the accuracy and reduce the uncertainty of the estimates.45,46

This study combined both data from randomized and non-randomized clinical trials as well as observational series to obtain as a large a cohort as possible. However, a meta-analysis not solely consisting of randomized controlled trials has the potential to be biased. It was not possible to verify all the individual patient data from each study, including age and histology of the lesions, which is another limitation because these are important risk factors for IBTR. Furthermore, the lack of a dose-response analysis for RT treatment limits the conclusions of this study because the favorable effect of a boost dose on the number of IBTRs has been demonstrated.48

A further potential bias is the variable duration of follow-up between studies. The median follow-up time of the included studies was 84 months (interquartile range, 63.15 to 102 months). Given this variability and the fact that simple proportions were used to quantify the risk of IBTR between patient cohorts, a potential source of error could be introduced. Furthermore, although our study selection criteria were stringent, there could be an element of selection bias imposed by their use.

Despite these caveats, this examination of a large international data set confirms that margins clear of disease are the gold standard for BCS followed by RT in the management of DCIS. This meta-analysis also demonstrates that 2-mm margins provide equivalent local control when compared with larger margins. Consequently, for unifocal DCIS, the evidence suggests that no further advantage in local control is obtained with the routine use of margins greater than 2 mm. It is important to emphasize that margin width is only one of several factors to consider when assessing the adequacy of surgical excision and should be used in conjunction with patient age, extent of disease in proximity to the margin, and the results of postexcision mammography when determining the need for re-excision. For example, a 65-year-old patient with a single microscopic focus of DCIS 1 mm from a margin and a postexcision mammogram that is free of calcifications is unlikely to derive benefit from a re-excision, whereas a 45-year-old patient with DCIS 2 mm from multiple margin surfaces over a 3-cm area would be considered for re-excision in our practices. It is likely that in the future, as the genes that govern the behavior of DCIS are characterized, molecular markers will play a greater role in defining the appropriate extent of surgical resection. In the interim, our data suggest that wide resections or conversion from BCS to mastectomy because of the inability to achieve a 1-cm margin are unnecessary in women treated with excision and RT.

The author(s) indicated no potential conflicts of interest.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Clive Dunne, Monica Morrow, Malcolm R. Kell
Financial support: Malcolm R. Kell
Administrative support: Malcolm R. Kell
Provision of study materials or patients: Malcolm R. Kell
Collection and assembly of data: Clive Dunne, Malcolm R. Kell
Data analysis and interpretation: Clive Dunne, John P. Burke, Monica Morrow, Malcolm R. Kell
Manuscript writing: John P. Burke, Monica Morrow, Malcolm R. Kell
Final approval of manuscript: Clive Dunne, John P. Burke, Monica Morrow, Malcolm R. Kell

REFERENCES


45. Stewart LA, Tierney JF: To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. Eval Health Prof 25:76-97, 2002

Dunne et al

1620 © 2009 by American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY