Breast-conserving surgery and radiotherapy for ductal carcinoma in situ of the breast: Meta-analysis of randomized controlled trials

Nickolas Myles, MD, PhD, FRCPC, St. Paul’s Hospital, Vancouver

ABSTRACT

The addition of radiotherapy (RT) to breast-conserving surgery (BCS) is common clinical practice in the treatment of patients with ductal carcinoma in situ (DCIS). The objective of this meta-analysis is to assess the cumulative evidence of the benefit of RT in this situation. The analysis includes all available English-language randomized controlled trials (RCT) comparing outcomes in patients who received BCS alone and those who received BCS and RT. Only 4 eligible RCTs were identified. Statistical analysis was carried out to compare relative and absolute risk of mortality, as well as ipsilateral, contralateral and total recurrence of either DCIS or invasive disease. Heterogeneity between trials was assessed. A reduction in total breast cancer recurrence was observed, with a pooled estimate of an absolute risk reduction of 10% (95% CI 7–14%) and a relative risk reduction (risk ratio) of 0.66 (95% CI 0.54–0.79) in the intervention arms of all 4 trials. There was significant intertrial heterogeneity in these estimates. The reduction was due primarily to a reduction in ipsilateral recurrence in patients treated with RT as well as BCS compared to those receiving BCS alone. There was no significant reduction in overall mortality between BCS and BCS+RT groups across all 4 trials, and no significant heterogeneity was observed. Potential sources of bias were identified that point to the need for further analysis and should inform future trials. Keywords: Breast cancer, ductal carcinoma in situ, breast-conserving surgery, radiotherapy, breast cancer recurrence, meta-analysis.

Ductal carcinoma in situ (DCIS) is a preinvasive cancer of the breast that is unable to spread and cause death, but may progress to life-threatening invasive carcinoma if left untreated. Current clinical practice considers DCIS as a precursor to invasive breast cancer and thus dictates that it be detected early through breast screening and treated aggressively to reduce the patient’s risk of developing invasive breast cancer. The clinical outcomes of untreated DCIS are unknown, as randomized clinical trials compare interventions against each other, and no baseline untreated population comparison is possible. Clinical outcomes of treated DCIS are excellent: observational studies refer to 98% 10-year breast cancer-specific survival. At the same time, invasive recurrence following initial diagnosis and treatment of DCIS are common and occur in up to one-third of patients over a 5- to 10-year followup period. Current clinical practice aims to eradicate DCIS by means of surgery and radiation therapy, and it has recently been proposed that these be accompanied by prophylactic antiestrogen systemic therapy. The efficiency of these interventions at reducing mortality in patients with DCIS remains unproven. Several large multicentre randomized controlled trials involving patients with DCIS have attempted to find out whether the addition of radiotherapy (RT) to breast conserving surgery (BCS) leads to improved long-term outcomes by reducing the risk of invasive breast cancer recurrence. The present meta-analysis searched for a comprehensive sample of such randomized controlled trials (RCTs), using prespecified inclusion and exclusion criteria to find out whether, in a population of women with DCIS who have undergone BCS, the addition of RT reduces mortality and recurrence of breast cancer compared to BCS alone.

MATERIAL AND METHODS

Only studies published in peer-reviewed journals were considered, and no grey literature search was performed. The PubMed search was conducted using the key words “DCIS and randomized control trials,” unrestricted as to age, sex, time and language of publication. All retrieved publications were screened for relevance using the following inclusion and exclusion criteria:

INCLUSION CRITERIA

To be included in the analysis, studies had to involve RCT design with any duration of followup. BCS could be lumpectomy or any local excision less than total mastectomy, and DCIS had to be confirmed by final pathology after surgical excision. Outcome measures had to be reported,
including ipsilateral and contralateral recurrence of DCIS or invasive carcinoma, deaths of any cause and/or breast-cancer deaths. Multiarm studies that at least partially addressed the research question were considered, even if the comparison of BCS alone vs BCS and RT was not the trial’s primary objective.

**EXCLUSION CRITERIA**

Observational studies, reviews and case reports were excluded from the analysis, as were studies that included invasive breast carcinomas, involved mastectomy, or did not specify the type of carcinoma. Studies were also excluded if full-text publication could not be obtained or required translation, and the abstract did not provide sufficient numeric data for extraction.

After the initial title screening and exclusion of irrelevant studies, relevant abstracts were rescreened in order to identify a comprehensive sample of RCTs that addressed the research question. Full-text papers based on selected relevant abstracts were retrieved and read. In cases where a trial was published several times, the publication containing the most recent update on followup and outcomes was used, though earlier publications of the same trials were used to extract background information and methodology. The data extraction protocol was based on the key elements for assessment of randomized trials with binary outcomes recommended by the CONSORT statement and included the following elements: study name; risk of bias (randomization method, allocation concealment, unknown data fractions); study size, including intervention arm and control arm numbers; and time to outcomes. Primary outcomes were: a) death in the intervention arm (total and/or breast cancer-related, whichever is declared); b) death from breast cancer in the control arm (total and/or breast cancer related, whichever is declared); c) invasive recurrence in the intervention arm (total, ipsilateral, contralateral); and d) invasive recurrence in the control arm (total, ipsilateral, contralateral). Secondary outcomes were: a) noninvasive recurrence (DCIS only) in the intervention arm (total, ipsilateral, contralateral); and b) noninvasive recurrence (DCIS only) in the intervention arm (total, ipsilateral, contralateral).

**ANALYSIS**

**Rationale and entry assumptions**

DCIS may recur as the same pathologic process (i.e. as DCIS) or as invasive cancer. Both can occur in the same breast, contralateral breast, or both. From a clinical and patient perspective, reduction in overall local recurrence may seem a more sensible measure of the success of RT in DCIS than reduction of only ipsilateral recurrence, as patients are directly interested in becoming breast-cancer-free, rather than cancer-free in only one breast. Of total local recurrences, invasive recurrences are considered potentially life-threatening and should thus, in the author’s opinion, be analyzed separately. Also, RT is a local treatment delivered to the particular area of the breast or total breast on one side, therefore the direct effect of RT should be also measured through assessment of ipsilateral local recurrences (DCIS or invasive carcinoma). Finally, and most importantly, mortality (overall and breast cancer-specific) should be compared between the intervention (RT+BCS) and comparator groups (BCS only).

**Statistical analysis**

Statistical analysis was carried out using Review Manager (RevMan) software v.5.1 and the methodologic approach taught at the Essential Medical Statistics module. The data on ipsilateral and contralateral invasive or DCIS recurrences and mortality in the intervention (RT+BCS) and control (BCS only) groups were analyzed as dichotomous data using the Mantel-Haenszel method with fixed-effect model, indicating the relative risk of recurrence as the effect measure. Absolute risk (risk difference) was also calculated for the same outcomes. Sensitivity analyses were carried out using the random-effect model. Statistical heterogeneity between individual studies was measured with the I² statistic and chi-square test for heterogeneity. Due to the small number of eligible studies, the p-value 0.1 was used to determine statistical significance (heterogeneity). Forest plots were constructed in order to visualize relative risk from the individual studies, the relative weight of each study, and the estimates of pooled relative or absolute risk (where appropriate).

Analysis of risk was prespecified and performed for: a) any kind of local recurrence (invasive, DCIS, ipsilateral, contralateral); b) total local invasive recurrence (ipsi- and contralateral); c) ipsilateral invasive recurrence; d) contralateral invasive recurrence; e) total local DCIS recurrence (ipsi- and contralateral); f) ipsilateral DCIS recurrence; and g) contralateral DCIS recurrence. Meta-regression analysis was considered, but not performed, due to the small number of published trials available for this meta-analysis (see Discussion).
RESULTS

Evidence search
Of the 108 studies identified in the initial search, only 5 were RCTs relevant to the research question. One study was unfortunately excluded due to language of publication and the unavailability of translation. Thus only 4 studies were included in the meta-analysis: The Swedish randomized trial – SweDCIS, the European Organization for Research and Treatment of Breast Cancer randomized phase 3 trial - EORTC 10853; the UK-ANZ trial, and the NSABP B17 trial. The search results are represented in Figure 1.

Meta-analysis
The results of the meta-analysis for each of the outcome measures are summarized as forest plots and represented in Figures 2 to 5.

Ipsilateral recurrence
The effect of RT on ipsilateral recurrence is represented in Tables 2a and 2b. There is a significant reduction of local ipsilateral DCIS recurrences (an effect significant in 3 out of 4 trials) and ipsilateral invasive recurrences in RT+BCS (intervention) group (showed consistently in all 4 trials). There was moderate heterogeneity in degree of reduction of DCIS recurrences (I^2=34%), but no significant heterogeneity in measurement of reduction of invasive ipsilateral recurrences between the studies (I^2=0%).

Contralateral recurrences
As was expected and shown in all 4 trials, there was no significant reduction in contralateral DCIS and invasive recurrences with RT+BCS vs BCS alone. There was a trend towards heterogeneity in the assessment of RT effect on contralateral DCIS recurrences between the studies. There was no apparent heterogeneity when contralateral invasive recurrences were considered (Figures 3a and 3b).

Overall (total) recurrence
This analysis considered reduction in DCIS recurrence, total invasive recurrence and combined overall recurrence in either breast (Figure 3a-d). It was performed in order to measure the contributory effect of a reduction in local recurrence against contralateral recurrence. This outcome was considered of high practical relevance, showing the contributory effect of ipsilateral DCIS and reduction in invasive recurrence on overall recurrence of breast cancer. There was a significant reduction in total DCIS recurrence in 3 of 4 trials, and significant heterogeneity was noted (Figure 4a). Also, there was a reduction in total invasive recurrence in the intervention arms of 2 of 4 trials, again with heterogeneity (Figure 4b). A reduction in total breast cancer recurrence was observed, with a pooled estimate of an absolute risk reduction of 10% (95% CI 7–14%), and a relative risk reduction (risk ratio) of 0.66 (95% CI 0.54–0.79) in the intervention arms of all 4 trials. There was significant intertrial heterogeneity in these estimates (Figure 4c and 4d).
Mortality
The most clinically important effectiveness measure of treatment in breast cancer is reduction in mortality in a given patient population. This meta-analysis found no significant reduction in overall mortality between intervention and comparator groups across all 4 trials, and no significant heterogeneity was observed between trials (Figure 5). Though breast cancer-specific mortality was initially considered in the analysis plan, it was later dropped due to lack of sufficient information in 2 of 4 trials.

Sensitivity analysis
Repeated analyses with all outcome groupings were performed using the random-effect meta-analysis model. All results were nearly identical (minor changes in a second digit points for all estimates) and are not displayed.

DISCUSSION
Radiotherapy of DCIS has become routine clinical practice. Although the secondary literature on the role of RT in management of DCIS is overwhelming, the primary highest level of evidence is currently based on only 4 published RCTs. The number of studies is surprisingly small given the entry assumption that there would be an abundance of evidence on this topic supporting clinical practice. The number of studies was too small to permit meta-regression analysis, and thus a number of important clinical questions remain unanswered, notably regarding factors associated with higher risk of local DCIS or invasive recurrence in some patients. This is one of the significant limitations of this meta-analysis. Any future analysis of clinical parameters (e.g. covariates) in the intervention and comparison cohorts of the published trials should aim to detect potential sources of bias and confounding, as some may be associated with increased risk of recurrence. These include the histopathologic features of DCIS (e.g. nuclear grade and comedonecrosis) and distance of DCIS from surgical margins. As randomization of patients into intervention and control groups did not consider these factors in any of the published trials, some subtle imbalance due to these factors may lead to biased estimates of the effectiveness of RT (i.e. either overestimation or underestimation of recurrence risk reduction due to the background pathology, rather than to RT alone). The Cochrane collaboration published a systematic review on the role of RT in management of DCIS that could be used as further guidance on the final status of research evidence, although it did not focus on mortality as a primary outcome.

DCIS is a systemic disease
Clinically and biologically, breast cancer is considered a systemic rather than local disease. Nevertheless, it starts with a localized non-invasive phase called carcinoma in situ. From that point of view, eradication of preinvasive disease would prevent progression to invasive carcinoma — a potentially life-threatening cancer. To complicate the matter, the carcinoma in situ may develop in a few separate areas of the same breast, or in the other breast. This development is
<table>
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<th>Study or subgroup</th>
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Heterogeneity: Tau² = 0.08; Chi² = 8.86, df = 3 (p = 0.03); F = 66%

Test for overall effect: Z = 3.72 (p = 0.0002)

Favours radiotherapy + surgery

Favours surgery

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<td><strong>Total (95% CI)</strong></td>
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<td>0.71 [0.55, 0.91]</td>
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Heterogeneity: Tau² = 0.03; Chi² = 6.52, df = 3 (p = 0.09); F = 54%

Test for overall effect: Z = 2.74 (p = 0.006)

Favours radiotherapy + surgery

Favours surgery

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Heterogeneity: Tau² = 0.02; Chi² = 4.52, df = 3 (p = 0.02); F = 68%

Test for overall effect: Z = 4.38 (p < 0.0001)

Favours radiotherapy + surgery

Favours surgery

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Heterogeneity: Tau² = 0.00; Chi² = 4.52, df = 3 (p = 0.02); F = 68%

Test for overall effect: Z = 6.42 (p < 0.00001)
usually asynchronous, and may be responsible for recurrences. Still, as most recurrences are on the same side (ipsilateral), there is still a role for local treatment. According to the results of all 4 large RCTs concluded to date, RT, when added to BCS as local treatment, reduces the risk of ipsilateral local DCIS recurrence and invasive recurrence, yet has no noticeable effect on mortality.

**Risk and potential sources of bias**

**Mammographic lesion or palpable mass?**

There was moderate statistical heterogeneity between the studies, most likely due to intrinsic differences in background characteristics of the study populations. Some studies included only mammography-detected nonpalpable lesions, while others included clinically palpable masses or did not specify this parameter. It is possible that palpable breast masses, as opposed to mammography-detected lesions, are more likely to be high-grade DCIS associated with higher risk of progression to invasive carcinoma.

**Low-grade or high-grade DCIS?**

Grading DCIS is a topic of controversy in diagnostic breast pathology. It has been observed that high-grade DCIS is more likely to be multicentric and may also be responsible for a higher rate of contralateral and ipsilateral recurrence. Unfortunately, the information on grade of DCIS is incomplete and is provided in only 2 of 4 trials, the EORTC11,14 and UK ANZ.13,16

**Status of surgical margins: was DCIS completely excised prior to radiation therapy?**

The status of surgical margins of patients included in the trials differed or was not stated explicitly in the trials’ eligibility criteria. In addition, the marginal clearance or distance of surgical margin to DCIS was not stated in the trial protocols, despite the fact that observational studies link the recurrence of DCIS to marginal clearance measured in millimeters. The SweDCIS trial8–10 explicitly reported that margin status was unknown in 22% of the patients. In the EORTC trial,11–14 the inclusion criteria mention that only patients with complete excision of DCIS (i.e. clear margins) were included, but the analysis included a group of patients with “not free margins,” although these patients were not eligible according to the published inclusion criteria. This signifies a risk of bias.22

**Followup duration: is 5 years or even 10 years enough to judge the clinical efficacy of intervention in DCIS?**

Invasive recurrences tend to accrue with age, thus age adjustment is of vital importance in the assessment of recurrence rates and mortality. Long-term followup updates on all 4 trials will become crucial in the future to determine the long-term effects of RT on mortality in patients with DCIS. It is unclear whether the factors discussed above were considered during the randomization procedure in any of the 4 published trials, and they may have caused imbalances and biased estimates of risk reduction. While it is not within the scope of the present meta-analysis, further investigation and potential adjustment for these factors is required before we can draw firm conclusions on the clinical utility of RT in DCIS. These and potentially other factors need to be scrutinized in future systematic reviews and through the use of metaregression analysis for all existing DCIS trials.

**CONCLUSION**

There is a statistical significant difference in reduction of any recurrence in the RT arms of all 4 trials, which is due to a reduction in ipsilateral DCIS recurrence. However, no evidence of a reduction in mortality at 5 to 10 years follow-up was observed in patients who received BCS and RT compared to patients who were treated with BCS alone.

**References:**

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6. Stevens R (course director). Essential Medical Statistics course, University of Oxford, September 2012. Includes the following lectures and texts:


