Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ

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CRD summary
The review concluded that surgical margins of 2mm (visible normal tissue removed with an excised tumour) seemed as good as larger margins for reducing ipsilateral breast tumour recurrence risk in women with breast cancer undergoing breast-conserving surgery and postoperative radiation therapy. The limitations of the review process and the included studies make the reliability of the authors’ conclusions unclear.

Authors’ objectives
To evaluate the adequacy of surgical margins related to ipsilateral breast tumour recurrence in patients receiving breast-conserving surgery and postoperative radiation therapy for ductal carcinoma in situ.

Searching
MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to January 2007 for publications in English. Search terms were reported.

Study selection
Randomised and non-randomised trials, and prospective and retrospective series of patients with a primary diagnosis of ductal carcinoma in situ, who were treated with breast-conserving surgery and postoperative radiation therapy using standardised surgery, were eligible for inclusion. All studies with standardised surgery were eligible for inclusion, regardless of margin threshold or radiation therapy dose or the exact radiation therapy schedule (as long as it was standardised to the treatment arm). Studies of patients with a prior personal history of breast cancer were excluded. If two studies reported on patients at the same institution with an overlapping time period, the study with the shortest period of follow-up was excluded. Studies were also excluded if radiotherapy was not used on all patients or not specified, or if no differentiation was made between negative and positive margins. Ongoing trials for which no peer-reviewed reports had been published were also excluded.

The primary outcome was margin status as a risk factor for ipsilateral breast tumour recurrence, and not the effect of specific radiation therapy regimes. Studies that did not describe the margin threshold were excluded; as were studies where data were not clear.

The included studies were in the USA or Europe. The median age of included patients ranged from 48 to 57 years; and included both pre-menopausal and post-menopausal women. The radiotherapy dose of the patients ranged from 45 to 66Gy; the number of patients receiving a radiotherapy boost ranged from 48 to 100% and the boost dose ranged from 6 to 20Gy.

Two independent researchers were involved in the literature search and study selection, with disagreements resolved by consensus.

Assessment of study quality
The authors stated that they assessed randomisation, allocation concealment, number of withdrawals per arm and blinding, but did not report the designs of the included studies or the results of the quality assessment.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
The number of events for each outcome were extracted in order to calculate odds ratio (OR) and 95% confidence intervals (CI). Extracted study data included: radiation therapy regimen used including radiotherapy dose, percentage of
patients receiving a radiotherapy boost, boost dose, and local recurrence in the preserved breast. Regional nodal failures were not scored as recurrences. When results for the same group of patients were reported more than once, the data for the longest period of follow-up were extracted.

The authors did not state how many reviewers performed the extraction.

**Methods of synthesis**
Odds ratios were pooled for all the included studies using both fixed-effect and random-effects models. Between study heterogeneity was determined using $\chi^2$ tests and the $I^2$ statistic. In order to assess specific margin thresholds, data were pooled from combined randomised and non-randomised studies when a specific margin could be identified related to ipsilateral breast tumour recurrence; these were divided into groups according to individual margin widths, and the odds ratios examined in relation to the highest margin. All statistical tests were two tailed.

**Results of the review**
Twenty-two relevant studies were identified (n=4,660 women); seven were multicentre trials. Of the patients in the included studies, 806 were in randomised controlled trials (RCTs). The median time to ipsilateral breast tumour recurrence was 60 months (interquartile range, 47.5 to 78 months). The median follow-up time was 85.2 months (range 36 to 132 months). The authors reported an even distribution in the populations studied for age, detection method and receptor status, but patient selection criteria for breast-conserving surgery and radiation therapy were poorly defined. Publication bias could not be totally excluded, as there was evidence that smaller studies gave different results to larger studies.

**Negative margin versus positive margin status:** Negative margins were defined as ranging from tumour not touching the ink to 10mm margin in individual studies. There was a significant reduction in risk of ipsilateral breast tumour recurrence with a negative margin after breast-conserving surgery compared with patients with a positive margin (OR 0.36, 95% CI 0.27 to 0.47; 20 studies; $I^2=0\%$).

**Negative margin versus close margin status:** Close margins were defined as between the study margin thresholds and positive margins, ranging from under 1 to under 5mm. There was a significant reduction in risk of ipsilateral breast tumour recurrence for a negative margin after breast-conserving surgery compared with patients with a close margin (OR 0.59, 95% CI 0.42 to 0.83; seven studies; $I^2=0\%$).

**Negative margin versus unknown margin status:** There was a significant reduction in risk of ipsilateral breast tumour recurrence for a negative margin after breast-conserving surgery compared with patients with an unknown margin (OR 0.56, 95% CI 0.36 to 0.87; 13 studies; $I^2=42.2\%$).

**Close margin versus positive margin status:** There was a significant reduction in risk for a close margin after breast-conserving surgery compared with patients with a positive margin (OR 0.43, 95% CI 0.24 to 0.77; four studies; $I^2=12.1\%$).

**Specific margin thresholds:** Analysis was performed for different negative margin widths to help define an optimum margin threshold. Compared with a margin of 5mm or more, there was no significant difference in the risk of ipsilateral breast tumour recurrence with a 2mm margin, but there was an increased risk with a margin of 1mm (OR 2.89, 95% CI 1.3 to 8.1) and with a margin of ‘no cells on the ink’ (OR 2.56, 95% CI 1.1 to 7.3). Additionally, a margin of 2mm or more was superior to a margin of less than 2mm (OR 0.53, 95% CI 0.26 to 0.96).

**Authors’ conclusions**
Surgical margins negative for ductal carcinoma in situ should be obtained after breast-conserving surgery for ductal carcinoma in situ. A margin threshold of 2mm was as good as a larger margin when breast-conserving surgery for ductal carcinoma in situ was combined with radiation therapy.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched, but no start dates were given. The authors commented that a number of
the studies identified did not have extractable data. Study quality was assessed using suitable criteria, but little relevant data was reported. Although study selection was carried out with efforts to reduce error and bias, it was not clear whether this process applied to other aspects of the review process.

Relevant study details were reported, but no details of individual study types were given. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of all studies seemed appropriate and was used to derive odds ratios, but odds ratios were not determined for different individual types of studies.

In view of some potential limitations arising from the review process, uncertainties about the quality of included studies, increased bias by the pooling of results from both randomised and non-randomised trials, and the authors’ own reservations about margin measurement in the studies, the extent to which the authors’ conclusions are reliable is unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that there was no consensus on what was a negative margin. Margins of 2mm provided equivalent local control when compared with larger margins. Wide resections or conversion from breast-conserving surgery to mastectomy because of an inability to achieve a 1 cm margin are unnecessary in women treated with excision and radiation therapy.

**Research:** The authors did not state any implications for research.

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