Does locoregional radiation therapy improve survival in breast cancer: a meta-analysis

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Authors' objectives
To assess the effectiveness and toxicity of locoregional radiation therapy in people treated with definitive surgery and adjunctive systemic therapy.

Searching
MEDLINE, Cancerlit, and the reference lists of retrieved articles were searched for peer-reviewed studies published between 1967 and July 1999; the search headings were reported. The authors also handsearched relevant journals published in the first half of 1999. There were no language restrictions. Abstracts and full reports were eligible. If the same trial was published more than once, the most up-to-date data were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a median follow-up of at least 5 years were eligible for inclusion.

Specific interventions included in the review
Studies were eligible for inclusion if they assessed locoregional radiotherapy targeting regional lymph nodes and the chest wall or breast following definitive surgery (radical or modified mastectomy, or lumpectomy plus an auxiliary dissection) and adjuvant systemic therapy (chemotherapy or hormonal therapy). Systemic therapy had to be the same for the treatment and control groups. The doses of radiation, sites irradiated and techniques used varied between the included trials; details of these were tabulated. It was not stated in the review, but the control appears to have been definitive surgery and adjuvant systemic therapy with no radiation therapy.

Participants included in the review
Studies of women with node-positive and node-negative breast cancer treated with definitive surgery and adjuvant systemic therapy were eligible for inclusion. The included studies had varying inclusion criteria. Most of the studies contained pre- and postmenopausal women with node-positive breast cancer who underwent modified radical mastectomy. The authors did not report demographic details such as age and ethnicity.

Outcomes assessed in the review
Outcomes were not specified as inclusion criteria. Data were extracted on the following outcomes: recurrence, local recurrence, mortality, or toxicity. Since limited data on toxicity were available, toxicity data were not reported in the review.

How were decisions on the relevance of primary studies made?
At least two authors reviewed citations and potential papers independently. Decisions to select an article were based on information in the published report. Any disagreements were resolved by consensus or review by a third investigator.

Assessment of study quality
The authors used the Jadad instrument to assess methodological quality. This assesses randomisation method, double-blinding (not applicable in this case), and descriptions of withdrawals and drop-outs. The scores range from 0 (low quality) to 5 (high quality). The authors assumed that randomisation was adequate and that follow-up was completed unless otherwise reported in the articles. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

Data extraction
Two authors abstracted the data independently. Data were abstracted on the following: publication details, number of participants, disease stage, type of surgery, extent of dissection, systemic treatment, radiation regimen, dose and timing, sites irradiated, sequencing of chemotherapy and irradiation, median follow-up, recurrence at any site, local recurrence, mortality, and the number of people who experienced treatment-related toxicity. The maximum published follow-up for data were used. Raw numbers were extracted where possible, but where necessary the numbers were estimated from survival curves (2 studies). The validity of the data extracted was assessed by repeated cross-checking.

**Methods of synthesis**

**How were the studies combined?**

To estimate treatment effects, findings on morbidity and recurrence were pooled quantitatively. The authors combined odds ratios (ORs) from each study using precision-based weights (Woolf estimators) using fixed-effect and random-effects models. The random-effects model was reported as these findings were more conservative. Pooled treatment effects were expressed as ORs. Findings about toxicity were reported narratively.

**How were differences between studies investigated?**

Chi-squared tests were used to test for statistical heterogeneity. The authors performed an exploratory univariate analysis and random-effects regression of factors that might influence the effect of treatment on mortality, including disease stage, anthracycline-based chemotherapy, radiation technique, extent of radiation, radiation dose, timing of radiation and methodological quality. The degree of auxiliary dissection and rate of locoregional failure in controls were considered only in univariate analysis.

**Results of the review**

The review included 18 RCTs with 6,367 participants.

Locoregional radiation statistically significantly reduced the risk of any recurrence (13 trials; OR 0.69, 95% confidence interval, CI: 0.58, 0.83, P=0.00004), local recurrence of breast cancer (13 trials; OR 0.25, 95% CI: 0.19, 0.34, P=0.000001) and death (18 trials, OR 0.83, 95% CI: 0.74, 0.94, P=0.004). Multivariate analysis revealed that the timing of radiation (within 6 months of beginning chemotherapy) and radiation technique had statistically significant effects on mortality (regression P=0.03 and P=0.05, respectively).

Eight out of 18 trials reported toxicity data. Acute toxicity to locoregional radiation was infrequent and included severe skin toxicity, myelosuppression and radiation pneumonitis. Arm oedema was reported in 3 trials and cardiac toxicity, primarily congestive heart failure, in 6 trials.

Most studies were of low methodological quality as none involved blinded treatment allocation. Seven of the 18 trials had a Jadad score of 1 out of 5, seven had a score of 2, and four had a score of 3.

**Cost information**

No

**Authors’ conclusions**

In women with breast cancer treated with systemic therapy, locoregional radiation following surgery reduced mortality and disease recurrence.

**CRD commentary**

The research question for this review was well defined. The inclusion criteria for the intervention, participants and study types were clearly specified, as were the methods used to assess the relevance and quality of the included studies. However, only studies published in peer-reviewed journals were eligible. The authors did not report the possibility of publication bias. The techniques used to pool the data appear to have been appropriate, but it is unclear whether pooling is acceptable in this instance: as the trials included many different treatment regimens and were of
varying quality, it is likely that there would have been some heterogeneity between the studies. The authors examined the effect of certain factors on the treatment effect using regression analysis. However, although heterogeneity tests were conducted, they were not reported.

It was appropriate not to pool data on toxicity, given the limited information available from the included trials. The authors presented ranges of the incidence of different toxicities, but this information is of limited value when it is not in the context of specific treatment regimens.

Overall, the data presented in this review support the authors' conclusions.

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

**Practice:** The authors stated that locoregional control is important in people undergoing systemic therapy because locoregional recurrence may prevent secondary systemic spread and prolong survival. However, it is unclear how it should be incorporated into clinical practice.

**Research:** The authors stated that adequately powered studies are needed to investigate how locoregional radiation should be incorporated into current practice, and the potential impact of radiation technique and timing on mortality and toxicity.

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