Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases


CRD summary
This meta-analysis compared pain relief achieved with various dose-fractionation schedules of localised radiotherapy in patients treated for painful bone metastases of cancer. The authors found no difference between single- and multiple-fraction radiotherapy. The evidence presented supports the authors' conclusions but some of the review methods were not reported so it is difficult to evaluate the reliability of the conclusions.

Authors' objectives
To compare pain relief among various dose-fractionation schedules of localised radiotherapy (RT) in the treatment of painful bone metastases.

Searching
Two independent literature searches were conducted: PubMed was from 1966 to 2000; and MEDLINE, PREMEDLINE, Cancerlit and the Cochrane Library from 1998 to 2001. Both searches were conducted without language restrictions. The search strategies were described in the paper.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were eligible for the review.

Specific interventions included in the review
Trials comparing two or more dose-fractionation schedules of localised RT were reviewed. Trials involving the use of hemibody RT or radionuclides were excluded.

Participants included in the review
Trials of patients undergoing treatment for painful bone metastases were included. In most of the included studies, the primary site of the cancer was not restricted and the life expectancy of the patients was not discussed. The prescription point (spine) for each trial was given in the review.

Outcomes assessed in the review
The primary outcomes of interest for the review were complete pain response and overall pain response. The secondary outcomes were median response duration, reduction in analgesic dose, acute adverse effects, pathologic fracture rate, re-irradiation rate, remineralisation, and quality of life.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
All the included studies, except one that had been reported as an abstract only, were assessed using the Jadad scale (both the 3- and 6-item versions). The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The data were extracted by one reviewer and checked by another. Pain relief response data were extracted; if only percentage data were reported, the number of responders was calculated.

Methods of synthesis
How were the studies combined?
The trials were combined in a meta-analysis. The trials were divided into three groups: comparisons of different doses of single-fraction RT (2 trials); comparisons of single- versus multiple-fraction RT (8 trials); and comparisons of different doses of multiple-fraction RT (6 trials). The complete and overall pain responses for trials comparing single- and multiple-fraction RT were pooled in a meta-analysis using a random-effects model. The main analysis used the number of patients randomised, while a sensitivity analysis used the number of assessable patients. Other outcome data not included in the meta-analyses were summarised.

**How were differences between studies investigated?**
For those trials considered suitable for meta-analysis, heterogeneity was tested using the chi-squared test.

**Results of the review**
Sixteen trials (4,486 assessable patients) were included.

Comparisons of different doses of single-fraction RT (2 trials): both trials found the overall response rates were significantly lower with 4 Gy than with 8 Gy, but there was no significant difference for the complete response rate.

Comparisons of single- and multiple-fraction RT (8 trials): the pooled intention-to-treat complete response rates were 33.4% for single-fraction and 32.3% from multiple-fraction, with a relative risk (RR) of 1.03 (95% confidence interval, CI: 0.94, 1.13, P=0.5). For overall response rate, the values were 62.1% and 58.7%, respectively, (RR 1.05, 95% CI: 1.00, 1.11, P=0.04). The results of the analysis using assessable patients only found no treatment differences. Trial quality did not affect the response rates.

Comparisons of different doses of multiple-fraction RT (6 trials): these results were not discussed.

Dose response: the effects of high versus low doses, with the cut-off set at various doses, failed to identify any dose response.

For secondary outcome measures, only the re-irradiation rates were consistently different between the treatment arms, being more common in lower-dose treatment arms.

**Authors' conclusions**
A meta-analysis of RCTs found no difference in complete and overall pain relief between single- and multiple-fraction RT for bone metastases. No dose-response relationship could be detected by including data from the multi-fraction versus multi-fraction trials. Additional trials are needed to evaluate the role of re-irradiation and the impact of RT on other treatment end points such as quality of life.

**CRD commentary**
This review used clear inclusion and exclusion criteria. The literature search was adequate, although sources other than electronic databases do not appear to have been explored. Only limited details of the conduct of the review were reported, so it is difficult to assess the efforts made to reduce reviewer bias. The results of the quality assessment were not reported and neither were details of an analysis of the impact of quality on the trial results, although the authors stated that there was no effect. A meta-analysis was used appropriately to combine clinically homogeneous trials. It was unclear why studies comparing different multi-fraction regimens were not discussed as a group. Overall, the authors' conclusions are supported by the review findings.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that more evidence is needed on the role of re-irradiation in bone metastases and on other relevant palliative end points.

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Linked records

- Update on the systematic review of palliative radiotherapy trials for bone metastases

Other publications of related interest

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.