Palliation of metastatic bone pain: single fraction versus multifraction radiotherapy. A systematic review of randomised trials

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CRD summary
This review found single fraction radiotherapy to have similar efficacy to multifraction radiotherapy in relieving metastatic bone pain. However, the rates of re-treatment, and possibly pathological fracture, were higher after single fraction radiotherapy. The interpretation of the findings was limited by the lack of detail on the primary studies.

Authors' objectives
To assess the efficacy of single fraction radiotherapy, compared with multifraction radiotherapy, in relieving metastatic bone pain and preventing pathological fracture and spinal cord compression.

Searching
MEDLINE (from 1966 to November 2002), EMBASE (from 1980 to November 2002), Cancerlit (from 1975 to November 2002) and the Cochrane Controlled Trials Register were searched. Studies were also identified from the reference lists of retrieved papers, textbooks and review articles. In addition, some major cancer conference proceedings and journals were handsearched up to November 2002.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for the review.

Specific interventions included in the review
Studies comparing single fraction radiotherapy with multifraction radiotherapy were eligible for the review. Studies comparing radioisotopes or drugs were excluded.

Participants included in the review
The inclusion criteria for the participants were not stated explicitly. Studies of patients undergoing treatment for pain associated with bony metastases from any primary cancer were included in the review.

Outcomes assessed in the review
Studies that included at least one outcome measure of pain were eligible. All types of pain outcome assessment were eligible. The outcomes reported in the review were the overall pain response, complete pain response, re-treatment rate, pathological fracture rate, spinal cord compression rate and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies.

Assessment of study quality
Each study was quality assessed using the Jadad scale (1 to 5); the resultant scores were not used to weight the studies for the analysis. The authors did not state who performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The data for overall pain response and complete pain response were extracted as categorical data (response or no
response), with the criteria for response used in each original study. The data for pain response were those at 4 weeks, or as near to 4 weeks as were available. Data were extracted on an intention-to-treat basis to minimise bias due to the high drop-out rates.

**Methods of synthesis**

**How were the studies combined?**
Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Where there was no significant heterogeneity, the ORs were pooled using a fixed-effect model (Peto).

**How were differences between studies investigated?**
Statistical heterogeneity was investigated using a chi-square test with a significance level of 0.05.

**Results of the review**

Twelve trials (3,508 patients) were included.

Overall pain response (12 trials): there was no significant statistical heterogeneity. The overall response was similar for single fraction radiotherapy (60%) and multifraction radiotherapy (59%), with a pooled OR of 1.03 (95% CI: 0.90, 1.19) (no significant difference).

Complete pain response (8 trials): there was no significant statistical heterogeneity. The complete response rate was similar for single fraction radiotherapy (34%) and multifraction radiotherapy (32%), with a pooled OR of 1.10 (95% CI: 0.94, 1.30) (no significant difference).

Re-treatment rate (5 trials): there was no significant statistical heterogeneity. The re-treatment rate was higher for single fraction radiotherapy (21.5%) than for multifraction radiotherapy (7.4%), with a pooled OR of 3.44 (95% CI: 2.67, 4.43) (significant difference).

Pathological fracture rate (5 trials): there was no significant statistical heterogeneity. The pathological fracture rate was higher for single fraction radiotherapy (3%) than for multifraction radiotherapy (1.6%), with a pooled OR of 1.82 (95% CI: 1.06, 3.11) (significant difference).

Spinal cord compression (3 trials): there was no significant statistical heterogeneity. The rate of spinal cord compression was 1.9% for single fraction radiotherapy and 1.4% for multifraction radiotherapy, with a pooled OR of 1.42 (95% CI: 0.72, 2.75) (no significant difference). When this analysis was recalculated using only data from patients with spine metastases, the trend was the same.

Adverse effects (10 trials): similar rates of adverse effects (mainly nausea and vomiting) with both treatments were reported.

**Authors’ conclusions**

Both single and multifraction radiotherapy were effective for the relief of the pain of bony metastases, although two thirds of patients did not achieve complete pain relief. With the exception of the rates of re-treatment and pathological fracture, which were higher after single fraction radiotherapy, there was no difference between the two types of therapy.

**CRD commentary**

The review addressed a clear question with well-defined inclusion criteria for the interventions, comparators, participants, study design and outcomes. The quality of the trials was assessed, but the results of this assessment were not reported.

The main limitation of the review, as reported, was the lack of information on the primary studies. Differences between the methods used in the primary trials to assess pain relief might have impacted on the review's results. The differences
did not translate into statistical heterogeneity, but this might have been due to the limit of significance adopted; as the review's authors did not provide further details, the significance of such differences cannot be discerned. The results derived for the primary studies and pooled analysis were well reported. However, it was not clear how the figures for patients reporting 'overall pain response' were derived; it is possible that some unreported transformation of continuous data was used. It was also unclear how this might have influenced the results of the review. The authors' conclusions are generally supported by the review, although the efficacy of treatment relative to placebo or no treatment was not established and the treatment difference for pathological fracture only just reached statistical significance.

Implications of the review for practice and research
Practice: The authors suggested that the incorporation of different modalities (e.g. radioisotopes or bisphosphonates) may further improve the efficacy of these two treatments.

Research: The authors stated that studies testing the optimal use of various modalities, and reporting on effects on quality of life and cost-effectiveness, are warranted.

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