Palliative radiotherapy for painful bone metastases, single versus multiple fraction treatment: a literature review

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CRD summary
This review concluded that single fraction radiotherapy provided adequate pain relief and response duration in the palliation of painful bone metastases; however, there were concerns over fracture and re-treatment rates. Given the limitations of the review, the diverse group of studies included, and the effects of confounding variables on the results, the author's conclusions should be treated with caution.

Authors' objectives
To determine whether single or multiple dose radiotherapy is more effective at providing pain relief in patients with bone metastases.

Searching
PubMed and the Cochrane Library were searched; the search terms were reported, but the search dates were unclear. Only studies published in English in the previous 20 years were included in the review. The reference lists of four review articles were also checked for additional references.

Study selection
Study designs of evaluations included in the review
Any type of comparative study was eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing single with multiple dose radiotherapy regimens were eligible for inclusion. The treatment regimens varied between studies: most used a single 8-Gy fraction (range: 6 to 10); in multiple fraction studies the dose schedules ranged from 20 Gy in 5 fractions up to 46 Gy in 23 fractions. Beam energy varied from orthovoltage X-rays to cobalt-60 to 10 MV X-ray. The body sites treated included cervical spine, thoracic spine, lumbar spine, ribs/sternum, pelvis, long bones and hip. Only one study reported the details of the margins used and the field sizes treated.

Participants included in the review
Studies including patients with painful bone metastases were eligible for inclusion. Where reported, the median age ranged from 60 to 67 years and 40 to 100% of the participants were men. The primary tumour sites varied between studies and included breast, lung, prostate, non-small-cell lung and kidney cancer.

Outcomes assessed in the review
Studies that assessed the following measures of pain were eligible for inclusion: the use of analgesics; patients's pain response; the onset of pain; and the duration of the pain. Other outcomes reported in the review were mortality, re-treatment rates, incidence of bone fractures, and quality of life.

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

Assessment of study quality
The author did not state that they assessed validity.

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

The proportion of patients receiving each treatment was calculated for each study for response and re-treatment rates; different scales were used for analgesic consumption and pain response.

**Methods of synthesis**

How were the studies combined?
The studies were combined in a narrative, grouped according to outcome.

How were differences between studies investigated?
Some differences between the studies were evident from the data tables and were discussed in the text of the review.

**Results of the review**

The author reported that 8 studies were included in the review, but the data tables and 'Results' section reported the findings from 9 studies (n=3,288). Seven studies appeared to be randomised controlled trials (RCTs), one a non-randomised controlled trial, and another either a cohort or case-control study.

Analgesic use (7 studies).

Three RCTs (n=1,692) concluded that there were no differences between single and multiple fraction therapies either pre- or post-treatment. Overall, the studies showed that analgesic use was not a helpful indicator of pain response, as the development of additional metastatic sites over time increased the requirement of pain relief.

Pain response (7 studies).

One RCT (n=241) using the visual analogue scale (VAS) and 2 RCTs (n=1,049) using a 4-point categorical pain scale reported no significant difference in VAS scores between single and multiple fraction treatments.

One RCT (n=1,171) reported a more favourable complete response rate for the single treatment arm (37% versus 33%). A non-randomised controlled trial (n=205) concluded that complete response was better in patients receiving 40 to 46 Gy in 20 to 23 fractions (81%) than in those receiving 30 to 36 Gy in 10 to 12 fractions (65%) or 8 to 28 Gy in 1 to 4 fractions (46%), as were 3-year pain freedom rates (85%, 76% and 32%, respectively).

One RCT (n=287) and the cohort/case-control study (n=26) favoured the multiple treatment over the single fraction treatment arm, though not significantly so.

Onset of pain response (5 studies).

Of 3 RCTs, one (n=288) reported a reduction in pain 4 to 6 weeks post-treatment, one (n=241) no difference in pain response between single and multiple fraction therapies, and the third (n=761) a reduction after 2 weeks that continued for several weeks. The non-randomised controlled trial (n=205) reported maximum pain reduction at 2 to 3 weeks post-treatment. The cohort/case-control study (n=26) reported that patients in the single fraction group reported an earlier onset of pain relief than those in the multiple fraction group (24 to 48 hours versus 1 to 2 weeks.

Response duration (6 studies).

Four RCTs (n=1,570) found no significant differences in response duration between patients receiving single fraction therapy and those receiving multiple fraction therapy. The non-randomised controlled trial reported that the maximum response occurred 2 to 3 weeks post-treatment; however, this was directly impacted by the response the patient had to the radiotherapy treatment. One RCT (n=1,171) reported no difference in time to progression between the treatment groups. The cohort/case-control study (n=26) reported a shorter time to relapse with single fraction therapy (2.8 months versus 6 to 11 months).
Re-treatment rates (6 studies).

Five RCTs (n=2,490) reported that re-treatment was more common in single fraction treatment groups than in those receiving multiple fraction treatment. One RCT (n=280) did not show a higher re-treatment rate for single fraction therapy.

Quality of life (1 study).

One RCT (n=280) reported no significant difference in quality of life between patients receiving single fraction therapy and those receiving multiple fraction therapy.

Authors' conclusions
Single fraction radiotherapy provided adequate pain relief and response duration in the palliation of painful bone metastases; however, there were concerns over fracture and re-treatment rates.

CRD commentary
This review was based on a clear research question. The literature search was somewhat limited, and the dates and exact databases searched were unclear. Only English language articles were retrieved and little attempt was made to search for unpublished material, so it is possible that relevant studies were missed. It was difficult to assess whether appropriate steps were taken to reduce the risk of errors and bias since insufficient detail of the review methodology was provided. The author did not assess the methodological quality of the studies and, given there were very few details about the included study designs, it is not possible for the reader to make any assessment of their quality either. Similarly, it was difficult to check and compare the author's findings with those of the authors of the original studies as, in many instances, insufficient details were provided in the text and data tables. The author was, however, justified in using a qualitative synthesis given the apparent variability in study populations, interventions and outcome measures.

One omission from the review was an assessment of treatment side-effects. The author discussed side-effects but did not seem to specifically assess this in the review. Given these omissions and the fact that the data were subject to the effects of confounding variables, the author's conclusions should be treated with caution. The suggestion that single fraction therapy may be associated with an increased fracture rate and re-treatment rate was also worrying, and the author is justified in recommending further research to investigate these findings.

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

Research: The author stated that further research in the form of large, well-conducted RCTs is required to confirm her findings and to determine the best single fraction dose regimen and the best end points. In particular, further research is needed to determine whether a single 8 to 10 Gy dose can achieve that same level of pain relief with fewer side-effects. The influence of potential confounding factors such as primary disease site on response rate should also be assessed. Future studies should ensure that re-treatment definitions and criteria and outcome measures are fully defined. Further research is also required to determine patients' treatment preferences.

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Record Status
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.