Update on the systematic review of palliative radiotherapy trials for bone metastases
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CRD summary
The review concluded that overall and complete response rates were similar in single and multiple fraction regimens of palliative radiotherapy for bone metastases but significantly higher re-treatment rates were experienced by patients who received single fractions. Given potential bias in the review process, lack of quality assessment and potential clinical heterogeneity, the authors’ conclusions should be considered with caution.

Authors’ objectives
To compare single fraction regimens with multiple fraction regimens of palliative radiotherapy for bone metastases.

Searching
PubMed, EMBASE, CANCERLIT and The Cochrane Library were searched without language restriction from January 1950 to November 2010 for relevant studies. Google Scholar and the reference lists of retrieved studies were searched for any additional studies.

Study selection
Published randomised controlled trials (RCTs) that compared single fraction with multiple fraction regimens of external beam radiotherapy for the palliation of uncomplicated bone metastases were eligible for inclusion in the review. The primary outcomes of interest were complete response and overall response rates as reported and defined in the included studies. Secondary outcomes included re-treatment rates, spinal cord compression, pathological fracture rates and acute toxicities. Trials that involved the use of hemibody radiotherapy and radionuclides were excluded.

In the five additional RCTs in this updated review, complete response was defined (where reported) as either a pain score of 0 at the treated site, score of 0 on the 10 point visual analogue scale, no pain without increase of analgesia or reduction of at least 2 out of 4 points on a pain questionnaire. Rates were measured at variable time periods that ranged from three to eight weeks, where reported. In the five additional RCTs, single fraction arms always used 8Gy; the multiple fraction arms included 20Gy in five fractions, 30Gy in 10 fractions, or 40Gy in 20 fractions. Overall, five studies had three treatment arms of radiotherapy; four of these had a single fraction radiotherapy arm compared to two different multiple fraction arms and one had two different single fraction arms compared to one multiple fraction arm.

Three reviewers independently selected studies for the review.

Assessment of study quality
The authors did not report whether studies were assessed for quality.

Data extraction
Data were extracted on the outcomes to enable calculation of risk ratios (RRs) and 95% confidence intervals (CIs).

The authors did not report the number of reviewers who extracted data from the studies.

Methods of synthesis
The results of most of the outcomes were combined in meta-analyses using a random-effects model. Summary effect risk ratios and 95% confidence intervals were calculated. Analyses were presented based on intention-to-treat patients and assessable patients (excluding drop-outs). Heterogeneity was assessed using $\chi^2$ and $I^2$. Sensitivity analyses were undertaken to determine whether the inclusion of the control arm twice from three arm studies in the meta-analyses influenced the findings. Prevalence of acute toxicities such as nausea and vomiting, lethargy and tiredness, diarrhoea and skin reactions was reported in narrative format.

Results of the review
Twenty-five RCTs (numbers of participants not reported) were included in the review. Five additional RCTs and one retrospective study that included long term trial results of a previous RCT were added to 19 RCTs included in previous
systematic reviews (see Other Publications of Related Interest). Five of the 25 studies had three arms with each study being included in two comparisons in relevant meta-analyses.

**Intention-to-treat primary outcomes:**

For overall response rates (21 studies, 26 comparisons), there was no evidence of statistically significant differences in overall response rates when single was compared with multiple fraction regimens (RR 0.98, 95% CI 0.95 to 1.02; no significant heterogeneity).

For complete response rates (17 studies, 19 comparisons), there was no evidence of statistically significant differences in complete response rates when single was compared with multiple fraction regimens (RR 0.97, 95% CI 0.89 to 1.06; no significant heterogeneity).

**Intention-to-treat secondary outcomes:**

For re-treatment rates (13 studies, 16 comparisons), single fraction regimens were associated with a significantly greater risk of re-treatment when compared with multiple fraction regimens (RR 2.58, 95% CI 1.92 to 3.47; significant heterogeneity, I²=54%).

When single was compared with multiple fraction regimens, there was no evidence of statistically significant differences in pathological fracture rates (RR 1.10, 95% CI 0.65 to 1.86, significant heterogeneity, I²=47%; 10 studies), spinal cord compression rates (RR 1.44, 95% CI 0.90 to 2.30; no significant heterogeneity; six studies) or spinal cord compression rates in patients with spinal metastases (RR 1.40, 95% CI 0.73 to 2.67; no significant heterogeneity; three studies). Three studies found that acute toxicities were more prevalent in patients who received multiple fractions. One study found that pain flare was worse in patients who received single fraction radiotherapy.

Analyses of outcomes that used only assessable patients did not markedly change the results.

**Authors' conclusions**

Overall and complete response rates were similar in single and multiple fraction regimens of palliative radiotherapy for bone metastases but significantly higher re-treatment rates were experienced by patients who received single fractions.

**CRD commentary**

The aim of the review was to update previous meta-analyses that investigated the same research question. The most recent of these analyses, including 19 studies, was published in 2007 by the same principal author. The research question was supported by appropriate inclusion criteria. Relevant sources were searched to identify studies without language restriction. No specific attempts were made to find unpublished studies, so publication bias could not be ruled out. Appropriate methods were used to select studies, but the authors did not state how many reviewers extracted data for the review and did not report whether studies were assessed for quality. Five additional RCTs and a retrospective study that contained RCT results were identified from the updated search. Appropriate methods were used to synthesize studies and assess heterogeneity. Substantial heterogeneity was identified in the analyses of re-treatment and pathological fracture rates, but this was not explored by the authors.

The presentation of results from the control group twice from multi-arm studies in the meta-analyses was not appropriate, as this practice inflated the number of participants in the control groups. No details were reported on the previous 19 studies which were included in this review which made if difficult to determine how clinical heterogeneity impacted on the results. There was variation in the multiple fraction regimens, response definitions, follow-up time periods, and assessment criteria in included studies. There was also a discrepancy in the text reporting the number of trials used in the different outcome analyses and the number of trials presented in the forest plots.

Given considerable potential bias in the review process, lack of quality assessment and potential clinical heterogeneity, the authors’ conclusions should be considered with caution.

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

**Practice:** The authors stated that single fraction radiotherapy was an efficient and efficacious method of palliating uncomplicated painful bone metastases and should be implemented as standard of care.
Research: The authors stated that future trials should follow the guidelines from international consensus on palliative radiotherapy to improve the ability to make trial comparisons.

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- Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases
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- Palliative radiotherapy trials for bone metastases: a systematic review

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