Dose-effect relation in stereotactic radiotherapy for brain metastases: a systematic review

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CRD summary
This review concluded that local control of brain metastases by single fraction stereotactic radiotherapy was highly dependent on dose. High levels of control were achieved by doses above 21 Gy and low levels of control by doses below 15 Gy. Uncertainty about the validity of included studies and the conduct of the review make the reliability of the conclusions unclear.

Authors' objectives
To assess the relationship between dose and the probability of local control in stereotactic radiotherapy of brain metastases.

Searching
PubMed and EMBASE were searched for papers published in English, Dutch, German or French between 1990 and 2009. Only studies reported in peer-reviewed journal were eligible for inclusion.

Study selection
Studies (case series) of at least 10 patients who received stereotactic radiotherapy as a primary treatment for brain metastases or for recurrence following whole brain irradiation were eligible for inclusion. Only studies that reported actuarial local control rates for the irradiated metastases and in which these rates could be related to the radiation dose applied were included. Studies in which all patients received a planned stereotactic radiotherapy boost after whole brain irradiation were excluded from the review.

Patients in the included studies had mixed primary diagnoses except for one study that included only patients with non-small cell lung cancer and one that enrolled patients with melanoma, sarcoma or renal cell carcinoma. Techniques used included circular arc, conformal beam, dynamic arc, gamma knife and intensity-modulated radiation therapy. The percentage of patients who had received whole brain radiation therapy ranged from zero to 76%. The estimated diameters of tumours varied but was less than 4cm in the majority of studies.

The authors did not state how many reviewers selected the papers for the review.

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

Data extraction
Data were extracted on the radiation dose prescribed, the given minimum dose related to tumour dimensions, treatment machine and technique, local control rates at six and 12 months, 12-month survival and radiation necrosis rate. Definitions of local control in the primary studies were accepted. Definitions were absence of increase in size, absence of significant increase in size or no increase of at least 25% in size. It was not clear whether increases due to radiation necrosis constituted failures of local control. Biological effective doses were calculated to enable comparison of different treatment schemes.

The authors did not state how many reviewers carried out the data extraction.

Methods of synthesis
The data were combined in a narrative synthesis and summarised using line plots to explore relationships between radiation doses, diameter of treated metastases and 12-month local control rates.

Results of the review
Eleven studies (1,079 patients with at least 1,586 metastases) were included in the review. All studies were retrospective.
Six-month local control was over 80% for all except one single-fraction patient series and over 90% for all fractionated stereotactic radiotherapy patient series.

There was much greater variation in rates of local control at 12 months. In the single fraction patient series these were reported to be above 80% for doses over 20 Gy and above 60% for doses over 18 Gy. Discrepancies between the text and tables indicated that two studies of 20 to 24 Gy may have had lower control rates. Doses below 15 Gy showed control rates of less than 50% in all instances except one. Fractionated stereotactic radiotherapy studies reported rates higher than 70%.

Radiation necrosis rates were inconsistently reported; the highest rate was 12% which was seen after 3x13 Gy or 3x14 Gy.

**Authors’ conclusions**
Local control after single fraction stereotactic radiotherapy was highly dependent on dose. It was high (above 80%) after at least 21 Gy but low (under 50%) after 15 Gy or lower.

**CRD commentary**
The review question and the inclusion criteria were clear. Two relevant databases were searched. The restriction to published studies reported in specified languages may have led to the introduction of selection biases and omission of relevant studies. The inclusion criteria may have caused omission of relevant studies that reported local control data by different methods. There was no assessment of the validity of the included studies. The authors did not report using methods designed to reduce reviewer bias and error at other stages of the review process. The synthesis appeared appropriate.

The authors’ conclusions reflected the results of the review but their reliability is unclear due to uncertainties about the quality of the included studies and the conduct of the review.

**Implications of the review for practice and research**
**Practice:** The authors stated that stereotactic radiotherapy for brain metastases should preferably be applied with a biologically effective dose of at least 40 Gy which would correspond to a single fraction of 20 Gy, two fractions of 11.6 Gy or three fractions of 8.5 Gy.

**Research:** The authors did not state any recommendations for further research.

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