Effectiveness of stereotactic radiosurgery alone or in combination with whole brain radiotherapy compared to conventional surgery and/or whole brain radiotherapy for the treatment of one or more brain metastases: a systematic review and meta-analysis

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CRD summary
The authors concluded that adding stereotactic radiosurgery to whole brain radiotherapy improves survival in patients with one brain metastasis and improves local tumour control and functional independence in all patients. This was a well-conducted review but the small number of included studies suggest a more cautious conclusion may be appropriate.

Authors' objectives
To assess the effectiveness of stereotactic radiosurgery (SRS) with or without whole brain radiotherapy (WBRT) compared with conventional surgery and/or WBRT in patients with brain metastases.

Searching
Electronic databases (covering biomedical, clinical, social sciences and health service management) were searched using the reported search terms; details were reported to be available from the reviewers. Sources of non peer-reviewed unpublished studies such as the Internet and a series of reference databases of ‘grey’ literature were also searched, as were recent issues of five named relevant journals and conference proceedings of five named societies from the past 5 years. Experts in the field, corresponding authors of identified studies, and manufacturers of stereotactic radiosurgical equipment were contacted. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs; including pseudo- or quasi-randomised trials), and prospective and retrospective cohort studies with concurrent control groups, were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared any of the following interventions were eligible for inclusion: SRS versus SRS plus WBRT; SRS versus WBRT with or without surgical resection; SRS versus surgical resection alone; and SRS plus WBRT versus WBRT alone. Studies could include chemotherapeutic cointerventions that were given independently of the treatment group. The review evaluated SRS plus WBRT versus WBRT and SRS plus WBRT versus SRS.

Participants included in the review
Studies of adults (aged 18 years or older) who had been diagnosed with one or more brain metastases less than 4 cm in diameter using computerised tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) were eligible for inclusion. Participants were eligible regardless of the primary tumour histology and status as long as they had not received prior cranial irradiation.

Outcomes assessed in the review
The primary review outcomes were survival following treatment or randomisation, quality of life measured using a validated health-related quality of life scale, and functional independence measured using the Karnofsky Performance Score. The secondary outcomes were local tumour control measured using follow-up CT, MRI or PET, neurological death, and adverse effects defined as early (within 30 days of treatment) or delayed (within 90 days of treatment) morbidity.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected studies and resolved any disagreements through discussion.
Assessment of study quality
Two reviewers independently assessed validity and resolved any disagreements through discussion. RCTs were graded according to the level of allocation concealment, from A for adequate to C for inadequate. The validity of RCTs was assessed and scored using the Jadad scale, which considers randomisation, blinding and withdrawals. The maximum possible score was 5 points. The validity of RCTs, non-randomised controlled trials and concurrently controlled comparative studies was assessed using criteria described by Downs and Black (reporting, external validity, internal validity-bias, internal validity-confounding and power). The maximum possible score was 29 points.

Data extraction
Two reviewers independently extracted the data onto a standardised form and resolved any disagreements through discussion. For each study, where possible, the median duration of survival and time to local failure were extracted either directly or from survival curves, and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for time to event data. Relative risks with 95% CIs were calculated for dichotomous data, whilst mean differences with 95% CIs were calculated for continuous data. Data on other outcomes of interest were also extracted. Where required, authors were contacted for additional information. All analyses were performed on an intention-to-treat basis.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and outcome. Homogeneous data were pooled in meta-analyses. Pooled HRs with 95% CIs were calculated for time to event data using a random-effects model. Weighted mean differences with 95% CIs were calculated for continuous data, whilst pooled relative risks with 95% CIs were calculated for dichotomous data.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. A predefined subgroup analysis was used to examine the influence on the results of the number of metastases; there were insufficient data to examine the influence of other prognostic factors. Differences in the quality of studies were discussed with respect to sample size, selection bias, performance and attrition bias, and detection bias.

Results of the review
Four studies (n=1,000) were included: 3 RCTs (n=431) and 1 retrospective concurrently controlled cohort study (n=569). One of the RCTs was published as an abstract. The sample size ranged from 27 to 569.

Study quality.
Sample sizes were small in two of the RCTs (n=27 and n=104). There were no obvious baseline differences between treatment groups in the RCTs. The cohort study attempted to adjust for baseline differences in the analysis. In none of the studies were the patients and clinicians blinded. None of the studies reported details of salvage treatments. Clinicians were not blinded to treatment during the follow-up. The Jadad validity scores for RCTs were 3, 3 and 1. The Downs and Black validity scores were 22, 23 and 7 for the RCTs and 19 for the cohort study.

Survival. WBRT plus SRS versus WBRT (3 RCTs): there was no statistically significant difference in survival between treatments; the HR was 0.86 (95% CI: 0.70, 1.05, p=0.54) based on 2 RCTs. The third RCT reported no significant treatment difference but provided no data. The presence of extracranial metastases did not influence the results. Survival was significantly longer in patients with single metastases who received WBRT plus SRS compared with WBRT alone (HR 0.77, 95% CI: 0.60, 0.98), but there was no significant treatment difference for patients with multiple metastases (1 RCT, n=300).

WBRT plus SRS versus SRS (1 cohort study and 1 RCT): neither study reported any significant difference in survival between treatments. There were no significant treatment differences in survival for patients with either single or multiple metastases.
Health-related quality of life.

None of the studies assessed quality of life.

Functional independence. WBRT plus SRS versus WBRT (1 RCT, n=300): functional independence was significantly better at 6 months in patients receiving WBRT plus SRS.

WBRT plus SRS versus SRS: none of the studies assessed functional independence.

Local tumour control. WBRT plus SRS versus WBRT (3 RCTs): patients receiving WBRT plus SRS were significantly less likely to have lost local tumour control at 24 months; the HR was 0.49 (95% CI: 0.33, 0.74, p<0.005) based on 2 RCTs. The third RCT reported that more patients who received WBRT plus SRS maintained local control at 12 months (91% versus 62%), but the statistical significance of this was not reported. WBRT plus SRS versus SRS: none of the studies provided data.

Neurological death. WBRT plus SRS versus WBRT (1 RCT): the RCT reported no significant difference between treatments in neurological death.

WBRT plus SRS versus SRS: none of the studies provided data.

Adverse events.

WBRT plus SRS versus WBRT (2 RCTs): neither study reported any significant difference between treatments in adverse events (1 study reported no difference between early and late toxicities, while the other reported no difference in the type or frequency of adverse events).

WBRT plus SRS versus SRS: none of the studies provided any data.

Authors’ conclusions
The addition of SRS to WBRT improves survival in patients with one brain metastasis, whilst the combination of SRS and WBRT improves local tumour control and functional independence in all patients.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. The strategy undertaken to identify trials appeared extensive and included attempts to minimise publication and language bias. The validity of the included studies was assessed using checklists and the quality of the studies was discussed. Adequate information about the included studies was given. Methods were used to minimise reviewer errors and bias in the study selection, validity assessment and data extraction processes. Only homogeneous data were pooled using meta-analysis, and appropriate methods were used to analyse time to event data. This was a well-conducted review but the small number of included studies suggest a more cautious conclusion may be appropriate.

Implications of the review for practice and research
Practice: The authors suggested that patients with multiple metastases should continue to receive WBRT, keeping SRS for salvage therapy if required, and that patients with a single metastasis should be offered SRS plus WBRT.

Research: The authors stated the need for more evidence about the effects of SRS, including direct comparisons of SRS versus WBRT and ‘field evaluations’ of SRS. Future studies should most importantly assess health-related quality of life as well as time to re-treatment and neurological deficits.

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