The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline

CRD summary
The authors recommended the use of surgical resection plus postoperative whole brain radiation therapy in patients in good general condition. Different doses of whole brain radiation therapy presented similar findings. Given the small number of studies included for some comparisons and their unclear quality, and the potential for review bias, these recommendations should be interpreted with some caution.

Authors' objectives
To assess the role of whole brain radiation therapy in the treatment of patients with newly-diagnosed brain metastases.

Searching
MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and DARE were searched for English articles published from 1990 onwards (1970 onwards for RCTs assessing optimal dosing/fractionation schedules for whole brain radiation therapy). The search strategy was available from a previous publication (see Other Publications of Related Interest). In addition, references of included studies were manually searched.

Study selection
Studies that compared whole brain radiation therapy versus surgery plus whole brain radiation therapy in patients with newly diagnosed single brain metastases were eligible for inclusion. Also eligible for inclusion were studies that assessed the optimal dosing/fractionation schedule for whole brain radiation therapy, and studies that assessed whether tumour histopathology had an impact on whole brain radiation therapy treatment outcomes. Eligible studies were required to include at least five participants per study arm for comparative studies and at least five participants overall for non-comparative studies. Where studies included mixed populations, baseline information on patients with newly diagnosed brain metastases was required to be reported separately.

The outcomes of interest were six-month mortality, overall survival and neurologic function.

Included studies that compared whole brain radiation therapy with whole brain radiation therapy plus surgery provided patients with a radiation dose of 2 or 3 Gray (Gy) in 10 or 12 daily fractions, to provide a total dose of 30, 36, or 40Gy. Randomised controlled trials (RCTs) evaluating different whole brain radiation therapy regimens used a total dose ranging from 10 to 70.4Gy, given as between one and 44 fractions.

Two reviewers independently screened studies for inclusion, with any discrepancies referred to a third reviewer.

Assessment of study quality
Study quality was reported to have been assessed using the PEDro scale for RCTs and assessed using a modified eight item scale to assess non-randomised studies.

The authors did not state how many reviewers performed study validity.

Data extraction
Median survival and significance levels were extracted from individual studies to calculate relative risks (RRs) and their 95% confidence intervals (CIs).

One reviewer extracted the data and this was checked by a second reviewer.
Methods of synthesis
Where possible, relative risks and 95% confidence intervals were pooled using a random-effects model. The \( \chi^2 \) test and \( I^2 \) statistics were used to assess statistical heterogeneity. Where pooling was not appropriate, data were presented as a narrative synthesis and in tables. Studies that assessed whole brain radiation therapy/fractionation schedules were grouped by high (biologically effective dose (BED) of more than \( 39\text{ Gy}_{10} \)) or low dose (BED of less than \( 39 \text{ Gy}_{10} \)) versus control dose (BED=39 \text{ Gy}_{10} ).

Publication bias was assessed using funnel plots.

Results of the review
Twenty four studies (31 papers) were included in the review; 13 RCTs, eight retrospective cohort studies, one prospective non-randomised study, one prospective cohort study with historical controls, and one case series. Validity scores for studies were not reported, but blinding of the RCTs was not possible due to the nature of the procedures.

Surgical resection plus whole brain radiotherapy versus whole brain radiation therapy alone (n=515 patients; three RCTs, two retrospective cohort studies, one prospective non-randomised trial): Two of three RCTs, and all three non-randomised studies showed that patients who underwent surgery followed by whole brain radiation therapy demonstrated statistically significantly improved survival compared with patients who received whole brain radiation therapy alone.

Whole brain radiation therapy dosing/fractionation schedule (n=5,519 patients; nine RCTs, one randomised phase I/II trial, six retrospective cohorts, one prospective cohort with historical controls): None of the studies showed a statistically significant improvement in outcomes relative to dose. This was supported using meta-analysis to assess overall survival and mortality at six months in low dose versus control groups (two studies) and high dose versus control groups (five studies). \( I^2 \) was less than 50% for all these subgroup analyses. There were no statistically significant differences for neurological function, but data were not presented.

Impact of tumour histopathology on whole brain radiotherapy treatment outcomes (one study): Tumour histopathology did not statistically significantly alter overall survival rates.

Authors’ conclusions
The use of surgical resection plus postoperative whole brain radiation therapy compared with whole brain radiation therapy alone was supported for use in patients in good general condition (functionally independent and spending less than 50% of time in bed) and limited extracranial disease. Different dose/fractionation schedules of whole brain radiation therapy did not result in significant differences in median survival, local control or neurocognitive outcomes compared with standard dose/fractionation. There was insufficient evidence to determine the optimal dose/fractionation regimen based on tumour histopathology.

CRD commentary
The review question and supporting inclusion criteria were clearly stated. An appropriate search of the literature was conducted to include ongoing studies, but as the search was restricted by language, language bias could not be ruled out. Publication bias was assessed, but findings were not reported. Study selection and data extraction were performed in duplicate to minimise reviewer error and bias, but the process was not reported for quality assessment.

Although the authors stated that study validity was performed, quality scores were not reported and few details were presented on quality criteria. Appropriate methods were used to combine the results. Where meta-analysis was undertaken, appropriate methods were used to assess for statistical heterogeneity.

Given the uncertain quality of the studies, some potential for bias in the review, and the small number of studies included for different treatment comparisons, the authors’ recommendations should be interpreted with some caution.

Implications of the review for practice and research
Practice: The authors stated that they support surgical resection followed by postoperative whole brain radiation therapy compared with whole brain radiation therapy alone in patients with newly diagnosed brain metastases and good performance status. Recommendations regarding surgical resection plus whole brain radiation therapy versus whole brain radiation therapy alone do not apply to patients with relatively radiosensitive tumour histologies (i.e. small cell lung cancer, leukaemia, lymphoma, germ cell tumours and multiple myeloma).

Research: The authors stated that further studies are needed to assess the effectiveness of whole brain radiation therapy in patients with different tumour types.

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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.