

Radiation Therapy for Brain Metastases

Evidence Summary



Main Points

- We identified a large number of relevant radiation therapy studies (97 studies reported in 190 publications). Studies assessed whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS), alone and in combination with or without systemic therapy, and for resected or unresected lesions.
- Most studies evaluated WBRT as initial treatment, with or without SRS; 10 randomized controlled trials (RCTs) evaluated post-surgery interventions.
- Risk of bias varied, 25 RCTs were terminated early, predominantly due to poor accrual.
- Due to the variation in interventions, co-interventions, comparators, and outcome measures and reporting, the number of studies that could be combined for analyses was limited.
- There is insufficient evidence for important outcomes including quality of life, functional status, and cognitive effects.
- Studies evaluating WBRT as initial treatment addressed a variety of questions, including the use of radiosensitizers, the effect of neuroprotection, and the addition of systemic therapy.
- Data on neuroprotective strategies is sparse. We did not detect effects of hippocampal sparing WBRT on overall survival, disease-free survival, or quality of life, but time to cognitive decline likely increased.
- The addition of systemic therapy to WBRT was assessed in 19 RCTs. Effects were small and not statistically significant across studies. The combination treatment SRS plus WBRT compared to SRS alone or WBRT alone found no statistically significant difference in overall survival or deaths due to brain metastases.

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- Adding postoperative radiation therapy (WBRT or SRS) (moderate strength of evidence [SoE]) or postoperative WBRT specifically (moderate SoE) did not improve survival over surgery alone.
- Evidence was insufficient for several SRS evaluations and outcomes of interest. Studies varied by intervention, comparator, measures used to assess effects, and reported detail.
- Postoperative radiation (WBRT or SRS) therapy or postoperative WBRT specifically did not improve survival over surgery alone.
- We detected no difference between postoperative SRS and postoperative WBRT in overall survival across studies.
- We did not detect consistent differences in serious adverse events, number of reported adverse events, radiation necrosis, headaches, fatigue and seizures across interventions. WBRT plus systemic therapy was associated with increased risk for vomiting.
- There is insufficient evidence for important clinical outcomes including cognitive effects and functional status. The strength of evidence for quality of life is insufficient to low.



Background and Purpose

Brain metastases are a common problem in cancer care and the incidence is increasing as diagnostic tools are refined and advances in cancer therapy improve survival. The development of brain metastases may have substantial prognostic implications by causing neurologic symptoms or death.

Treatment options for brain metastases include WBRT, SRS, surgery, and systemic therapies. WBRT is administered to the entire brain, typically over multiple treatments (although hippocampal-avoidance WBRT is more selective regarding the dose for different areas of the brain). SRS is a treatment option that delivers precisely-targeted radiation to the brain metastases. Surgery for brain metastases aims to remove the tumor. Systemic therapy includes chemotherapy, targeted therapy or immunotherapy regimens. For some patients, supportive care alone may be appropriate. Each of these treatment options may be considered alone or in combination. Other therapies have been investigated as co-interventions with radiation therapy to either increase efficacy or reduce toxicity. Radiosensitizers are agents that make cancer cells more sensitive to radiation therapy. Memantine is a N-methyl-D-aspartate receptor antagonist that may have neuroprotective effects.

Outcomes including efficacy, impact on quality of life and neurocognition, and adverse effects are important to guide policy makers, clinicians, patients and caregivers. For radiation therapy options, information on the optimal technique (e.g. hippocampal avoidance WBRT), dose and fractionation, and efficacy of co-interventions is needed to inform decisions.

This Agency for Healthcare Research and Quality (AHRQ) evidence report, commissioned and funded by the Patient-Centered Outcomes Research Institute® (PCORI®), synthesizes the available evidence on radiation therapy for brain metastases.

The synthesis aims to support an update of the American Society for Radiation Oncology (ASTRO) guidelines.



Methods

We employed methods outlined in the AHRQ EPC Program Methods Guidance (<https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview>), as described in the full report. The protocol was informed by Key Informants. The systematic review was supported by a Technical Expert Panel and is registered in PROSPERO (CRD42020168260).

We searched PubMed®, Embase®, Web of Science, Scopus, CINAHL®, clinicaltrials.gov, and published guidelines in July 2020; assessed independently submitted data, consulted with experts, and contacted authors.

We included studies evaluating radiation therapy, including WBRT and SRS alone or in combination, as initial or postoperative treatment, with or without systemic therapy (immunotherapy, chemotherapy or targeted therapy) for adults with brain metastases. Eligible studies included RCTs as well as large non-randomized controlled trials and cohort studies comparing two cohorts (for safety and sensitivity analyses).

Studies had to report on effects of radiation therapy in the 1990s or later and we included studies published to July 2020 at the time of the draft report. We restricted to studies that included patients with non-small cell lung cancer, breast cancer, and melanoma. Two reviewers independently screened citations, data were abstracted by one reviewer and checked by an experienced reviewer.

A Technical Expert Panel advised on key outcomes: overall survival, disease-free survival, deaths due to brain metastases, intracranial progression, quality of life, functional status, cognitive effects, serious adverse events, adverse events, radiation necrosis, headaches, fatigue, seizure, vomiting. Random effects meta-analyses computed hazard ratios (HRs), relative risks (RRs), and standardized mean differences (SMDs) together with a 95 percent confidence interval (CI) of the effect estimate where possible. We assessed the SoE as either high, moderate, low, or insufficient. The systematic review is registered in PROSPERO (CRD42020168260).



Results

We identified 97 studies reported in 190 publications in the 9,265 identified citations. Studies assessed WBRT and SRS, alone and in combination with or without systemic therapy, and for resected or unresected lesions. Only 10 RCTs evaluated post-surgery intervention, all other studies evaluated WBRT or SRS as initial treatment. Throughout, data for quality of life, functional status, and cognitive function were often too limited to determine effect estimates across studies. Risk of bias varied, 25 trials were terminated early and the quality of adverse assessment and reporting showed large variation.

WBRT Effects

Sixty studies addressed WBRT, but co-interventions, comparators, and assessed outcomes varied.

Ten RCTs assessed the addition of radiosensitizers to WBRT alone but the analysis found no statistically significant differences between treatment groups for deaths due to brain metastases (RR 1.02; CI 0.13 to 8.24; 2 RCTs; low SoE).

We found no consistent effect of combining WBRT and surgery compared to WBRT alone for overall survival (HR 1.11; CI 0.31 to 3.96; 3 RCTs; low SoE) across studies.

We did not detect consistent effects of prognosis, WBRT dose or primary tumor type (all low SoE) but the number of studies contributing to these analyses was limited.

Data on neuroprotective effects is limited and we did not detect effects of memantine or hippocampal sparing WBRT on overall survival, disease-free survival, or quality of life (all low SoE); but time to cognitive decline increased as documented in one RCT each (WBRT plus memantine HR 0.78; CI 0.62 to 0.99; 1 RCT; low SoE; hippocampal sparing WBRT HR 0.76; CI 0.60 to 0.98; 1 RCT, low SoE).

The addition of systemic therapy to WBRT was assessed in 19 RCTS. Effects were small and not statistically significant across studies (overall survival HR 0.94; CI 0.82 to 1.08; 11 RCTs; low SoE; disease-free survival HR 0.92, CI 0.71 to 1.19; 7 RCTs; low SoE; deaths due to brain metastases RR 1.37, CI 0.66 to 2.85; 5 RCTs; low SoE).

Although key outcomes, data were insufficient for assessing effects of included interventions on quality of life, functional status, and cognitive effects.

SRS Effects

Twenty-nine studies assessed SRS interventions, alone or in combination with WBRT.

The combination treatment SRS plus WBRT compared to SRS alone or WBRT alone found no statistically significant difference in overall survival (HR 1.09; CI 0.69 to 1.73; 4 RCTs; low SoE) or deaths due to brain metastases (RR 0.93; CI 0.48 to 1.81; 3 RCTs; low SoE).

We found no difference in quality of life for SRS plus WBRT compared to SRS alone (-0.04; CI -1.59 to 1.51; 2 RCTs; low SoE) across studies but only two studies contributed to the analysis and results for different time points in individual studies varied.

One study reported a beneficial effect for intracranial progression favoring the combination of SRS plus WBRT but the effect size could not be determined (low SoE). Three studies reported on neurocognitive decline and two favored the SRS alone group compared to SRS plus WBRT but summary effect estimates could not be determined (low SoE).

We did not detect a systematic effect of SRS fractionation schedule (low SoE), patient prognosis (low SoE), or primary tumor type (low SoE), but analyses were limited due to a small number of contributing studies.

We found no evidence suggesting that adding systemic therapy to SRS is beneficial but available data are sparse.

Evidence was insufficient for several SRS evaluations and outcomes of interest. Studies varied by intervention, comparator, measures used to assess effects, and reported detail.

Effects of Post-Surgery Interventions

We identified 10 RCTs assessing postsurgical interventions.

Postoperative radiation (WBRT or SRS) therapy (overall survival HR 0.98; CI 0.76 to 1.26; 5 RCTs; moderate SoE) or postoperative WBRT specifically (overall survival HR 0.93; CI 0.68 to 1.27; 4 RCTs; low SoE; disease-free survival HR 0.79; CI 0.07 to 8.50; 2 RCTs; low SoE) did not improve survival over surgery alone.

Individual studies reported effects on quality of life favoring observation rather than WBRT after surgery (SMD -0.51; CI -0.72 to -0.30; 1 RCT, low SoE). One study favored SRS regarding local recurrence compared to no radiation after surgery (HR 0.46; CI 0.24 to 0.88; 1 RCT, low SoE).

We detected no difference between SRS and WBRT in overall survival across studies (HR 1.17; CI 0.61 to 2.25; 3 RCTs; low SoE). One RCT favored WBRT over SRS regarding intracranial progression rates (HR 2.45; CI 1.61 to 3.72; 1 RCT, low SoE) but SRS over WBRT regarding cognitive function (SMD -0.82; CI 1.11 to 0.53; 1 RCT; low SoE).

There was insufficient evidence for important outcomes including disease-free survival, intracranial progression, quality of life, functional status and cognitive effects.

Adverse Events

We found no difference in serious adverse events when comparing WBRT plus SRS with WBRT or SRS alone (RR 1.05; CI 0.12 to 8.89; 4 studies; moderate SoE), comparing WBRT plus radiosensitizers with WBRT (RR 1.16; CI 0.42 to 3.21; 3 studies, low SoE), comparing WBRT plus systemic therapy versus WBRT alone (RR 1.46; CI 0.77 to 2.45; 8 studies, low SoE), or comparing surgery plus SRS versus surgery plus WBRT (RR 1.33; CI 0.79 to 2.25; 2 studies; low SoE).

We found no difference in radiation necrosis but only WBRT plus SRS compared to WBRT alone or SRS alone (RR 0.93; CI 0.17 to 5.12; 4 studies; low SoE) and WBRT plus systemic therapy compared to WBRT alone (RR 0.89; CI <0.00 to 41413124; 2 studies; moderate SoE) had been assessed in more than one study.

We found no difference in headaches but only WBRT plus systemic therapy compared to WBRT alone (RR 1.16; CI 0.95 to 1.42; 12 studies, moderate SoE) had been assessed in more than one study.

We found no difference in fatigue but only WBRT plus systemic therapy (RR 1.03; CI 0.86 to 1.23; 10 studies; moderate SoE) had been assessed in more than one study.

We found no difference in seizures comparing WBRT plus SRS versus WBRT alone or SRS alone (RR 0.37; CI 0.03 to 5.38; 3 studies, low SoE) and WBRT plus systemic therapy versus WBRT alone (RR 0.74; CI 0.16 to 3.44; 4 studies, low SoE).

WBRT plus systemic therapy showed an increased risk for vomiting compared to WBRT alone (RR 1.58; CI 1.12 to 2.24; 15 studies; moderate SoE). We found no difference for the outcome vomiting comparing WBRT plus SRS with WBRT alone or SRS alone (RR 1.20; CI 0.43 to 3.37; 3 studies; low SoE).

Effects of Patient Characteristics

Across interventions and outcomes, we did not detect systematic differences in study results based on primary tumor type (low SoE) and patient prognosis (low SoE), but the results should be interpreted with caution as they were based on limited data and indirect comparisons. Most identified studies used mixed samples in terms of primary tumor type and prognosis, only WBRT studies allowed analyses at all, and analyses were only possible for selected outcomes.



Strengths and Limitations

This report provides a comprehensive collection of research on radiation treatment in brain metastases. Despite the large number of identified research studies, analyses were limited as studies evaluated unique intervention and comparator combinations and reported insufficient detail on outcomes of interest. Most research was available for WBRT. Fewer studies assessed SRS and post-surgery interventions. Throughout, data are missing on important patient-centered outcomes such as quality of life.



Implications and Conclusions

Despite the substantial research literature on radiation therapy, comparative effectiveness information is limited. The effects of interventions such as memantine and hippocampal avoidance WBRT have only been reported in individual studies and summary estimates across multiple studies do not exist yet. Other intervention characteristics did not show consistent effects or have only been reported in individual studies. We did not detect consistent advantages of combining SRS and WBRT or radiation therapy and systemic therapy, but information was only available for selected outcomes. There is a need for more data on patient-relevant outcomes such as quality of life, functional status, and cognitive effects. Standardizing the use of validated scales and standardizing outcome reporting in studies would allow for better data synthesis in the future. Existing data should be made available through journal publications or data repositories of trial record.

Full Report

Garsa A, Jang JK, Baxi S, Chen C, Akinniranye O, Hall O, Larkin J, Motala A, Newberry S, Hempel S. Radiation Therapy for Brain Metastases. Comparative Effectiveness Review No. 242. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2015-00001-I.) AHRQ Publication No. 21-EHC021. PCORI Publication No. 2020-SR-02. Rockville, MD: Agency for Healthcare Research and Quality; June 2021. DOI: <https://doi.org/10.23970/AHRQEPCCER242>, Posted final reports are located on the Effective Health Care Program [search page](#).

