JUNE 2021

SYSTEMATIC REVIEW

Radiation Therapy for Brain Metastases

In Partnership with

Comparative Effectiveness Review

Number 242

Radiation Therapy for Brain Metastases

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Rockville, MD 20857
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Contract No. 290-2015-00010-I

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AHRQ Publication No. 21-EHC021 **PCORI® Publication No. 2020-SR-02**
June 2021

This report is based on research conducted by the Southern California Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00010-I). The Patient-Centered Outcomes Research Institute® (PCORI®) funded the report (No. 2020-SR-02). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ or PCORI. Therefore, no statement in this report should be construed as an official position of PCORI, AHRQ, or the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

Suggested citation: 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.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

The Patient-Centered Outcomes Research Institute® (PCORI®) was established to fund research that helps patients and caregivers make better informed healthcare choices. To fulfill its authorizing mandate, PCORI partners with AHRQ to generate evidence synthesis products and make comparative effectiveness research more available to patients and providers.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Lionel Bañez, Jennie Dalton Bowen, Lisa Bradfield, and Ethan Balk for helpful comments. We also thank the authors Paul Brown, Lois Browne, Peter Graham, Siow Ming Lee, Mark Middleton, Alan Nichol, Stephanie Pugh, Srinivas Raman, and Daniel Roos for additional data or clarifications regarding data. In addition, we would like to thank Armenda Bialas and Lea Xenakis for project assistance.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Radiation Therapy for Brain Metastases

Structured Abstract

Objective. This evidence report synthesizes the available evidence on radiation therapy for brain metastases.

Data sources. 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.

Review methods. The protocol was informed by Key Informants. The systematic review was supported by a Technical Expert Panel and is registered in PROSPERO (CRD42020168260). Two reviewers independently screened citations; data were abstracted by one reviewer and checked by an experienced reviewer. We included randomized controlled trials (RCTs) and large observational studies (for safety assessments), evaluating whole brain radiation therapy (WBRT) and stereotactic radiosurgery (SRS) alone or in combination, as initial or postoperative treatment, with or without systemic therapy for adults with brain metastases due to non-small cell lung cancer, breast cancer, or melanoma.

Results. In total, 97 studies, reported in 190 publications, were identified, but the number of analyses was limited due to different intervention and comparator combinations as well as insufficient reporting of outcome data. Risk of bias varied; 25 trials were terminated early, predominantly due to poor accrual. Most studies evaluated WBRT, alone or in combination with SRS, as initial treatment; 10 RCTs reported on post-surgical interventions.

The combination treatment SRS plus WBRT compared to SRS alone or WBRT alone showed no statistically significant difference in overall survival (hazard ratio [HR], 1.09; confidence interval [CI], 0.69 to 1.73; 4 RCTs; low strength of evidence [SoE]) or death due to brain metastases (relative risk [RR], 0.93; CI, 0.48 to 1.81; 3 RCTs; low SoE). Radiation therapy after surgery did not improve overall survival compared with surgery alone (HR, 0.98; CI, 0.76 to 1.26; 5 RCTs; moderate SoE). Data for quality of life, functional status, and cognitive effects were insufficient to determine effects of WBRT, SRS, or post-surgical interventions.

We did not find systematic differences across interventions in serious adverse events radiation necrosis, fatigue, or seizures (all low or moderate SoE). WBRT plus systemic therapy (RR, 1.44; CI, 1.03 to 2.00; 14 studies; moderate SoE) was associated with increased risks for vomiting compared to WBRT alone.

Conclusion. Despite the substantial research literature on radiation therapy, comparative effectiveness information is limited. There is a need for more data on patient-relevant outcomes such as quality of life, functional status, and cognitive effects.

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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.
- 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 records.

Introduction

Background

The development of secondary malignant growths has particular implications when cancer metastasizes to the brain. The management of brain metastases is challenging due to the effects of the disease and treatment on patients. This systematic review synthesizes the literature on the effects of radiation therapy to treat brain metastases.

Brain metastases are a common problem in cancer care, occurring in 10 to 30 percent of adult patients.[1] The apparent incidence of brain metastases is increasing as diagnostic tools are refined, and advances in systemic therapy that improve survival may also be leading to an actual increase.[2, 3] The development of brain metastases may have substantial prognostic implications by causing neurologic symptoms or death.

Historically, patients with brain metastases had a poor prognosis, and little thought was given to determining each individual's prognosis and optimal treatment.[4] However, the patient population affected by brain metastases is heterogeneous, and recent studies have shown that prognosis can vary substantially. Prognostic indices such as the diagnosis-specific graded prognostic assessment (DS-GPA) have been developed using diagnosis and DS-GPA score to estimate median survival.[5-8] Brain metastases occur with a variety of cancers, which may result in different subtypes or molecular profiles that respond differently to treatment.[3] Primary tumors that most commonly metastasize to the brain are lung cancer (30-60% of all brain metastases), breast cancer (5-30% of brain metastases in women), and melanoma (5-21%); this systematic review focuses on these primary cancer types.[3]

Treatment options for brain metastases include whole brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgery, and systemic therapies. WBRT is administered to the entire brain, typically over multiple treatments (although hippocampal-avoidance WBRT is more selective to avoid the memory-specific neural stem cell compartment in the hippocampi). 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. 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.

Palliative care also serves an important role in the management of patients with brain metastases. The American Society of Clinical Oncology (ASCO) recommends that all patients diagnosed with advanced cancer, including patients with distant metastasis, should receive dedicated palliative care services early in the disease course, concurrent with active treatment.[9] For some patients with a very poor prognosis, palliative care alone may be appropriate.[10]

Several guidelines for the management of brain metastases have been published.[11-16] The American Society of Radiation Oncology (ASTRO) published guidelines for the radiotherapeutic and surgical management of brain metastases in 2012.[11] The ASTRO guidelines recommended using estimated prognosis and aims of treatment to guide management decisions. The use of histology-specific prognostic indices was recommended to estimate prognosis. For patients with an expected survival of 3 months or more, the number, size and resectability of metastases were identified as important factors to consider. For patients with a single brain metastasis and good prognosis, potential management options include surgery and WBRT or SRS, SRS alone,

WBRT, or combined WBRT and SRS. For patients with multiple brain metastases and a good prognosis, WBRT, SRS alone, or combined WBRT and SRS were recommended options for consideration. For patients with poor prognosis (expected survival less than three months), palliative care with or without WBRT was recommended. Regarding radiation dose fractionation for WBRT, the guideline noted that no altered dose fractionation scheme improved survival or symptom control compared with the commonly used 30 Gray (Gy) in ten daily fractions or 20 Gy in five daily fraction schemes. The ASTRO guidelines highlighted the limited neurocognitive outcomes data available at the time and recommended further trials to address this shortcoming.

The focus of this review is on radiation therapies, although the effects of combining other treatments with radiation are also addressed. For each of the available radiation treatments, several important clinical questions must be considered. Regarding WBRT, additional information on the optimal technique (e.g., hippocampal avoidance WBRT), dose, and fractionation is needed. Does the efficacy of WBRT depend on tumor histology and patient prognosis? What are the benefits and harms of WBRT on quality of life and neurocognition that need to be communicated to patients and caregivers? Do co-interventions such as memantine mitigate the neurocognitive effects, and if so, should they be offered in conjunction with WBRT? Is there a benefit to adding SRS to WBRT? And does the addition of systemic therapy change the efficacy or toxicity of WBRT?

For SRS, clinicians need to know how does the effectiveness compare to that of WBRT? Does the effectiveness depend on tumor type or the number or volume of brain metastases, and, if so, should the treatment plan be adapted accordingly? Does the effectiveness depend on tumor size or radiation dose and fractionation? Does the addition of systemic therapy change the efficacy or toxicity of SRS?

Several Key Questions must be considered for patients who undergo surgical resection of brain metastases. How do the outcomes compare among no radiation postoperative WBRT, postoperative SRS and preoperative SRS? To decide on the best treatment approach, patients and providers need to evaluate existing evidence on whether the effectiveness or toxicity and adverse events varies with tumor type, size, or dose and fractionation.

In addition, updated information is needed on adverse events associated with the interventions to guide policy makers, clinicians, patients, and caregivers. Critical questions include the following: What adverse cognitive effects are to be expected with the different radiation treatment options? What adverse effects of SRS do patients and caregivers need to consider, and how do they compare with those of WBRT? Does systemic therapy change the toxicity of treatment so that patients need to carefully weigh the advantages and disadvantages? In patients undergoing surgical resection, how do adverse events compare among those who also undergo postoperative WBRT or SRS therapy, compared with observation alone, to inform decisions?

Although aspects of these questions have been addressed in published systematic reviews,[12-14, 17-74] and there is some clinical guidance on the topic,[11-16, 49] our literature searches and stakeholder input indicated the need for an up-to-date, comprehensive evidence review on radiation therapy for brain metastases.

Purpose and Scope of the Systematic Review

This Agency for Healthcare Research and Quality (AHRQ) evidence report, commissioned 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 ASTRO guidelines. The focus of this review is radiation therapies, although the effects of combining other treatments with radiation are also addressed.

Methods

Review Approach

The methods for this evidence review follow the Methods Guide for the Evidence-based Practice Center (EPC) Program. Appendix A provides more detail on the methods. Appendix B provides the list of excluded and background studies. Appendix C provides more details on the results and Appendix D provides the evidence tables. The topic of this report was developed by the Patient-Centered Outcomes Research Institute (PCORI) in consultation with the Agency for Healthcare Research and Quality (AHRQ). Initially a panel of Key Informants provided input on the Key Questions to be addressed. The Key Questions were posted on AHRQ's Effective Health Care (EHC) website for public comment for 3 weeks in July 2019, and PCORI conducted a stakeholder call to discuss the Key Questions in August 2019. The EPC revised the questions in response to comments. A panel of Technical Experts provided high-level content and methodological expertise throughout development of the review protocol. Further details regarding expert guidance and review are provided in Appendixes E and F. The final protocol is posted on the EHC website at https://effectivehealthcare.ahrq.gov/products/radiation-brain-metastases/protocol. The PROSPERO registration is CRD42020168260.

Key Questions

The report was guided by four Key Questions, addressing initial and post-surgery treatment effects and adverse events.

Key Question 1. What is the effectiveness of whole brain radiation therapy (WBRT), alone or in combination with stereotactic radiosurgery (SRS) or systemic therapies, as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

a. How does effectiveness vary by dose fractionation schedule and technique?

b. How does effectiveness differ by patient prognosis and primary tumor site?

c. How does effectiveness differ by the addition of systemic therapies?

Key Question 2. What is the effectiveness of SRS/fractionated stereotactic radiation as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

a. How does effectiveness vary by dose fractionation schedule and technique?

b. How does effectiveness differ by patient prognosis and primary tumor site?

c. How does effectiveness differ by the addition of systemic therapies?

Key Question 3. What is the effectiveness (or comparative effectiveness) of postoperative SRS compared to WBRT, observation, or preoperative SRS in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

a. How does effectiveness vary by dose fractionation schedule?

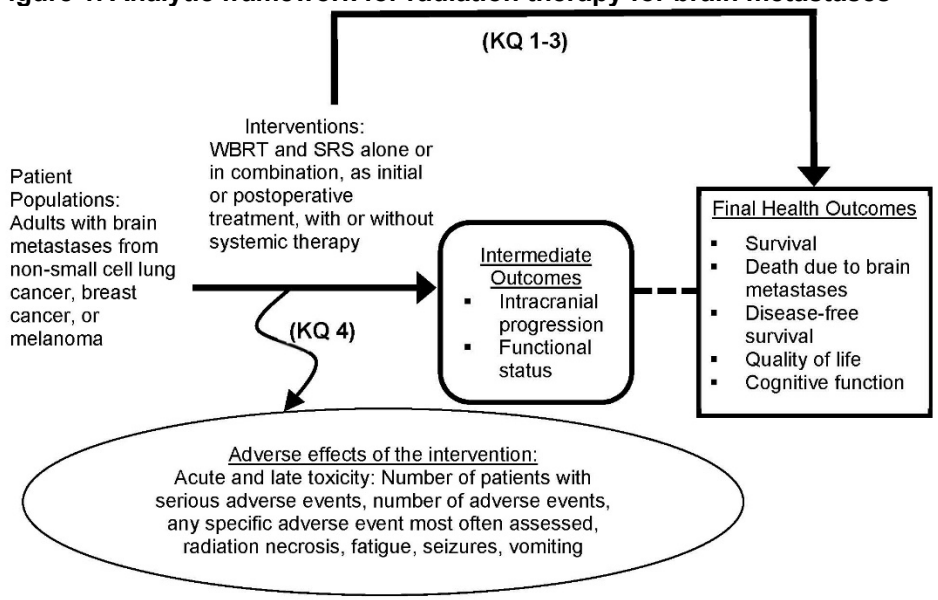
Key Question 4. What are the adverse effects (i.e., serious harms) of WBRT, SRS, and systemic therapies for patients with brain metastases (either alone or in combination)?

a. Do adverse effects vary by important patient characteristics (i.e., age, performance status, patient prognosis, disease status, primary tumor site) or dose fractionation schedule and technique?

Analytic Framework

The analytic framework (Figure 1) outlines the patient population, the interventions, and the outcomes that are addressed in the evidence synthesis.

Figure 1. Analytic framework for radiation therapy for brain metastases



Abbreviations: KQ = Key Question, SRS = stereotactic radiosurgery, WBRT = whole brain radiation therapy

Study Selection

We included randomized controlled trials (RCTs) 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 due to non-small cell lung cancer, breast cancer, and melanoma. Studies had to report on effects of radiation therapy in the 1990s or later, and we included studies published to July 2020. We also included large (N≥200) clinical controlled trials and cohort studies comparing two cohorts to address adverse effects of the interventions. The details of the sources, search strategies, screening procedure, and the eligibility criteria are described in detail in Appendix A.

Data Extraction and Risk of Bias Assessment

We abstracted study, patient, intervention and comparator details, and documented the results for clinical and patient-centered outcomes as well as adverse events. Publications reporting on the same patient group were consolidated. To facilitate comparisons across studies, we standardized descriptions (e.g., intervention characteristics) and converted study characteristics to proportions. Results were converted to measure-independent variables such as relative risks and standardized mean differences and effect estimates were presented together with 95-percent confidence intervals. Time to event data were analyzed as the hazard ratio.

Risk of bias assessed selection bias and risk of bias arising from the randomization process, performance bias and bias due to deviations from intended interventions, attrition bias and bias due to missing outcome data, detection bias and bias in measurement of the outcome, reporting bias and bias in selection of the reported results, and other sources of bias (lack of use of validated measures). In addition, we evaluated the data collection of adverse events and the reporting of adverse events.

The procedures are described in detail in Appendix A.

Data Synthesis and Analysis

We synthesized the effects of WBRT (Key Question [KQ] 1), SRS (KQ2), post-surgery treatment (KQ3), and any adverse events (KQ4) associated with the interventions. Where outcomes, interventions, and comparators allowed, we determined pooled effects across studies for the following outcomes: overall survival, disease-free survival, deaths due to brain metastases, intracranial progression, quality of life, functional status, cognitive effects, serious adverse events, number of adverse events, radiation necrosis, headaches, fatigue, seizure, and vomiting. We assessed statistical heterogeneity with the I-squared statistic and explored publication bias (Begg, Egger test). To address the subquestions, we conducted meta-regressions to detect effect modifiers such as the role of prognosis and the primary cancer site in indirect analyses across studies. The analytic methods are documented in detail in Appendix A.

Contacting Authors

To allow for more analyses, we contacted all RCTs' authors and asked specifically about the 14 outcomes of interest and the effect measure we were using (e.g., time to event data to compute hazard ratios, mean and standard deviation for intervention and control group to compute mean differences between groups). We asked authors to send us the data or to submit to clinicaltrials.gov.

Grading the Strength of the Body of Evidence

We formulated evidence statements for the interventions and outcomes of interest. We then graded the strength of evidence to describe our confidence in effect estimates as high, moderate, low, and insufficient evidence. The assessment is based on our analysis of the study limitations, directness, consistency, precision, and reporting bias (see Appendix A for more details).

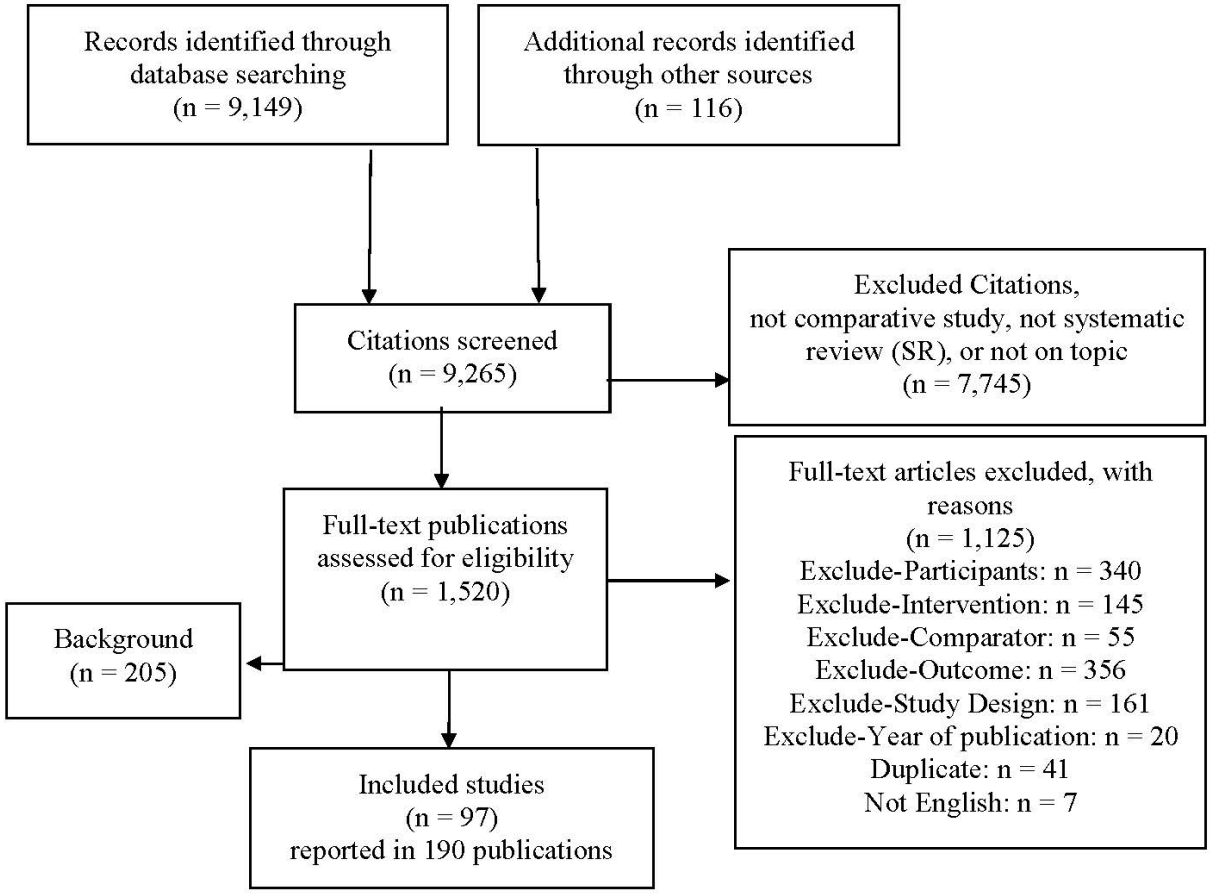
Results

For each Key Question, we summarize key points, synthesize the data, and summarize the strength of evidence. The list of excluded studies and the reasons for exclusion are documented in Appendix B. Details on results of literature search results and included studies are described in Appendix C. The evidence table of included studies is documented in Appendix D.

Description of Included Evidence

We identified 97 studies published in 190 publications.[10, 75-263] Of the 9,265 identified citations, 1,520 were assessed as full text. Of these, 1,125 were excluded and 205 were retained as background (e.g., systematic reviews to reference mine). Figure 2 shows the literature flow diagram.

Figure 2. Study flow diagram

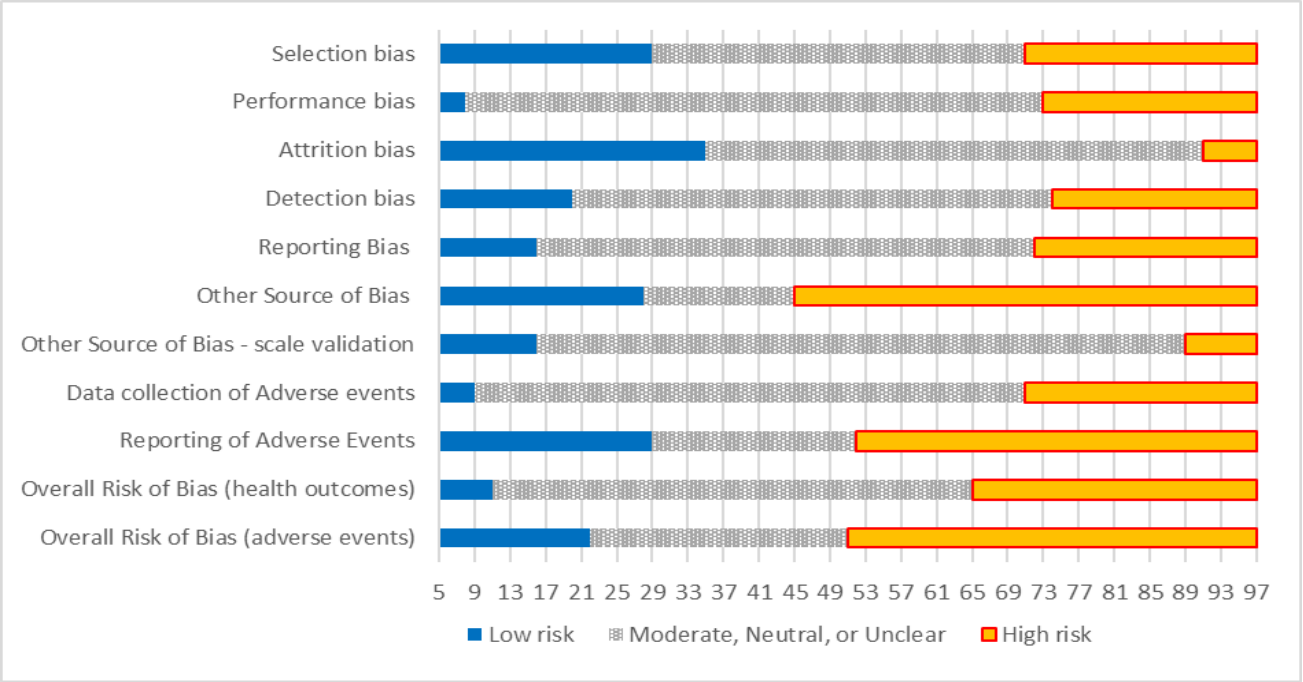


Samples included patients with breast cancer, lung cancer, and melanoma, but the largest set of studies included combinations of patients with different cancer origins. Twenty-two studies were observational studies comparing two treatment cohorts, all other 75 studies were randomized controlled trials (RCTs). The largest proportion of studies evaluated whole brain radiation therapy (WBRT) (60 RCTs), alone or in combination with other treatments, which is addressed in Key Question 1. Key Question 2 focuses on the smaller set of studies that assessed stereotactic radiosurgery (SRS) intervention groups (13 RCTs). Key Question 3 synthesizes the

evidence for the 10 identified post-surgery RCTs. Key Question 4 addresses adverse events across all interventions (81 RCTs and cohort studies). All included studies reported at least one outcome of interest, but the reporting varied in quality and some studies did not report sufficient detail for meta-analyses.

The risk of bias assessment is documented in detail in Appendix C. Noteworthy is the large proportion of trials that were terminated prematurely and the wide variation in how adverse events were assessed and reported. In 19/25 cases, studies were terminated early due to slow accrual of participants. Figure 3 summarizes results across studies and domains.

Figure 3. Risk of bias summary



The remainder of this chapter reports on the outcomes that have been identified as key outcomes: *overall survival, disease-free survival, deaths due to brain metastases, intracranial progression, quality of life, functional status, cognitive effects, number of patients with serious adverse events, number of adverse events, headache, radiation necrosis, fatigue, seizures,* and *vomiting*.

Studies reported a variety of measures. Most included studies reported on overall survival. Some studies reported sufficient detail to compute effects for disease-free survival and for deaths due to brain metastases. While many studies reported on intracranial progression, the individual measures varied widely, which limited analyses across studies. While some studies reported on quality of life scales, including scales that could be combined in scale-independent analyses, the majority did not report sufficient detail to allow effect sizes to be computed. Functional status has been addressed in some studies but either not in sufficient detail or using unique measures, so that only few analyses were possible based on the outcome. Cognitive effects were reported only in some studies and these studies used a variety of different measures, rarely reporting sufficient detail to allow us to compute effect sizes.

Other outcomes reported in individual studies are documented in Appendix D. In addition, the appendix shows results for studies that reported insufficient detail to allow us to compute

effect sizes. The results chapter focuses on effect estimates that are based on more than one study. All individual study results are documented in Appendix D.

Key Question 1. What is the effectiveness of WBRT, alone or in combination with SRS or systemic therapies, as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

Key findings for WBRT as initial treatment (assessed in 60 RCTs) include the following:

Key Points

- 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 (relative risk [RR] 1.02; confidence interval [CI] 0.13 to 8.24; 2 RCTs; low strength of evidence [SoE]) across studies.
- We found no consistent effect of combining WBRT and surgery compared to WBRT alone for overall survival (hazard ratio [HR] 1.11; CI 0.31 to 3.96; 3 RCTs; low SoE) across studies.
- We did not detect consistent effects of WBRT dose, prognosis, or primary tumor site (all low SoE) but the number of studies that could be combined for these analyses was limited.
- Data on neuroprotective effects is sparse 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.

The RCTs evaluated different aspects of WBRT therapy as initial treatment and we have stratified the evidence accordingly.

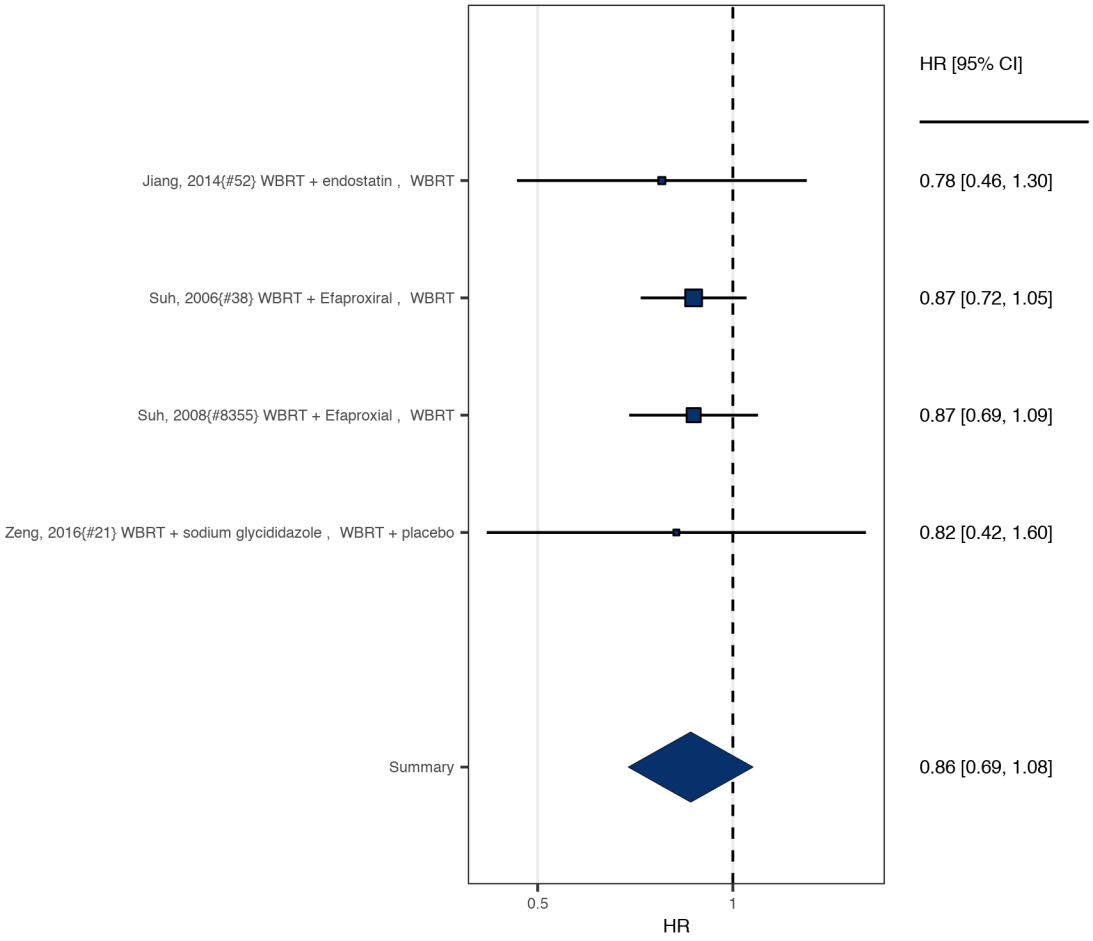
WBRT Plus Steroids Versus WBRT Alone

Wolfson et al. assessed administering steroids (dexamethasone) with WBRT.[163] The high risk of bias study indicated an advantage to WBRT plus dexamethasone over that of WBRT alone with regard to functional status as reported by the authors, but effect sizes could not be computed due to lack of sufficient detail.

WBRT Plus Radiosensitizers Versus WBRT Alone

We identified 10 RCTs that assessed the effect of adding potential radiosensitizers to WBRT treatment.[94, 107, 109, 127, 128, 138, 149, 155, 156, 168] Figure 4 shows the effect on overall survival in the RCTs reporting on this outcome in sufficient detail.[109, 155, 156, 168]

Figure 4. WBRT plus radiosensitizers versus WBRT alone: overall survival



Abbreviations: CI confidence interval; HR hazard ratio; WBRT whole brain radiation therapy

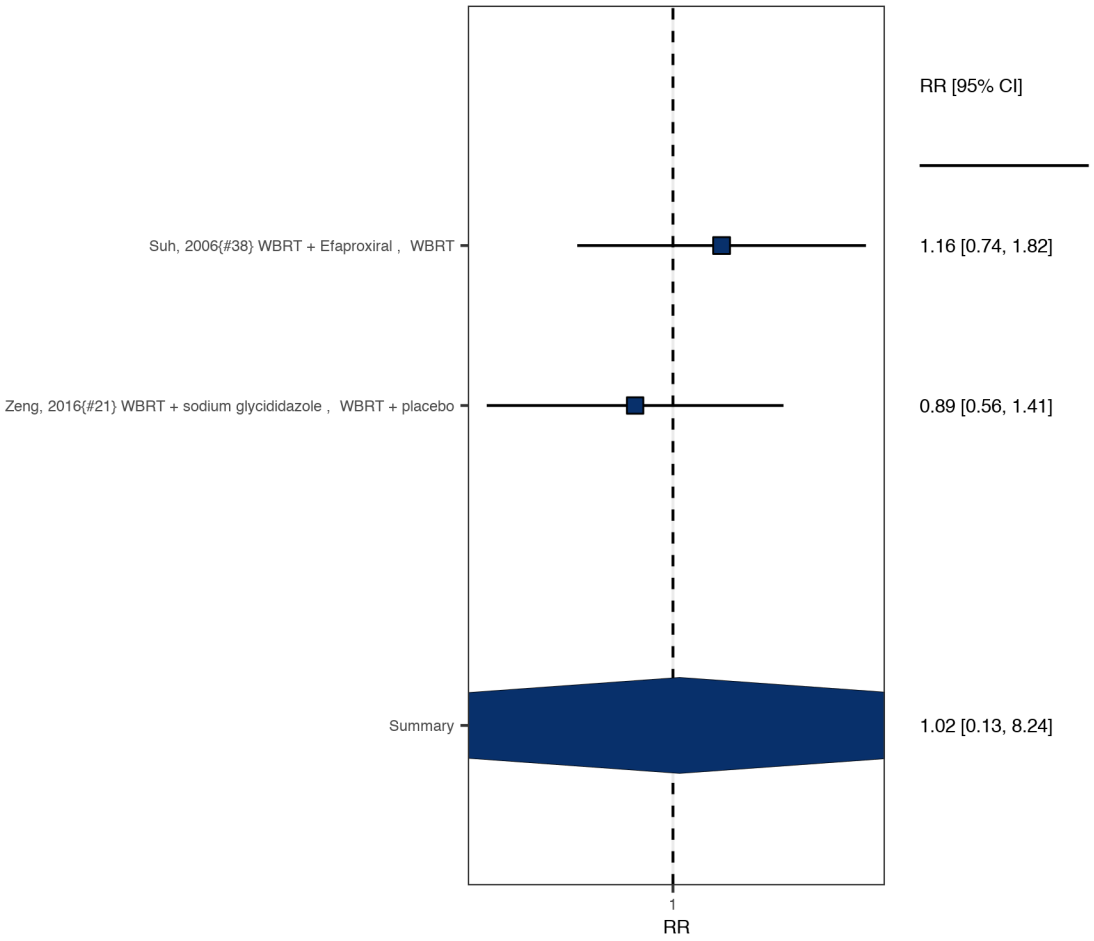
All individual studies (low to medium risk of bias) that added radiosensitizers to WBRT showed higher overall survival in the radiosensitizer than the control group but the effect was not statistically significant for individual studies or across studies (HR 0.86; CI 0.69 to 1.08; 4 RCTs) and there was no indication of heterogeneity (I^2 0). Five additional RCTs evaluating radiosensitizers that reported other survival data could not be included in the pooled analysis; the individual studies reported also no statistically significant differences between interventions (Phillips et al. for bromodeoxyuridine, Rojas-Puentes et al. for chloroquine, El-Hamamsy et al. for simvastatin, and Mehta et al. in 2 RCTs for motexafin gadolinium).[94, 127, 128, 138, 149]

Five RCTs reported on progression-free survival but the pooled effect size could not be established due to insufficient data. Only Mehta et al. (2009)[128] reported sufficient detail to compute the hazard ratio (HR 0.78; CI 0.57 to 1.06; 1 RCT), the effect of motexafin gadolinium

was not statistically significant. Rojas-Puentes et al.[149] reported results that favored the WBRT plus placebo rather than the WBRT plus chloroquine group (statistical significance not given) and Zeng et al.[168] reported longer median central nervous system (CNS) progression-free survival when adding sodium glycididazole (p=0.04). El-Hamamsy et al. (simvastatin),[94] and Suh et al.[155] (efaproxiral) reported no significant difference between treatment groups.

Two studies assessed deaths due to brain metastases and reported sufficient detail to compute effect sizes as shown in Figure 5.

Figure 5. WBRT plus radiosensitizers versus WBRT alone: deaths due to brain metastases



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

The pooled effect suggested no difference between the intervention approaches but the individual studies reported conflicting results and the confidence interval is wide (RR 1.02; CI 0.13 to 8.24; 2 RCTs). Statistical heterogeneity was not detected. An additional study by Mehta[127] using motexafin gadolinium could not be combined in the analysis; the RCT reported no differences in deaths from CNS causes (p=0.60).

Mehta et al. reported significant time differences to progression in one of two RCTs[127, 128] in favor of the motexafin gadolinium group. Phillips et al.[138] reported three patients out of 21 patients with progression at three months in the radiosensitizer group compared to none out of 23 patients in the WBRT group.

Some of the identified RCTs reported on quality of life but effect sizes could only be calculated for one study. Mehta et al.[127] reported no significant difference between groups for motexafin gadolinium (HR 1.14; CI 0.74 to 1.75; 1 RCT). Suh et al.[155] indicated that a larger percentage of patients in the efaproxiral group had stable or improving quality of life scores. Rojas-Puentes, 2013[149] reported no differences between groups with chloroquine and El-Hamamsy et al.[94] reported no significant differences for simvastatin.

Mehta et a.[127] and Suh et al.[156] reported no significant difference in functional status.

One other RCT by Mehta et al.[128] reported on cognitive effects; the authors reported a longer time interval to neurocognitive progression (p=0.057).

Another identified RCT by Hosseini et al. reported only on adverse events of interest (see KQ4).[107]

WBRT Plus SRS Versus WBRT Alone

We identified three RCTs that assessed the combination of WBRT and SRS to determine whether adding SRS improves outcomes compared with receiving WBRT alone.[75, 93, 117] With the exception of Andrews et al.,[75] the studies did not report outcomes in sufficient detail to compute effect sizes independently and the studies could not be combined.

None of the studies reported a survival benefit or fewer deaths due to brain metastases for the combination treatment compared to WBRT alone. However, the Radiation Therapy Oncology Group (RTOG) 9508 trial (Andrews et al.) reported a survival benefit in a subgroup of patients with a single brain metastasis favoring the combination treatment (all patients HR 1.14; CI 0.74 to 1.75; 1 RCT).[75] The number of risks due to brain metastases was lower in the combination group but not statistically different (RR 0.86; CI 0.06 to 1.25; 1 RCT).

Kondziolka et al. reported better local control in the combination treatment group (p=0.002).[117]

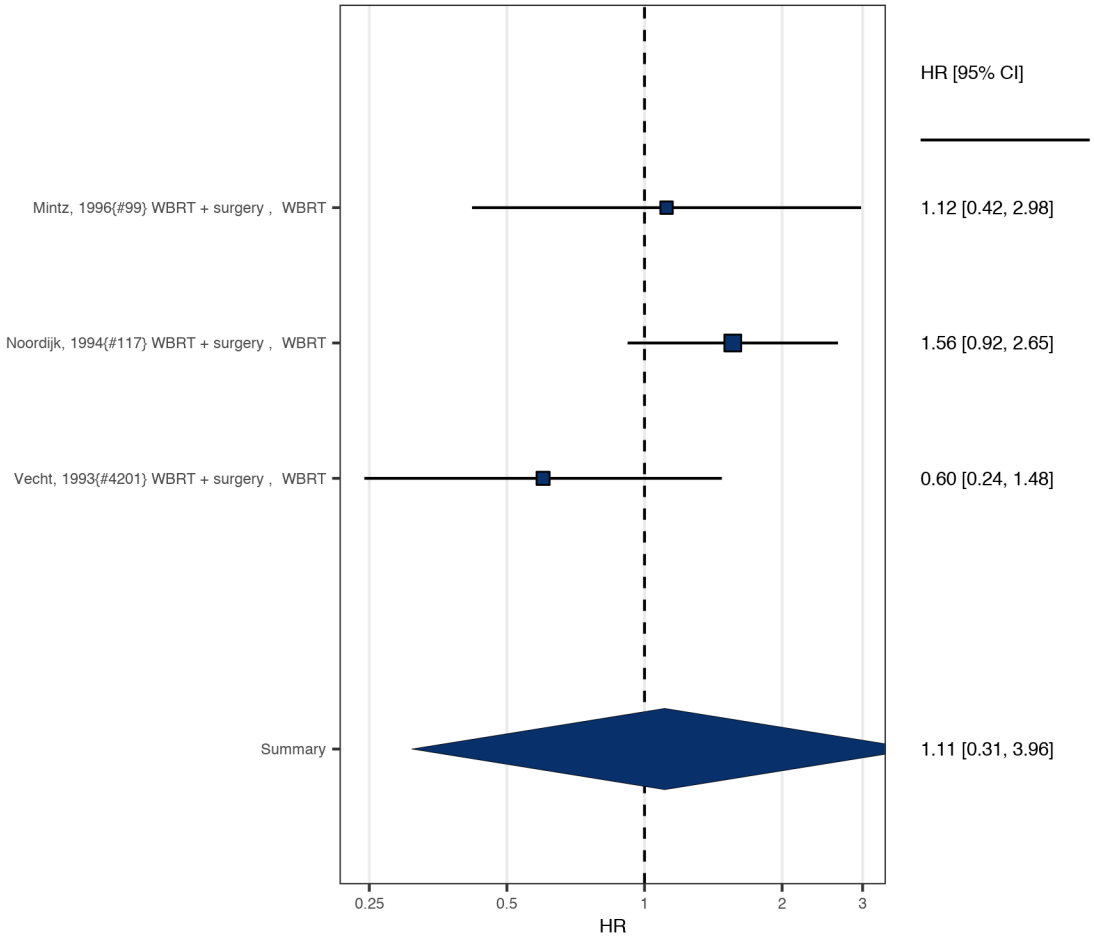
Andrews et al.[75] reported improvements in Karnofsky Performance Status[75] in the combination treatment group (patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status score at 6 months: 43% vs 27%; p=0.03) but no other study reported on this outcome. Andrews et al.[75] found no difference in mental status.

We combined the results reported by Andrews with other WBRT plus SRS combination studies that compared to SRS alone, see KQ2.

WBRT Plus Surgery Versus WBRT Alone

We identified three RCTs that evaluated the comparative effects of adding surgery to WBRT treatment; the study results for overall survival are shown in Figure 6.[131, 136, 160]

Figure 6. WBRT plus surgery versus WBRT alone: overall survival

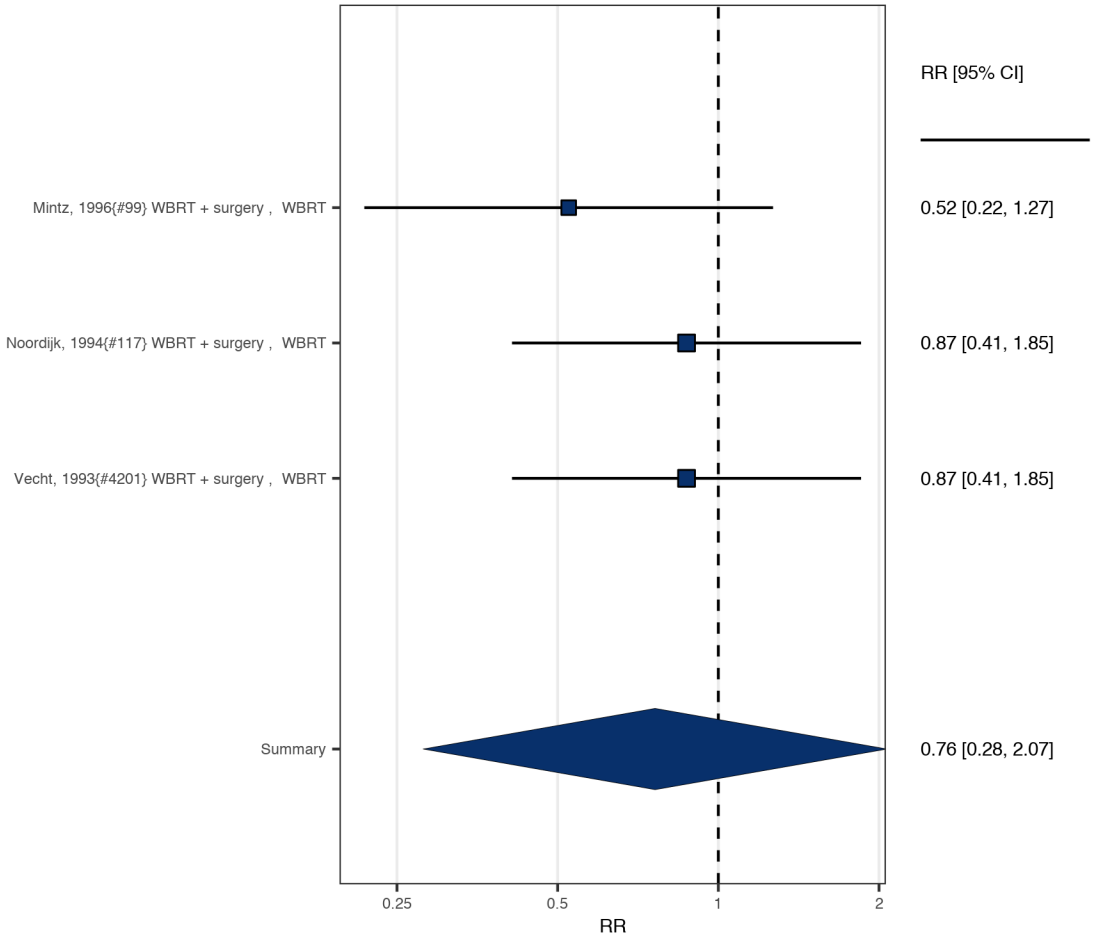


Abbreviations: CI confidence interval; HR hazard ratio; WBRT whole brain radiation therapy

Two studies reported conflicting results and across studies there was no systematic difference (HR 1.11; CI 0.31 to 3.96; 3 RCTs). The analysis detected heterogeneity despite the small number of studies (I^2 40%). Neither of the studies was high or low risk of bias and it was not possible to assign more weight to one than the other.

The studies also reported on the number of deaths due to brain metastases as shown in Figure 7.

Figure 7. WBRT plus surgery versus WBRT alone: deaths due to brain metastases



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

Across studies, the combination treatment showed a lower risk of death due to brain metastases but the effect was not statistically significant (RR 0.76; CI 0.28 to 2.07; 3 RCTs).

With regard to other effectiveness outcomes, Mintz et al.[131] reported no statistically significant difference in quality of life (standardized mean difference (SMD) 0.09; CI -0.34, 0.52; 1 RCT) or functional status (SMD 0.00; CI -0.43 to 0.43). Vecht et al. indicated that improvement in functional status occurred more rapidly and for longer periods of time after the combination treatment but the effect was not statistically significant.[160]

Adjunctive WBRT Versus Supportive Care Alone

We identified only one (low risk of bias) study that evaluated whether patients receiving supportive care benefit from additional WBRT.[10] Mulvenna et al. reported no difference in overall survival or quality of life compared to supportive care alone but there was insufficient detail to compute effect sizes and no other study was identified that reported on the research question.

Adjunctive WBRT Plus Systemic Therapy Versus Systemic Therapy Alone

Some of the identified studies assessed the effect of WBRT as adjunctive therapy, i.e., adding WBRT to systemic therapy and compared the effects to patients receiving only systemic therapy, including three RCTs.[132, 148, 164]

Robinet et al. reported no statistically significant difference in overall survival (HR 1.14; CI 0.82 to 1.59; 1 RCT).[148] Mornex et al.[132] reported insufficient detail to compute hazard ratios but the authors reported no statistically significant difference in overall survival but improvement in time to cerebral progression. Yang et al.[164] compared patients that received WBRT plus platinum-based doublet first line and pemetrexed or docetaxel as second line treatment compared to patients receiving only icotinib and no WBRT. Patients did not differ in overall survival but patients only receiving icotinib reported longer progression-free survival and there were fewer cases with progressive disease in the study period. Robinet et al. reported no statistically significant difference in disease-free survival (HR 1.18; CI 0.84 to 1.66; 1 RCT).[148] Of note, a cohort study published by Jiang et al.[108] that compared epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors plus WBRT to systemic therapy alone also found no statistically significant difference for overall survival, disease-free survival, or progressive disease.

Robinet et al. found no systematic difference for the number of deaths due to brain metastases (RR 0.94; CI 0.81 to 1.09).[148]

Yang, 2017[164] reported 23 percent of patients with progressive disease for WBRT versus 12 percent in the icotinib group. Yang, 2017[165] reported 4 percent (WBRT + bevacizumab + gefitinib) versus 27 percent (WBRT alone) patients with progressive disease.

Yang et al.[164] reported also on cognitive function; the observed difference of Mini-Mental State Examination (MMSE) scores was not significant between groups (p=0.663).

KQ1a. Dose Fractionation Schedule and Technique

We identified seven RCTs that compared different doses in head-to-head trials.[87, 90, 99, 134, 141, 152, 169] The evaluations varied widely, with no studies addressing the same dyad of intervention and comparator, and the intervention in one study served as the control group in another study (e.g., 20 Gy vs 30 Gy, and 30 vs 50 Gy).

Only one of the head-to-head trials that provided sufficient information to compute effect sizes reported a statistically significant superiority of a particular intervention for the outcomes of interest.[99] Graham et al. reported results favoring the 40 Gy in 20 twice-daily fractions for CNS progression-free survival (HR 0.55; CI 0.31 to 1.00; 1 RCT) and deaths due to brain metastases (RR 0.63; CI 0.4 to 1.00; 1 RCT) but not other outcomes compared to 20 Gy in four daily fractions.[99] All other comparisons are documented in Table 1. Of note, one included observational study concluded that the simultaneous delivery of WBRT with reduced fraction dose and boost proved to be advantageous prolonging overall survival with shortened treatment time and reduced probability for cognitive decline development even for patients with poor performance status and progressing extracranial disease.[92]

As all studies reported on different outcome measures, the maximum number of studies that could be combined was three studies for overall survival. Therefore, we could not explore a dose-response relationship.

We also computed meta-regressions across studies to determine whether we could detect a relationship of the dose and the study results in the WBRT studies. Perhaps not surprisingly

given the diversity of the radiation interventions, the co-interventions, and comparators, we could not detect systematic dose-repose effects for the analyzable outcomes of overall survival (p=0.97), disease-free survival (p=0.65) or deaths due to brain metastases (p=0.09).

WBRT With Neuroprotection

Studies assessed the addition of memantine and hippocampal avoidance-WBRT.

Memantine

One identified study assessed the effect of the addition of memantine to WBRT treatment. The RCT, RTOG 0614, published by Brown et al.[82] was classified as medium risk of bias. It reported on a number of outcomes of interest for this review but we identified no other study reporting on the same intervention and comparison group. The individual study showed no differences between WBRT alone and WBRT plus memantine for overall survival and progression-free survival. However, the authors reported that WBRT plus memantine delayed the risk of cognitive decline (HR 0.78, CI 0.62 to 0.99; 1 RCT) and reduced the rates of decline in memory, executive function, and processing speed compared with WBRT alone (insufficient detail to compute standardized mean differences).

Hippocampal Avoidance-WBRT

The literature review also identified three RCTs that tested the potential advantages of hippocampal avoidance-WBRT over those of traditional WBRT.[80, 104, 166] The studies could not be combined because they did not report the same outcomes; two of the studies were determined to be high risk, one low risk of bias.

Brown et al., reporting results of the low risk of bias NRG CC001 trial, found no statistically significant difference in overall or intracranial-progression free survival and indicated no differences between arms in quality of life. However, comparing patients treated with hippocampal avoidance WBRT with memantine versus those treated with WBRT with memantine alone, hippocampal avoidance WBRT was associated with a lower risk of cognitive failure, with less deterioration of executive function and learning and memory.[80] The other RCT reported by Hauswald et al.[104] was stopped early due to slow patient recruitment and the authors reported that data for quality of life for the seven patients were not analyzable. Overall survival was five months versus four months comparing hippocampal-sparing WBRT with standard WBRT.

Yang et al. applied multiple cognitive tests. Results varied by test and follow up date; the authors concluded that hippocampal-avoidant conformal WBRT without memantine has better preservation in late verbal memory, but not in verbal fluency or executive function, compared to conformal WBRT without hippocampal avoidance.[166]

KQ1b. Patient Prognosis and Primary Tumor Site

The evidence table in Appendix D shows the study characteristics in detail and Appendix C outlines in detail that studies typically used patient samples that varied widely. Hence, it is difficult to determine whether effectiveness differs systematically by patient characteristics.

To address this Key Question, we identified studies of patients with good prognosis and studies in patients with poor prognosis. We conducted meta-regressions to assess the effect of the prognosis on the study's effect size estimate indirectly across studies. We did not detect a systematic effect of patient prognosis on overall survival (p=0.34). However, this finding should

be interpreted with caution as most studies were in mixed samples and only four studies could be classified as patient samples with a good prognosis[81, 112, 126, 139] and only four studies of patients with poor prognosis[10, 94, 135, 168] were identified. All other studies were in patients with unclear or mixed prognosis samples and did not meaningfully contribute to the analysis. We also did not detect differences in results for other outcomes (number of patients with death due to brain metastases p=0.82) that might be attributable to prognosis.

We also aimed to determine whether the primary tumor site affects the outcomes of interventions. Visual inspections of forest plots stratified by tumor site did not indicate clear trends but most studies were in mixed samples and did not contribute to the analyses. We combined all studies with a passive comparator (e.g., supportive care or base treatment given to both arms) and conducted meta-regressions across studies. Compared to studies in patients with breast cancer only (reference standard for the analysis), studies in patients with lung cancer only (overall survival p=0.51) and studies in patients with different cancer types (overall survival p=0.39) did not indicate apparent differences in study results for the outcomes overall survival, disease-free survival, and number of deaths due to brain metastases (i.e., the primary tumor site was not a significant predictor of the estimated effect size). However, these findings should be regarded with caution given the small number of pertinent studies.

KQ1c. Addition of Systemic Therapies

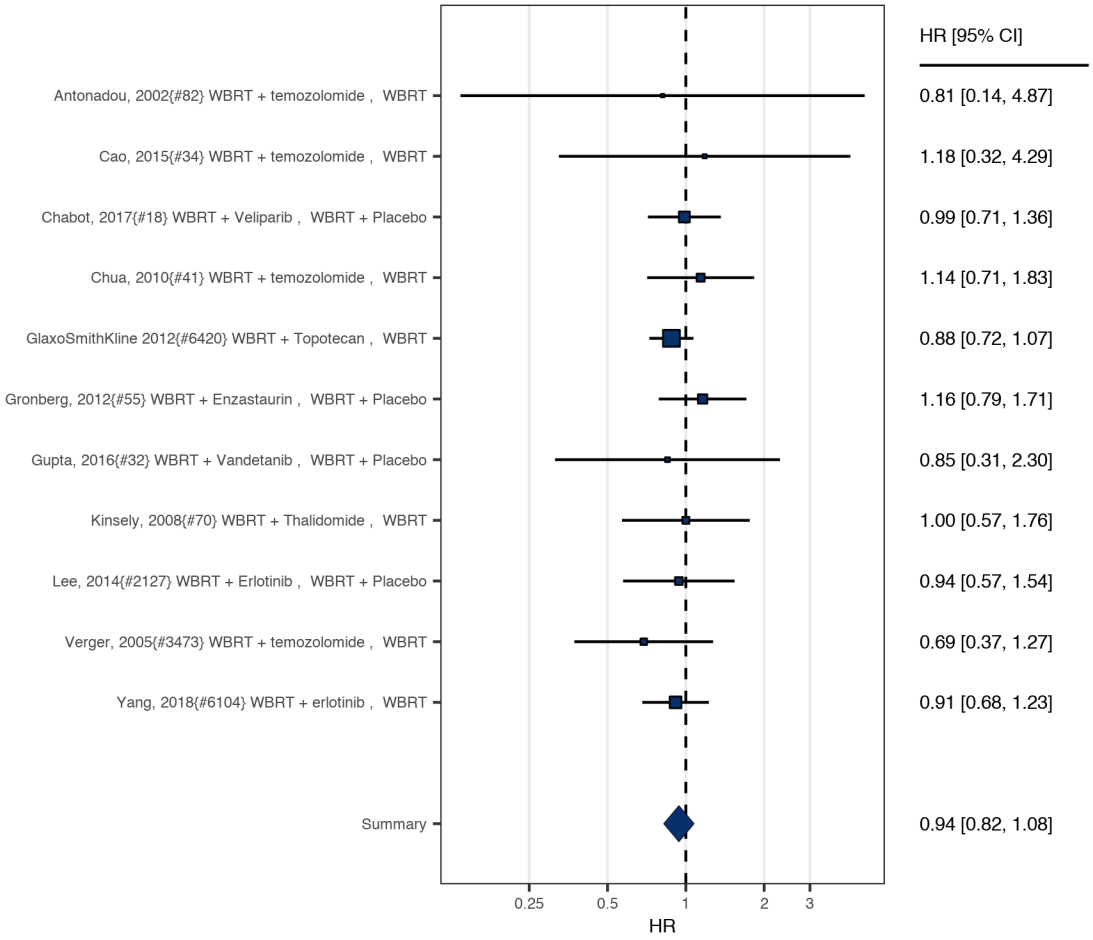
All but two studies evaluated chemotherapy.

WBRT Plus Chemotherapy Versus WBRT Alone

A large group of studies assessed whether the addition of systemic therapy benefits patients receiving WBRT. Temozolomide, a drug shown to be effective in cancers that originate in the brain, was the systemic therapy most often assessed. Other studies evaluated veliparib, topotecan, enzastaurin, vandetanib, endostatin, thalidomide, erlotinib, fotemustine, gefitinib, and the combination of bevacizumab and gefitinib.[76, 84, 85, 89, 96, 97, 100-103, 105, 115, 120, 122, 129, 159, 161, 165, 167]

Figure 8 shows all studies evaluating WBRT plus systemic therapy compared to WBRT alone, with or without placebo, that reported on overall survival.

Figure 8. WBRT plus systemic therapy versus WBRT alone: overall survival



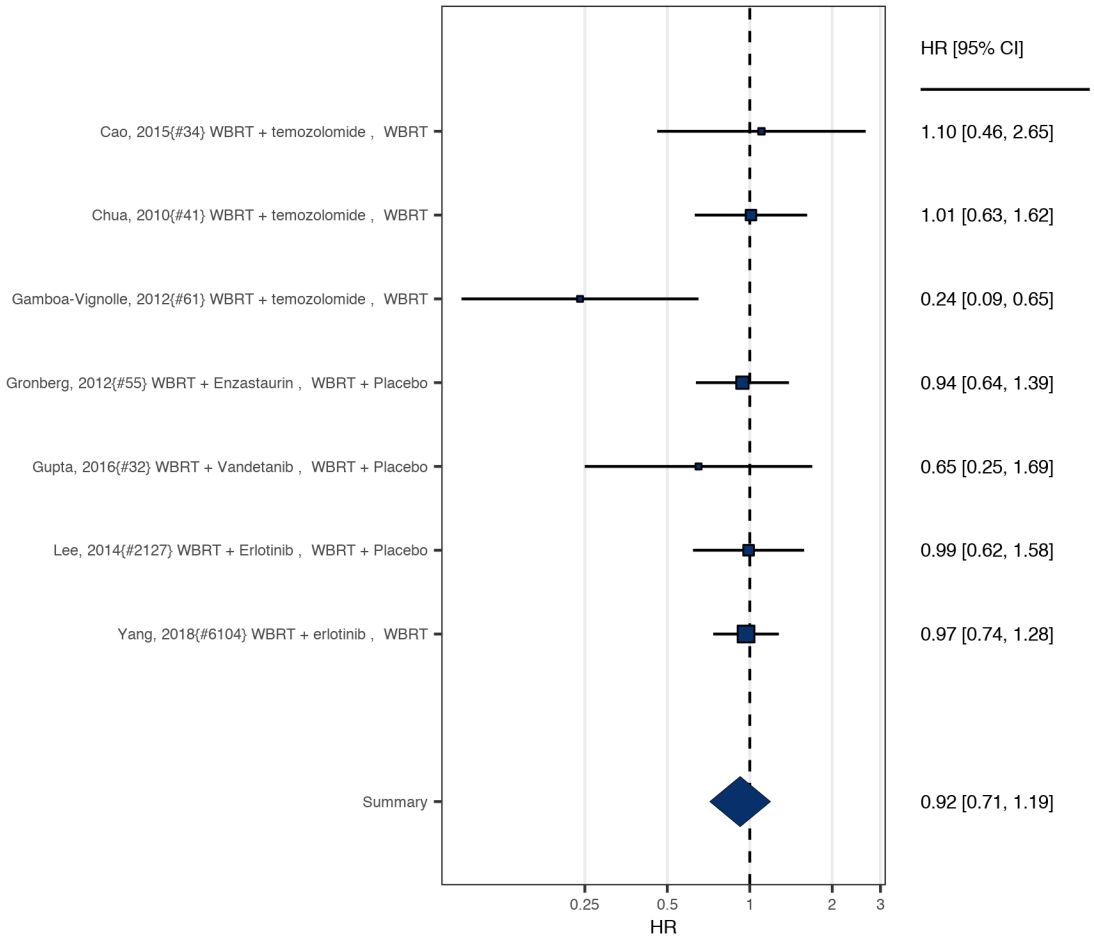
Abbreviations: CI confidence interval; HR hazard ratio; WBRT whole brain radiation therapy

Across studies, there was no statistically significant difference in overall survival between arms (HR 0.94; CI 0.82 to 1.08; 11 RCTs) but some arms with chemotherapeutic agent reported small advantages. We did not detect statistical heterogeneity and although only two low risk of bias studies were included in the analysis, no high risk of bias study contributed to the effect estimate (assuring that the analysis is not mainly driven by poor quality studies). As a sensitivity analysis, we assessed whether the combination of WBRT and systemic therapy is superior to either WBRT or systemic therapy alone. We also found no consistent difference (HR 0.95; CI 0.84 to 1.08; 13 RCTs). The RCTs by Gamboa-Vignolle et al. (temozolomide),[96] Guerrieri et al. (carboplatin),[101] Hassler et al. (temozolomide),[103] Liu et al. (temozolomide),[122] Ushio et al. (Methyl-CCNU/ACNU + tegafur),[159] Verger et al. (temozolomide),[161] Yang et al. (bevacizumab + gefitinib),[165] and a Hoffmann-LaRoche-funded trial (capecitabine) could not be combined with the others; with one exception in a temozolomide RCT,[122] the study authors did not report significant differences in overall survival in the individual studies or did not report statistical tests.

Furthermore, the figure above combines chemotherapy and targeted therapies. Separating out the subgroups did not substantially alter the results (chemotherapy HR 0.95; CI 0.81 to 1.11; 9 RCTs; targeted therapy HR 0.92; CI 0.18 to 4.75; 2 RCTs).

Some of the studies that assessed the combination of WBRT and systemic therapy versus WBRT alone also assessed disease-free survival as shown in Figure 9.[89, 96, 100, 102, 120, 167]

Figure 9. WBRT plus systemic therapy versus WBRT alone: disease-free survival



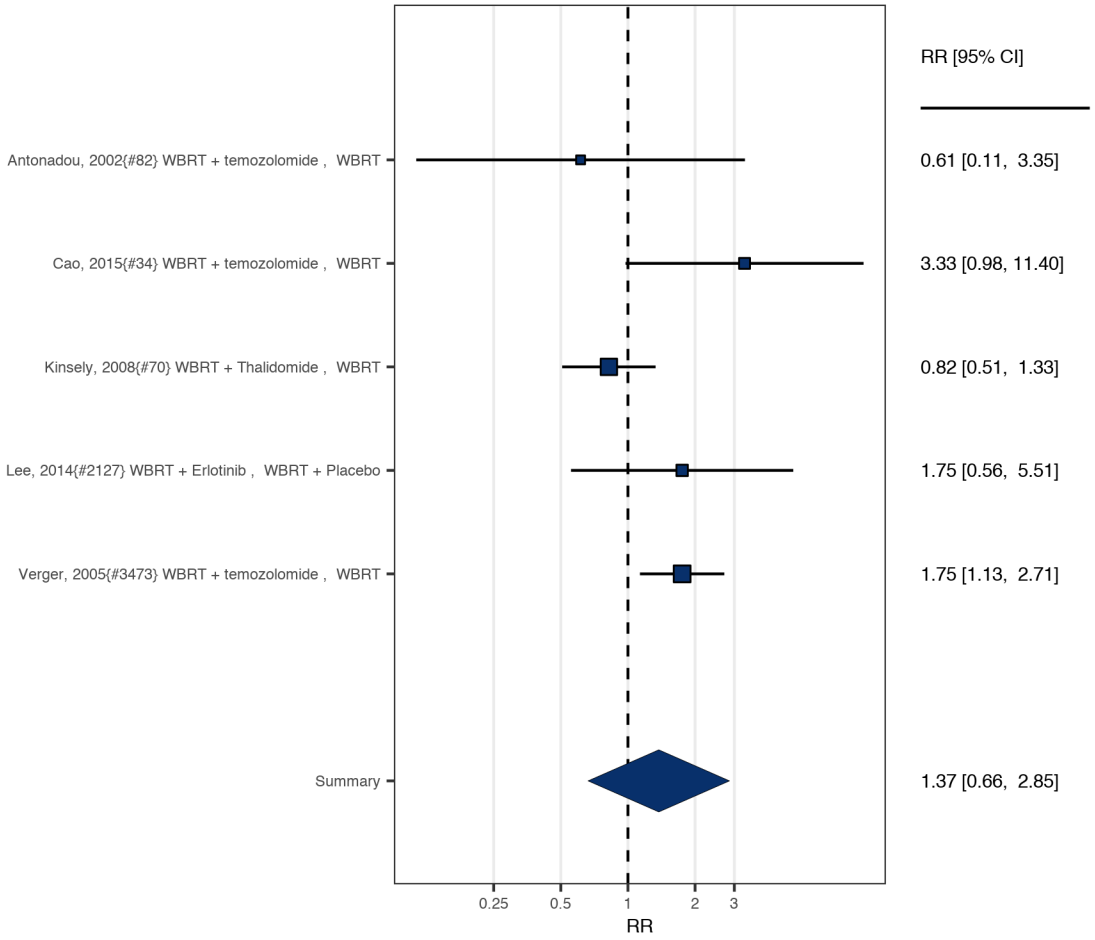
Abbreviations: CI confidence interval; HR hazard ratio; WBRT whole brain radiation therapy

Most individual studies reported no difference or favored the combination slightly. Results across studies showed no statistically significant difference between arms (HR 0.92; CI 0.71 to 1.19; 7 RCTs). The analysis included only one low risk of bias study[100] but none of the other studies was determined to be high risk of bias. Statistical heterogeneity was not detected. A sensitivity analysis that compared the effects of combination treatment with those of either WBRT or SRS alone also showed no evidence of a systematic difference (HR 1.01, CI 0.81 to 1.26). The RCTs by Liu et al.,[122] Verger et al.,[161] Yang et al.[165] and the trial funded by Merck (temozolomide)[129] could not be combined with the other studies; the published RCTs reported favorable results for the combination treatment, however the trial record for the Merck trial did not provide information about the statistical significance of the difference across treatment arms.

Separating out the subgroups into chemotherapy and targeted therapy did not substantially alter the results (chemotherapy HR 0.77; CI 0.39 to 1.51; 5 RCTs; targeted therapy 0.97; CI 0.21 to 4.55; 2 RCTs).

Figure 10 shows three studies reporting on deaths due to brain metastases evaluating WBRT alone compared to WBRT plus systemic therapy.[76, 84, 115]

Figure 10. WBRT plus systemic therapy versus WBRT alone: deaths due to brain metastases



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

Across studies, there was no difference between arms in the number of deaths due to brain metastases (RR 1.37; CI 0.66 to 2.85; 5 RCTs), individual studies reported conflicting results, and the pooled result indicated moderate heterogeneity (I^2 52%). Neither included study was high or low risk of bias, hence it was not possible to assign more weight to one or the other.

The RCTs by Chabot et al.,[85] Chua et al.,[89] Knisely et al.,[115] Liu et al.,[122] Ushio et al.,[159] Verger et al.,[161] Yang et al.,[165] and a GlaxoSmith trial[97] reported on intracranial progression, but the studies reported no difference between treatment group or did not report the statistical significance of the differences between groups. Only Chua et al. reported sufficient detail to compute the effect size for the time to progression (HR 1.01; CI 0.63 to 1.62; 1 RCT); the others did not provide sufficient detail for an independent evaluation.

Gronberg et al.,[100] El-Hamamsy,[94] and Lee et al.[120] reported no differences in quality of life while Liu et al.[122] reported positive results for the combination treatment. The studies could not be combined as they reported insufficient details with the exception of Lee et al. (SMD 0.03; CI -0.41 to 0.47; 1 RCT).

Antonadou et al.[76] concluded that the addition of chemotherapy did not diminish the improvements in neurologic function that was achieved with WBRT alone and the study described improvement in functional status in the combination group. A Hoffman-La Roche trial

reported cognitive decline in the WBRT group but not the combination group (SMD 2.56; CI 1.06 to 6.18; 1 RCT).

Other Systemic Therapy Analyses

Three RCTs assessed the comparative effectiveness and safety of different chemotherapy agents adjunctive to WBRT.[137, 142, 162] Pesce et al.[137] compared gefitinib and temozolomide given in addition to WBRT; the study reported no statistically significant differences in overall survival between groups (HR 1.29; CI 0.47 to 3.55; 1 RCT) but the number of deaths due to CNS progression (RR 0.43; CI 0.18 to 0.98; 1 RCT) favored gefitinib over temozolomide.[137] Quantin et al.[142] compared an adjunctive regimen of cisplatin-vinorelbine-ifosfamide versus adjunctive ifosfamide alone; the authors reported no significant difference in median survival and the number of patients with progressive disease at the end of the study period.[142] Wang et al.[162] compared the combination of velcade-melphalan-prednisone to gefitnib. The study reported insufficient detail to compute hazard ratios but the authors concluded that gefitinib is an effective method for patients with brain metastases from non-small cell lung cancer based on median survival time; the number of patients with progressive disease at two months was similar.

Furthermore, Lee et al.[119] assessed whether WBRT should be followed by chemotherapy or chemotherapy should be given first. The study reported no significant difference in overall survival or progression-free survival and the study did not report on additional effectiveness outcomes of interest.

Finally, Berk et al.[78] evaluated the effect of melatonin. The authors did not find improved survival or differences in cognitive effects.

Summary of Findings, KQ1

Table 1 summarizes results across studies.

Table 1. Summary of findings and strength of evidence for WBRT

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1: WBRT + steroids vs WBRT alone	Functional status	Effect estimate not possible	Effect estimate not possible *Wolfson, 1994[163] reported 29% patients improved, 57% with no change, 14% deteriorated in the WBRT + steroids group vs 80% no change and 20% deteriorated in the WBRT alone group*	Insufficient [study limitations, precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1: WBRT + radio-sensitizer vs WBRT alone	Overall survival	4 RCTs (N 1024); Jiang, 2014;[109] Suh, 2006;[155] Suh, 2008;[156] Zeng, 2016[168]	HR 0.86; CI 0.69 to 1.08: The direction across studies consistently favors WBRT + radiosensitizers but there was no statistically significant difference compared to WBRT alone across studies where the effect size could be computed. *In addition, Mehta, 2003[127] reported no significant difference (median, 5.2 vs 4.9 months, p=0.48) using motexafin gadolinium. Mehta, 2009[128] reported an HR of 1.02 between groups for motexafin gadolinium. Rojas-Puentes, 2013[149] reported a median survival of 8.4 vs 10.2 months for chloroquine. Phillips, 1995[138] reported no significant difference between arms (median 4.3 vs 6.12 months) for WBRT with bromodeoxyuridine vs WBRT alone.*	Insufficient [study limitations, precision, consistency]
KQ1: WBRT + radiosensitizer vs WBRT alone	Disease-free survival	1 RCT (N 554); Mehta, 2009[128]	HR 0.78; CI 0.57 to 1.06: No significant differences in progression-free survival with motexafin gadolinium. *In addition, Suh, 2006[155] reported a median progression-free survival of 4 vs 3.5 months with efaproxiral (p=0.21). Rojas-Puentes, 2013[149] reported survival rates at 1-year of 84% vs 55% for chloroquine. Zeng, 2016[168] reported longer median CNS progression-free survival with sodium glycididazole (7 vs 4 months, p=0.038).*	Insufficient [study limitations, precision, consistency]
KQ1: WBRT + radiosensitizer vs WBRT alone	Death due to brain metastases	2 RCTs (N 579); Suh, 2006;[155] Zeng, 2016[168]	RR 1.02; CI 0.13 to 8.24: Pooled across RCTs where the effect size could be computed, WBRT + radiosensitizers likely do not differ in deaths to brain metastases compared to WBRT alone. *In addition, Mehta, 2003[127] reported no difference in deaths from CNS causes by treatment arm using motexafin gadolinium (p=0.60).*	Low SoE for no consistent effect [study limitations, precision]
KQ1: WBRT + radiosensitizer vs WBRT alone	Intra-cranial progression	1 RCT (N 554); Mehta, 2009[128]	HR 0.78; CI 0.57 to 1.06: WBRT + motexafin gadolinium did not statistically significantly delay intracranial progression in a study where the effect size could be computed. *However, Mehta, 2003[127] reported a significant difference in time to neurologic progression (p=0.018) in favor of motexafin gadolinium. Phillips, 1995[138] reported 3/21 vs 0/23 patients with progressive disease at 3 months favoring the addition of bromodeoxyuridine.*	Low SoE for no consistent effect [study limitations, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1: WBRT + radiosensitizer vs WBRT alone	Quality of life	1 RCT (N 554); Mehta, 2009[128]	HR 1.14; CI 0.74 to 1.75: No significant difference between groups for motexafin gadolinium. *In addition, Suh, 2006[155] reported a larger percentage of patients in the efaproxiral group had stable or improving quality of life scores. Rojas-Puentes, 2013[149] reported no differences between groups with chloroquine. El-Hamamsy et al.[94] reported no significant differences for simvastatin.*	Low SoE for no effect [study limitation, precision]
KQ1: WBRT + radiosensitizer vs WBRT alone	Functional status	Effect estimate not possible	Effect estimate not possible *Mehta, 2003[127] reported no significant difference between groups with motexafin gadolinium. Suh, 2008[156] also reported no statistically significant differences between groups with efaproxial.*	Low SoE for no effect [study limitation, precision]
KQ1: WBRT + motexafin gadolinium vs WBRT alone	Cognitive effects	Effect estimate not possible	Effect estimate not possible *Mehta, 2009[128] reported a longer time interval to neurocognitive progression favoring motexafin gadolinium.*	Low SoE for longer time interval to neurocognitive progression with motexafin gadolinium [precision, consistency]
KQ1: WBRT + SRS vs WBRT alone	Overall survival	1 RCT (N 331); Andrews, 2004[75]	HR 1.14; CI 0.74 to 1.75: WBRT + SRS did not improve overall survival compared to SRS alone according to an RCT that provided an effect size estimate. *In addition, El Gantery, 2014[93] reported a non-significant survival benefit for WBRT + SRS compared to WBRT alone. Kondziolka, 1999[117] reported no statistically significant difference in median survival (p=0.22).*	Low SoE for no effect [study limitation, precision]
KQ1: WBRT + SRS vs WBRT alone	Death due to brain metastases	1 RCT (N 331); Andrews, 2004[75]	RR 0.86; CI 0.60 to 1.25: WBRT + SRS did not systematically improve overall survival compared to SRS alone.	Low SoE for no consistent effect [precision, consistency]
KQ1: WBRT + SRS vs WBRT alone	Intra-cranial progression	Effect estimate not possible	Effect estimate not possible *Kondziolka, 1999[117] reported the median time to any brain failure was 34 months after WBRT + SRS and 5 months after WBRT alone (p=0.002).*	Low SoE for slower intracranial progression favoring WBRT + SRS vs WBRT alone [precision, consistency]
WBRT + SRS vs WBRT alone	Functional status	Effect estimate not possible	Effect estimate not possible *Andrews, 2004[75] noted a significant improvement in Karnofsky Performance Status in the combination group (p=0·0331) .*	Low SoE for improved functional status favoring SRS + WBRT vs WBRT alone [precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
WBRT + SRS vs WBRT alone	Cognitive status	Effect estimate not possible	Effect estimate not possible *Andrews, 2004[75] reported no difference in mental status based on the mini mental state examination between groups.*	Insufficient [study limitation, precision, consistency]
KQ1: WBRT + surgery vs WBRT alone	Overall survival	3 RCTs (N 210); Mintz, 1996;[131] Noordijk, 1994;[136] Vecht, 1993[160]	HR 1.11; CI 0.31 to 3.96: Conflicting results across studies, no systematic difference across studies.	Low SoE for no effect [precision, consistency]
KQ1: WBRT + surgery vs WBRT alone	Deaths due to brain metastases	3 RCTs (N 210); Mintz, 1996;[131] Noordijk, 1994;[136] Vecht, 1993[160]	RR 0.76; CI 0.28 to 2.07: Direction of effects consistently favored the combination treatment but the effect was not statistically significant.	Insufficient [study limitation, precision]
KQ1: WBRT + surgery vs WBRT alone	Quality of life	1 RCT (N 84); Mintz, 1996[131]	SMD 0.09; CI -0.34 to 0.52: Direction of effects favored WBRT alone but the effect was not statistically significant in an RCT that provided an effect size estimate.	Low SoE for no effect [precision, consistency]
KQ1: WBRT + surgery vs WBRT alone	Functional status	1 RCT (N 84); Mintz, 1996[131]	SMD 0.00; CI -0.43 to 0.43: WBRT + surgery in an RCT that provided an effect size estimate. *However, Vecht, 1993[160] indicated that improvements in functional status occurred more rapidly and for longer periods of time after combination treatment but the effect was not statistically significant.*	Low SoE for no effect [study limitation, consistency]
KQ1: WBRT + supportive therapy vs supportive therapy alone	Overall survival	1 RCT (N 538); Mulvenna, 2016[10]	HR 1.06; CI 0.89 to 1.26: WBRT + supportive did not improve overall survival compared to supportive care alone.	Low SoE for no effect [precision, consistency]
KQ1: WBRT + supportive therapy vs supportive therapy alone	Quality of life	Effect estimate not possible	Effect estimate not possible *Mulvenna, 2016[10] reported the number of patients with maintained or improved quality of life was similar between the groups.*	Low SoE for no effect [precision, consistency]
KQ1: Chemotherapy + WBRT vs chemotherapy alone	Overall survival	1 RCT (N 171); Robinet, 2001[148]	HR 1.14; CI 0.82 to 1.59: No systematic difference between cisplatin and vinorelbine + immediate WBRT vs chemotherapy alone in one RCT that provided an effect size estimate. *In addition, Mornex, 2003[132] reported a median survival 105 vs 86 days in the combination group. Yang, 2017[164] reported no significant difference between arms (20.5 months for icotinib + WBRT vs 18.0 months for icotinib alone, p<0.001).*	Low SoE for no effect [study limitation, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1: Chemotherapy + WBRT vs chemotherapy alone	Disease-free survival	1 RCT (N 171); Robinet, 2001[148]	HR 1.18; CI 0.84 to 1.66: No systematic difference for cisplatin and vinorelbine + immediate WBRT vs chemotherapy alone in an RCT that provided an effect estimate. *In addition, Yang, 2017[164] reported intracranial progression-free survival in favor of icotinib (HR 0.44; CI 0.31, 0.63) in favor of Icotinib.*	Low SoE for no effect [study limitation, consistency]
KQ1: cisplatin and vinorelbine + WBRT vs cisplatin and vinorelbine alone	Deaths due to brain metastases	1 RCT (N 171); Robinet, 2001[148]	RR 0.94; CI 0.81 to 1.09: No systematic difference between cisplatin and vinorelbine + immediate WBRT and chemotherapy alone.	Low SoE for no effect [study limitation, consistency]
KQ1: chemotherapy + WBRT vs icotinib alone	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Yang, 2017[164] reported 23% of patients with progressive disease for WBRT vs 12% in the icotinib group. Yang, 2017[165] reported 4% (WBRT + bevacizumab + gefitinib) vs 27% (WBRT alone) patients with progressive disease*	Insufficient [study limitation, precision]
KQ1: chemotherapy + WBRT vs icotinib alone	Cognitive function	Effect estimate not possible	Effect estimate not possible *Yang, 2017[164] reported no difference in MMSE scores between groups (p=0·663).*	Insufficient [study limitation, precision, consistency]

Abbreviations: CI confidence interval; HR hazard ratio; MMSE Mini-Mental State Examination; N number of participants; RCT randomized controlled trial; RR relative risk; SMD standardized mean difference; SoE strength of evidence; WBRT whole brain radiation therapy

‡The column reports the findings across studies starting with the pooled effect when it can be calculated; findings from additional studies not included in the effect estimate calculation or from relevant studies when an effect estimate cannot be calculated are included and italicized.
‡‡SoE strength of evidence and reason for downgrading.

Reasons for downgrading: study limitations: the estimate is based on studies with high risk of bias, there are equally or more studies where no effect estimate could be determined, the comparator is problematic because of co-interventions, the study is not designed to detect differences between groups in the outcome of interest; precision: the effect size could not be determined, wide confidence intervals, a beneficial effect could not be ruled out; consistency: the effect is based on a single study and the evaluation has not yet been replicated in another study, heterogeneity, conflicting direction of effects.

Table 2 summarizes the results for the subquestions addressing possible effect modifiers regarding the radiation intervention (KQ1a), patient or tumor characteristics (KQ1b), or the role of chemotherapy (KQ1c).

Table 2. Summary of findings and strength of evidence for WBRT – effect modifiers

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1a: WBRT dose	Overall survival, disease-free survival, deaths due to brain metastases	Meta-regression	No systematic relationship was detected between the dose of WBRT and the outcomes overall survival, disease-free survival, and deaths due to brain metastases.	Low SoE for no effect [indirectness, study limitations]
KQ1a: WBRT intensity modulated RT with integrated boost 30 GY vs WBRT intensity modulated RT with integrated boost 25Gy	Overall survival	Effect estimate not possible	Effect estimate not possible *Zhu, 2018[169] reported median survival of 8 (CI 4.4, 11.6) months in the 30 Gy group and 13 (CI 11.4, 14.6) months in the 25 Gy group (p=0.025).*	Insufficient [study limitation, precision, consistency]
WBRT intensity modulated RT with integrated boost 30 GY vs WBRT intensity modulated RT with integrated boost 25Gy	Disease-free survival	Effect estimate not possible	Effect estimate not possible *Zhu, 2018[169] reported median intracranial progression-free survival of 8 months (CI 4.4, 11.6) in the 30 Gy group and 11 (CI 8.7, 13.3) months in the 25 Gy group (p=0.104).*	Insufficient [study limitation, precision, consistency]
KQ1a: WBRT intensity modulated RT with integrated boost 30 GY vs WBRT intensity modulated RT with integrated boost 25Gy	Cognitive function	1 RCT (N 75); Zhu, 2018[169]	SMD -0.05; CI -0.50 to 0.40: No statistically significantly difference in mini-mental state examination.	Low SoE for no difference [study limitation, consistency]
KQ1a: Accelerated WBRT vs WBRT	Overall survival	Effect estimate not possible	Effect estimate not possible *Davey, 2008[90] reported 19 weeks median survival in both groups. Murray, 1997[134] also compared accelerated hyperfractionated WBRT with standard WBRT and found no significant difference in 1-year survival rates (16 vs 19%).*	Low SoE for no difference [study limitation, precision]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1a: Accelerated WBRT vs WBRT	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Davey, 2008[90] reported longer median time to retreatment in the accelerated WBRT group for intracranial relapse (p=0.03).*	Low SoE for beneficial effects of accelerated WBRT on intracranial progression [precision, consistency]
KQ1a: Accelerated WBRT vs WBRT	Functional status	Effect estimate not possible	Effect estimate not possible *Davey, 2008[90] reported no difference in neurological function between groups.*	Insufficient [study limitation, precision, consistency]
KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions	Overall survival	1 RCT (N 113) Graham, 2010[99]	HR 1.08; CI 0.6 to 1.96: No systematic difference between treatment groups.	Low SoE for no difference [study limitation, consistency]
KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions	Disease-free survival	1 RCT (N 113) Graham, 2010[99]	HR 0.55; CI 0.31 to 1: Results favoring 40 Gy.	Low SoE for benefits for 40 Gy vs 20 Gy on disease-free survival [precision, consistency]
KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions	Deaths due to brain metastases	1 RCT (N 113) Graham, 2010[99]	RR 0.63; CI 0.40 to 1.00: Results favoring 40 Gy	Low SoE for benefits for 40 Gy vs 20 Gy for deaths due to brain metastases [precision, consistency]
KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions	Intracranial progression	1 RCT (N 113) Graham, 2010[99]	HR 1.56; CI 0.94 to 2.60: The difference between groups was not statistically significant.	Insufficient [study limitation, precision, consistency]
KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions	Quality of life	1 RCT (N 113) Graham, 2010[99]	SMD -0.17; CI -0.54 to 0.20 The difference between groups was not statistically significant.	Insufficient [study limitation, precision, consistency]
KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions	Cognitive function	Effect estimate not possible	Effect estimate not possible *Graham, 2010[99] reported no difference between the 20 Gy and 40 Gy group in a cognitive subscale.*	Insufficient [study limitation, precision, consistency]
KQ1a: Dose 30 Gy in 10 fractions vs 20 Gy in 5 fractions	Overall survival	1 RCT (N 56) Saha, 2014[152]	HR 0.98; CI 0.55 to 1.75: No systematic difference between treatment groups.	Low SoE for no difference [study limitation, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1a: Dose 30 Gy in 10 fractions vs 20 Gy in 5 fractions	Functional status	1 RCT (N 56) Saha, 2014[152]	SMD 0.12; CI -0.40 to 0.65: No statistically significant difference between groups.	Low SoE for no difference [study limitation, consistency]
KQ1a: 30 Gy in 10 fractions vs 12 Gy in 2 fractions	Overall survival	1 RCT (N 533) Priestman, 1996[141]	HR 0.93; CI 0.77 to 1.12: No systematic difference between treatment groups.	Low SoE for no difference [study limitation, consistency] [precision, consistency]
KQ1a: 30 Gy in 10 fractions vs 12 Gy in 2 fractions	Deaths due to brain metastases	1 RCT (N 533) Priestman, 1996[141]	RR 0.99; CI 0.92 to 1.06: No systematic difference between treatment groups.	Low SoE for no difference [study limitation, consistency]
KQ1a: 30 Gy vs 25 Gy	Cognitive function	1 RCT (N 75) Zhu, 2018[169]	SMD -0.05; CI -0.50 to 0.40: No systematic difference between treatment groups.	Low SoE for no difference [study limitation, consistency]
KQ1a: WBRT with neuroprotection: WBRT + memantine vs WBRT alone	Overall survival	1 RCT (N 252); Brown, 2013[82]	HR 1.06; CI 0.86 to 1.31: WBRT + memantine did not improve overall survival compared to supportive care alone.	Low SoE for no effect [study limitation, consistency]
KQ1a: WBRT with neuroprotection: WBRT + memantine vs WBRT alone	Disease-free survival	1 RCT (N 252); Brown, 2013[82]	HR 1.06; CI 0.86 to 1.30: WBRT + memantine did not improve disease-free survival compared to WBRT plus placebo.	Low SoE for no effect [study limitation, consistency]
KQ1a: WBRT with neuroprotection: WBRT + memantine vs WBRT alone	Cognitive function	Effect estimate not possible	Effect estimate not possible *Brown et al.[82] reported that adding memantine delayed the risk of cognitive decline (HR 0.78, CI 0.62 to 0.99) and reduced the rates of decline in memory, executive function, and processing speed.*	Low SoE for beneficial effect of memantine on cognitive function [precision, consistency]
KQ1a: WBRT with neuroprotection – hippocampal sparing vs standard WBRT	Overall survival	1 RCT (N 519); Brown, 2020[80]	HR 1.13; CI 0.19 to 6.59: Hippocampal sparing WBRT + memantine vs WBRT + memantine alone did not significantly differ in overall survival based on one RCT that provided effect estimates. *In addition, Hauswald, 2019[104] reported median overall survival of 5 months (hippocampal sparing WBRT) vs 4 months (standard WBRT).*	Low SoE for no effect [study limitation, precision]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1a: WBRT with neuroprotection – hippocampal sparing vs standard WBRT	Disease-free survival	1 RCT (N 519); Brown, 2020[80]	HR 1.14; CI 0.92 to 1.41: No systematic difference between treatment groups.	Low SoE for no effect [precision, consistency]
KQ1a: WBRT with neuroprotection - hippocampal sparing vs standard WBRT	Quality of life	Effect estimate not possible	Effect estimate not possible *Brown, 2020[80] reported no differences in EQ-5D-5L.*	Low SoE for no effect [precision, consistency]
KQ1a: WBRT with neuroprotection – hippocampal sparing vs standard WBRT	Cognitive effects	Effect estimate not possible	Effect estimate not possible *Brown, 2020[80] reported HR 0.76; CI 0.60 to 0.98 (p=0.03) for cognitive decline in favor of hippocampal-sparing WBRT+ memantine compared to WBRT + memantine alone. Yang, 2019[166] reported better preservation in late verbal memory but not verbal fluency or executive function with hippocampal avoidance WBRT.*	Low SoE for beneficial effect of hippocampal sparing WBRT on cognitive function [study limitation, precision]
KQ1b: Prognosis and WBRT	Overall survival, deaths due to brain metastases	Meta-regression	No systematic relationship was detected between the patient prognosis and effects of WBRT for overall survival.	Low SoE for no effect [indirectness, study limitations]
KQ1b: Primary tumor site and WBRT	Overall survival, disease-free survival, deaths due to brain metastases	Meta-regression	No systematic relationship was detected between the primary tumor type and overall survival.	Low SoE for no effect [indirectness, study limitations]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1c: WBRT + systemic therapy vs WRBT alone	Overall survival	11 RCTs (N 1,606); Antonadou, 2002;[76] Cao, 2015;[84] Chabot, 2017;[85] Chua, 2010;[89] GlaxoSmithKline 2012;[97] Gronberg, 2012;[100] Gupta, 2016;[102] Knisely, 2008;[115] Lee, 2014;[120] Berger, 2005;[161] Yang, 2018[167]	HR 0.94; CI 0.82 to 1,08: Additional systemic therapy did not show a systematic benefit compared to WBRT alone in studies that provided effect estimates. *In addition, Gamboa-Vignolle, 2012[96] reported no significant difference in overall survival between groups. Guerrieri, 2004[101] reported a median survival of 4.4 months in the WBRT alone arm and 3.7 months in the combined treatment arm (p=0.64). Hassler, 2013[103] reported median overall survival of 3 vs 6.3 months comparing radiochemotherapy and radiation alone. Hoffmann-La Roche, 2011[105] reported 4.6 vs 9.8 months survival. Liu, 2017[122] reported significantly longer survival with temozolomide. Ushio, 1991[159] reported median survival of 29 weeks in the WBRT + methyl-CCNU/ACNU + tegafur group compared to 27 weeks in the WBRT alone group and 30.5 weeks in the WBRT + methylCCNU/ACNU group. Verger, 2005[84] reported no differences between groups. Yang, 2017[165] reported that the WBRT + bevacizumab + gefitinib had the most favorable survival status.*	Low SoE for no effect [study limitation, consistency]
KQ1c: WBRT + systemic therapy vs WRBT alone	Disease-free survival	7 RCTs (N 679); Cao, 2015;[84] Chua, 2010;[89] Gamboa-Vignolle, 2012;[96] Gronberg, 2012;[100] Gupta, 2016;[102] Lee, 2014;[120] Yang, 2018[167]	HR 0.92; CI 0.71 to 1,19: Adding systemic therapy did not show a systematic benefit compared to WBRT alone across studies that reported effect estimates. *In addition, El-Hamamsy, 2016[94] reported 1-year progression free survival rates of 17.7% and 5.2% (p=0.392). Liu, 2017[122] reported significantly longer survival with temozolomide compared to WBRT alone. A trial by Merck, 2008[129] reported that 8/18 patients in the WBRT + temozolomide vs 8/13 in the WBRT group alone were still alive after 6 months. Yang, 2017[165] reported that the WBRT + bevacizumab + gefitinib had the most favorable survival status*.	Low SoE for no effect [precision, consistency]
KQ1c: WBRT + systemic therapy vs WRBT alone	Deaths due to brain metastases	5 RCTs (N 486); Antonadou, 2002;[76] Cao, 2015;[84] Knisely, 2008;[115] Lee, 2014;[120] Verger, 2005[161]	RR 1.37; CI 0.66 to 2.85: Conflicting results across studies, 2 favoring the WBRT plus systemic therapy, 3 the comparator WBRT alone.	Low SoE for no effect [precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1c: WBRT + systemic therapy vs WRBT alone	Intracranial progression	1 RCT (N 95); Chua, 2010[89]	HR 1.01; CI 0.63 to 1.62: No systematic difference between treatment groups in the RCT that provided an effect estimate. *In addition, Chabot, 2017[85] also reported no significant differences in intracranial response rate and time to clinical or radiographic progression. Hassler, 2013[103] reported 2.4 months vs 2.0 months favoring systemic therapy (not significant). Liu, 2017[122] reported no difference between groups in the number of patients with progressive disease (p=0.2327). Mornex, 2003[132] reported 56 vs 49 days to cerebral progression (p=0.028) with fotemustine. Ushio, 1991[159] reported 1/19 patients in the WBRT + methyl-CCNU/ACNU + tegafur group, 4/14 in the WBRT alone group, and 2/16 patients in the WBRT + methylCCNU/ACNU group with progressive disease. Verger, 2005[161] reported 3/41 (WBRT + temozolomide) vs 9/41 (WBRT alone) patients with progressive disease. Yang, 2017[165] reported 4% (WBRT + bevacizumab + gefitinib) vs 27% (WBRT alone) patients with progressive disease (12% in WBRT + gefitinib group).*	Low SoE for no effect [study limitation, consistency]
KQ1c: WBRT + systemic therapy vs WRBT alone	Quality of life	1 RCT (48) Lee, 2014[120]	SMD 0.03; CI -0.41 to 0.47 No systematic difference between groups in the RCT providing an effect size estimate. *In addition, El-Hamamsy, 2016[94] reported no significant differences between groups of which one received chemotherapy. Gronberg, 2012[100] also reported no statistical differences for enzastaurin. Liu, 2017[122] reported improvement with temozolomide group (p=0.0007).*	Low SoE for no effect [study limitation, consistency]
KQ1c: WBRT + systemic therapy vs WRBT alone	Functional status	Effect estimate not possible	Effect estimate not possible *Antonadou, 2002[76] described improved functional status in the combination group but the statistical significance was not reported and the effect size could not be determined).*	Insufficient [study limitation, precision, consistency]
KQ1c: WBRT + capecitabine vs WRBT alone	Cognitive function	1 RCT (N 95); Hoffmann-La Roche, 2011[105]	SMD 2.56; CI 1.06 to 6.18: WBRT + capecitabine showed less decline in cognitive function compared to WBRT alone.	Low SoE for improved cognitive function with capecitabine [precision, consistency]
KQ1c: WBRT + temozolomide vs WBRT + gefitinib	Overall survival	1 RCT (N 59) Pesce, 2012[137]	HR 1.29; CI 0.47 to 3.55: No systematic difference between groups.	Low SoE for no effect [precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ1c: WBRT + temozolomide vs WBRT + gefitinib	Deaths due to brain metastases	1 RCT (N) Pesce, 2012[137]	RR 0.43; CI 0.18 to 0.98: No systematic difference between groups.	Low SoE for no effect [study limitation, consistency]
KQ1c: WBRT + cisplatin, vinorelbine, ifosfomide vs ifosfamide	Overall survival	Effect estimate not possible	Effect estimate not possible *Quantin, 2010[142] reported a median survival of 8.5 months in the combination and 5.7 months in the ifosfamide group (p=0.82).*	Low SoE for no effect [study limitation, consistency]
KQ1c: WBRT + cisplatin, vinorelbirne, ifosfomide vs WBRT + ifosfomide	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Quantin, 2010[142] reported 4/37 (WBRT + cisplatin, Vinorelbirne, ifosfomide) vs 5/33 (WBRT + cisplatin) patients with progressive disease.*	Insufficient [study limitation, precision, consistency]
KQ1c: WBRT followed by chemotherapy vs chemotherapy followed by WBRT	Overall survival	Effect estimate not possible	Effect estimate not possible *Lee, 2008[119] reported no statistically significantly difference between groups.*	Insufficient [study limitation, precision, consistency]
KQ1c: WBRT followed by chemotherapy vs chemotherapy followed by WBRT	Progression-free survival	Effect estimate not possible	Effect estimate not possible *Lee, 2008[119] reported no statistically significantly difference between groups.*	Insufficient [study limitation, precision, consistency]
KQ1c: WBRT + gefitinib vs WBRT + VMP	Overall survival	Effect estimate not possible	Effect estimate not possible *Wang, 2015[162] reported the median survival time was 13.3 for gefitinib and 12.7 for VMP (p<0.05).*	Low SoE for no difference [precision, consistency]
KQ1c: WBRT + gefitinib vs WBRT + VMP	Overall survival	Effect estimate not possible	Effect estimate not possible *Wang, 2015[162] reported 5.4% (gefitinib) vs 5.8% (VMP) of patients with progressive disease.*	Low SoE for no difference [precision, consistency]
KQ1c: WBRT + melatonin vs WBRT	Overall survival	Effect estimate not possible	Effect estimate not possible *Berk, 2007[78] reported the median survival were 2.8 vs 3.4*	Low SoE for no effect [precision, consistency]
KQ1c: WBRT + melatonin vs WBRT	Cognitive effects	Effect estimate not possible	Effect estimate not possible *Berk, 2007[78] reported 57% vs 55% new MMSE failures*	Low SoE for no effect [precision, consistency]

Abbreviations: CI confidence interval; HR hazard ratio; N number of participants; RCT randomized controlled trial; RR relative risk; SMD standardized mean difference; SoE strength of evidence; WBRT whole brain radiation therapy.

‡The column reports the findings across studies starting with the pooled effect when it can be calculated; findings from additional studies not included in the effect estimate calculation or from relevant studies when an effect estimate cannot be calculated are included and italicized.
‡‡SoE strength of evidence and reason for downgrading.

Reasons for downgrading: study limitations: the estimate is based on studies with high risk of bias, there are equally or more studies where no effect estimate could be determined, the comparator is problematic because of co-interventions, the study is not designed to detect differences between groups in the outcome of interest; precision: the effect size could not be determined, wide confidence intervals, a beneficial effect could not be ruled out; consistency: the effect is based on a single study and the evaluation has not yet been replicated in another study, heterogeneity, conflicting direction of effects.

Key Question 2. What is the effectiveness of SRS/fractionated stereotactic radiation as initial treatment in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

Key findings regarding SRS as initial treatment include the following:

Key Points

- The combination treatment SRS plus WBRT compared to SRS alone or WBRT alone found no consistent 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 RCT 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 RCTs 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 site (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 very limited due to the small number of available studies.
- Evidence was insufficient for several SRS evaluations and outcomes of interest. Studies varied by intervention, comparator, measures used to assess effects, and reported detail.

The identified number of RCTs addressing the effects of SRS was considerably smaller than the WBRT evidence base. This summary focuses on the results for SRS as an initial treatment across studies for the key outcomes. Other outcomes are documented in the evidence table in Appendix D.

SRS Versus WBRT

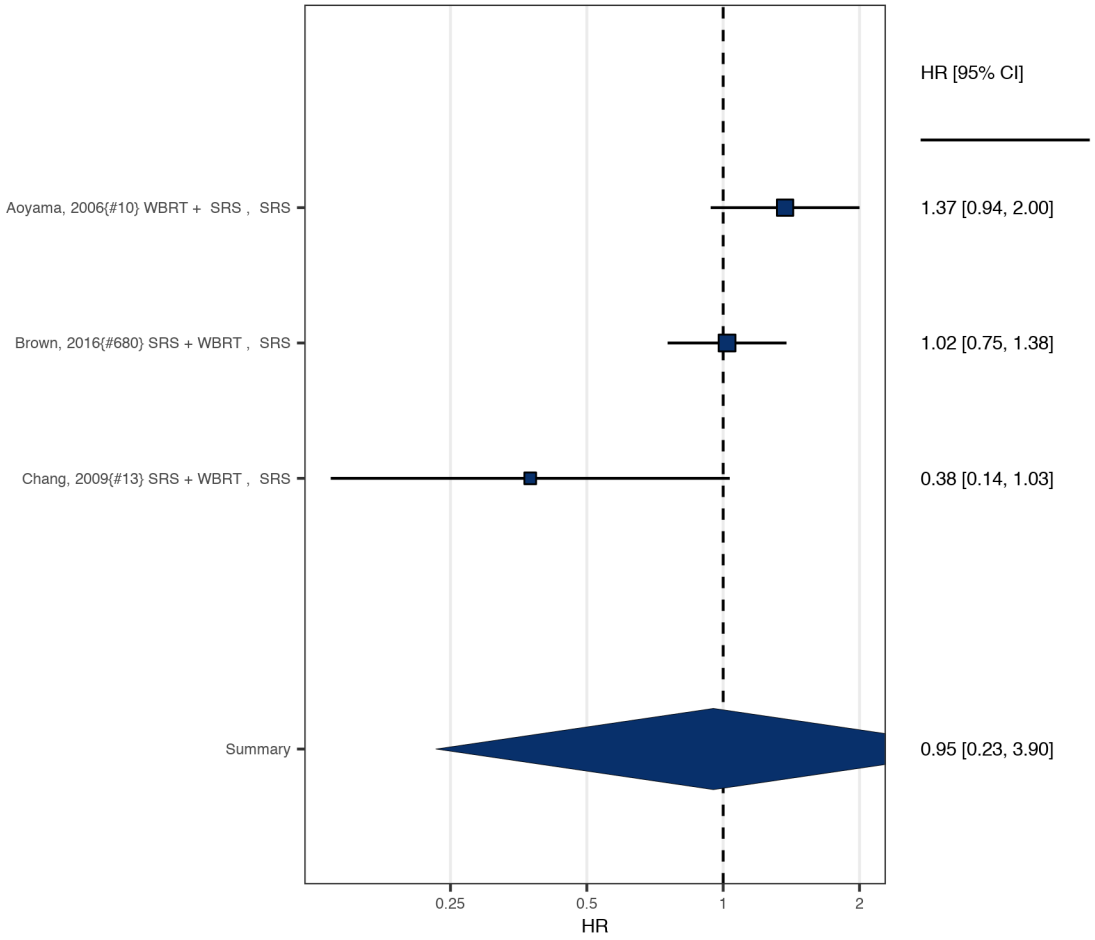
Two RCTs compared SRS and WBRT as initial treatment.[135, 145] Raman, 2020[145] compared SRS and WBRT in patients with poor prognosis; the author reported that an RCT in this patient group is feasible. Overall survival (HR 2.00; CI 0.78 to 5.17; 1 RCT), progression-free survival (HR 3.10; CI 0.74 to 12.93; 1 RCT) and death due to brain metastases (RR 3.00; CI 0.79 to 11.44; 1 RCT) favored WBRT but were not statistically significantly different. The time to intracranial progression was 2.5 months for SRS, and 12.8 months for WBRT). There was no difference in cognitive function (SMD -0.02; CI -0.91 to 0.87; 1 RCT) and the difference in functional status was not statistically significant (SMD 0.55; CI -0.36 to 1.46; 1 RCT).

A National Cancer Institute trial[135] also compared SRS and WBRT but the trial record only reported adverse events for the five study participants. Both studies contribute to KQ4.

SRS Plus WBRT Versus SRS Alone

We identified three RCTs that evaluated SRS plus WBRT compared to SRS alone.[77, 81, 86] The results for overall survival are documented in Figure 11.

Figure 11. SRS plus WBRT versus SRS alone: overall survival

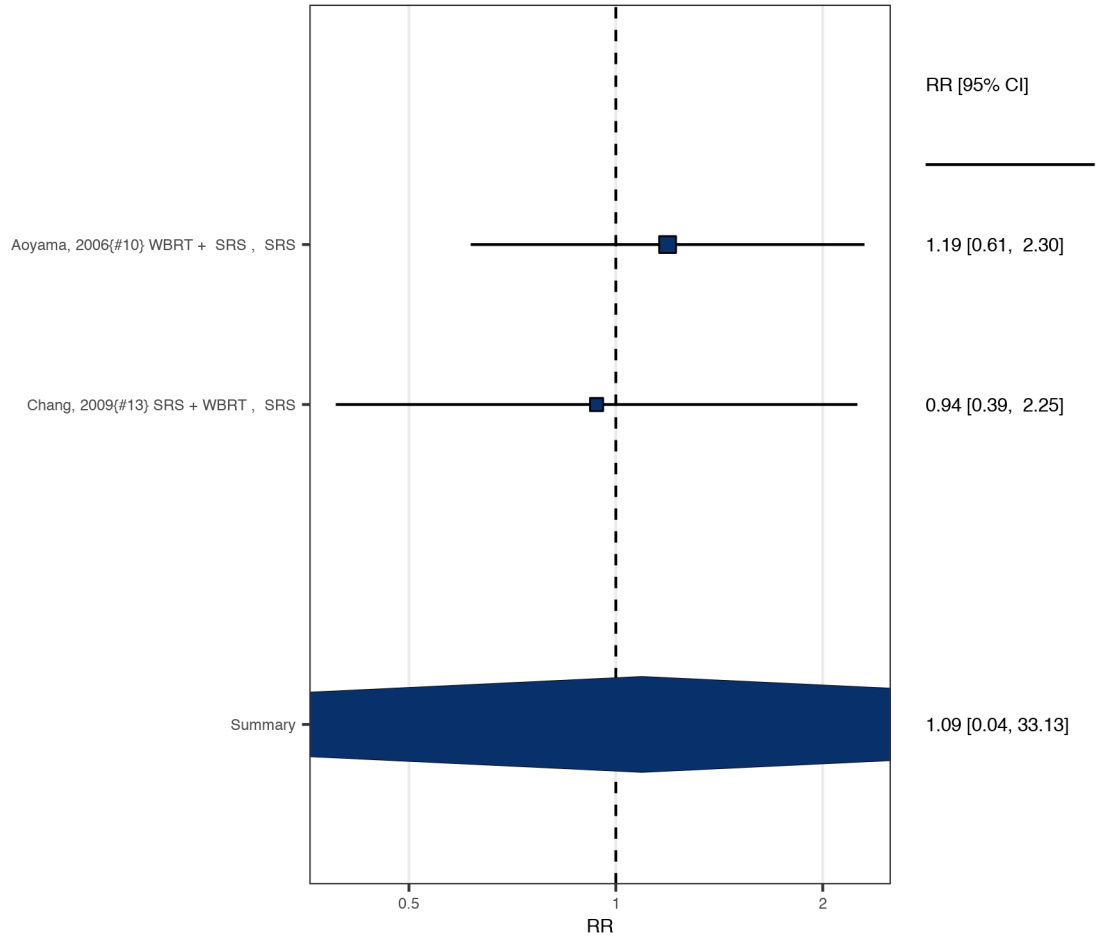


Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Individual studies reported conflicting results and overall there was no systematic difference in overall survival between treatment groups (HR 0.95; CI 0.23 to 3.90; 3 RCTs). Heterogeneity was not detected. None of the studies included in the analysis was high risk of bias. The low risk of bias study by Brown et al.[81] reported no difference between intervention groups.

Two RCTs assessed the outcome number of deaths due to brain metastases as shown in Figure 12.[77, 86]

Figure 12. SRS plus WBRT versus SRS alone: death due to brain metastases



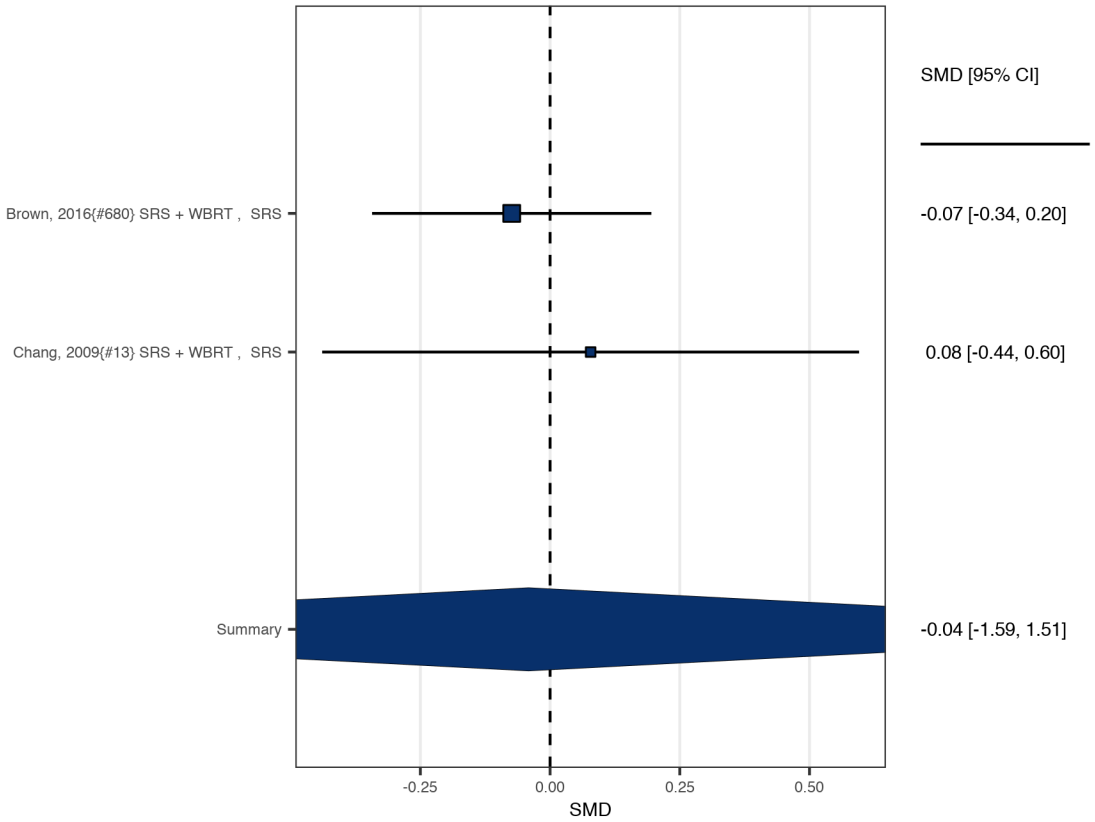
Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Both studies did not report statistically significant differences between groups and across studies there was also no systematic difference between treatments (RR 1.09; CI 0.04 to 33.13; 2 RCTs). Heterogeneity was not detected.

Aoyama et al. reported a 12-month brain tumor recurrence rate was 47 percent in the combination group compared to 76 percent for the SRS alone group ($p<.001$).[77]

Two of the studies assessed quality of life and reported sufficient detail to compute effect sizes.[81, 86] The results are shown in Figure 13.

Figure 13. SRS plus WBRT versus SRS alone: quality of life



Abbreviations: CI confidence interval; SMD standardized mean difference; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Both studies reported small effects and the risk of bias did not differ (neither high nor low risk), but the direction of effects varied (one favoring the combination, the other the SRS group). The pooled point estimate indicated no difference between the combination of SRS plus WBRT compared to SRS alone, but the resulting confidence interval surrounding the point estimate was wide (SMD -0.04; CI -1.59 to 1.51; 2 RCTs). Statistical heterogeneity was not detected. The graph is based on the mean and standard deviation but Brown et al.[81] reports positive results at the 3-months follow up based on the mean difference from baseline.

Aoyama et al. reported no significant difference in systematic functional preservation at 12 months.[77] Brown et al. also assessed functional independence; the study reported no difference between SRS plus WBRT and SRS alone (SMD -0.07; CI -0.34 to 0.20; 1 RCT).[81] The studies could not be combined as they used different outcome operationalizations.

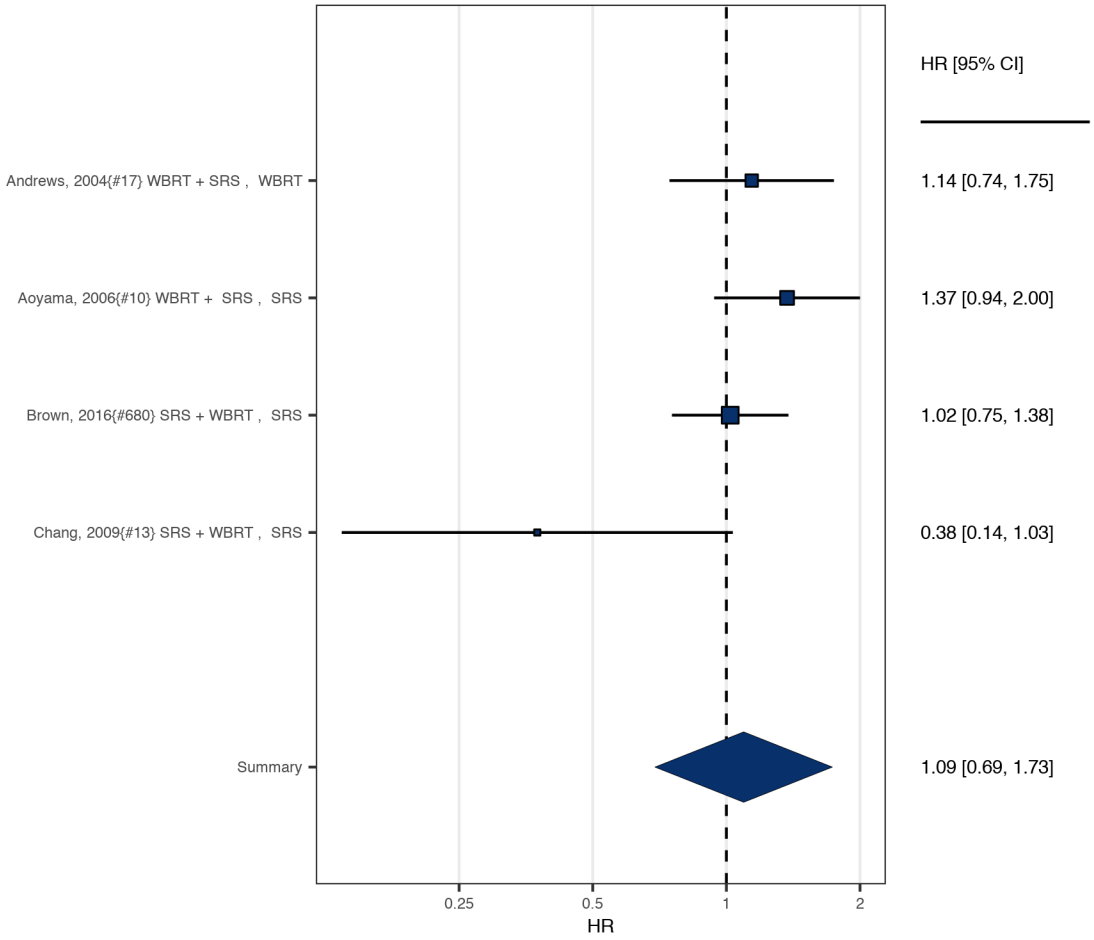
Three of the RCTs reported on cognitive function.[77, 81, 86] Studies reported insufficient details to compute effect sizes and could not be combined statistically. Aoyama et al.[77] reported no statistically significantly difference in improvement or deterioration between the treatment groups using the Mini-Mental State Examination (time to deterioration 13.6 vs 6.8 months). Chang, 2009[86] used the Hopkins Verbal Learning Test-Revised and reported a greater risk of significant neurocognitive decline for patients receiving WBRT and SRS (52%) compared with the group receiving SRS alone (24%). Brown et al.[81] also reported greater decline in the combination treatment group: a decline of more than one standard deviation on at least one out of

seven cognitive tests was less frequent after SRS alone than after SRS plus WBRT (63.5% vs 91.7%; p<.001) but results for individual tests varied.

SRS Plus WBRT Versus SRS Alone or WBRT Alone

Four RCTs compared the combination of SRS plus WBRT to SRS alone or to WBRT alone and reported on overall survival as shown in Figure 14.[75, 77, 81, 86]

Figure 14. SRS plus WBRT versus SRS alone or WBRT alone: overall survival

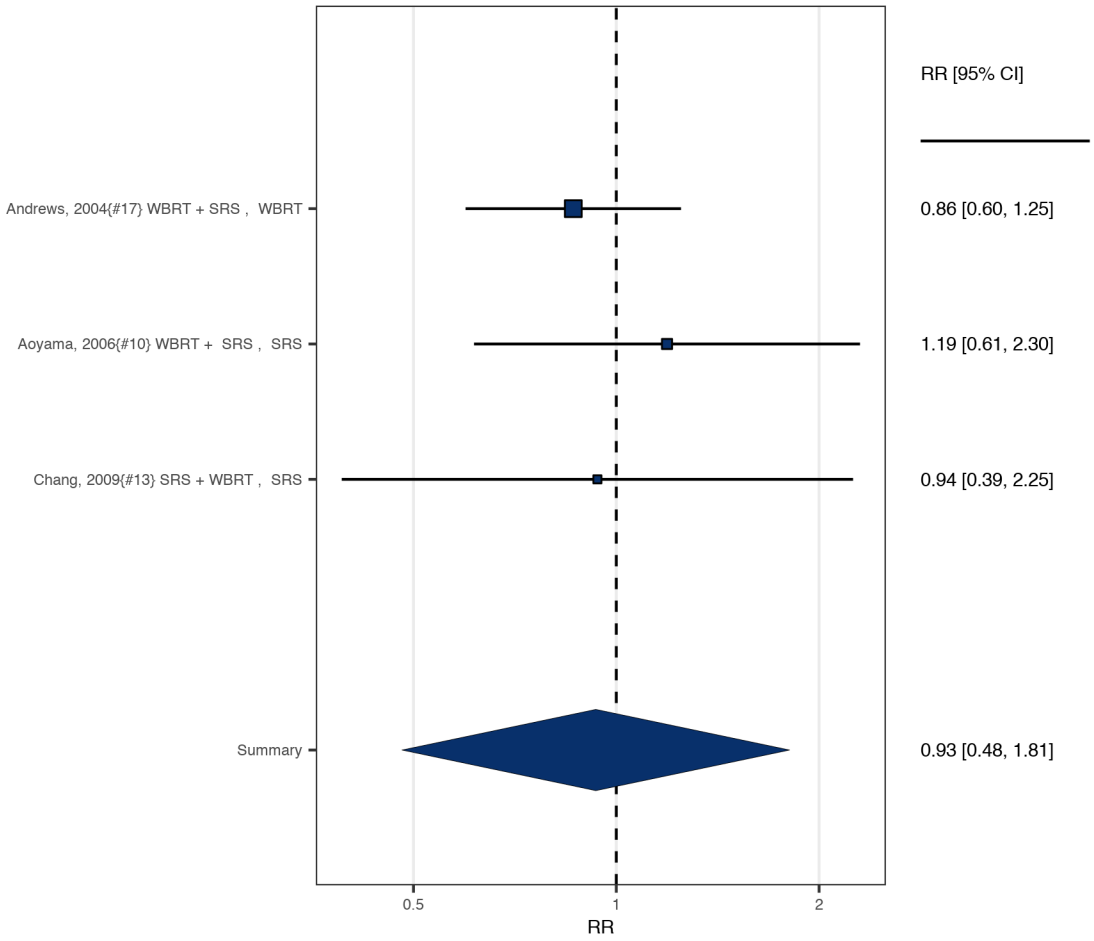


Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Combining Aoyama et al., Brown et al., and Chang et al. (comparator SRS)[77, 81, 86] with Andrews et al. (comparator WBRT),[75] we found no statistically significant differences in individual studies or across studies (HR 1.09; CI 0.69 to 1.73; 4 RCTs). As a sensitivity analysis, we also combined the RCTs with a cohort study published by Gonda et al.[98] and a cohort study published by Sneed et al.[153] Across studies we found no difference in overall survival (HR 0.99; CI 0.81 to 1.21; 4 studies). Pooling the combination treatment of SRS plus WBRT versus SRS or versus WBRT[75, 77, 81, 86, 93, 98, 117] also did not find that overall survival improved in the combination (HR 0.72; CI 0.00 to 755; 2 RCTs). Finally, a sensitivity analysis pooling all combination treatment studies SRS plus WBRT versus SRS or WBRT across RCTs and cohort studies showed a similar result (HR 1.01; CI 0.87 to 1.18, 6 studies).

Three RCTs also reported on the number of deaths that could be attributed to brain metastases as shown in Figure 15.

Figure 15. SRS plus WBRT versus SRS alone or WBRT alone: deaths due to brain metastases



Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

The difference between treatment groups was not statistically significant for the individual nor the combined studies (RR 0.93; CI 0.48 to 1.81; 3 RCTs). No heterogeneity was detected.

Results for other outcomes could not be combined across the studies comparing to SRS and WBRT; the individual comparison to SRS and to WBRT are reported in the individual sections.

SRS Plus Surgery Versus SRS Alone or Radiation

We did not identify any RCTs that reported on this comparison.

Of note, three cohort studies reported on the comparison SRS plus surgery versus SRS alone[110, 140, 144] and one reported on SRS plus surgery versus radiation.[83] Johnson et al. reported a trend for improved survival in the resection group,[110] Rades et al. found no difference in overall survival rates but better intracranial control rates in the SRS plus surgery group,[144] and Prabhu et al. found longer survival and better local recurrence control in the combination group.[140] The studies could not be combined for effectiveness outcomes but they contribute to KQ4 analyses. Cagney et al.[83] reported only on adverse events.

Adjunctive SRS Versus Supportive Care Alone

Studies assessed different intervention combinations and research questions relevant to SRS but none of the identified studies compared SRS and observation or supportive care alone.

Of note, our searches identified one cohort study that is included in KQ4 that assessed supportive care. Kim et al.[113] compared patients who had received WBRT or SRS and that were then either treated with chemotherapy or supportive care. The study reported longer median survival in the chemotherapy group ($p<0.001$) but this finding has not been replicated in an RCT and the study reported no other effectiveness outcomes.

SRS Plus Systemic Therapy Versus Systemic Therapy Alone

We identified one medium risk of bias RCT that evaluated whether patients receiving systemic therapy benefit from additional SRS; the study compared patients who received SRS followed by systemic therapy to patients who received systemic therapy upfront.[121] Lim et al. reported no statistically significant difference in overall survival (HR 1.20; CI 0.76 to 1.89; 1 RCT), intracranial progression-free survival, time to CNS disease progression, functional status, or cognitive effects between the two treatment arms.

Of note, two cohort studies also reported on systemic therapy. Magnuson et al.[123] concluded that use of EGFR-tyrosine kinase inhibitors and deferral of radiotherapy is associated with inferior overall survival in some patients and more research is needed. Tetu et al.[157] concluded that adding radiation therapy may be associated with a decrease in deaths in patients treated with systemic therapy.

SRS Plus WBRT Versus Surgery Plus WBRT

Roos et al.[150] evaluated whether SRS added to WBRT is as effective as surgery adjunctive to WBRT. The study reported on overall survival (HR 0.53; CI 0.2 to 1.43; 1 RCT), progression-free survival (HR 0.55; CI 0.22 to 1.38; 1 RCT), intracranial progression (similar rate, no effect size), quality of life (SMD 1.22; CI 0.26 to 2.18; 1 RCT), functional status (no significant differences between arms), and neurological function (no significant differences between arms). The authors stated they encountered accrual difficulties and had low statistical power to detect differences between groups.

Surgery Plus WBRT Versus SRS

Muacevic et al.[133] compared SRS to surgery plus WBRT and reported that length of survival did not differ across groups (HR 1.08; CI 0.30 to 3.94; 1 RCT). The rate of neurological deaths was lower in the SRS group (RR 3.13; CI 0.95 to 10.33; 1 RCT) and the local control rate was higher (no effect size estimate) but the differences between groups were not statistically significant. The authors also reported a difference in quality of life scales seen at 6 weeks favoring SRS was not maintained 6 months after treatment and the difference in stabilized KPS or deterioration was not significant ($p>0.1$) between groups.

Of note, an observational study comparing SRS alone versus resection plus WBRT concluded that SRS alone appeared to be as effective as resection plus WBRT in the treatment of one or two brain metastases.[143]

KQ2a. Dose Fractionation Schedule and Technique

Some of the identified studies specifically assessed the effect of intervention characteristics. One RCT randomized by lesion to 1 mm margin SRS or 3 mm margin SRS; the study (classified as high risk of bias) reported no difference in local recurrence at the site of radiosurgery in a head-to-head comparison and addressed no other outcomes of interest.[114]

Of note, two additional cohort studies specifically addressed effects of fractionated SRS and single fraction SRS but the studies did not report sufficient detail for further effect size analyses and contributed only to KQ4 (adverse events).[95, 130]

None of the identified studies compared the effects of fractionation schedules directly in a head-to-head comparison. Fractionation schedules varied in the 24 identified studies evaluating SRS (ranging from 1260 cGy to 1750 cGy in 1 fraction[77] to 4000 cGy in 10 fractions[95]). A meta-regression aiming to detect an effect of the dose across studies did not indicate a systematic effect on overall survival (p=0.55). However, due to the multiplicity of other differences among the studies (e.g., co-treatment, comparator), the failure to detect an effect should be interpreted with caution. No other outcome could be assessed due to insufficient data.

KQ2b. Patient Prognosis and Primary Tumor Site

The evidence table in Appendix D shows that SRS study samples typically comprised patients with a mixture of primary cancers. Thus, it is difficult to assess potential effect modifiers among patient characteristics. A meta-regression categorizing studies by prognosis did not detect a systematic effect for any of the outcomes that allowed analyses (overall survival p=0.67). However, the result should be interpreted with caution because of the small number of studies contributing to the analysis, the narrow range of differences in prognosis (patient prognosis for all analyzable studies was mixed or good), and the result is based on the outcome of overall survival only (data for other outcomes were insufficient).

Among the SRS studies, one RCT enrolled only lung cancer patients.[121] Of note, one identified cohort study assessing SRS included only patients with lung cancer[113] and another cohort study included only breast cancer patients.[135] All other studies were in mixed patient samples. Meta-regressions did not detect differences based on the primary tumor type (overall survival p=0.51); however, the result should be interpreted with caution as only a few studies that restricted to a particular primary tumor type contributed to the analyses.

KQ2c. Addition of Systemic Therapies

The identified SRS studies evaluated different research questions. As described in the introduction of the KQ2 section, one RCT by Lim et al. assessed whether the effects of the combination of SRS and systemic therapy are superior to those of systemic therapy alone (data were limited and did not indicate systematic differences).[121]

Sperduto et al.[154] assessed whether the combination of SRS plus WBRT and temozolomide or erlotinib is superior to SRS plus WBRT alone. The RCT was stopped early due to slow accrual and the authors did not report a statistically significant effect on overall survival (effect estimate HR 1.43; CI 0.89 to 2.31), disease-free survival (8.1 vs 4.8 months), and intracranial progression. The authors found less deterioration in performance status at 6 months in the SRS plus WBRT group than in the arms with added temozolomide or erlotinib.

One RCT funded by the University of Michigan assessed whether patients receiving ipilimumab prior to SRS had more favorable outcomes than patients who received SRS followed

by ipilimumab. However, the trial has only been published in a conference abstract and reported only adverse events in detail for the four participants (see KQ4).[158]

Of note, we identified four cohort studies that compared effects in patients receiving SRS plus immunotherapy to those in patients receiving SRS alone, but with one exception, effect sizes were computable only for adverse events (see KQ4) or the statistical significance of the difference between arms was not reported for effectiveness outcomes.[118, 125, 170] Chen et al.[88] concluded that concurrent stereotactic radiosurgery-stereotactic radiation therapy and immune checkpoint inhibitors may be associated with favorable survival outcomes.

A trial funded by the National Institute of Cancer compared SRS plus R04929097, a gamma secretase inhibitor, with WBRT plus R04929097 but the trial record only reported adverse events (see KQ4).[135] In addition, an observational study that compared SRS or WBRT in combination with either immunotherapy or targeted therapy, reported that SRS and immunotherapy achieved the highest overall survival rates and that for combinations of radiation therapy and targeted therapy, the sequence is important.[146]

Summary of Findings, KQ2

Table 3 summarizes results across studies.

Table 3. Summary of findings and strength of evidence for SRS

Intervention and Comparison	Outcome	Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ2: SRS vs WBRT	Overall survival	1 RCT (N 20) Raman, 2020[145]	HR 2.00; CI 0.78 to 5.17: The results favored WBRT but the difference was not statistically significant.	Insufficient [study limitation, precision, consistency]
KQ2: SRS vs WBRT	Disease-free survival	1 RCT (N 20) Raman, 2020[145]	HR 3.00; CI 0.79 to 11.44: The results favored WBRT but the difference was not statistically significant.	Insufficient [study limitation, precision, consistency]
KQ2: SRS vs WBRT	Deaths due to brain metastases	1 RCT (N 20) Raman, 2020[145]	RR 3.00; CI 0.79 to 11.44: The results favored WBRT but the difference was not statistically significant.	Insufficient [study limitation, precision, consistency]
KQ2: SRS vs WBRT	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Raman, 2020[145] reported a 6-month local recurrence-free survival rate of 58.3% for SRS and 71.4% for WBRT.*	Insufficient [study limitation, precision, consistency]
KQ2: SRS vs WBRT	Functional status	1 RCT (N 20) Raman, 2020[145]	SMD 0.55; CI -0.36 to 1.46: No statistically significant difference between groups.	Insufficient [study limitation, precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ2: SRS vs WBRT	Cognitive function	1 RCT (N 20) Raman, 2020[145]	SMD -0.02; CI -0.91 to 0.87: No difference between groups.	Low for no difference [precision, consistency]
KQ2: SRS + WBRT vs SRS alone	Overall survival	3 RCTs (N 403); Aoyama, 2006;[77] Brown, 2016;[81] Chang, 2009[86]	HR 0.95; CI 0.23 to 3.90: Conflicting results across studies with no systematic difference between treatment groups.	Low SoE for no effect [precision, consistency]
KQ2: SRS + WBRT vs SRS alone	Deaths due to brain metastases	2 RCTs (N 190); Aoyama, 2006;[77] Chang, 2009[86]	RR 1.09; CI 0.04 to 33.13: No systematic difference between treatment groups.	Low SoE for no effect [precision, consistency]
KQ2: SRS + WBRT vs SRS alone	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Aoyama, 2006[77] reported the 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group (p<.001).*	Low SoE for beneficial effect on brain tumor recurrence favoring SRS + WBRT [precision, consistency]
KQ2: SRS + WBRT vs SRS alone	Quality of life	2 RCTs (N 271); Brown, 2016;[81] Chang, 2009[86]	SMD -0.04; CI -1.59 to 1.51: SRS + WBRT compared to SRS alone suggested no systematic differences for quality of life across studies but one study reported SRS alone to be superior at the 3-month follow up point.	Low SoE for no effect [study limitations, consistency]
KQ2: SRS + WBRT vs SRS alone	Functional status	1 RCT (N 213); Brown, 2016[81]	SMD -0.07; CI -0.34 to 0.20: The combination treatment SRS plus WBRT compared to SRS alone suggested no differences in functional status. In addition, Aoyama, 2006[77] reported no significant difference in systemic functional preservation rates between groups.	Low SoE for no effect [study limitation, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ2: SRS + WBRT vs SRS alone	Cognitive status	Effect estimate not possible	Effect estimate not possible *Aoyama, 2006[77] reported no significantly difference in improvement or deterioration between the groups but time to deterioration marginally favored the combination group (14 vs 7 months, p=0.05). Chang, 2009[86] reported a mean posterior probability of decline of 52 percent for the SRS + WBRT group and 24 percent for SRS alone. Brown, 2016[81] reported that a decline of >1 SD on at least 1/7 cognitive tests was less frequent after SRS alone than after SRS + WBRT (p<.001) but results for individual tests varied.*	Low SoE for beneficial effect on cognitive status favoring SRS alone [study limitation, precision, consistency]
KQ2: SRS + WBRT vs SRS or WBRT alone	Overall survival	4 RCTs (N 734); Andrews, 2004;[75] Aoyama, 2006;[77] Brown, 2016;[81] Chang, 2009[86]	HR 1.09; CI 0.69 to 1.73: The combination treatment SRS + WBRT compared to SRS alone or WBRT alone found no statistically significant difference between groups.	Low SoE for no effect [study limitation, precision]
KQ2: SRS + WBRT vs SRS or WBRT alone	Deaths due to brain metastases	3 RCTs (N 521); Andrews, 2004;[75] Aoyama, 2006;[77] Chang, 2009[86]	RR 0.93; CI 0.48 to 1.81: The combination treatment SRS + WBRT compared to SRS alone or WBRT alone found no statistically significant difference in deaths due to brain metastases.	Low for no effect [study limitation, precision]
KQ2: SRS + chemotherapy vs chemotherapy alone	Overall survival	1 RCT (N 98); Lim, 2015[121]	HR 1.20; CI 0.76 to 1.89: The combination treatment SRS + chemotherapy compared to chemotherapy alone found no statistically significant difference in overall survival.	Insufficient [study limitation, precision, consistency]
KQ2: SRS + systemic therapy vs systemic therapy alone	Intracranial progression-free survival, time to CNS disease progression, functional status, cognitive effects	Effect estimate not possible	Effect estimate not possible *Lim, 2015[121] reported no statistically significant difference in overall survival, intracranial progression-free survival, time to CNS disease progression, functional status, and cognitive effects between groups.*	Insufficient [study limitation, precision, consistency]
KQ2: WBRT + SRS vs WBRT + surgery	Overall survival	1 RCT (N 21); Roos, 2011[150]	HR 0.53; CI 0.20 to 1.43: No systematic difference between groups.	Insufficient [study limitation, precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ2: WBRT + SRS vs WBRT + surgery	Disease-free survival	1 RCT (N 21); Roos, 2011[150]	HR 0.55; CI 0.22 to 1.38: No systematic difference for failure-free survival between groups.	Insufficient [study limitation, precision, consistency]
KQ2: WBRT + SRS vs WBRT + surgery	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Roos, 2011[150] reported that 3/11 in the SRS + WBRT had distant brain recurrence and 2/11 local failure vs 3/10 (distant) failure in the surgery + WBRT group*	Insufficient [study limitation, precision, consistency]
KQ2: WBRT + SRS vs WBRT + surgery	Quality of life	1 RCT (N 21); Roos, 2011[150]	SMD 1.22; CI 0.26 to 2.18: No systematic difference between groups	Insufficient [study limitation, precision, consistency]
KQ2: WBRT + SRS vs WBRT + surgery	Functional status, cognitive function	Effect estimate not possible	Effect estimate not possible *Roos, 2011[150] reported no significant differences between arms at 2 months.*	Insufficient [study limitation, precision, consistency]
KQ2: Surgery + WBRT vs SRS	Overall survival	1 RCT (N 33) Muacevic, 2008[133]	HR 1.08; CI 0.30 to 3.94: No systematic difference between groups.	Insufficient [study limitation, precision, consistency]
KQ2: Surgery + WBRT vs SRS	Deaths due to brain metastases	1 RCT (N 33) Muacevic, 2008[133]	RR 3.13; CI 0.95 to 10.33: No systematic difference between groups.	Insufficient [study limitation, precision, consistency]
KQ2a: SRS dose	Overall survival	Meta-regression	No systematic relationship between SRS dose and SRS effect estimates was detected but the analysis was limited.	Low for no effect [directness, study limitations]
KQ2a: SRS technique	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Knisely, 2008[114] randomized by lesion to 1mm margin SRS or 3 mm margin SRS and reported no difference in local recurrence at the site of radiosurgery.*	Insufficient [study limitation, precision, consistency]
KQ2b: Prognosis and SRS	Overall survival	Meta-regression	No systematic relationship between prognosis and SRS effect estimates was detected but the analysis was limited.	Low for no effect [directness, study limitations]
KQ2b: Primary tumor site and SRS	Overall survival	Meta-regression	No systematic relationship between primary tumor type and SRS effect estimates was detected but the analysis was limited.	Low for no effect [directness, study limitations]

Intervention and Comparison	Outcome	Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone	Overall survival	1 RCT (N 126); Sperduto, 2013[154]	HR 1.43; CI 0.89 to 2.31 No systematic difference between groups combining SRS + WBRT and temozolomide vs SRS + WBRT alone. SRS + WBRT + erlotinib vs SRS + WBRT also found no difference: HR 1.47; CI 0.92 to 2.36.	Insufficient [study limitation, precision, consistency]
KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone	Disease-free survival	Effect estimate not possible	Effect estimate not possible *Sperduto, 2013[154] reported median CNS progression-free survival of 4.6 (+temozolomide), 8.1 (SRS+WBRT alone), 4.8 (+erlotinib) months.*	Insufficient [study limitation, precision, consistency]
KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone	Intracranial progression	Effect estimate not possible	Effect estimate not possible *Sperduto, 2013[154] reported times to CNS progression for the three arms were not statistically significant.*	Insufficient [study limitation, precision, consistency]
KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone	Functional status	Effect estimate not possible	Effect estimate not possible *Sperduto, 2013[154] reported SRS + WBRT produced less deterioration in performance status at 6 months than the chemotherapy arms.*	Insufficient [study limitation, precision, consistency]

Abbreviations: CI confidence interval; HR hazard ratio; MMSE Mini-Mental State Examination; N number of participants; N/A not applicable; RCT randomized controlled trials; RR relative risk; SMD standardized mean difference; SoE strength of evidence; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy.

‡the column reports the findings across studies starting with the pooled effect when it can be calculated; findings from additional studies not included in the effect estimate calculation or from relevant studies when an effect estimate cannot be calculated are included and italicized.
‡‡SoE strength of evidence and reason for downgrading.
Reasons for downgrading: study limitations: the estimate is based on studies with high risk of bias, there are equally or more studies where no effect estimate could be determined, the comparator is problematic because of co-interventions, the study is not designed to detect differences between groups in the outcome of interest; precision: the effect size could not be determined, wide confidence intervals, a beneficial effect could not be ruled out; consistency: the effect is based on a single study and the evaluation has not yet been replicated in another study, heterogeneity, conflicting direction of effects.

Key Question 3. What is the effectiveness (or comparative effectiveness) of postoperative SRS compared to WBRT, observation, or preoperative SRS in patients with brain metastases on patient-relevant outcomes, such as overall survival and quality of life?

The identified studies assessed a variety of postoperative interventions and compared to different management strategies. Key points were as follows:

Key Points

- Postoperative radiation therapy (WBRT or SRS) (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, 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.

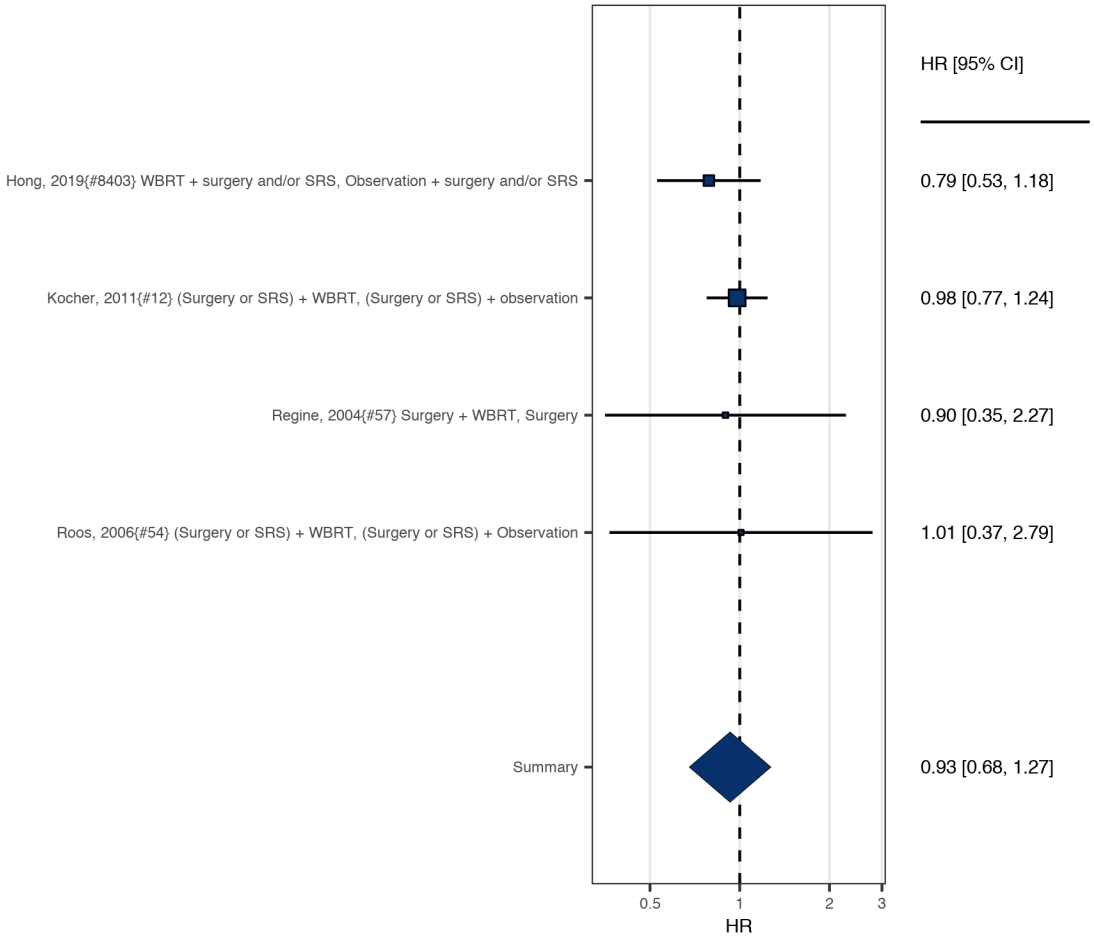
The results for the 10 RCTs are reported separately for WBRT after surgery, SRS after surgery, and radiation therapy after surgery, compared with observation or different interventions.

WBRT After Local Treatment Versus Local Treatment Alone

Most identified studies that assessed postoperative interventions evaluated the use of postsurgical WBRT. This included four RCTs[106, 116, 147, 151] and one observational study.[126]

Figure 16 shows all RCTs reporting on overall survival.[106, 116, 147, 151] The analysis includes studies where patients may have received SRS in addition, or in some cases instead of undergoing surgery.

Figure 16. WBRT post-surgery versus surgery alone: overall survival

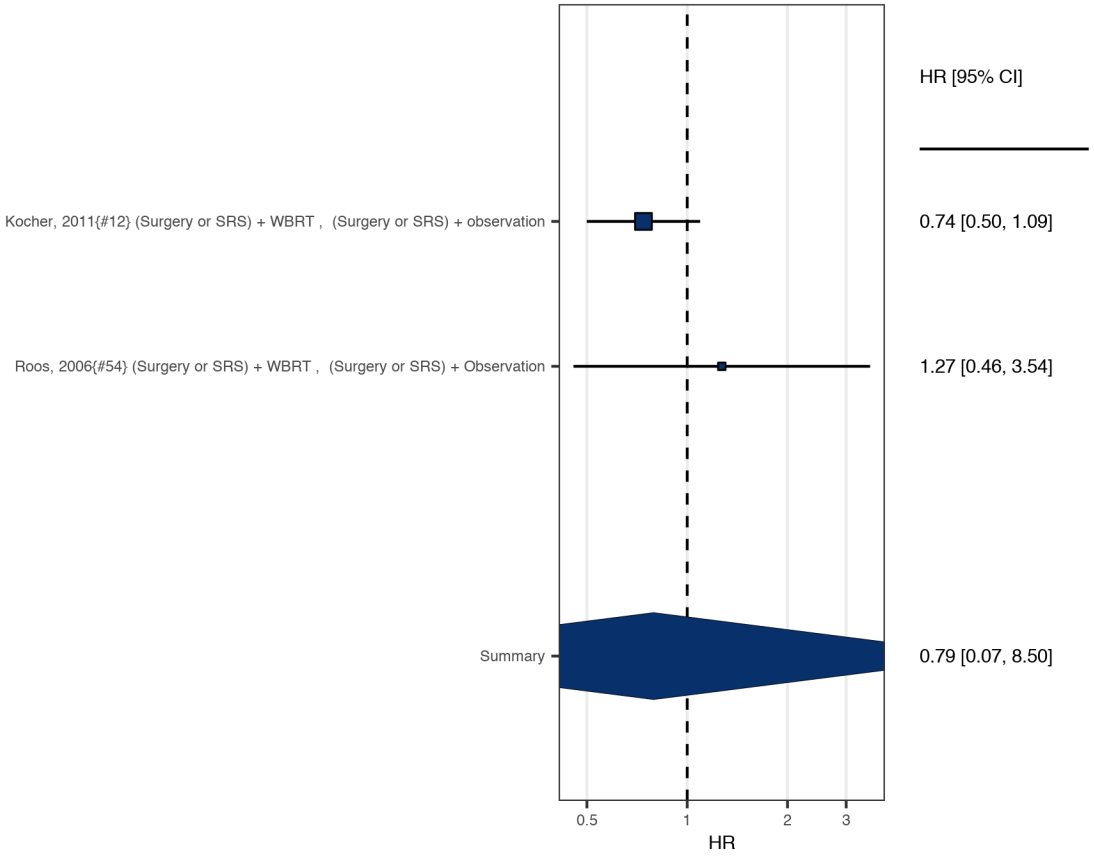


Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Neither individual studies, nor results pooled across studies, showed a statistically significant difference between study arms for the outcome overall survival comparing patients that received WBRT and those that did not (HR 0.93; CI 0.68 to 1.27; 4 RCTs). Heterogeneity was not detected and studies did not differ in their risk of bias, none was high or low risk of bias. As a sensitivity analysis, we compared all studies reporting on the intervention and outcome, thereby adding a cohort study[126] to the analysis, but the pooled results were similar (HR 0.86; CI 0.68 to 1.09; 5 studies).

Two RCTs reported on the outcome disease-free survival as shown in Figure 17.

Figure 17. WBRT post-surgery versus surgery alone: disease-free survival

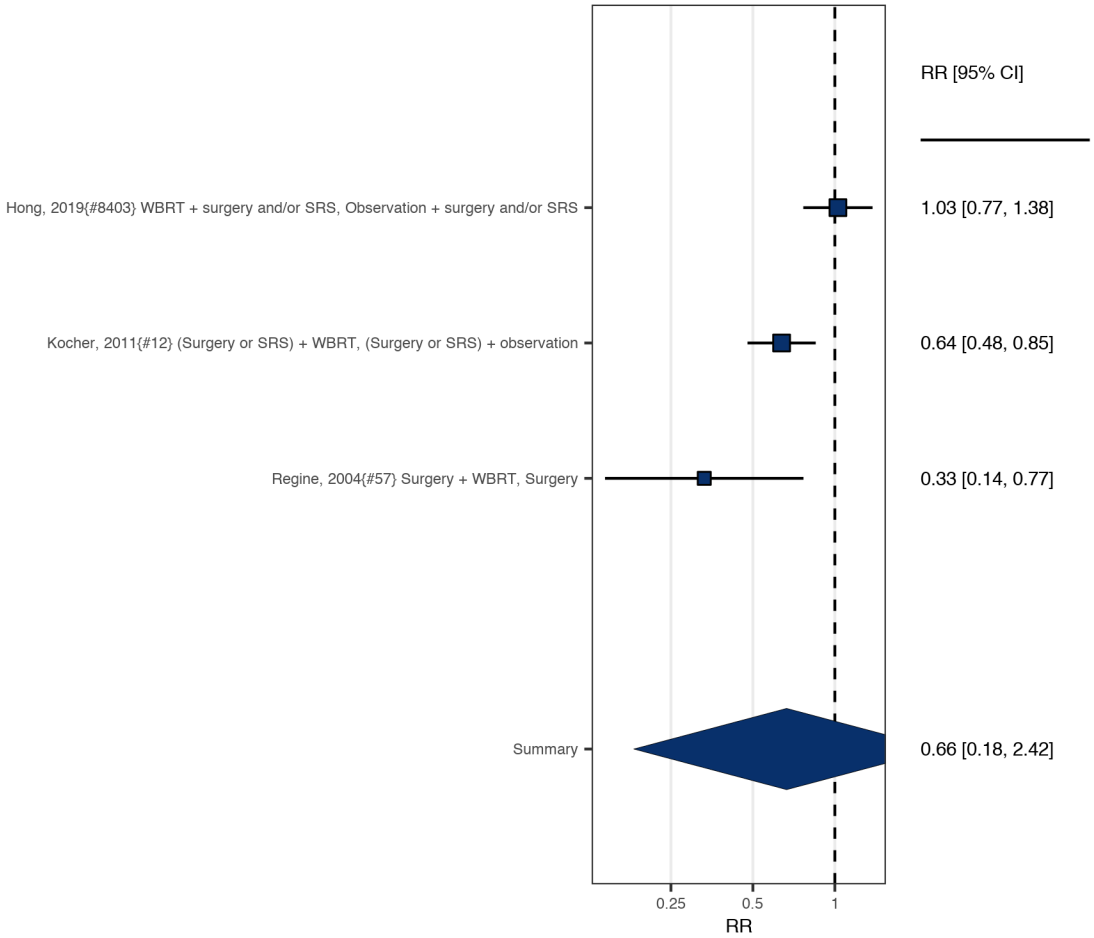


Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

The individual studies reported conflicting results, one favoring the WBRT, one the surgery or SRS plus observation arm.[116, 151] The pooled result did not suggest that a meaningful summary can be obtained from the identified data (HR 0.79; CI 0.07 to 8.50; 2 RCTs).

We identified three RCTs that reported on the outcome of deaths due to brain metastases and that allowed us to calculate the relative risk as shown in Figure 18.[106, 116, 147]

Figure 18. WBRT post-surgery versus surgery alone: deaths due to brain metastases



Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Although the results of both studies favored the WBRT addition, the effect estimates varied widely and no precise summary estimate could be determined (RR 0.66; CI 0.18 to 2.42; 3 RCTs). The analysis detected considerable heterogeneity (I^2 83%). All included studies were classified as medium risk of bias.

Hong et al.[106] reported no difference in intracranial failure (p=0.28). Kocher et al.[116] reported that local recurrence was similar between groups (HR 1.15; CI 0.72 to 1.83); patients undergoing SRS had a lower risk of early (0-3 months) local recurrence (HR 5.94; CI 1.72 to 20.45) but the risk increased with time (HR for 3-6 months 1.37; CI 0.64 to 2.90; HR for 6-9 months 0.75; CI 0.28 to 2.00; HR at 9 months or longer 0.36; CI 0.14 to 0.93). Regine et al.[147] reported local recurrence of metastatic cancer in the brain was six percent in the radiation and 13 percent in the observation group. Roos et al.[151] reported a trend of reduced CNS relapse with WBRT but the difference was not statistically significant (p=0.12). Of note, an observational study by McPhearson et al. reported that withholding WBRT was an independent predictor of local and distant recurrence.[126] Combining the RCT by Roos and the observational study by McPhearson in a sensitivity analysis showed that no meaningful effect estimate for the time to intracranial progression can be determined (HR 1.12; CI 0.00 to 22143; 2 studies).

The EORT 22952-26001 trial group of Kocher et al.[116] reported better quality of life scores for patients in the observation group (SMD -0.51; CI -0.72 to -0.30; 1 RCT). Hong et al.[106]

assessed quality of life but did not report sufficient detail for effect size calculations; the authors concluded no difference between groups. Similarly, Roos et al.[151] concluded that their limited analysis of quality of life data revealed no evidence of differences between groups.

Kocher et al.[116] reported no difference between arms in the duration of functional independence (HR 0.96; 95% CI 0.76 to 1.20; p=0.71). Regine et al.[147] also found no statistically significant difference in the length of time the Karnofsky score remained at 70 percent or more (p=0.61). Roos et al.[151] similarly reported no statistically significant difference between arms (p=0.80) for the time to functional status deterioration.

Hong et al.[106] reported no difference in time to cognitive failure or in the proportion of patients with global cognitive impairment, but the authors found a change in Hopkins Verbal Learning Test Revised, Delayed Recall at four months favoring the observation group (p=0.0018). Roos et al.[151] concluded that their limited analysis of neurocognitive function showed no evidence of differences between groups.

SRS After Surgery Versus Surgery Alone

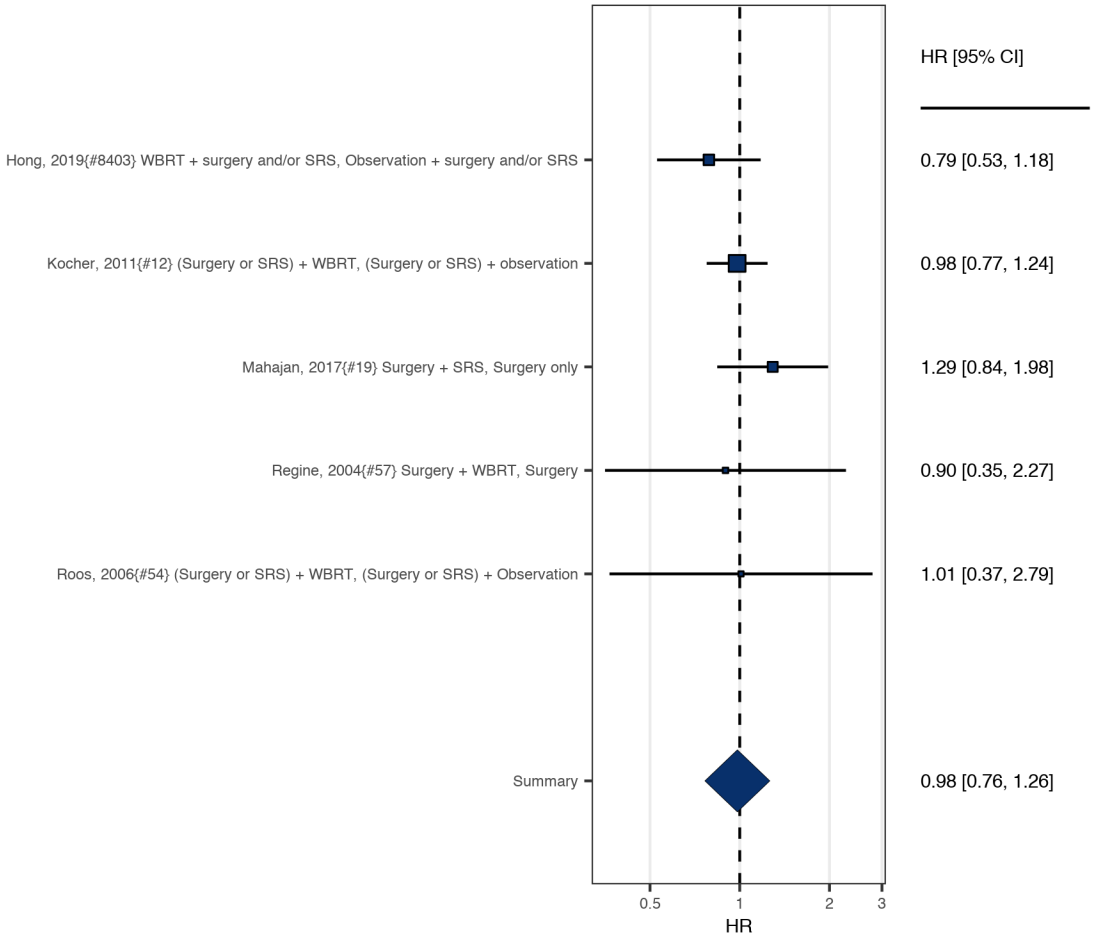
One (low risk of bias) RCT reported by Mahajan et al. assessed whether offering SRS after surgery improves patient outcomes compared with surgery alone.[124] The findings for the analyzable outcomes of overall survival (HR 1.29; CI 0.84 to 1.98; 1 RCT) and deaths due to brain metastases (RR 0.91; CI 0.58 to 1.43; 1 RCT) favored the observation after surgery arm, but the effects in this single study were not statistically significant. However, the study found a statistically significant benefit of SRS for local recurrence (HR 0.46; CI 0.24 to 0.88; 1 RCT).

All studies comparing WBRT or SRS to observation after surgery are combined in the next section.

Radiation Therapy After Surgery Versus Surgery Alone

The results of five identified RCTs, all investigating whether radiation therapy (SRS or WBRT) improves outcomes after surgery, are shown in Figure 19.[116, 124, 147, 151]

Figure 19. Radiation therapy post-surgery versus surgery alone: overall survival

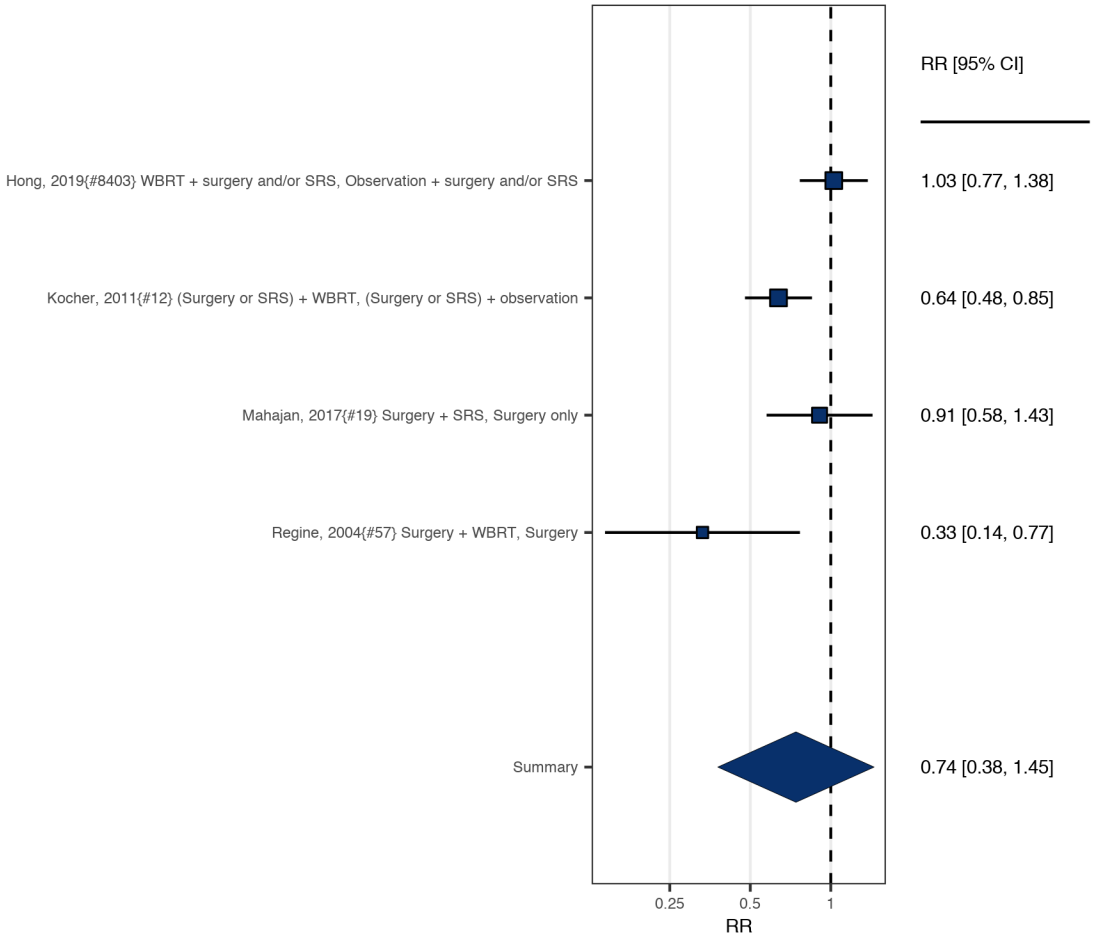


Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Individual studies did not indicate an advantage of radiation therapy and the pooled result for overall survival was also not different between study arms (HR 0.98; CI 0.76 to 1.26; 5 RCTs). The analysis included one low risk of bias study[124] and no high risk of bias study; statistical heterogeneity was not detected. Two of the studies also reported on disease-free survival, both evaluated WBRT and were documented in the previous section.

The RCTs evaluating SRS or WBRT post-surgery that reported on deaths due to brain metastases are shown in Figure 20.[106, 116, 124, 147]

Figure 20. Radiation therapy post-surgery versus surgery alone: deaths due to brain metastases

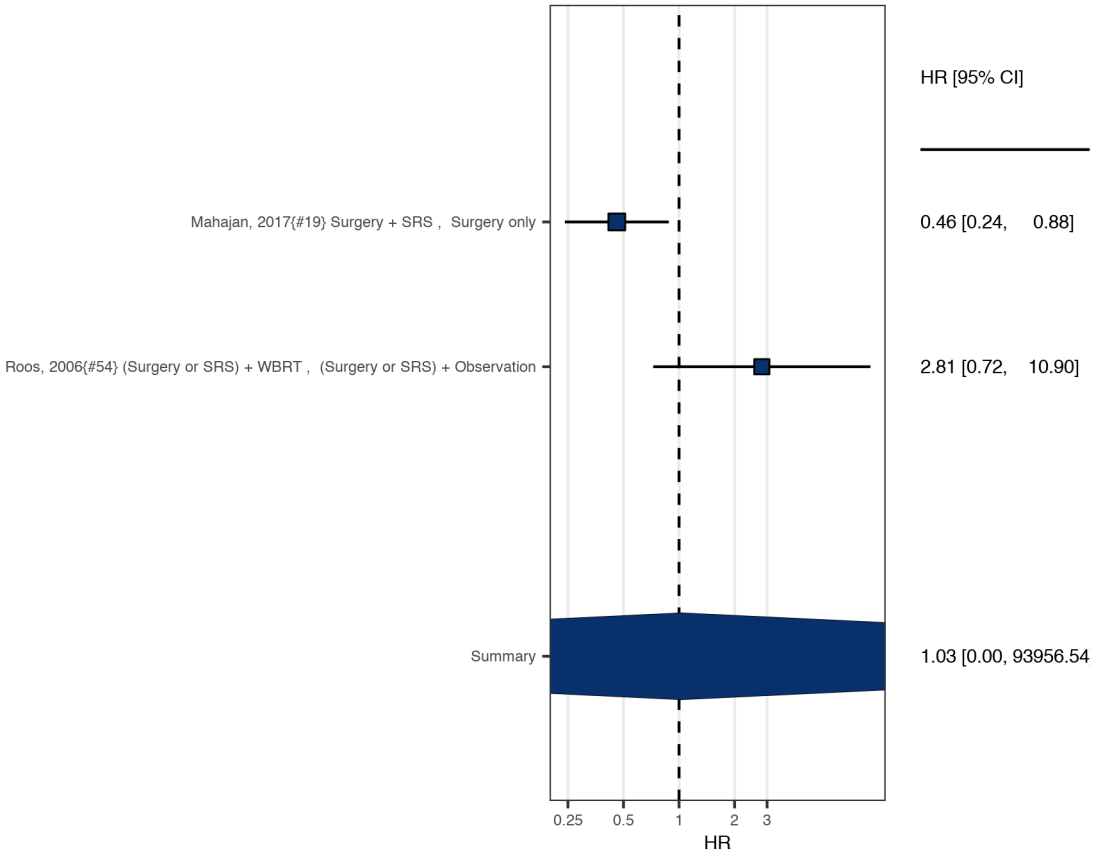


Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Results favored participants who had received radiation therapy, but effect estimates varied considerably across the small number of studies and consequently, the pooled effect was not statistically significant (RR 0.74; CI 0.38 to 1.45; 4 RCTs). The analysis included a low risk of bias study[124] and no high risk of bias studies contributed to the effect estimate. The statistical heterogeneity was moderate (I^2 70%).

Two of the RCTs reported on time to intracranial progression as shown in Figure 21.[124, 151]

Figure 21. Radiation therapy post-surgery versus surgery alone: intracranial progression



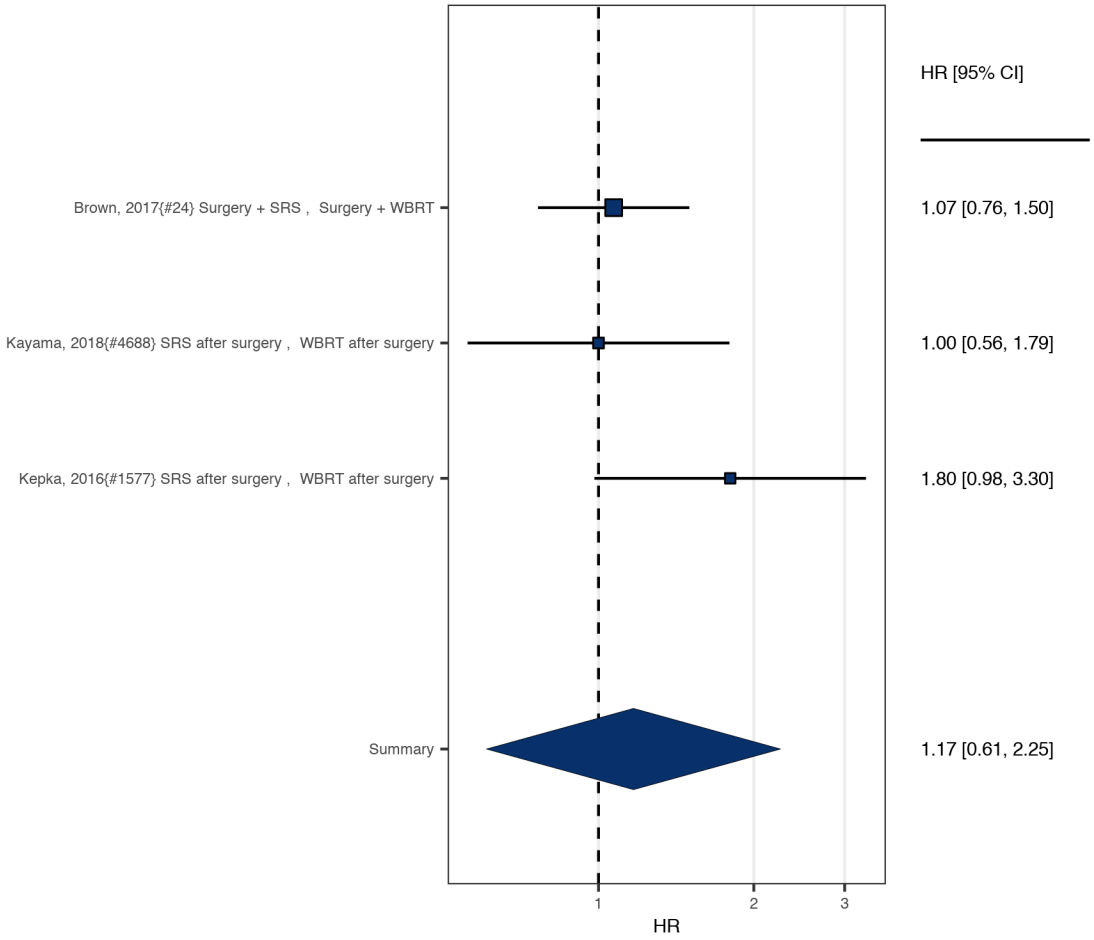
Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

The two studies reported conflicting results and overall, there was no difference in the point estimate with wide confidence intervals (HR 1.03; CI 0.00 to 93956; 2 RCTs); heterogeneity was substantial (I^2 82%).

SRS After Surgery Versus WBRT After Surgery

Three RCTs compared post-surgical WBRT and post-surgical SRS in head-to-head trials.[79, 111, 112] Figure 22 shows results for overall survival.

Figure 22. SRS post-surgery versus WBRT post-surgery: overall survival



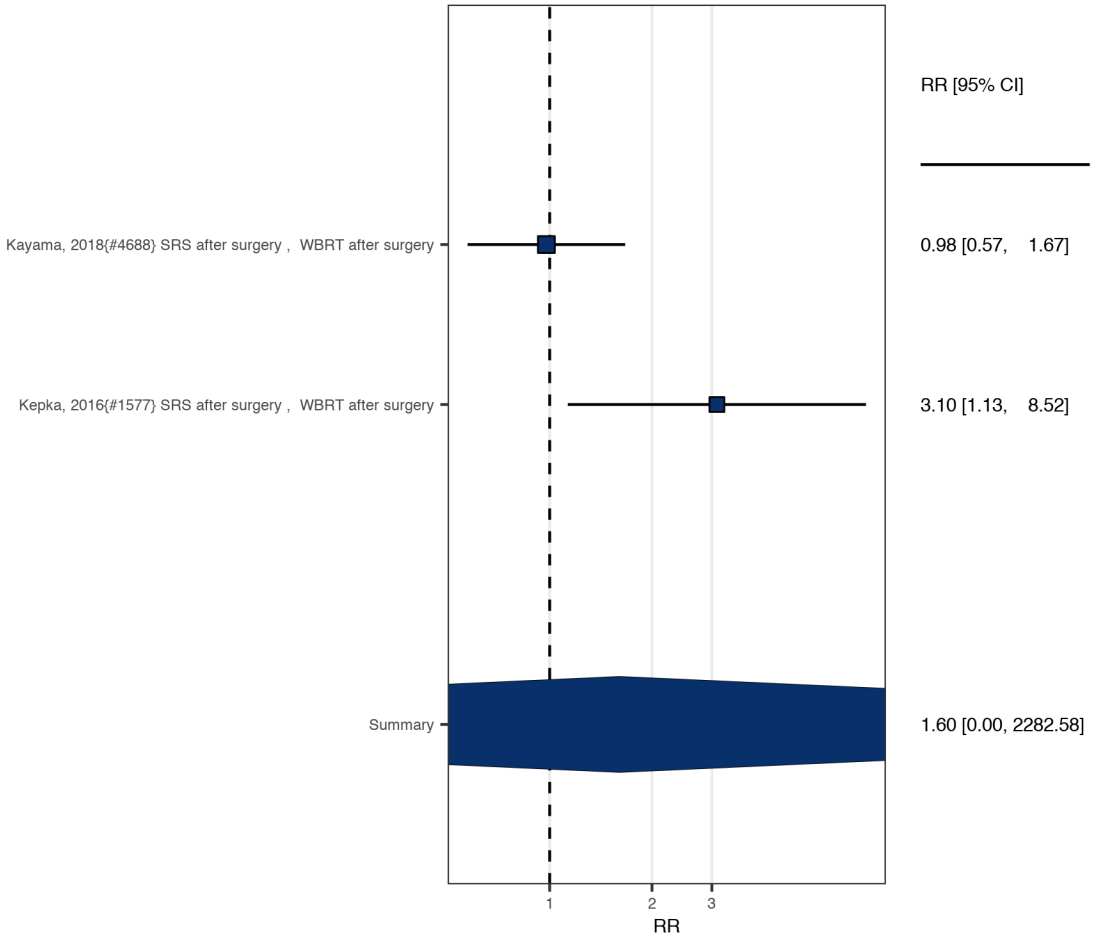
Abbreviations: CI confidence interval; HR hazard ratio; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

The estimates varied substantially and the difference was not statistically significant (HR 1.17; CI 0.61 to 2.25; 3 RCTs). The RCTs were categorized as low, medium, and high risk of bias. The low risk of bias study[79] reported a smaller effect; both individual studies did not show statistically significant differences between arms.

Kayama et al.[111] reported that median intracranial progression-free survival was longer in the WBRT treatment group but we were unable to compute effect sizes.

Two of the RCTs reported on deaths due to brain metastases as shown in Figure 23.[111, 112]

Figure 23. SRS post-surgery versus WBRT post-surgery: death due to brain metastases



Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

The estimates varied substantially and the difference across studies was not statistically significant (RR 1.60; CI <0.00 to 2282; 2 RCTs). Despite the small number of studies, the analysis detected heterogeneity (I^2 75%). The RCT by Kayama et al.[111] and Kepka et al.[112] were rated similarly with regard to risk of bias (both were neither high nor low) and it was not possible to assign one study more weight than the other.

Brown et al.[79] reported slower intracranial progression in the WBRT group (HR 2.45; CI 1.61 to 3.72; 1 RCT).[79] Kepka et al.[112] reported rates of 86 percent in the SRS and 68 percent in the WBRT group,

The RCT by Brown et al. also reported on quality of life.[79] Results varied by quality of life scale component and details were insufficient to allow effect sizes to be computed. The authors reported clinically significant improvement was more frequent in the SRS group compared with WBRT for physical wellbeing but no significant differences between treatment groups in social, emotional, or functional wellbeing, brain-specific concerns, or overall Functional Assessment of Cancer Therapy-Brain (FACT-Br) were found.

Brown et al. reported functional independence at three months was higher after SRS than after WBRT but at 6 months, no significant difference between groups was noted.[79] Kayama et al. reported the proportions of patients whose performance status scores did not worsen at 12 months were similar in both treatment groups.[111]

Brown et al.[79] reported less cognitive deterioration in patients who received SRS rather than WBRT (SMD -0.82; CI -1.11 to -0.53; 1 RCT). Kayama et al. reported that the proportion of patients whose mini mental status examination did not worsen at 12 months was similar across treatment arms but 16 percent of patients in the WBRT arm experienced grade two to four cognitive dysfunction after 91 days post-enrollment compared to only eight percent in the SRS arm (p=0.048).[111]

KQ3a. Dose Fractionation Schedule

We did not identify any studies that conducted direct comparisons of post-surgical radiation fractionation schedules. Only a small number of post-surgery studies were found overall, and these studies varied in several aspects in addition to fractionation schedules, making indirect comparisons difficult.

Summary of Findings, KQ3

Table 4 summarizes results across studies.

Table 4. Summary of findings and strength of evidence for postoperative interventions

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment	Overall survival	4 RCTs (N 680); Hong, 2019;[106] Kocher, 2011;[116] Regine, 2004;[147] Roos, 2006[151]	HR 0.93; CI 0.68 to 1.27: No systematic difference between groups.	Low SoE for no effect [precision, consistency]
KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment	Disease-free survival	2 RCTs (N 378); Kocher, 2011;[116] Roos, 2006[151]	HR 0.79; CI 0.07 to 8.50: No systematic difference between treatment groups.	Low SoE for no effect [precision, consistency]
KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment	Deaths due to brain metastases	3 RCTs (N 661); Hong, 2019[106]; Kocher, 2011;[116] Regine, 2004[147]	RR 0.66; CI 0.18 to 2.42: Two studies reported fewer deaths due to brain metastases, one reported no difference.	Insufficient [study limitation, precision, consistency]
KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment	Intracranial progression	1 RCT (N 19) Roos, 2006[151]	HR 2.81; CI 0.72 to 10.9: Results favor WBRT but the effect was not statistically significant. *In addition, Hong, 2019[106] reported no difference in intracranial failure (p=0.28). Kocher, 2011[116] reported that in adjusted models, local recurrence was similar between the SRS and surgical resection groups (HR 1.15; CI, 0.72-1.83). Regine, 2004[147] reported a*	Insufficient [study limitation, precision, consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
			rate of 6 vs 13% local recurrence of metastatic cancer in the brain.	
KQ3: WBRT after surgery vs no radiation after surgery	Quality of life	1 RCT (N 359); Kocher, 2011[116]	SMD -0.51; CI -0.72 to -0.30: Patients in the observation group reported better quality of life than patients in the WBRT group based on the RCT that provided effect sizes. *In addition, Hong, 2019[106] reported no difference in quality of life (p=0.083). Roos, 2006[151] found no differences between groups but analyses were limited.*	Low SoE for beneficial effect on quality of life favoring observation [study limitation, consistency]
KQ3: WBRT after surgery or SRS vs no radiation after surgery	Functional status	Effect estimate not possible	Effect estimate not possible *Kocher, 2011[116] reported no difference between the two arms (p=0.71). Regine, 2004[147] reported no difference in the length of time the Karnofsky score remained at ≥ 70% (p=0.61). Roos, 2006[151] reported no statistically significant difference between time to deterioration of WHO performance status to >1 (HR 1.16, 0.38 to 3.48).*	Low SoE for no effect [study limitation, precision]
KQ3: WBRT after surgery or SRS vs no radiation after surgery	Cognitive function	Effect estimate not possible	Effect estimate not possible *Hong, 2019[106] reported no difference in in time to cognitive failure or in proportions with global cognitive impairment and patients in the observation group showed a 20.9% improvement vs a 2.7% decline in WBRT patients. Roos, 2006[151] found no differences between groups.*	Insufficient [study limitation, precision, consistency]
KQ3: SRS after surgery vs no radiation after surgery	Overall survival	1 RCT (N 128); Mahajan, 2017[124]	HR 1.29; CI 0.84 to 1.98: No systematic difference between groups.	Low SoE for no effect [precision, consistency]
KQ3: SRS after surgery vs no radiation after surgery	Deaths due to brain metastases	1 RCT (N 128); Mahajan, 2017[124]	RR 0.91; CI 0.58 to 1.43: No systematic difference between groups.	Low SoE for no effect [precision, consistency]
KQ3: SRS after surgery vs no radiation after surgery	Intracranial progression	1 RCT (N 128); Mahajan, 2017[124]	HR 0.46; CI 0.24 to 0.88: Favors SRS after surgery compared to observation after surgery regarding local recurrence.	Low SoE for beneficial effect on local recurrence favoring SRS [study limitation, consistency]
KQ3: Radiation therapy after surgery vs no radiation after surgery	Overall survival	5 RCTs (N 808); Hong, 2019;[106] Kocher, 2011;[116] Mahajan, 2017;[124] Regine, 2004;[147] Roos, 2006[151]	HR 0.98; CI 0.76 to 1.26: No systematic difference between treatment groups.	Moderate SoE for no effect [consistency]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ3: Radiation therapy after surgery vs no radiation after surgery	Deaths due to brain metastases	4 RCTs (N 789); Hong, 2019;[106] Kocher, 2011;[116] Mahajan, 2017;[124] Regine, 2004[147]	RR 0.74; CI 0.38 to 1.45: No systematic difference between treatment groups.	Low SoE for no effect [precision, consistency]
KQ3: Radiation therapy after surgery vs no radiation after surgery	Intracranial progression	2 RCTs (N 147); Mahajan, 2017;[124] Roos, 2006[151]	HR 1.03; CI <0.00 to 93956: Studies reported conflicting results.	Insufficient [study limitation, precision, consistency]
KQ3a: SRS vs WBRT post-surgery	Overall survival	3 RCTs (N 515); Brown, 2017;[79] Kayama, 2018;[111] Kepka, 2016[112]	HR 1.17; CI 0.61 to 2.25: Across studies there were no systematic differences between WBRT and SRS.	Low SoE for no difference [precision]
KQ3a: SRS vs WBRT post-surgery	Disease-free survival	Effect estimate not possible	Effect estimate not possible *Kayama, 2018[111] reported a median intracranial progression-free survival of 10 months for WBRT and 4 months for salvage SRS.*	Insufficient [study limitation, precision, consistency]
KQ3a: SRS vs WBRT post-surgery	Deaths due to brain metastases	2 RCT (N 330); Kayama, 2018;[111] Kepka, 2016[112]	RR 1.60; CI <0.00 to 2282: Direction of effects favors WBRT but the effect is not statistically significant.	Insufficient [study limitation, precision, consistency]
KQ3a: SRS vs WBRT post-surgery	Intracranial progression	1 RCT (N 185); Brown, 2017[79]	HR 2.45; CI 1.61 to 3.72: Results favoring WBRT based on one RCT that provided effect estimates. *In addition, Kepka, 2016[112] reported intracranial progression rates of 86% in the SRS vs 68% in the WBRT group.*	Low SoE for beneficial effects on intracranial progression favoring WBRT [study limitation, precision]
KQ3a: SRS vs WBRT post-surgery	Quality of life	Effect estimate not possible	Effect estimate not possible *Brown, 2017[79] reported clinically significant improvement was more frequent in the SRS group compared with WBRT for physical wellbeing; no significant differences between treatment groups in social, emotional, or functional wellbeing, brain-specific concerns, or overall FACT-Br.*	Insufficient [study limitation, precision, consistency]
KQ3a: SRS vs WBRT post-surgery	Functional status	Effect estimate not possible	Effect estimate not possible *Brown, 2017[79] reported no significant difference between groups in functional independence at the latest follow up.* *Kayama, 2018[111] reported the proportions of patients whose performance status scores did not worsen at 12 months were similar in both treatment groups.*	Low SoE for no difference [study limitation, precision]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies‡ *Additional Individual Study Findings*	Conclusion and SoE‡‡ [Reasons for Downgrading]
KQ3a: SRS vs WBRT post-surgery	Cognitive function	1 RCT (N 185); Brown, 2017[79]	SMD -0.82; CI -1.11 to -0.53: Results favored SRS in an RCT that provided effect estimates. *In addition, Kayama, 2018[111] reported the proportion of patients whose mini mental status examination did not worsen at 12 months was similar across treatment arms but 16% of patients in the WBRT arm experienced grade 2-4 cognitive dysfunction after 91 days post-enrollment compared to 8% in the SRS arm (p=0.048).*	Low SoE for beneficial effects on cognitive function favoring SRS [study limitation, precision,]

Abbreviations: CI confidence interval; FACT-Br Functional Assessment of Cancer Therapy-Brain; HR hazard ratio; N number of participants; RCT randomized controlled trial; RR relative risk; SMD standardized mean difference; SoE strength of evidence; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy.

‡The column reports the findings across studies starting with the pooled effect when it can be calculated; findings from additional studies not included in the effect estimate calculation or from relevant studies when an effect estimate cannot be calculated are included and italicized.
‡‡SoE strength of evidence and reason for downgrading.
Reasons for downgrading: study limitations: the estimate is based on studies with high risk of bias, there are equally or more studies where no effect estimate could be determined, the comparator is problematic because of co-interventions, the study is not designed to detect differences between groups in the outcome of interest; precision: the effect size could not be determined, wide confidence intervals, a beneficial effect could not be ruled out; consistency: the effect is based on a single study and the evaluation has not yet been replicated in another study, heterogeneity, conflicting direction of effects.

Key Question 4. What are the adverse effects (i.e., serious harms) of WBRT, SRS, and systemic therapies for patients with brain metastases (either alone or in combination)?

This summary focuses on adverse events reported across studies in the identified radiation therapy RCTs and large cohort studies. Key findings include the following:

Key Points

- 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.

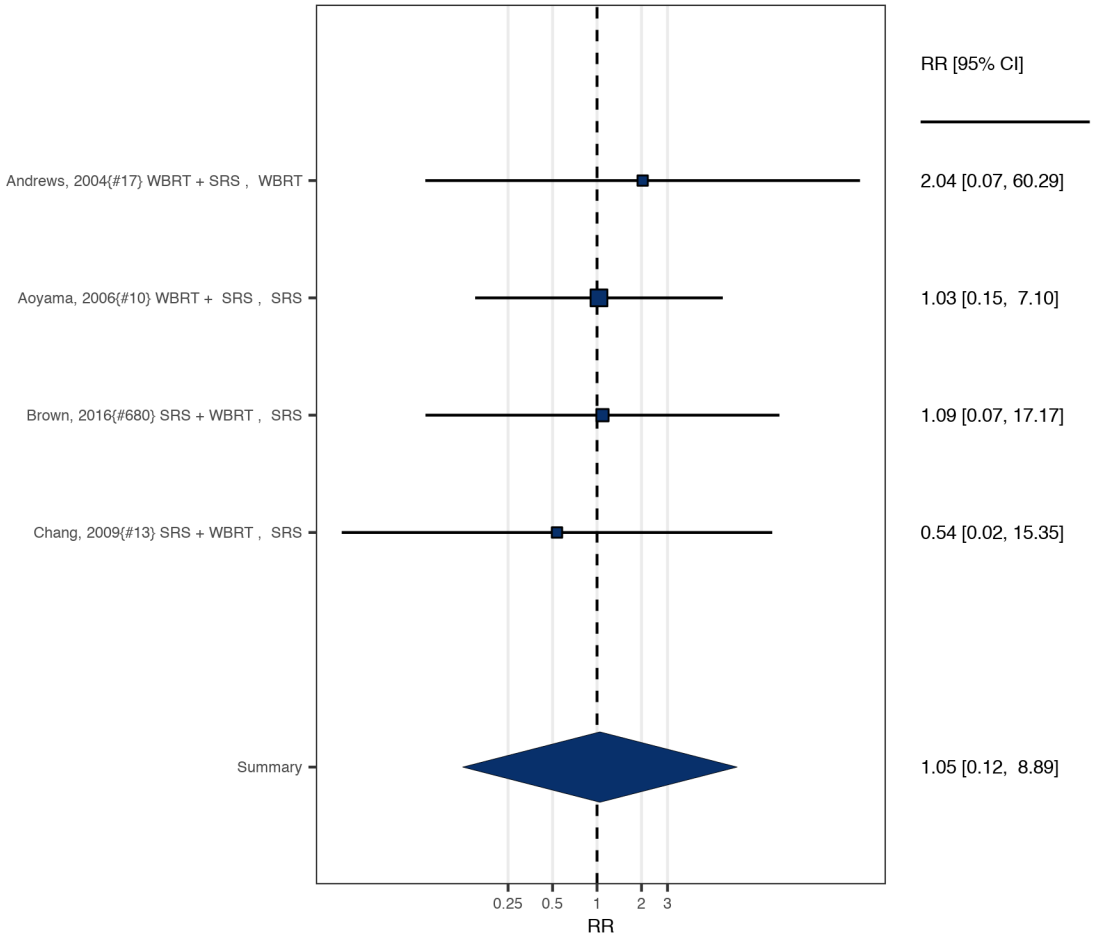
- We found no difference in fatigue but only WBRT plus systemic therapy (RR 1.03; CI 0.86 to 1.23; 10 studies; moderate SoE) had been assessed in more than one study.
- We found no difference in seizures comparing WBRT plus SRS versus WBRT alone or SRS alone (RR 0.37; CI 0.03 to 5.38; 3 studies, low 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).

The chapter is organized by adverse event category that had been selected with the help of the Technical Expert Panel and addressed number of patients with serious adverse events, number of adverse events, headaches, radiation necrosis, fatigue, seizure, and vomiting. Other adverse events reported in individual studies are documented in Appendix D. The narrative synthesis focuses on interventions that have been evaluated in more than one study. Single studies detecting a statistically significant risk for an intervention are also included in the synthesis.

Serious Adverse Events

The studies evaluating the effect of the combination of WBRT plus SRS are shown in Figure 24. Studies compared to either WBRT or SRS alone.[75, 77, 81, 86]

Figure 24. WBRT plus SRS versus WBRT or SRS alone: serious adverse events

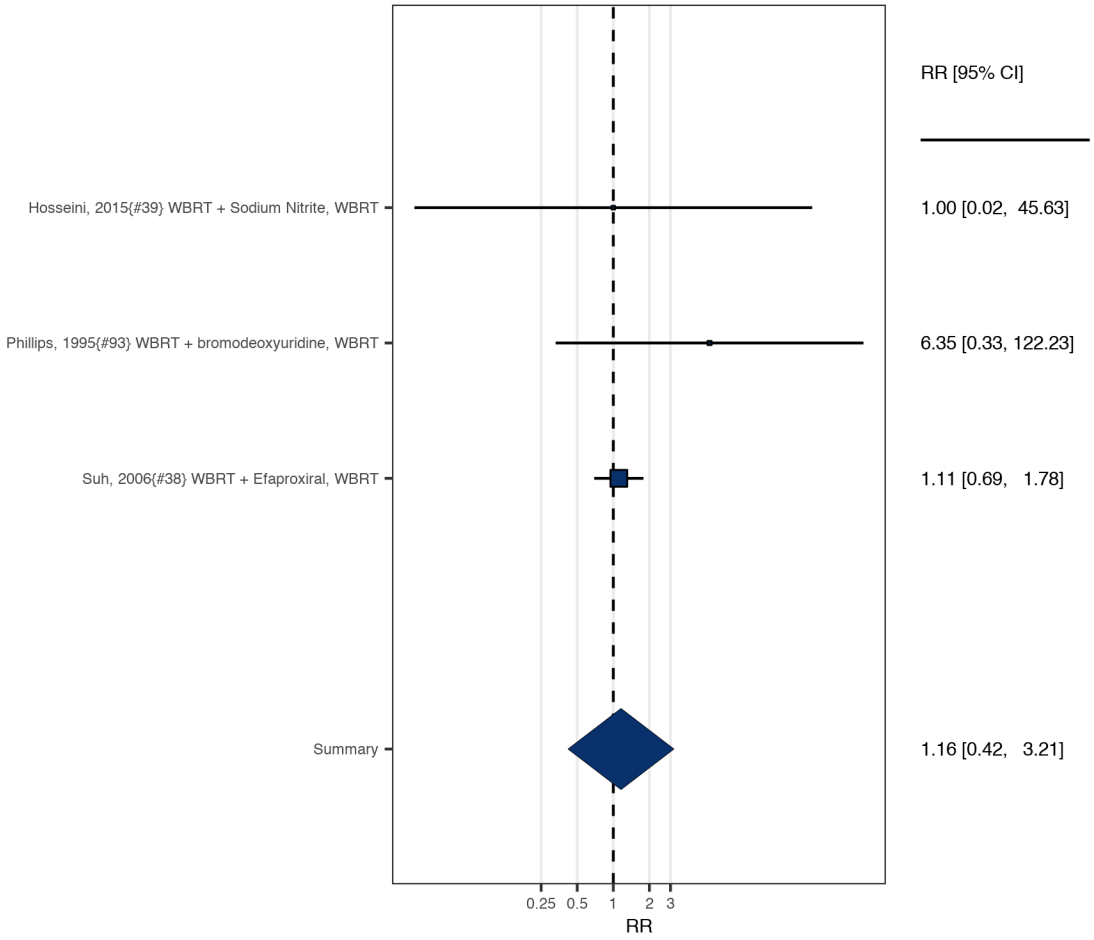


Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Individual study results varied but across studies no difference between the combination and the individual treatments could be found (RR 1.05; CI 0.12 to 8.89; 4 studies). Individual studies reported different adverse events across treatment arms, such as radiation necrosis and leukoencephalopathy,[77] neurological toxicities and not further defined,[75] grade 3 or 4 of late radiation toxic effects,[81] and pathologically proven radiation necrosis.[86] The analysis includes one low risk of bias study[75] and no high risk of bias studies contributed to the effect estimate. The analysis detected no statistical heterogeneity.

Three studies evaluating radiosensitizer in WBRT reported on the number of patients with serious adverse events as shown in Figure 25.[107, 138, 155]

Figure 25. WBRT plus radiosensitizer or WBRT alone: serious adverse events

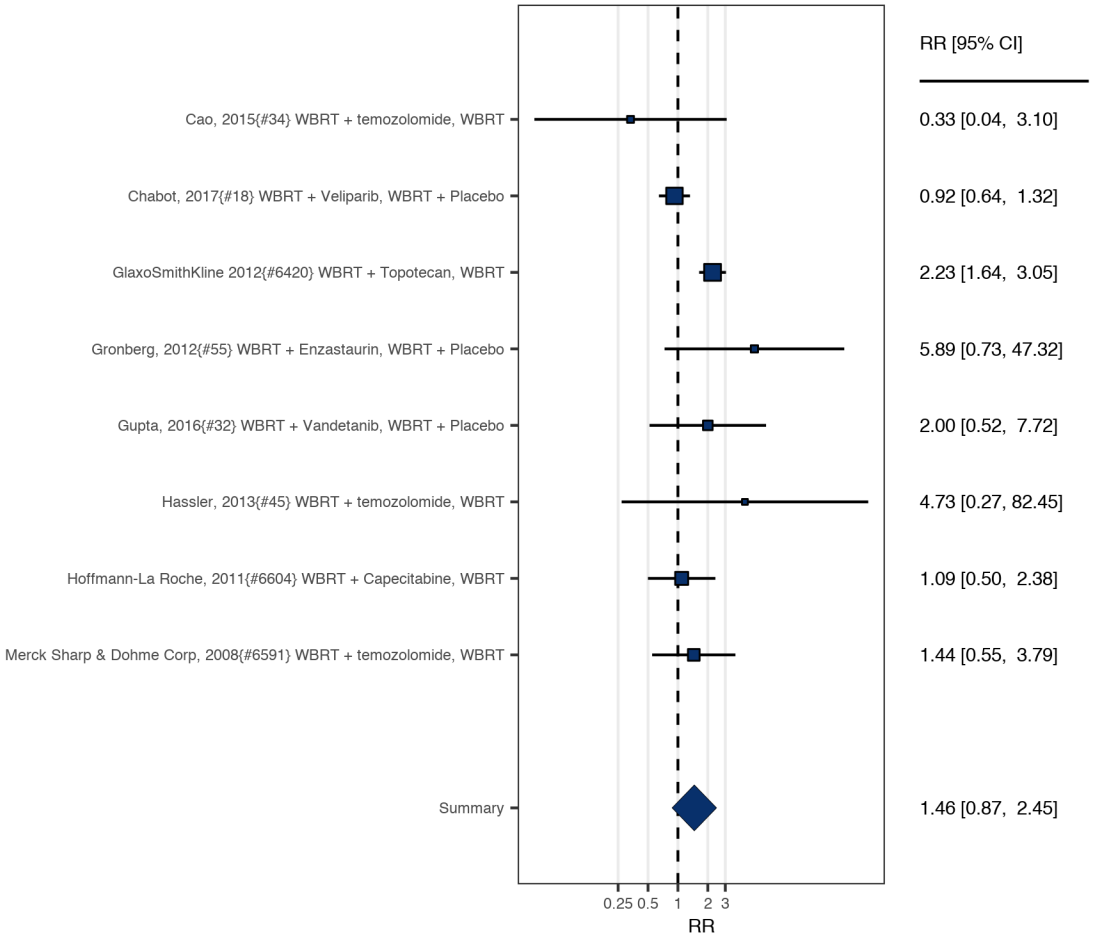


Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

Two studies indicated an increased risk, but none were statistically significant (RR 1. 16; CI, 0.42 to 3.21; 3 studies). Suh et al.[155] reported more incidences grade 3 or 4 treatment-emergent adverse events (hypoxemia, headache), Philips reported three fatal toxicities in the radiosensitizer group (Stevens-Johnson type total skin reaction, neutropenia).[138] The studies were similar in their overall risk of bias assessment for adverse events (neither high nor low risk).

Several studies compared systemic therapy given in addition to WBRT and reported on serious adverse events as shown in Figure 26.[84, 85, 97, 100, 102, 103, 105, 154]

Figure 26. WBRT plus systemic therapy versus WBRT alone: serious adverse events



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

As shown in the figure, some individual studies suggested an increased risk of serious adverse events to be associated with the addition of systemic therapy, but the effect was not statistically significant across studies (RR 1.46; CI 0.87 to 2.45; 8 studies). In studies that reported more events in the systemic therapy arm, the GlaxoSmith trial[97] reported 41% of patients with a serious adverse event, including neutropenia and thrombocytopenia, in the topotecan group compared to 18% in the WBRT alone group. Gronberg et al.[100] reported six patients with a serious adverse event including a death of unknown cause compared to one event in the placebo group (death from pulmonary embolism). Gupta et al.[102] reported confusion as the most common serious adverse event. Hassler et al.[103] reported more incidences of lymphocytopenia. Sperduto et al.[154] reported an incident of myocardial ischemia, brain necrosis, and hemorrhagic stroke in the temozolomide as well as the erlotinib group but not in the WBRT plus SRS group without systemic therapy. There was moderate heterogeneity (I^2 52%). The analysis did not include any high risk of bias studies and five of the eight studies were classified as low risk of bias due to the assessment and reporting methods for adverse events.

Kocher et al (medium risk of bias) study comparing WBRT with observation in patients who had received surgery or SRS as initial treatment reported more incidences of grade 4 late toxicities (RR 4.31; CI 1.25 to 14.86; 1 study) and the authors suspected one patient in the

WBRT arm died of toxicity (radionecrosis), but the evaluation has not been replicated in another study yet.[116]

Two studies evaluating surgery plus SRS compared to surgery plus WBRT reported on the number of patients who experienced a serious adverse event.[79, 112] Across studies there was no statistically significant difference between studies (RR 1.33; CI 0.79 to 2.25; 2 studies). The risk of bias varied but no heterogeneity was detected and the low risk of bias study by Brown et al[79] also reported no statistically significant difference between treatment arms. While Kepka et al. reported no serious adverse events in both groups, Brown et al. reported 10 incidences of serious adverse events, including respiratory failure, in the WBRT group of 92 patients, compared to seven incidences in 93 patients in the SRS group. Kayama et al.[111] did not report the number of patients experiencing a serious adverse events but the authors reported no grade 4 event in the SRS group and 8 events in the WBRT group including cognitive dysfunction.

Number of Adverse Events

We reviewed the total number of adverse events reported for the interventions across studies. For this outcome, no statistical test could be performed as reported adverse events are likely clustered within patients, i.e., the same patient can suffer multiple adverse events.

Across WBRT studies, most adverse events were seen in the combination of WBRT plus radiosensitizer compared to WBRT alone (2,255 vs 1,009 events)[107, 127, 128, 138, 168] and WBRT plus systemic therapy (1,570 vs 1,150).[76, 84, 85, 89, 91, 100, 102, 103, 105, 115, 129, 165] The number of events was similar for WBRT as adjunctive therapy (211 vs 204),[148, 164] WBRT plus SRS versus WBRT alone (174 vs 160),[75, 93] and WBRT plus surgery versus WBRT alone (11 vs 8).[131]

SRS studies showed some differences for SRS plus WBRT versus SRS alone (182 vs 145);[77, 81, 86] SRS plus WBRT versus WBRT (171 vs 157};[75] and the combination of SRS plus WBRT versus SRS alone or WBRT alone (353 vs 302).[75, 77, 81, 86]

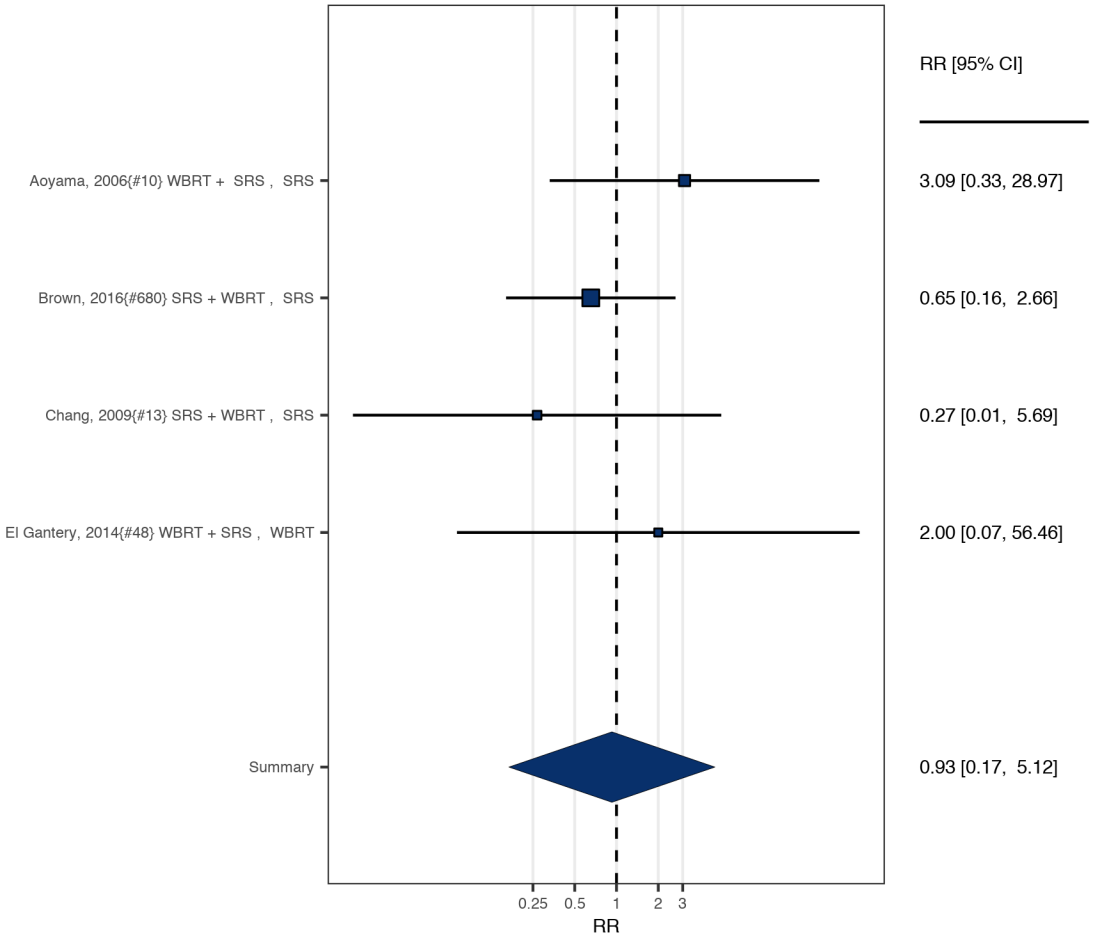
Post-surgery studies reported more adverse events for WBRT when comparing SRS versus WBRT after surgery (338 vs 541)[79, 111] but WBRT versus observation showed no marked differences (721 vs 691).[116] The results should be interpreted with caution as the effect size and the statistical significance could not be computed.

Radiation Necrosis

In addition to the broad categories of adverse events, the Technical Expert Panel also helped select specific adverse events, one of them was radiation necrosis (for more information on the selection process see Appendix A). It should be noted that the method of assessing and grading radiation necrosis varied across studies and we accepted the authors definition and assessment method.

The findings of studies comparing SRS plus WBRT versus WBRT alone or SRS alone are shown in Figure 27.[77, 81, 86, 93]

Figure 27. SRS plus WBRT versus SRS or WBRT alone: radiation necrosis



Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Individual study results varied and across studies no systematic difference was found between treatments (RR 0.93; CI 0.17 to 5.12; 4 studies); no statistical heterogeneity was detected. All individual studies, including the low risk of bias study by Brown et al.[81] did not report statistically significant differences between arms either. While the figure shows the comparison to WBRT for El Gantery et al.,[93] the study also reports on a comparison of WBRT plus SRS versus SRS alone; there was one case of radiation necrosis in the SRS and one in the combination group. The sensitivity analysis found a similar pooled estimate (RR 0.85; CI 0.16 to 4.51; 4 studies).

Gupta et al.[102] and Lee et al.[120] evaluated systemic therapy added to WBRT and both reported no cases of radiation necrosis in either group (RR 0.89; CI 0 to 41413124; 2 studies).

A cohort study (determined to be high risk of bias) evaluated the effect of immunotherapy added to SRS treatment and found more incidences in the immunotherapy arm (RR 2.92; CI 1.73 to 4.94; 1 study); but the effect published by Martin et al. has not been replicated in another study.[125]

One (medium risk of bias) study by Kocher et al. comparing WBRT with observation in patients who had received surgery or SRS as initial treatment reported more incidences in the WBRT arm (RR 1.99; CI 0.18 to 21.74; 1 study), but the evaluation has not been replicated in another study yet.[116]

Two studies comparing SRS with WBRT after surgery reported more incidences of radiation necrosis in the SRS treatment group than the WBRT treatment group (6 vs 3 or 0 incidences); however, the individual and the pooled result is not statistically significant (RR 3.07; CI 0 to 38255; 2 studies). The confidence interval was very wide after combining the two studies by Brown et al.[79] and Kayama et al.[111] that reported on a very rare event and no other study reported on the outcome and the same intervention and comparator combination.

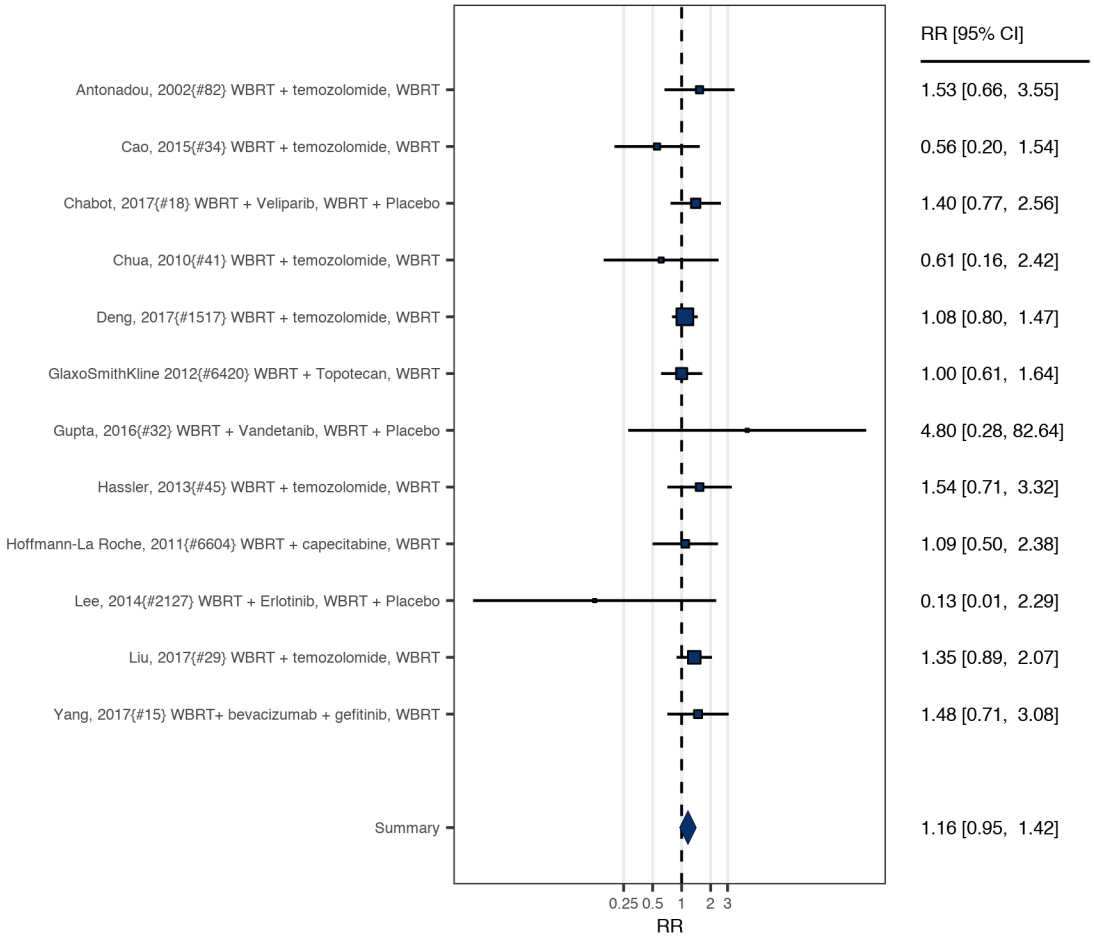
Headaches

Two studies that evaluated the combination of SRS plus WBRT reported on headaches. El Gantery et al.[93] evaluated WBRT plus SRS versus WBRT alone or SRS alone and Brown et al. evaluated SRS plus WBRT versus SRS alone.[81] One study found no difference between all three arms, the other one favored the combination treatment (not statistically significant). Studies could not be combined for a meaningful effect estimate as indicated by the wide confidence interval surrounding the estimate regardless of the comparator (vs WBRT or SRS RR 0.46; CI <0.00 to 22602; 2 studies; vs SRS RR 0.43; CI 0 to 7810.73; 2 studies). The individual estimates differed substantially and no other study reporting on the same intervention and comparator was found to substantiate the estimate. Both studies were low risk of bias studies hence it was not possible to assign one more weight than the other.

Two studies evaluated radiosensitizers in WBRT[128, 155] and reported on headaches. Mehta et al. and Suh et al. reported more events in the radiosensitizer arms, but effect estimates varied substantially, hence the confidence interval surrounding the pooled effect was wide (RR 1.14; CI 0.22 to 5.91; 2 studies). Both individual studies did not report statistically significant effects between arms, including the low risk of bias study by Mehta et al.[128]

A large number of studies investigated the effect of adding systemic therapy to WBRT as shown in Figure 28.[76, 84, 85, 89, 91, 97, 102, 103, 120, 122, 165]

Figure 28. WBRT plus systemic therapy versus WBRT alone: headaches



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

The analysis suggested a slightly increased risk of headaches associated with combined WBRT and systemic therapy, but the effect was not statistically significant (RR 1.16; CI 0.95 to 1.42; 12 studies); statistical heterogeneity was not detected. Half of the included studies were classified as low risk of bias and no high risk of bias study contributed to the effect estimate. Results were similar when restricting to chemotherapy agents (RR 1.22; CI 0.95 to 1.58; 11 studies). A further sensitivity analysis across all combination treatment studies and comparing to WBRT alone or systemic therapy alone also found no systematically increased risk (RR 1.18; CI 0.97 to 1.43; 13 studies).

One (medium risk of bias) study that compared WBRT with observation in patients who had received surgery or SRS as initial treatment reported more headaches in the WBRT study arm but the effect estimate was imprecise (RR 1.99 CI 0.18 to 21.74; 1 study), and the evaluation published by Kocher et al. has not been replicated in another study yet.[116]

Fatigue

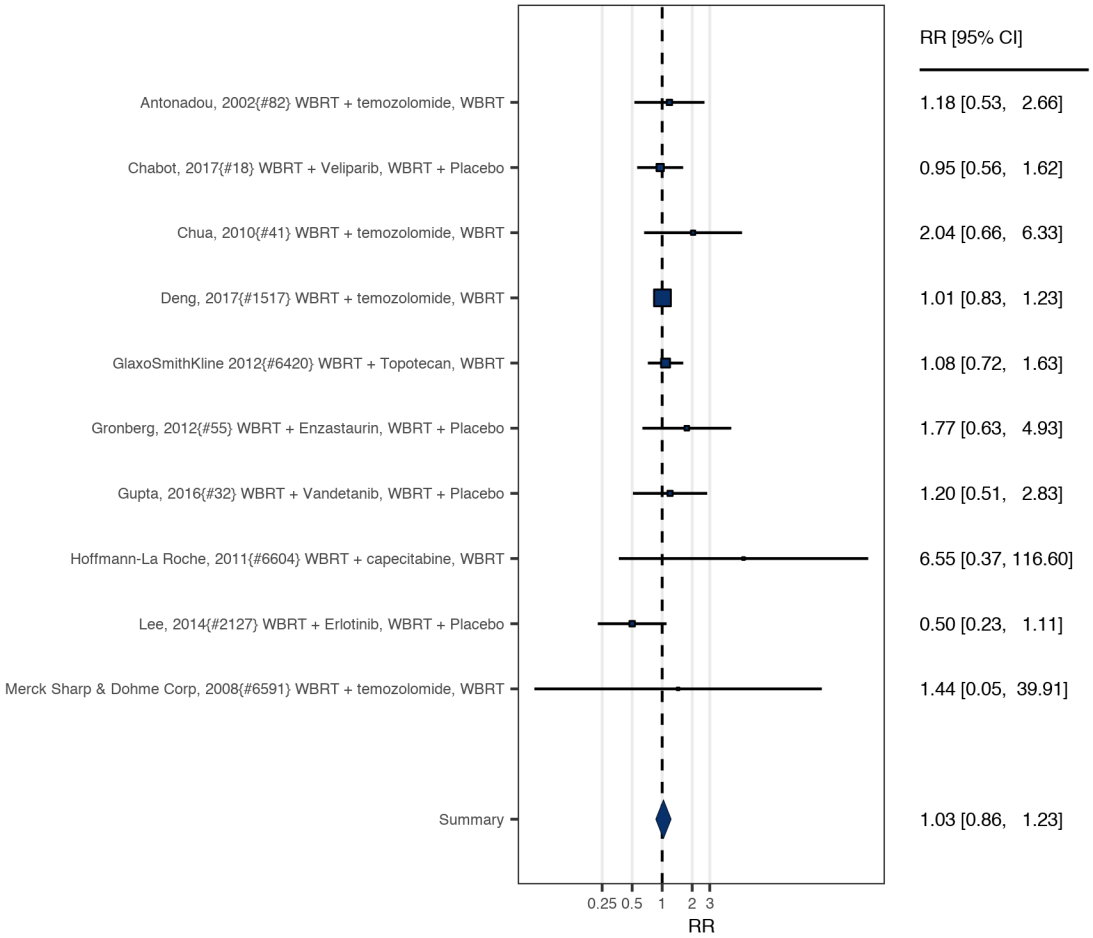
Two studies evaluated SRS plus WBRT compared to SRS alone and reported on fatigue in participants.[77, 81] The studies by Aoyama et al. and Brown et al. reported conflicting findings, resulting in a large confidence interval of possible effects and no meaningful summary effect

estimate could be determined (RR 0.82; CI <0.00 to 1523; 2 studies). Both individual studies, including the low risk of bias study by Brown et al.[81] did not find not statistically significant differences between treatment groups.

A study published by Yang et al.[164] reported more incidences of fatigue in the group that combined WBRT and chemotherapy compared to icotinib alone (RR 2.86; CI 1.53 to 5.35; 1 study).

Several studies evaluated systemic therapy given in addition to WBRT and reported on the incidence of fatigue among patients as shown in Figure 29.[76, 85, 89, 91, 97, 100, 102, 120]

Figure 29. WBRT plus systemic therapy versus WBRT alone: fatigue



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

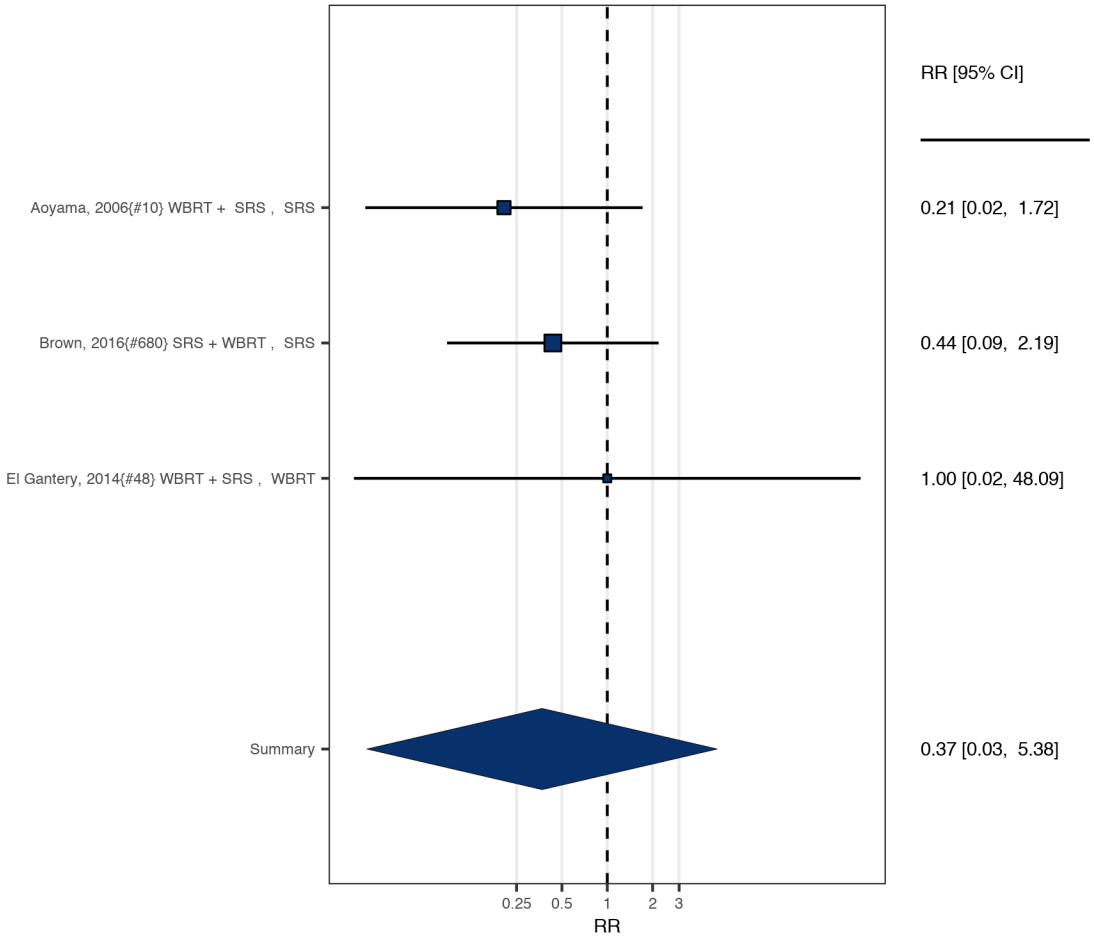
Some studies favored the combination, some the WBRT arm, and across studies there was no difference between treatment arms in the number of patients reporting fatigue (RR 1.03; CI 0.86 to 1.23; 10 studies); statistical heterogeneity was not detected. Half the studies were classified as low risk of bias and no high risk of bias study contributed to the effect estimate.

Brown et al. (low risk of bias) who compared WBRT and SRS post-surgery reported better results for the SRS arm (RR 0.19; CI 0.07 to 0.53; 1 study) but, but the evaluation has not been replicated in other studies yet.[79]

Seizures

The method of grading seizures varied across studies. The studies comparing the combination of WBRT plus SRS compared to WBRT or SRS alone and that reported on the incidence of seizures are shown in Figure 30.[77, 81, 93]

Figure 30. WBRT plus SRS versus WBRT or SRS alone: seizure

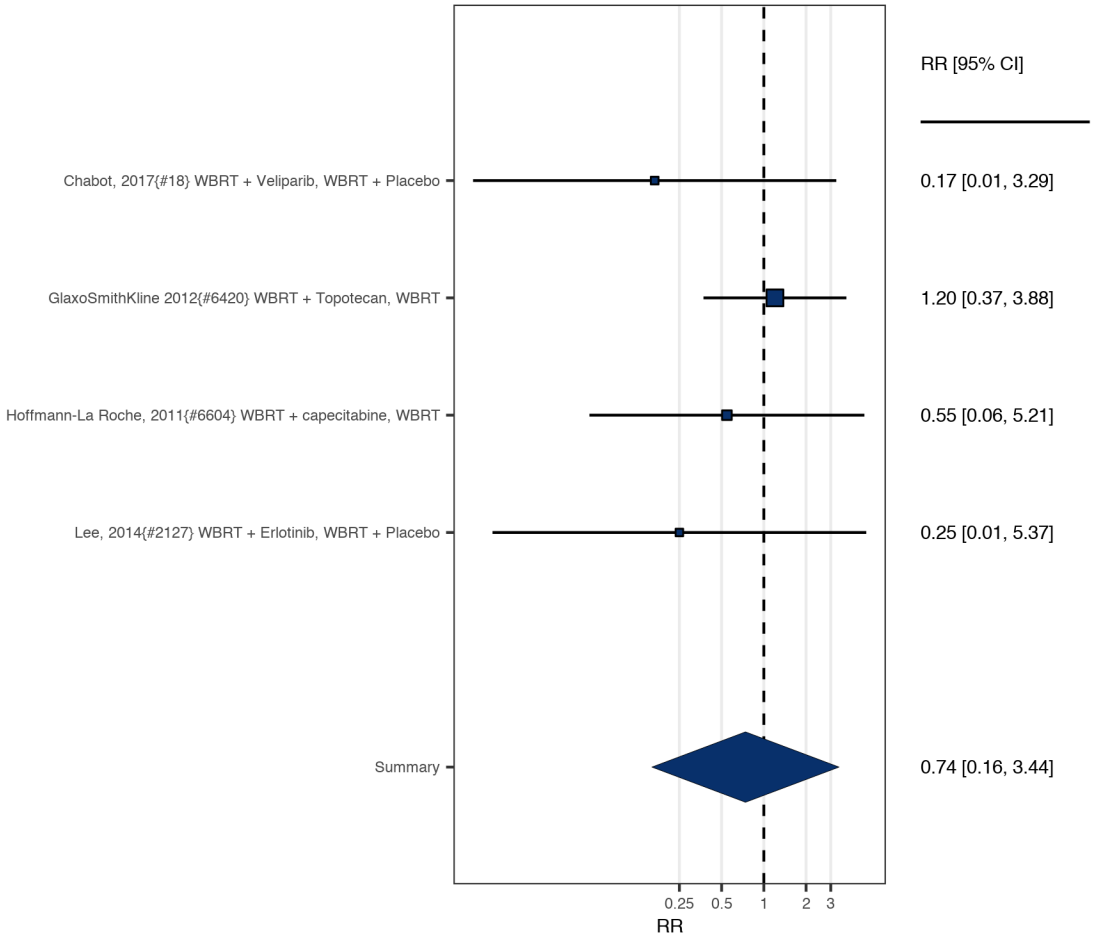


Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

Two studies, including a low risk of bias study by Brown et al.,[81] favored the combination treatment, one found no difference. The pooled effect was not statistically significant across treatment groups (RR 0.37; CI 0.03 to 5.38; 3 studies); statistical heterogeneity was not detected. El Gantery et al. also reported on a comparison to SRS alone; the authors reported one patient in the SRS group with a grade 2 seizure compared to no patients in the combination or the WBRT group.[93] The sensitivity analysis using the comparison to SRS found a similar pooled estimate (RR 0.34; CI 0.02 to 4.76; 3 studies).

Several studies were identified that evaluated the addition of systemic therapy and reported on the presence or absence of seizures as shown in Figure 31.[85, 97, 120]

Figure 31. WBRT plus systemic therapy versus WBRT alone: seizure



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

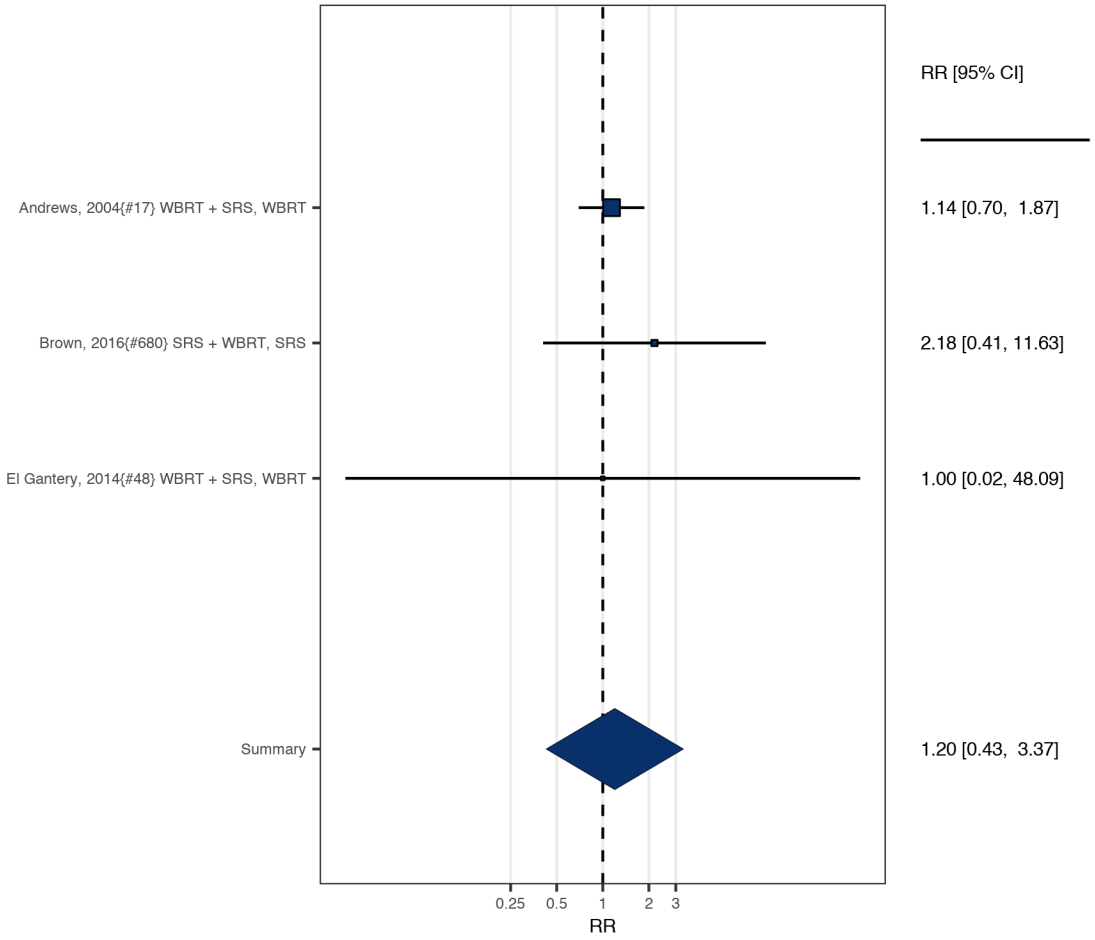
There were conflicting results across studies and the pooled effect did not show a statistically significant effect (RR 0.74; CI 0.16 to 3.44; 4 studies). Heterogeneity was low (I^2 1%) and three of the studies were classified as low risk of bias due to the adverse events assessment and reporting. Excluding the targeted therapy agent, results were similar (RR 0.83; CI 0.1 to 7.21; 3 studies).

Kocher et al. (medium risk of bias) who compared WBRT with observation in patients who had received surgery or SRS as initial treatment reported more incidences of seizures in the WBRT arm (RR 5.97; CI 0.3 to 118; 1 study) but the effect estimate was imprecise and the evaluation has not been replicated in other studies.[116]

Vomiting

The studies evaluating the combination of WBRT plus SRS compared to WBRT or SRS alone that reported on incidence of vomiting are shown in Figure 32.[75, 81, 93]

Figure 32. WBRT plus SRS versus WBRT or SRS alone: vomiting



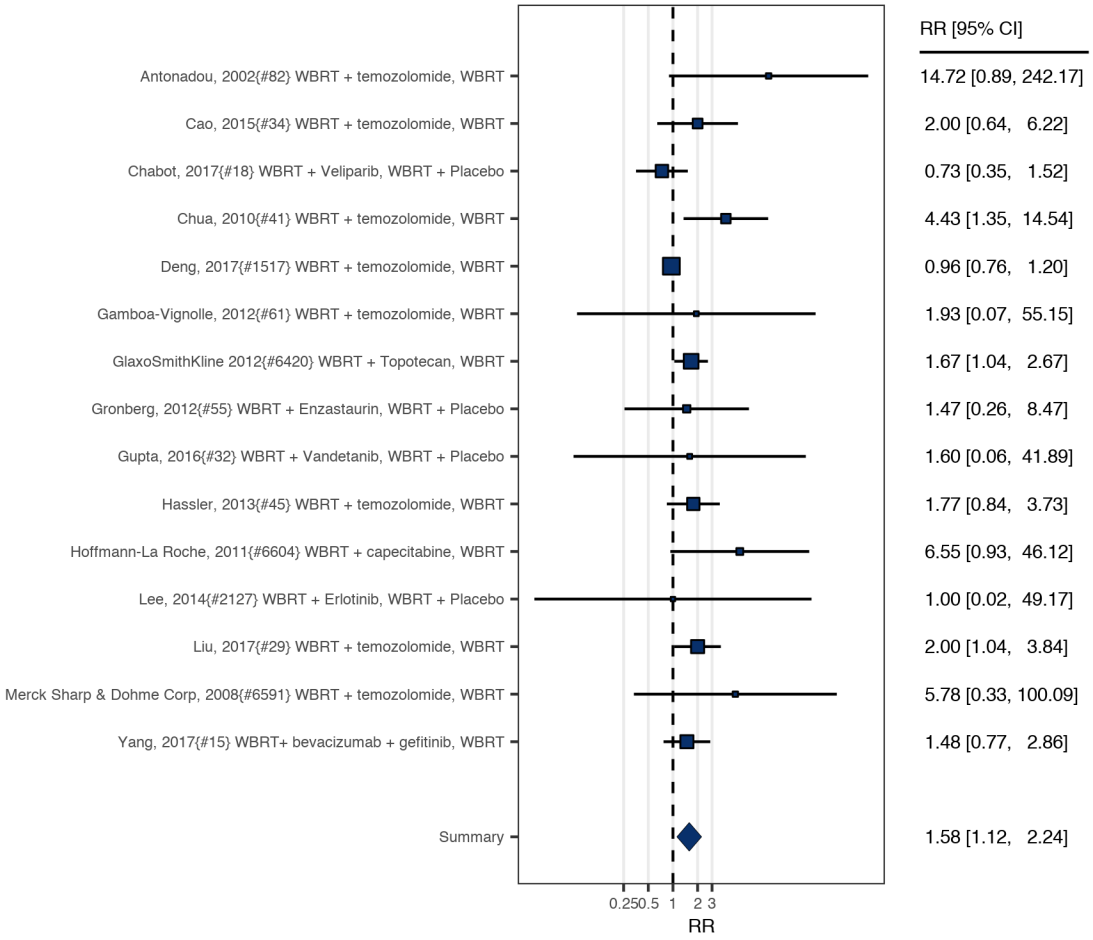
Abbreviations: CI confidence interval; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy

Individual study results varied and the effect across studies was not statistically significantly different (RR 1.20; CI 0.43 to 3.37; 3 studies). Two of the included studies were classified as low risk of bias, no high risk of bias contributed to the finding, and statistical heterogeneity was not detected. El Gantery et al. reported one case in the SRS group, the other treatment groups reported no incidences of vomiting.[93] The sensitivity analysis using the SRS comparator showed a similar result (RR 1.18; CI 0.42 to 3.3; 3 studies).

Two studies that evaluated the use of radiosensitizers in WBRT compared to traditional WBRT reported on the outcome vomiting.[128, 155] Suh et al., and Mehta et al. both found more incidences of vomiting in the radiosensitizer groups but the effect was not statistically significant (RR 1.67; CI 0.36 to 7.63; 2 studies).

Several studies that evaluated the effect of adding systemic therapy to WBRT reported on the outcome vomiting as shown in Figure 33.[76, 84, 85, 89, 91, 96, 97, 100, 103, 120, 122, 132, 148, 165]

Figure 33. WBRT plus systemic therapy versus WBRT alone: vomiting



Abbreviations: CI confidence interval; RR relative risk; WBRT whole brain radiation therapy

The studies indicated an increased risk of patients reporting vomiting in the combination of WBRT plus systemic therapy arm (RR 1.58; CI 1.12 to 2.24; 15 studies). The analysis includes four low risk of bias studies and no high risk of bias study contributed to the treatment effect estimate. There was limited heterogeneity (I^2 42%). However, there was some indication of publication bias (Egger p=0.033, Begg p=0.92). A sensitivity analysis across combination studies that compared to either WBRT alone or chemotherapy alone also found more patients reporting vomiting (RR 1.55; CI 1.13 to 2.11; 17 studies); in this analysis there was no indication of publication bias. Similarly, restricting to chemotherapy agents, results were similar (RR 1.71; CI 1.26 to 2.33; 16 studies) and there was also no indication of publication bias.

Two studies assessed WBRT as adjunctive therapy to chemotherapy.[148, 164] Yang et al. found more patients reporting vomiting in the combination group compared to icotinib alone while Robinet et al. reported no incidences; across studies there was no statistically significantly increased risk but the estimate was imprecise (RR 2.1; CI 0.03 to 159.09; 2 studies).

One (low risk of bias) study by Brown et al. that compared WBRT and SRS post-surgery reported better results for the outcome for the SRS arm (RR 0.02; CI <0.00 to 0.37; 1 study) but the evaluation has not been conducted in another study to confirm the finding.[79]

KQ4a. Important Patient Characteristics or Dose Fractionation Schedule and Technique

We also investigated whether adverse events associated with the radiation therapy treatments vary by patient or intervention characteristics such as neuroprotection.

Serious Adverse Events

We explored the potential effect of cancer origin site, the prognosis, and the dose fractionation schedule on the risk of serious adverse events.

Meta-regressions did not indicate that compared to patients with breast cancer, patients with different cancer types (p=0.46), lung cancer (p=0.44), or melanoma (p=0.56) have an increased risk of serious adverse events when undergoing WBRT or SRS. We also did not detect systematic effects in the SRS subgroup (different cancer types vs lung cancer p=0.69 or vs melanoma only p=0.62) for the outcome serious adverse events, but the analysis was based on only five studies.[81, 86, 121, 154, 158]

We also investigated whether adverse events are associated with the clinical prognosis of patients. We did not identify associations of the prognosis with serious adverse events (p=0.50), i.e., patients with a poor prognosis were not more likely to experience a serious adverse event than other patients undergoing WBRT. However, the analysis should be regarded with caution as most studies included mixed samples and the dataset was not well suited to identify effect modifiers.

Two studies (both medium risk of bias) reported direct comparisons of the risk for serious adverse events between patients on different dose fractionation schedules.[87, 99] Neither Chatani et al. nor Graham et al. found a statistically significant difference between arms; the studies could not be combined because they compared different doses.

Indirect comparisons that explored whether the WBRT (p=0.42) or the SRS (p=0.97) radiation dose might act as an effect modifier did not indicate an association. However, the analysis should be interpreted with caution as studies varied in multiple aspects that hindered the detection of effects.

Finally, we explored whether the publication year of the included studies is associated with the number of patients experiencing serious adverse events, suggesting, for example, that newer treatments are safer than older. The meta-regression did not detect a systematic effect (p=0.56).

Number of Adverse Events

Results in studies with lung cancer patients that received WBRT or SRS did not differ systematically from studies in mixed tumor type samples regarding experiencing adverse events (p=0.27). However, the analysis should be interpreted with caution as it is based on the number of patients with adverse events rather than the number of adverse events, and the analysis was only based on two studies that enrolled exclusively patients with lung cancer.[97, 120]

Indirect comparisons across studies to explore the role of the total WBRT radiation dose as a potential effect modifier did not indicate an association (p=0.99) but the analysis should be interpreted with caution as it is based on the number of patients with adverse events rather than the number of adverse events and studies varied in multiple aspects that hindered the detection of effects.

Radiation Necrosis

Treatment effects in lung cancer patients that received WBRT or SRS did not differ systematically from patients in mixed tumor type studies regarding experiencing adverse events (p=0.97) nor did patients with melanoma (p=0.74). However, the finding should be interpreted with caution as the analysis included only two studies that enrolled only lung cancer patients.[120, 154] Similarly, we found no effect when restricting to SRS studies (mixed samples vs lung cancer only p=0.88).

We also aimed to explore whether the risk of experiencing radiation necrosis when undergoing SRS is associated with the patients' prognosis. We did not identify a statistically significant association (p=0.13), but the analysis must be interpreted with caution, as no study that evaluated patients with consistently poor prognosis provided data for this analysis.

Indirect comparisons exploring the WBRT (p=0.92) or the SRS (p=0.45) radiation dose as a potential effect modifier did not indicate an association, but the analyses should be interpreted with caution as it is based on a small number of studies that varied in multiple aspects, which hindered the detection of effect modifiers.

An analysis of the publication year across studies did not suggest systematic differences in radiation necrosis results between older and newer studies (p=0.83).

Headaches

We did not identify systematic differences in reported headaches based on the primary tumor type in studies evaluating WBRT or SRS (mixed samples p=0.24, lung cancer p=0.42, melanoma p=0.27 compared to patients with breast cancer). However, the findings should be interpreted with caution, as the analysis was based on only three studies exclusively in patients with breast cancer and one study exclusively enrolling patients with melanoma.[84, 102, 105, 135]

We also explored whether the risk of experiencing headaches when undergoing SRS is associated with the patients' prognosis. We did not identify an association (p=0. 89). However, the finding should be interpreted with caution, as no studies of patients with poor prognosis provided data for this analysis, hence only patients with good or moderate prognosis were compared.

Two studies (one medium, one high risk of bias) reported direct comparisons between dose fractionation schedules and the associated risk for headaches.[87, 141] Chatani et al. and Priestman et al. did not find a statistically significant difference between arms and the studies could not be combined because they compared different doses.

Indirect comparisons that explored the WBRT radiation dose as an effect modifier did not suggest an association between dose and the number of patients who experience headaches (p=0.11).

Two studies assessed hippocampus sparing WBRT. Across Brown et al. and Hauswald et al. no systematic effect on headaches was detected (RR 1.17; CI 0.26 to 5.31; 2 studies).[80, 104]

We found no effect of the study publication year and the relative risk of experiencing headaches (p=0.97).

Fatigue

We did not identify systematic differences in reported fatigue based on the primary tumor type in studies evaluating WBRT or SRS (mixed samples p=0.21, lung cancer p=0.23, melanoma p=0.30 compared to patients with breast cancer). However, the findings should be interpreted

with caution, as the analysis was based on only one study exclusively in patients with breast cancer and one exclusively in patients with melanoma.[102, 105]

Indirect comparisons that assessed the potential role for WBRT radiation dose as an effect modifier did not indicate an association (p=0.16), but the analysis should be interpreted with caution, as studies varied in multiple aspects, which hindered the detection of effects.

Two studies assessed hippocampus sparing WBRT. Across Brown et al. and Hauswald et al. no systematic effect on fatigue was detected (RR 1.20; CI 0.01 to 126; 2 studies).[80, 104]

Exploring the potential effect of the study publication year did not suggest a systematic effect on patients experiencing fatigue (p=0.89).

Seizures

We did not identify systematic differences in experiencing seizures based on the primary tumor type in studies evaluating WBRT or SRS (mixed samples p=0.78, lung cancer p=0.78 compared to breast cancer). However, the analysis should be interpreted with caution as it is based on only one study that enrolled only patients with breast cancer.[105]

We also explored whether the risk of experiencing seizures when undergoing SRS is associated with the patients' prognosis. We did not identify an association between the size of the treatment effect compared to the control group and the prognosis (p=0.81). However, the finding from this analysis should be interpreted with caution, as no studies that enrolled only patients with poor prognosis contributed data to this analysis.

Indirect comparisons that explored the radiation dose as a potential effect modifier did not indicate an association (WBRT p=0.51, SRS p=0.69) but the findings should be interpreted with caution as studies varied in multiple aspects that hindered the detection of effects.

We did not identify an association between the year of the published data and the risk of experiencing seizures (p=0.36).

Vomiting

We did not identify systematic differences in patients reporting vomiting based on the primary tumor type in studies that evaluated WBRT or SRS treatment (mixed samples p=0.39, lung cancer p=0.23, melanoma p=0.15 compared to breast cancer patients). However, the findings should be interpreted with caution, as the analysis was based on only two studies exclusively enrolling patients with breast cancer and only two studies in patients with melanoma.[84, 102, 105, 132]

Indirect comparisons that explored the WBRT radiation dose as a potential effect modifier for the risk of vomiting did not indicate an association (p=0.63), but the finding should be interpreted with caution, as studies varied in multiple aspects, which hindered the detection of effects.

Two studies assessed hippocampus sparing WBRT. Across Brown et al. and Hauswald et al. no systematic effect on patients reporting vomiting was detected (RR 1.23; CI 0.09 to 17.39; 2 studies).[80, 104]

Exploring the potential effect of the study publication year did not suggest a systematic effect on the risk of vomiting, i.e., older research studies did not report more incidences of the interventions compared to control groups (p=0.43).

Summary of Findings, KQ4

Table 5 summarizes the findings and evaluates the quality of evidence.

Table 5. Summary of findings and strength of evidence for adverse events

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies ‡ *Additional Individual Study Findings*	Conclusion and SoE ‡‡ [Reasons for Downgrading]
KQ4: WBRT + SRS vs WBRT or SRS alone	Serious adverse events	4 studies (N 734) Andrews, 2004;[75] Aoyama, 2006;[77] Brown, 2016;[81] Chang, 2009[86]	RR 1.05; CI 0.12 to 8.89: Across studies there was no difference between the combination of WBRT plus SRS and the individual interventions WBRT alone or SRS alone in serious adverse events.	Moderate SoE for no increased risk [study limitation]
KQ4: WBRT + radiosensitizer vs WBRT alone	Serious adverse events	3 studies (N 605) Hosseini, 2015;[107] Phillips, 1995; [138]Suh, 2006[155]	RR 1.16; CI 0.42 to 3.21: Across studies there was no difference between WBRT plus radiosensitizer and WBRT alone in serious adverse events.	Low SoE for no increased risk [consistency, precision]
KQ4: WBRT + systemic therapy vs WBRT alone	Serious adverse events	8 studies (N 992) Cao, 2015;[84] Chabot, 2017;[85] GlaxoSmithKline 2012[97] Gronberg, 2012;[100] Gupta, 2016;[102] Hassler, 2013;[103] Hoffmann-La Roche, 2011;[105] Merck Sharp & Dohme Corp, 2008[129]	RR 1.46; CI 0.87 to 2.45: We did not detect a consistent difference in WBRT plus systemic therapy compared to WBRT alone for serious adverse events. Pooled study results suggested an increased risk with WBRT plus systemic therapy compared to WBRT alone, but the effect was not statistically significant and individual study results varied favoring sometimes the combination, sometimes WBRT alone.	Low SoE for no increased risk [consistency, precision]
KQ4: SRS post-surgery vs WBRT post-surgery	Serious adverse events	2 studies (N 244) Brown, 2017;[79] Kepka, 2016[112]	RR 1.33; CI 0.78 to 2.25: No consistent difference comparing surgery plus SRS with surgery plus WBRT. *Kayama, 2018;[111] reported more events in the WBRT group.*	Low SoE for no difference [precision, consistency]
KQ4: WBRT + SRS vs WBRT or SRS alone	Radiation necrosis	4 studies (N 445) Aoyama, 2006;[77] Brown, 2016;[81] Chang, 2009;[86] El Gantery, 2014[93]	RR 0.93; CI 0.17 to 5.12: Across studies there was no difference between the combination of WBRT and SRS and the individual interventions WBRT alone or SRS alone.	Low SoE for no increased risk [precision, consistency]
KQ4: WBRT + systemic therapy vs WBRT alone	Radiation necrosis	2 studies (N 98) Gupta, 2016;[102] Lee, 2014[120]	RR 0.89; CI 0 to 41413124: No cases in either group.	Moderate SoE for no increased risk [precision]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies ‡ *Additional Individual Study Findings*	Conclusion and SoE ‡‡ [Reasons for Downgrading]
KQ4: SRS post-surgery vs WBRT post-surgery	Radiation necrosis	2 studies (N 456) Brown, 2017;[79] Kayama, 2018[111]	RR 3.07; CI 0 to 38255): The results show more instances of radiation necrosis in the SRS groups but the effect was not statistically significant.	Insufficient [study limitation, precision]
KQ4: WBRT + systemic therapy vs WBRT alone	Headaches	12 studies (N 1,536) Antonadou, 2002;[76] Cao, 2015;[84] Chabot, 2017;[85] Chua, 2010;[89] Deng, 2017;[91] GlaxoSmithKline 2012;[97] Gupta, 2016;[102] Hassler, 2013;[103] Hoffmann-La Roche, 2011;[105] Lee, 2014;[120] Liu, 2017;[122] Yang, 2017[165]	RR 1.16; CI 0.95 to 1.42: No consistent difference in WBRT + systemic therapy versus WBRT alone regarding headaches. Pooled across studies, WBRT plus systemic therapy showed a slightly increased risk of headaches compared to WBRT alone but the effect was not statistically significant and individual studies results varied, showing no difference, or sometimes favoring WBRT plus systemic therapy, sometimes WBRT alone.	Moderate SoE for no increased risk [consistency]
KQ4: WBRT + systemic therapy vs WBRT alone	Fatigue	10 studies (N 1,318) Antonadou, 2002;[76] Chabot, 2017;[85] Chua, 2010;[89] Deng, 2017; [91] GlaxoSmithKline 2012;[97] Gronberg, 2012;[100] Gupta, 2016;[102] Hoffmann-La Roche, 2011;[105] Lee, 2014;[120] Merck Sharp & Dohme Corp, 2008[129]	RR 1.03; CI 0.86 to 1.23: Across studies there was no difference between WBRT plus systemic therapy and WBRT alone for the outcome fatigue.	Moderate SoE for no increased risk [consistency]
KQ4: WBRT + SRS vs WBRT or SRS alone	Seizures	3 studies (N 387) Aoyama, 2006;[77] Brown, 2016;[81] El Gantery, 2014[93]	RR 0.37; CI 0.03 to 5.38: No consistent difference between WBRT + SRS and SRS or WBRT alone in the reported number of patients with seizures. Pooled across studies, WBRT plus SRS showed a lower risk for seizures in some studies than did WBRT or SRS alone, but there was no statistically significant difference between studies.	Low SoE for no increased risk [consistency, precision]

Intervention and Comparison	Outcome	Number of Studies (Participants) Contributing to Effect Estimate; Citations	Results Across Studies ‡ *Additional Individual Study Findings*	Conclusion and SoE ‡‡ [Reasons for Downgrading]
KQ4: WBRT + systemic therapy vs WBRT alone	Seizures	4 studies (N 779) Chabot, 2017;[85] GlaxoSmithKline 2012;[97] Hoffmann-La Roche, 2011;[105] Lee, 2014[120]	RR 0.74; CI 0.16 to 3.44: No consistent difference in seizures comparing WBRT + systemic therapy to WBRT alone. Across studies there was no statistically significant difference between groups receiving WBRT plus systemic therapy or WBRT alone but individual study results varied.	Low SoE for no increased risk [consistency, precision]
KQ4: WBRT + SRS vs WBRT or SRS alone	Vomiting	3 studies (N 586) Andrews, 2004;[75] Brown, 2016;[81] El Gantery, 2014[93]	RR 1.20; CI 0.43 to 3.37: No consistent difference for the outcome vomiting comparing WBRT plus SRS to WBRT or SRS alone. Across studies, WBRT plus SRS showed a slightly increased risk for vomiting compared to WBRT or SRS alone but the effect was not statistically significant.	Low SoE for no increased risk [consistency, precision]
KQ4: WBRT + radiosensitizer vs WBRT alone	Vomiting	2 studies (N 1,069) Mehta, 2009;[128] Suh, 2006[155]	RR 1.67; CI 0.36 to 7.63: Both studies reported more incidences in the radiosensitizer group (one statistically significant) but the effect was not statistically significant.	Insufficient [study limitation, precision, inconsistency]
KQ4: WBRT plus systemic therapy vs WBRT alone	Vomiting	15 studies (N 1,731) Antonadou, 2002;[76] Cao, 2015;[84] Chabot, 2017;[85] Chua, 2010; [89] Deng, 2017;[91] Gamboa-Vignolle, 2012;[96] GlaxoSmithKline 2012;[97] Gronberg, 2012;[100] Gupta, 2016;[102] Hassler, 2013;[103] Hoffmann-La Roche, 2011;[105] Lee, 2014;[120] Liu, 2017;[122] Merck Sharp & Dohme Corp, 2008;[129] Yang, 2017[165]	RR 1.58; CI 1.12 to 2.24: Patients receiving WBRT plus systemic therapy reported more instances of vomiting than patients receiving WBRT alone.	Moderate SoE for increased risk of vomiting with systemic therapy [consistency]

Abbreviations: CI confidence interval; N number of participants; RCT randomized controlled trial; RR relative risk; SoE strength of evidence; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy.

‡The column reports the findings across studies starting with the pooled effect when it can be calculated; findings from additional studies not included in the effect estimate calculation or from relevant studies when an effect estimate cannot be calculated are included and italicized.
‡‡SoE strength of evidence and reason for downgrading.

Reasons for downgrading: study limitations: the estimate is based on studies with high risk of bias, there are equally or more studies where no effect estimate could be determined, the comparator is problematic because of cointerventions; precision: the effect size could not be determined, wide confidence intervals, a beneficial effect could not be ruled out; consistency: the effect is based on a single study and the evaluation has not yet been replicated in another study, heterogeneity, conflicting direction of effects.

Discussion

This systematic review identified a substantial number of studies that addressed the effect of radiation therapy, but analyses were limited due to the variety of interventions, comparators, measures, and lack of reported detail for several outcomes of interest.

Findings in Relation to the Decisional Dilemmas

WBRT (Key Question 1)

Regarding the effectiveness of whole brain radiation therapy (WBRT) alone or in combination with other treatments, we identified a small number of studies that assessed the role of adding stereotactic radiosurgery (SRS) or surgery to WBRT. Two identified studies compared WBRT alone or in combination with SRS.[75, 93] Due to differences in reported outcomes a combined analysis could not be performed. The individual study results showed no survival benefit for the addition of SRS, with the exception of the subgroup of patients with a single brain metastasis in the Radiation Therapy Oncology Group (RTOG) 9508 trial.[75] Local control was improved with the addition of SRS in both studies. The previously reported American Society for Radiation Oncology (ASTRO) guideline found that SRS added to WBRT improves survival for good prognosis patients with single brain metastasis, and it improves local control. Based on the results from individual studies, our findings are consistent.

For WBRT alone versus WBRT plus surgery, the three identified studies reported conflicting results, and there was no systematic difference across studies (low strength of evidence [SoE]).[131, 160] The previously reported ASTRO guideline concluded that selected patients with good performance status, limited extracranial disease, and a single brain metastasis may have improved survival with the addition of surgery to WBRT.[11] Of note, one of the studies referenced by the ASTRO guideline was excluded from our analysis because it was conducted before 1990.[264] This excluded study by Patchell et al. showed an improvement in survival with the addition of surgery to WBRT for patients with a single brain metastasis.

The addition of radiosensitizers to WBRT showed no significant difference in overall survival. The studies evaluated different radiosensitizing agents in different tumor types, and none of the individual studies showed a survival advantage.

For the potential effects of dose fractionation of WBRT, the variation in interventions and comparators among studies limited the analysis, but there was no significant effect of dose on overall survival, disease-free survival or deaths due to brain metastases (low SoE). This finding is consistent with the findings of the previously reported ASTRO guideline.[11]

Only one identified study assessed the effect of the addition of memantine to WBRT treatment.[82] WBRT plus memantine delayed the risk of cognitive decline and reduced the rates of decline in memory, executive function, and processing speed compared with WBRT alone. However, the finding has not yet been replicated in other studies and definitive effect estimates are still missing to guide patients, providers, and policy makers.

Three randomized controlled trials (RCTs) evaluated hippocampal avoidance WBRT versus conventional WBRT and reported sufficient information for effect estimates.[80, 104, 166] The individual studies did not report statistically significant differences for effectiveness outcomes of interest. NRG CC001 trial reported detailed neurocognitive outcomes for hippocampal avoidance WBRT.[80] Comparing patients treated with hippocampal avoidance WBRT with memantine versus those treated with WBRT with memantine, hippocampal avoidance WBRT was

associated with a lower risk of cognitive failure, with less deterioration of executive function and learning and memory.[80] However, the finding has not yet been replicated in other studies, and definitive effect estimates are still missing to guide patients, providers, and policy makers.

For WBRT, our analyses detected no systematic effect of prognosis on overall survival, however the number of studies with patients with predominantly good or poor prognosis was very limited, hindering meaningful analyses (low SoE). More research targeting patients with exclusively good prognosis and exclusively poor prognosis are needed to detect effects of the prognosis. The majority of existing studies on radiation therapy comprises patient samples with mixed or unclear prognosis; hence results should be treated with caution. The previously reported ASTRO guideline recommended the use of histology-specific prognostic indices for research and clinical decision making.[11] Prognostic indices such as the diagnosis-specific graded prognostic assessment (DS-GPA) have been developed using diagnosis and DS-GPA score to estimate median survival.[5-8] The prognostic index studies did not meet eligibility criteria for this review, however they remain an important resource to guide providers, patients, researchers and policy makers .

The addition of systemic therapy to WBRT may be beneficial with regard to overall survival, but the effect was small and not statistically significant (low SoE). Individual study results varied; studies evaluated many different chemotherapy or targeted therapy approaches. Meta-regressions did not suggest that a specific type of chemotherapy or targeted therapy is associated with larger treatment effects, hence we were unable to determine subgroups of systemic therapy that showed positive effects. It should be noted that most identified studies evaluated chemotherapy or targeted therapy rather than immunotherapy. Research on immunotherapy and targeted therapy is rapidly expanding and evolving, and future research may change the role of systemic therapy.[4]

Strength of evidence was insufficient to assess the effects of treatment on functional status and cognitive effects and we were unable to formulate evidence statements. In addition, data on quality of life that allows accurate treatment effect estimates are also lacking. While 12 RCTs reported quality of life and cognitive effects, and 11 studies reported functional status, the measures and reported details varied (e.g., no measure of dispersion was reported), or the intervention, co-intervention, and comparator combination could not be combined. Hence, there was insufficient data to compute effect sizes despite the large number of identified research studies on radiation therapy. This is particularly unfortunate as Key Informants and Technical Expert Panel members had repeatedly indicated that these patient-centered outcomes are critical and that information on these outcomes would meaningfully inform decisional dilemmas regarding treatment choice following a diagnosis of brain metastases. These outcomes are as important as the clinical effectiveness and adverse events information and the lack of reporting of sufficient detail is problematic for patients and their caregivers.

SRS (Key Question 2)

Regarding SRS as initial treatment, there was no significant difference in overall survival or death due to brain metastases for SRS alone versus SRS plus WBRT, based on pooled analysis (low SoE).[75, 77, 81, 86] The previously reported ASTRO guideline supported SRS alone as a treatment option for selected patients (good prognosis, metastases ≤3-4 cm).[11] However, the individual trials they reviewed were noted to be underpowered for survival. Our pooled analysis indicates that survival is not impacted by the omission of WBRT.

Three studies reported on cognitive function for SRS alone versus SRS plus WBRT.[77, 81, 86] Reported results varied by intervention, comparator, and measures used to assess effects; the studies reported insufficient details to compute effect sizes (low SoE favoring SRS alone). It is important to note that two of these studies, Chang et al. 2009[86] and Brown et al.[81], utilized rigorous neurocognitive assessments and the individual study results showed significantly greater risk of cognitive decline for patients receiving WBRT and SRS compared with SRS alone.

Patient prognosis had no significant effect on overall survival, however the analyzable studies had a narrow range of differences in prognosis (all analyzable studies were mixed or good prognosis), so the results should be interpreted with caution (low SoE). We found no difference in survival based on primary cancer type. This result should also be interpreted with caution, since there were only several studies limited to a particular primary tumor type to contribute to the analyses and the findings were based on indirect comparisons across studies (low SoE). In addition, this review already included only the most common primary tumor types and represents a more homogenous study pool, hence the finding may not generalize to other cancer origin sites.

Unlike the evidence base for WBRT, regarding the role of systemic therapy with SRS, only a small number of studies was identified. There was insufficient information to analyze several key efficacy outcomes. Furthermore, evidence on immunotherapy and targeted therapy is emerging and its role in patients with brain metastases should be explored further.

Combination With Surgery (Key Question 3)

For patients who had surgery (Key Question 3), postoperative WBRT or SRS did not show a significant difference in overall survival compared with surgery alone (moderate SoE). Radiation therapy may decrease the risk of dying from brain metastases (low SoE). There were no RCTs for preoperative radiation therapy that contributed to the analyses. The number of identified post-surgery studies was small and due to the lack of reporting of details, analyses were very restricted. In particular, robust effect estimates are missing for important outcomes including intracranial progression, quality of life, functional status and cognitive effects, which can help patients decide whether additional treatment should be undertaken (insufficient SoE). The previously reported ASTRO guideline found that post-operative WBRT improved treated brain metastasis control and overall brain control without improving survival, and recommended post-operative WBRT (level 1 evidence) or post-operative SRS (level 3 evidence).[11] While our analysis found that data were insufficient to compute effect sizes for intracranial progression, radiation therapy may reduce the risk of death due to brain metastases.

Post-surgical WBRT and post-surgical SRS were compared in three RCTs.[79, 111, 112] SRS after surgery may improve overall survival compared to WBRT but no effect estimate could be determined (low SoE). Other outcomes were either reported in a single study or could not be combined for analysis. The larger North Central Cancer Treatment Group (NCCTG) N107C/CEC·3 trial had a low risk of bias.[79] Results from the NCCTG N107C/CEC·3 trial showed shorter time to intracranial progression with post-surgical SRS compared with post-surgical WBRT, but no difference in overall survival. Post-surgical SRS was associated with improved cognitive function and quality of life.

Adverse Effects (Key Question 4)

A substantial number of identified studies reported on adverse events. Review of adverse events (Key Question 4) showed no increased risk of serious adverse events or the reported

number of adverse events with the combination of WBRT plus SRS compared to WBRT alone or SRS alone (moderate SoE). We also did not detect differences in serious adverse events for surgery plus SRS compared to surgery plus WBRT (low SoE).

One RCT that compared WBRT with observation in patients who had received surgery or SRS as initial treatment reported more serious adverse events and a higher incidence of radiation necrosis in the WBRT arm.[116] However, this evaluation has not yet been replicated in another study; we did not identify studies confirming the increased risk or contributing to a reliable treatment effect estimate across multiple, independent studies.

Individual radiosensitizer studies[138, 155] indicated an increased risk of serious adverse events, but no meaningful summary effect across available studies could be determined. Studies evaluating systemic therapy with WBRT show an increased risk of vomiting with the addition of systemic therapy (moderate SoE).

We did not detect differences in number of adverse events based on tumor type for patients receiving WBRT or SRS. Other effects were not detected but the findings should be interpreted with caution as studies varied in multiple aspects that hindered the detection of effect modifiers. Indirect comparisons of SRS dose did not find an association between dose and adverse events, but only a small number of studies has been identified and these varied in multiple aspects that hindered the detection of effects.

Strengths and Limitations

This report provides a comprehensive collection of research relevant to radiation treatment in brain metastases. A total of 97 studies reported in 190 publications are included in this review. We screened a large amount of existing literature on radiation therapy for brain metastases and aimed to identify all study reports for studies meeting inclusion criteria. Many identified studies addressed unique research questions beyond the Key Questions addressed in this evidence report and we hope the research collection will be used as a resource for practitioners and researchers.

The studies compare a variety of treatments or combinations of treatment. The reported outcomes in individual studies also varied. Overall survival was the most commonly reported outcome, the evidence base for other important outcomes is sparse. For many of the Key Questions and subquestions, the limited number of studies with the same intervention, co-intervention, comparator, and outcome restricted the possible analyses, often resulting in insufficient strength of evidence. The synthesis focused on effect estimates that were based on more than one published study, hence conclusions were based on analyses that have been replicated and investigated by more than one independent author group. Some of the analyses performed for this report were hindered by differences across studies. Within broad intervention categories there was variation in approach as the existing studies addressed unique questions and some analyses were based on only two studies, resulting in large confidence intervals surrounding the effect estimate

Despite the large number of identified research studies, analyses were limited as studies reported insufficient detail or variation in outcome measures to assess the effect of interventions. In particular, data are missing on important patient-centered outcomes such as quality of life. For adverse outcomes, studies did not use a consistent method of reporting radiation necrosis and seizures. Furthermore, while we assessed the potential for publication bias, there were often too few studies to detect potential effects.

Applicability

Some issues may impact the applicability of our findings. The population for this review includes studies of adult patients with at least 50 percent of patients with brain metastases from non-small cell lung cancer, breast cancer, or melanoma. The results may not be applicable to brain metastases from other primary cancer types (particularly radiosensitive histologies such as small cell lung cancer, leukemia, lymphoma, or germ cell tumor) or the pediatric population. In addition, patients with very poor prognosis are often excluded from clinical trials, and the results of this review may not be applicable to this patient population. The 2012 ASTRO guideline for patients with expected survival less than three months recommended palliative care with or without WBRT.

Most of the studies in this review compared initial treatments for patients with brain metastases. Patients may subsequently develop new brain metastases or progression of treated lesions. As a result, patients may receive multiple treatments for brain metastases over time. The implications and effects of subsequent treatments are important for patients and providers, but not well captured by many of the RCTs or this review.

The review was purposefully limited to studies conducted in 1990 or later to ensure that the review can advise on current decisional dilemmas. This decision was informed by input from the Technical Expert Panel that specifically considered the applicability of the review findings. Because of advancements in imaging and treatment, and improved understanding of prognosis and management, studies from the 1990s or later were believed to be most relevant for this review.

Implications for Clinical Practice, Education, Research, or Health Policy

The patient population with brain metastases is diverse and heterogenous. A combination of factors including tumor type, number, size and location of brain metastases, performance status, extracranial disease burden and prognosis may affect the feasibility, effect and toxicity of a treatment for an individual patient. Due to limited data, many important analyses are missing or the findings for the Key Questions in this review had insufficient or limited strength of evidence. Clinical guidance will need to be based on additional consideration as the existing evidence base provides only limited information.

For future research to help address these questions, we propose the following:

- Participants: Assessing the effects of prognosis was limited because most studies enrolled patients with mixed or unclear prognosis. Future studies should clearly report patient prognosis and consider subgroup analyses.
- Interventions: There is growing research interest in immunotherapy and targeted therapies for brain metastases, but there is a lack of studies comparing these treatments with established treatments. RCTs evaluating immunotherapy or targeted therapies alone or in combination with other treatment options are needed. Promising studies showed reduced cognitive decline with memantine and hippocampal avoidance WBRT. Additional studies of hippocampal avoidance WBRT or memantine would provide definitive effect estimates to guide patients, providers, and policy makers. Further research is needed to assess the role of radiosensitizers. We identified no RCTs evaluating preoperative SRS; studies on the effects of preoperative SRS are needed to support patients and clinicians. Research on the effects of cointerventions such as

physical therapy, occupational therapy, speech therapy and psycho-oncology would be useful for patients and their caregivers.

- Comparators: More research on palliative care, alone or in combination with treatment, is needed to address important decisional dilemmas for patients and their care providers.
- Outcomes: Despite the large number of published studies, we note that many studies do not report on outcomes that have been determined to be important to patients and clinicians, or they do not report on it in sufficient detail.
    - Future funded studies should use validated scales to assess and rigorously report data for quality of life, functional status, and cognitive effects, and report data in sufficient detail. Assessing patient reported outcomes is important in understanding the effects of treatment from the patient's perspective. More information is needed on how treatment-associated adverse events such as sleeping disturbance, drowsiness, poor appetite or distress from treatment, impacts quality of life and broad tolerability assessments of the interventions.
    - Standardizing the validated scales and outcomes used in studies, reporting counts and denominators (categorical data), means and standard deviations (continuous data) for all study arms, and reporting on relevant effect sizes such as hazard ratios (time to event data) would allow for better data synthesis in the future.
    - The identified evidence base indicates that several research studies have already assessed these outcomes that are critical for patients. While journal manuscripts require brief result presentations, online appendices and data repositories can be used to provide more detail on existing studies. In addition, patient registries may provide additional information on this critical patient group to help clinicians and patients make decisions about the best available approach to care after diagnosis with brain metastases.
    - Research registries such as clinicaltrials.gov should be used to add information such as the general tendency for both study arms and a measure of dispersion for both study arms which would allow systematic reviews to estimate treatment effects across studies. In particular the 2016 change in the regulatory requirements and procedures for submitting registration and summary results information of clinical trials has already greatly improved reporting of adverse events. Similar efforts should be made for effectiveness outcomes and it is critical that federal funding is used to initiate but also to facilitate the documentation of research in sufficient detail. While many individual studies may not have sufficient statistical power to show differences between treatment arms, data aggregation in meta-analyses may be able to advance this important field of research.

Conclusions

Despite the substantial research literature on radiation therapy that has been published to date, comparative effectiveness information for the intervention WBRT, SRS, and post-surgery interventions is limited. In particular this is due to studies analyzing unique dyads of interventions and comparators and reporting different outcomes that hinder comparisons across studies. The use of radiosensitizers appear to improve overall survival. The radiosensitizer studies evaluated different radiosensitizing agents in different tumor types, and none of the individual studies showed a survival advantage. The applicability of this finding is unclear, and more research is needed. The effects of memantine and hippocampal avoidance WBRT are

promising but have only been reported in individual studies and summary estimates across multiple studies do not exist yet. SRS alone showed no difference in overall survival or death due to brain metastases compared to SRS plus WBRT. Postoperative WBRT or SRS did not improve survival but may decrease the risk of dying from brain metastases. We did not detect statistically significant differences of radiation therapy plus systemic therapy across studies. However, it should be noted that some studies showed clinical benefits that should be explored in future research and data were only available for selected outcomes, hindering analyses (e.g., important outcomes such as functional status and quality of life could not be analyzed). There is a need for more data on patient-relevant outcomes such as quality of life, functional status, and cognitive effects. Existing data should be made available, through journal publications or data repositories of trial records.

References

Note: This list of references includes references from both the main report and the appendixes.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ASTRO	American Society for Radiation Oncology
bid	twice daily
cGy	centigray
CI	confidence interval
EPC	Evidence-based Practice Center
DFS	disease-free survival
GPA	Graded Prognostic Assessment
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
KQ	Key Question
N	number of participants
OS	overall survival
PCORI	Patient-Centered Outcomes Research Institute
PICOTSS	population, intervention, comparator, outcomes, timing, setting, study design
RCT	randomized controlled trial
RoB	risk of bias
RR	relative risk
SD	standard deviation
SMD	standardized mean difference
SRS	stereotactic radiosurgery
TEP	Technical Expert Panel
US	United States
WBRT	whole brain radiation therapy

Appendix A. Methods

This appendix summarizes the methods used for this evidence report. Note: The references in this appendix can be found in the list at the end of the main report.

Details of Study Selection

The scope of the review was to evaluate the efficacy and safety of radiation therapy for brain metastases in adults with primary melanoma, breast cancer, or non-small cell lung cancer.

Search Strategy

For this review, we searched a variety of sources and applied several measures to reduce potential reviewer errors and bias.

Sources

We searched the research databases PubMed, EMBASE, Web of Science, Scopus, and CINAHL. PubMed indexes biomedical literature, EMBASE emphasizes pharmacological and European journals, CINAHL includes nursing literature, and the Web of Science and Scopus index many technology journals.

We also reference-mined published systematic reviews to ensure that all relevant studies were identified, i.e., rather than summarizing the reviews, we used them as sources to identify available research studies. In addition, we searched the ECRI Guidelines Trust (to be included in the guideline database, guidelines have to be based on a systematic review of the evidence base). We also searched the trial registry, clinicaltrials.gov. Increasingly, authors provide results in trial records, and particularly for new technology developments, trial registries are an important source of research information.

Furthermore, we sought input from content experts on the TEP and a Supplemental Evidence and Data for Systematic review (SEADS) portal was available and a Federal Register Notice was posted for this review to ensure that all relevant evidence has been considered.

Search Strategy

This section describes the search strategies. The search strategies for the individual databases were developed, executed, and documented by an experienced EPC librarian and were peer-reviewed by an experienced methodologist.

PubMed

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((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR “gamma knife”[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
RCT filter OR systematic review filter
OR
((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR “gamma knife”[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
AND clinical trial*[tiab] OR cohort stud*[tiab] OR “case series”[tiab])
OR
((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])

AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR “gamma knife”[tiab] OR CyberKnife[tiab] OR LINAC[tiab])
AND random[tiab] OR RCT[tiab] OR clinical trial*[tiab] OR cohort stud*[tiab] OR “case series”[tiab]
AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb]))
OR
Guideline*[ti]
AND ((brain[tiab] OR head[tiab] OR Brain[mesh]) AND (metastasis[tiab] OR metastatic[tiab] OR metastases[tiab] OR metastasectomy OR cancer*[tiab] OR neoplasm*[tiab] OR carcinoma*[tiab])
AND radiation[tiab] OR radiosurgery[MeSH] OR radiosurgery[tiab] OR radiosurgeries[tiab] OR radiotherapy[tiab] OR radiotherapies[tiab] OR irradiation[tiab] OR WBRT[tiab] OR “gamma knife”[tiab] OR CyberKnife[tiab] OR LINAC[tiab])

ECRI Guidelines Trust Search
“brain metastasis” = 6 = 1 unique (and relevant*)
“brain metastases” = 10 = 1 unique (and relevant)
“metastatic brain” = 8 all duplicates no unique or relevant
TOTAL = 2
*must contain something about radio/radiation or one of the specific terms from the pubmed searches.

Embase
20 July 2020
Limit: Article/Review/Article in Press
('brain'/exp OR brain:ab,ti) AND (metastasis:ab,ti OR metastatic:ab,ti OR metastases:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR carcinoma*:ab,ti OR metastasectomy:ab,ti)
AND
'radiosurgery'/exp OR radiation:ab,ti OR radiosurgery:ab,ti OR radiosurgeries:ab,ti OR radiotherapy:ab,ti OR radiotherapies:ab,ti OR irradiation:ab,ti OR wbrt:ab,ti OR 'gamma knife':ab,ti OR cyberknife:ab,ti OR linac:ab,ti
AND
([systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)
OR
('brain'/exp OR brain:ab,ti) AND (metastasis:ab,ti OR metastatic:ab,ti OR metastases:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR carcinoma*:ab,ti OR metastasectomy:ab,ti)
AND
'radiosurgery'/exp OR radiation:ab,ti OR radiosurgery:ab,ti OR radiosurgeries:ab,ti OR radiotherapy:ab,ti OR radiotherapies:ab,ti OR irradiation:ab,ti OR wbrt:ab,ti OR 'gamma knife':ab,ti OR cyberknife:ab,ti OR linac:ab,ti
AND
“clinical trial*” OR “cohort stud*”
OR
Limit: Conference Abstract
('brain'/exp OR brain:ab,ti) AND (metastasis:ab,ti OR metastatic:ab,ti OR metastases:ab,ti OR cancer*:ab,ti OR neoplasm*:ab,ti OR carcinoma*:ab,ti OR metastasectomy:ab,ti)
AND
'radiosurgery'/exp OR radiation:ab,ti OR radiosurgery:ab,ti OR radiosurgeries:ab,ti OR radiotherapy:ab,ti OR radiotherapies:ab,ti OR irradiation:ab,ti OR wbrt:ab,ti OR 'gamma knife':ab,ti OR cyberknife:ab,ti OR linac:ab,ti
AND
[randomized controlled trial]/lim

Scopus
Limit: Article, 1980-present, Human
TITLE-ABS((brain) AND (metastasis OR metastatic OR metastases OR cancer* OR neoplasm* OR carcinoma* OR metastasectomy)) AND (LIMIT-TO (DOCTYPE , "ar"))
AND
TITLE-ABS(radiation OR radiosurgery OR radiosurgeries OR radiotherapy OR radiotherapies OR irradiation OR wbrt OR “gamma knife” OR cyberknife OR linac) AND (LIMIT-TO (DOCTYPE , "ar"))
AND
TITLE-ABS-KEY-AUTH(“clinical trial*” OR “cohort stud*”) AND (LIMIT-TO (DOCTYPE , "ar"))

Web of Science
Limit: Article, 1980-present Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI
(TS=(brain) AND TS=(metastasis OR metastatic OR metastases OR cancer* OR neoplasm* OR carcinoma* OR metastasectomy))
AND

TS=(radiation OR radiosurgery OR radiosurgeries OR radiotherapy OR radiotherapies OR irradiation OR wbrt OR “gamma knife” OR cyberknife OR linac)

CINAHL
1980-present; Academic Journals
(((MH "Brain") OR TI brain OR AB brain) AND (TI(metastasis OR metastatic OR metastases OR cancer* OR neoplasm* OR carcinoma* OR metastasectomy) OR AB(metastasis OR metastatic OR metastases OR cancer* OR neoplasm* OR carcinoma* OR metastasectomy)))
AND
(MH "Radiosurgery") OR TI(radiation OR radiosurgery OR radiosurgeries OR radiotherapy OR radiotherapies OR irradiation OR wbrt OR “gamma knife” OR cyberknife OR linac) OR AB(radiation OR radiosurgery OR radiosurgeries OR radiotherapy OR radiotherapies OR irradiation OR wbrt OR “gamma knife” OR cyberknife OR linac)
AND
clinical trial* OR cohort stud*)
NOT
(SU Animal studies)

Inclusion and Exclusion Criteria

The citations were screened by two independent literature reviewers. Citations deemed relevant by at least one reviewer were obtained as full text. Full text articles and grey literature material were screened by two independent reviewers against the explicit eligibility criteria. Any discrepancies in inclusion decisions were discussed among the full review team.

Table A-1 describes the eligibility criteria in a PICOTSS (population, intervention, comparator, outcomes, timing, setting, and study design) framework.

Table A-1. Eligibility criteria

PICOTS	Inclusion	Exclusion
Population	• Primary research studies that include a majority (50% or more) of adult patients with metastases in the brain resulting from non-small cell lung cancer, breast cancer, or melanoma	• Study samples comprising patients with cancer from other origins or primary brain tumors (e.g., glioblastomas) and pediatric samples
Interventions	• Studies evaluating radiation therapy, including WBRT and SRS alone or in combination, as initial or postoperative treatment, with or without systemic therapy (immunotherapy and chemotherapy) • Studies have to report on effects of radiation therapy in the 1990s or later	• Studies without WBRT or SRS treatment arms • Studies based exclusively on pre-1990 data
Comparators	• Studies comparing eligible interventions to other eligible interventions or other management approaches (no intervention; waitlist; delayed intervention [radiation to be given at a later time]; placebo; observation, watchful waiting, or surveillance; supportive care, palliative care, or steroid treatment; usual care; systemic therapy, immunotherapy, or chemotherapy; WBRT; SRS; surgery; different dose fractionation schedules; different radiation therapy approaches; different intervention combinations)	• Studies comparing only non-intervention features (e.g., comparing two patient subgroups)
Outcomes	• Studies reporting on patient health outcomes, such as overall survival, progression-free survival; recurrence/cancer control (local tumor control, intracranial control / complete response, partial response, stable response of all metastases); symptom burden, health status or health-related quality of life; functional status (physical, affective or neurocognition functions); or adverse events, including acute and late toxicity (e.g., radiation necrosis or nausea) • Patient health outcomes may include patient- and caregiver-reported outcomes as well as clinical, physician assessed, and hospital record outcomes and measures may include quantitative as well as qualitative reports and no restrictions will be imposed regarding the specific measurement, metric, aggregation method (e.g., mean, proportion), or timepoint.	• Studies reporting only on therapy acceptance, provider variables (e.g., provider knowledge), organizational measures (e.g., wait times), treatment utilization, or costs
Timing	• Studies will not be limited by the duration of the intervention or the length of follow up	• No exclusions apply
Setting(s)	• Studies may include inpatient and outpatient settings • Studies may include national and international settings	• Studies in resource-limited settings such as developing countries will be reviewed for comparability with US settings

PICOTS	Inclusion	Exclusion
Study design	**All KQs** • RCTs • Studies with results published in clinicaltrial.gov will be included regardless of whether a journal publication is available • English-language publications **KQ4 (adverse events)** • Prospective experimental and observational studies (including non-randomized controlled trials and cohort studies comparing 2 or more intervention cohorts) of 200 patients or more or those that report a statistical power analysis for adverse events	• Studies without comparator • Evaluations reported only in abbreviated format (e.g., in a conference abstract) and that are not registered in a research registry • Studies exclusively reported in non-English publications will be retained as a resource but will not be eligible for inclusion • Systematic reviews will be retained for reference mining

Systematic reviews identified in the searches were retained for reference mining, as a source to identify potentially relevant studies.

The scope of the review is to evaluate radiation therapy for brain metastases in adults with melanoma, breast cancer, or non-small lung cancer. Although studies did not have to include these patients exclusively, these patients had to comprise the majority of participants for a study to be eligible for inclusion, or results had to be presented for eligible cancer origin subgroups. These cancer origins represent the most common cancer types in adults. While treatment for brain metastases from other primary cancers and in pediatric patients is equally important, it was deemed to be outside the scope of this project and should be addressed in future reviews.

In response to public comments on the posted review questions and preliminary inclusion criteria, we further restricted the studies of lung cancer brain metastases to those including only patients with non-small cell lung cancer. This restriction ensured a more homogeneous evidence base. A further change since the initial posting of the Key Questions is the expansion of the eligible study designs for Key Question 4 from RCTs and observational studies to non-randomized experimental studies (e.g., controlled clinical trials) as well. RCTs were eligible for all Key Questions. The broader inclusion criteria for adverse event data take into account that rare adverse events are difficult to detect in smaller and short-term trials.

The eligible outcomes encompassed several categories of patient outcomes—including health, wellbeing, and side effects. Key Informant input consistently emphasized the importance of patient-relevant outcomes. Patients need to weigh many aspects of treatment outcomes in addition to effectiveness and toxicity. These include effects on survival as well as quality of life during and after treatment. Functional status in general as well as retention of normal function—for example being able to care for one's child—are other key considerations for patients. Furthermore, the extent and the potential consequences of cognitive changes are very important considerations.

The Technical Expert Panel provided input on the restricting inclusion to studies reporting data from 1990 or later for intervention evaluations. Because of technological advances, especially in the area of imaging, results of older studies may not be relevant to current clinical decisions. We decided to exclude non-English studies, as non-English language studies may not contribute substantially to the evidence base in this research area. The inclusion of non-English

language studies can make the evidence base less transparent and might impede ASTRO's guideline committee members from using individual studies to formulate guidance.

Data Abstraction

Data were abstracted in an online data abstraction program for systematic reviews (DistillerSR). The abstraction forms included detailed instructions, definitions, and descriptions of categories to guide reviewers and to avoid ambiguities. Data were abstracted by one reviewer and the data abstraction was checked for accuracy and consistency across studies by a second, experienced literature reviewer; a content expert reviewed abstracted participant and intervention details. The progress was monitored frequently, questions were discussed among the review team, and further guidance was added to the online forms as needed.

The data abstraction process captured all information published about the study, including information in the trial record in a trial registry, study protocol, interim analyses, main analysis, and subgroup analyses. Multiple publications reporting on the same participant groups were counted as single studies and did not enter the review analysis multiple times. Throughout the data abstraction process, publications reporting on the same participant group were consolidated.

The data abstraction included study-level variables that are displayed in the evidence table and variables that were used in the review analysis, critical appraisal of the study, or assessment of applicability:

- Study characteristics
    - Author and publication year of the main publication, country, trial registration number, additional publications reporting on the study, type of publication (journal manuscript, trial record), study status (e.g., early trial termination, preliminary data only), study design (parallel RCT randomizing participants, cluster RCT, controlled clinical trial, cohort study, other RCT [e.g., randomized by lesion]), Key Question contribution of non-randomized studies (adverse events, effects, or both), number of participants (study size indication), power calculation, and funding type and potential for conflict of interest (industry-funded, author conflicts of interest, industry-funded but unrestricted grant, unclear, non-industry funded)
- Participant characteristics
    - Age (mean, standard deviation [SD]), gender (% female)
    - Diagnosis and cancer origin (melanoma; breast; non-small cell lung cancer; combination of melanoma, breast, and lung cancer; combination of cancer diagnoses)
    - Extent of metastases: number of metastases (mean, SD, other measures), volume of metastases (mean, SD, other measures), size of metastases (mean, SD, other measures)
    - Prognostic information (using the authors' classification or descriptive information on the proportion of patients with poor or good prognosis, limited/favorable versus extensive brain metastases), prognosis classification for analysis (poor; unclear or mixed; good)
- Intervention arms
    - Intervention type (initial WBRT, initial SRS, post-surgery WBRT, post-surgery SRS), intervention description (e.g., hippocampus-sparing WBRT), radiation dose and fractionation (e.g., 4000 cGy, 20 fractions bid)

        - The more or most intense intervention was classified as the main intervention
    - Co-treatment type (systemic therapy, additional WBRS or SRS, other), co-treatment description (e.g., chemotherapy, genotype-directed [yes/no], dose, duration), pre-treatment description (e.g., repeat SRS)
    - N randomized (or initially included), N analyzed
- Control and comparator arms
    - Type, description, dose, fractionation, and co-treatment
        - The less or least intense intervention was classified as the main comparator
- Outcomes and results
    - Type (survival, disease-free survival, deaths due to brain metastases, intracranial progression, quality of life, functional status, cognitive effects, serious adverse events, number of adverse events, headache, radiation necrosis, fatigue, seizure, vomiting), measure description and origin (e.g. assessment scale, hospital record data), follow up calculated from start of the intervention, follow up calculated from end of the intervention,
    - Results at latest follow up comparing intervention and control arm, intervention and additional comparator arm, and control arm and additional comparator arm

To facilitate comparisons across studies, we standardized descriptions throughout (e.g., reporting intervention characteristics in a clear structure) and converted study characteristics to proportions (e.g., % female). Results were converted to measure-independent variables such as standardized mean differences (SMDs), relative risks (RRs), and hazard ratios (HRs). All results were presented together with the 95% confidence interval (CI). We used SMDs to analyze continuous data, RR for categorical data, and HRs for time to event data. In many studies, the HR was not reported. Where reported, we used the median survival and the number of deaths per arm to compute the HR. For all other studies we reported the outcomes as reported by the study authors as we could not combine the information statistically.

We organized reported outcomes by outcome category (e.g., cognitive measures). For adverse events, when studies reported events for one arm only, we assumed that no event occurred in the other study arm. We used the authors' classification of serious adverse events. However, where not specified, we applied the FDA definition of serious adverse events (death, life-threating, requiring hospitalization, disability or permanent damage, congenital anomaly, requiring intervention to prevent permanent impairment, or other serious events).[265]

Risk of Bias Assessment of Individual Studies

All included studies were assessed for key sources of bias that may have influenced the reported results. The assessment was conducted by one reviewer; a second reviewer checked the assessment for accuracy and consistency across studies, and unclear cases were discussed in the review team. Studies contributing to Key Questions 1 through 3 were assessed for the following sources of bias:

- Selection bias, including risk of bias arising from the randomization process
- Performance bias, including bias due to deviations from intended interventions
- Attrition bias, including bias due to missing outcome data
- Detection bias, including bias in measurement of the outcome
- Reporting bias, including bias in selection of the reported results

- Other sources of bias

The risk of bias domain selection was informed by established risk of bias assessment approaches and the latest revision of the Cochrane Risk of Bias Tool (RoB 2) that is currently being applied in practice.[266] For *selection bias*, we assessed the randomization sequence and allocation concealment in RCTs as well as baseline differences and potential confounders in all studies. *Performance bias* evaluated whether patient- or caregiver knowledge of the intervention allocation or circumstances such as the trial context may have affected the outcome, and whether any deviations from intended interventions were balanced between groups. *Attrition bias* considered the number of dropouts, any imbalances across study arms, and whether missing values may have affected the reported outcomes. *Detection bias* assessed whether outcome assessors were aware of the intervention allocation, whether this knowledge could have influenced the outcome measurement, and whether the outcome ascertainment could differ between arms. *Reporting bias* assessment included an evaluation of whether a pre-specified analysis plan was described (e.g., a published protocol), whether the numerical results likely have been selected on the basis of the results, and whether key outcomes were not reported (e.g., an obvious effectiveness indicator is missing) or inadequately reported (e.g., anecdotal adverse event reporting). In addition, we assessed *other potential sources of bias* such as early termination of trials, inadequate reporting of intervention details, and lack of intention-to-treat analyses. For the outcomes, *functional status* and *quality of life*, we assessed whether the outcome assessment used scales that have been validated for patients with brain tumors.

Given that the reliability and validity of the data are critical to answer Key Question 4 and adverse event reporting is often lacking in rigor, we applied an additional critical appraisal tool for adverse event research, assessing the following:[267, 268]

- Data collection of adverse events
- Reporting of adverse events

The appraisal of the data collection method evaluated the rigor of the adverse event assessment (e.g., use of a scale or checklist) and whether adverse events were collected actively (e.g., all participants were asked about the occurrence of specific harms) or passively (e.g., participants might have reported events at their discretion but without structured assessment or specific prompts). The reporting also assessed whether adverse events, including serious adverse events, were defined by the study authors. In addition, we reviewed whether the authors specified the number of participants affected by each type of adverse event (some patients experience multiple events).

For each risk-of-bias criterion, we assessed high, moderate or unclear, and low risk of bias. In addition, we determined two overall summary assessments, one for the outcome domain, patient health outcomes, and one for adverse events. The assessments determined the suitability of the study to answer Key Questions 1 through 3 and Key Question 4, respectively. The critical appraisal result was used for sensitivity analyses where appropriate (e.g., excluding high risk of bias studies). The summary assessments were incorporated into the strength of evidence assessment.

Data Synthesis and Analysis

The included studies were broadly characterized based on study characteristics, participant details, intervention categories, identified comparator, and outcome categories employed. Study details and results of all included studies are documented in the evidence table (Appendix D), which allows a concise overview. The included studies represented a multitude of

comparisons—such as SRS versus WBRT or SRS plus surgery versus surgery alone. Thus, we mapped the network of available research for the Key Questions to provide an overview of the evidence base.

Key Questions 1 through 3 aim to evaluate the effects and comparative effects of different radiation therapy interventions (WBRT, SRS, post-surgery treatment) and intervention combinations. For all interventions where a similar comparator was employed (e.g., all evaluated interventions compared to surgery alone), individual and summary results are shown in forest plots to answer the Key Questions (measure comparability permitted). The forest plots provide a clear overview of the individual study effects, study size, direction of effects across studies, and outliers in the study pool. The risk of bias is discussed when summarizing the forest plot results. We present the data stratified by broad categories (e.g., WBRT, WBRT plus SRS) to organize the research studies. To determine the comparative effects of interventions, we used direct evidence from head-to-head comparisons (e.g., WBRS vs SRS) wherever possible. In addition, we explored effects through indirect comparisons across studies. Specifically, we assessed whether combination treatments of WBRT plus SRS are more effective than the individual interventions WBRT or SRS.

Meta-Analytic Approach

Given the evidence base and review questions, we assessed the suitability of the available research for network meta-analyses. Network analyses can incorporate direct and indirect evidence. However, the identified studies evaluated interventions and comparators that were often unique dyads. In addition, only a few outcomes were available for pooled analyses. While studies may have reported on an outcome domain, the data were often insufficient to allow effect sizes to be calculated (e.g., studies may have reported narrative results or reported means without a measure of dispersion). Hence, we decided to use pairwise analyses and traditional meta-regressions to analyze direct and indirect evidence. Where only unique outcome, intervention, and comparator combinations were identified, we computed effect sizes for the individual study to facilitate comparisons across studies.

Outcome domains (e.g., survival, quality of life, functional status) for analyses were selected with input from the Technical Expert Panel. The panel also provided input on outcome measures within outcome domains (e.g., disease-free survival vs overall survival; see Table A-2.). For eligible interventions for which no RCTs had been identified, we reviewed the studies that met inclusion criteria for Key Question 4. However, these analyses were interpreted with caution given the study limitations of observational and non-randomized studies. For Key Question 4, the synthesis focused on key adverse events, which were also selected with input from the panel. All analyses considered the number of studies that assessed an adverse event and the observed events. The analysis reported on the presence and the absence of events. For this Key Question, a number of study designs were eligible to contribute information. Given the nature of the clinical condition, we assessed the frequency of adverse events for an intervention compared to those for a similar control group, i.e., in comparison to a sample of patients also affected by brain metastases but receiving a different or no treatment.

Synthesis

Throughout the project, where possible, study results were synthesized in statistically pooled analyses to provide a numerical estimate of the size of the treatment effect across all available research evidence. For Key Question 1, the analysis was centered around WBRT as initial

treatment. For Key Question 2, the analysis was centered around SRS as initial treatment. For Key Question 3, the analysis focused on postoperative treatment. The analyses for Key Question 4 addressed adverse events associated with all eligible interventions and was organized by event first and intervention second. The review aimed to inform decisional dilemmas for patients (e.g., how do the intervention options compare, what are the effects on critical outcomes such as survival and quality of life after treatment; Key Question 1-3) and what adverse effects are to be expected (Key Question 4)? We followed the principle of "first lumping, then splitting." While differentiation is important where studies are clinically and empirically different, an analysis that is too granular will also not be adequate to answer the Key Questions. The meta-analyses used random effects models with Knapp-Hartung corrections where appropriate using the metafor package in R.[269] Heterogeneity was documented using the I-squared statistic.

Analyses were conducted for the outcomes of interest identified in the strength of evidence assessment using the longest follow-up reported in the individual studies. Where outcome domains did not specify a metric or method of aggregation (e.g., mean differences or counts), we chose the measure that allowed the most studies to enter the analysis. If considerable heterogeneity had been detected in analyses, we would have explored potential sources. For example, the publication year could be a potential source of heterogeneity. If a systematic effect had been detected for an effect modifier, we would have reported sensitivity analyses (e.g., omitting older studies) or stratified the results by publication year cluster (e.g., 2010 to date). For comparisons that showed statistically significant differences across studies, we assessed publication bias using the Begg's rank test and Egger's regression test.[270] Where publication bias was indicated, we would have used the trim and fill method to provide adjusted estimates. Sensitivity analyses explored the robustness of key results by reviewing the number of studies with high risk of bias. All studies meeting inclusion criteria were summarized in the narrative synthesis and Appendix D. The synthesis was structured by interventions, comparators, and outcomes; these are also documented in the summary of findings table used for documenting the strength of evidence assessment. Summary results across studies reported the magnitude of the effect as well as the direction of effects.

Subquestions

Subquestions 1a-c, 2a-c, 3a, and 4a addressed intervention and patient characteristics. We used direct evidence to answer the subquestions whenever possible, for example where dose fractionation schedules have been assessed in head-to-head comparisons. In addition, especially in the absence of direct evidence, we compared studies indirectly. Where meta-analysis was possible, we added a variable of interest to the meta-analytic model to determine whether study findings varied systematically depending on the variable (e.g., whether the addition of radiosensitizers systematically influenced treatment effects). The meta-regressions used qualitative categories (e.g., primary tumor type) or quantitative operationalizations (e.g., number of metastases). We set out to assess the effects of all characteristics called out in the subquestions (dose fractionation schedule and technique, patient characteristics, patient prognosis, primary tumor site, addition of systematic therapies). However, only some analyses were possible due to the lack of data. Where analyses indicated systematic differences across studies, we stratified studies and presented data for the subgroups of interest separately. Finally, we aimed to present analyses according to how the evidence will be used. For example, if the ASTRO guideline committee plans to stratify recommendations by specific prognostic or tumor characteristics, we aimed to provide an equivalent evidence summary for the area of interest.

Grading the Strength of the Body of Evidence

We reviewed the quality of evidence across studies for the selected outcomes. For each Key Question, we considered the outcomes listed in Table A-2 to ensure a concise overview. Outcome domains and individual outcome measures were selected for their relevance and importance, and these selections were made *a priori*—i.e., before the results of studies were known—to ensure an unbiased evidence assessment. As part of the review process, we gathered input from TEP members regarding potential outcomes of importance based on published studies and existing systematic reviews. Outcomes were ranked and checked for conceptual overlap.

Table A-2. Key outcomes

Key Question	Outcomes
Key Questions 1-3	1. Overall survival (time to death, hazard ratio) 2. Quality of life as measured by validated scales 3. Cognitive function measured by any scale 4. Deaths due to brain metastases (number of patients, relative risk) 5. Disease-free survival (time to event, hazard ratio) 6. Intracranial progression/central nervous system failure (development of new or progressive metastases) 7. Functional status as measured by any scale or measure (standardized mean differences)
Key Question 4 (adverse events)	1. Number of patients with serious adverse events 2. Number of adverse events 3. Any specific adverse event most often assessed 4. Radiation necrosis 5. Fatigue 6. Seizure 7. Vomiting

The most assessed, specific adverse event, apart from the other selected outcomes was reported headaches. We used the authors' definition of serious adverse event. The evidence table shows definitions where reported, other studies referenced the FDA definition of serious adverse events.[265] The outcomes were used to answer the review questions. The summary of findings tables document the presence and the absence of evidence for each of the selected outcomes. The findings across studies were presented together with the quality of the evidence and our confidence in effect estimates. The strength of evidence assessment used the AHRQ EPC program strength of evidence assessment categories taking the following domains into account:

- Study limitations
- Directness
- Consistency
- Precision
- Reporting bias

Study limitations can be judged as low, medium, or high level, reflecting the risk of bias in the included studies. Study limitations include inadequate sample sizes to detect effects and inadequate comparators for the research question as well as more studies exist that do not contribute to the pooled effect than that contribute to the pooled effect. Directness differentiates between direct (head-to-head) and indirect (across studies) evidence. The domain consistency differentiates among consistent and inconsistent study findings across studies, and unknown in the case of a result that is based on a single study and that has not been replicated yet. Precision is scored as either precise or imprecise, where precise indicates the result reflects a clinically

unambiguous conclusion. Reasons for imprecision were the study reported insufficient detail to compute effect sizes or the confidence intervals were wise. If results were based primarily on network meta-analysis findings, the strength of evidence assessment would informed by the new Cochrane guidance on network meta-analysis.[271] The domain, reporting bias, differentiates between suspected bias (e.g., there is indication of publication bias, selective outcome reporting, or selective reporting of the analysis) and undetected bias (no bias indicated).

Each evidence statement was assessed with these criteria to determine the overall strength of evidence and we differentiated the strength of evidence levels outlined in Table A-3.

Table A-3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

The categories communicate the confidence in the summary estimates for the findings across studies. The evidence statements were drafted by one literature reviewer and discussed among the team to ensure quality control and consistency of interpretation. The findings highlight the direction and size of effect narratively in addition to providing the numerical point estimate and confidence interval. Throughout, results were interpreted with caution: for comparative effectiveness assessments (Key Questions 1 through 3) that do not show a statistically significant difference between interventions, we took evidence of statistical power to detect differences into account before making non-inferiority statements for interventions. The interpretation of Key Question 4 results considered that frequentist approaches are problematic for rare adverse events (rare events require large samples to detect effects). Associations of adverse events with an intervention are based on comparative evaluations, and events in the intervention group were reported relative to results in a comparable control group not exposed to the intervention.

To facilitate comparisons, we based all results on measure-independent effect estimates, such as relative risks or standardized mean differences. However, for important results we translated effect sizes into absolute effects or mean differences on known scales to help the interpretation of the effect where appropriate. Throughout the Results section, we call out specific areas of uncertainty such as large effects that are not statistically significant (given that the number and the size of studies also affect statistical significance) and outline the range of possible effects consistent with the data. For areas where we determined that there was 'insufficient' evidence, we aimed to provide information about the specific data limitations to assist in decision-making.

The review documents available research as well as remaining research gaps. The gap presentation was structured by Key Question and subquestion and used the eligibility criteria framework PICO (participants, intervention, comparator, outcome) to provide specific recommendations for future research.

Peer Review and Public Commentary

Experts in radiosurgery, neurosurgery, nursing and palliative care, systemic therapy, patient-centered outcomes, and radiation therapy synthesis, and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ website for four weeks to elicit public comment. All reviewer comments have been addressed in the final report, revising the text as appropriate. A disposition of comments table of peer and public comments will be posted on the EHC website 3 months after the Agency posts the final systematic review.

Appendix B. List of Excluded Studies

Note: after each reference is the aspect of the eligibility criteria the study failed to meet for inclusion.

1. Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission. Cochrane Database Syst Rev. 2000(4):Cd002805. doi: 10.1002/14651858.Cd002805. PMID: 11034766. *Population*

2. Stereotactic Radiosurgery Keeps Brain Metastases at Bay. Cancer Discov. 2016 Nov;6(11):Of2. doi: 10.1158/2159-8290.Cd-nb2016-124. PMID: 27807104. *Study design*

3. Challenging Current Conventions: Up-Front Stereotactic Radiosurgery Alone for Limited Brain Metastases in Small Cell Lung Cancer. Pergamon Press - An Imprint of Elsevier Science; 2019. p. 1031-2. *Population*

4. Abbott Medical D. Supporting Patients Undergoing HIgh-Risk PCI Using a High-Flow PErcutaneous Left Ventricular Support Device (SHIELD II). 2020. *Outcome*

5. AbbVie. Study Evaluating ABT-414 in Japanese Subjects With Malignant Glioma. 2020. *Population*

6. AbbVie, AbbVie. A Phase I Study of ABT-888 in Combination With Conventional Whole Brain Radiation Therapy (WBRT) in Cancer Patients With Brain Metastases. 2013. *Outcome*

7. AbdelWahab MMR, Wolfson AH, Raub W, et al. The role of hyperfractionated re-irradiation in metastatic brain disease - A single institutional trial. American Journal of Clinical Oncology-Cancer Clinical Trials. 1997 Apr;20(2):158-60. doi: 10.1097/00000421-199704000-00011. PMID: WOS:A1997WQ31500011. *Intervention*

8. Abramson Cancer Center of the University of P. F18 EF5 PET/CT Imaging in Patients With Brain Metastases From Breast Cancer. 2016. *Intervention*

9. Abramson Cancer Center of the University of P. Proton Radiation For Meningiomas and Hemangiopericytomas. 2017. *Population*

10. Abramson Cancer Center of the University of P. Radvax™: A Stratified Phase I/Ii Dose Escalation Trial of Hypofractionated Radiotherapy Followed by Ipilimumab in Metastatic Melanoma. 2019. *Intervention*

11. Abramson Cancer Center of the University of P, National Cancer I. MRI Mapping in Planning Radiation Therapy to the Base of Skull and Brain in Patients With Nonmetastatic Head and Neck Cancer. 2011. *Population*

12. Abramson Cancer Center of the University of P, United States Department of D. Skull Base and Low Grade Glioma Neurocognitive Magnetic Resonance Imaging (MRI) Study. 2017. *Population*

13. Addeo R, Caraglia M, Vincenzi B, et al. Efficacy and Safety of Cetuximab plus Radiotherapy in Cisplatin-Unfit Elderly Patients with Advanced Squamous Cell Head and Neck Carcinoma: A Retrospective Study. Chemotherapy. 2019;64(1):48-56. doi: 10.1159/000500714. PMID: 31242489. *Population*

14. Adnexus AB-MSR, Company D. CT-322 in Combination With Radiation Therapy and Temozolomide to Treat Newly Diagnosed Glioblastoma Multiforme. 2010. *Population*

15. Affiliated Hospital to Academy of Military Medical S. Hippocampal-sparing Whole Brain Radiotherapy for Brain Metastases From Breast Cancer. 2017. *Outcome*

16. Agarwal JP, Chakraborty S, Laskar SG, et al. Applying the QUARTZ Trial Results in Clinical Practice: Development of a Prognostic Model Predicting Poor Outcomes for Non-small Cell Lung Cancers with Brain Metastases. Clinical Oncology. 2018;30(6):382-90. doi: 10.1016/j.clon.2018.02.002. PMID: 129374746. Language: English. Entry Date: 20180502. Revision Date: 20180502. Publication Type: Article. *Study design*

17. Ain Shams U. Simvastatin Effect on Radiation Therapy of Brain Metastases. 2015. *Outcome*

18. Akanda ZZ, Hong W, Nahavandi S, et al. Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis. Radiother Oncol. 2020 Jan;142:27-35. doi: 10.1016/j.radonc.2019.08.024. PMID: 31563407. *Study design*

19. Akyurek S, Chang EL, Mahajan A, et al. Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer. American Journal of Clinical Oncology: Cancer Clinical Trials. 2007;30(3):310-4. doi: 10.1097/01.coc.0000258365.50975.f6. *Study design*

20. Al-Saleh K, El-Sherify M, Safwat R, et al. Phase II/III Randomized Controlled Trial of Concomitant Hyperfractionated Radiotherapy plus Cetuximab (Anti-EGFR Antibody) or Chemotherapy in Locally Advanced Head and Neck Cancer. Gulf J Oncolog. 2019 May;1(30):6-12. PMID: 31242976. *Population*

21. Albert Einstein College of M. Phase I Study of Fractionated Stereotactic Radiation Therapy. 2021. *Outcome*

22. Albert Einstein College of M. A Simple Walking Program to Enhance Concurrent Chemoradiotherapy Delivery. 2021. *Outcome*

23. Albert Einstein College of M, National Cancer I. Voxel Based Diffusion Tensor Imaging in Predicting Response in Patients With Brain Metastases Undergoing Whole Brain Radiation Therapy or Stereotactic Radiosurgery. 2016. *Outcome*

24. Albert Einstein College of M, National Cancer I. PET-Adjusted Intensity Modulated Radiation Therapy and Combination Chemotherapy in Treating Patients With Stage II-IV Non-small Cell Lung Cancer. 2017. *Population*

25. Alberta AHSCC. Identification of Clinically Occult Glioma Cells and Characterization of Glioma Behavior Through Machine Learning Analysis of Advanced Imaging Technology. 2017. *Population*

26. Alberta Health S, Alberta AHSCC. Prophylactic Cranial Irradiation in Patients With HER-2-Positive Metastatic Breast Cancer. 2011. *Intervention*

27. Alberta Health S, Tom Baker Cancer C, Alberta AHSCC. Frameless Stereotactic Radiosurgery for Brain Metastases. 2012. *Outcome*

28. Alliance for Clinical Trials in O, National Cancer I. Temozolomide and Radiation Therapy in Treating Patients With Stage IV Malignant Melanoma With Measurable and Unresectable Cancer of the Central Nervous System. 2005. *Outcome*

29. Alliance for Clinical Trials in O, National Cancer I. Donepezil and Vitamin E to Prevent Side Effects Caused By Radiation Therapy to the Head in Patients Receiving Treatment for Small Cell Lung Cancer. 2005. *Population*

30. Alliance for Clinical Trials in O, National Cancer I. EGb761 in Maintaining Mental Clarity in Women Receiving Chemotherapy for Newly Diagnosed Breast Cancer. 2006. *Population*

31. Alliance for Clinical Trials in O, National Cancer I, Genentech I. Corticosteroids + Bevacizumab vs. Corticosteroids + Placebo (BEST) for Radionecrosis After Radiosurgery for Brain Metastases. 2020. *Outcome*

32. Amaral T, Kiecker F, Schaefer S, et al. Combined immunotherapy with nivolumab and ipilimumab with and without local therapy in patients with melanoma brain metastasis: a DeCOG* study in 380 patients. J Immunother Cancer. 2020 Mar;8(1). doi: 10.1136/jitc-2019-000333. PMID: 32221017. *Intervention*

33. Amaral T, Tampouri I, Eigentler T, et al. Immunotherapy plus surgery/radiosurgery is associated with favorable survival in patients with melanoma brain metastasis. Immunotherapy. 2019 Mar;11(4):297-309. doi: 10.2217/imt-2018-0149. PMID: 30606066. *Study design*

34. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363(9422):1665-72. doi: 10.1016/S0140-6736(04)16250-8. *Duplicate*

35. Anglo Celtic Cooperative Oncology G, National Cancer I. Radiation Therapy to the Head in Preventing Brain Metastases in Women Receiving Trastuzumab and Chemotherapy for Metastatic or Locally Advanced Breast Cancer. 2010. *Intervention*

36. Annick D, Amgen, Duke U. Panitumumab and Irinotecan for Malignant Gliomas. 2011. *Outcome*

37. Aposense L. 18F ML-10 for Early Detection of Response of Brain Metastases to WBRT. 2008. *Outcome*

38. Aposense L. 18F ML-10 for Early Detection of Response of Brain Metastases to SRS. 2009. *Outcome*

39. Aposense L. Evaluation of the Efficacy and Safety of 18F -ML-10, as a PET Imaging Radiotracer, in Early Detection of Response of Brain Metastases of Solid Tumors to Radiation Therapy. 2010. *Outcome*

40. Armstrong JG, Wronski M, Galicich J, et al. Postoperative radiation for lung cancer metastatic to the brain. Journal of Clinical Oncology. 1994;12(11):2340-4. doi: 10.1200/JCO.1994.12.11.2340. *Study design*

41. Aroney RS, Aisner J, Wesley MN, et al. Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma. Cancer Treat Rep. 1983 Jul-Aug;67(7-8):675-82. PMID: 6307516. *Population*

42. Ashworth A, Rodrigues G, Boldt G, et al. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. Lung Cancer. 2013 Nov;82(2):197-203. doi: 10.1016/j.lungcan.2013.07.026. PMID: 24051084. *Year*

43. Assistance Publique - Hôpitaux de P. Non Invasive Methods for Differential Diagnosis Radionecrosis/Recurrence After Radiosurgery of Brain Metastases. 2015. *Outcome*

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122. Case Comprehensive Cancer C, National Cancer I. Stereotactic Radiation Therapy in Treating Patients With Brain Metastases. 2001. *Outcome*

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134. Center HLMC, Research I, National Comprehensive Cancer N, et al. Study Bendamustine Concurrent Whole Brain Radiation Brain Metastases From Solid Tumors. 2012. *Outcome*

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138. Center MDAC. Fatigue, Sleep and Cytokines in Primary Brain Tumor (PBT) Patients. 2013. *Population*

139. Center MDAC. Treatment of Tumors of the Choroid Plexus Epithelium. 2017. *Population*

140. Center MDAC. Prophylactic Cranial Irradiation (PCI) for Small Cell Carcinoma of the Urothelium. 2019. *Intervention*

141. Center MDAC. Single Versus Multifraction Salvage Spine Stereotactic Radiosurgery for Previously Irradiated Spinal Metastases. 2022. *Intervention*

142. Center MDAC, BioMed Valley Discoveries I, Merck S, et al. Pembrolizumab With Intratumoral Injection of Clostridium Novyi-NT. 2020. *Outcome*

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144. Center MDAC, National Cancer I. Neurological Effects of Acupuncture to Prevent Radiation-induced Xerostomia. 2019. *Intervention*

145. Center MDAC, National Cancer I. Frameless Fractionated Stereotactic Radiation in Treating Patients With Brain Metastases. 2020. *Outcome*

146. Center MDAC, National Cancer I. Nivolumab and Radiation Therapy With or Without Ipilimumab in Treating Patients With Brain Metastases From Non-small Cell Lung Cancer. 2020. *Study design*

147. Center MDAC, National Cancer I. Stereotactic Radiosurgery in Treating Patients With Greater Than 3 Melanoma Brain Metastases. 2020. *Outcome*

148. Center MDAC, National Cancer I. DECT in Imaging Patients With Solid Organ Cancer With Intracranial Metastasis. 2020. *Outcome*

149. Center MDAC, National Cancer I. nTMS in Planning Stereotactic Radiosurgery in Patients With Brain Metastases in the Motor Cortex. 2021. *Outcome*

150. Center MDAC, National Cancer I. Pre-operative SRS or Post-operative SRS in Treating Cancer Patients With Brain Metastases. 2022. *Outcome*

151. Center MDAC, Pharmaceuticals OSI. Tarceva With Whole Brain Radiation Therapy - Brain Mets From Non-Small Cell Lung Cancer. 2019. *Comparator*

152. Center UNCLCC. FLT PET/MR for Evaluation of Pseudoprogression in Patients With Brain Lesions. 2018. *Intervention*

153. Center UNCLCC. MRI Biomarkers for Radiation-Induced Neurocognitive Decline Following SRS of Newly Diagnosed Brain Mets. 2022. *Outcome*

154. Center UNCLCC, National Cancer I. Whole-Brain Radiation Therapy and Pemetrexed in Treating Patients With Brain Metastases From Non-Small Cell Lung Cancer. 2008. *Study design*

155. Center VUUM. Safety Study of Radiotherapy and Concurrent Erlotinib (Tarceva®) for Brain Metastases From a Non-Small Cell Lung Cancer. 2007. *Outcome*

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159. Centre Francois B, Anocef/Igcno, Groupement Interrégional de Recherche Clinique et dI. Stereotactic Radiotherapy for Cerebral Metastases With Recent Hemorrhagic Signal. 2022. *Outcome*

160. Centre Francois B, National Cancer Institute F, Roche Pharma AG, et al. Safety Evaluation of a Combination of Brain Radiation Therapy and Bevacizumab (Avastin®) for Treatment of Brain Metastasis. 2013. *Comparator*

161. Centre Francois Baclesse L. Stereotactic Radiotherapy for Brain Metastases. 2019. *Outcome*

162. Centre Francois Baclesse L. Cerebral Prophylactic Irradiation With Saving Hippocampus and Amygdala. 2019. *Outcome*

163. Centre Georges Francois L. Study Evaluating the Efficacy of Radiotherapy With SIB-IMRT, Associated With Temozolomide in Glioblastomas. 2017. *Outcome*

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165. Centre Hospitalier Intercommunal C, Groupe Francais De P-C. Therapeutic Strategies in Patients With Non-squamous Non-small Cell Lung Cancer With Brain Metastases. 2018. *Outcome*

166. Centre Hospitalier Universitaire A. Astrocytoma Desmoplastic Gamliogliomes (DIA DIG) - Study of the French Cohort of the Last 20 Years : Clinical, Anatomopathological, Molecular and Radiological Charactersics. 2017. *Population*

167. Centre Hospitalier Universitaire de N. Cerebral Metabolism in Patients With Refractory Chronic Cluster Headache Treated by Occipital Nerve Stimulation. 2015. *Population*

168. Centre Hospitalier Universitaire de Saint E. Structural and Functional Brain Reorganization in Neuropathic Pain: Basal State of Local Cerebral Blood Flow and Functional Connectivity. 2019. *Outcome*

169. Centre Hospitalier Universitaire de Saint E. Structural and Functional Brain Reorganization in Neuropathic Pain. Influences of the Loss of Sensitivity and the Atrophy Cortical on Activations Due to Stimulation Allodynic. 2019. *Outcome*

170. Centre Leon B. Study of SBRT Efficacy on Intra and Extra -Cranial Tumors or Metastasis in Pediatrics Population (SBRT Pediatrics). 2019. *Outcome*

171. Centre of Postgraduate Medical E. Assessment of Left Atrial Appendage Morphology in Patients After Ischemic Stroke. 2016. *Population*

172. Centre Oscar L. TraStuzumAb-Radiotherapy : Impact on the Cerebral Prevention. 2012. *Outcome*

173. Centre Oscar L, Centre Hospitalier Universitaire de B. Prospective Assessment of Quality of Life in Patients Treated by Radiosurgery for Brain Metastases (PRAMECE-1302). 2018. *Outcome*

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623. National Cancer I. Trametinib With or Without Whole Brain Radiation Therapy in Treating Patients With Brain Metastases. 2016. *Study design*

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626. National Cancer I. VX-970 and Whole Brain Radiation Therapy in Treating Patients With Brain Metastases From Non-small Cell Lung Cancer, Small Cell Lung Cancer, or Neuroendocrine Tumors. 2019. *Outcome*

627. National Cancer I. Cisplatin With or Without Veliparib in Treating Patients With Recurrent or Metastatic Triple-Negative and/or BRCA Mutation-Associated Breast Cancer With or Without Brain Metastases. 2021. *Intervention*

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633. National Cancer I, National Institutes of Health Clinical C. Dose Escalation Trial of Re-irradiation in Good Prognosis Recurrent Glioblastoma. 2020. *Outcome*

634. National Cancer I, National Institutes of Health Clinical C. T-DM1 Alone Versus T-DM1 and Metronomic Temozolomide in Secondary Prevention of HER2-Positive Breast Cancer Brain Metastases Following Stereotactic Radiosurgery. 2022. *Outcome*

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638. National Cancer I, National Institutes of Health Clinical C. A Pilot Study of 1H-Nuclear Magnetic Resonance Spectroscopic Imaging in Pediatric Patients With Primary and Metastatic Brain Tumors. May 6, 2019. *Intervention*

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640. National Cancer I, Radiation Therapy Oncology G, Oncology NRG. Dasatinib in Treating Patients With Recurrent Glioblastoma Multiforme or Gliosarcoma. 2011. *Population*

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645. National Institute of C. Gene-expression Profiles in CNS-metastatic Non-small Cell Lung Cancer. 2012. *Intervention*

646. National Institute of Neurological D, Stroke, National Institutes of Health Clinical C. Surgery Versus Radiosurgery to Treat Metastatic Brain Tumors. *Outcome*

647. National Institute of Neurological D, Stroke, National Institutes of Health Clinical C. Gene Therapy for the Treatment of Brain Tumors. 2010. *Intervention*

648. National Institute of Neurological D, Stroke, National Institutes of Health Clinical C. Cytokine Microdialysis for Real-Time Immune Monitoring in Glioblastoma Patients Undergoing Checkpoint Blockade. 2021. *Outcome*

649. National Institute of Neurological D, Stroke, National Institutes of Health Clinical C. Detecting Malignant Brain Tumor Cells in the Bloodstream During Surgery to Remove the Tumor. January 2005. *Intervention*

650. National Institute of Neurological D, Stroke, National Institutes of Health Clinical C. OGT 918-006: A Phase I/II Randomized, Controlled Study of OGT 918 in Patients With Neuronopathic Gaucher Disease. March 21, 2007. *Population*

651. National Institute of Neurological D, Stroke, National Institutes of Health Clinical C. Direct Injection of Alcohol for the Treatment of Spinal Tumors. May 2002. *Outcome*

652. National Institutes of Health Clinical C. Stereotactic Radiosurgery in Treating Patients With Brain Tumors. May 2002. *Outcome*

653. National Institutes of Health Clinical C, National Cancer I. Conformal Radiation Therapy in Treating Patients With Metastatic Cancer Outside the Brain. 2010. *Population*

654. National Taiwan University H. Vorinostat and Concurrent Whole Brain Radiotherapy for Brain Metastasis. 2013. *Outcome*

655. National Taiwan University H. Fractionated Stereotactic Radiosurgery With Concurrent Bevacizumab for Brain Metastases: A Phase I Dose-escalation Trial. 2018. *Outcome*

656. National Taiwan University H. Bevacizumab, Etoposide and Cisplatin Followed by Whole Brain Radiotherapy in Breast Cancer With Brain Metastases. 2019. *Outcome*

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958. University Hospital T. FluoroAv45 Imaging Research-in Alzheimer's Disease. 2011. *Intervention*

959. University Hospital T. Evaluation of Safety and Efficacy of Patients With Four and More Symptomatic Brain Metastases of Melanoma. 2021. *Outcome*

960. University Hospital T. Effects of Closed-loop Automatic Control of FiO2 in Extremely Preterm Infants. 2022. *Outcome*

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981. University of California I. A Pilot Study of Irinotecan in Patients With Breast Cancer and CNS Metastases. 2017. *Outcome*

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986. University of California SF, National Cancer I. Irinotecan and Temozolomide in Treating Patients With Breast Cancer Who Have Received Previous Treatment for Brain Metastases. 2013. *Intervention*

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988. University of California SF, North American Gamma Knife C. A Single Arm Study of Neurocognitive Outcomes in Patients With Brain Metastases Managed With Stereotactic Radiosurgery (SRS). 2015. *Outcome*

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990. University of Colorado D, Children's Hospital C. Gemcitabine in Newly-Diagnosed Diffuse Intrinsic Pontine Glioma. 2019. *Outcome*

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995. University of F. Proton Therapy for Lymph Nodes in Breast Cancer. 2014. *Population*

996. University of F, Florida Academic Cancer Center A. Imaging the Patterns of Breast Cancer Early Metastases. 2018. *Intervention*

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999. University of L. Study of Intraoperative Radiotherapy for Patients With Large Brain Metastases Treated With Neurosurgical Resection. 2029. *Outcome*

1000. University of L, Biomedical Research Centre R, Leicester Clinical Trials U, et al. Anti-ST2 (MSTT1041A) in COPD (COPD-ST2OP). 2020. *Population*

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1005. University of Michigan Rogel Cancer C. MRI Study of Radiation-Induced Damage to White Matter and Blood-Brain-Barrier. 2014. *Intervention*

1006. University of Minnesota C, Translational Science I. Zoledronic Acid in Preventing Osteoporosis in Patients Undergoing Donor Stem Cell Transplant. 2011. *Population*

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1008. University of P. Pre-operative Stereotactic Radiosurgery Followed by Resection for Brain Metastases. 2019. *Outcome*

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Appendix C. Results

This appendix provides additional information on the included studies. Note: The references in this appendix can be found in the list at the end of the main report

Results of Literature Searches

The literature search identified 9,265 citations across all sources. Of these, 1,520 were obtained as full text. We identified 97 studies reported in 190 citations that met inclusion criteria.

Description of Included Studies

The included studies were published between 1991 and 2020. All studies reported on data collected using radiation therapy methods from 1990 or later to capture evidence that is relevant to today's standard of care. Given that the included studies spanned a period of 30 years, we used meta-regressions to determine whether the reported effect sizes in newer studies tended to be larger than in older studies (because treatment effectiveness may have generally improved). We did not detect effects for all key outcomes that reported sufficient data (overall survival p=0.90, disease-free survival p=0.52, deaths due to brain metastases p=0.83, intracranial progression p=0.38, quality of life p=o.31, serious adverse events p=0.45, adverse events p=0.91, radiation necrosis p=0.71, headaches p= 0.95, fatigue p=0.91, seizure p=0.93, vomiting p=0.44). Hence, we did not pursue subgroup analyses for newer publications.

Half of the included studies had a unique trial identifier (the link to the study details can be found in the evidence table in Appendix D). A third of the included studies was based in the USA. The other studies were conducted in Australia, Austria, Canada, China, Egypt, France, Germany, Greece, India, Iran, Italy, Japan, Mexico, Netherlands, Poland, South Korea, Spain, Switzerland, Taiwan, and the UK. Six studies combined data from different countries. The large majority of studies (n=75) were RCTs, the remaining ones were cohort studies comparing two intervention cohorts. Study size varied from four participants included in an RCT that was closed early[158] to 3,536 participants included in a cohort study.[98]

Most identified studies reported on WBRT as initial treatment and were relevant to Key Question 1. Twenty-four studies were relevant to Key Question 2. Only a dozen studies reported on post-surgery interventions (Key Question 3). With few exceptions, most studies contributed to Key Question 4 and reported on the presence or absence of at least one adverse event.

More than half of the included studies recruited patients with different primary tumor types, followed by studies in lung cancer patients, patients with melanoma, and patients with breast cancer. Similarly, the large majority of studies included patients with a range of prognoses. The number and volume of metastases was rarely described (see Appendix D).

Risk of Bias

The methodological quality of studies varied widely. Twenty-eight randomized studies reported adequate random sequence generation methods, with eighteen of them also describing allocation concealment. Seven studies state that a central office carried out the randomization, but did not provide the actual methods for randomization.[102, 120, 131, 133, 141, 148, 163] Another thirty-five studies were described as randomized without further details. Twenty-four studies were classified as high risk of selection bias because they were not randomized. Three randomized studies were determined to have high risk of selection bias for our review.[78, 89, 114] One study

randomly assigned patients to treatment but compared outcomes to a historical group in their primary analyses, one randomized metastatic lesions but not the patients, and one did not report the randomization method and the treatment groups had important differences in baseline characteristics that could affect outcome.

Seven studies were described as double-blinded,[82, 85, 100, 102, 120, 149, 168] although only two of those studies adequately reported their methods of blinding.[102, 168] An additional study designated itself as single-blinded, but blinded both patients and examiners.[166] Patients were not blinded in 65 randomized studies, and therefore these studies had an unclear or moderate risk of performance bias. While not blinding participants probably did not affect the reliable determination of survival, it could have affected other outcomes such as neurocognitive endpoints and quality of life. Twenty-three studies were non-randomized observational studies, and therefore had higher risk of performance bias. One study was a non-randomized phase I study and therefor had higher risk of performance bias for the primary endpoints.[135]

Thirty-four studies adequately reported attrition with no significant differences between treatment arms. Fifty-seven studies had moderate or unclear risk of attrition bias, mostly because attrition was unclear for some endpoints. Six studies had high risk of attrition bias, as they had significant attrition and/or attrition differed between treatment groups.[81, 84, 94, 103, 105, 129]

Twenty studies had low risk of detection bias. In addition to the previously discussed double-blinded studies, twelve studies blinded the radiologists or neuropsychologists, or had a blinded review committee making assessments.[76, 79-81, 84, 96, 107, 124, 127, 128, 155, 161] While the studies might be at risk for detection bias for some of their endpoints, we separated these studies from the remaining 53 without any blinding that were at moderate or unclear risk of detection bias. Twenty-three studies were non-randomized observational studies and were considered at higher risk of detection bias. A non-randomized phase I study was also determined to be at higher risk of detection bias.[135]

Sixteen studies had low risk of reporting bias, with ten of these studies having their protocol readily available online or in a previous publication.[10, 78-81, 106, 111, 115, 124, 164] In fifty-six studies the risk for reporting bias was unclear, mostly because the language that described which analyses were planned was not explicit, especially with subgroup and multivariable analyses. Twenty-five studies had high risk of reporting bias. Of those studies, 23 were observational studies. One randomized study did not report survival data and reported only significant results from their analyses.[107] Another randomized study did not report results from all of the outcomes collected and qualitatively reported some results.[103]

Twenty-seven randomized studies analyzed their data by intent-to-treat and did not close early. Seventeen randomized studies had unclear risk of other biases, mostly because details were missing. Fifty-three studies had high risk of other biases. Of the interventional studies with high risk of bias, 25 were terminated early, either because of results during interim analyses or because of poor participant accrual (which was stated as a reason in 17 studies). One study was not analyzed by intent-to-treat[159] and another study's modified intent-to-treat analysis was potentially problematic, as significant differences in exclusion were found between treatment arms.[164]

Fifteen studies used quality of life assessments that were well-validated in brain metastases or brain tumor patients (e.g., FACT-Br, EORTC QLQ-C30 with BN20) or robust neurocognitive tests (e.g., HVLT-R). Forty-four studies did not assess quality of life or neurocognitive function. An additional seven studies collected data but did not completely report outcomes related to these endpoints.[103, 104, 129, 135, 154, 165] The remaining twenty-three studies with moderate rating did

not specify the assessment tool used, used an assessment validated in other disease settings, or used cognitive tests such as the MMSE that are used in the assessment of dementia. Eight studies used performance scales (e.g. ECOG performance scale) with only one measure usually assessed subjectively by a clinician,[76, 97, 101, 122, 136, 147, 156, 160] and are therefore considered more problematic in assessing quality of life or function.

Eleven studies were determined to have low risk of overall bias for effectiveness outcomes.[10, 79, 80, 85, 90, 99, 100, 124, 149, 155, 168] Fifty-three had moderate or unclear risk of bias, with 18 of those studies not having enough details for assessment. The remaining were considered high risk of bias.

Nine studies collected adverse event data systematically and prospectively.[10, 79-81, 90, 97, 111, 116, 135] Sixty prospective studies reported adverse events, but it was unclear how events were collected. Of the studies rated as high risk in their collection of adverse events, 17 did not report adverse events or simply stated that no adverse events occurred. The remaining studies either collected their events retrospectively, or collected only specific events (e.g., radionecrosis or surgical complications). Twenty-nine studies reported adverse events rigorously, including severity and a variety of adverse events by treatment groups. Twenty-three studies reported adverse events for only a limited number of non-hematological events. Of the 45 studies rated as high risk, 17 did not report adverse events. The remaining studies reported adverse events for their whole cohort but not by treatment arm, did not report rates of events, or reported only on specific adverse events (e.g., radionecrosis). Taking into consideration the method of collection and reporting of adverse events, 22 studies were considered relatively low risk, 29 were considered moderate or unclear, and 46 were considered high risk in their adverse event assessment.

Details on Strength of Evidence

We used the criteria outlined in Appendix A to assess the strength of the body of evidence for each Key Question. All findings started at high strength of evidence as the results were mostly based on RCTs. We did not upgrade any findings. Most often we downgraded results due to imprecision, study limitations, or indirect evidence. The reasons for downgrading are included in the summary of findings tables.

Table C-1. Critical appraisal for individual studies

Study	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Other Source of Bias	Other Source of Bias - Scale Validation	Data Collection of Adverse Events	Reporting of Adverse Events	Overall RoB (Health Outcomes)	Overall RoB (Adverse Events)
Andrews, 2004[75]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Antonadou, 2002[76]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Aoyama, 2006[77]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear
Berk, 2007[78]	High risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear
Brown, 2013[82]	Moderate/ Unclear	Low risk	Moderate /Unclear	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Brown, 2016[81]	Low risk	Moderate/ Unclear	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate/ Unclear	Low risk
Brown, 2017[79]	Low risk	Moderate/ Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Brown, 2020[80]	Low risk	Moderate/ Unclear	Moderate /Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cagney, 2019[83]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Cao, 2015[84]	Low risk	Moderate/ Unclear	High risk	Low risk	Low risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Chabot, 2017[85]	Moderate/ Unclear	Low risk	Low risk	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Low risk	Low risk
Chang, 2009[86]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Chatani, 1994[87]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Chen, 2018[88]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Chua, 2010[89]	High risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Davey, 2008[90]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk	High risk	Low risk	High risk
Deng, 2017[91]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Low risk	High risk	Low risk	High risk	Moderate/ Unclear
Dobi, 2020[92]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk

Study	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Other Source of Bias	Other Source of Bias - Scale Validation	Data Collection of Adverse Events	Reporting of Adverse Events	Overall RoB (Health Outcomes)	Overall RoB (Adverse Events)
El Gantery, 2014[93]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
El-Hamamsy, 2016[94]	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Fokas, 2012[95]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Gamboa-Vignolle, 2012[96]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
GlaxoSmithKline 2012[97]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	Low risk	Low risk	Moderate/ Unclear	Low risk
Gonda, 2014[98]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Graham, 2010[99]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear
Gronberg, 2012[100]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate/ Unclear	Low risk	Low risk	Low risk
Guerrieri, 2004[101]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk
Gupta, 2016[102]	Moderate/ Unclear	Low risk	Low risk	Low risk	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Hassler, 2013[103]	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	Low risk
Hauswald, 2019[104]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear
Hoffmann-La Roche, 2011[105]	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	Low risk
Hong, 2019[106]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Hosseini, 2015[107]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Low risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk
Jiang 2016[108]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Jiang, 2014[109]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear

Study	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Other Source of Bias	Other Source of Bias - Scale Validation	Data Collection of Adverse Events	Reporting of Adverse Events	Overall RoB (Health Outcomes)	Overall RoB (Adverse Events)
Johnson, 2016[110]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Kayama, 2018[111]	Low risk	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk
Kepka, 2016[112]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Kim, 2005[113]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Knisely, 2008[115]	Low risk	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Low risk	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Kirkpatrick, 2015[114]	High risk	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Kocher, 2011[116]	Low risk	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Low risk	Low risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Kondziolka , 1999[117]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Lanier, 2019[118]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Lee, 2008[119]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Lee, 2014[120]	Moderate/ Unclear	Low risk	Moderate /Unclear	Low risk	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Lim, 2015[121]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk
Liu, 2017[122]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear
Magnuson, 2017[123]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Mahajan, 2017[124]	Low risk	Moderate/ Unclear	Low risk	Low risk	Low risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Low risk	High risk
Martin, 2018[125]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
McPherson , 2010[126]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Mehta, 2003[127]	Low risk	Moderate/ Unclear	Moderate /Unclear	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Mehta, 2009[128]	Low risk	Moderate/ Unclear	Moderate /Unclear	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk

Study	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Other Source of Bias	Other Source of Bias - Scale Validation	Data Collection of Adverse Events	Reporting of Adverse Events	Overall RoB (Health Outcomes)	Overall RoB (Adverse Events)
Merck Sharp & Dohme Corp, 2008[129]	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	Low risk
Minniti, 2016[130]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Mintz, 1996[131]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk
Mornex, 2003[132]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Muacevic, 2008[133]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear
Mulvenna, 2016[10]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk	Low risk	Low risk	Low risk
Murray, 1997[134]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
National Cancer Institute 2011[135]	High risk	High risk	Moderate /Unclear	High risk	Moderate/ Unclear	High risk	Moderate/ Unclear	Low risk	Low risk	High risk	Low risk
Noordijk, 1994[136]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Pesce, 2012[137]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Phillips, 1995[138]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Pirzkall, 1998[139]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Prabhu, 2017[140]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Priestman, 1996[141]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Quantin, 2010[142]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Rades, 2007[143]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Rades, 2017[144]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk

Study	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Other Source of Bias	Other Source of Bias - Scale Validation	Data Collection of Adverse Events	Reporting of Adverse Events	Overall RoB (Health Outcomes)	Overall RoB (Adverse Events)
Raman, 2020[145]	Low risk	High risk	Low risk	Moderate/ Unclear	High risk	Low risk	Low risk	High risk	High risk	Moderate/ Unclear	High risk
Rauschenberg, 2019[146]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	High risk
Regine, 2004[147]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	High risk	High risk	Moderate/ Unclear	High risk
Robinet, 2001[148]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear
Rojas-Puentes, 2013[149]	Low risk	Low risk	Moderate /Unclear	Low risk	Low risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Low risk	Low risk
Roos, 2006[151]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk	High risk	Low risk	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Roos, 2011[150]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk
Saha, 2014[152]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Sneed, 2002[153]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Sperduto, 2013[154]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Suh, 2006[155]	Low risk	Moderate/ Unclear	Low risk	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear
Suh, 2008[156]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Tetu, 2019[157]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	Low risk	High risk	Moderate/ Unclear
University of Michigan, 2016 [158]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	Moderate/ Unclear
Ushio, 1991[159]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk
Vecht, 1993[160]	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Verger, 2005[161]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Low risk	Moderate/ Unclear	High risk	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear

Study	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias	Other Source of Bias	Other Source of Bias - Scale Validation	Data Collection of Adverse Events	Reporting of Adverse Events	Overall RoB (Health Outcomes)	Overall RoB (Adverse Events)
Wang, 2015[162]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk
Wolfson, 1994[163]	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk
Yang, 2017[164]	Low risk	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Low risk	High risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Moderate/ Unclear	Low risk
Yang, 2017[165]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear
Yang, 2018[167]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk
Yang, 2019[166]	Moderate/ Unclear	Low risk	Moderate /Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	High risk	High risk	Moderate/ Unclear	High risk
Zeng, 2016[168]	Low risk	Low risk	Low risk	Low risk	Moderate/ Unclear	Low risk	Moderate/ Unclear	Moderate/ Unclear	Low risk	Low risk	Low risk
Zhu, 2018[169]	Moderate/ Unclear	Moderate/ Unclear	Moderate /Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	Moderate/ Unclear	High risk	High risk	Moderate/ Unclear	High risk
Zhuang, 2020[170]	High risk	High risk	Moderate /Unclear	High risk	High risk	High risk	Moderate/ Unclear	High risk	High risk	High risk	High risk

Appendix D. Evidence Table

Table D-1. Evidence table

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Andrews, 2004[75] Sperduto, 2014[251]; Group Radiation Therapy Oncology, 2002[236] NCT00002708 RCT Power calculation: Yes USA Non industry Journal article N: 333	Age: WBRT+stereotactic: 34% > 65, WBRT alone: 40% > 65 Gender: WBRT+stereotactic surgery : 48% female and WBRT alone: 47% Primary tumor type: Different cancer types; 78% lung, breast or melanoma Metastases: Number: 1.56 [mean] Volume: n/a Size: unclear (<= 4cm) Prognosis: good to moderate	WBRT + SRS WBRT: 3750 cGy, 15 fractions, qd. SRS: 1500-2400 cGy, 1 fraction WBRT 3750 cGy, 15 fractions, qd	Intervention: 164 randomized, 164 analyzed Comparator: 167 randomized, 167 analyzed Followup: 7 [median] months	Intervention vs Comparator: Mean survival time HR 1.14; CI (0.74, 1.75) Brain metastases cause of death RR 0.86; CI (0.6, 1.25) Karnofsky Performance Status at 6 months A significant improvement in KPS was noted in the WBRT + SRS group Mental status at 6 months No difference in mental status between groups	Intervention vs Comparator: Grade 4 acute toxicities RR 2.04; CI (0.07, 60.29) Number of events (acute toxicities) Late toxicities WBRT+SRS: 40; WBRT alone: 32 Acute vomiting RR 1.14; CI (0.7, 1.87) Late - WBRT+SRS: 5, WBRT alone: 3

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Antonadou, 2002[76] Antonadou, 2003[175] N/A RCT Power calculation: Not relevant outcome Greece Unclear funding source Journal article N: 52	Age: WBRT + temozolomide: 61 [median], WBRT: 62 [median] Gender: 27% female Primary tumor type: Different cancer types; 72% lung or breast Metastases: Number: WBRT + temozolomide: 76% have multiple metastases, WBRT: 30% have multiple metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + temozolomide 4000 cGy, 20 fractions, qd Temozolomide 75 mg/m2 /d during radiation treatment and 200 mg/m2/d for 5 days every 28 days after treatment for 6 cycles; corticosteroids at the lowest dose necessary to maintain neurologic stability WBRT 4000 cGy, 20 fractions, qd Corticosteroids at the lowest dose necessary to maintain neurologic stability	Intervention: 26 randomized, 25 analyzed Comparator: 26 randomized, 23 analyzed Followup: 4 [median] months	Intervention vs Comparator: Overall survival HR 0.81; CI (0.14, 4.87) Survival: 8.6 vs 7.0 months Neurological deaths RR 0.61; CI (0.11, 3.35) Progressive disease 0/24 vs 2/21 with progressive disease Neurologic functional status (level I, fully functional; level II, fully functional not able to work; level III, stays in bed and needs help half the time; level IV, requires help all the time) In WBRT + TMZ, the proportion of patients with level I and II status increased from 80% to 92%, the proportion of patients with level III status decreased from 20% to 8%; in WBRT group, the proportion of patients with level I and II status increased from 74% to 81%, whereas the proportion of patients with level III status decreased from 26% to 19% Objective response rate The objective response rate was significantly higher in WBRT + temozolomide than in WBRT alone	Intervention vs Comparator: Number of events (grade 2 and above nonhematologic adverse events) 39 vs 16 Fatigue RR 1.18; CI (0.53, 2.66) Vomiting RR 14.72; CI (0.89, 242.17) Grade 2 and above nausea was significantly increased in WBRT + temozolomide, compared to WBRT. Headache RR 1.53; CI (0.66, 3.55)

Aoyama, 2006[77] Aoyama, 2007[176]; Aoyama, 2015[177] (JROSG 99-1); Japanese Radiation Oncology Study Group[208]; Hokkaido University[202] C000000412 RCT Power calculation: Yes Japan Non industry Journal article N: 132	Age: WBRT+ SRS: 62.5 [mean], SRS: 62.1 [mean] Gender: WBRT+ SRS: 29% female and SRS: 21% Primary tumor type: Different cancer types; 73% lung or breast Metastases: Number: 1-4 brain metastases (mean not stated) Volume: N/A Size: WBRT+ SRS: 1.53(0.78) and SRS: 1.42(0.79) Prognosis: mixed good to moderate prognosis	WBRT + SRS WBRT: 3000 cGy, 10 fractions, qd, SRS: 1260 cGy to 1750 cGy, 1 fraction SRS metastases 2 cm or smaller: 2200 to 2500 cGy in 1 fraction, and larger than 2 cm were treated with 1800 to 2000 cGy in 1 fraction	Intervention: 65 randomized, 65 analyzed Comparator: 67 randomized, 67 analyzed Followup: 8 [median] months	Intervention vs Comparator: Overall survival HR 1.37; CI (0.94, 2) Median survival time and 1-year actuarial survival rate were 7.5 months and 38.5% (CI 26.7%-50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (CI 17.6%-39.2%) for SRS alone (P = .42). Deaths due to neurologic causes RR 1.19; CI (0.61, 2.3) Brain tumor recurrence at either distant or local sites in the brain 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group (P<.001) Systemic functional preservation rates (KPS score >=70) at 12 months No significant difference in systemic functional preservation rates at 12 months between groups. MMSE No significantly difference in improvement or deterioration was found post treatment between the groups. Time to deterioration was marginally different between the two groups favoring the combination group (13.6 vs. 6.8 months, p=0.05) 1-year actuarial survival rate; 12-month brain tumor recurrence rate; Salvage brain treatment	Intervention vs Comparator: Grade 4 neurotoxic effects based on Common Toxicity Criteria version 2.0 RR 1.03; CI (0.15, 7.1) Acute and late toxicity, radiological leukoencephalopathy 18 vs 13 Radiation necrosis RR 3.09; CI (0.33, 28.97) Lethargy RR 2.06; CI (0.07, 60.4) Seizure from both acute and late toxicity RR 0.21; CI (0.02, 1.72)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
				The 1-year actuarial survival rate were not significantly different between groups (38.5% vs. 28.4%). The 12-month brain tumor recurrence rate was significantly lower in the WBRT + SRS group than in the SRS alone group (46.8% vs.76.4%). Salvage brain treatment was significantly less frequent in the WBRT + SRS group than with SRS alone (n = 10 vs. 29)	
Berk, 2007[78] Radiation Therapy Oncology Group[237] NCT00031967 RCT Power calculation: No USA Non industry Journal article N: 126	Age: Intervention: 52% <65, control: 60% <65 Gender: Intervention: 45% female, control: 52% female Primary tumor type: Different cancer types; 83% lung, breast, melanoma Metastases: Number: NA Volume: NA Size: NA Prognosis: Recursive partitioning analysis class 2	WBRT + melatonin 3000 cGy in 10 fractions 20mg melatonin in the evening WBRT 3000 cGy in 10 fractions to the whole brain 20 mg melatonin in the morning (should have no effect)	Intervention: randomized, 62 analyzed Comparator: randomized, 64 analyzed Followup: 29 [median] (survivors) months	Intervention vs Comparator: Overall survival time Median survivals of the morning and evening melatonin treatments were 3.4 and 2.8 months Mini-Mental State Examination (MMSE) Control: 55% new MMSE failures, intervention: 57% new MMSE failures	Intervention vs Comparator: Fatigue RR 0.7; CI (0.42, 1.17) Vomiting RR 2.06; CI (0.65, 6.51) Headaches RR 1.03; CI (0.38, 2.77) Other AE Allergy (1 event in control group), auditory (4 intervention), blood/bone marrow (1 control), dermatology/skin (control 17, intervention 12), infection / febrile neutropenia (1 control), muscolosketal (1 intervention), neurology (control 22, intervention 10), ocular (control 3, intervention 1)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Brown, 2013[82] Laack, 2019[214]; Radiation Therapy Oncology Group[238] NCT00566852 RCT Power calculation: Underpowered USA Non industry Journal article N: 508	Age: WBRT + Memantine: 60 [median] and WBRT + Placebo: 59 [median] Gender: 56% female Primary tumor type: Different cancer types; 85% lung or breast Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: 44% RPA class 1, 55% RPA class 2 (majority moderate to good prognosis)	WBRT + memantine 3750 cGy, 15 fractions, qd Memantine 20 mg/day WBRT + placebo 3750 cGy, 15 fractions, qd	Intervention: 278 randomized, 256 analyzed Comparator: 276 randomized, 252 analyzed Followup: 12 [median] months	Intervention vs Comparator: Overall survival HR 1.06; CI (0.86, 1.31) Progression-free survival HR 1.06; CI (0.86, 1.3) HVLT-R for Delayed Recall (HVLT-R DR) There was less decline in HVLT-R DR in the Memantine arm (median decline of 0) compared with the placebo arm (median decline of -0.90) at 24 weeks, but the difference did not reach statistical significance. The memantine arm had a significantly longer time to cognitive decline (HR 0.78, 95% CI 0.62-0.99). Significantly superior results were seen in the memantine arm for executive function at 8 and 16 weeks and for processing speed and delayed recognition at 24 weeks	Intervention vs Comparator: Grade 5 RR 1.64; CI (0.4, 6.79) Number of patients (Grade 3/4 events) RR 1; CI (0.76, 1.32)

Brown, 2016[81] Churilla 2017[184]; Oncology Alliance for Clinical Trials, 2014[173] NCT00377156 RCT Power calculation: Yes USA Non industry Journal article N: 213	Age: SRS + WBRT: 61.4 (10.6), SRS: 59.8 (10.4) Gender: 48% female Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: SRS + WBRT: 54.9% have one brain metastases and SRS alone: 49.5% had one metastases Volume: N/A Size: N/A Prognosis: majority good to moderate prognosis	SRS + WBRT SRS: 1800-2200 cGy, 1 fraction, WBRT: 3000 cGy, 12 fractions, qd SRS 2000-2400 cGy, 1 fraction	Intervention: 102 randomized, 102 analyzed Comparator: 111 randomized, 111 analyzed Followup: 7 [median] months	Intervention vs Comparator: Time from randomization until death due to any cause HR 1.02; CI (0.75, 1.38) Time to intracranial failure Time to intracranial failure was significantly shorter for SRS alone compared with SRS plus WBRT (HR, 3.6; 95% CI, 2.2-5.9; P < .001) Functional Assessment of Cancer Therapy-Brain SMD -0.07; CI (-0.34, 0.2) SRS vs SRS+WBRT mean change from baseline, _1.3 vs _10.9; mean difference,9.6 points, CI 3.6-15.6 points (p=.002) Barthel Index of Activities of Daily Living SMD -0.07; CI (-0.34, 0.2) SRS vs SRS+WBRT mean change from baseline 0.4 vs _21.9; mean difference, 21.5; 95% CI, 4.6-38.4; p=.03 Percent of patients with cognitive deterioration A decline of >1 SD on at least 1/7 cognitive tests was less frequent after SRS alone than after SRS+WBRT (63.5% vs 91.7%; difference, _28.2%; 90% CI, _41.9, _14.4%; p<.001); HLVT-R Immediate Recall: SRS vs SRS+WBRT MD 0.8; CI 0.3, 1.3; HVLT-R Delayed Recall: SRS vs SRS+WBRT MD 1.2; CI 0.6, 1.8; TMT-B: SRS vs SRS+WBRT MD 0.6; CI -2.1, 0.9; COWAT: SRS vs SRS+WBRT MD 0.3; CI 0, 0.6)	Intervention vs Comparator: Number of grade 5 events RR 1.09; CI (0.07, 17.17) Number of participants with adverse events RR 1.04; CI (0.76, 1.42) Number of events (Grade 3-5): 153 vs 129 Pathologic confirmation of necrosis on surgically resected lesions consistent with treatment effect in lesions previously treated by radiosurgery RR 0.65; CI (0.16, 2.66) Fatigue RR 0.73; CI (0.21, 2.5) Seizure RR 0.44; CI (0.09, 2.19) Vomiting RR 2.18; CI (0.41, 11.63) Headaches RR 0.18; CI (0.02, 1.48)

Brown, 2017[79] Trifiletti, 2019[258]; Brown, 2017[174]; Roberge, 2017[241]; Trifiletti, 2020[259] NCT01372774, NCCTG N107C/CEC 3) RCT Power calculation: Yes Multinational USA and Canada Non industry Journal article N: 194	Age: SRS: 61 [median], WBRT: 62 [median] Gender: SRS: 53% female, WBRT: 48% female Primary tumor type: Different cancer types; 59% lung, other types not broken down Metastases: Number: SRS: 77% have one metastases and WBRT: 77% have one metastases Volume: N/A Size: N/A Prognosis: mixed	Surgery + SRS 1200-2000 cGy, 1 fraction One resected brain metastasis, resection cavity <5.0 cm Surgery + WBRT 3000 cGy, 10 fractions, qd OR 3750 cGy, 15 fractions, qd One resected brain metastasis, resection cavity <5.0 cm	Intervention: 98 randomized, 93 analyzed Comparator: 96 randomized, 92 analyzed Followup: 11 [median] months	Intervention vs Comparator: Overall survival HR 1.07; CI (0.76, 1.5) Time from randomization to recurrence in the local surgical bed, progression of unresected metastases, distant brain recurrence, or development of leptomeningeal disease HR 2.45; CI (1.61, 3.72) Change from baseline to 6 months in Functional Assessment of Cancer Therapy - Brain (FACT-Br) and LASA (linear analogue self-assessment) for quality of life Clinically significant improvement more frequent in the SRS group compared with WBRT for physical well being; no significant differences between treatment groups in social, emotional, or functional wellbeing, brain-specific concerns, or overall FACT-Br Barthel ADL index Functional independence at 3 months was higher after SRS than after WBRT; At 6 months, no significant difference between groups was noted Time from randomization to a drop of greater than 1 SD from baseline in at least one of the six cognitive tests SMD -0.82; CI (-1.11, -0.53) Cognitive deterioration at 6 months was significantly less frequent in patients who received SRS than those who received WBRT (52% vs 85% of evaluable patients). Median cognitive-deterioration-free	Intervention vs Comparator: Serious adverse events FDA definition RR 1.34; CI (0.72, 2.51) Number of events (individual toxicities of any grade) The most common grade 3 or 4 adverse events reported were hearing impairment (3% vs. 9%) and cognitive disturbance (3% vs. 5%). CNS radiation necrosis RR 11.87; CI (0.67, 209.49) Fatigue RR 0.19; CI (0.07, 0.53) Seizure RR 1.32; CI (0.3, 5.73) Vomiting RR 0.02; CI (0, 0.37) Headaches RR 3.96; CI (0.18, 86.58) Leptomeningeal disease No difference in the development of leptomeningeal disease between treatment groups

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
				survival was longer after SRS to the surgical cavity than after WBRT (HR 0ß47 [95% CI 0ß35-0ß64], p<0ß0001); overall outcome for cognitive deterioration MD -33.6 (95%CI -45.3 to -21.8)	
Brown, 2020[80] Gondi, 2019[198]; National Cancer Institute, 2018[228]; Gondi, 2018[197]; Armstrong, 2019[178] NCT02360215 RCT Power calculation: Yes USA Non industry Journal article N: 518	Age: Median 61.5 Gender: 58% female Primary tumor type: Different cancer types; details not published Metastases: Number: WBRT Plus Memantine (38.1%) HA-WBRT Plus Memantine (37.5%) Volume: N/A Size: N/A Prognosis: mostly moderate	Hippocampal-sparing WBRT + Memantine 3000 cGy, 10 fractions, qd Memantine scaled up to 10mg bid or 28mg qd for extended release formulation WBRT + Memantine 3000 cGy, 10 fractions, qd Memantine scaled up to 10mg bid or 28mg qd for extended release formulation	Intervention: 261 randomized, 261 analyzed Comparator: 257 randomized, 257 analyzed Followup: 8 [median] (survivors) months	Intervention vs Comparator: Survival HR 1.13; CI (0.19, 6.59) Intracraninal progression-free survival HR 1.14; CI (0.92, 1.41) EQ-5D-5L No differences were seen between arms at baseline or over time for the EQ-5D-5L Time to cognitive failure HR 0.76; 95% CI, 0.60-0.98; P = .03 in favor of HA-WBRT + Memantine. At 6 months, HA-WBRT + Memantine reported significantly less difficulty with remembering things (P = .01), and less difficulty with speaking (P = .049). The HA-WBRT + memantine arm experienced significantly less symptom interference and fewer cognitive symptoms at 6 months. HA-WBRT+M was associated with lower risk of NCF failure (adjusted HR=0.739, 95% CI: 0.577-0.945, p=0.0.016), with differences first noted at 4 mos in Trail Making Test Part-B (23.3% vs. 40.4% deteriorated, p=0.012 (from abstract (from ref ID 9273).	Intervention vs Comparator: Serious adverse events RR 0.91; CI (0.74, 1.13) Toxicities No difference between arms in toxicity Fatigue RR 1.08; CI (0.93, 1.25) Seizure RR 1.75; CI (0.79, 3.89) Vomiting (mild) RR 1.25; CI (0.82, 1.89) Headache (not serious) RR 1.17; CI (0.93, 1.48)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Cagney, 2019[83] N/A Cohort Power calculation: No USA Non industry Journal article N: 1188	Age: surgery: 58.9 (11.5), radiation: 58.9 (12.1) Gender: 59% female Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: surgery: 1 (median), radiation: 2 (median) Volume: N/A Size: N/A Prognosis: mixed	Surgery + SRS 2500-3000 cGy, 5 fractions Resection of at least 1 brain metastasis Radiation (no details) details not provided	Intervention: 318 randomized, 318 analyzed Comparator: 870 randomized, 870 analyzed Followup: 29 [median] (survivors) months	Not reported	Intervention vs Comparator: Leptomeningeal disease; pachymeningeal seeding No significant difference in development of leptomeningeal disease between groups (HR 1.14; 95% CI, 0.73-1.77). Resection was significantly associated with pachymeningeal seeding.
Cao, 2015[84] Curie Institut, 2009[204] NCT00875355 RCT Power calculation: No France Non industry Journal article N: 100	Age: 55 [median] 29-79 [range] Gender: 100% female Primary tumor type: Breast cancer only; Metastases: Number: WBRT: 4.6 and WBRT + temozolomide: 3.6 Volume: N/A Size: N/A Prognosis: mixed	WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m(2)/day WBRT 3000 cGy, 10 fractions, qd	Intervention: 50 randomized, 50 analyzed Comparator: 50 randomized, 50 analyzed Additional comparator: randomized, analyzed Followup: 9 [median] months	Intervention vs Comparator: Time from date of diagnosis of BM to the date of death resulting from any cause HR 1.18; CI (0.32, 4.29) In the intervention, median overall survival was 9.4 months, in the comparator 11.1 months. Progression-free survival HR 1.1; CI (0.46, 2.65) Death due to tumor progression RR 3.33; CI (0.98, 11.4) Progressive disease Objective remission rate The objective remission rates at 6 weeks were not significantly different between groups	Intervention vs Comparator: Grade 4 adverse events RR 0.33; CI (0.04, 3.1) Any adverse event grade 2 or above 74 vs 55 Vomiting (any grade) RR 2; CI (0.64, 6.22) Headaches RR 0.56; CI (0.2, 1.54)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Chabot, 2017[85] AbbVie, 2015[171] NCT01657799 RCT Power calculation: No USA Industry funded Journal article N: 307	Age: Placebo+WBRT: 60 [median], Veliparib 50 mg+WBRT: 60 [median], and Veliparib 200 mg+WBRT: 62 [median] Gender: Placebo+WBRT: 45% female, Veliparib 50 mg+WBRT: 41% female, Veliparib 200 mg+WBRT : 35% Primary tumor type: Lung cancer only; Metastases: Number: unclear (majority had >3) Volume: N/A Size: N/A Prognosis: mixed	WBRT + Veliparib 3000 cGy, 10 fractions, qd Veliparib 200mg bid WBRT + Placebo 3000 cGy, 10 fractions, qd Placebo WBRT+ Veliparib 50mg 3000 cGy, 10 fractions, qd Veliparib 50mg bid	Intervention: 102 randomized, 102 analyzed Comparator: 102 randomized, 102 analyzed Additional comparator: 103 randomized, 103 analyzed Followup: 36 months	Intervention vs Comparator: Median overall survival HR 0.99; CI (0.71, 1.36) Radiographic progression found in either target lesions or new lesions Intracranial response rate; time to clinical or radiographic progression No significant differences in intracranial response rate and time to clinical or radiographic progression between any of the treatment arms were noted. Intervention vs additional comparison: Median overall survival HR 0.97; CI (0.7, 1.33)	Intervention vs Comparator: Serious adverse events, FDA definition RR 0.92; CI (0.64, 1.32) Any adverse event 90 vs 91 Fatigue RR 0.95; CI (0.56, 1.62) Convulsion RR 0.17; CI (0.01, 3.29) Vomiting RR 0.73; CI (0.35, 1.52) Headaches RR 1.4; CI (0.77, 2.56) Intervention vs additional comparison: Serious adverse events, FDA definition RR 1.17; CI (0.79, 1.74) Fatigue RR 0.79; CI (0.48, 1.3) Convulsion RR 1.01; CI (0.02, 50.41) Vomiting RR 2.22; CI (0.8, 6.17) Headaches RR 1.18; CI (0.67, 2.08)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Chang, 2009[86] Lal, 2012[215]; Marko, 2010[219]; Anderson Cancer Center, 2019[180] NCT00548756 RCT Power calculation: Yes USA Non industry Journal article N: 58	Age: SRS 63 [median], SRS + WBRT: 64 [median] Gender: SRS: 60% female; SRS + WBRT: 39% female Primary tumor type: Different cancer types; 81% lung, breast or melanoma Metastases: Number: 1.6 [median] (1-3) [range] Volume: SRS alone: median 1.4 cm3 (SD 4.6), SRS+WBRT: median 2.3 cm3 (SD 6.3) Size: N/A Prognosis: mixed good to moderate (17.2% RPA class 1, 82.8% RPA class 2)	SRS + WBRT WBRT: 3000 cGy, 12 fractions, qd. SRS: 1500-2400 cGy, 1 fraction SRS SRS: 1500-2400 cGy in 1 fraction	Intervention: 28 randomized, 28 analyzed Comparator: 30 randomized, 30 analyzed Followup: 10 [median] months	Intervention vs Comparator: Median survival HR 0.38; CI (0.14, 1.03) Median and 1-year survival was higher for the SRS alone group than for patients in the SRS plus WBRT group (15.2 vs 5.7 months, 63% vs 21%; p=0ß003) Neurological deaths RR 0.94; CI (0.39, 2.25) Symptomatic intracranial progression At 1 year, 73% of combination and 27% of SRS patients were free from CNS recurrence Functional Assessment of Cancer Therapy-Brain (FACT-BR) at 4 months SMD 0.08; CI (-0.44, 0.6) Difference between groups at 4 months was inconclusive (mean difference 2.8; 95% CI -26 to 21; p=.76). Significant deterioration (a drop of at least 5 points from baseline) in Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months Mean posterior probability of decline was 52% for the SRS+WBRT group and 24% for the SRS alone group One-year CNS recurrence rate Significant more patients in the SRS+WBRT group were free from CNS recurrence at 1 year than those in the SRS group (73% vs. 27%)	Intervention vs Comparator: Grade 4 toxicity RR 0.54; CI (0.02, 15.35) Grade 3/4 toxicity 1 vs 3 Pathologically proven radiation necrosis RR 0.27; CI (0.01, 5.69)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Chatani, 1994[87] Chatani 1989[183]; Chatani, 1994[182] N/A RCT Power calculation: No Japan Unclear funding source Journal article N: 162	Age: 51% >60 years Gender: 23% female Primary tumor type: Different cancer types; 64% lung (nsclc) Metastases: Number: 65% had multiple metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT 50 Gy 5000 cGy, 20 fractions, qd WBRT 30 Gy 3000 cGy, 10 fractions, qd WBRT 20 Gy 2000 cGy, 5 fractions, qd	Intervention: 46 randomized, 46 analyzed Comparator: 46 randomized, 46 analyzed Additional comparator: 35 randomized, analyzed Followup: 5 [median] months	Intervention vs Comparator: Survival time One-year survival rates were 17% in WBRT 50Gy and 21% in WBRT 30Gy. Neurologic function Improvement in neurologic function appeared to increase with total dosage, 41% in WBRT 50Gy vs. 45% in WBRT 30Gy	Intervention vs Comparator: WHO grade 3 or more (including serious adverse events) RR 1; CI (0.02, 49.33) Nausea/vomiting RR 0.14; CI (0.02, 1.12) Headache RR 0.67; CI (0.12, 3.81)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Chen, 2018[88] N/A Cohort Power calculation: No USA Unclear funding source Journal article N: 260	Age: SRS without immunotherapy: 77% <70, Nonconcurrent SRS and immunotherapy: 82% <70, Concurrent SRS and immunotherapy: 86% <70 Gender: N/A Primary tumor type: Different cancer types; majority lung or melanoma Metastases: Number: 2 (median) Volume: N/A Size: N/A Prognosis: mixed	SRS + immunotherapy 1500-2400 cGy, 1 fraction OR 1800-2400 cGy, 3 fractions OR 2500 cGy, 5 fractions Immune checkpoint inhibition (anti-PD-1, anti-CTLA-4, concurrent dual anti-PD-1 and anti-CTLA-4, or sequential anti-CTLA-4 and anti-PD-1) within 2 weeks before or after SRS SRS 1500-2400 cGy, 1 fraction OR 1800-2400 cGy, 3 fractions OR 2500 cGy, 5 fractions Nonconcurrent SRS-SRT and ICI 1500-2400 cGy, 1 fraction OR 1800-2400 cGy, 3 fractions OR 2500 cGy, 5 fractions Immune checkpoint inhibition (anti-PD-1, anti-CTLA-4, concurrent dual anti-PD-1 and anti-CTLA-4, or sequential anti-CTLA-4 and anti-PD-1) >2 weeks apart from SRS	Intervention: randomized, 28 analyzed Comparator: randomized, 181 analyzed Additional comparator: randomized, 51 analyzed Followup: 9 [median] months	Intervention vs Comparator: Time to death HR 1.74; CI (1.01, 3) Concurrent stereotactic radiosurgery-stereotactic radiation therapy and immune checkpoint inhibitors may be associated with favorable survival outcomes Intervention vs additional comparison: Time to death HR 2.02; CI (1.25, 3.27)	Intervention vs Comparator: Grade 4 immune-related adverse events or acute neurologic toxicity RR 1.62; CI (0.07, 34.93) Number of events (immune-related adverse events or acute neurologic toxicity) 24 vs 143 Intervention vs additional comparison: Grade 4 immune-related adverse events or acute neurologic toxicity RR 1.82; CI (0.04, 89.33)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Chua, 2010[89] Merck Sharp[224] NCT00076856 RCT Power calculation: Yes Multinational China, Poland, France, Argentina, Colombia, Israel, USA, Greece Industry funded Journal article N: 95	Age: WBRT + temozolomide: 59 [median] and WBRT: 62 [median] Gender: 35% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m2 daily for 21 or 28 consecutive days WBRT 3000 cGy, 10 fractions, qd	Intervention: 47 randomized, 47 analyzed Comparator: 48 randomized, 48 analyzed Followup: 7 [median] months	Intervention vs Comparator: Time from the date of randomization to death HR 1.14; CI (0.71, 1.83) CNS progression-free survival HR 1.01; CI (0.63, 1.62) Time to CNS progression HR 1.01; CI (0.63, 1.62)	Intervention vs Comparator: Number of adverse events Number of adverse events: n=85 vs. 45 Fatigue RR 2.04; CI (0.66, 6.33) Vomiting RR 4.43; CI (1.35, 14.54) Headache RR 0.61; CI (0.16, 2.42) Nausea, alopecia, and anorexia Adding temozolomide to WBRT also increased the frequency of nausea (36% vs. 10%), alopecia (28% vs. 6%), and anorexia (15% vs. 6%).
Davey, 2008[90] N/A RCT Power calculation: Yes Canada Non industry Journal article N: 90	Age: Accelerated WBRT: 69% <65, Control WBRT: 67% <65 Gender: N/A Primary tumor type: Different cancer types; 70% lung, breast, melanoma Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: mixed	Accelerated WBRT 4000 cGy, 20 fractions, bid WBRT 2000 cGy, 5 fractions, qd	Intervention: 45 randomized, 45 analyzed Comparator: 45 randomized, 45 analyzed Followup: 5 [median] months	Intervention vs Comparator: Time to death The median survival was 19 weeks in both groups. Time to retreatment for intracranial relapse Accelerated WBRT arm had a significantly longer median time to retreatment for intracranial relapse (p=0.03). Modified Barthel Index No statistically significant difference in neurological function between the two arms	Intervention vs Comparator: Side effects and late toxicity No statistically significant differences in acute side effects (WHO epilation score) and late toxicity (LENT/SOMA) between the two arms. Epilation Trends for more severe epilation in the accelerated arm did not reach statistical significance.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Deng, 2017[91] N/A Cohort Power calculation: No China Non industry Journal article N: 238	Age: WBRT+temozolomide: 55% >60, WBRT: 65.1% <60 Gender: 43% female Primary tumor type: Lung cancer only; Metastases: Number: 73% had > 3 brain metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m2/day during radiation treatment; 100 mg/m2/day for 14 days every 28 days for 6 cycles after radiation WBRT 3000 cGy, 10 fractions, qd	Intervention: randomized, 129 analyzed Comparator: randomized, 109 analyzed Followup: 7 [median] months	Intervention vs Comparator: Overall survival Longer survival in combination group but no significant difference between groups (0.11) Intracranial progression-free survival Median PFS of RCT arm was significantly longer than that of RT arm (5.9 vs. 4.9 months, p = 0.002) Functional Assessment of Cancer Treatment-Lung (FACT-L) No significant difference in the declined number of scores for QOL between two groups (p > 0.05). Revised Hopkins Verbal Learning Test, Controlled Oral Word Association test and Trail-making Test No significant difference in the declined number of scores for neurocognitive function between groups (p>0.05). Intracranial objective response rate; disease control rate The WBRT+temozolomide group had significantly higher intracranial objective response and disease control rates (34.9% vs. 20.2% and 98.4% vs. 92.7%, respectively), compared to the WBRT group	Intervention vs Comparator: Number of adverse events 574 vs 485 Fatigue RR 1.01; CI (0.83, 1.23) Vomiting RR 0.96; CI (0.76, 1.2) Headaches RR 1.08; CI (0.8, 1.47)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Dobi, 2020[92] N/A Cohort Power calculation: No Other Hungary Non industry Journal article N: 468	Age: 60.7 Gender: 47% female Primary tumor type: Different cancer types; NSCLC, breast, melanoma, SCLC, renal, colorectal Metastases: Number: 3.6 Volume: N/A Size: N/A Prognosis: 56.2% KPS>70, 11% RPA 1, 45% RPA 2, 44% RPA 3 class	WBRT + boost (sequential or simultaneous integrated SIB) WBRT 3000 cGy, 10 fractions qd or 3600 cGy, 18 fractions qd + sequential boost 2000 cGy, 10 fractions qd OR WBRT 3300 cGy, 15 fractions qd + SIB 1050 cGy, 15 fractions qd 12 mg methylprednisolone during radiation WBRT 3000 cGy, 10 fractions qd 12 mg methylprednisolone during radiation	Intervention: randomized, 195 analyzed Comparator: randomized, 273 analyzed Followup: N/A months	Intervention vs Comparator: Time to death HR 1.26; CI (1.02, 1.55)	Intervention vs Comparator: Alopecia Alopecia was equal among groups

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
El Gantery, 2014[93] N/A RCT Power calculation: No Egypt Non industry Journal article N: 60	Age: N/A Gender: N/A Primary tumor type: Different cancer types; specific breakdown not provided Metastases: Number: 1-3 metastases Volume: N/A Size: N/A Prognosis: unclear	WBRT + SRS WBRT: 3000 cGy, 10 fractions, qd. SRS: 1400-2000 cGy, 1 fraction WBRT 3000 cGy, 10 fractions, qd SRS 1800-2000 cGy, 1 fraction	Intervention: 21 randomized, 21 analyzed Comparator: 21 randomized, 21 analyzed Additional comparator: 18 randomized, 18 analyzed Followup: 9 [median] months	Intervention vs Comparator: Overall survival There was non significant survival benefit for WBRT + SRS compared to SRS alone & WBRT alone Median local control Median local control was significantly better for WBRT + SRS compared to SRS alone & WBRT alone (10 vs 6 vs 5 months)	Intervention vs Comparator: Number of participants with acute toxicities RR 1; CI (0.23, 4.4) Radionecrosis RR 2; CI (0.07, 56.46) Seizures RR 1; CI (0.02, 48.09) Vomiting RR 1; CI (0.02, 48.09) Headache RR 1; CI (0.16, 6.45) Intervention vs additional comparison: Number of participants with acute toxicities RR 2.57; CI (0.29, 22.61) Radionecrosis RR 0.86; CI (0.06, 12.75) Seizures RR 0.43; CI (0.02, 12.04) Vomiting RR 0.43; CI (0.02, 12.04) Headache RR 0.86; CI (0.13, 5.48)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
El-Hamamsy, 2016[94] N/A RCT Power calculation: No Egypt Non industry Journal article N: 50	Age: WBRT + simvastatin: 53.6 (10.6), WBRT: 55.2 (11.8) Gender: 50% female Primary tumor type: Different cancer types; 88% breast or lung Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: 68% RPA class 3	WBRT + Simvastatin 3000 cGy, 10 fractions, qd Simvastatin 80 mg WBRT 3000 cGy, 10 fractions, qd	Intervention: 25 randomized, 15 analyzed Comparator: 25 randomized, 15 analyzed Followup: 12 months	Intervention vs Comparator: 1-year overall survival Overall survival rates were 8% and 12% (p = 0.880) for the simvastatin and the control group 1-year progression-free survival 1-year progression free survival rates of 17.7% and 5.2% comparing the combination group to WBRT alone (p = 0.392) EORTC QLQ-C30 at 4 weeks No significant differences between groups. Response rates There were no significant differences in response rates (60% vs. 78.6%)	Not reported
Fokas, 2012[95] N/A Cohort Power calculation: No Multinational Germany and UK Non industry Journal article N: 260	Age: SRS: 51% <63, fractionated stereotactic radiotherapy 7x 5Gy: 56% <63, FSRT 10x 4Gy: 54% <63 Gender: 56% female Primary tumor type: Breast cancer only; Metastases: Number: SRS: 90% have one metastases, FSRT 7x 5Gy: 67% have one metastases, FSRT 10x 4Gy: 59% have one metastases Volume: SRS: 0.87 cm3 (median), FSRT 7x5: 2.04 cm3 (median), FSRT 10x4: 5.93 cm3 (median) Size: N/A Prognosis: mixed	Fractionated SRS SRS in multiple treatments: 4000 cGy, 10 fractions SRS 1500 cGy - 2400 cGy; median dose 20 Gy Fractionated SRT 7 x 5 Gy 3500 cGy, 7 fractions	Intervention: randomized, 61 analyzed Comparator: randomized, 138 analyzed Additional comparator: randomized, 61 analyzed Followup: 28 [mean] months	Intervention vs Comparator: Overall survival 10 vs 8 months, no statistically significant difference between arms	Intervention vs Comparator: Grades 1-3 acute and chronic toxicities SRS was associated with a significantly higher rate of toxicity (grades 1-3) as compared to the Fractionated SRT 7 x 5 Gy and Fractionated SRT groups (14 vs. 6 vs. 2 %, respectively). Radionecrosis RR 0.28; CI (0.02, 5.27) Intervention vs additional comparison: Radionecrosis RR 0.5; CI (0.02, 14.63)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Gamboa-Vignolle, 2012[96] Instituto Nacional de Cancerologia de Mexico[205] NCT01015534 RCT Power calculation: Not relevant outcome Mexico Unrestricted grant Journal article N: 55	Age: WBRT + temozolomide: 49.5 [median], WBRT: 53.8 [median] Gender: 85% female Primary tumor type: Different cancer types; 62% breast, majority of remainder lung Metastases: Number: TMZ + WBI arm: 61% have less than 4 and Control arm: 41% have less than 4 Volume: N/A Size: N/A Prognosis: mixture of good, moderate and poor prognosis	WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 200 mg/day 3x/week and 300 mg/day 2x/week WBRT 3000 cGy, 10 fractions, qd Dexamethasone 8-16 mg/day or prednisone 50 mg/day	Intervention: 28 randomized, 28 analyzed Comparator: randomized, 27 analyzed Followup: 8 [median] months	Intervention vs Comparator: Overall survival was measured at the date of death or the last follow-up No significant difference in overall survival between groups Progression-free survival of brain metastases HR 0.24; CI (0.09, 0.65) Objective response rate The objective response rate was significantly higher in WBRT + temozolomide than in WBRT	Intervention vs Comparator: Grade 3 RR 1.93; CI (0.07, 55.15)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
GlaxoSmithKline 2012[97] Ramlau, 2013[239] NCT00390806 RCT Power calculation: No USA Industry funded Trial record N: 472	Age: 58.6 (8.6) Gender: 34% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT + Topotecan 3000 cGy, 10 fractions, qd Topotecan 1.1 mg/m2/day p.o. two hours post WBRT WBRT 3000 cGy, 10 fractions, qd	Intervention: 236 randomized, 236 analyzed Comparator: 236 randomized, 236 analyzed Followup: 49 months	Intervention vs Comparator: Time from randomization until the date of death due to any cause HR 0.88; CI (0.72, 1.07) Progressive disease Complete response rate; overall response rate; time to response; time to neurologic symptoms and signs Complete response and overall response rates in WBRT + topotecan vs. WBRT were 10% and 27% vs. 5% and 26%, respectively. There were no significant differences in time to response or neurologic symptoms and signs	Intervention vs Comparator: Untoward medical occurrence that, at any dose: results in death; is life threatening; requires hospitalization or prolongation of existing hospitalization; results in disability/incapacity; is a congenital anomaly/birth defect RR 2.23; CI (1.64, 3.05) Number of participants with any adverse event RR 1.38; CI (1.23, 1.54) Fatigue RR 1.08; CI (0.72, 1.63) Convulsions and epilepsy RR 1.2; CI (0.37, 3.88) Vomiting RR 1.67; CI (1.04, 2.67) Headaches RR 1; CI (0.61, 1.64) Hematologic toxicity; febrile neutropenia; diarrhea Hematologic toxicity, febrile neutropenia, and diarrhea were more frequent in WBRT+topotecan than in WBRT alone.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Gonda, 2014[98] N/A Cohort Power calculation: No Multinational USA and Japan Non industry Journal article N: 3536	Age: San Diego Gamma Knife Center cohort: 58 [median], Katsuta Hospital cohort: 65 [median] Gender: SDGKC (San Diego Gamma Knife Center) cohort: 50% female, Katsuta Hospital cohort: 39% female Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: SDGKC: 41.4% 3 or more metastases and Katsuta Hospital: 55.9% have 3 or more metastases Volume: SDGKC: 45% >4 cm3, Katsuta Hospital: 56% >4cm3 Size: N/A Prognosis: mixed	SRS + WBRT SRS: SDGKC 1900 cGy [median], 1 fraction, Katsuta Hospital 2110 cGy [median], 1 fraction. WBRT: no details SRS SRS: SDGKC 1900 cGy [median], 1 fraction, Katsuta Hospital 2110 cGy [median], 1 fraction	Intervention: randomized, 464 analyzed Comparator: randomized, 3072 analyzed Followup: 24 months	Intervention vs Comparator: Time to death HR 0.99; CI (0.85, 1.15)	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Graham, 2010[99] N/A RCT Power calculation: Yes Australia Non industry Journal article N: 113	Age: 62 [mean] 28-83 [range] Gender: 36% female Primary tumor type: Different cancer types; 70% lung, breast, melanoma Metastases: Number: 61% had multiple metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT 40Gy 4000 cGy, 20 fractions, bid WBRT 20Gy 2000 cGy, 4 fractions, qd	Intervention: 57 randomized, 57 analyzed Comparator: 56 randomized, 56 analyzed Followup: 7 [median] months	Intervention vs Comparator: Overall survival HR 1.08; CI (0.6, 1.96) CNS progression-free survival HR 0.55; CI (0.29, 1.07) Death due to CNS progression RR 0.63; CI (0.4, 1) Intracranial progression HR 1.56; CI (0.94, 2.6) QLQ-C30 SMD -0.17; CI (-0.54, 0.2) The QOL improve by a clinically significant degree in WBRT (20Gy) but was not significantly different statistically from WBRT (40Gy). QLQ-C30 cognitive subscale No significant difference was found by treatment group. Salvage treatment Salvage surgery or radiotherapy was used significantly less in 40 Gy patients than in 20 Gy patients (4% vs 21%)	Intervention vs Comparator: Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Gronberg, 2012[100] Eli Lilly Company[191] NCT00415363 RCT Power calculation: Yes Multinational Norway, Romania, Finland, Sweden, Denmark, Austria, USA Industry funded Journal article N: 107	Age: Enzastaurin: 61.5 [median] and Placebo: 65.2 [median] Gender: 41% female Primary tumor type: Different cancer types; 75% NSCLC Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: mix of good, moderate and poor prognosis	WBRT + Enzastaurin WBRT: 2000 cGy, 4 -5 fractions, qd OR 3000 cGy, 10 fractions, qd 1125 mg Enzastaurin on day 1 followed by 500 mg daily), supportive care with corticosteroids WBRT + Placebo WBRT: 2000 cGy, 4 -5 fractions, qd OR 3000 cGy, 10 fractions, qd Supportive care with corticosteroids	Intervention: 55 randomized, 55 analyzed Comparator: 54 randomized, 54 analyzed Followup: 9 [minimum] months	Intervention vs Comparator: Time from the date of study enrollment to the date of death from any cause HR 1.16; CI (0.79, 1.71) Progression-free survival HR 0.94; CI (0.64, 1.39) Time to progression of brain metastases No statistical difference in median time to progression of brain metastases between arms. QLQ-C30 No statistical differences between arms in change from baseline in any of the HRQoL scores. Overall response rate The overall response rates were not significantly different for extracranial disease (0% vs. 4.5%) and for intracranial disease (9.3% vs. 6.8%)	Intervention vs Comparator: Serious treatment-emergent adverse event RR 5.89; CI (0.73, 47.32) Number of events (Grade 3/4 toxicities) 44 vs 31 Number of events (Grade 3/4) RR 1.77; CI (0.63, 4.93) Number of events (Grade 3/4) RR 1.47; CI (0.26, 8.47) Treatment-related adverse events Grade 4 hematologic treatment-emergent adverse events were thrombocytopenia (5.6% vs. 1.9%) and neutropenia (5.6% vs. 0%). There was one treatment-related death in each arm.
Guerrieri, 2004[101] N/A RCT Power calculation: Yes Australia Unclear funding source Journal article N: 42	Age: WBRT + carboplatin: 60 [median] , WBRT: 63 [median] Gender: 29% female Primary tumor type: Lung cancer only; Metastases: Number: 74% had multiple metastases (not specified further) Volume: N/A Size: N/A Prognosis: mixed	WBRT + Carboplatin 2000 cGy, 5 fractions, qd Carboplatin 70 mg/m2 /day intravenously for 5 days; steroids given at the discretion of the investigator WBRT 2000 cGy, 5 fractions, qd Steroids given at the discretion of the investigator	Intervention: 21 randomized, 21 analyzed Comparator: 21 randomized, 21 analyzed Followup: 4 [median] months	Intervention vs Comparator: Median survival Median survival was 4.4 months in the radiotherapy alone arm and 3.7 months in the combined treatment arm (p = 0.64) Objective response rate The objective response rates were not significantly different between groups (29% vs 10%	Intervention vs Comparator: Gastrointestinal and hematological toxicities No significant differences in gastrointestinal or hematological toxicities between groups.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Gupta, 2016[102] Oxford University, 2016[233] ISRCTN 20253034 RCT Power calculation: No UK Non industry Journal article N: 24	Age: WBRT + vandetanib: 57 [mean], WBRT + placebo: 64 [mean], safety cohort: 69 [mean] Gender: 50% female Primary tumor type: Melanoma only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: mixed	WBRT + Vandetanib 3000 cGy, 10 fractions, qd Vandetanib 100 mg qd WBRT + Placebo 3000 cGy, 10 fractions, qd Placebo (identical appearance)	Intervention: 10 randomized, 10 analyzed Comparator: 8 randomized, 8 analyzed Followup: 5 [median] months	Intervention vs Comparator: Median overall survival HR 0.85; CI (0.31, 2.3) Median overall survival was 4.6 months (90% CI: 1.6-6.3) in the vandetanib and 2.5 months (90% CI: 0.2-7.2) in the control group (P=0.54) Intracraninal progression-free survival HR 0.65; CI (0.25, 1.69) Median progression free survival was 3.3 months in the vandetanib group and 2.5 months in the placebo group (P=0.34)	Intervention vs Comparator: RR 2; CI (0.52, 7.72) Number of events (all grades) 43 vs 16 Radiation necrosis RR 0.8; CI (0.02, 36.05) Fatigue RR 1.2; CI (0.51, 2.83) Vomiting RR 1.6; CI (0.06, 41.89) Headache RR 4.8; CI (0.28, 82.64)
Hassler, 2013[103] N/A RCT Power calculation: Yes Austria Industry funded Journal article N: 35	Age: RCT arm: 69 [median] and RT arm: 64 [median] Gender: 40% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: mixed, 77% RPA class 2	WBRT + temozolomide 4000 cGy, 20 fractions, qd OR 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m2 for 2 weeks followed at day 28 by 100 mg/m2/day 2 weeks on/2 weeks off for up to 6 months; WBRT 4000 cGy, 20 fractions, qd OR 3000 cGy, 10 fractions, qd Anti-emetics, anti-epileptic drugs, corticosteroids and other medications at the discretion of the treating physician	Intervention: 22 randomized, 22 analyzed Comparator: 13 randomized, 13 analyzed Followup: 6 [median] months	Intervention vs Comparator: Overall survival Median overall survival was 3 months vs 6.3 months comparing radiochemotherapy and radiation alone Time to progression 2.4 months vs 2.0 months (not significant)	Intervention vs Comparator: Severe haematological toxicity RR 4.73; CI (0.27, 82.45) Number of events (non-haematological toxicities) 43 vs 16 Vomiting RR 1.77; CI (0.84, 3.73) Headache RR 1.54; CI (0.71, 3.32) Thrombocytopenia, leucocytopenia, lymphocytopenia WHO grade 3 and 4 thrombocytopenia in 3/22 vs. 0/13, leucocytopenia in 1/22 vs. 0/13 and lymphocytopenia in 7/22 vs. 12/13 patients.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Hauswald, 2019[104] Hauswald, 2013[201]; Universitètsklinikum Heidelberg[260] DRKS00005127 RCT Power calculation: No Germany Industry funded Journal article N: 7	Age: 49 [median] Gender: 43% female Primary tumor type: Melanoma only; Metastases: Number: 10 [median] Volume: N/A Size: 14 [median] Prognosis: mixed moderate to poor	Hippocampal-sparing WBRT 3000 cGy, 10 fractions, qd WITH hippocampus sparing boost to tumors (5000 cGy in 10 fractions, qd) WBRT 3000 cGy, 10 fractions, qd	Intervention: 4 randomized, 4 analyzed Comparator: 3 randomized, 3 analyzed Followup: 5 [median] months	Intervention vs Comparator: Overall survival Median overall survival 5 months (hippocampal sparing WBRT) versus 4 months (standard WBRT) Local control The local control in every individual brain metastasis was significantly longer in the Hippocampal-sparing WBRT than in the WBRT arm	Intervention vs Comparator: Fatigue RR 4.5; CI (0.34, 60.15) Vomiting RR 0.75; CI (0.07, 7.73) Headaches RR 1.5; CI (0.07, 31.57)
Hoffmann-La Roche, 2011[105] NCT00977379 RCT Power calculation: No France Industry funded Trial record N: 24	Age: 56.2 (14.2) Gender: 100% female Primary tumor type: Breast cancer only; Metastases: Number: NR Volume: NR Size: NR Prognosis: NR	WBRT + Capecitabine 3000 cGy in 10 fractions Capecitabine 825 mg/m2 p.o. bid Days 1-14 every 21 days for 1 cycle, followed by capecitabine 1000 mg/m2 p.o. bid Days 1-14 every 21 days starting with Cycle 2 WBRT 3000 cGy in 10 fractions Standard care	Intervention: 12 randomized, 11 analyzed Comparator: 12 randomized, 12 analyzed Followup: 18 months	Intervention vs Comparator: Time to death 4.6 vs 9.8 months Change from baseline in Mini Mental State (MMS) SMD 0.94; CI (0.06, 1.82)	Intervention vs Comparator: Number of participants with serious adverse events RR 1.09; CI (0.5, 2.38) Number of adverse events 75 vs 77 Number of events RR 6.55; CI (0.37, 116.6) Number of events RR 0.55; CI (0.06, 5.21) Number of events RR 6.55; CI (0.93, 46.12) Number of events RR 1.09; CI (0.5, 2.38)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Hong, 2019[106] Fogarty, 2011[194]; Hong, 2014[203]; Lo, 2019[217]; Martinage, 2018[220]; Melanoma Skin Cancer Trials Limited, 2017[223]; Fogarty, 2015[195]; Fogarty, 2019[193] NCT01503827, ACTRN16070000512426 RCT Power calculation: No Multinational Australia, UK, Norway Non industry Preliminary data N: 215	Age: 64 [median], 62 [mean] Gender: 33% female Primary tumor type: Melanoma only; Metastases: Number: Observation: 61.7% have one metastases, WBRT: 49% have one metastases Volume: N/A Size: Observation: 1.9 cm [median], WBRT: 2.4 cm [median] Prognosis: mixed	WBRT + surgery and/or SRS 3000 cGy, 10 fractions, qd Local treatment by either surgery and/or SRS Observation + surgery and/or SRS Local treatment by either surgery and/or SRS and observation	Intervention: 107 randomized, 100 analyzed Comparator: 108 randomized, 107 analyzed Followup: 48 [median] months	Intervention vs Comparator: Overall survival HR 0.79; CI (0.53, 1.18) At 12 months, 41.5% of patients in the WBRT group and 51.4% of patients in the observation group had died (P = .28) Neurologic death RR 1.03; CI (0.77, 1.38) No significant difference in neurologic death incidence between the two groups (43.6% and 45.8%; P = .38) Local or any intracranial failure The cumulative incidence of any intracranial failure over the study period was similar in the two groups (61.0% and 68.2%, p = .28) QLQC30+BN20 No difference in effect on global QOL (p=0.083) Time to cognitive failure There was no difference in time to cognitive failure or in proportions with global cognitive impairment but a change in Hopkins Verbal Learning Test Revised, Delayed Recall at 4 months: 20.9% improvement in observation vs -2.7% decline in WBRT arm; overall adjusted average intervention effect 23.6% (CI 9, 38.2; p=0.0018)	Intervention vs Comparator: Fatigue grade 3 RR 0.54; CI (0.02, 15.77) Vomiting RR 0.54; CI (0.02, 15.77)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Hosseini, 2015[107] Ahvaz Jundishapur University of Medical sciences[172] IRCT2013101515026N1 RCT Power calculation: Underpowered Iran Non industry Journal article N: 20	Age: WBRT: 57 [median] and WBRT + SN: 52 [median] Gender: 60% female Primary tumor type: Different cancer types; 40% breast, 60% other Metastases: Number: 80% has less than 4 metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + Sodium Nitrite 3000 cGy, 10 fractions, qd Sodium nitrite (radiosensitizer) 267 microg/kg/h before each fraction of radiation WBRT 3000 cGy, 10 fractions, qd Steroids and anticonvulsant agents at the lowest dose, as needed	Intervention: 10 randomized, 10 analyzed Comparator: 10 randomized, 10 analyzed Followup: 2 months	Intervention vs Comparator: Objective response rate There was no significant difference in the objective response rate between groups (n=4 vs. 3). Intervention vs additional comparison:	Intervention vs Comparator: Symptomatic acute toxicity (including SAE) RR 1; CI (0.02, 45.63) Symptomatic acute toxicity No symptomatic acute toxicity was observed
Jiang 2016[108] N/A Cohort Power calculation: No China Non industry Journal article N: 230	Age: 74% <65 Gender: 58% female Primary tumor type: Lung cancer only; Metastases: Number: 56% have more than 10 metastases Volume: N/A Size: N/A Prognosis: mixed	EGFR TKI + WBRT 3000 cGy, 10 fractions, qd Gefitinib 250mg/day, erlotinib 150 mg/day, and icotinib 125 mg tid EGFR TKI Gefitinib 250mg/day, erlotinib 150 mg/day, and icotinib 125 mg tid	Intervention: randomized, 30 analyzed Comparator: randomized, 91 analyzed Followup: 22 [median] months	Intervention vs Comparator: Overall survival HR 1.56; CI (0.67, 3.63) Intracranial progression-free survival HR 1.32; CI (0.78, 2.23) Progressive disease Progressive disease status in 14/51 (combination) and 24/116 (systemic therapy alone)	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Jiang, 2014[109] Jiang 2014[209]; Jiangsu Simcere Pharmaceutical Co, Ltd[210] NCT01410370 RCT Power calculation: No China Non industry Journal article N: 80	Age: 65 [median] Gender: 46% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT + endostatin 3000 cGy, 10 fractions, qd Intravenous RHES (Endostar) 7.5 mg/m2/day during radiotherapy WBRT 3000 cGy, 10 fractions, qd	Intervention: 40 randomized, 40 analyzed Comparator: randomized, 40 analyzed Followup: 9 [median] months	Intervention vs Comparator: Overall survival time HR 0.78; CI (0.46, 1.3)	Intervention vs Comparator: Adverse reactions There were no statistical differences in adverse reactions between two groups. Other AE measures Compared with the WBRT group, brain edema was significantly relieved in the WBRT+ endostatin group.
Johnson, 2016[110] N/A Cohort Power calculation: No USA Author COI Journal article N: 330	Age: 62% <65 Gender: 57% female Primary tumor type: Different cancer types; 63% lung, 15% breast, 5% melanoma Metastases: Number: 87% have less than 3 metastases Volume: N/A Size: N/A Prognosis: mixed, majority moderate	Surgery + postoperative SRS 2100-2400 cGy for lesions <=2 cm, 1800 cGy for lesions 2 to 3 cm, and 1500 cGy for lesions >3 cm Surgical resection of at least 1 lesion SRS 2100-2400 cGy for lesions <=2 cm, 1800 cGy for lesions 2 to 3 cm, and 1500 cGy for lesions >3 cm	Intervention: randomized, 112 analyzed Comparator: randomized, 218 analyzed Followup: 9 [median] months	Intervention vs Comparator: Overall survival Median survival in the SRS plus surgery group were 12.9 compared to 10.6 for SRS alone	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Kayama, 2018[111] Japan Clinical Oncology Group (JCOG)[207]; Fukuda Haruhiko, 2013[200] NCT00280475, C000000307 RCT Power calculation: Yes Japan Non industry Journal article N: 271	Age: WBRT: 61 [mean], SRS: 63 [mean] Gender: 50% female Primary tumor type: Different cancer types; 67% lung or breast Metastases: Number: WBRT: 73% have single metastases, SRS: 73.9% have a single metastases Volume: N/A Size: N/A Prognosis: unclear	SRS after surgery no details Surgical resection WBRT after surgery 3750 cGy, 15 fractions, qd Surgical resection	Intervention: 134 randomized, 134 analyzed Comparator: 137 randomized, 137 analyzed Followup: 16 [median] months	Intervention vs Comparator: Time to death HR 1; CI (0.56, 1.79) Median survival was not different (p=0.27) Intracraninal progression-free survival Median intracranial progression-free survival of patients in the WBRT arm was 10.4 months compared to 4.0 months in the salvage SRS group Neurologic death RR 0.98; CI (0.57, 1.67) Eastern Cooperative Oncology Group PS scores The proportion of PS scores that did not worsen in the WBRT and SRS arms were 64.2% and 64.9% after 6 months and 46.0% and 46.3% after 12 months, respectively, with no significant difference. MMSE (worsening: decrease in category) THe proportion of patients whose mini mental status examination did not worsen at 12 months was similar across treatment arms but 16% of patients in the WBRT arm experienced grade 2 to 4 cognitive dysfunction after 91 days post-enrollment compared to 8% in the SRS arm (p=0.048)	Intervention vs Comparator: Number of grade 4 events at 91 days RR 0.06; CI (0, 1.1) Number of adverse events at 91 days 118 vs 179 Radiation necrosis at 91 days RR 2.04; CI (0.52, 8.01) Memory disturbance; cognitive dysfunction Memory disturbance (16.4% vs. 6.8%) and cognitive dysfunction (16.4% vs. 7.7%) were significantly more common in the WBRT arm than in the SRS arm after day 91.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Kepka, 2016[112] Kepka, 2018[211]; Maria Sklodowska-Curie Institute[218]; Kepka, 2017[212] NCT01535209 RCT Power calculation: Yes Poland Non industry Journal article N: 59	Age: 60 [median] Gender: 56% female Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: 1 (all patients had 1 brain metastasis) Volume: N/A Size: N/A Prognosis: good to moderate population	SRS after surgery 1500 cGy, 1 fraction OR 2500 cGy, 5 fractions Total/subtotal resection of single brain metastasis WBRT after surgery 3000 cGy, 10 fractions, qd Total/subtotal resection of single brain metastasis	Intervention: 30 randomized, 29 analyzed Comparator: 30 randomized, 30 analyzed Followup: 29 [median] (survivors) months	Intervention vs Comparator: Two-year overall survival HR 1.8; CI (0.98, 3.3) Neurological death RR 3.1; CI (1.13, 8.52) Two-year cumulative incidence of neurological death HR = 2.51 (95% CI: 1.19-5.29) in favor of WBRT Total intracranial progression (in the tumor bed and/or at new sites of the brain) 86% in the SRS, 68% in the WBRT group	Intervention vs Comparator: Grade 3 or higher RTOG radiotherapy toxicity (including SAE) RR 1.03; CI (0.02, 50.42) Grade 3 or higher RTOG radiotherapy toxicity No grade 3 or higher RTOG radiotherapy toxicity was recorded in either group.
Kim, 2005[113] N/A Cohort Power calculation: No South Korea Non industry Journal article N: 63	Age: WBRT + chemotherapy: 54.2 [median] , non-chemotherapy arm: 57.7 [median] Gender: 32% female Primary tumor type: Lung cancer only; Metastases: Number: 59% had > 2 metastases Volume: N/A Size: N/A Prognosis: unclear	Radiation therapy (WBRT and/or SRS) + chemotherapy WBRT 3000-4000 cGy (number of treatments not provided), no SRS treatment details Platinum-based combination therapies for at least 6 cycles; corticosteroids administered during radiation therapy RT + supportive care WBRT or SRS; 3000-4000 cGy (number of treatments not provided). No SRS treatment details Best supportive care, corticosteroids administered during radiation therapy	Intervention: randomized, 31 analyzed Comparator: 32 randomized, 32 analyzed Followup: 15 [median] months	Intervention vs Comparator: Overall survival Median survival was longer in the combination group (58.1 vs. 19.0 weeks, p<0.001)	Intervention vs Comparator: Toxicity Toxicity in the chemotherapy group was tolerable

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Knisely, 2008[115] Corn, 2008[188]; National Cancer Institute, 2006[230] NCT00033254 RCT Power calculation: Yes USA Non industry Journal article N: 183	Age: WBRT + thalidomide: 58.5 [median] and WBRT alone: 59 [median] Gender: 55% female Primary tumor type: Different cancer types; 90% lung, breast, melanoma Metastases: Number: WBRT + thalidomide: 82% have > 3 brain metastases, WBRT: 79% have >3 brain metastases Volume: N/A Size: N/A Prognosis: mixture of good and moderate prognosis (75% RPA class 2, 25% RPA class 1)	WBRT + Thalidomide 3750 cGy, 15 fractions, qd 200 mg of thalidomide per day and had a weekly dose escalation of 200 mg per day during WBRT WBRT 3750 cGy, 15 fractions, qd	Intervention: 90 randomized, 84 analyzed Comparator: 93 randomized, 92 analyzed Followup: 2 [median] months	Intervention vs Comparator: Time of randomization until death HR 1; CI (0.57, 1.76) Median survival was 3.9 months for both arms Rate of deaths due to brain metastases RR 0.82; CI (0.51, 1.33) CNS progression The time to progression curves were not different (p = 0.097)	Intervention vs Comparator: Number of events (Grade 4) 8 vs 1 Number of adverse events 255 vs 146
Kirkpatrick, 2015[114] Duke University[190] NCT01017497 RCT (other) Power calculation: No USA Non industry Journal article N: 49	Age: 61 [median] Gender: 67.3% female Primary tumor type: Different cancer types; 80% lung, breast, melanoma Metastases: Number: 1-3 metastases (mean unclear) Volume: NA Size: NA Prognosis: Life expectancy 3 months or more	SRS 1-mm volume 1-mm uniform expansion of the gross target volume SRS 3-mm volume 3-mm uniform expansion of the gross target volume	Intervention: randomized, analyzed Comparator: randomized, analyzed Followup: 48 months	Intervention vs Comparator: Local recurrence at the site of radiosurgery 12 month local control 95% vs 91% (p=0.51)	Intervention vs Comparator: Lesion with radionecrosis 0.028 versus 0.152 (p=0.10)

Kocher, 2011[116] Churilla, 2017[187]; Churilla, 2018[185]; Mueller, 2009[227]; Organization for European Research, 2007[192]; Soffietti, 2008[248]; Churilla, 2019[186]; Soffietti, 2013[247] NCT00002899 RCT Power calculation: Yes Multinational Germany, Italy, Turkey, Spain, France, Netherlands, Israel, Finland, Latvia, Belgium Non industry Journal article N: 359	Age: 60 [median] Gender: 35% female Primary tumor type: Different cancer types; 70% lung, breast or melanoma Metastases: Number: 1.25 (mean) Volume: N/A Size: unclear Prognosis: good to moderate prognosis: WHO performance status 0: 44%, 1: 45%, 2: 11%	(Surgery or SRS) + WBRT 3000 cGy, 10 fractions, qd Complete surgery or SRS (Surgery or SRS) + observation Complete surgery or SRS and observation	Intervention: 180 randomized, 180 analyzed Comparator: 179 randomized, 179 analyzed Followup: 49 [median] (survivors) months	Intervention vs Comparator: Overall survival HR 0.98; CI (0.77, 1.24) Progression-free survival HR 0.74; CI (0.5, 1.09) Deaths due to intracranical progression RR 0.64; CI (0.48, 0.85) Progression at both initial sites and new sites In adjusted models, local recurrence was similar between the SRS and surgical resection groups (HR 1.15; CI, 0.72-1.83); patients with surgical resection had a much higher risk of early (0-3 months) local recurrence compared with those undergoing SRS (HR 5.94; CI, 1.72-20.45), but their risk decreased with time (HR for 3-6 months, 1.37; CI, 0.64-2.90]; HR for 6-9 months, 0.75; CI, 0.28-2.00]); at 9 months or longer, the surgical resection group had a lower risk of local recurrence (HR, 0.36; 95% CI, 0.14-0.93) HRQOL SMD -0.51; CI (-0.72, -0.3) Median time to WHO PS more than 2 No difference was found between the two arms (HR 0.96; 95% CI, 0.76 to 1.20; P =.71). Salvage treatment Salvage therapies for intracranial relapses were more frequent in patients after observation than in those who received adjuvant WBRT(51% vs. 16%)	Intervention vs Comparator: Serious acute toxicities related to surgery and radiosurgery evaluated by serious adverse event forms RR 4.31; CI (1.25, 14.86) Grade 4 late toxicities (number of events): WBRT 41, observation 40 Number of events (late toxicities) Number of events (grade 2-4 late toxicity): WBRT 63, observation 70; Number of patients (grade 4 late toxicity): WBRT 22, observation 23 Severe acute toxicity - radiation necrosis RR 1.99; CI (0.18, 21.74) Severe acute toxicity - seizure RR 5.97; CI (0.3, 118.26) Number of patients with headaches (grade 4 late toxicity) RR 1.99; CI (0.18, 21.74) Number of headaches (grade 2-4 late toxicity): WBRT 85, observation 98

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Kondziolka, 1999[117] Kondziolka, 2000[213] N/A RCT Power calculation: Yes USA Non industry Journal article N: 27	Age: WBRT + SRS: 59 [mean], WBRT: 58 [mean] Gender: 41% female Primary tumor type: Different cancer types; 78% lung, breast, melanoma Metastases: Number: 2 to 4 brain metastases Volume: N/A Size: N/A Prognosis: unclear	WBRT + SRS WBRT: 3000 cGy, 12 fractions, qd, SRS: 1600 cGy, 1 fraction WBRT 3000 cGy, 12 fractions, qd	Intervention: 13 randomized, 13 analyzed Comparator: 14 randomized, 14 analyzed Followup: 11 [median] months	Intervention vs Comparator: Overall survival Patients who received WBRT alone lived a median of 7.5 months, patients who received WBRT+SRS lived 11 months (p = 0.22) Median time to any brain failure (progression of the initial tumors or the development of new tumors) The median time to any brain failure was 5 months (95% CI, 3.2-6.8) after WBRT alone and 34 months after WBRT plus radiosurgery (p = 0.002)	Not reported
Lanier, 2019[118] N/A Cohort Power calculation: No USA Non industry Journal article N: 271	Age: SRS: 67 (59-74), SRS+immunotherapy: 63 (55-71) [intervention: median (IQR)] Gender: 45% Primary tumor type: Lung, breast, or melanoma cancer; NSCLC and melanoma Metastases: Number: 93 patients with 1 metastases, 108 patients with 2-4 metastases, 70 patients with 5 or more metastases Volume: Size: Prognosis: less than 9% have KPS <70, about 90% have DS-GPA between 0-2.5, about 40% with widespread disease, more than 50% with progressive disease	SRS plus immunotherapy 1800 cGy (1650, 2000), 1 fraction [median (IQR)] SRS (1800 cGy, IQR 1650-2000) with immunotherapy (before, concurrent, or after; varied agents) SRS alone 1800 cGy (1650, 2000), 1 fraction [median (IQR)]	Intervention: randomized, 101 analyzed Comparator: 170 randomized, 170 analyzed Followup: 29.9 [median] months	Intervention vs Comparator: Time to death 1 year cumulative incidence of death due to neurologic decline (i.e., death with progressive neurologic decline) cumulative incidence 9% in arm 1 versus 23% in control group; HR 0.35 (95% CI 0.19 to 0.66) 1 year cumulative incidence of distant brain failure 1 year cumulative incidence of distant brain failure 54% in arm 1 versus 34% in control arm	Intervention vs Comparator: Overall rates of neurologic toxicity requiring intervention Overall rates of neurologic toxicity requiring intervention only reported for whole study 33% (also reported for RTOG grade 3 or 4 CNS toxicity for SRS + immunotherapy arm only 21%)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Lee, 2008[119] N/A RCT Power calculation: No South Korea Non industry Journal article N: 48	Age: chemotherapy: 60 [median], WBRT: 62[median] Gender: 21% female Primary tumor type: Lung cancer only; Metastases: Number: chemotherapy: 64% 3 or more metastases, WBRT: 65% three or more metastases Volume: N/A Size: N/A Prognosis: unclear	WBRT followed by chemotherapy 3000 cGy, 10 fractions, qd Gemcitabine 900 mg/m2 and vinorelbine 25 mg/m2 on days 1 and 8 and repeated every 3 weeks up to 6 cycles Chemotherapy first followed by WBRT 3000 cGy, 10 fractions, qd Gemcitabine 900 mg/m2 and vinorelbine 25 mg/m2 given on Days 1 and 8 and repeated every 3 weeks	Intervention: 23 randomized, 23 analyzed Comparator: 25 randomized, 25 analyzed Followup: 40 [median] months	Intervention vs Comparator: Time to death Overall survival 9.1 vs 9.9 months (n.s.) Progression-free survival Progression-free survival not statistically significantly different (3.6 vs 4.4 months) Overall response rate The overall response rates were not significantly different between the groups (28.0% vs 39.1%)	Intervention vs Comparator: Number of events (grade 4 hematologic and non-hematologic toxicities) 6 vs 2 Number of events (hematologic and non-hematologic toxicities) 220 vs 237 Fatigue RR 0.77; CI (0.62, 0.94) Vomiting RR 1.3; CI (0.46, 3.7) Headaches RR 1; CI (0.58, 1.73) Neutropenia; alopecia; mild headache or dizziness Grade 3 or 4 neutropenia occurred significantly more frequently in the WBRT-first arm (79% vs 40%). Alopecia and mild headache or dizziness were more frequent in the WBRT-first arm.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Lee, 2014[120] University College London Cancer Research U. K.[261] NCT00554775 RCT Power calculation: Yes UK Non industry Journal article N: 80	Age: WBRT+placebo: 62.2 [median], WBRT+erlotinib: 61.3 [median] Gender: 55% female Primary tumor type: Lung cancer only; Metastases: Number: WBRT+placebo: 65% < 3, WBRT+erlotinib: 57.5% < 3 metastases Volume: N/A Size: N/A Prognosis: mostly moderate to good	WBRT + Erlotinib 2000 cGy, 5 fractions, qd Erlotinib 100ng/day starting on day 1 of WBRT and 150mg/day after WBRT until disease progression with symptomatic deterioration; dexamethasone at least 4mg during WBRT and for one week after WBRT + Placebo 2000 cGy, 5 fractions, qd Matching placebo; dexamethasone at least 4mg during WBRT and for one week after	Intervention: 40 randomized, 40 analyzed Comparator: 40 randomized, 40 analyzed Followup: 3 [median] months	Intervention vs Comparator: Overall survival HR 0.94; CI (0.57, 1.54) Neurological progression-free survival HR 0.99; CI (0.62, 1.58) RR 1.75; CI (0.56, 5.51) EuroQol EQ- 5D SMD 0.03; CI (-0.41, 0.47) There was no significant differences in the QoL scores between groups at one or two months, adjusting for baseline scores (all P <.40)	Intervention vs Comparator: Number of participants with grade 3 or 4 toxicities RR 1; CI (0.75, 1.33) Number of events (grade 3 or 4 toxicities) erlotinib: 59; placebo: 68 Radiation necrosis RR 1; CI (0.02, 49.17) Grade 3 or 4 fatigue RR 0.5; CI (0.23, 1.11) Grade 3 or 4 seizure RR 0.25; CI (0.01, 5.37) Vomiting RR 1; CI (0.02, 49.17) Grade 3 or 4 headache RR 0.13; CI (0.01, 2.29) Rash More patients in WBRT + erlotinib group experienced rash (20.0% vs 5.0%)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Lim, 2015[121] Samsung Medical Center[243] NCT01301560 RCT Power calculation: Yes South Korea Non industry Journal article N: 105	Age: SRS: 58 [mean], Upfront chemotherapy group: 57 [mean] Gender: 28% female Primary tumor type: Lung cancer only; Metastases: Number: SRS: 2.18 (1.17), Upfront chemo: 1.82 (1.07) Volume: SRS: 1.92 cm3, Upfront chemo: 1.54 cm3 Size: N/A Prognosis: moderate	SRS + Chemotherapy Gamma knife radiosurgery, no dose details First-line chemotherapy then cisplatin or carboplatin upon progression Chemotherapy only First-line chemotherapy then cisplatin or carboplatin upon progression	Intervention: randomized, 49 analyzed Comparator: randomized, 49 analyzed Followup: 43 [median] months	Intervention vs Comparator: Time of randomization to date of death HR 1.2; CI (0.76, 1.89) Intracranial progression-free survival Median survival was 9.4 (SRS followed by chemotherapy) vs 6.6 (chemotherapy upfront) months Barthel ADL and Korean version of Instrumental ADL (K-IADL) No significant differences in improvement or worsening of K-IADL (P = 0.4252) and Barthel ADL scores (P = 0.9657) between two groups over time MoCA-K (Korean version of Montreal Cognitive Assessment) and K-MMSE (Korean version of Mini-Mental State Examination) There were no significant differences in improvement or worsening of MoCA-K (p=0.9932) and K-MMSE (p=0.3798) between the groups over time Symptomatic progression Symptomatic progression of brain metastases was more frequent in the chemotherapy group than in the SRS +chemotherapy group (26.5% vs. 18.4%) but without statistical significance	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Liu, 2017[122] N/A RCT Power calculation: No China Non industry Journal article N: 72	Age: 59 [median] Gender: 26% female Primary tumor type: Different cancer types; 62.5% lung (NSCLC) or breast Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT + temozolomide 4000 cGy, 20 fractions, qd Temozolomide (150-200 mg/m(2)/day WBRT 4000 cGy, 20 fractions, qd	Intervention: 36 randomized, 36 analyzed Comparator: 36 randomized, 36 analyzed Followup: 9 [median] months	Intervention vs Comparator: Overall survival Overall survival 8.5 in WBRQ + temozolomide vs 5 months in WBRT alone (p<0.0001) Progression-free survival Significantly longer progression-free survival (p<0.001) Progressive disease No difference between groups (p=0.2327) KPS increase >=10 as quality of life measure Scores were improved in 32 patients in WBRT + TMZ group and 19 in WBRT group (p=0.0007) Objective remission rate; disease control rate; symptoms The objective remission rate in WBRT + temozolomide group was significantly higher than that of in WBRT group ((77.78% vs. 47.22%). The disease control rates were not significantly different between groups (94.44% vs. 86.11%). Compared to WBRT group, WBRT + temozolomide group showed significantly better improvement in symptoms and signs	Intervention vs Comparator: Adverse response No significant difference in the rates between groups. Vomiting RR 2; CI (1.04, 3.84) Headaches RR 1.35; CI (0.89, 2.07)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Magnuson, 2017[123] N/A Cohort Power calculation: No USA Author COI Journal article N: 351	Age: EGFR: 60 (53-70), WBRT: 58 (51-65), SRS: 63 (54-70) [intervention: median (IQR)] Gender: 67% Primary tumor type: Lung cancer only; Metastases: Number: 69 patients with 1 metastasis, 129 patients with 2-4 metastases, 82 patients with 5-10 metastases, 71 patients with >10 metastases Volume: Size: Prognosis: about 37% with DS-GPA between 2-3.5, >70% with ECOG 0-1	SRS followed by tyrosine kinase inhibitor SRS followed by tyrosine kinase inhibitor (98% patients received erlotinib, dose and duration not specified) Tyrosine kinase inhibitor alone WBRT followed by tyrosine kinase inhibitor	Intervention: randomized, 100 analyzed Comparator: randomized, 131 analyzed Additional comparator: randomized, 120 analyzed Followup: 22 [median] months	Intervention vs Comparator: Time to death HR 0.39; CI (0.26, 0.58) Time to intracranial progression HR 0.92; CI (0.66, 1.29) Intervention vs additional comparison: Time to death HR 0.7; CI (0.5, 0.98)	Not reported
Mahajan, 2017[124] M.D. Anderson Cancer Center[181] NCT00950001 RCT Power calculation: Not relevant outcome USA Non industry Journal article N: 132	Age: 59 [median] Gender: 47% female Primary tumor type: Different cancer types; 60% lung, breast, melanoma Metastases: Number: 1.5 (mean) Volume: N/A Size: 3 cm (median) Prognosis: mixed, majority moderate	Surgery + SRS 1200-1600 cGy, 1 fraction Complete resection of brain metastases Surgery only Complete resection of brain metastases	Intervention: 63 randomized, 63 analyzed Comparator: 65 randomized, 65 analyzed Followup: 11 [median] months	Intervention vs Comparator: Overall survival HR 1.29; CI (0.84, 1.98) Neurologic deaths RR 0.91; CI (0.58, 1.43) Local recurrence HR 0.46; CI (0.24, 0.88) 12-month freedom from local recurrence 12-month freedom from local recurrence was significantly high in the SRS group than in the observation group (72% vs. 43%; HR 0.46 [95% CI 0.24-0.88])	Intervention vs Comparator: Adverse events No patients experienced adverse events related to placement of a stereotactic frame or treatment with SRS. Leptomeningeal disease The incidence of Leptomeningeal disease did not differ between study arms at 12 months

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Martin, 2018[125] Cagney, 2019[83] (same database, different patients) N/A Cohort Power calculation: No USA Author COI Trial record N: 480	Age: Immunotherapy: 61 (11), No-immunotherapy: 62 (11) Gender: 44% female Primary tumor type: Different cancer types; majority NSCLCs melanoma Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	SRS + Immunotherapy Tumors <2cm : 1800-2000 cGy, 1 fraction, 2-3cm 1800 cGy, 1 fraction, and >3cm 2500-3000 cGy, 5 fractions Immunotherapy (ipilimumab, pembrolizumab, nivolumab) SRS Tumors <2cm : 1800-2000 cGy, 1 fraction, 2-3cm 1800 cGy, 1 fraction, and >3cm 2500-3000 cGy, 5 fractions	Intervention: randomized, 115 analyzed Comparator: randomized, 365 analyzed Followup: 25 [median] (survivors) months	Intervention vs Comparator: Surviving median followup Median survival was 23.1 (IQR 15.4-42.1) vs 25.1 (15.2-34.3)	Intervention vs Comparator: Symptomatic radiation necrosis RR 2.92; CI (1.73, 4.94)
McPherson, 2010[126] N/A Cohort Power calculation: No USA Non industry Journal article N: 358	Age: 55 [median] Gender: 42% female Primary tumor type: Different cancer types; majority lung, melanoma, breast Metastases: Number: 1 (all patients had 1 brain metastasis) Volume: N/A Size: 76% < 3 cm Prognosis: All RPA 1 (48%) or 2 (52%)	Surgery + WBRT 3000 cGy, 10-15 fractions Resection of single brain metastases Surgery alone Resection of single brain metastases	Intervention: randomized, 142 analyzed Comparator: randomized, 216 analyzed Followup: 60 [median] months	Intervention vs Comparator: Survival HR 0.77; CI (0.6, 0.98) Local tumor recurrence (at site of surgery) HR 0.58; CI (0.34, 0.98) HR 0.58; CI 0.35, 0.98; p=0.04 for local recurrence, HR 0.43; CI 0.30, 0.61, p<.001 for distant recurrence , both favoring WBRT; withholding WBRT was an independent predictor of local and distant recurrence	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Mehta, 2003[127] Meyers, 2004[225]; Mehta, 2002[222] PCI-P120-9801, 9801 RCT Power calculation: Yes USA Non industry Journal article N: 401	Age: WBRT: 58 [median], MGd and WBRT: 58 [median] Gender: 55% female Primary tumor type: Different cancer types; 81% lung or breast Metastases: Number: WBRT: 33.2% 2-3 metastases and MGd and WBRT: 33.9% metastases Volume: N/A Size: N/A Prognosis: mixed good to moderate	WBRT + motexafin gadolinium 3000 cGy, 10 fractions, qd Motexafin gadolinium (radiosensitizer) 5 mg/kg/d, 2 to 5 hours before each fraction of WBRT WBRT 3000 cGy, 10 fractions, qd	Intervention: 193 randomized, 193 analyzed Comparator: 208 randomized, 208 analyzed Followup: 5 [median] months	Intervention vs Comparator: Overall survival No significant difference by treatment arm in survival (median, 5.2 months for combination vs 4.9 months for WBRT alone, p=.48) Neurologic deaths No difference was seen in deaths from CNS causes by treatment arm (48.6% vs 51.6% in WBRT; P=.60) Time to neurologic progression Significant difference in time to progression (p=0.018) in favor of the motexafin gadolinium group Time to progression of brain-specific quality-of-life (FACT-BR) No significant differences between arms Barthel Index No significant differences between arms	Intervention vs Comparator: Number of adverse events 763 vs 155

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Mehta, 2009[128] N/A RCT Power calculation: Yes Multinational USA, Canada, France, Germany, Austria, Belgium, Netherlands, Australia Industry funded Journal article N: 554	Age: 59.3 [mean] Gender: 43% female Primary tumor type: Lung cancer only; Metastases: Number: 81.2% had multiple metastases Volume: N/A Size: N/A Prognosis: moderate	WBRT + motexafin gadolinium 3000 cGy, 10 fractions, qd Motexafin gadolinium 5 mg/kg/d 2-5 hours before each fraction WBRT 3000 cGy, 10 fractions, qd	Intervention: 279 randomized, 279 analyzed Comparator: 275 randomized, 275 analyzed Followup: 24 [median] months	Intervention vs Comparator: Time to death HR:1.02 Progression-free survival No significant difference in progression-free survival Median interval to neurologic progression (based on standardized and commonly used scales) HR 0.78; CI (0.57, 1.06) The median interval to neurologic progression HR = 0.78, 95% CI, 0.58-1.06 in favor of the MGd Group (p = 0.109). Interval to neurocognitive progression The interval to neurocognitive progression (HR 0.78) was in favor of the MGd Group (p=0.057). Salvage treatment WBRT patients required significantly more salvage brain surgery or radiosurgery than did the WBRT+MGd patients (54 vs. 25)	Intervention vs Comparator: Number of adverse events 1012 vs 369 Nausea and vomiting RR 1.65; CI (1.3, 2.1) Number of patients RR 1.09; CI (0.84, 1.42) Liver function; asthenia; hypertension The most common MGd-related Grade 3 and above adverse events included liver function abnormalities (5.5%), asthenia (4.0%), and hypertension (4%).

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Merck Sharp & Dohme Corp, 2008[129] NCT00266812 RCT Power calculation: No USA Industry funded Trial record N: 35	Age: 64.3 (11.3) Gender: 40% female Primary tumor type: Lung cancer only; Metastases: Number: NR Volume: NR Size: NR Prognosis: NR	WBRT + temozolomide 4000 cGy in 20 fractions or 30 Gy in 10 fractions Temozolomide 75mg/m2/day p.o. for 14 days during radiation, 100 mg/m2/day at 14 days on/14 days off until intolerable or progression WBRT 40 Gy in 20 fractions or 30 Gy in 10 fractions	Intervention: 22 randomized, 18 analyzed Comparator: 13 randomized, 13 analyzed Followup: 6 months	Intervention vs Comparator: Progression-free survival at 6 months 8/18 (WBRT + temozolomide) vs 8/13 (WBRT alone)	Intervention vs Comparator: Number of participants with serious adverse events RR 1.44; CI (0.55, 3.79) Number of adverse events 70 vs 21 Number of events RR 1.44; CI (0.05, 39.91) Number of events RR 5.78; CI (0.33, 100.09)
Minniti, 2016[130] N/A Cohort Power calculation: No Italy Non industry Journal article N: 289	Age: Single fraction SRS: 64 [median], multifraction SRS: 62 Gender: Single-fraction SRS: 49% female, multifraction SRS: 50% female Primary tumor type: Different cancer types; 42% NSCLC, 17% breast Metastases: Number: Single-fraction SRS: 52% have multiple metastases, multifraction SRS: 51% have multiple metastases Volume: singe fraction SRS: 8.8 cm3 [median], multifration SRS: 12.5 cm3 [median] Size: N/A Prognosis: mixed	Single-Fraction SRS 1800 cGy for metastases of 2-3 cm and 1500-1600 cGy for metastases >=3 cm Multifraction SRS 2700 cGy, 3 fractions	Intervention: randomized, 151 analyzed Comparator: randomized, 138 analyzed Followup: 29 [median] months	Intervention vs Comparator: Alive at time of last analysis 11% in the single fraction and 22% in the multi-fraction group were still alive Recurrence One-year cumulative local control rate One-year cumulative local control rate was significantly higher in the multifraction SRS group than in the single-fraction SRS groups (91% vs. 77%)	Intervention vs Comparator: Radiation necrosis as suggested by MRI and PET-CT RR 2.58; CI (1.35, 4.92)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Mintz, 1996[131] N/A RCT Power calculation: No Canada Non industry Journal article N: 84	Age: Surgery + WBRT: 58.9 (8.98) and Radiation Alone: 58 (9.86) Gender: 45% female Primary tumor type: Different cancer types; 70% lung, breast, melanoma Metastases: Number: 1 (all had 1 brain metastasis) Volume: N/A Size: N/A Prognosis: mixed	WBRT + surgery 3000 cGy, 10 fractions, qd Craniotomy to achieve gross total removal of the metastases or lobectomy WBRT 3000 cGy, 10 fractions, qd	Intervention: 41 randomized, 41 analyzed Comparator: 43 randomized, 43 analyzed Followup: 6 [median] months	Intervention vs Comparator: Survival HR 1.12; CI (0.42, 2.98) There were no significant differences in the 30-day morbidity between groups Neurologic deaths RR 0.52; CI (0.22, 1.27) Spitzer quality of life score (4-6 months) SMD 0.09; CI (-0.34, 0.52) mean proportion of days KPS >= 70 SMD 0; CI (-0.43, 0.43)	Intervention vs Comparator: Number of events (surgical and radiation-related complications) 11 vs 8

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Mornex, 2003[132] Mornex, 2003[226] N/A RCT Power calculation: Underpowered France Non industry Journal article N: 76	Age: Fotemustine alone: 53.1 [mean], fotemustine+WBRT: 49.2 [median] Gender: 50% female Primary tumor type: Melanoma only; Metastases: Number: 66% had > 1 metastasis Volume: N/A Size: N/A Prognosis: mixed	WBRT + Fotemustine 3750 cGy, 15 fractions, qd Fotemustine 100 mg/m2 intravenously days 1, 8 and 15 weekly for 3 weeks; maintenance therapy to non-progressive patients 100 mg/m2 every three weeks until cerebral and/or extracerebral relapse or unacceptable toxicity; systemic corticosteroids (methylprednisolone 240 mg/day or dexamethasone 2 x 4 mg/day at the start of the treatment and adjusted according to the symptoms of intracranial hypertension) Fotemustine Fotemustine 100 mg/m2 intravenously days 1, 8 and 15 weekly for 3 weeks; maintenance therapy to non-progressive patients 100 mg/m2 every three weeks until cerebral and/or extracerebral relapse or unacceptable toxicity; systemic corticosteroids (methylprednisolone 240 mg/day or dexamethasone 2 x 4 mg/day at the start of the treatment and adjusted according to the symptoms of intracranial hypertension)	Intervention: 37 randomized, 37 analyzed Comparator: 39 randomized, 39 analyzed Followup: 4 [median] months	Intervention vs Comparator: Overall survival Median survival 105 (combination) vs 86 (WBRT alone) days Progressive disease Time to progression 56 vs 49 days (p=0.028) Objective response rate; control rate There was no significant difference in cerebral response (10.0% vs. 7.4%) or control rates (objective responses plus stable disease) after 7 weeks (47% vs. 30%).	Intervention vs Comparator: Number of events (hematological and non-hematological toxicities) 122 vs 125 Vomiting RR 0.53; CI (0.1, 2.71)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Muacevic, 2008[133] N/A RCT Power calculation: Yes Germany Industry funded Journal article N: 64	Age: SRS: 54.3 (11.7), surgery + WBRT: 58.3 (9.6) Gender: 58% female Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: 1 (all patients had 1 brain metastasis) Volume: N/A Size: SRS: 2.1 cm (0.8), Surgery + WBRT: 2.4 cm (0.6) Prognosis: mixed good to moderate	Surgery + WBRT 4000 cGy, 20 fractions, qd Complete resection using microsurgery SRS 1400-2700 cGy, 1 fraction	Intervention: 33 randomized, 33 analyzed Comparator: 31 randomized, 31 analyzed Followup: 12 months	Intervention vs Comparator: Length of survival HR 1.08; CI (0.3, 3.94) Overall survival did not differ between groups (p=0.8) Neurological death RR 3.13; CI (0.95, 10.33) 1-year local tumor control rate 82% in the surgery and WBRT vs 97% in the SRS group (p=0.,06) Health related quality of life Improved scores for the domains role functioning and quality of life favoring SRS were seen 6 weeks after SRS but differences were not maintained after 6 months KPS The difference in stabilized KPS or deterioration was not significant (p>0.1)	Intervention vs Comparator: Number of events (grade 4 acute and late toxicities) Number of events (acute and late toxicities) SRS had significantly lower frequency of grade 1/2 toxicities.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Mulvenna, 2016[10] Langley, 2013[216]; Medical Research Council[221] NCT00403065 RCT Power calculation: Yes Multinational UK and Australia Non industry Journal article N: 538	Age: 66 [median] Gender: 42% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: poor prognosis (37.5% RPA class 3, 55.9% RPA class 2, 5.6% RPA class 1)	WBRT + supportive care 2000 cGy, 5 fractions, qd Optimal supportive care with dexamethasone dexamethasone (given with a proton pump inhibitor with the dose determined by the patients ₣ symptoms) Supportive care alone Optimal supportive care with dexamethasone dexamethasone (given with a proton pump inhibitor with the dose determined by the patients ₣ symptoms)	Intervention: 269 randomized, 269 analyzed Comparator: 269 randomized, 269 analyzed Followup: 3 months	Intervention vs Comparator: Time to death HR 1.06; CI (0.89, 1.26) EQ-5D The number of patients with maintained or improved quality of life compared with baseline was similar between the groups at 4, 8, and 12 weeks. The difference in quality-adjusted life-years days was -4.7 days in favor of WBRT (90% CI 12.7 to 3.3)	Intervention vs Comparator: Any serious adverse events RR 1.09; CI (0.85, 1.39)
Murray, 1997[134] Gaspar, 2000[196]; Regine, 2001[240] RTOG 9104 RCT Power calculation: No USA Unclear funding source Journal article N: 429	Age: 59.8 [mean] Gender: 44% female Primary tumor type: Different cancer types; 83% lung, breast, melanoma Metastases: Number: 72% had multiple metastases Volume: N/A Size: N/A Prognosis: mixed	Accelerated hyperfractionated WBRT 5440 cGy, 34 fractions, bid (note: 2440 cGy of treatment was a focal boost to the metastases) Accelerated fractionated (standard) WBRT 3000 cGy, 10 fractions, qd	Intervention: randomized, 216 analyzed Comparator: randomized, 213 analyzed Followup: 5 [median] months	Intervention vs Comparator: Survival measured from the date of randomization The 1-year survival rates were not significantly different between groups (16% vs. 19%)	Intervention vs Comparator: Number of events (Grade 5) 1 vs 0 Number of events (acute and late tocixities) 275 vs 196

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
National Cancer Institute 2011[135] NCT01217411 RCT Power calculation: No USA Non industry Trial record N: 5	Age: WBRT + R04929097: 49 [median] , SRS + RO4929097: 49 [median] Gender: WBRT + R04929097: 33% female, SRS + RO4929097: 0% female Primary tumor type: Breast cancer only; Metastases: Number: 60% with 4 or more lesions Volume: NA Size: NA Prognosis: 60% with 4 or more brain lesions or otherwise not eligible for SRS	SRS + RO4929097 3000-4000 cGy in 10-20 fractions R04929097 (gamma secretase inhibitor) 5mg WBRT + R04929097 2000 cGy for tumors up to 1cm diameter, 1800 cGy for tumors from 1.1-2.5 cm, 1600 cGy for tumors >2.5 cm for patients with 3 or fewer brain lesions R04929097 5mg	Intervention: 2 randomized, 2 analyzed Comparator: 3 randomized, 3 analyzed Followup: 4 months	Not reported	Intervention vs Comparator: Death, not treatment related RR 0.75; CI (0.04, 13.43) Fatigue RR 0.75; CI (0.04, 13.43) Seizure RR 0.75; CI (0.04, 13.43) Vomiting RR 0.75; CI (0.04, 13.43) Headaches RR 0.75; CI (0.04, 13.43)
Noordijk, 1994[136] N/A RCT Power calculation: No Netherlands Non industry Journal article N: 63	Age: surgery + WBRT: 59.2 [mean], WBRT: 59.8 [median] Gender: 48% female Primary tumor type: Different cancer types; 81% lung, breast, melanoma Metastases: Number: 1 (all patients had 1 brain metastasis) Volume: N/A Size: N/A Prognosis: mixed	WBRT + surgery 4000 cGy, 20 fractions, bid Macroscopical excision of the metastasis, dexamethasone 16 mg/day started 4-5 days preoperatively and withdrawn postoperatively in about 10 days WBRT 4000 cGy, 20 fractions, bid Dexamethasone 16 mg/day started 4-5 days preoperatively and withdrawn postoperatively in about 10 days	Intervention: 32 randomized, 32 analyzed Comparator: 31 randomized, 31 analyzed Followup: 78 months	Intervention vs Comparator: Overall survival HR 1.56; CI (0.92, 2.65) Neurologic deaths RR 0.87; CI (0.41, 1.85)	Intervention vs Comparator: Number of patients with complications of radiotherapy (headache, nausea, and vomiting) RR 1.08; CI (0.51, 2.29)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Pesce, 2012[137] Research Swiss Group for Clinical Cancer, 2009[256] NCT00238251 RCT Power calculation: Yes Switzerland Industry funded Journal article N: 59	Age: WBRT + temozolomide: 63 [median], WBRT + gefitinib: 57 [median] Gender: 39% female Primary tumor type: Lung cancer only; Metastases: Number: WBRT + temozolomide: 58% had more than 4 metastases, WBRT + gefitinib: 50% had more than four metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m2 p.o. daily for 21 days every 28 days WBRT + gefitinib 3000 cGy, 10 fractions, qd Gefitinib 250 mg p.o. daily continuously	Intervention: 43 randomized, 43 analyzed Comparator: 16 randomized, 16 analyzed Followup: 34 [median] (survivors) months	Intervention vs Comparator: Overall Survival HR 1.29; CI (0.47, 3.55) Median overall survival in the gefitinib arm was 6.3 months (95% CI 2.1-14.6), and 4.9 months (95% CI 2.3-5.6) in TMZ treated patients Deaths due to CNS progression RR 0.43; CI (0.18, 0.98)	Intervention vs Comparator: Number of events (grade 4) 1 vs 1 Number of adverse events 36 vs 11 Fatigue RR 1.49; CI (0.67, 3.29) Nausea/vomiting RR 4.47; CI (0.26, 75.46)
Phillips, 1995[138] RTOG 8905 RCT Power calculation: No USA Non industry Journal article N: 72	Age: WBRT + bromodeoxyuridine : 60.7 [mean], and radiotherapy: 59.5 [mean] Gender: 44% female Primary tumor type: Different cancer types; 73% lung or breast Metastases: Number: 66% had multiple metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + bromodeoxyuridine 3750 cGy, 15 fractions, qd Bromodeoxyuridine 0.8 g/m2 per day, continuous 96 h i.v. infusion WBRT 3750 cGy, 15 fractions, qd	Intervention: 35 randomized, 34 analyzed Comparator: 37 randomized, 36 analyzed Followup: 6 [median] months	Intervention vs Comparator: Survival No significant difference between treatment arms (median 4.3 vs 6.12 months for combination vs WBRT alone) Progressive disease Progression 3/21 (combination) vs 0/23 (WBRT only) at 3 months	Intervention vs Comparator: Grade 5 SAE RR 6.35; CI (0.33, 122.23) Number of adverse events 30 vs 37

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Pirzkall, 1998[139] N/A Cohort Power calculation: No Germany Non industry Journal article N: 236	Age: SRS: 57.4 [median], SRS+WBRT: 55.6 [median] Gender: 32% female Primary tumor type: Different cancer types; predominantly lung cancer Metastases: Number: Predominantly solitary brain metastasis Volume: NA Size: RS: 20 mm median diameter (range 3-38), RS+WBRT: 20 (3-36) Prognosis: Excluded patients with >3 metastases or recurrent metastases	SRS + WBRT SRS: 1000-2700 cGy; total radiation dose 3000-5000 cGy (median 3600 cGy) SRS 1000-3000 cGy	Intervention: randomized, 158 analyzed Comparator: 78 randomized, 78 analyzed Followup: 6 [median] months	Intervention vs Comparator: 1 and 2 year survival rates Intervention: 1-year survival 30.4%, 2-year survival 13.9%; 1-year survival 19.2%, 2-year survival 8.3% Local control rates Intervention: 1-year 92%, 2-year 86%; control: 1-year 89%, 2-year 72% (p=0.13) Disease control rate Disease control rates were not significantly different between the groups	Not reported
Prabhu, 2017[140] N/A Cohort Power calculation: No USA Non industry Journal article N: 213	Age: SRS+surgery: 59.5 (IQR 51-68), SRS alone: 58 (IQR 48-66) Gender: N/A Primary tumor type: Different cancer types; lung, breast, melanoma, renal, other Metastases: Number: 66% has 1 metastasis Volume: SRS+surgery: 9.6 cm3, SRS: 5.9 cm3 Size: N/A Prognosis: mixed	Surgery + pre- or post-surgery SRS SRS: 1800 cGy for lesions 2.1 to 3 cm and 1500 cGy for lesions 3.1 to 4 cm; the preoperative SRS dose was reduced by 20% Gross total resection SRS 1800 cGy for lesions 2.1 to 3 cm and 1500 cGy for lesions 3.1 to 4 cm	Intervention: randomized, 153 analyzed Comparator: randomized, 60 analyzed Followup: 13 [median] months	Intervention vs Comparator: Overall survival One-year local recurrence rate The local recurrence rate was significantly lower with surgery and SRS (36.7% vs 20.5%)	Intervention vs Comparator: Radiation necrosis (development of contrast-enhancing mass with previous radiation treatment fields and conventional imaging features, including soap-bubble appearance; additional imaging where necessary, neuro-oncology tumor board consensus No significant difference in RN rates between groups at 1 year and 2 years. Adjusted HR = 1.32; 95% CI, 0.53-3.27; p=.55. Leptomeningeal disease No significant difference in leptomeningeal disease between groups (p=.13). Adjusted analysis not performed.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Priestman, 1996[141] Royal College of Radiologists' Trial RCT Power calculation: Yes UK Non industry Journal article N: 533	Age: 2 fractions Group: 51% < 60, 10 fractions Group : 49% < 60 Gender: 50% female Primary tumor type: Different cancer types; 58% lung or breast, 17% other Metastases: Number: 56% had multiple metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT 30 Gy 3000 cGy, 10 fractions, qd WBRT 12 Gy 1200 cGy, 2 fractions, qd	Intervention: 270 randomized, 263 analyzed Comparator: 274 randomized, 270 analyzed Followup: 40 months	Intervention vs Comparator: Survival was measured from the date of diagnosis of brain metastases and from the time of randomization HR 0.93; CI (0.77, 1.12) Death due to tumor progression RR 0.99; CI (0.92, 1.06) Overall response Overall responses were not significantly different between the groups (44% vs. 39%)	Intervention vs Comparator: Number of participants (excluding alopecia) RR 0.46; CI (0.24, 0.87) Nausea/vomiting RR 0.23; CI (0.05, 1.05) Headache RR 0.17; CI (0.02, 1.41) Morbidity Drowsiness (7 vs 6), dizziness (2 vs 4), cerebral hemorrhage (0 vs 1), blurred vision (0 vs 1), fits (1 vs 1)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Quantin, 2010[142] N/A RCT Power calculation: Not relevant outcome France Non industry Journal article N: 70	Age: Group A: 59.1(7.8), Group B: 56(9.5) Gender: 24% female Primary tumor type: Lung cancer only; Metastases: Number: Group A: 54.05% have one metastases, Group B: 48.48% have one metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + Cisplatin-Vinorelbine-Ifosfomide 5400 cGy, 30 fractions, qd (3600 cGy to whole brain, 1800 cGy boost to metastases) Vinorelbine 30 mg/m2 on days 1 and 8 of the radiotherapy; Ifosfamide 1.5 g/m2 5-hour infusion, qd (day 1-3) plus uroprotection by uromitexan 2 g/m2; Cisplatin 100 mg/m2 on day 2 with hyper-hydration, methyl-prednisolone 120 mg per day from day 1 to day 4, then 40 mg per day from day 5 to day 12; recombinant-HuG-CSF permitted WBRT + Ifosfamide 5400 cGy, 30 fractions, qd (3600 cGy to whole brain, 1800 cGy boost to metastases) Ifosfamide 3 g/m2 intravenously and daily from day 1 to day 4 of radiotherapy plus uroprotection by uromitexan 3.5 g/m2, methylprednisolone from day 1 to day 12, and hemotopoietic support with r-HuG-CSF day 5 to day 14	Intervention: 37 randomized, 37 analyzed Comparator: 33 randomized, 33 analyzed Followup: 21 [minimum] months	Intervention vs Comparator: Time from random assignment to the date of death Median overall survival did not significantly differ between the two groups (8.5 months [6.4-10.8] in combination and 5.7 months [4.6-11.9] in ifosfamide group; p= 0.82) Progressive disease 4/37 (combination) vs 5/33 (cisplatin) patients with progressive disease Overall response rate The overall response rates did not significantly differ between the groups (45.9% vs. 33.3%)	Intervention vs Comparator: Number of events (grade 4 hematological toxicity) 55 vs 38 events Number of events (hematological toxicity) 140 vs 132 Febrile neutropenia; infections; transfusion and readmission Febrile neutropenia and documented infections were more frequently observed in the WBRT + Cisplatin-Vinorelbine-Ifosfomide group than in the WBRT + Ifosfomide but the differences were not significant. Red blood cell transfusions and readmission for antibiotic infusions significantly affected more patients in WBRT + Cisplatin-Vinorelbine-Ifosfomide group than in WBRT + Ifosfomide group.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Rades, 2007[143] N/A Cohort Power calculation: No Germany Unclear funding source Journal article N: 206	Age: Group A: 53% <60, Group B: 52% <60 Gender: 52% female Primary tumor type: Lung, breast, or melanoma cancer; Metastases: Number: 1-2 brain metastases (median of 1) Volume: N/A Size: N/A Prognosis: mostly moderate to good	Surgery + WBRT 3000 cGy, 10 fractions or 4000 cGy, 20 fractions Resection of metastases SRS 1800-2500 cGy, 1 fraction	Intervention: randomized, 112 analyzed Comparator: randomized, 94 analyzed Followup: 9 [median] (survivors) months	Intervention vs Comparator: Overall survival No significantly difference in overall survival between groups. No significantly difference in local or distant intracerebral failure between groups	Intervention vs Comparator: Grade 3 acute toxicity rates (Common Toxicity Criteria (version 2.0) Surgery-related complications, such as brain abscess, occurred in 2% of Group B patients. Grade 3 late toxicity rates according to the RTOG criteria were 4% in Group A and 3% in Group B.
Rades, 2017[144] N/A Cohort Power calculation: No Germany Non industry Journal article N: 252	Age: WBRT + SRS: 52% ≤58, WBRT: 52% ≤58 Gender: 60% female Primary tumor type: Different cancer types; majority lung or breast Metastases: Number: WBRT + SRS: 52% have 2 -3, WBRT: 52% have 2-3 Volume: N/A Size: N/A Prognosis: mixed mostly moderate to good	WBRT + SRS WBRT: 2000 cGy, 5 fractions or 3000 cGy, 10 fractions or 4000 cGy, 20 fractions. SRS: 1500-2500 cGy or SRS with two to five fractions of 400-800 cGy WBRT WBRT: 2000 cGy, 5 fractions or 3000 cGy, 10 fractions or 4000 cGy, 20 fractions	Intervention: 84 randomized, 84 analyzed Comparator: 168 randomized, 168 analyzed Followup: 11 [median] months	Intervention vs Comparator: Overall survival The overall survival rates were not significantly different between the groups Intracranial control rate WBRT + SRS had significantly better intracranial control rates, compared to the WBRT group	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Raman, 2020[145] British Columbia Cancer, 2019[179] NCT02220491 RCT Power calculation: Not relevant outcome Canada Non industry Journal article N: 20	Age: 65 (46-85) [median (range)] Gender: 50% female Primary tumor type: Different cancer types; Lung, breast Metastases: Number: 2.5 [median] (1-7) [range] Volume: N/A Size: 11.5 [median] (6-34) [range] mm Prognosis: Poor prognosis (50% DS-GPA 0.0-1.0; 45% DS-GPA 1.5-2.0; 5% DS-GPA 2.5-3.0)	SRS 1500 cGy, 1 fraction, qd WBRT 2000 cGy, 5 fractions qd	Intervention: 10 randomized, 10 analyzed Comparator: 10 randomized, 10 analyzed Followup: 7 [median] months	Intervention vs Comparator: Median survival HR 2; CI (0.78, 5.17) Progression free survival HR 3.1; CI (0.74, 12.93) Number of deaths due to brain metastases RR 3; CI (0.79, 11.44) Local and distant recurrence rate 3- and 6-month local recurrence-free survivals were 72.9% and 58.3% in SRS and 85.7% and 71.4% in WBRT; distant brain recurrence-free survivals were 17.8% and 0% in SRS and 87.5% and 87.5% in WBRT KPS score at 3 months SMD 0.55; CI (-0.36, 1.46) Montreal Cognitive Assessment (max score 30) SMD -0.02; CI (-0.91, 0.87) Retreatment rate The cumulative rates of retreatment were 40% in SRS and 40% in WBRT	Intervention vs Comparator: Number of toxicities (events) 25 vs 22 Radionecrosis RR 1; CI (0.02, 45.63) Patients experiencing fatigue RR 0.1; CI (0.01, 1.6) Grade 3 and above seizure RR 2; CI (0.08, 53.13) Patients experiencing headaches RR 0.25; CI (0.01, 4.88)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Rauschenberg, 2019[146] N/A Cohort Power calculation: No Germany Author COI Journal article N: 208	Age: 60.1 (26.6-92.7) [median (range)] Gender: 36% Primary tumor type: Melanoma only; Metastases: Number: WBRT: 5 (1-100) [median (range)], SRS: 2 (1-7) [median (range)] Volume: N/A Size: N/A Prognosis: mixed, 80% ECOG performance of 0-1 (10% unknown, 10% >1), but RPA classification would have been at least RPA class 2 as 84% had extracranial metastases	SRS plus immunotherapy 2000 cGy [median, range (900-6000 cGy)], single fraction [median, range (240-2500 cGy fractions)] immunotherapy (anti-PD-1 and/or anti-CTLA-4) of unknown intensity or dose WBRT plus immunotherapy 3000 cGy, 10 fractions qd (range 750-5400 cGy) immunotherapy (anti-PD-1 and/or anti-CTLA-4) of unknown intensity or dose SRS plus targeted therapy (BRAF or BRAF + MEK inhibitors) 2000 cGy [median, range (900-6000 cGy)], single fraction [median, range (240-2500 cGy fractions)] BRAF inhibitor OR BRAF inhibitor plus MEK inhibitor (targeted therapy, unknown intensity or dose)	Intervention: randomized, 87 analyzed Comparator: randomized, 51 analyzed Followup: 7.3 [median] months	Intervention vs Comparator: Time to death SRS and immunotherapy achieved the highest overall survival rates	Intervention vs Comparator: Radiation necrosis RR 4.69; CI (0.25, 86.91) Intervention vs additional comparison: Radiation necrosis RR 2.48; CI (0.14, 45.49)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Regine, 2004[147] Patchell, 1998[235] N/A RCT Power calculation: Not relevant outcome USA Non industry Journal article N: 95	Age: Surgery + WBRT: 60 [median], Surgery alone: 58 [median] Gender: 42% female Primary tumor type: Different cancer types; 71% NSCLC, breast, melanoma Metastases: Number: 1 (all patients had single metastasis) Volume: N/A Size: N/A Prognosis: mixed	Surgery + WBRT 5040 cGy, 28 fractions, qd Complete surgical resection Surgery Complete surgical resection	Intervention: 49 randomized, 49 analyzed Comparator: 46 randomized, 46 analyzed Followup: 11 [median] months	Intervention vs Comparator: Overall Survival HR 0.9; CI (0.35, 2.27) RR 0.91 (95%CI 0.59-1.40) Neurologic deaths RR 0.33; CI (0.14, 0.77) Brain recurrence (original and distant) Local recurrence of metastatic cancer in the brain was 6% in the radiation and 13% in the observation group Length of time KPS remaining 70% or more No statistical difference between two groups	Not reported
Robinet, 2001[148] GFPC 95-1 RCT Power calculation: Yes France Industry funded Journal article N: 176	Age: Arm A: 57 [median], Arm B: 57 [median] Gender: 14/% female Primary tumor type: Lung cancer only; Metastases: Number: 64% have multiple metastases Volume: N/A Size: N/A Prognosis: mixed	Chemotherapy + WBRT 3000 cGy, 10 fractions, qd Cisplatin 100 mg/m2 on day 1 and vinorelbine 30 mg/m2 on days 1, 8, 15, 22 for 2 cycles Chemotherapy + delayed WBRT 3000 cGy, 10 fractions, qd delayed WBRT (for nonreponders after at least 2 cycles of chemotherapy) Cisplatin 100 mg/m2 on day 1 and vinorelbine 30 mg/m2 on days 1, 8, 15, 22 for 2 cycles	Intervention: 85 randomized, 85 analyzed Comparator: 86 randomized, 86 analyzed Followup: 6 [median] months	Intervention vs Comparator: Overall survival Progression-free survival Objective response There were no significant differences in overall objective response rates (20% vs. 21%) and intracranial objective response rates (33% vs. 27%) between groups	Intervention vs Comparator: Toxic deaths RR 1.18; CI (0.41, 3.37) Number of events (hematologic toxicity and non-hematologic side effects) 147 vs 129 events Nausea and vomiting (grade 3-4) RR 1.01; CI (0.21, 4.87) Neutropenia; treatment-related deaths Severe or life-threatening neutropenia (grade 4) occurred in 35% of delayed WBRT patients and 36% of WBRT patients. There were thirteen treatment-related deaths (six in delayed WBRT and seven in WBRT).

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Rojas-Puentes, 2013[149] Instituto Nacional de Cancerologia de Mexico[206] NCT01894633 RCT Power calculation: Not relevant outcome Mexico Non industry Journal article N: 73	Age: Chloroquine: 55.7 [median], control: 52 [median] Gender: 73% female Primary tumor type: Different cancer types; 94% lung or breast Metastases: Number: CLQ: 71.8% had less than 4 and Control: 64.7% had less than 4 Volume: N/A Size: N/A Prognosis: mostly moderate	WBRT + chloroquine 3000 cGy, 10 fractions, qd Chloroquine 150 mg/day 1 hour prior to WBRT for 28 days WBRT + Placebo 3000 cGy, 10 fractions, qd	Intervention: 40 randomized, 39 analyzed Comparator: 36 randomized, 34 analyzed Followup: 8 [median] months	Intervention vs Comparator: Overall survival to the date of death or the last follow-up visit Median survival was 8.4 vs 10.2 months (n,s,) Progression-free survival Rates at 1-year were 84% vs 55% Quality of life No differences between the treatment arms Overall response rate; 1-year progression-free survival of brain metastases rate The overall response rates were not significantly different between arms (54% vs. 55%). The progression-free survival of the brain metastases rate at one year was significantly higher for the CLQ arm than the control arm (83.9% vs. 55.1%)	Intervention vs Comparator: Toxicity in either arm No toxicity (grade 4 or 5) was observed in either arm, and there were no significant differences in toxicity between the arms.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Roos, 2006[151] TROG 98.05 RCT Power calculation: Underpowered Australia Non industry Journal article N: 19	Age: WBRT arm: 51.5 [median] and Observation arm: 61 [median] Gender: 26% female Primary tumor type: Different cancer types; 63% lung or melanoma Metastases: Number: 1 (all patients had a single metastasis) Volume: N/A Size: N/A Prognosis: good to moderate	(Surgery or SRS) + WBRT WBRT: 3000 cGy, 10 fractions, qd OR 3600 cGy, 18 fractions, qd Surgery or SRS for solitary brain metastases, dexamethasone and anti-convulsants as required (Surgery or SRS) + Observation Surgery or SRS for solitary brain metastases, dexamethasone and anti-convulsants as required	Intervention: 10 randomized, 10 analyzed Comparator: 9 randomized, 9 analyzed Followup: 74 [median] months	Intervention vs Comparator: Overall survival HR 1.01; CI (0.37, 2.79) Progression-free survival HR 1.27; CI (0.46, 3.54) No significant difference in CNS failure-free survival between the arms (5.7 vs. 4.5 months) CNS relapse HR 2.81; CI (0.72, 10.9) 30% in the WBRT vs 78% (p-0.12) reported CNS relapse Quality of life No evidence of difference between the groups Time to deterioration of WHO performance status to >1 There was no statistically significant difference between the arms (P = 0.80, HR = 1.16, 95% CI = 0.38-3.48) Neurocognitive function No evidence of difference between the groups	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Roos, 2011[150] Royal Adelaide Hospital, 2009[242] NCT00124761 RCT Power calculation: Yes Australia Non industry Journal article N: 21	Age: SRS + WBRT: 63 [median], surgery + WBRT: 58 [median] Gender: 48% female Primary tumor type: Different cancer types; 48% lung, 33% other Metastases: Number: 1 (all patients had 1 brain metastsis) Volume: N/A Size: SRS + WBRT: 17 mm [median], Surgery + WBRT: 24 mm [median] Prognosis: mixture, majority moderate prognosis	SRS + WBRT SRS: 1500-2000 cGy, 1 fraction. WBRT: 3000 cGy, 10 fractions, qd Corticosteroid use at clinician's discretion Surgery + WBRT 3000 cGy, 10 fractions, qd Standard stereotactic guided neurosurgical technique surgery, corticosteroid use at clinician's discretion	Intervention: 11 randomized, 11 analyzed Comparator: 11 randomized, 10 analyzed Followup: 16 [minimum] (survivors) months	Intervention vs Comparator: Overall survival was measured from randomisation to death from any cause HR 0.53; CI (0.2, 1.43) Progression-free survival HR 0.55; CI (0.22, 1.38) Local or distant brain recurrence 3/11 in the SRS + WBRT had distant brain recurrence, 2/11 local failure compared to 3/10 (distant) failure in the surgery+ WBRT group QLQ-C30 global scale SMD 1.22; CI (0.26, 2.18) KS No significant differences between arms at 2 months Neurological function No significant differences between arms at 2 months	Intervention vs Comparator: Grade 4 toxicities RR 0.91; CI (0.02, 41.68) Severe or loss of ability to perform RR 5.45; CI (0.31, 96.09)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Saha, 2014[152] N/A RCT Power calculation: No India Non industry Journal article N: 56	Age: Arm A: 50% │50-<60, Arm B: 46.15% │50-<60 Gender: 48% female Primary tumor type: Different cancer types; 88% breast or lung Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: mixed	WBRT 30Gy 3000 cGy, 10 fractions, qd Dexamethasone 8 mg bid at the beginning and tapered to 4 mg/day; antiemetics, hematinics and proton pump inhibitors throughout the treatment period; blood transfusions and anti-seizure medications as needed WBRT 20Gy 2000 cGy, 5 fractions, qd Dexamethasone 8 mg bid at the beginning and tapered to 4 mg/day; antiemetics, hematinics and proton pump inhibitors throughout the treatment period; blood transfusions and anti-seizure medications as needed	Intervention: randomized, 30 analyzed Comparator: randomized, 26 analyzed Followup: 7 [median] months	Intervention vs Comparator: Time to death HR 0.98; CI (0.55, 1.75) Progressive disease 7% (30 Gy) vs 19% (20 Gy) of patients with progressive disease Barthel's ADL at 6 weeks SMD 0.12; CI (-0.4, 0.65)	Intervention vs Comparator: Number of events (grade 4) No SAE in either group Number of adverse events 120 vs 104 events
Sneed, 2002[153] N/A Cohort Power calculation: No Multinational Brazil and USA Unclear funding source Journal article N: 569	Age: RS +WBRT: 59 [median], RS: 61 [median] Gender: N/A Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: SRS +WBRT: 58% have one brain metastases, SRS: 63% have one brain metastases Volume: N/A Size: N/A Prognosis: mixed	SRS + WBRT WBRT 3000 cGy in 10 fractions, 3000 cGy in 12 fractions, 3500 cGy in 14 fractions, 3750 cGy in 15 fractions, 4000 Gy in 20 fractions, or 5040 cGy in 28 fractions; SRS no details were collected SRS No details of SRS were collected	Intervention: 301 randomized, 301 analyzed Comparator: 268 randomized, 268 analyzed Followup: 43 [median] (survivors) months	Intervention vs Comparator: Time to death HR 0.99; CI (0.83, 1.18)	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Sperduto, 2013[154] Sperduto, 2013[231] NCT00096265 RCT Power calculation: Yes USA Non industry Journal article N: 126	Age: Arm 1: 64, (median) Arm 2: 63 (median), and Arm 3: 61 (median) Gender: N/A Primary tumor type: Lung cancer only; Metastases: Number: 1-3 brain metastases (mean not provided) Volume: N/A Size: N/A Prognosis: mixed	SRS+WBRT + temozolomide SRS: 1500-2400 cGy, 1 fraction; WBRT: 3750 cGy, 15 fractions, qd Temozolomide (150-200 mg/m(2)/day x 5 days/month) SRS+WBRT SRS: 1500-2400 cGy, 1 fraction; WBRT: 3750 cGy, 15 fractions, qd SRS+WBRT + erlotinib SRS: 1500-2400 cGy, 1 fraction; WBRT: 3750 cGy, 15 fractions, qd Erlotinib 150 mg/day	Intervention: 40 randomized, 40 analyzed Comparator: 44 randomized, 44 analyzed Additional comparator: 41 randomized, 41 analyzed Followup: 34 [median] (survivors) months	Intervention vs Comparator: Overall survival HR 1.43; CI (0.89, 2.31) Multi-variate HR SRS+WBRT + temozolomide 1.46; CI 0.91, 2.36; SRS +WBRT + erlotinib vs WBRT + SRS: 1.46; CI 0.91, 2.34 CNS progression-free survival Median CNS progression-free survival: 4.6 (+temozolomide), 8.1 (SRS+WBRT alone), 4.8 (+erlotinib) months Time to CNS progression Times to CNS progression for the three arms were not statistically significant Zubrod score WBRT + SRS produced less deterioration in performance status at 6 months than did either drug arm	Intervention vs Comparator: Grade 5 toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) RR 2.2; CI (0.08, 63.82) The rates of serious toxicity related to therapy for WBRT + SRS, WBRT + SRS + TMZ, and WBRT+ SRS+ ETN were 11%, 41%, and 49% (P<.001), respectively. Brain necrosis RR 2.2; CI (0.08, 63.82) Intervention vs additional comparison: Grade 5 toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) RR 1.02; CI (0.07, 15.83) Brain necrosis RR 1.02; CI (0.07, 15.83)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Suh, 2006[155] Scott, 2007[244]; Stea, 2006[253]; Spectrum Pharmaceuticals, 2000[250], Nabid, 2004[229], Shaw, 2004[245], Stea, 2004[252], Suh, 2004[255], Suh, 2004[254] NCT00005887 RCT Power calculation: Yes USA Non industry Journal article N: 515	Age: Efaproxiral: 72% <65 and Control: 73% <65 Gender: 56% female Primary tumor type: Different cancer types; 78% lung or breast Metastases: Number: Efaproxiral: 52% had 3 or more metastases and Control: 47% had 3 or more metastases Volume: N/A Size: N/A Prognosis: mixed	WBRT + Efaproxiral 3000 cGy, 10 fractions, qd Efaproxiral (radiosensitizer) 75 or 100 mg/kg intravenous, supplemental oxygen WBRT 3000 cGy, 10 fractions, qd Supplemental oxygen	Intervention: 265 randomized, 265 analyzed Comparator: 250 randomized, 250 analyzed Followup: 15 [median] months	Intervention vs Comparator: Survival measured from the time of random assignment until death or January 31, 2003 HR 0.87; CI (0.72, 1.05) Intracranial progression-free survival Median 4 vs 3.5 months (p=0.21) Neurologic deaths RR 1.16; CI (0.74, 1.82) Quality of life A larger percentage of patients in the efaproxiral arm had stable or improving quality-of-life scores over the course of the follow-up visits. Response rate Response rates (radiographic complete response plus partial response) were not significantly different between groups	Intervention vs Comparator: Grade 4 events RR 1.11; CI (0.69, 1.78) Vomiting RR 1.89; CI (0.72, 4.95) Headache RR 1.68; CI (0.75, 3.73)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Suh, 2008[156] Spectrum Pharmaceuticals, 2007[249] NCT00083304 RCT Power calculation: Not relevant outcome USA Industry funded Trial record N: 368	Age: N/A Gender: N/A Primary tumor type: Breast cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT + Efaproxial 3000 cGy, 10 fractions, qd Efaproxiral; supplemental oxygen WBRT 3000 cGy, 10 fractions, qd Supplemental oxygen	Intervention: randomized, 182 analyzed Comparator: randomized, 183 analyzed Followup: 13 [median] months	Intervention vs Comparator: Overall survival HR 0.87; CI (0.69, 1.09) KPS KPS, and neurological signs and symptoms improvement in WBRT+Efaproxiral failed to achieve statistical significance. Overall response rate; neurological signs and symptoms The overall response rates in the brain at 3 months (complete response plus partial response, 31% vs. 27%) and neurological signs and symptoms improvement were not significantly different between the groups	Not reported
Tetu, 2019[157] Assistance Publique - Hopitaux de Paris[234] NCT02828202 Cohort Power calculation: No France Non industry Journal article N: 262	Age: 61 [median] Gender: 42% female Primary tumor type: Melanoma only; Metastases: Number: 44% had < 3 brain metastases Volume: N/A Size: N/A Prognosis: mixed	RT + Immunotherapy/targeted WBRT, SRS or WBRT after SRS as per local practices (insufficient details) Targeted therapy (anti-BRAF anti-MEK) or immunotherapy (ipilimumab or anti-PD1), according to investigator ƒs choice Immunotherapy/targeted Targeted therapy (anti-BRAF anti-MEK) or immunotherapy (ipilimumab or anti-PD1), according to investigator ƒs choice	Intervention: randomized, 93 analyzed Comparator: randomized, 169 analyzed Additional comparator: randomized, analyzed Followup: 7 [median] months	Intervention vs Comparator: Overall survival HR 0.6; CI (0.45, 0.8) Progression-free survival Progressive disease	Intervention vs Comparator: Adverse events (any grade) The incidence of AEs of any grade was 73% in the combined treatment group and 61% in the immunotherapy/targeted therapy group (p = 0.4).

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
University of Michigan, 2016 [158] Silk, 2015[246] NCT02097732 RCT Power calculation: No USA Industry funded Trial record N: 4	Age: 58 [mean] 48-69 [range] Gender: 25% Primary tumor type: Melanoma only; Metastases: Number: NA Volume: NA Size: NA Prognosis: unclear	Induction ipilimumab + SRS N/A Ipilimumab 3mg/kg given intravenously every 3 weeks, total of 4 doses SRS followed by ipilimumab NA Ipilimumab 3mg/kg given intravenously prior to SRS, every 3 weeks, total of 4 doses	Intervention: 3 randomized, 3 analyzed Comparator: 1 randomized, 1 analyzed Followup: NA months	Not reported	Intervention vs Comparator: Serious adverse events (event that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect) RR 0.33; CI (0.01, 8.18)
Ushio, 1991[159] N/A RCT Power calculation: No Japan Non industry Journal article N: 100	Age: Group A: 62 [mean], Group B: 56 [mean], Group C: 58 [mean] Gender: 15% female Primary tumor type: Different cancer types; majority NSCLC (some SCLC) Metastases: Number: 33% had multiple metastases Volume: N/A Size: N/A Prognosis: unclear	WBRT + Methyl-CCNU/ACNU + Tegafur 4000 cGy, 20 fractions Chloroethylnitrosoureas methyl-CCNU 100 to 120 mg/m2 p.o. or ACNU 80 to 100 mg/m2 i.v. every 6 to 8 weeks; Tegafur 300mg/m2/day; conventional doses of corticosteroids as needed WBRT 4000 cGy, 20 fractions Conventional doses of corticosteroids as needed WBRT + Methyl-CCNU/ACNU 4000 cGy, 20 fractions Chloroethylnitrosoureas methyl-CCNU 100 to 120 mg/m2 p.o. or ACNU 80 to 100 mg/m2 i.v. every 6 to 8 weeks; conventional doses of corticosteroids as needed	Intervention: 33 randomized, 29 analyzed Comparator: 31 randomized, 25 analyzed Additional comparator: 36 randomized, 34 analyzed Followup: 82 months	Intervention vs Comparator: Time to death Median survival 27 (control) ,30.5, (comparator) and 29 (intervention) weeks; 1 long-term survivor (more than 5 years) in the control group, 3 in the comparison group, 1 in the intervention group Progressive disease Patients with progression: 1/19 (intervention) vs 4/14 (control), 2/16 (comparator) Complete resolution of tumor Complete resolution of the tumor was noted in 63%, 69%, and 29% of the patients. Tumor regression of greater than or equal to 50% was seen in 74%, 69%, and 36% of the patients. The difference in the response rates between WBRT + Methyl-CCNU/ACNU + Tegafur and WBRT alone was significant	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Vecht, 1993[160] N/A RCT Power calculation: No Netherlands Non industry Journal article N: 63	Age: surgery + WBRT: 59.2 (10.3) and WBRT: 59.8 (12) Gender: 48% female Primary tumor type: Different cancer types; majority lung, breast, melanoma Metastases: Number: 1 (all patients had 1 brain metastasis) Volume: N/A Size: N/A Prognosis: unclear	WBRT + surgery 4000 cGy, 20 fractions, bid Neurosurgical excision, dexamethasone up to 16 mg/day during radiation therapy WBRT 4000 cGy, 20 fractions, bid	Intervention: 33 randomized, 32 analyzed Comparator: 33 randomized, 31 analyzed Followup: 70 months	Intervention vs Comparator: Overall survival HR 0.6; CI (0.24, 1.48) Neurologic death RR 0.87; CI (0.41, 1.85) World Health Organization performance status <= 1 Improvement in functional status occurred more rapidly and for longer periods of time after WBRT+surgery than after WBRT alone but the result did not reach statistical significance	Intervention vs Comparator: Number of participants with complications of radiotherapy such as headache, nausea, or vomiting RR 1.08; CI (0.51, 2.29)
Verger, 2005[161] N/A RCT Power calculation: Yes Spain Non industry Journal article N: 82	Age: WBRT: 58.3 (11.6), WBRT+TMZ: 57.8 (12.2) Gender: 65% female Primary tumor type: Different cancer types; majority lung or breast Metastases: Number: WBRT: 3 [median], WBRT + TMZ: 2 [median] Volume: N/A Size: N/A Prognosis: mixed, majority moderate to poor	WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m2 /d during WBRT, 5 d/wk for 2 weeks, followed by two 5-day cycles of 200 mg/m2 /d (150 mg/m2 in heavily pretreated patients) every 28 days; dexamethasone (initial dose 4 mg/d) at the lowest dose needed; anticonvulsant agents only used in patients with seizure; antiemetic metoclopramide 10 mg/6 h or ondansetron 4 mg/12 h WBRT 3000 cGy, 10 fractions, qd Dexamethasone (initial dose 4 mg/d) at the lowest dose needed; anticonvulsant agents only used in patients with seizure; antiemetic metoclopramide 10 mg/6 h or ondansetron 4 mg/12 h	Intervention: 41 randomized, 41 analyzed Comparator: 41 randomized, 41 analyzed Followup: 5 [median] months	Intervention vs Comparator: Overall survival HR 0.69; CI (0.37, 1.27) No significant difference between arms Percentage of patients with progression-free survival at 90 days 72% vs 54% favoring the combination Death from brain metastases RR 1.75; CI (1.13, 2.71) Progressive disease at 90 days 3/41 (WBRT + temozolomide) vs 9/41 (WBRT alone) patients with progressive disease Objective response rate The objective response rates at 30 and 90 days were similar in both arms	Intervention vs Comparator: Grade 3 or worse vomiting Nausea and vomiting were reported in 32% of patients in the WBRT + temozolomide arm (one grade 3 or worse) and 22% in the WBRT arm. Grade 3 or worse hematologic toxicity Grade 3 or worse hematologic toxicity was seen in 3 patients of the WBRT + temozolomide arm.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Wang, 2015[162] N/A RCT Power calculation: No China Unclear funding source Journal article N: 73	Age: Gefitinib: 61 [median], VMP chemotherapy: 62[median] Gender: 34% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT + Gefitinib 5000 cGy, 25 fractions, qd Gefitinib 250 mg/day p.o. started at first day of radiation therapy WBRT + VMP chemotherapy 5000 cGy, 25 fractions, qd Intravenous infusion of 100 mg/day VM-26 from day 1 to day 3; intravenous infusion of cisplatin 25 mg/m2 from day 1 to day 3; one cycle was defined as a 21-day therapy duration, with a total of 2 cycles; radiotherapy starting from the first day of chemotherapy	Intervention: 37 randomized, 37 analyzed Comparator: 36 randomized, 34 analyzed Followup: 14 [median] months	Intervention vs Comparator: Overall survival Median survival time was 13.3 (gefitinib) vs 12.7 (VMP) ($p<0.05$) Progressive disease at 2 months 5.4% (gefitinib) vs 5.8% (VMP) of patients with progressive disease Total response rate There was no significant difference in the short-term effects in total response rate (complete response and partial response) at 2 months between the two groups	Intervention vs Comparator: Toxicity Toxicity of Gefitinib groups were characterized by rash (70.3 %), whereas chemotherapy resulted in hematologic toxicities, which included III/IV leucopenia (17.6 %), anemia (8.8 %), and thrombocytopenia (14.7 %), and less serious non-hematological toxicity including gastrointestinal disorders (79.4 %), hair loss, etc. No treatment-related deaths occurred.
Wolfson, 1994[163] Protocol 90/01, IRB M1 196 RCT Power calculation: No USA Unclear funding source Journal article N: 12	Age: 58 [median] Gender: 58% female Primary tumor type: Different cancer types; 92% lung or breast Metastases: Number: A third each with 1, 2, or >2 Volume: NA Size: A third each with <2, 2-4, and >4 cm Prognosis: unclear	WBRT + dexamethasone 3000 cGy, 10 fractions, qd dexamethasone 4 mg PO q6h WBRT alone 3000 cGy, 10 fractions, qd	Intervention: 7 randomized, 7 analyzed Comparator: 5 randomized, 5 analyzed Followup: 24 months	Intervention vs Comparator: General performance status (5 categories ranging from normal to 100% bedridden) Intervention: 29% improved, 57% no change, 14% deteriorated; control: 80% no change, 20% deteriorated	Intervention vs Comparator: Side effects (including serious adverse events) RR 0.71; CI (0.02, 30.32)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Yang, 2017[164] Guangdong Association of Clinical Trials, 2015[199]; Wu, 2017[263] NCT01724801 RCT Power calculation: Yes China Non industry Journal article N: 176	Age: WBRT: 58 [median], Icotinib: 57 [median] Gender: 59% female Primary tumor type: Lung cancer only; Metastases: Number: patients had at least 3 metastases (no further details) Volume: N/A Size: N/A Prognosis: unclear	WBRT with concurrent or sequential chemotherapy 3000 cGy, 10 fractions, qd 71% received chemotherapy (first line: platinum-based doublet; second line: pemetrexed or docetaxel) Icotinib 125 mg orally tid	Intervention: 91 randomized, 73 analyzed Comparator: 85 randomized, 85 analyzed Followup: 17 [median] months	Intervention vs Comparator: Time from randomization to death from any cause HR 0.93; CI (0.6, 1.44) Median survival showed no significant difference between arms (21 months for WBRT + chemotherapy vs 18 months for icotinib alone) Progression-free survival HR 0.44; CI (0.31, 0.63) Intracranial progression-free survival HR 0.56 (CI 0.36-0.90); p=0.014 in favor of Icotinib Progressive disease 23% vs 12% with progressive disease MMSE Difference of MMSE scores was not significant between groups (p=0ß663)	Intervention vs Comparator: Number of participants with adverse events RR 0.99; CI (0.88, 1.12) Number of patients reporting fatigue RR 2.86; CI (1.53, 5.35) Number of patients reporting vomiting RR 2.46; CI (1.19, 5.09) Number of patients RR 1.55; CI (0.69, 3.47) Most common adverse events Elevated alanine aminotransferase and rash were the most common adverse events of any grade in both groups, occurring in around 20-30% of each group.

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Yang, 2017[165] CNSDQFSH010 RCT Power calculation: No China Unclear funding source Journal article N: 218	Age: Bevacizumab+gefitinib+WBRT: 58.42(14.88), Gefitinib+WBRT: 60.64 (13.57) WBRT: 58.78(10.92) Gender: Bevacizumab+gefitinib+WBRT: 41% female, Gefitinib+WBRT: 48% female WBRT: 40% female Primary tumor type: Lung cancer only; Metastases: Number: bevacizumab+gefitinib+WBRT: 36% more than 5 metasases, Gefitinib+WBRT: 39% had 5 or more metastases, WBRT: 40% had more than 5 metastases Volume: N/A Size: N/A Prognosis: good to moderate prognosis	WBRT+ bevacizumab + gefitinib 4000 cGy, 20 fractions, qd Bevacizumab (5 mg/kg every 14 days) and gefitinib (250 mg/day) WBRT 3000 cGy, 10 fractions, qd WBRT + gefitinib 4000 cGy, 20 fractions, qd Gefitinib 250 mg/day	Intervention: 76 randomized, 76 analyzed Comparator: 75 randomized, 75 analyzed Additional comparator: 77 randomized, 77 analyzed Followup: NA months	Intervention vs Comparator: Overall survival WBRT + bevacizumab + gefitinib group had the most favorable survival status; survival rates in the WBRT + bevacizumab + gefitinib, WBRT + gefitinib, and WBRT groups were 48.6, 36.7, and 9.8% Progression-free survival WBRT + bevacizumab + gefitinib had the most favorable survival status; median progression-free survival rates in the WBRT + bevacizumab + gefitinib, WBRT + gefitinib, and WBRT were 29.8, 29.6, and 14.6% Progressive disease determined if the product of tumor diameters increased more than 25% or new lesions appeared 4% (WBRT + bevacizumab + gefitinib) vs 27% (WBRT alone) patients with progressive disease (12% in WBRT + gefitinib group) Response rate, disease control rate Compared to WBRT, WBRT + bevacizumab + gefitinib significantly enhanced response rate and disease control rate. Compared to WBRT+ gefitinib, WBRT + bevacizumab + gefitinib significantly improved disease control rate but not response rate	Intervention vs Comparator: Number of events (NCICTC version 2.0) 198 vs 160 events Nausea/vomiting RR 1.48; CI (0.77, 2.86) Headache RR 1.48; CI (0.71, 3.08) Intervention vs additional comparison: Nausea/vomiting RR 1.3; CI (0.7, 2.43) Headache RR 1.17; CI (0.6, 2.29)

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Yang, 2018[167] Daping Hospital[189] NCT01887795 RCT Power calculation: No China Non industry Trial record N: 222	Age: N/A Gender: N/A Primary tumor type: Lung cancer only; Metastases: Number: all patients had at least 2 brain metastases Volume: N/A Size: N/A Prognosis: unclear	WBRT + erlotinib 4000 cGy, 20 fractions, qd Erlotinib p.o. 150 mg/day WBRT 4000 cGy, 20 fractions, qd	Intervention: 107 randomized, 107 analyzed Comparator: 115 randomized, 115 analyzed Followup: 11 [median] months	Intervention vs Comparator: Overall survival HR 0.91; CI (0.68, 1.23) Progression-free survival HR 0.97; CI (0.74, 1.28) Median intracranial progression-free survival was 11.2 months (95% CI: 7.2-13.7) with WBRT + Erlotinib versus 9.2 months (95% CI: 6.7-10.9) with WBRT alone (HR 0.926; 95% CI:0.695-1.234; p=0.601). Intervention vs additional comparison: Overall survival	Not reported
Yang, 2019[166] National Taiwan University, 2019[232] NCT02393131 RCT Power calculation: No Taiwan Industry funded Trial record N: 70	Age: 59.5 [median] Gender: N/A Primary tumor type: Different cancer types; 95% lung Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	Hippocampal-sparing WBRT 3000 cGy, 10 fractions, qd WBRT 3000 cGy, 10 fractions, qd	Intervention: randomized, 33 analyzed Comparator: randomized, 32 analyzed Followup: 7 [median] months	Intervention vs Comparator: Hopkins Verbal Learning Test-Revised [HVLT-R], Trail Making Test [TMT], and Controlled Oral Word Association [COWA] at 4 months Better preservation better preservation in late verbal memory but not verbal fluency or executive function; n0 differences in any neurocognitive assessments between two arms at 4 months; HA-WBRT had favorable perpetuation of HVLT-R total recall and significantly better preservation of HVLT-R recognition-discrimination index compared to WBRT at 6 months; no differences in trail making test at any time point; WBRT had significantly superior controlled oral word association than HA-WBRT in patients who survived 12 months or longer	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Zeng, 2016[168] N/A RCT Power calculation: No China Industry funded Journal article N: 64	Age: WBRT + sodium glycididazole: 57 [median]. WBRT: 56 [median] Gender: 39% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: poor, more than 80% were ECOG 3-4	WBRT + sodium glycididazole 3000 cGy, 10 fractions, qd Radiosensitizer sodium glycididazole 700mg/m(2) intravenous infusion 30 minutes before radiotherapy, 3x a week WBRT + placebo 3000 cGy, 10 fractions, qd Placebo (100 mL of saline as intravenous infusion)	Intervention: 32 randomized, 32 analyzed Comparator: 32 randomized, 32 analyzed Followup: 10 [median] months	Intervention vs Comparator: Time from the first day of enrollment to death or last follow-up HR 0.82; CI (0.42, 1.6) No significant difference between study and control group (11 vs 9 months, p=0.418) CNS progression-free survival Longer median CNS progression-free survival time in study vs control group (7 vs 4 months, p=0.038) Neurological deaths RR 0.89; CI (0.56, 1.41) Disease control rate Disease control rate was significantly better in the WBRT + Sodium Glycididazole group than in the WBRT + Placebo group at 3 months of follow-up (90.6% vs 65.6%)	Intervention vs Comparator: Number of adverse events 450 vs 448 events Fatigue 2 vs 1 Vomiting 3 vs 1 Headaches 0 vs 0
Zhu, 2018[169] Taizhou Hospital of Zhejiang Province[257] ChiCTR-INR-17013204 RCT Power calculation: No China Unclear funding source Trial record N: 75	Age: N/A Gender: N/A Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear	WBRT intensity modulated radiation therapy with simultaneous integrated boost 30Gy WBRT: 3000 cGy, 10 fractions, qd AND concomitant tumor boost of 5000 cGy, 10 fractions, qd WBRT intensity modulated radiation therapy with simultaneous integrated boost 25Gy 2500 cGy, 10 fractions, qd AND concomitant tumor boost of 5000 cGy, 10 fractions, qd	Intervention: 37 randomized, 37 analyzed Comparator: 38 randomized, 38 analyzed Followup: 15 [median] months	Intervention vs Comparator: Overall survival Median survival was 8 (95%CI:4.4-11.6) months in the 30 Gy group and 13 (95%CI:11.4-14.6) months in the 25Gy group (p=0.025) Intracranial progression-free survival Median survival was 8 months (CI 4.4, 11.6) in the 30 Gy group and 11 (CI 8.7, 13.3) months in the 25Gy group (p=0.104) MMSE at 12 months SMD -0.05; CI (-0.51, 0.4)	Not reported

Study	Participants	Intervention	N and Followup	Effects	Adverse Events
Zhuang, 2020[170] ChiCTR1900022750 Cohort Power calculation: No China Non industry Journal article N: 361	Age: 59.6 (10.5) Gender: 56.80% Primary tumor type: Lung cancer only; Metastases: Number: 1.4 (mean) Volume: median 2844.9 (IQR 871.6, 7866.2) Size: Prognosis: limited to no more than 4 brain metastases and had to have at least 10 months of follow up	SRS (with or without WBRT) + tyrosine kinase inhibitor 7040 cGy (6000, 7590) [median BED (interquartile range)], 2 fractions qd Tyrosine kinase inhibitors (gefitinib, erlotinib, or icotinib), unknown intensity and dose SRS (with or without WBRT) 7040 cGy (6000, 7590) [median BED (interquartile range)], 2 fractions (1,3) [median (interquartile range)] qd can include other types of chemotherapy but excluding tyrosine kinase inhibitors (not description of other types of chemotherapy, intensity or dose)	Intervention: randomized, 196 analyzed Comparator: randomized, 165 analyzed Followup: >10 months months	Not reported	Intervention vs Comparator: Radiation necrosis RR 4.8; CI (2.53, 9.09)

Appendix E. Expert Guidance and Review

Stakeholder Input in Formulating the Research Protocol

Stakeholders, participated in a virtual workshop by PCORI in August 2019 to discuss the draft Key Questions and PICOTs. Details on the virtual workshop, including a list of participants, can be found at https://www.pcori.org/events/2019/pcori-stakeholder-webinar-radiation-therapy-brain-metastases-systematic-review.

Stakeholders in the workshop represented different viewpoints which included patients, patient advocates, clinicians, guideline developers and researches.

During the virtual workshop, stakeholders provided input and guidance on the Key Questions and PICOTs. Based upon the from the workshop, the protocol was developed by the EPC and the Key Questions were modified with guidance from PCORI and AHRQ.

Stakeholders did not do analysis of any kind or contribute to the writing of this draft report. They will be given the opportunity to review the report through the peer or public review mechanisms.

Appendix F. PCORI Checklist

This systematic review adheres to the PCORI Methodology Standards enumerated below.

PCORI Methodology Standards Checklist: Systematic Review (SR)

Contract No.	**290-2015-00010I**
Task Order No.	**70**
EPC	**Southern California Evidence-based Practice Center**
Project Title	**Radiation Therapy for Brain Metastases**

Standard Category	Abbrev.	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard?
Cross-Cutting Standards for PCOR					
Standards for Formulating Research Questions	RQ-1	Identify gaps in evidence.	Yes	Discussion chapter	
	RQ-2	Develop a formal study protocol.	Yes	Available on AHRQ website	
	RQ-3	Identify specific populations and health decision(s) affected by the research.	Yes	Abstract	
	RQ-4	Identify and assess participant subgroups.	Yes	KQ1b, KQ2b, KQ1a	
	RQ-5	Select appropriate interventions and comparators.	Yes	Methods appendix	
	RQ-6	Measure outcomes that people representing the population of interest notice and care about.	Yes	Methods appendix	
Standards Associated with Patient-Centeredness	PC-1	Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context.	Yes	Frontmatter (KI and TEP)	
	PC-2	Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants.	Yes	Methods appendix	
	PC-3	Use patient-reported outcomes when patients or people at risk of a condition are the best source of information for outcomes of interest.	Yes	Result chapter	
	PC-4	Support dissemination and implementation of study results.	Yes	Accompanying manuscript	

Standard Category	Abbrev.	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard?
Standards for Data Integrity and Rigorous Analyses	IR-1	A priori, specify plans for quantitative data analysis that correspond to major aims.	Yes	Published protocol	
	IR-2	Assess data source adequacy.	Yes	Risk of bias assessment	
	IR-3	Describe data linkage plans, if applicable.	Yes	SRDR	
	IR-4	Document validated scales and tests.	Yes	Evidence table in appendix	
	IR-5	Provide sufficient information in reports to allow for assessments of the study's internal and external validity.	Yes	Methods appendix	
	IR-6	Masking should be used when feasible.	N/A	N/A	
	IR-7	In the study protocol, specify a data management plan that addresses, at a minimum, the following elements: collecting data, organizing data, handling data, describing data, preserving data, and sharing data.	Yes	Published protocol	
Standards for Preventing and Handling Missing Data	MD-1	Describe methods to prevent and monitor missing data.	Yes	Methods appendix	
	MD-2	Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.	Yes	SoE assessment, result section	
	MD-3	Record and report all reasons for dropout and missing data, and account for all patients in reports.	Yes	Methods appendix	
	MD-4	Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.	Yes	Result chapter	
Standards for Heterogeneity of Treatment Effect (HTE)	HT-1	State the goals of HTE analyses, including hypotheses and the supporting evidence base.	Yes	Result chapter	
	HT-2	For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods.	Yes	Methods appendix	

Standard Category	Abbrev.	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard?
	HT-3	Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed.	Yes	Result chapter	
Standards for Specific Study Designs and Methods					
Standards for Data Registries	DR-1	Requirements for the design of registries.	N/A		
	DR-2	Documentation and reporting requirements of registry materials, characteristics, and bias.	N/A		
	DR-3	Adapting established registries for PCOR.	N/A		
	DR-4	Documentation requirements when using registry data.	N/A		
Standards for Data Networks as Research-Facilitating Structures	DN-1	Requirements for the design and features of data networks.	N/A		
	DN-2	Selection and use of data networks.	N/A		
Causal Inference Standards	CI-1	Specify the causal model underlying the research question (cross-cutting standard, applies to all PCOR/CER studies).	Yes	Key questions	
	CI-2	Define and appropriately characterize the analysis population used to generate effect estimates.	Yes	Result chapter, evidence table	
	CI-3	Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure.	Yes	Evidence table in appendix	
	CI-4	Measure potential confounders before start of exposure and report data on potential confounders with study results.	Yes	Result chapter, meta-regressions	
	CI-5	Report the assumptions underlying the construction of propensity scores and the comparability of the resulting groups in terms of the balance of covariates and overlap.	N/A		
	CI-6	Assess the validity of the instrumental variable (i.e., how the assumptions are met) and report the balance of covariates in the groups created by the instrumental variable.	N/A		

Standard Category	Abbrev.	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard?
Standards for Adaptive and Bayesian Trial Designs	AT-1	Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations.	N/A		
	AT-2	Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs.	N/A		
	AT-3	Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent interim analyses.	N/A		
	AT-4	When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications.	N/A		
Standards for Studies of Medical Tests	MT-1	Specify clinical context and key elements of the medical test.	N/A		
	MT-2	Assess the effect of factors known to affect performance and outcomes.	N/A		
	MT-3	Focus studies of medical tests on patient-centered outcomes, using rigorous study designs with a preference for randomized controlled trials.	N/A		
Standards for Systematic Reviews	SR-1	Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate.	Yes	Protocol, report	
Standards on Research Designs Using Clusters	RC-1	Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level.	N/A		
	RC-2	Justify the choice of cluster randomization.	N/A		
	RC-3	Power and sample size estimates must use appropriate methods to account for the dependence of observations within clusters and the degrees of freedom available at the cluster level.	N/A		
	RC-4	Data analyses must account for the dependence of observations within clusters regardless of its magnitude.	N/A		
	RC-5	Stratified randomization should be used when feasible.	N/A		

Standard Category	Abbrev.	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard?
Standards for Studies of Complex Interventions	SCI-1	Fully describe the intervention and comparator and define their core functions.	N/A		
	SCI-2	Specify the hypothesized causal pathways and their theoretical basis.	N/A		
	SCI-3	Specify how adaptations to the form of the intervention and comparator will be allowed and recorded.	N/A		
	SCI-4	Plan and describe a process evaluation.	N/A		
	SCI-5	Select patient outcomes informed by the causal pathway.	N/A		
Standards for Qualitative Methods	QM-1	State the qualitative approach to research inquiry, design, and conduct.	Yes	Methods appendix	
	QM-2	Select and justify appropriate qualitative methods sampling strategy.	Yes	Methods appendix	
	QM-3	Link the qualitative data analysis, interpretations, and conclusions to the study question.	Yes	Result chapter	
	QM-5	Establish trustworthiness and credibility of qualitative research.	Yes	Result chapter	
Standards for Mixed Methods Research	MM-2	Specify how mixed methods are integrated across design, data sources, and/or data collection phases.	N/A		
	MM-2	Select and justify appropriate mixed methods sampling strategy.	N/A		
	MM-3	Integrate data analysis, data interpretation, and conclusions.	N/A		
	IPD-1	Specify the research question(s) that will be addressed through the IPD-MA and describe the specific information it will provide that other approaches would not.	N/A		

Standard Category	Abbrev.	Standard	Is this standard applicable to this SR?	List sections and pages of the SR report where you address this standard	If applicable, describe how and why the SR deviated from this standard?
Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)	IPD-2	Describe the proposed governance structure for the IPD-MA in the protocol and study reports.	N/A		
	IPD-3	Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA.	N/A		
	IPD-4	Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications.	N/A		