Radiation Therapy for Brain Metastases
Radiation Therapy for Brain Metastases

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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.

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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.

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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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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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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. 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. 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. 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. Brain metastases occur with a variety of cancers, which may result in different subtypes or molecular profiles that respond differently to treatment. 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.

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. For some patients with a very poor prognosis, palliative care alone may be appropriate.

Several guidelines for the management of brain metastases have been published. The American Society of Radiation Oncology (ASTRO) published guidelines for the radiotherapeutic and surgical management of brain metastases in 2012. 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, and there is some clinical guidance on the topic, 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. 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. 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. Figure 4 shows the effect on overall survival in the RCTs reporting on this outcome in sufficient detail.

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

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).

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) 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.\textsuperscript{149} reported results that favored the WBRT plus placebo rather than the WBRT plus chloroquine group (statistical significance not given) and Zeng et al.\textsuperscript{168} reported longer median central nervous system (CNS) progression-free survival when adding sodium glycididazole ($p=0.04$). El-Hamamsy et al. (simvastatin),\textsuperscript{94} and Suh et al.\textsuperscript{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**

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\textsuperscript{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\textsuperscript{127, 128} in favor of the motexafin gadolinium group. Phillips et al.\textsuperscript{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.\textsuperscript{127} reported no significant difference between groups for motexafin gadolinium (HR 1.14; CI 0.74 to 1.75; 1 RCT). Suh et al.\textsuperscript{155} indicated that a larger percentage of patients in the efaproxiral group had stable or improving quality of life scores. Rojas-Puentes, 2013\textsuperscript{149} reported no differences between groups with chloroquine and El-Hamamy et al.\textsuperscript{94} reported no significant differences for simvastatin.

Mehta et al.\textsuperscript{127} and Suh et al.\textsuperscript{156} reported no significant difference in functional status.

One other RCT by Mehta et al.\textsuperscript{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).\textsuperscript{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.\textsuperscript{75, 93, 117} With the exception of Andrews et al.,\textsuperscript{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).\textsuperscript{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).\textsuperscript{117}

Andrews et al.\textsuperscript{75} reported improvements in Karnofsky Performance Status\textsuperscript{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.\textsuperscript{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.\textsuperscript{131, 136, 160}
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.
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. Robinet et al. reported no statistically significant difference in overall survival (HR 1.14; CI 0.82 to 1.59; 1 RCT). Mornex et al. 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. 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). Of note, a cohort study published by Jiang et al. 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). Yang, 2017 reported 23 percent of patients with progressive disease for WBRT versus 12 percent in the icotinib group. Yang, 2017 reported 4 percent (WBRT + bevacizumab + gefitinib) versus 27 percent (WBRT alone) patients with progressive disease.

Yang et al. 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. 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. 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. 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.

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. 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. 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. The other RCT reported by Hauswald et al. 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.

**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 and only four studies of patients with poor prognosis 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.

Figure 8 shows all studies evaluating WBRT plus systemic therapy compared to WBRT alone, with or without placebo, that reported on overall survival.
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), Guerrieri et al. (carboplatin), Hassler et al. (temozolomide), Liu et al. (temozolomide), Ushio et al. (Methyl-CCNU/ACNU + tegafur), Verger et al. (temozolomide), Yang et al. (bevacizumab + gefitinib), and a Hoffmann-LaRoche-funded trial (capecitabine) could not be combined with the others; with one exception in a temozolomide RCT, 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**

![Graph showing disease-free survival](image)

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 study100 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
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 (I² 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 trial97 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. Pesce et al. 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. Quantin et al. 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. Wang et al. compared the combination of velcade-melphalan-prednisone to gefitinib. 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. 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. 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>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies (Participants) Contributing to Effect Estimate; Citations</th>
<th>Results Across Studies‡ Additional Individual Study Findings</th>
<th>Conclusion and SoE‡‡ [Reasons for Downgrading]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1: WBRT + steroids vs WBRT alone</td>
<td>Functional status</td>
<td>Effect estimate not possible Wolfson, 1994 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</td>
<td>Insufficient [study limitations, precision, consistency]</td>
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<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies(^\d) Additional Individual Study Findings</td>
<td>Conclusion and SoE(^\ddagger) [Reasons for Downgrading]</td>
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<tr>
<td>KQ1: WBRT + radiosensitizer vs WBRT alone</td>
<td>Overall survival</td>
<td>4 RCTs (N 1024); Jiang, 2014;(^{109}) Suh, 2006;(^{155}) Suh, 2008;(^{156}) Zeng, 2016(^{168})</td>
<td>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.</td>
<td>Insufficient [study limitations, precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + radiosensitizer vs WBRT alone</td>
<td>Disease-free survival</td>
<td>1 RCT (N 554); Mehta, 2009(^{128})</td>
<td>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)).</td>
<td>Insufficient [study limitations, precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + radiosensitizer vs WBRT alone</td>
<td>Death due to brain metastases</td>
<td>2 RCTs (N 579); Suh, 2006;(^{155}) Zeng, 2016(^{168})</td>
<td>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)).</td>
<td>Low SoE for no consistent effect [study limitations, precision]</td>
</tr>
<tr>
<td>KQ1: WBRT + radiosensitizer vs WBRT alone</td>
<td>Intra-cranial progression</td>
<td>1 RCT (N 554); Mehta, 2009(^{128})</td>
<td>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.</td>
<td>Low SoE for no consistent effect [study limitations, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies Additional Individual Study Findings</td>
<td>Conclusion and SoE‡‡ [Reasons for Downgrading]</td>
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<tr>
<td>KQ1: WBRT + radiosensitizer vs WBRT alone</td>
<td>Quality of life</td>
<td>1 RCT (N 554); Mehta, 2009\textsuperscript{128}</td>
<td>HR 1.14; CI 0.74 to 1.75: No significant difference between groups for motexafin gadolinium. \textit{In addition, Suh, 2006\textsuperscript{155} reported a larger percentage of patients in the efaproxial group had stable or improving quality of life scores. Rojas-Puentes, 2013\textsuperscript{141} reported no differences between groups with chloroquine. El-Hamamsy et al.\textsuperscript{94} reported no significant differences for simvastatin.}</td>
<td>Low SoE for no effect [study limitation, precision]</td>
</tr>
<tr>
<td>KQ1: WBRT + radiosensitizer vs WBRT alone</td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible \textit{Mehta, 2003\textsuperscript{127} reported no significant difference between groups with motexafin gadolinium. Suh, 2008\textsuperscript{156} also reported no statistically significant differences between groups with efaproxial.}</td>
<td>Low SoE for no effect [study limitation, precision]</td>
</tr>
<tr>
<td>KQ1: WBRT + motexafin gadolinium vs WBRT alone</td>
<td>Cognitive effects</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible \textit{Mehta, 2009\textsuperscript{124} reported a longer time interval to neurocognitive progression favoring motexafin gadolinium.}</td>
<td>Low SoE for longer time interval to neurocognitive progression with motexafin gadolinium [precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + SRS vs WBRT alone</td>
<td>Overall survival</td>
<td>1 RCT (N 331); Andrews, 2004\textsuperscript{73}</td>
<td>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. \textit{In addition, El Gantery, 2014\textsuperscript{93} reported a non-significant survival benefit for WBRT + SRS compared to WBRT alone. Kondziolka, 1999\textsuperscript{12} reported no statistically significant difference in median survival (p=0.22).}</td>
<td>Low SoE for no effect [study limitation, precision]</td>
</tr>
<tr>
<td>KQ1: WBRT + SRS vs WBRT alone</td>
<td>Death due to brain metastases</td>
<td>1 RCT (N 331); Andrews, 2004\textsuperscript{73}</td>
<td>RR 0.86; CI 0.60 to 1.25: WBRT + SRS did not systematically improve overall survival compared to SRS alone.</td>
<td>Low SoE for no consistent effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + SRS vs WBRT alone</td>
<td>Intra-cranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible \textit{Kondziolka, 1999\textsuperscript{17} reported the median time to any brain failure was 34 months after WBRT + SRS and 5 months after WBRT alone (p=0.002).}</td>
<td>Low SoE for slower intracranial progression favoring WBRT + SRS vs WBRT alone [precision, consistency]</td>
</tr>
<tr>
<td>WBRT + SRS vs WBRT alone</td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible \textit{Andrews, 2004\textsuperscript{23} noted a significant improvement in Karnofsky Performance Status in the combination group (p=0.0331).}</td>
<td>Low SoE for improved functional status favoring SRS + WBRT vs WBRT alone [precision, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies(^2) Additional Individual Study Findings</td>
<td>Conclusion and SoE(^\dagger) [Reasons for Downgrading]</td>
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<tr>
<td>WBRT + SRS vs WBRT alone</td>
<td>Cognitive status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Andrews, 2004(^1) reported no difference in mental status based on the mini mental state examination between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + surgery vs WBRT alone</td>
<td>Overall survival</td>
<td>3 RCTs (N 210); Mintz, 1996(^1); Noordijk, 1994(^1); Vecht, 1993(^1); Vecht, 1993 (^1);</td>
<td>HR 1.11; CI 0.31 to 3.96: Conflicting results across studies, no systematic difference across studies.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + surgery vs WBRT alone</td>
<td>Deaths due to brain metastases</td>
<td>3 RCTs (N 210); Mintz, 1996(^1); Noordijk, 1994(^1); Vecht, 1993(^1); Vecht, 1993 (^1);</td>
<td>RR 0.76; CI 0.28 to 2.07: Direction of effects consistently favored the combination treatment but the effect was not statistically significant.</td>
<td>Insufficient [study limitation, precision]</td>
</tr>
<tr>
<td>KQ1: WBRT + surgery vs WBRT alone</td>
<td>Quality of life</td>
<td>1 RCT (N 84); Mintz, 1996(^1); Mintz, 1996(^1); Vecht, 1993(^1); Vecht, 1993 (^1);</td>
<td>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.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + surgery vs WBRT alone</td>
<td>Functional status</td>
<td>1 RCT (N 84); Mintz, 1996(^1); Mintz, 1996(^1); Vecht, 1993(^1); Vecht, 1993 (^1);</td>
<td>SMD 0.00; CI -0.43 to 0.43: WBRT + surgery in an RCT that provided an effect size estimate. However, Vecht, 1993(^2) 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.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + supportive therapy vs supportive therapy alone</td>
<td>Overall survival</td>
<td>1 RCT (N 538); Mulvenna, 2016(^1);</td>
<td>HR 1.06; CI 0.89 to 1.26: WBRT + supportive did not improve overall survival compared to supportive care alone.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ1: WBRT + supportive therapy vs supportive therapy alone</td>
<td>Quality of life</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Mulvenna, 2016(^1) reported the number of patients with maintained or improved quality of life was similar between the groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ1: Chemotherapy + WBRT vs chemotherapy alone</td>
<td>Overall survival</td>
<td>1 RCT (N 171); Robinet, 2001(^1);</td>
<td>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(^2) reported a median survival 105 vs 86 days in the combination group. Yang, 2017(^1) reported no significant difference between arms (20.5 months for icotinib + WBRT vs 18.0 months for icotinib alone, p&lt;0.001).</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
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<tr>
<td>KQ1: Chemotherapy + WBRT vs chemotherapy alone</td>
<td>Disease-free survival</td>
<td>1 RCT (N 171); Robinet, 2001(^{148})</td>
<td>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. (\text{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.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1: cisplatin and vinorelbine + WBRT vs cisplatin and vinorelbine alone</td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N 171); Robinet, 2001(^{148})</td>
<td>RR 0.94; CI 0.81 to 1.09: No systematic difference between cisplatin and vinorelbine + immediate WBRT and chemotherapy alone.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1: chemotherapy + WBRT vs icotinib alone</td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible (\text{Yang, 2017}^{164}) reported 23% of patients with progressive disease for WBRT vs 12% in the icotinib group. (\text{Yang, 2017}^{165}) reported 4% (WBRT + bevacizumab + gefitinib) vs 27% (WBRT alone) patients with progressive disease</td>
<td>Insufficient [study limitation, precision]</td>
</tr>
<tr>
<td>KQ1: chemotherapy + WBRT vs icotinib alone</td>
<td>Cognitive function</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible (\text{Yang, 2017}^{164}) reported no difference in MMSE scores between groups ((p=0.663)).</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
</tbody>
</table>

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

\(^{\ddagger}\)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.

\(^{\ddagger\ddagger}\)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>
<thead>
<tr>
<th>Intervention and Comparison</th>
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<th>Number of Studies (Participants) Contributing to Effect Estimate; Citations</th>
<th>Results Across Studies(^2) Additional Individual Study Findings</th>
<th>Conclusion and SoE(^{12}) [Reasons for Downgrading]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ1a: WBRT dose</strong></td>
<td>Overall survival, disease-free survival, deaths due to brain metastases</td>
<td>Meta-regression</td>
<td>No systematic relationship was detected between the dose of WBRT and the outcomes overall survival, disease-free survival, and deaths due to brain metastases.</td>
<td>Low SoE for no effect [indirectness, study limitations]</td>
</tr>
<tr>
<td><strong>KQ1a: WBRT intensity modulated RT with integrated boost 30 Gy vs WBRT intensity modulated RT with integrated boost 25Gy</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Zhu, 2018(^{66}) 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).</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>WBRT intensity modulated RT with integrated boost 30 Gy vs WBRT intensity modulated RT with integrated boost 25Gy</strong></td>
<td>Disease-free survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Zhu, 2018(^{66}) 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).</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: WBRT intensity modulated RT with integrated boost 30 Gy vs WBRT intensity modulated RT with integrated boost 25Gy</strong></td>
<td>Cognitive function</td>
<td>1 RCT (N 75); Zhu, 2018(^{69}) SMD -0.05; CI -0.50 to 0.40: No statistically significantly difference in mini-mental state examination.</td>
<td>Effect estimate not possible Davey, 2008(^{60}) reported 19 weeks median survival in both groups. Murray, 1997(^{13}) also compared accelerated hyperfractionated WBRT with standard WBRT and found no significant difference in 1-year survival rates (16 vs 19%).</td>
<td>Low SoE for no difference [study limitation, precision]</td>
</tr>
<tr>
<td><strong>KQ1a: Accelerated WBRT vs WBRT</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Davey, 2008(^{60}) reported 19 weeks median survival in both groups. Murray, 1997(^{13}) also compared accelerated hyperfractionated WBRT with standard WBRT and found no significant difference in 1-year survival rates (16 vs 19%).</td>
<td>Low SoE for no difference [study limitation, precision]</td>
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<tr>
<td><strong>KQ1a: Accelerated WBRT vs WBRT</strong></td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Davey, 2008(^9) reported longer median time to retreatment in the accelerated WBRT group for intracranial relapse (p=0.03).</td>
<td>Low SoE for beneficial effects of accelerated WBRT on intracranial progression [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Accelerated WBRT vs WBRT</strong></td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Davey, 2008(^9) reported no difference in neurological function between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions</strong></td>
<td>Overall survival</td>
<td>1 RCT (N 113) Graham, 2010(^9)</td>
<td>HR 1.08; CI 0.6 to 1.96: No systematic difference between treatment groups.</td>
<td>Low SoE for no difference [study limitation, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions</strong></td>
<td>Disease-free survival</td>
<td>1 RCT (N 113) Graham, 2010(^9)</td>
<td>HR 0.55; CI 0.31 to 1: Results favoring 40 Gy.</td>
<td>Low SoE for benefits for 40 Gy vs 20 Gy on disease-free survival [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions</strong></td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N 113) Graham, 2010(^9)</td>
<td>RR 0.63; CI 0.40 to 1.00: Results favoring 40 Gy</td>
<td>Low SoE for benefits for 40 Gy vs 20 Gy for deaths due to brain metastases [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions</strong></td>
<td>Intracranial progression</td>
<td>1 RCT (N 113) Graham, 2010(^9)</td>
<td>HR 1.56; CI 0.94 to 2.60: The difference between groups was not statistically significant.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions</strong></td>
<td>Quality of life</td>
<td>1 RCT (N 113) Graham, 2010(^9)</td>
<td>SMD -0.17; CI -0.54 to 0.20 The difference between groups was not statistically significant.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 20 Gy in 4 fractions vs 40 Gy in 20 fractions</strong></td>
<td>Cognitive function</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Graham, 2010(^9) reported no difference between the 20 Gy and 40 Gy group in a cognitive subscale.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: Dose 30 Gy in 10 fractions vs 20 Gy in 5 fractions</strong></td>
<td>Overall survival</td>
<td>1 RCT (N 56) Saha, 2014(^1)</td>
<td>HR 0.98; CI 0.55 to 1.75: No systematic difference between treatment groups.</td>
<td>Low SoE for no difference [study limitation, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies Additional Individual Study Findings</td>
<td>Conclusion and SoE [Reasons for Downgrading]</td>
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<tr>
<td>KQ1a: Dose 30 Gy in 10 fractions vs 20 Gy in 5 fractions</td>
<td>Functional status</td>
<td>1 RCT (N 56) Saha, 2014&lt;sup&gt;133&lt;/sup&gt;</td>
<td>SMD 0.12; CI -0.40 to 0.65: No statistically significant difference between groups.</td>
<td>Low SoE for no difference [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1a: 30 Gy in 10 fractions vs 12 Gy in 2 fractions</td>
<td>Overall survival</td>
<td>1 RCT (N 533) Priestman, 1996&lt;sup&gt;141&lt;/sup&gt;</td>
<td>HR 0.93; CI 0.77 to 1.12: No systematic difference between treatment groups.</td>
<td>Low SoE for no difference [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1a: 30 Gy in 10 fractions vs 12 Gy in 2 fractions</td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N 533) Priestman, 1996&lt;sup&gt;141&lt;/sup&gt;</td>
<td>RR 0.99; CI 0.92 to 1.06: No systematic difference between treatment groups.</td>
<td>Low SoE for no difference [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1a: 30 Gy vs 25 Gy</td>
<td>Cognitive function</td>
<td>1 RCT (N 75) Zhu, 2018&lt;sup&gt;169&lt;/sup&gt;</td>
<td>SMD -0.05; CI -0.50 to 0.40: No systematic difference between treatment groups.</td>
<td>Low SoE for no difference [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1a: WBRT with neuroprotection: WBRT + memantine vs WBRT alone</td>
<td>Overall survival</td>
<td>1 RCT (N 252); Brown, 2013&lt;sup&gt;132&lt;/sup&gt;</td>
<td>HR 1.06; CI 0.86 to 1.31: WBRT + memantine did not improve overall survival compared to supportive care alone.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1a: WBRT with neuroprotection: WBRT + memantine vs WBRT alone</td>
<td>Disease-free survival</td>
<td>1 RCT (N 252); Brown, 2013&lt;sup&gt;132&lt;/sup&gt;</td>
<td>HR 1.06; CI 0.86 to 1.30: WBRT + memantine did not improve disease-free survival compared to WBRT plus placebo.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>KQ1a: WBRT with neuroprotection: WBRT + memantine vs WBRT alone</td>
<td>Cognitive function</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Brown et al.&lt;sup&gt;13&lt;/sup&gt; 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.</td>
<td>Low SoE for beneficial effect of memantine on cognitive function [precision, consistency]</td>
</tr>
<tr>
<td>KQ1a: WBRT with neuroprotection – hippocampal sparing vs standard WBRT</td>
<td>Overall survival</td>
<td>1 RCT (N 519); Brown, 2020&lt;sup&gt;19&lt;/sup&gt;</td>
<td>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&lt;sup&gt;116,117&lt;/sup&gt; reported median overall survival of 5 months (hippocampal sparing WBRT) vs 4 months (standard WBRT).</td>
<td>Low SoE for no effect [study limitation, precision]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies(^\ddagger) Additional Individual Study Findings</td>
<td>Conclusion and SoE(^\ddagger) [Reasons for Downgrading]</td>
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</tr>
<tr>
<td><strong>KQ1a: WBRT with neuroprotection – hippocampal sparing vs standard WBRT</strong></td>
<td>Disease-free survival</td>
<td>1 RCT (N 519); Brown, 2020(^\text{10})</td>
<td>HR 1.14; CI 0.92 to 1.41: No systematic difference between treatment groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: WBRT with neuroprotection - hippocampal sparing vs standard WBRT</strong></td>
<td>Quality of life</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Brown, 2020(^\text{10}) reported no differences in EQ-5D-5L.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ1a: WBRT with neuroprotection – hippocampal sparing vs standard WBRT</strong></td>
<td>Cognitive effects</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Brown, 2020(^\text{10}) 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(^\text{186}) reported better preservation in late verbal memory but not verbal fluency or executive function with hippocampal avoidance WBRT.</td>
<td>Low SoE for beneficial effect of hippocampal sparing WBRT on cognitive function [study limitation, precision]</td>
</tr>
<tr>
<td><strong>KQ1b: Prognosis and WBRT</strong></td>
<td>Overall survival, deaths due to brain metastases</td>
<td>Meta-regression</td>
<td>No systematic relationship was detected between the patient prognosis and effects of WBRT for overall survival.</td>
<td>Low SoE for no effect [indirectness, study limitations]</td>
</tr>
<tr>
<td><strong>KQ1b: Primary tumor site and WBRT</strong></td>
<td>Overall survival, disease-free survival, deaths due to brain metastases</td>
<td>Meta-regression</td>
<td>No systematic relationship was detected between the primary tumor type and overall survival.</td>
<td>Low SoE for no effect [indirectness, study limitations]</td>
</tr>
</tbody>
</table>
| Intervention and Comparison | Outcome | Number of Studies (Participants) Contributing to Effect Estimate; Citations | Results Across Studies Additional Individual Study Findings | Conclusion and SoE

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

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, 201220 reported no significant difference in overall survival between groups. Guerrieri, 200417 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, 2013101 reported median overall survival of 3 vs 6.3 months comparing radiochemotherapy and radiation alone. Hoffmann-La Roche, 2011105 reported 4.6 vs 9.8 months survival. Liu, 2017122 reported significantly longer survival with temozolomide compared to WBRT alone. A trial by Merck, 2008129 reported that 8/18 patients in the WBRT + temozolomide vs 8/13 in the WBRT group alone were still alive after 6 months. Yang, 2017165 reported that the WBRT + bevacizumab + gefitinib had the most favorable survival status.

Low SoE for no effect [study limitation, consistency]

Disease-free survival

7 RCTs (N 679); Cao, 2010;84 Chua, 2010;84 Gamboa-Vignolle, 2012;96 Gronberg, 2012;100 Gupta, 2016;102 Lee, 2014;120 Yang, 2018

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, 2016101 reported 1-year progression free survival rates of 17.7% and 5.2% (p=0.392). Liu, 2017122 reported significantly longer survival with temozolomide compared to WBRT alone. A trial by Merck, 2008129 reported that 8/18 patients in the WBRT + temozolomide vs 8/13 in the WBRT group alone were still alive after 6 months. Yang, 2017165 reported that the WBRT + bevacizumab + gefitinib had the most favorable survival status.

Low SoE for no effect [precision, consistency]

Deaths due to brain metastases

5 RCTs (N 486); Antonadou, 2002;76 Cao, 2015;84 Knisely, 2008;115 Lee, 2014;120 Verger, 2005

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]
<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies (Participants) Contributing to Effect Estimate; Citations</th>
<th>Results Across Studies Additional Individual Study Findings</th>
<th>Conclusion and SoE</th>
<th>[Reasons for Downgrading]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ1c: WBRT + systemic therapy vs WRBT alone</td>
<td>Intracranial progression</td>
<td>1 RCT (N 95); Chua, 2010&lt;sup&gt;9&lt;/sup&gt;</td>
<td>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&lt;sup&gt;10&lt;/sup&gt; also reported no significant differences in intracranial response rate and time to clinical or radiographic progression. Hassler, 2013&lt;sup&gt;11&lt;/sup&gt; reported 2.4 months vs 2.0 months favoring systemic therapy (not significant). Liu, 2017&lt;sup&gt;12&lt;/sup&gt; reported no difference between groups in the number of patients with progressive disease (p=0.2327). Mornex, 2003&lt;sup&gt;13&lt;/sup&gt; reported 56 vs 49 days to cerebral progression (p=0.028) with fotemustine. Ushio, 1994&lt;sup&gt;14&lt;/sup&gt; 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&lt;sup&gt;15&lt;/sup&gt; reported 3/41 (WBRT + temozolomide) vs 9/41 (WBRT alone) patients with progressive disease. Yang, 2017&lt;sup&gt;16&lt;/sup&gt; reported 4% (WBRT + bevacizumab + gefitinib) vs 27% (WBRT alone) patients with progressive disease (12% in WBRT + gefitinib group).</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
<td></td>
</tr>
<tr>
<td>KQ1c: WBRT + systemic therapy vs WRBT alone</td>
<td>Quality of life</td>
<td>1 RCT (48) Lee, 2014&lt;sup&gt;17&lt;/sup&gt;</td>
<td>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&lt;sup&gt;18&lt;/sup&gt; reported no significant differences between groups of which one received chemotherapy. Gronberg, 2012&lt;sup&gt;19&lt;/sup&gt; also reported no statistical differences for enzastaurin. Liu, 2017&lt;sup&gt;12&lt;/sup&gt; reported improvement with temozolomide group (p=0.0007).</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
<td></td>
</tr>
<tr>
<td>KQ1c: WBRT + systemic therapy vs WRBT alone</td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible</td>
<td>Insufficient [study limitation, precision, consistency]</td>
<td></td>
</tr>
<tr>
<td>KQ1c: WBRT + capecitabine vs WRBT alone</td>
<td>Cognitive function</td>
<td>1 RCT (N 95); Hoffmann-La Roche, 2011&lt;sup&gt;20&lt;/sup&gt;</td>
<td>SMD 2.56; CI 1.06 to 6.18: WBRT + capecitabine showed less decline in cognitive function compared to WBRT alone.</td>
<td>Low SoE for improved cognitive function with capecitabine [precision, consistency]</td>
<td></td>
</tr>
<tr>
<td>KQ1c: WBRT + temozolomide vs WBRT + gefitinib</td>
<td>Overall survival</td>
<td>1 RCT (N 59) Pesce, 2012&lt;sup&gt;21&lt;/sup&gt;</td>
<td>HR 1.29; CI 0.47 to 3.55: No systematic difference between groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
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</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies&lt;sup&gt;‡&lt;/sup&gt; Additional Individual Study Findings</td>
<td>Conclusion and SoE&lt;sup&gt;‡‡&lt;/sup&gt; [Reasons for Downgrading]</td>
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<tr>
<td><strong>KQ1c: WBRT + temozolomide vs WBRT + gefitinib</strong></td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N ) Pesce, 2012&lt;sup&gt;137&lt;/sup&gt;</td>
<td>RR 0.43; CI 0.18 to 0.98: No systematic difference between groups.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT + cisplatin, vinorelbine, ifosfamide vs ifosfamide</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Quantin, 2010&lt;sup&gt;142&lt;/sup&gt; reported a median survival of 8.5 months in the combination and 5.7 months in the ifosfamide group (p=0.82).</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT + cisplatin, vinorelbirne, ifosfamide vs WBRT + ifosfamide</strong></td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Quantin, 2010&lt;sup&gt;142&lt;/sup&gt; reported 437 (WBRT + cisplatin, Vinorelbirne, ifosfamide) vs 533 (WBRT + cisplatin) patients with progressive disease.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT followed by chemotherapy vs chemotherapy followed by WBRT</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Lee, 2008&lt;sup&gt;116&lt;/sup&gt; reported no statistically significantly difference between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT followed by chemotherapy vs chemotherapy followed by WBRT</strong></td>
<td>Progression-free survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Lee, 2008&lt;sup&gt;116&lt;/sup&gt; reported no statistically significantly difference between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT + gefitinib vs WBRT + VMP</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Wang, 2015&lt;sup&gt;162&lt;/sup&gt; reported the median survival time was 13.3 for gefitinib and 12.7 for VMP (p&lt;0.05).</td>
<td>Low SoE for no difference [precision, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT + gefitinib vs WBRT + VMP</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Wang, 2015&lt;sup&gt;162&lt;/sup&gt; reported 54% (gefitinib) vs 58% (VMP) of patients with progressive disease.</td>
<td>Low SoE for no difference [precision, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT + melatonin vs WBRT</strong></td>
<td>Overall survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Berk, 2007&lt;sup&gt;17&lt;/sup&gt; reported the median survival were 2.8 vs 3.4</td>
<td>Low SoE for no effect [precision, consistency]</td>
<td></td>
</tr>
<tr>
<td><strong>KQ1c: WBRT + melatonin vs WBRT</strong></td>
<td>Cognitive effects</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Berk, 2007&lt;sup&gt;17&lt;/sup&gt; reported 57% vs 55% new MMSE failures</td>
<td>Low SoE for no effect [precision, consistency]</td>
<td></td>
</tr>
</tbody>
</table>

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.

<sup>‡</sup>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.

<sup>‡‡</sup>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. Raman, 2020 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 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. The results for overall survival are documented in Figure 11.

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

![Graph showing overall survival comparison](image)

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. reported no difference between intervention groups.

Two RCTs assessed the outcome number of deaths due to brain metastases as shown in Figure 12.
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.
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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{81} The studies could not be combined as they used different outcome operationalizations.

Three of the RCTs reported on cognitive function.\textsuperscript{77, 81, 86} Studies reported insufficient details to compute effect sizes and could not be combined statistically. Aoyama et al.\textsuperscript{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\textsuperscript{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.\textsuperscript{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](image)

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

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 WBRT75, 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**

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 fraction77 to 4000 cGy in 10 fractions95). 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 cancer113 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**

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations</th>
<th>Results Across Studies† Additional Individual Study Findings</th>
<th>Conclusion and SoE‡‡ [Reasons for Downgrading]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ2: SRS vs WBRT</strong></td>
<td>Overall survival</td>
<td>1 RCT (N 20) Raman, 2020145</td>
<td>HR 2.00; CI 0.78 to 5.17; The results favored WBRT but the difference was not statistically significant.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: SRS vs WBRT</strong></td>
<td>Disease-free survival</td>
<td>1 RCT (N 20) Raman, 2020145</td>
<td>HR 3.00; CI 0.79 to 11.44; The results favored WBRT but the difference was not statistically significant.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: SRS vs WBRT</strong></td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N 20) Raman, 2020145</td>
<td>RR 3.00; CI 0.79 to 11.44; The results favored WBRT but the difference was not statistically significant.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: SRS vs WBRT</strong></td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Raman, 2020145 reported a 6-month local recurrence-free survival rate of 58.3% for SRS and 71.4% for WBRT.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: SRS vs WBRT</strong></td>
<td>Functional status</td>
<td>1 RCT (N 20) Raman, 2020145</td>
<td>SMD 0.55; CI -0.36 to 1.46: No statistically significant difference between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations</td>
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<tr>
<td>KQ2: SRS vs WBRT</td>
<td>Cognitive function</td>
<td>1 RCT (N 20) Raman, 2020</td>
<td>SMD -0.02; CI -0.91 to 0.87: No difference between groups.</td>
<td>Low for no difference [precision, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS alone</td>
<td>Overall survival</td>
<td>3 RCTs (N 403); Aoyama, 2006; Brown, 2016; Chang, 2009</td>
<td>HR 0.95; CI 0.23 to 3.90: Conflicting results across studies with no systematic difference between treatment groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS alone</td>
<td>Deaths due to brain metastases</td>
<td>2 RCTs (N 190); Aoyama, 2006; Chang, 2009</td>
<td>RR 1.09; CI 0.04 to 33.13: No systematic difference between treatment groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS alone</td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Aoyama, 2006 reported the 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group (p&lt;.001).</td>
<td>Low SoE for beneficial effect on brain tumor recurrence favoring SRS + WBRT [precision, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS alone</td>
<td>Quality of life</td>
<td>2 RCTs (N 271); Brown, 2016; Chang, 2009</td>
<td>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.</td>
<td>Low SoE for no effect [study limitations, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS alone</td>
<td>Functional status</td>
<td>1 RCT (N 213); Brown, 2016</td>
<td>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 reported no significant difference in systemic functional preservation rates between groups.</td>
<td>Low SoE for no effect [study limitation, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations</td>
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<tr>
<td>KQ2: SRS + WBRT vs SRS alone</td>
<td>Cognitive status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Aoyama, 2006\textsuperscript{67} 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\textsuperscript{68} reported a mean posterior probability of decline of 52 percent for the SRS + WBRT group and 24 percent for SRS alone. Brown, 2016\textsuperscript{69} reported that a decline of &gt;1 SD on at least 1/7 cognitive tests was less frequent after SRS alone than after SRS + WBRT (p&lt;.001) but results for individual tests varied.</td>
<td>Low SoE for beneficial effect on cognitive status favoring SRS alone [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS or WBRT alone</td>
<td>Overall survival</td>
<td>4 RCTs (N 734); Andrews, 2004;\textsuperscript{70} Aoyama, 2006;\textsuperscript{71} Brown, 2016;\textsuperscript{72} Chang, 2009\textsuperscript{73}</td>
<td>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.</td>
<td>Low SoE for no effect [study limitation, precision]</td>
</tr>
<tr>
<td>KQ2: SRS + WBRT vs SRS or WBRT alone</td>
<td>Deaths due to brain metastases</td>
<td>3 RCTs (N 521); Andrews, 2004;\textsuperscript{74} Aoyama, 2006;\textsuperscript{75} Chang, 2009\textsuperscript{76}</td>
<td>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.</td>
<td>Low for no effect [study limitation, precision]</td>
</tr>
<tr>
<td>KQ2: SRS + chemotherapy vs chemotherapy alone</td>
<td>Overall survival</td>
<td>1 RCT (N 98); Lim, 2015\textsuperscript{77}</td>
<td>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.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ2: SRS + systemic therapy vs systemic therapy alone</td>
<td>Intracranial progression-free survival, time to CNS disease progression, functional status, cognitive effects</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Lim, 2015\textsuperscript{78} reported no statistically significant difference in overall survival, intracranial progression-free survival, time to CNS disease progression, functional status, and cognitive effects between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ2: WBRT + SRS vs WBRT + surgery</td>
<td>Overall survival</td>
<td>1 RCT (N 21); Roos, 2011\textsuperscript{79}</td>
<td>HR 0.53; CI 0.20 to 1.43: No systematic difference between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) and Study Design Contributing to Effect Estimate; Citations</td>
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<td>------------------------------------------</td>
</tr>
<tr>
<td><strong>KQ2: WBRT + SRS vs WBRT + surgery</strong></td>
<td>Disease-free survival</td>
<td>1 RCT (N 21); Roos, 2011(^{50})</td>
<td>HR 0.55; CI 0.22 to 1.38: No systematic difference for failure-free survival between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: WBRT + SRS vs WBRT + surgery</strong></td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible (^{150}) Roos, 2011 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</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: WBRT + SRS vs WBRT + surgery</strong></td>
<td>Quality of life</td>
<td>1 RCT (N 21); Roos, 2011(^{50})</td>
<td>SMD 1.22; CI 0.26 to 2.18: No systematic difference between groups</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: WBRT + SRS vs WBRT + surgery</strong></td>
<td>Functional status, cognitive function</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible (^{150}) Roos, 2011 reported no significant differences between arms at 2 months.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: Surgery + WBRT vs SRS</strong></td>
<td>Overall survival</td>
<td>1 RCT (N 33); Muacevic, 2008(^{133})</td>
<td>HR 1.08; CI 0.30 to 3.94: No systematic difference between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2: Surgery + WBRT vs SRS</strong></td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N 33); Muacevic, 2008(^{133})</td>
<td>RR 3.13; CI 0.95 to 10.33: No systematic difference between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2a: SRS dose</strong></td>
<td>Overall survival</td>
<td>Meta-regression</td>
<td>No systematic relationship between SRS dose and SRS effect estimates was detected but the analysis was limited.</td>
<td>Low for no effect [directness, study limitations]</td>
</tr>
<tr>
<td><strong>KQ2a: SRS technique</strong></td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible (^{114}) Knisely, 2008 randomized by lesion to 1mm margin SRS or 3mm margin SRS and reported no difference in local recurrence at the site of radiosurgery.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ2b: Prognosis and SRS</strong></td>
<td>Overall survival</td>
<td>Meta-regression</td>
<td>No systematic relationship between prognosis and SRS effect estimates was detected but the analysis was limited.</td>
<td>Low for no effect [directness, study limitations]</td>
</tr>
<tr>
<td><strong>KQ2b: Primary tumor site and SRS</strong></td>
<td>Overall survival</td>
<td>Meta-regression</td>
<td>No systematic relationship between primary tumor type and SRS effect estimates was detected but the analysis was limited.</td>
<td>Low for no effect [directness, study limitations]</td>
</tr>
</tbody>
</table>
### Intervention and Comparison

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
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</tr>
</thead>
<tbody>
<tr>
<td>KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone</td>
<td>Overall survival</td>
<td>1 RCT (N 126); Sperduto, 2013&lt;sup&gt;134&lt;/sup&gt;</td>
<td>HR 1.43; CI 0.89 to 2.31</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone</td>
<td>Disease-free survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone</td>
<td>Intracranial progression</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ2c: SRS+WBRT+temozolomide or erlotinib vs SRS+WBRT alone</td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
</tbody>
</table>

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.

<sup>‡</sup>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.

<sup>‡‡</sup>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
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\textsuperscript{106, 116, 147, 151} and one observational study.\textsuperscript{126} Figure 16 shows all RCTs reporting on overall survival.\textsuperscript{106, 116, 147, 151} The analysis includes studies where patients may have received SRS in addition, or in some cases instead of undergoing surgery.
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 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.
The individual studies reported conflicting results, one favoring the WBRT, one the surgery or SRS plus observation arm\textsuperscript{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.\textsuperscript{106, 116, 147}
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 (I² 83%). All included studies were classified as medium risk of bias.

Hong et al.\textsuperscript{106} reported no difference in intracranial failure (p=0.28). Kocher et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{151} concluded that their limited analysis of quality of life data revealed no evidence of differences between groups.

Kocher et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{151} similarly reported no statistically significant difference between arms (p=0.80) for the time to functional status deterioration.

Hong et al.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{116, 124, 147, 151}
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\textsuperscript{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.\textsuperscript{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\textsuperscript{124} and no high risk of bias studies contributed to the effect estimate. The statistical heterogeneity was moderate (I\textsuperscript{2} 70%).

Two of the RCTs reported on time to intracranial progression as shown in Figure 21.\textsuperscript{124, 151}
Figure 21. Radiation therapy post-surgery versus surgery alone: intracranial progression

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 (I² 82%).

**SRS After Surgery Versus WBRT After Surgery**

Three RCTs compared post-surgical WBRT and post-surgical SRS in head-to-head trials. The figure 22 shows results for overall survival.
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\textsuperscript{79} reported a smaller effect; both individual studies did not show statistically significant differences between arms.

Kayama et al.\textsuperscript{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.\textsuperscript{111,112}
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 (I² 75%). The RCT by Kayama et al. and Kepka et al. 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. reported slower intracranial progression in the WBRT group (HR 2.45; CI 1.61 to 3.72; 1 RCT). Kepka et al. 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. 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. Kayama et al. reported the proportions of patients whose performance status scores did not worsen at 12 months were similar in both treatment groups.
Brown et al. 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).

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

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies (Participants)</th>
<th>Results Across Studies Additional Individual Study Findings</th>
<th>Conclusion and SoE [Reasons for Downgrading]</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment</td>
<td>Overall survival</td>
<td>4 RCTs (N 680); Hong, 2019; Kocher, 2011; Regine, 2004; Roos, 2006</td>
<td>HR 0.93; CI 0.68 to 1.27: No systematic difference between groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
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<tr>
<td>KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment</td>
<td>Disease-free survival</td>
<td>2 RCTs (N 378); Kocher, 2011; Roos, 2006</td>
<td>HR 0.79; CI 0.07 to 8.50: No systematic difference between treatment groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment</td>
<td>Deaths due to brain metastases</td>
<td>3 RCTs (N 661); Hong, 2019; Kocher, 2011; Regine, 2004</td>
<td>RR 0.66; CI 0.18 to 2.42: Two studies reported fewer deaths due to brain metastases, one reported no difference.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ3: WBRT after surgery (or after SRS) vs no radiation after local treatment</td>
<td>Intracranial progression</td>
<td>1 RCT (N 19)</td>
<td>HR 2.81; CI 0.72 to 10.9: Results favor WBRT but the effect was not statistically significant. In addition, Hong, 2019 reported no difference in intracranial failure (p=0.28). Kocher, 2011 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 reported a</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies(\ddagger) Additional Individual Study Findings</td>
<td>Conclusion and SoE(\ddagger) [Reasons for Downgrading]</td>
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<tr>
<td><strong>KQ3: WBRT after surgery vs no radiation after surgery</strong></td>
<td>Quality of life</td>
<td>1 RCT (N 359); Kocher, 2011(^{116})</td>
<td>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. <em>In addition, Hong, 2019(^{106}) reported no difference in quality of life (p=0.083). Roos, 2006(^{114}) found no differences between groups but analyses were limited.</em></td>
<td>Low SoE for beneficial effect on quality of life favoring observation [study limitation, consistency]</td>
</tr>
<tr>
<td><strong>KQ3: WBRT after surgery or SRS vs no radiation after surgery</strong></td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Kocher, 2011(^{116}) reported no difference between the two arms (p=0.71). Regine, 2004(^{117}) reported no difference in the length of time the Karnofsky score remained at (\geq 70%) (p=0.61). Roos, 2006(^{114}) reported no statistically significant difference between time to deterioration of WHO performance status to &gt;1 (HR 1.16, 0.38 to 3.48).</td>
<td>Low SoE for no effect [study limitation, precision]</td>
</tr>
<tr>
<td><strong>KQ3: WBRT after surgery or SRS vs no radiation after surgery</strong></td>
<td>Cognitive function</td>
<td>Effect estimate not possible</td>
<td>Hong, 2019(^{106}) reported no difference 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(^{114}) found no differences between groups.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
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<tr>
<td><strong>KQ3: SRS after surgery vs no radiation after surgery</strong></td>
<td>Overall survival</td>
<td>1 RCT (N 128); Mahajan, 2017(^{124})</td>
<td>HR 1.29; CI 0.84 to 1.98: No systematic difference between groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ3: SRS after surgery vs no radiation after surgery</strong></td>
<td>Deaths due to brain metastases</td>
<td>1 RCT (N 128); Mahajan, 2017(^{124})</td>
<td>RR 0.91; CI 0.58 to 1.43: No systematic difference between groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ3: SRS after surgery vs no radiation after surgery</strong></td>
<td>Intracranial progression</td>
<td>1 RCT (N 128); Mahajan, 2017(^{124})</td>
<td>HR 0.46; CI 0.24 to 0.88: Favors SRS after surgery compared to observation after surgery regarding local recurrence.</td>
<td>Low SoE for beneficial effect on local recurrence favoring SRS [study limitation, consistency]</td>
</tr>
<tr>
<td><strong>KQ3: Radiation therapy after surgery vs no radiation after surgery</strong></td>
<td>Overall survival</td>
<td>5 RCTs (N 808); Hong, 2019(^{106}); Kocher, 2011(^{116}); Mahajan, 2017(^{124}); Regine, 2004(^{117}); Roos, 2006(^{151})</td>
<td>HR 0.98; CI 0.76 to 1.26: No systematic difference between treatment groups.</td>
<td>Moderate SoE for no effect [consistency]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies Additional Individual Study Findings</td>
<td>Conclusion and SoE [Reasons for Downgrading]</td>
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<tr>
<td>KQ3: Radiation therapy after surgery vs no radiation after surgery</td>
<td>Deaths due to brain metastases</td>
<td>4 RCTs (N 789); Hong, 2019; Kocher, 2011; Mahajan, 2017; Regine, 2004</td>
<td>RR 0.74; CI 0.38 to 1.45: No systematic difference between treatment groups.</td>
<td>Low SoE for no effect [precision, consistency]</td>
</tr>
<tr>
<td>KQ3: Radiation therapy after surgery vs no radiation after surgery</td>
<td>Intracranial progression</td>
<td>2 RCTs (N 147); Mahajan, 2017; Roos, 2006</td>
<td>HR 1.03; CI &lt;0.00 to 93956: Studies reported conflicting results.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Overall survival</td>
<td>3 RCTs (N 515); Brown, 2017; Kayama, 2018; Kepka, 2016</td>
<td>HR 1.17; CI 0.61 to 2.25: Across studies there were no systematic differences between WBRT and SRS.</td>
<td>Low SoE for no difference [precision]</td>
</tr>
<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Disease-free survival</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Kayama, 2016 reported a median intracranial progression-free survival of 10 months for WBRT and 4 months for salvage SRS.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Deaths due to brain metastases</td>
<td>2 RCT (N 330); Kayama, 2018; Kepka, 2016</td>
<td>RR 1.60; CI &lt;0.00 to 2282: Direction of effects favors WBRT but the effect is not statistically significant.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Intracranial progression</td>
<td>1 RCT (N 185); Brown, 2017</td>
<td>HR 2.45; CI 1.61 to 3.72: Results favoring WBRT based on one RCT that provided effect estimates. In addition, Kepka, 2016 reported intracranial progression rates of 86% in the SRS vs 68% in the WBRT group.</td>
<td>Low SoE for beneficial effects on intracranial progression favoring WBRT [study limitation, precision]</td>
</tr>
<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Quality of life</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Brown, 2017 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.</td>
<td>Insufficient [study limitation, precision, consistency]</td>
</tr>
<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Functional status</td>
<td>Effect estimate not possible</td>
<td>Effect estimate not possible Brown, 2017 reported no significant difference between groups in functional independence at the latest follow up. Kayama, 2018 reported the proportions of patients whose performance status scores did not worsen at 12 months were similar in both treatment groups.</td>
<td>Low SoE for no difference [study limitation, precision]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies‡ Additional Individual Study Findings</td>
<td>Conclusion and SoE‡‡ [Reasons for Downgrading]</td>
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<tr>
<td>KQ3a: SRS vs WBRT post-surgery</td>
<td>Cognitive function</td>
<td>1 RCT (N 185); Brown, 201799</td>
<td>SMD -0.82; CI -1.11 to -0.53: Results favored SRS in an RCT that provided effect estimates. In addition, Kayama, 201811 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).</td>
<td>Low SoE for beneficial effects on cognitive function favoring SRS [study limitation, precision,]</td>
</tr>
</tbody>
</table>

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.\textsuperscript{75,77,81,86}
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, neurological toxicities and not further defined, grade 3 or 4 of late radiation toxic effects, and pathologically proven radiation necrosis. The analysis includes one low risk of bias study 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.
Figure 25. WBRT plus radiosensitizer or WBRT alone: serious adverse events

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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{84, 85, 97, 100, 102, 103, 105, 154}
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 GlaxoSmithKline trial\(^9\) 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.\(^10\) 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.\(^11\) reported confusion as the most common serious adverse event. Hassler et al.\(^12\) reported more incidences of lymphocytopenia. Sperduto et al.\(^13\) 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.\textsuperscript{116}

Two studies evaluating surgery plus SRS compared to surgery plus WBRT reported on the number of patients who experienced a serious adverse event.\textsuperscript{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\textsuperscript{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.\textsuperscript{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)\textsuperscript{107, 127, 128, 138, 168} and WBRT plus systemic therapy (1,570 vs 1,150).\textsuperscript{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),\textsuperscript{148, 164} WBRT plus SRS versus WBRT alone (174 vs 160),\textsuperscript{75, 93} and WBRT plus surgery versus WBRT alone (11 vs 8).\textsuperscript{131}

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

Post-surgery studies reported more adverse events for WBRT when comparing SRS versus WBRT after surgery (338 vs 541)\textsuperscript{79, 111} but WBRT versus observation showed no marked differences (721 vs 691).\textsuperscript{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.\textsuperscript{77, 81, 86, 93}
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.\textsuperscript{81} did not report statistically significant differences between arms either. While the figure shows the comparison to WBRT for El Gantery et al.,\textsuperscript{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.\textsuperscript{102} and Lee et al.\textsuperscript{120} evaluated systemic therapy added to WBRT and both reported no cases of radiation necrosis in either group (RR 0.89; CI 0 to 414; 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.\textsuperscript{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.\textsuperscript{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. and Kayama et al. 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. evaluated WBRT plus SRS versus WBRT alone or SRS alone and Brown et al. evaluated SRS plus WBRT versus SRS alone. 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 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.

A large number of studies investigated the effect of adding systemic therapy to WBRT as shown in Figure 28.
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. did not find not statistically significant differences between treatment groups.

A study published by Yang et al. 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.

![Figure 29. WBRT plus systemic therapy versus WBRT alone: fatigue](image)

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.
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
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 (I² 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
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
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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).
Table 5 summarizes the findings and evaluates the quality of evidence.

<table>
<thead>
<tr>
<th>Intervention and Comparison</th>
<th>Outcome</th>
<th>Number of Studies (Participants) Contributing to Effect Estimate; Citations</th>
<th>Results Across Studies Additional Individual Study Findings</th>
<th>Conclusion and SoE [Reasons for Downgrading]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ4: WBRT + SRS vs WBRT or SRS alone</strong></td>
<td>Serious adverse events</td>
<td>4 studies (N 734) Andrews, 2004; Aoyama, 2006; Brown, 2016; Chang, 2009</td>
<td>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.</td>
<td>Moderate SoE for no increased risk [study limitation]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT + radiosensitizer vs WBRT alone</strong></td>
<td>Serious adverse events</td>
<td>3 studies (N 605) Hosseini, 2015; Phillips, 1995; Suh, 2006</td>
<td>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.</td>
<td>Low SoE for no increased risk [consistency, precision]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT + systemic therapy vs WBRT alone</strong></td>
<td>Serious adverse events</td>
<td>8 studies (N 992) Cao, 2015; Chabot, 2017; GlaxoSmithKline 2012; Gronberg, 2012; Gupta, 2016; Hassler, 2013; Hoffmann-La Roche, 2011; Merck Sharp &amp; Dohme Corp, 2008</td>
<td>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.</td>
<td>Low SoE for no increased risk [consistency, precision]</td>
</tr>
<tr>
<td><strong>KQ4: SRS post-surgery vs WBRT post-surgery</strong></td>
<td>Serious adverse events</td>
<td>2 studies (N 244) Brown, 2017; Kepka, 2016</td>
<td>RR 1.33; CI 0.78 to 2.25: No consistent difference comparing surgery plus SRS with surgery plus WBRT. Kayama, 2018 reported more events in the WBRT group.</td>
<td>Low SoE for no difference [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT + SRS vs WBRT or SRS alone</strong></td>
<td>Radiation necrosis</td>
<td>4 studies (N 445) Aoyama, 2006; Brown, 2016; Chang, 2009; El Gantry, 2014</td>
<td>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.</td>
<td>Low SoE for no increased risk [precision, consistency]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT + systemic therapy vs WBRT alone</strong></td>
<td>Radiation necrosis</td>
<td>2 studies (N 98) Gupta, 2016; Lee, 2014</td>
<td>RR 0.89; CI 0 to 41413124: No cases in either group.</td>
<td>Moderate SoE for no increased risk [precision]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
<td>Outcome</td>
<td>Number of Studies (Participants) Contributing to Effect Estimate; Citations</td>
<td>Results Across Studies ‡ Additional Individual Study Findings</td>
<td>Conclusion and SoE ‡‡ [Reasons for Downgrading]</td>
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<tr>
<td>KQ4: SRS post-surgery vs WBRT post-surgery</td>
<td>Radiation necrosis</td>
<td>2 studies (N 456) Brown, 2017;76 Kayama, 2018111</td>
<td>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.</td>
<td>Insufficient [study limitation, precision]</td>
</tr>
<tr>
<td>KQ4: WBRT + systemic therapy vs WBRT alone</td>
<td>Headaches</td>
<td>12 studies (N 1,536) Antonadou, 2002;76 Chabot, 2017;44 Chua, 2010;89 Deng, 2017;91 GlaxoSmithKline 2012;97 Gupta, 2016;102 Hassler, 2013;103 Hoffmann-La Roche, 2011;105 Lee, 2014;129 Liu, 2017;122 Yang, 2017165</td>
<td>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.</td>
<td>Moderate SoE for no increased risk [consistency]</td>
</tr>
<tr>
<td>KQ4: WBRT + systemic therapy vs WBRT alone</td>
<td>Fatigue</td>
<td>10 studies (N 1,318) Antonadou, 2002;76 Chabot, 2017;44 Chua, 2010;89 Deng, 2017;91 GlaxoSmithKline 2012;97 Gronberg, 2012;100 Gupta, 2016;102 Hoffmann-La Roche, 2011;105 Lee, 2014;129 Merck Sharp &amp; Dohme Corp, 2008199</td>
<td>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.</td>
<td>Moderate SoE for no increased risk [consistency]</td>
</tr>
<tr>
<td>KQ4: WBRT + SRS vs WBRT or SRS alone</td>
<td>Seizures</td>
<td>3 studies (N 387) Aoyama, 2006;77 Brown, 2016;81 El Gantry, 201443</td>
<td>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.</td>
<td>Low SoE for no increased risk [consistency, precision]</td>
</tr>
<tr>
<td>Intervention and Comparison</td>
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<td>Results Across Studies‡ Additional Individual Study Findings</td>
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<tr>
<td><strong>KQ4: WBRT + systemic therapy vs WBRT alone</strong></td>
<td>Seizures</td>
<td>4 studies (N 779) Chabot, 2017; GlaxoSmithKline 2012; Hoffmann-La Roche, 2011; Lee, 2014</td>
<td>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.</td>
<td>Low SoE for no increased risk [consistency, precision]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT + SRS vs WBRT or SRS alone</strong></td>
<td>Vomiting</td>
<td>3 studies (N 586) Andrews, 2004; Brown, 2016; El Gantry, 2014</td>
<td>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.</td>
<td>Low SoE for no increased risk [consistency, precision]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT + radiosensitizer vs WBRT alone</strong></td>
<td>Vomiting</td>
<td>2 studies (N 1,069) Mehta, 2009; Suh, 2006</td>
<td>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.</td>
<td>Insufficient [study limitation, precision, inconsistency]</td>
</tr>
<tr>
<td><strong>KQ4: WBRT plus systemic therapy vs WBRT alone</strong></td>
<td>Vomiting</td>
<td>15 studies (N 1,731) Antonadou, 2002; Cao, 2015; Chabot, 2017; Chua, 2010; Deng, 2017; Gamboa-Vignolle, 2012; GlaxoSmithKline 2012; Gronberg, 2012; Gupta, 2016; Hassler, 2013; Hoffmann-La Roche, 2011; Lee, 2014; Liu, 2017; Merck Sharp &amp; Dohme Corp, 2008; Yang, 2017</td>
<td>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.</td>
<td>Moderate SoE for increased risk of vomiting with systemic therapy [consistency]</td>
</tr>
</tbody>
</table>

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.\(^32\) 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. 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. 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. 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.

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). The previously reported ASTRO guideline supported SRS alone as a treatment option for selected patients (good prognosis, metastases ≤3-4 cm). 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.\textsuperscript{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. \textsuperscript{2009} and Brown et al.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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 heterogeneous. 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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AHRQ</td>
<td>Agency for Healthcare Research and Quality</td>
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<tr>
<td>ASTRO</td>
<td>American Society for Radiation Oncology</td>
</tr>
<tr>
<td>bid</td>
<td>twice daily</td>
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<tr>
<td>cGy</td>
<td>centigray</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>EPC</td>
<td>Evidence-based Practice Center</td>
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<tr>
<td>DFS</td>
<td>disease-free survival</td>
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<tr>
<td>GPA</td>
<td>Graded Prognostic Assessment</td>
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<tr>
<td>GRADE</td>
<td>Grading of Recommendations Assessment, Development and Evaluation</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>KQ</td>
<td>Key Question</td>
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<tr>
<td>N</td>
<td>number of participants</td>
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<td>OS</td>
<td>overall survival</td>
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<tr>
<td>PCORI</td>
<td>Patient-Centered Outcomes Research Institute</td>
</tr>
<tr>
<td>PICOTSS</td>
<td>population, intervention, comparator, outcomes, timing, setting, study design</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RoB</td>
<td>risk of bias</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SMD</td>
<td>standardized mean difference</td>
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<tr>
<td>SRS</td>
<td>stereotactic radiosurgery</td>
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<tr>
<td>TEP</td>
<td>Technical Expert Panel</td>
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<tr>
<td>US</td>
<td>United States</td>
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<tr>
<td>WBRT</td>
<td>whole brain radiation therapy</td>
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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
20 July 2020
RCT filter OR systematic review filter
OR
AND clinical trial*[tiab] OR cohort stud*[tiab] OR "case series*[tiab])
OR
AND (inprocess[sb] OR publisher[sb] OR pubmednotmedline [sb])
OR
Guideline*[ti]

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
('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'" OR "cohort stud*"

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
(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>
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<tr>
<th>PICOTS</th>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
<td>• 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</td>
<td>• Study samples comprising patients with cancer from other origins or primary brain tumors (e.g., glioblastomas) and pediatric samples</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>• 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)</td>
<td>• Studies without WBRT or SRS treatment arms</td>
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<td></td>
<td>• Studies have to report on effects of radiation therapy in the 1990s or later</td>
<td>• Studies based exclusively on pre-1990 data</td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td>• 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)</td>
<td>• Studies comparing only non-intervention features (e.g., comparing two patient subgroups)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>• 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)</td>
<td>• Studies reporting only on therapy acceptance, provider variables (e.g., provider knowledge), organizational measures (e.g., wait times), treatment utilization, or costs</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>• Studies will not be limited by the duration of the intervention or the length of follow up</td>
<td>• No exclusions apply</td>
</tr>
<tr>
<td><strong>Setting(s)</strong></td>
<td>• Studies may include inpatient and outpatient settings</td>
<td>• Studies in resource-limited settings such as developing countries will be reviewed for comparability with US settings</td>
</tr>
<tr>
<td></td>
<td>• Studies may include national and international settings</td>
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</table>
### PICOTS

<table>
<thead>
<tr>
<th>Study design</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>All KQs</td>
<td>- RCTs</td>
<td>- Studies without comparator</td>
</tr>
<tr>
<td></td>
<td>- Studies with results published in clinicaltrial.gov will be included regardless of whether a journal publication is available</td>
<td>- Evaluations reported only in abbreviated format (e.g., in a conference abstract) and that are not registered in a research registry</td>
</tr>
<tr>
<td></td>
<td>- English-language publications</td>
<td>- Studies exclusively reported in non-English publications will be retained as a resource but will not be eligible for inclusion</td>
</tr>
<tr>
<td>KQ4 (adverse events)</td>
<td>- 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</td>
<td>- Systematic reviews will be retained for reference mining</td>
</tr>
</tbody>
</table>

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-threatening, 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.\textsuperscript{266} For \textit{selection bias}, we assessed the randomization sequence and allocation concealment in RCTs as well as baseline differences and potential confounders in all studies. \textit{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. \textit{Attrition bias} considered the number of dropouts, any imbalances across study arms, and whether missing values may have affected the reported outcomes. \textit{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. \textit{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:\textsuperscript{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. 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. 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

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **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. 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.\textsuperscript{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>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>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).</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
</tr>
<tr>
<td>Low</td>
<td>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.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.


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


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/i 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


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


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*


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*


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*


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

44. Assistance Publique - Hôpitaux de P. Clinical Features, Outcome and Prognosis of Human Metapneumovirus (hMPV) Lower Respiratory Tract Infections in Adult Inpatients. 2019. Population


47. Assistance Publique Hopitaux De M. Late Effects of Radiosurgery on Acromegaly Study. 2016. Population


50. Assuta Medical C, Rabin Medical C. Can Hybrid PET-MRI Differentiate Between Radiation Effects and Disease Progression? ; 2017. Outcome


56. Avid R. A Phase 0, Open Label, Multi-center Exploratory and Safety Study of F-18 T807. 2013. Intervention


58. Azienda Ospedaliera Universitaria di Bologna Policlinico SOM. Short Course Radiation Therapy in Palliative Treatment of Brain Metastases. 2022. Outcome

60. Badiyan SN, Bierhals AJ, Olsen JR, et al. Stereotactic body radiation therapy for the
treatment of early-stage minimally invasive adenocarcinoma or adenocarcinoma in situ (formerly
bronchioloalveolar carcinoma): a patterns of failure analysis. Radiat Oncol. 2013 Jan 3;8:4. doi:


62. Baptist Health South F. Observational Trial of the Impact of Radiation Dose in Children
With Brain and Skull Base Tumors. 2030. Outcome

63. Barretos Cancer H. Exclusive Hypofractionated Stereotactic Radiotherapy in Non-resectable
Single Brain Metastasis. 2010. Outcome

64. Barretos Cancer H. Phase I Dose Escalation in Patients With 1-3 Unresectable Brain
Metastases. 2011. Outcome

65. Barwon H, Deakin U, Peter MacCallum Cancer Centre A. A Feasibility Trial Using Lithium
As A Neuroprotective Agent In Patients Undergoing Prophylactic Cranial Irradiation For Small
Cell Lung Cancer. 2014. Intervention

Carcinoma in the Targeted Therapy Era: The University of Rochester Experience. American
Journal of Clinical Oncology: Cancer Clinical Trials. 2017;40(5):439-43. doi:
10.1097/COC.0000000000000186. Population

67. Bayer. SH L 562BB Phase II/III Dose Justification and Gadoteridol-controlled Comparative
Study. 2008. Intervention

68. Baylor Breast Care C. Brain Mets - Capecitabine Plus Sunitinib and WBRT. 2013. Study
design

69. Baylor College of M, Pediatric Brain Tumor C. Karenitecin in Pediatric Patients With
Refractory or Recurrent Solid Tumors N10010). 2011. Intervention

Chemotherapy Followed by Radiation for Infants With Brain Tumors. 2005. Population

2009;75(3):S126-S7. Study design

Metastasis in Advanced Unresectable Metastatic Melanoma. American Journal of Clinical
Oncology-Cancer Clinical Trials. 2011 Dec;34(6):603-10. doi:
10.1097/COC.0b013e3181f9456a. PMID: WOS:000297258800004. Population

73. Beijing Tiantan H. Supra-early Post-Surgery Chemotherapy in the Treatment on GBM
Patients. 2020. Outcome

brain metastases from small-cell lung cancer. Strahlenther Onkol. 2018 Feb;194(2):98-106. doi:
10.1007/s00066-017-1228-4. PMID: 29085978. Population

B-5
75. Beth Israel Deaconess Medical C, Dana-Farber Cancer I. A Phase II Study of Cyberknife Radiosurgery for Renal Cell Carcinoma. 2021. **Outcome**


77. Betta Pharmaceuticals Co L. Icotinib Combined With WBRT For NSCLC Patients With Brain Metastases and EGFR Mutation. 2013. **Outcome**

78. Betta Pharmaceuticals Co L. Icotinib With Whole Brain Radiation Therapy in NSCLC Patients With Brain Metastases. 2016. **Outcome**

79. Betta Pharmaceuticals Co L. Icotinib Combined With Radiation Therapy For NSCLC Patients With Brain Metastases and EGFR Mutation. 2020. **Outcome**

80. Betta Pharmaceuticals Co L. High Dose Icotinib With Sequential SRS For NSCLC Patients Harboring EGFR Mutation With Brain Metastases. 2021. **Outcome**


B-7


95. Brian L, University of M. Cytochlor, Tetrahydrouridine, and External-Beam Radiation Therapy in Treating Patients With Cancer That Has Spread to the Brain. 2014. Outcome


98. British Columbia Cancer A. Volumetric Modulated Arc Therapy (VMAT) for Brain Metastases. 2013. Study design


108. Burzynski Research I, National Cancer I. Antineoplaston Therapy in Treating Patients With Neuroendocrine Tumor That Is Metastatic or Unlikely to Respond to Surgery or Radiation Therapy. Population


114. CancerCare M, Health Sciences Centre Foundation M. Neurocognition After Gamma Knife Radiosurgery for Multiple Brain Metastases. 2015. Outcome


119. Case Comprehensive Cancer C. Osimertinib With Stereotactic Radiosurgery (SRS) in Brain Metastases From EGFR Positive NSCLC. 2019. Outcome

120. Case Comprehensive Cancer C. Multi-Parametric Quantitative MR Imaging in Evaluation of Brain Tumors. 2019. Outcome

121. Case Comprehensive Cancer C. 18F-Fluciclovine PET to Distinguish Tumor Progression From Radiation Necrosis. 2021. Outcome


123. Case Comprehensive Cancer C, National Cancer I. Acute Side Effects in Patients Who Are Undergoing Stereotactic Radiosurgery for Brain Tumors or Other Brain Disorders. 2008. Comparator


129. Cedars-Sinai Medical C. Dose Escalation Trial of Neoadjuvant Radiosurgery for the Treatment of Metastatic Brain Tumors. 2019. Outcome

130. Center ACCC, Carl Zeiss Meditec AG. Focal Intraoperative Radiotherapy of Brain Metastases. 2020. Outcome


133. Center HLMC, Research I, Cortice Biosciences I. Fractionated Stereotactic Radiotherapy (FSRT) in Treatment of Brain Metastases. 2018. *Outcome*

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


136. Center HLMC, Research I, Schering P. Phase I Study of Temozolomide, Valproic Acid and Radiation Therapy in Patients With Brain Metastases. 2009. *Outcome*

137. Center MDAC. Nuclear Imaging of Human CSF Flow Using Ga-67 Citrate and In-111 DTPA. 2009. *Intervention*

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


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


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*


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

156. Center VUUM, The Netherlands Cancer I, Utrecht UMC. Local Radiotherapy Following Complete Resection of a Brain Metastasis. 2017. *Outcome*


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


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*


164. Centre hospitalier de l'Université de M, Bristol-Myers S. Combining Radiosurgery and Nivolumab in the Treatment of Brain Metastases. 2021. *Outcome*

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 Gamliogiomes (DIA DIG) - Study of the French Cohort of the Last 20 Years : Clinical, Anatomopathological, Molecular and Radiological Characteristics. 2017. *Population*

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

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*


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*


175. Chang Gung Memorial H. A Prospective Study of the Impact of Hippocampal Avoidance During Whole Brain Radiotherapy on Neurocognitive Function Decline. 2019. *Outcome*


193. Chinese Academy of Medical S. FSRT Combined With TMZ for Large BMs: a PSM Study. 2017. Outcome

194. Chinese Academy of Medical S. Tomotherapy as Primary Radiotherapy for Multipule Brain Metastases. 2017. Comparator


197. Chinese Academy of Medical S. HFSRT With Concurrent TMZ for Large BMs. 2022. Outcome

198. Chinese Academy of Medical S, Cancer Foundation C. Stereotactic Radiotherapy Plus Temozolomide for Refractory Brain Metastases. 2015. Study design


208. City of Hope Medical C, National Cancer I. Temozolomide in Treating Patients With Primary Brain Tumors or Metastatic Brain Tumors. 2008. Intervention


223. Dana-Farber Cancer I. Treatment Response Assessment Maps to Delineate Necrosis From Tumor After Stereotactic Radiation in Brain Metastases. 2021. *Outcome*

224. Dana-Farber Cancer I. Stereotactic Radiation in Patients With Small Cell Lung Cancer and 1-6 Brain Metastases. 2021. *Outcome*

225. Dana-Farber Cancer I, Brigham, Women's H. Whole Brain Radiation Versus Stereotactic Radiation (SRS) in Patients With 5-20 Brain Metastases: A Phase III, Randomized Clinical Trial. 2021. *Outcome*

226. Dana-Farber Cancer I, Conquer Cancer F. Screening Magnetic Resonance Imaging of the Brain in Patients With Breast Cancer. 2022. *Outcome*


228. Dana-Farber Cancer I, National Cancer I. High-dose ICE With Amifostine. 2000. *Intervention*

229. Daping H, the Research Institute of Surgery of the Third Military Medical U. Phase III Trial of WBRT Versus Erlotinib Concurrent Whole-brain Radiation Therapy as first-line Treatment for Patients With Multiple Brain Metastases From Non-small-cell Lung Cancer(ENTER): a Multicentre, Open-label, Randomised Study. 2016. *Duplicate*


241. Dekk-Tec I, Tulane University Medical Center NOLA, Icahn School of Medicine at Mount S, et al. Study of 4-Demethyl-4-cholesteryloxy carbonylpenclole in Patients With Brain Tumors. 2016.


261. Dwight H, University of P. Radiosurgery for Patients Recurrent Oligometastatic Disease. 2019. Outcome


271. Emory U. Phase I Trial of Stereotactic Radiosurgery Following Surgical Resection of Brain Metastases. 2015. Outcome


274. Emory U. Hypofractionated Stereotactic Radiosurgery in Treating Patients With Large Brain Metastasis. 2022. Outcome


276. EpicentRx I. Dose-Escalation Study of RRx-001 in Combination With Whole Brain Radiation in Subjects With Brain Metastases. 2018. Comparator


284. Far Eastern Memorial H. A Phase II Multi-center Pilot Study of Concurrent Temozolomide and Whole Brain Irradiation in Lung Cancer and Breast Cancer Patients With Brain Metastases. 2015. *Outcome*


291. First Hospital of Jilin U. Concurrent Involved-field Radiotherapy and Intrathecal Chemotherapy for Leptomeningeal Metastases From Solid Tumors. 2018. *Outcome*

292. First Hospital of Jilin U. Concurrent Intrathecal-pemetrexed and Involved-field Radiotherapy for Leptomeningeal Metastasis From Solid Tumors. 2019. *Outcome*


299. Fondazione Irccs Istituto Nazionale dei Tumori M, University of M. Efficacy of Metformin in Preventing Glucocorticoid-induced Diabetes in Patients With Brain Metastases. 2021. *Outcome*

300. Fortis Memorial Research I. Radiation-Induced Alopecia in Patients Undergoing Radiation Therapy to the Brain. 2018. *Outcome*


316. General Hospital of Ningxia Medical U. HS-WBRT for Prophylactic Cranial Irradiation in Limited Stage Small Cell Lung Cancer. 2018. Intervention


324. gGmbH AIOS, ClinAssess Gmb H, Sanofi. A Study of Cabazitaxel for Patients With Breast or Lung Cancer and Recurrent or Progressive Brain Metastases - Cabazitaxel for Brain Metastases (CaBaMet). 2017. Outcome


341. Grupo Español Multidisciplinar de M, Bristol-Myers S. GEM STUDY: Radiation And Yervoy in Patients With Melanoma and Brain Metastases. 2016. Outcome

342. Grupo Español Multidisciplinar de M, Pierre Fabre M, S.L MCR. Encorafenib and Binimetinib Before Local Treatment in Patients With BRAF Mutant Melanoma Metastatic to the Brain. 2020. Outcome


353. Gustave Roussy CCGP. Comparison of Dosimetry After rhTSH or Withdrawal of Thyroid Hormone in Metastatic or Locally Advanced Thyroid Cancer. 2016. Population


369. Hebrew Rehabilitation Center B. Trial to Reduce Antimicrobial Use In Nursing Home Residents With Alzheimer's Disease and Other Dementias. 2020.


374. Hellenic Cooperative Oncology G. Lapatinib and WBRT for Patients With Brain Metastases From Lung or Breast Tumors. 2014.

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383. Hoffmann-La R. A Study of Herceptin (Trastuzumab) in Combination With Whole Brain Radiotherapy in Patients With HER-2 Positive Breast Cancer. 2012. Study design

384. Hoffmann-La R. A Study of Vemurafenib in Metastatic Melanoma Participants With Brain Metastases. 2015. Intervention

385. Hokkaido University H. Prospective Randomized Trial Between WBRT Plus SRS Versus SRS Alone for 1-4 Brain Metastases. Duplicate


387. Hologic I, Methodist H. GliaSite 1-3 Mets Study. 2007. Outcome


408. Indiana U. Pilot Phase 2 Study Whole Brain Radiation Therapy With Simultaneous Integrated Boost for Patients With Brain Metastases. 2021. *Outcome*

409. Indiana U. Pre-operative Stereotactic Radiosurgery Followed by Resection for Patients With Brain Metastases. 2021. *Outcome*

410. Institut Claudius R. A Multicentric Phase II, Open-label Study Evaluating the Efficacy of the Combination of Hypofractionated Stereotactic Radiation Therapy With the Anti-PDL1 Immune Checkpoint Inhibitor Durvalumab in NSCLC Patients With 1 to 4 Brain Metastases. 2019. *Outcome*


412. Institut de Cancérologie de la L, Institut de Recherche Biomedicale des A. Validation of Radio-induced Damage Biomarkers. 2019. *Outcome*


414. Institut du Cancer de Montpellier - Val dA. A Trial Evaluating Concurrent Whole Brain Radiotherapy and Iniparib in Multiple Non Operable Brain Metastases. 2014. *Outcome*

415. Institut du Cancer de Montpellier - Val dA. Patients With Brain Metastases From HER2-positive Breast Cancer. 2017. *Outcome*

416. Institut du Cancer de Montpellier - Val dA. Medical and Surgical Management of Patients With Brain Metastases. 2018. *Intervention*

418. Institut P-C, Eisai I. Eribulin in Brain Metastases From HER2-negative Breast Cancer. 2023. *Outcome*


420. Institute OKC, National Cancer I. Ferumoxytol MRI in Assessing Response to Pembrolizumab in Patients With Brain Tumors From Melanoma and Glioblastoma. 2019. *Outcome*

421. Instituto de Oncología Ángel HR. Supplementation of L-arginine in Patients With Non-resectable Brain Metastases. 2007. *Outcome*

422. Instituto Nacional de Cancerología de M. Whole Brain Radiotherapy With or Without Temozolomide at Daily Fixed-dose for Brain Metastases Treatment. 2009. *Duplicate*

423. Instituto Nacional de Cancerología de M. Prophylactic Cranial Irradiation in Patients With Lung Adenocarcinoma With High Risk of Brain Metastasis. 2017. *Outcome*

424. International Extranodal Lymphoma Study G. Study on Tailored Treatment in Elderly Patients With Newly Diagnosed Primary Lymphoma of Central Nervous System. 2023. *Outcome*


426. Ipsen. A Non-interventional Retrospective Study to Describe Early Clinical Experience With Cabozantinib in Patients With Advanced Renal Cell Carcinoma (RCC) in the UK. 2019. *Population*


428. Istituto Clinico H. Tumor Bed Hypofractionated IMRT After Surgery for Patients With Single,Large Brain Metastases From Solid Tumor. 2019. *Outcome*


434. Jeff Burns MD, University of Kansas Medical C. Dapagliflozin In Alzheimer's Disease. 2020. Outcome


448. Juergen D, Heidelberg U, University Hospital H. Whole Brain Radiation Therapy Alone vs. Radiosurgery for SCLC Patients With 1-10 Brain Metastases. 2019. Population
449. Juergen D, Heidelberg U, University Hospital H. Cyberknife Radiosurgery for Patients With Brain Metastases Diagnosed With Either SPACE or MPRAGE Sequence. 2019. **Outcome**

450. Jules Bordet I. Kadcyla In pAtients With bRAin Metastasis. 2018. **Intervention**


455. Kadmon Corporation LLC. Study of the Combination of KD019 and Trastuzumab in Subjects With HER2-Positive Metastatic Breast Cancer. 2015. **Intervention**

456. Kaohsiung Medical University Chung-Ho Memorial H. Memory Preservation of Hippocampal Avoidance Whole Brain Radiotherapy. 2020. **Outcome**


459. Kathleen D, University of P. Stem Cell Transplant in Patients With Severe Sickle Cell Disease. 2022. **Outcome**


498. Leo WJCC, East Carolina U. Treating NSCLC Minimal Stage IV With Curative Intent. 2017. *Outcome*


505. Li L, Huazhong University of S, Technology. VEGFRs Predict Bevacizumab Benefit in Advanced Non Small Cell Lung Cancer. 2014. Outcome


514. Limited HCAI. Investigating the Efficacy of Hair Sparing Radiotherapy Treatment to the Whole Brain. 2019. *Outcome*


Maasstricht Radiation O. Radiomics for Prediction of Long Term Survival and Local Failure After Stereotactic Radiotherapy for Brain Metastases. 2014. *Intervention*

Maasstricht Radiation O. Re-irradiation of High Grade Gliomas: a Quality of Life Study. 2015. *Population*

Maasstricht Radiation O. Tumor Hypoxia With HX4 PET in Several Diseases. 2017. *Intervention*

Maasstricht Radiation O, Maastricht University Medical C. Serial CT Scans in Fractionated Stereotactic Radiotherapy. July 2007. *Intervention*


Maasstricht Radiation O, University Medical Center G, The Netherlands Cancer I. Prophylactic Cranial Irradiation (PCI) vs Observation in Stage III NSCLC. 2014. *Intervention*

Maasstricht University Medical C, Nutricia R. Targeted Nutrient Supplement in COPD (NUTRECOVER-trial). 2023. *Outcome*

Main Line H. IDO2 Genetic Status Informs the Neoadjuvant Efficacy of Chloroquine (CQ) in Brain Metastasis Radiotherapy. 2013. *Outcome*


Martin L, Université de S. Predictive Value of Dynamic Contrast Enhancement MRI on a Cerebral Tumor Response to Gamma Knife Treatment. 2008. *Intervention*


552. Masonic Cancer Center UoM. Auto Transplant for High Risk or Relapsed Solid or CNS Tumors. 2020. Outcome


555. Massachusetts General H. A Pilot Study to Evaluate PBR PET in Brain Tumor Patients Treated With Chemoradiation or Immunotherapy. 2019. Population

556. Massachusetts General H. Local Control, Quality of Life and Toxicities in Adults With Benign or Indolent Brain Tumors Undergoing Proton Radiation Therapy. 2020. Outcome


571. Medical College of W. Advanced MRI Sequences for Radiation Therapy Treatment Planning. 2015. *Intervention*

572. Medical Research C, National Cancer I. Dexamethasone and Supportive Care With or Without Whole-Brain Radiation Therapy in Treating Patients With Non-Small Cell Lung Cancer That Has Spread to the Brain and Cannot Be Removed By Surgery. Duplicate

573. Medical University I. Intrafractional Head Movement During Radiosurgery. 2015. *Intervention*

574. Medical University I, Marcel Seiz-Rosenhagen Md PD, Meinhard Nevinny-Stickel Md P, et al. Sector Irradiation Versus Whole Brain Irradiation for Brain Metastasis. 2016. *Outcome*

575. Medical University of V. Glucocorticoids, Immunotherapy and Radiosurgery for Brain Metastases. 2023. *Outcome*


583. Memorial Sloan Kettering Cancer C. Phase II Trial of Stereotactic Radiosurgery Boost Following Surgical Resection for Brain Metastases. 2009. *Outcome*

584. Memorial Sloan Kettering Cancer C. A Feasibility Study of Image Guided Noninvasive Single Fraction Stereotactic Radiosurgery for the Treatment of Brain Metastases. 2010. *Outcome*

585. Memorial Sloan Kettering Cancer C. Assessment of Early Treatment Response by Diffusion and Perfusion MRI in Patients With Brain Metastasis. 2019. *Intervention*

586. Memorial Sloan Kettering Cancer C. PET Imaging of Patients With Melanoma and Malignant Brain Tumors Using an 124I-labeled cRGDY Silica Nanomolecular Particle Tracer: A Microdosing Study. 2019. *Intervention*

587. Memorial Sloan Kettering Cancer C. 18F-FLT-PET Imaging of the Brain in Patients With Metastatic Breast Cancer to the Brain Treated With Whole Brain Radiation Therapy With or Without Sorafenib: Comparison With MR Imaging of the Brain. 2020. *Outcome*

588. Memorial Sloan Kettering Cancer C. Study of Proton Radiation to the Brain and Spinal Cord for Patients With Leptomeningeal Metastases. 2020. *Outcome*

589. Memorial Sloan Kettering Cancer C. A Comparison of MRI Perfusion and FDG PET/CT to Distinguish Between Radiation Injury and Tumor Progression. 2020. *Outcome*


593. Memorial Sloan Kettering Cancer C, MedImmune LLC. Brain Irradiation and Tremelimumab in Metastatic Breast Cancer. 2020. *Outcome*


597. Memorial Sloan Kettering Cancer C, National Institutes of H. 18F-Fluorocholine (18F-FCho) to Distinguish Necrosis From Recurrence in Brain Metastases. 2020. Outcome


604. Monica T, Medical College of W. Phase 2 STIR Trial: Haploidentical Transplant and Donor Natural Killer Cells for Solid Tumors. 2019. Outcome

605. Monteris M. Laser Ablation After Stereotactic Radiosurgery. 2016. Intervention


607. Mt. Sinai Medical Center M, Northern California Melanoma C. Temozolomide Plus Bevacizumab in Patients With Metastatic Melanoma Involving the Central Nervous System. 2011. Intervention


621. National Cancer Center K, National Cancer I. Radiation Therapy to the Brain or Observation in Preventing Brain Metastases in Patients With Advanced Non-Small Cell Lung Cancer. May 2009. Intervention

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


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


629. 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. Population


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


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


659. New Mexico Cancer Care A. Whole Brain Radiation Using IMRT for Patients With Brain Metastases. 2020. Outcome


673. Northwestern U, Genentech I. Bevacizumab in Pats w/ Recurrent ST Brain Metas Who Have Failed Whole Brain Radiation Therapy. 2018. Study design


685. Ohio State University Comprehensive Cancer C. Carboplatin and Temozolomide (Temodar) for Recurrent and Symptomatic Residual Brain Metastases. 2008. Intervention


689. Oncology Institute of Southern S. Hypofractionated Brain Radiationcavity. 2020. Outcome

690. Oncology Institute of Southern S, National Cancer I. External-Beam Radiation Therapy With or Without Indinavir and Ritonavir in Treating Patients With Brain Metastases. 2009. Outcome

691. Oncology NRG, National Cancer I. Memantine Hydrochloride and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Reducing Neurocognitive Decline in Patients With Brain Metastases. 2018. Duplicate

692. Oncology NRG, National Cancer I, Radiation Therapy Oncology G. Whole-Brain Radiation Therapy With or Without Hippocampal Avoidance in Treating Patients With Limited Stage or Extensive Stage Small Cell Lung Cancer. 2022. Outcome


697. Oslo University H, Hospital of Southern Norway T, Ostfold Hospital T, et al. Improved Therapy Response Assessment in Metastatic Brain Tumors. 2020. Outcome

698. Ottawa Hospital Research I. MR Perfusion Methods in Patients With Suspected Recurrent High Grade Gliomas. 2018. Outcome


716. Peking Union Medical College H. A Multi-center Prospective Observational Biomarker Study on EGFRm+ Non-small Cell Lung Cancer Patients With Leptomeningeal Metastasis. 2016. *Intervention*


723. Pfizer. Study Of CP-751,871 In Combination With Exemestane In Postmenopausal Women With Hormone Receptor Positive Advanced Breast Cancer. 2012. *Intervention*


725. Pharmacyclics LLC. Study of Motexafin Gadolinium With Whole Brain Radiation Therapy Followed by Stereotactic Radiosurgery Boost in the Treatment of Patients With Brain Metastases. *Outcome*

726. Pharmacyclics LLC. Study of Neurologic Progression With Motexafin Gadolinium and Radiation Therapy (SMART). *Outcome*


728. Philogen SpA. 131I-L19SIP Radioimmunotherapy (RIT) in Combination With External Beam Radiation in Patients With Multiple Brain Metastases From Solid Tumors. 2012. *Intervention*


Study design

Population


742. Rabin Medical C. Intracranial Activity of AZD9291 (TAGRISSO) in Advanced EGFRm NSCLC Patients With Asymptomatic Brain Metastases. 2020. Outcome


752. Radiation Therapy Oncology G, National Cancer I, Oncology NRG. Adjuvant Cetuximab and Chemoradiotherapy Using Either Cisplatin or Docetaxel in Treating Patients With Resected Stage III or Stage IV Squamous Cell Carcinoma or Lymphoepithelioma of the Head and Neck. 2009. *Population*

753. Radiation Therapy Oncology G, National Cancer I, Oncology NRG. Memantine in Preventing Side Effects in Patients Undergoing Whole-Brain Radiation Therapy for Brain Metastases From Solid Tumors. 2011. *Duplicate*

754. Radiation Therapy Oncology G, National Cancer I, Oncology NRG. Avoiding the Hippocampus During Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases. 2013. *Study design*


757. Raffaele IS, Mundipharma KK. High-Dose Sequential Chemoimmunotherapy for B-Cell Lymphomas With Central Nervous System Involvement. 2010. *Population*


760. Rambam Health Care C. Cardiotoxicity in Metastatic Her 2 Positive Patients Treated With Trastuzumab ,Pertuzumab and Taxanes. 2016. *Intervention*


763. Reata Pharmaceuticals I. RTA 744 in Breast Cancer Patients With Progression of Previously Irradiated Brain Metastases. 2008. *Outcome*


766. Rennes University H. Neurovascular Non Contrast-Enhanced MR Angiography at 3T. 2016. *Intervention*

767. Research USO, Novartis P. STAR Cape+BKM120 MBC With Brain Met. 2019. *Intervention*


788. Samsung Medical C. Whole-Body Magnetic Resonance Imaging/Positron Emission Tomography (MRI/PET) in the Staging of Non-Small-Cell Lung Cancer (NSCLC). Intervention

789. Samsung Medical C. The Continuation of Erlotinib. 2010. Intervention


792. Samsung Medical C, Korean Radiation Oncology G. Hippocampus-sparing WBRT and Simultaneous Integrated Boost for Multiple Brain Metastases From NSCLC. 2019. Outcome


794. Sanofi. Investigate the Maximum Tolerated Dose of Vandetanib and Concurrent Whole Brain Radiotherapy (WBRT) in Patients With Non-small Cell Lung Cancer (NSCLC) and Brain Metastases. 2010. Outcome


807. Shandong Cancer H, Institute, AstraZeneca. Open Label, Prospective Study to Investigate Efficacy and Safety of AZD9291 in BM From NSCLC Patients With EGFR T790M. 2019. Outcome


809. Shanghai Chest H. Comparator-Controlled Study for EGFR(+) Patients With Multiple BMs From NSCLC (BROKE) (EGFR-epidermal Growth Factor Receptor;BM-brain Metastases). 2017. Outcome


815. Sheba Medical C. Adoptive Cell Therapy Following a Reduced Intensity, Non-myeloablative, Lymphodepleting Induction Regimen in Metastatic Ovarian. 2021. Outcome

816. Sheba Medical C, Assaf-Harofeh Medical C. Hyperbaric Oxygen Stimulation for Patients With Brain Malignancies After Radiation Therapy. 2018. Outcome


827. Sichuan Provincial People's H. Hypofractionated Brain Radiation In EGFR Mutated Adenocarcinoma Cranial Disease (Hybrid). 2020. Outcome

828. Sidney Kimmel Cancer Center at Thomas Jefferson U, Bayer, Thomas Jefferson U. Combination of Sorafenib and Radiation for Brain Metastases and Primary Brain Tumors. 2012. Outcome

829. Sidney Kimmel Cancer Center at Thomas Jefferson U, Bristol-Myers S, Thomas Jefferson U. Phase I Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma. 2015. Comparator


831. Sidney Kimmel Cancer Center at Thomas Jefferson U, Novartis, Thomas Jefferson U. Panobinostat and Stereotactic Radiation Therapy in Treating Patients With Brain Tumors. 2013. Study design


834. Sidney Kimmel Comprehensive Cancer Center at Johns H. SRS (Stereotactic Radiosurgery) Plus Ipilimumab. 2016. Outcome


836. Sidney Kimmel Comprehensive Cancer Center at Johns H. Neurocognitive Functioning With Genu-Sparing Whole Brain Radiation Therapy for Brain Metastases. 2022. Outcome


838. Sidney Kimmel Comprehensive Cancer Center at Johns H, Prostate Cancer F, Radiological Society of North A. Biodistribution and Pharmacokinetic Study of 18F-DCFBC Prostate Specific Membrane Antigen Based PET in Patients With Advanced Prostate Cancer. 2014. Population


848. St George Hospital A. Brain Metastases Study: Radiotherapy Fractionation Schemes in the Treatment of Brain Metastases. 2007. Outcome


854. St. Jude Children's Research H. A Phase II Trial of Intensity-Modulated Proton Therapy for Incompletely Resected Craniopharyngioma and Observation for Craniopharyngioma After Radical Resection. 2025. Outcome


860. St. Michael's Hospital T, Heart, Stroke Foundation of C. In-Centre Nocturnal Hemodialysis (INHD): A Long-Term Follow-Up Study. 2016. Population


862. Stanford U. Study of Fractionated Stereotactic Radiosurgery to Treat Large Brain Metastases. 2017. Study design

863. Stanford U, National Comprehensive Cancer N. Phase I Vorinostat Concurrent With Stereotactic Radiosurgery (SRS) in Brain Metastases From Non-Small Cell Lung Cancer. 2014. Comparator


873. Sun Yat-sen U. IMRT Combined With Erlotinib for EGFR Wild Type Non-small Cell Lung Cancer With 4-10 Brain Metastases. 2019. Outcome

874. Sun Yat-sen U, Fifth Affiliated Hospital SY-SU. A Clinical Trial on Whole-brain Radiotherapy With Temozolomide Concurrent Chemotherapy or Avoidance of Hippocampus for Patients of Brain Metastases. 2017. Outcome

875. Sunnybrook Health Sciences C. Role of Hyperpolarized 13C-Pyruvate MR Spectroscopy in Patients With Intracranial Metastasis Treated With (SRS). 2019. Outcome

876. Sunnybrook Health Sciences C. Stereotactic Radiotherapy for Oligometastatic Prostate Cancer. 2020. Outcome


880. Swedish Medical C. Markers of Prognosis and Response to Therapy in Patients With Metastatic Brain Tumors Undergoing Stereotactic Radiosurgery (SRS). 2015. Outcome


882. Swiss Group for Clinical Cancer R. Early Hippocampal Avoidance Prophylactic Cranial Irradiation in Patients With LD SCLC. 2018. Outcome


886. Taipei Medical University WanFang H. Protein Supplementation for Chronic Stroke Treatment. 2020. Outcome

887. Taipei Veterans General Hospital T, National Tsing Hua University T. Boron Neutron Capture Therapy (BNCT) for Locally Recurrent Head and Neck Cancer. 2012. Population


892. Technische Universität D. Vemurafenib Plus Cobimetinib After Radiosurgery in Patients With BRAF-mutant Melanoma Brain Metastases. 2022. Outcome

893. Tel-Aviv Sourasky Medical C. The Role of Posterior Fossa Irradiation (PFI) Plus Stereotactic Radiosurgery (SRS) for Cerebellar Metastases. 2009. Outcome

894. Tel-Aviv Sourasky Medical C. Stereotactic Radiosurgery to the Resection Cavity Following Surgical Removal of Brain Metastasis. June 2007. Outcome


896. The Chaim Sheba Medical C. Complementary/Integrative Medicine for Brain Cancer Patients. 2019. Intervention

897. The Cleveland C, National Cancer I. Radiation Therapy in Treating Patients Who Are Undergoing Surgery to Remove a Metastatic Brain Tumor. 2010. Outcome
898. The Cooper Health S. Stereotactic Radiosurgery (SRS) for Multiple CNS Mets. 2017. **Outcome**

899. The Hospital for Sick C. Biventricular Pacing in Children With Congenital Heart Disease. 2018. **Population**

900. The Methodist Hospital S. MRI-Guided LITT for Treatment Metastatic Brain Tumors. 2014. **Intervention**

901. The Netherlands Cancer I, Dutch Cancer S. Hippocampus Avoidance PCI vs PCI. 2019. **Intervention**


903. Therapeutics Ym, National Cancer I, Health NYUL. Radiolabeled Monoclonal Antibody Therapy in Treating Patients With Refractory, Recurrent, or Advanced CNS or Leptomeningeal Cancer. 2018. **Population**

904. Thomas Jefferson U. Neurocognitive and Functional Assessment of Patients With Brain Metastases. 2015. **Outcome**


906. Trans-Tasman Radiation Oncology G. A Study of Local Therapy for the Treatment of Brain Metastases From HER2 Positive Breast Cancer. 2020. **Outcome**


909. Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer. 2012;118(9):2486-93. doi: 10.1002/cncr.26515. **Study design**


911. Tuen Mun H. Prognosis of Patient Evaluated for Palliative Radiotherapy. 2019. **Outcome**


917. Unicancer, National Cancer Institute F. Standard Treatment +/- SBRT in Solid Tumors Patients With Between 1 and 3 Bone-only Metastases. 2020. Outcome

918. Unicancer, Oncology EEAoD. Stereotactic Radiosurgery Added to Binimetinib and Encorafenib in Patients With BRAFV600 Melanoma With Brain Metastasis. 2022. Outcome


921. Universitätsmedizin M. Intraoperative Radiotherapy After the Resection of Brain Metastases. 2019. Outcome


924. Université de S. IA Carboplatin + Radiotherapy in Relapsing GBM. 2020. Outcome


926. University College L, University College London H. RCT of the 4mm vs. the 8mm Collimator for GKR of Brain Micrometastases. 2020. Outcome


929. University Health Network T. Stereotactic Radiosurgery With Sunitinib for Brain Metastases. 2014. Outcome


932. University Health Network T. A Study of Neoadjuvant Stereotactic Radiosurgery for Large Brain Metastases. 2022. Outcome


935. University Health Network T, Princess Margaret Hospital C. Dexamethasone for Palliation - Brain Metastases. 2006. Intervention


937. University Health Network T, Princess Margaret Hospital C. Perfexion Brain Metastasis. 2016. Outcome

938. University Health Network T, Princess Margaret Hospital C. Palliative Radiotherapy (RT) for Liver Metastases (Mets) and Hepatocellular Carcinoma (HCC)(COLD 4). 2018. Population


940. University Hospital A. Study of Motor Representations in Healthy Subjects and Amnestic MCI. 2017. Population


942. University Hospital B. Pemetrexed Plus Cisplatin for Brain Metastasis of Advanced Non-Small Cell Lung Cancer (NSCLC). Comparator


946. University Hospital B. Prospective Comparison of 18F-choline PET/CT and 18F-FDG PET/CT in the Initial Work-up of Multiple Myeloma. 2020. Outcome


948. University Hospital B, Mundipharma Research Gmb H, Co KG. A Clinical Trial to Assess the Safety & Efficacy of the Treatment of Patients With Metastasis From Malignant Melanoma - Treatment Consists of the Substances Lomustine (Capsules) & Cytarabine (Injected Into an Area Near the Spinal Cord), Accompanied by Radiotherapy of the Brain. 2015. Outcome

950. University Hospital E. Whole-Brain Radiotherapy (WBRT) Versus WBRT and Integrated Boost Using Helical Tomotherapy for Multiple Brain Metastases. 2011. Outcome

951. University Hospital G. Hair-sparing Whole Brain Radiotherapy. 2013. Outcome

952. University Hospital G, SAS NHT. Radiosensitization of Multiple Brain Metastases Using AguIX Gadolinium Based Nanoparticles. 2019. Study design


955. University Hospital L, Bristol-Myers S. Ipilimumab Combined With a Stereotactic Radiosurgery in Melanoma Patients With Brain Metastases. 2015. Outcome


957. University Hospital M, Université M. Gait and REM Sleep Behavior Disorder. 2017. Population


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

961. University Hospital T, University Hospital D. Buparlisib in Melanoma Patients Suffering From Brain Metastases (BUMPER). 2017. Intervention

962. University Medical Center G. Pilot Viability of 11C-MET-PET as a Post-surgery Baseline Scan in High-grade Gliomas. 2017. Population

963. University of A. Combo of Abraxane, TMZ, Bevacizumab in Metastatic Melanoma With Brain Metastases. 2015. Outcome


965. University of A. Diagnostic Accuracy of FDG PET/CT of Cranial Arteries in GCA. 2017. Intervention


967. University of A, Genzyme aSC. Physical and Cognitive Performance During the Two First Years of Lemtrada Treatment. 2019. Outcome


970. University of Alabama at B. A Dose Escalation Trial of Five Fraction Stereotactic Radiation Therapy for Brain Metastases. 2020. Outcome

971. University of Alabama at B. HSV G207 in Children With Recurrent or Refractory Cerebellar Brain Tumors. 2022. Outcome


975. University of C. Evaluation of the Use of Trental and Vitamin E For Prophylaxis of Radiation Necrosis. 2016. Intervention


980. University of California D. Irinotecan and Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases From Solid Tumors. 2006. Outcome


984. University of California SF, GlaxoSmithKline. Dabrafenib and Trametinib With Radiosurgery in Melanoma Brain Mets. 2016. Study design


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


991. University of Erlangen-Nürnberg Medical S. Analysis of CMV Infections in Patients With Brain Tumors or Brain Metastases During and After Radio(Chemo)Therapy. 2018. Outcome


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


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


1003. University of Maryland CP, University of Maryland B. HER2-positive Breast Cancer With Brain Metastasis (GCC 1345). 2016. Outcome

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


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


1010. University of P, GlaxoSmithKline. CNS and Extracranial Tumor Tissues, CSF, and Blood From Patients With Melanoma Brain Metastases. 2019. Intervention

1011. University of P, Passage B. Natural History Study of Infantile and Juvenile GM1 Gangliosidosis (GM1) Patients. 2024. Outcome

1012. University of R. Study of Resection Combined With Stereotactic Radiosurgery for 1 to 3 Brain Metastases. 2019. Outcome


1016. University of Southern C, National Cancer I. Gadobutrol Versus Gadopentetate Dimeglumine or Gadobenate Dimeglumine Before DCE-MRI in Diagnosing Patients With Multiple Sclerosis, Grade II-IV Glioma, or Brain Metastases. 2014. Intervention


1018. University of T. Bevacizumab, Dacarbazine and Interferon-Alfa to Treat Metastatic Melanoma. 2008. Intervention


1020. University of Texas Southwestern Medical C. Hippocampal-Avoiding Whole Brain Irradiation With Simultaneous Integrated Boost for Treatment of Brain Metastases. 2020. Outcome

1021. University of Texas Southwestern Medical C. Stereotactic Radiosurgery (SRS) for Brain Metastasis. 2020. Outcome

1022. University of Texas Southwestern Medical C. SAbR For Oligometastatic Renal Cell Carcinoma. 2020. Outcome
1023. University of Texas Southwestern Medical C. Neurocognitive Decline in Patients With Brain Metastases. 2023. *Outcome*


1027. University of U. Assessment of Primary and Metastatic Brain Tumor Hypoxia With Fluoromisonidazole, FDG and Water. 2021. *Outcome*


1030. University of W, National Cancer I. 18F-FLT PET/CT in Measuring Cell Proliferation in Patients With Brain Tumors. 2018. *Intervention*


1032. University of Wisconsin M. Pilot Study of 18F-FLT PET. 2011. *Intervention*

1033. University of Z. Multicenter Validation of the AVICH Score. 2016. *Intervention*


1040. Vanderbilt-Ingram Cancer C, National Cancer I. Ph I Study of Lithium During Whole Brain Radiotherapy For Patients With Brain Metastases. 2009. *Outcome*


1042. Vanderbilt-Ingram Cancer C, National Cancer I. Sorafenib Tosylate and Stereotactic Radiosurgery in Treating Patients With Brain Metastases. 2015. *Study design*


10.3389/fsurg.2017.00035. PMID: 28691010. *Population*


1051. Virginia Commonwealth U. Impact of Cognitive Rehab and Physical Activity on Cognition in Patients With Metastatic Brain Tumors Undergoing RT. 2018. *Outcome*


1054. Virginia Commonwealth U, National Cancer I. SBRT + PD-1/PDL-1 Inhibiting Therapy for Advanced Solid Tumors After Dz Contro on PD-1/PDL-1 Tx. 2023. Outcome


1059. Wake Forest University Health S. The Brain Ketone Body Challenge Imaging Study. 2019. Intervention

1060. Wake Forest University Health S, National Cancer I. Phase II Studies Of Donepezil And Ginkgo Biloba In Irradiated Brain Tumor. 2005. Outcome

1061. Wake Forest University Health S, National Cancer I. Methylphenidate to Improve Quality of Life in Patients Undergoing Radiation Therapy for Brain Tumors. 2005. Outcome

1062. Wake Forest University Health S, National Cancer I. Donepezil in Treating Young Patients With Primary Brain Tumors Previously Treated With Radiation Therapy to the Brain. 2010. Population


1064. Wake Forest University Health S, National Cancer I. Immunotherapy With or Without SBRT in Patients With Stage IV Non-small Cell Lung Cancer. 2027. Outcome

1065. Wake Forest University Health S, Spectrum Pharmaceuticals I. Evaluation of Lucanthone to Whole Brain Radiation Therapy in Patients With Brain Metastases From Non-Small Cell Lung Cancer. 2017. Outcome


1067. wang s, Sun Yat-sen U. PCI in Advanced Triple Negative Breast Cancer Patients Who Response to 1st Line Chemotherapy. 2025. Outcome


1072. Washington Hospital C. Sestamibi Scans In Thyroglobulin Positive Scan Negative Differentiated Thyroid Cancer Patients. 2019. Population


1075. Washington University School of M. Temozolomide Chronotherapy for High Grade Glioma. 2020. Outcome


1077. Washington University School of M, AstraZeneca. MEDI4736 (Durvalumab) in Patients With Brain Metastasis From Epithelial-derived Tumors. 2017. Intervention


1079. Weill Medical College of Cornell U. Pembrolizumab And Stereotactic Radiosurgery (Srs) Of Selected Brain Metastases In Breast Cancer Patients. 2024. Outcome

1080. Weill Medical College of Cornell U, Genzyme aSC. Measuring Active Microglia in Progressive Multiple Sclerosis. 2020. Population


1087. Wuhan Union Hospital C. Endostar Combine With Radiotherapy in Brain Metastasis of NSCLC. 2018. Outcome


1090. Xinhua Hospital SJTUSoM. Fluoroglutamine PET/CT in Imaging Patients With Malignant Tumor. 2019. Outcome


1094. Yale U, Genentech I. Phase 2 Study of Neoadjuvant Vemurafenib in Melanoma Patients With Untreated Brain Metastases. 2014. Intervention


1106. Yun-fei X, Sun Yat-sen U. A Phase II Clinical Trial of Chemotherapy With or Without Endostar® Continuous Intravenous Infusion in Refractory NPC. 2018. Outcome


1116. Zhejiang Cancer H. Icotinib Combined With Whole Brain Radiotherapy in Treating Multiple Brain Metastases From Non-Small Cell Lung Cancer. 2014. *Outcome*


Background

Note: references below were either background articles that were cited in the report or systematic reviews used for reference mining.


5. Alliance for Clinical Trials in O, National Cancer I. Radiosurgery With or Without Whole-Brain Radiation Therapy in Treating Patients With Brain Metastases. 2005. Background


16. Barretos Cancer H. Surgery and Whole Brain Radiotherapy (RT) Versus Whole Brain Radiotherapy (RT) and Radiosurgery for 1-3 Resectable Brain Metastases. 2010. **Background**

17. Betta Pharmaceuticals Co L. A Study to Determine the Efficiency For Brain Metastasis NSCLC Patients Treated With Icotinib Alone or Combined With Radiation Therapy. 2022. **Background**


24. Center MDAC, National Cancer I. Stereotactic Radiosurgery or Whole Brain Radiation Therapy in Treating Patients With Newly Diagnosed Non-melanoma Brain Metastases. 2019. Background


51. Good Samaritan Hospital Medical Center NY. Phase II Trial of Conventional Versus IMRT Whole Brain Radiotherapy for Brain Metastases. 2017. Background


94. Maastricht Radiation O. Whole Brain Radiotherapy (WBRT) Versus Stereotactic Radiosurgery (SRS) for 4 Upto 10 Brain Metastases. 2019. Background


96. Mayo C, National Cancer I. Neo-Adjuvant vs. Post-Operative Stereotactic Radiosurgery for Operative Metastatic Brain Tumors. 2025. Background

Background


104. Mundipharma Research L. Study to Demonstrate the Safety of WBR Administered at the Same Time as Intrathecal Liposomal Cytarabine (DepoCyte®) Versus Intrathecal Liposomal Cytarabine (DepoCyte®) Administered After WBR for the Treatment of Solid Tumour Neoplastic Meningitis in Patients With or Without Brain Metastasis. 2012. Background


106. National Cancer I, Oncology NRG. Whole-Brain Radiation Therapy or Stereotactic Radiosurgery With or Without Lapatinib Ditosylate in Treating Patients With Brain Metastasis From HER2-Positive Breast Cancer. 2019. Background


121. Oslo University H. Whole Brain Radiation With or Without Erlotinib for Brain Metastases From Non-Small Cell Lung Cancer. 2017. Background


156. Sidney Kimmel Cancer Center at Thomas Jefferson U, Genentech I, Thomas Jefferson U. Vemurafenib Combined With Whole Brain Radiation Therapy or Radiosurgery in Patients With BRAF Mutation-Positive Melanoma and Brain Metastases. 2019. Background


169. Stanford U. Phase I Compare OS in Post-CyberKnife Radiosurgery Tx in 1-3 VS 4 or More Brain Metastases. 2019. *Background*

170. Stephanie C, Technische Universität M. Evaluation of Repeated Whole Brain Radiotherapy Versus Best Supportive Care for Multiple Brain Metastases. 2018. *Background*


172. Sun Yat-sen U. EGFR-TKI Concurrent With/Without WBRT in Brain Metastasis From NSCLC. 2021. *Background*

173. Sunnybrook Health Sciences C. Radiosurgery With or Without Whole Brain Radiation for Multiple Metastases. 2020. *Background*


177. Tel-Aviv Sourasky Medical C, Radiation Therapy Oncology G. Comparison Study of WBRT and SRS Alone Versus With Temozolomide or Erlotinib in Patients With Brain Metastases of NSCLC. May 2005. *Background*


179. Trans-Tasman Radiation Oncology G. A Randomised Phase II Trial of Osimertinib With or Without SRS for EGFR Mutated NSCLC With Brain Metastases. 2021. *Background*


188. University of Alabama at B. Glyburide vs Placebo as Prophylaxis Against Cerebral Edema in Patients Receiving Radiosurgery for Brain Metastases (RAD 1502/UAB 1593). 2021. Background

189. University of Erlangen-Nürnberg Medical S. Fractionated Stereotactic Radiotherapy vs. Single Session Radiosurgery in Patients With Larger Brain Metastases. 2024. Background


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 $p=0.31$, 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 to 3,536 participants included in a cohort study.

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. 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. 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 therefore 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-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\textsuperscript{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\textsuperscript{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\textsuperscript{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

<table>
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<th>Performance Bias</th>
<th>Attrition Bias</th>
<th>Detection Bias</th>
<th>Reporting Bias</th>
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<th>Data Collection of Adverse Events</th>
<th>Reporting of Adverse Events</th>
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<td>Low risk</td>
<td>Moderate/ Unclear</td>
<td>Low risk</td>
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<td>Moderate/ Unclear</td>
<td>Low risk</td>
<td>Moderate/ Unclear</td>
<td>High risk</td>
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<tr>
<td>Zeng, 2016&lt;sup&gt;168&lt;/sup&gt;</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Moderate/ Unclear</td>
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<td>Zhu, 2018&lt;sup&gt;169&lt;/sup&gt;</td>
<td>Moderate/ Unclear</td>
<td>Moderate/ Unclear</td>
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<td>Moderate/ Unclear</td>
<td>Moderate/ Unclear</td>
<td>High risk</td>
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<td>Zhuang, 2020&lt;sup&gt;170&lt;/sup&gt;</td>
<td>High risk</td>
<td>High risk</td>
<td>Moderate/ Unclear</td>
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<td>High risk</td>
<td>Moderate/ Unclear</td>
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### Appendix D. Evidence Table

**Table D-1. Evidence table**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews, 2004&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Age: WBRT+stereotactic: 34% &gt; 65, WBRT alone: 40% &gt; 65</td>
<td>WBRT + SRS WRB: 3750 cGy, 15 fractions, qd. SRS: 1500-2400 cGy, 1 fraction</td>
<td>Intervention: 164 randomized, 164 analyzed</td>
<td>Intervention vs Comparator: Mean survival time HR 1.14; CI (0.74, 1.75)</td>
<td>Intervention vs Comparator: Grade 4 acute toxicities RR 2.04; CI (0.07, 60.29)</td>
</tr>
<tr>
<td>Sperduto, 2014&lt;sup&gt;13&lt;/sup&gt;; Group Radiation Therapy Oncology, 2002&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Gender: WBRT+stereotactic surgery: 48% female and WBRT alone: 47%</td>
<td>WBRT 3750 cGy, 15 fractions, qd</td>
<td>Comparator: 167 randomized, 167 analyzed</td>
<td>Brain metastases cause of death RR 0.86; CI (0.6, 1.25)</td>
<td>Number of events (acute toxicities) Late toxicities WBRT+SRS: 40; WBRT alone: 32</td>
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<tr>
<td>NCT00002708 RCT Power calculation: Yes USA Non industry Journal article N: 333</td>
<td>Primary tumor type: Different cancer types; 78% lung, breast or melanoma</td>
<td>Followup: 7 [median] months</td>
<td>Karnofsky Performance Status at 6 months A significant improvement in KPS was noted in the WBRT + SRS group</td>
<td>Mental status at 6 months No difference in mental status between groups</td>
<td>Acute vomiting RR 1.14; CI (0.7, 1.87) Late - WBRT+SRS: 5, WBRT alone: 3</td>
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<td></td>
<td>Metastases: Number: 1.56 [mean] Volume: n/a Size: unclear (&lt;= 4cm) Prognosis: good to moderate</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
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<tr>
<td>Antonadou, 2002&lt;sup&gt;76&lt;/sup&gt;</td>
<td>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</td>
<td>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</td>
<td>Intervention: 26 randomized, 25 analyzed Comparator: 26 randomized, 23 analyzed Followup: 4 [median] months</td>
<td>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</td>
<td>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)</td>
</tr>
<tr>
<td>Antonadou, 2003&lt;sup&gt;77&lt;/sup&gt;</td>
<td>N/A RCT Power calculation: Not relevant outcome Greece Unclear funding source Journal article N: 52</td>
<td>WBRT 4000 cGy, 20 fractions, qd Corticosteroids at the lowest dose necessary to maintain neurologic stability</td>
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<td>N/A</td>
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<td>RCT</td>
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**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

**Comparator:** 67 randomized, 67 analyzed
**Followup:** 8 [median] months

**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)
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| Berk, 2007<sup>1</sup> | 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), musculoskeletal (1 intervention), neurology (control 22, intervention 10), ocular (control 3, intervention 1) |

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).
<table>
<thead>
<tr>
<th>Study</th>
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<th>Intervention</th>
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<th>Effects</th>
<th>Adverse Events</th>
</tr>
</thead>
</table>
| Brown, 2013[^1]  
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) |

[^1]: Radiation Therapy Oncology Group NCT00566852  
[^2]: RCT  
[^3]: Underpowered  
[^4]: USA  
[^5]: Non industry  
[^6]: Journal article  
[^7]: N: 508
<table>
<thead>
<tr>
<th>Brown, 2016</th>
<th>Churilla 2017; Oncology Alliance for Clinical Trials, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00377156</td>
<td>RCT</td>
</tr>
<tr>
<td>Power calculation: Yes USA Non industry Journal article</td>
<td>N: 213</td>
</tr>
</tbody>
</table>

| 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,.96 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, 4.6-36.4; 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); HVLT-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) |

<p>| 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) | 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 |
| Brown, 2017; Trifiletti, 2019; Brown, 2017; Roberge, 2017; Trifiletti, 2020 |
|---|---|---|---|
| <strong>Age:</strong> SRS: 61 [median], WBRT: 62 [median] | <strong>Surgery + SRS</strong> 1200-2000 cGy, 1 fraction One resected brain metastasis, resection cavity &lt;5.0 cm | <strong>Intervention vs Comparator:</strong> 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 |
| <strong>Gender:</strong> SRS: 53% female, WBRT: 48% female | <strong>Surgery + WBRT</strong> 3000 cGy, 10 fractions, qd OR 3750 cGy, 15 fractions, qd One resected brain metastasis, resection cavity &lt;5.0 cm | <strong>Serious adverse events FDA definition</strong> 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 |
| <strong>Primary tumor type:</strong> Different cancer types; 59% lung, other types not broken down | <strong>Volume:</strong> N/A <strong>Size:</strong> N/A | <strong>Followup:</strong> 11 [median] months |
| <strong>Metastases:</strong> Number: SRS: 77% have one metastases and WBRT: 77% have one metastases | <strong>Prognosis:</strong> mixed |
| | <strong>Intervention:</strong> 98 randomized, 93 analyzed <strong>Comparator:</strong> 96 randomized, 92 analyzed | <strong>Barthel ADL index</strong> 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 |</p>
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<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Brown, 2020&lt;sup&gt;88&lt;/sup&gt;</td>
<td>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</td>
<td>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</td>
<td>Intervention: 261 randomized, 261 analyzed Comparator: 257 randomized, 257 analyzed Followup: 8 [median] (survivors) months</td>
<td>Intervention vs Comparator: Survival HR 1.13; CI (0.19, 6.59) Intracranial 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=0.0016), 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).</td>
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<tr>
<td>Gondi, 2019&lt;sup&gt;108&lt;/sup&gt;; National Cancer Institute, 2018&lt;sup&gt;123&lt;/sup&gt;; Gondi, 2018&lt;sup&gt;197&lt;/sup&gt;; Armstrong, 2019&lt;sup&gt;178&lt;/sup&gt;</td>
<td>NCT02360215 RCT Power calculation: Yes USA Non industry Journal article</td>
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<td>N: 518</td>
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<td>Cagney, 2019&lt;sup&gt;13&lt;/sup&gt; &lt;br&gt; N/A Cohort &lt;br&gt; Power calculation: No USA &lt;br&gt; Non industry &lt;br&gt; Journal article &lt;br&gt; N: 1188</td>
<td>Age: surgery: 58.9 (11.5), radiation: 58.9 (12.1) &lt;br&gt; Gender: 59% female &lt;br&gt; Primary tumor type: Different cancer types; majority lung, breast, melanoma &lt;br&gt; Metastases: Number: surgery: 1 (median), radiation: 2 (median) &lt;br&gt; Volume: N/A &lt;br&gt; Size: N/A &lt;br&gt; Prognosis: mixed</td>
<td>Surgery + SRS 2500-3000 cGy, 5 fractions &lt;br&gt; Resection of at least 1 brain metastasis &lt;br&gt; Radiation (no details) details not provided</td>
<td>Intervention: 318 randomized, 318 analyzed &lt;br&gt; Comparator: 870 randomized, 870 analyzed &lt;br&gt; Followup: 29 [median] (survivors) months</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cao, 2015&lt;sup&gt;14&lt;/sup&gt; &lt;br&gt; Curie Institut, 2009&lt;sup&gt;21&lt;/sup&gt; &lt;br&gt; NCT00875355 RCT &lt;br&gt; Power calculation: No France &lt;br&gt; Non industry &lt;br&gt; Journal article &lt;br&gt; N: 100</td>
<td>Age: 55 [median] 29-79 [range] &lt;br&gt; Gender: 100% female &lt;br&gt; Primary tumor type: Breast cancer only; &lt;br&gt; Metastases: Number: WBRT: 4.6 and WBRT + temozolomide: 3.6 &lt;br&gt; Volume: N/A &lt;br&gt; Size: N/A &lt;br&gt; Prognosis: mixed</td>
<td>WBRT + temozolomide 3000 cGy, 10 fractions, qd &lt;br&gt; Temozolomide 75 mg/m(2)/day &lt;br&gt; WBRT 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 50 randomized, 50 analyzed &lt;br&gt; Comparator: 50 randomized, 50 analyzed &lt;br&gt; Additional comparator: randomized, analyzed &lt;br&gt; Followup: 9 [median] months</td>
<td>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) &lt;br&gt; In the intervention, median overall survival was 9.4 months, in the comparator 11.1 months. &lt;br&gt; Progression-free survival HR 1.1; CI (0.46, 2.65) &lt;br&gt; Death due to tumor progression RR 3.33; CI (0.98, 11.4) &lt;br&gt; Progressive disease &lt;br&gt; Objective remission rate &lt;br&gt; The objective remission rates at 6 weeks were not significantly different between groups</td>
</tr>
<tr>
<td>Study</td>
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<td>Intervention</td>
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<tr>
<td>Chabot, 2017&lt;sup&gt;165&lt;/sup&gt; AbbVie, 2015&lt;sup&gt;171&lt;/sup&gt; NCT01657799 RCT</td>
<td>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 &gt;3) Volume: N/A Size: N/A Prognosis: mixed</td>
<td>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</td>
<td>Intervention: 102 randomized, 102 analyzed Comparator: 102 randomized, 102 analyzed Additional comparator: 103 randomized, 103 analyzed Followup: 36 months</td>
<td>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)</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
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<td>Chang, 2009&lt;sup&gt;96&lt;/sup&gt; Lal, 2012&lt;sup&gt;215&lt;/sup&gt;, Marko, 2010&lt;sup&gt;219&lt;/sup&gt;, Anderson Cancer Center, 2019&lt;sup&gt;100&lt;/sup&gt; NCT00548756 RCT</td>
<td>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)</td>
<td>SRS + WBRT WBRT: 3000 cGy, 12 fractions, qd. SRS: 1500-2400 cGy, 1 fraction SRS SRS: 1500-2400 cGy in 1 fraction</td>
<td>Intervention: 28 randomized, 28 analyzed Comparator: 30 randomized, 30 analyzed Followup: 10 [median] months</td>
<td>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=0.003) 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%)</td>
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<td>Study</td>
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<tr>
<td>Chatani, 1994</td>
<td>Age: 51% &gt;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</td>
<td>WBRT 50 Gy 5000 cGy, 20 fractions, qd</td>
<td>Intervention: 46 randomized, 46 analyzed; Comparator: 46 randomized, 46 analyzed; Additional comparator: 35 randomized, analyzed; Followup: 5 [median] months</td>
<td>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</td>
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<td>Study</td>
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<tr>
<td>Chen, 2018&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Age: SRS without immunotherapy: 77% &lt;70, Nonconcurrent SRS and immunotherapy: 82% &lt;70, Concurrent SRS and immunotherapy: 86% &lt;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</td>
<td>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) &gt;2 weeks apart from SRS</td>
<td>Intervention: randomized, 28 analyzed Comparator: randomized, 181 analyzed Additional comparator: randomized, 51 analyzed Followup: 9 [median] months</td>
<td>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)</td>
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<tr>
<td>Study</td>
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</tbody>
</table>
| Chua, 2010<sup>69</sup>  
Merck Sharp<sup>224</sup>  
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 | 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<sup>90</sup>  
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. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng, 2017</td>
<td>Age: WBRT+temozolomide: 55% &gt;60, WBRT: 65.1% &lt;60</td>
<td>WBRT + temozolomide 3000 cGy, 10 fractions, qd</td>
<td>Intervention: randomized, 129 analyzed</td>
<td>Intervention vs Comparator: Overall survival Longer survival in combination group but no significant difference between groups (0.11)</td>
<td>Intervention vs Comparator: Number of adverse events 574 vs 485</td>
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<td></td>
<td>Gender: 43% female</td>
<td>Temozolomide 75 mg/m2/day during radiation treatment; 100 mg/m2/day</td>
<td>Comparator: randomized, 109 analyzed</td>
<td>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)</td>
<td>Fatigue RR 1.01; CI (0.83, 1.23)</td>
</tr>
<tr>
<td>Cohort N/A</td>
<td>Primary tumor type: Lung cancer only;</td>
<td>WBRT 3000 cGy, 10 fractions, qd</td>
<td>Followup: 7 [median] months</td>
<td>Functional Assessment of Cancer Treatment-Lung (FACT-L) No significant difference in the declined number of scores for QOL between two groups (p &gt; 0.05).</td>
<td>Vomiting RR 0.96; CI (0.76, 1.2)</td>
</tr>
<tr>
<td>China</td>
<td>Metastases: Number: 73% had &gt; 3 brain metastases</td>
<td></td>
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<td>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&gt;0.05).</td>
<td>Headaches RR 1.08; CI (0.8, 1.47)</td>
</tr>
<tr>
<td>Non industry</td>
<td>Volume: N/A</td>
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<td>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.</td>
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<tr>
<td>Journal article N: 238</td>
<td>Size: N/A</td>
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<td>Study</td>
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<td>Dobi, 2020[12]</td>
<td>N/A</td>
<td>Intervention: randomized, 195 analyzed</td>
<td>Intervention vs Comparator: Time to death HR 1.26; CI (1.02, 1.55)</td>
<td>Intervention vs Comparator: Alopecia Alopecia was equal among groups</td>
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<tr>
<td>Cohort</td>
<td>N/A</td>
<td>Comparator: randomized, 273 analyzed</td>
<td>Followup: N/A months</td>
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<td>Power calculation: No</td>
<td>N/A</td>
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<td>Other Hungary</td>
<td>N/A</td>
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<td>Non industry</td>
<td>N/A</td>
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<td>Journal article</td>
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<tr>
<td>N: 468</td>
<td>Age: 60.7</td>
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<tr>
<td></td>
<td>Gender: 47% female</td>
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<tr>
<td></td>
<td>Primary tumor type: Different cancer types: NSCLC, breast, melanoma, SCLC, renal, colorectal</td>
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<td></td>
<td>Metastases:  Number: 3.6</td>
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<td>Volume: N/A</td>
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<td>Size: N/A</td>
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<td>Prognosis: 56.2% KPS&gt;70, 11% RPA 1, 45% RPA 2, 44% RPA 3 class</td>
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<td></td>
<td>WBRT + boost (sequential or simultaneous integrated SIB)</td>
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<td></td>
<td>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</td>
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<td>12 mg methylprednisolone during radiation</td>
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<td>WBRT 3000 cGy, 10 fractions qd</td>
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<td>12 mg methylprednisolone during radiation</td>
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<tr>
<td>El Gantery, 2014(^{91})</td>
<td>Age: N/A</td>
<td>WBRT + SRS</td>
<td>Intervention: 21 randomized, 21 analyzed</td>
<td>Intervention vs Comparator: Overall survival There was no significant survival benefit for WBRT + SRS compared to SRS alone &amp; WBRT alone</td>
<td>Intervention vs Comparator: Number of participants with acute toxicities RR 1; CI (0.23, 4.4)</td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: N/A</td>
<td>WBRT: 3000 cGy, 10 fractions, qd. SRS: 1400-2000 cGy, 1 fraction</td>
<td>Comparator: 21 randomized, 21 analyzed</td>
<td>Median local control was significantly better for WBRT + SRS compared to SRS alone &amp; WBRT alone</td>
<td>Radionecrosis RR 2; CI (0.07, 56.46)</td>
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<tr>
<td>RCT</td>
<td>Primary tumor type: Different cancer types; specific breakdown not provided</td>
<td>WBRT 3000 cGy, 10 fractions, qd SRS 1800-2000 cGy, 1 fraction</td>
<td>Additional comparator: 18 randomized, 18 analyzed</td>
<td>RR 1; CI (0.02, 48.09)</td>
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<tr>
<td>Power calculation: No</td>
<td>Metastases: Number: 1-3 metastases</td>
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<td>Followup: 9 [median] months</td>
<td>Vomiting RR 1; CI (0.02, 48.09)</td>
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<tr>
<td>Egypt</td>
<td>Volume: N/A</td>
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<td></td>
<td>Headache RR 1; CI (0.16, 6.45)</td>
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<tr>
<td>Non industry</td>
<td>Size: N/A</td>
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<td>Intervention vs additional comparison: Number of participants with acute toxicities RR 2.57; CI (0.29, 22.61)</td>
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<tr>
<td>Journal article</td>
<td>Prognosis: unclear</td>
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<td>Radionecrosis RR 0.86; CI (0.06, 12.75)</td>
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<td>N: 60</td>
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<td>Seizures RR 0.43; CI (0.02, 12.04)</td>
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<td>Vomiting RR 0.43; CI (0.02, 12.04)</td>
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<td>Headache RR 0.86; CI (0.13, 5.48)</td>
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<td>Study</td>
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<tr>
<td>El-Hamamsy, 2016&lt;sup&gt;44&lt;/sup&gt;</td>
<td>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</td>
<td>WBRT + Simvastatin 3000 cGy, 10 fractions, qd Simvastatin 80 mg WBRT 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 25 randomized, 15 analyzed Comparator: 25 randomized, 15 analyzed Followup: 12 months</td>
<td>Intervention vs Comparator: 1-year overall survival Overall survival rates were 8% and 12% (p = 0.880) for the simvastatin and 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%)</td>
<td>Not reported</td>
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<tr>
<td>Fokas, 2012&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Age: SRS: 51% &lt;63, fractionated stereotactic radiotherapy 7x 5Gy: 56% &lt;63, FSRT 10x 4Gy: 54% &lt;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 cm&lt;sup&gt;3&lt;/sup&gt; (median), FSRT 7x5: 2.04 cm&lt;sup&gt;3&lt;/sup&gt; (median), FSRT 10x4: 5.93 cm&lt;sup&gt;3&lt;/sup&gt; (median) Size: N/A Prognosis: mixed</td>
<td>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</td>
<td>Intervention: randomized, 61 analyzed Comparator: randomized, 138 analyzed Additional comparator: randomized, 61 analyzed Followup: 28 [mean] months</td>
<td>Intervention vs Comparator: Overall survival 10 vs 8 months, no statistically significant difference between arms</td>
<td>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)</td>
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<tr>
<td>Gamboa-Vignolle, 2012&lt;sup&gt;96&lt;/sup&gt; Instituto Nacional de Cancerologia de Mexico&lt;sup&gt;205&lt;/sup&gt; NCT01015534 RCT</td>
<td>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</td>
<td>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</td>
<td>Intervention: 28 randomized, 28 analyzed Comparator: randomized, 27 analyzed Followup: 8 [median] months</td>
<td>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</td>
<td>Intervention vs Comparator: Grade 3 RR 1.93; CI (0.07, 55.15)</td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline 2012</td>
<td>Age: 58.6 (8.6)</td>
<td>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</td>
<td>Intervention: 236 randomized, 236 analyzed Comparator: 236 randomized, 236 analyzed Followup: 49 months</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Ramla, 2013 NCT00390806</td>
<td>Gender: 34% female Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear</td>
<td>Topotecan 1.1 mg/m2/day p.o. two hours post WBRT</td>
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USA Industry funded Trial record N: 472
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<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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<tr>
<td>Gonda, 2014*</td>
<td>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% &gt;4 cm³, Katsuta Hospital: 56% &gt;4 cm³ Size: N/A Prognosis: mixed</td>
<td>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</td>
<td>Intervention: randomized, 464 analyzed Comparator: randomized, 3072 analyzed Followup: 24 months</td>
<td>Intervention vs Comparator: Time to death HR 0.99; CI (0.85, 1.15)</td>
<td>Not reported</td>
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<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
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<tr>
<td>Graham, 2010</td>
<td>Age: 62 [mean] 28-83 [range]</td>
<td>WBRT 40Gy 4000 cGy, 20 fractions, bid</td>
<td>Intervention: 57 randomized, 57 analyzed</td>
<td>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%)</td>
<td>Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6</td>
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<tr>
<td>N/A RCT</td>
<td>Gender: 36% female</td>
<td>WBRT 20Gy 2000 cGy, 4 fractions, qd</td>
<td>Comparator: 56 randomized, 56 analyzed</td>
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<tr>
<td>Power</td>
<td>Primary tumor type: Different cancer types; 70% lung, breast, melanoma</td>
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<td>Followup: 7 [median] months</td>
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<tr>
<td>calculation:</td>
<td>Metastases: Number: 61% had multiple metastases</td>
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<td>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%)</td>
<td>Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6</td>
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<td>Australia</td>
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<td>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%)</td>
<td>Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6</td>
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<td>Non industry</td>
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<td>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%)</td>
<td>Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6</td>
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<td>Journal article</td>
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<td>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%)</td>
<td>Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6</td>
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<td>N: 113</td>
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<td>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%)</td>
<td>Grade 5 CNS toxicity RR 1.96; CI (0.07, 57.4) Number of events (acute toxicities) 18 vs 6</td>
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<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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<tr>
<td>Gronberg, 2012¹⁰⁰</td>
<td>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</td>
<td>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</td>
<td>Intervention: 55 randomized, 55 analyzed Comparator: 54 randomized, 54 analyzed Followup: 9 [minimum] months</td>
<td>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%)</td>
<td>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.</td>
</tr>
<tr>
<td>Eli Lilly Company¹⁹¹</td>
<td>NCT00415363</td>
<td>RCT</td>
<td>Power calculation: Yes Multinational Norway, Romania, Finland, Sweden, Denmark, Austria, USA Industry funded Journal article N: 107</td>
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<td>Guerrieri, 2004¹⁰¹</td>
<td>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</td>
<td>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</td>
<td>Intervention: 21 randomized, 21 analyzed Comparator: 21 randomized, 21 analyzed Followup: 4 [median] months</td>
<td>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%)</td>
<td>Intervention vs Comparator: Gastrointestinal and hematological toxicities No significant differences in gastrointestinal or hematological toxicities between groups.</td>
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<td>Study</td>
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<tr>
<td>Gupta, 2016[102]</td>
<td>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</td>
<td>WBRT + Vandetanib 3000 cGy, 10 fractions, qd Vandetanib 100 mg qd WBRT + Placebo 3000 cGy, 10 fractions, qd Placebo (identical appearance)</td>
<td>Intervention: 10 randomized, 10 analyzed Comparator: 8 randomized, 8 analyzed Followup: 5 [median] months</td>
<td>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) Intracranial 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)</td>
<td>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)</td>
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<td>Oxford University, 2016[13]</td>
<td>N/A</td>
<td>RCT</td>
<td>Power calculation: No UK Non industry Journal article N: 24</td>
<td>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</td>
<td>WBRT + temozolomide 4000 cGy, 20 fractions, qd OR 3000 cGy, 10 fractions, qd</td>
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<tr>
<td>Hassler, 2013[103]</td>
<td>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</td>
<td>WBRT + temozolomide 4000 cGy, 20 fractions, qd OR 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 22 randomized, 22 analyzed Comparator: 13 randomized, 13 analyzed Followup: 6 [median] months</td>
<td>Treatment 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)</td>
<td>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.</td>
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<td>Study</td>
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<tr>
<td>Hauswald, 2019(^{104})</td>
<td>Age: 49 [median] Gender: 43% female</td>
<td>Hippocampal-sparing WBRT 3000 cGy, 10 fractions, qd WITH hippocampus sparing boost to tumors (5000 cGy in 10 fractions, qd)</td>
<td>Intervention: 4 randomized, 4 analyzed</td>
<td>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</td>
<td>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)</td>
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<td>Hauswald, 2013(^{201}); Universitätsklinikum Heidelberg(^{260}) DRKS00005127 RCT</td>
<td>Primary tumor type: Melanoma only; Metastases: Number: 10 [median] Volume: N/A Size: 14 [median] Prognosis: mixed moderate to poor</td>
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<td>Hoffmann-La Roche, 2011(^{105}) NCT00977379 RCT</td>
<td>Age: 56.2 (14.2) Gender: 100% female Primary tumor type: Breast cancer only; Metastases: Number: NR Volume: NR Size: NR Prognosis: NR</td>
<td>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</td>
<td>Intervention: 12 randomized, 11 analyzed</td>
<td>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)</td>
<td>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)</td>
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<tr>
<td>Industry funded Journal article</td>
<td>N: 7</td>
<td>WBRT 3000 cGy in 10 fractions Standard care</td>
<td>Followup: 5 [median] months</td>
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<td>Industry funded Trial record</td>
<td>N: 24</td>
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<td>Hong, 2019(^{106}); Fogarty, 2011(^{194}); Hong, 2014(^{203}); Lo, 2019(^{217}); Martinage, 2018(^{219}); Melanoma Skin Cancer Trials Limited, 2017(^{223}); Fogarty, 2015(^{196}); Fogarty, 2019(^{193})</td>
<td>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</td>
<td>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</td>
<td>Intervention: 107 randomized, 100 analyzed Comparator: 108 randomized, 107 analyzed Followup: 48 [median] months</td>
<td>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)</td>
<td>Intervention vs Comparator: Fatigue grade 3 RR 0.54; CI (0.02, 15.77) Vomiting RR 0.54; CI (0.02, 15.77)</td>
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<td>Study</td>
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<tr>
<td>Hosseini, 2015</td>
<td>Age: WBRT: 57 [median] and WBRT + SN: 52 [median]</td>
<td>WBRT + Sodium Nitrite 3000 cGy, 10 fractions, qd Sodium nitrite (radiosensitizer) 267 microg/kg/h before each fraction of radiation</td>
<td>Intervention: 10 randomized, 10 analyzed Comparator: 10 randomized, 10 analyzed Followup: 2 months</td>
<td>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:</td>
<td>Intervention vs Comparator: Symptomatic acute toxicity (including SAE) RR 1; CI (0.02, 45.63) Symptomatic acute toxicity No symptomatic acute toxicity was observed</td>
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<tr>
<td>Ahvaz Jundishapur University of Medical sciences</td>
<td>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</td>
<td>WBRT 3000 cGy, 10 fractions, qd Steroids and anticonvulsant agents at the lowest dose, as needed</td>
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<td>IRCT2013101515026N1</td>
<td>RCT Power calculation: Underpowered Iran Non industry Journal article N: 20</td>
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<tr>
<td>Jiang 2016</td>
<td>Age: 74% &lt;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</td>
<td>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</td>
<td>Intervention: randomized, 30 analyzed Comparator: randomized, 91 analyzed Followup: 22 [median] months</td>
<td>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 status in 14/51 (combination) and 24/116 (systemic therapy alone)</td>
<td>Not reported</td>
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<tr>
<td>Study</td>
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<tr>
<td>Jiang, 2014(^{109})</td>
<td>Age: 65 [median]</td>
<td>WBRT + endostatin 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 40 randomized, 40 analyzed</td>
<td>Intervention vs Comparator: Overall survival time HR 0.78; CI (0.46, 1.3)</td>
<td>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.</td>
</tr>
<tr>
<td>Jiang 2014(^{109}); Jiangsu Simcere Pharmaceutical Co, Ltd(^{110})</td>
<td>Gender: 46% female</td>
<td>Intravenous RHES (Endostar) 7.5 mg/m2/day during radiotherapy</td>
<td>Comparator: randomized, 40 analyzed</td>
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<tr>
<td>NCT01410370 RCT</td>
<td>Primary tumor type: Lung cancer only;</td>
<td>WBRT 3000 cGy, 10 fractions, qd</td>
<td>Followup: 9 [median] months</td>
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<td>Power calculation: No China</td>
<td>Metastases: Number: N/A</td>
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<tr>
<td>Non industry Journal article</td>
<td>Size: N/A</td>
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<tr>
<td>N: 80</td>
<td>Prognosis: uncertain</td>
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<td>Johnson, 2016(^{110})</td>
<td>Age: 62% &lt;65</td>
<td>Surgery + postoperative SRS 2100-2400 cGy for lesions &lt;=2 cm, 1800 cGy for lesions 2 to 3 cm, and 1500 cGy for lesions &gt;3 cm Surgical resection of at least 1 lesion SRS 2100-2400 cGy for lesions &lt;=2 cm, 1800 cGy for lesions 2 to 3 cm, and 1500 cGy for lesions &gt;3 cm</td>
<td>Intervention: randomized, 112 analyzed Comparator: randomized, 218 analyzed Followup: 9 [median] months</td>
<td>Intervention vs Comparator: Overall survival Median survival in the SRS plus surgery group were 12.9 compared to 10.6 for SRS alone</td>
<td>Not reported</td>
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| Kayama, 2018<sup>111</sup>  
Japan Clinical Oncology Group (JCOG)<sup>107</sup>; Fukuda Haruhiko, 2013<sup>200</sup>  
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)  
Intracranial 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. |
<table>
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<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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</thead>
<tbody>
<tr>
<td>Kepka, 2016&lt;sup&gt;112&lt;/sup&gt;</td>
<td>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</td>
<td>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</td>
<td>Intervention: 30 randomized, 29 analyzed Comparator: 30 randomized, 30 analyzed Followup: 29 [median] (survivors) months</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Kepka, 2018&lt;sup&gt;211&lt;/sup&gt;; Maria Sklodowska-Curie Institute&lt;sup&gt;218&lt;/sup&gt;; Kepka, 2017&lt;sup&gt;212&lt;/sup&gt;</td>
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<tr>
<td>NCT01535209 RCT</td>
<td>Power calculation: Yes Poland Non industry Journal article N: 59</td>
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<tr>
<td>Kim, 2005&lt;sup&gt;113&lt;/sup&gt;</td>
<td>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 &gt; 2 metastases Volume: N/A Size: N/A Prognosis: unclear</td>
<td>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</td>
<td>Intervention: randomized, 31 analyzed Comparator: 32 randomized, 32 analyzed Followup: 15 [median] months</td>
<td>Intervention vs Comparator: Overall survival Median survival was longer in the combination group (58.1 vs. 19.0 weeks, p&lt;0.001)</td>
<td>Intervention vs Comparator: Toxicity Toxicity in the chemotherapy group was tolerable</td>
</tr>
<tr>
<td>N/A Cohort</td>
<td>Power calculation: No South Korea Non industry Journal article N: 63</td>
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</table>

**Notes:**
- **HR** (Hazard Ratio), **CI** (Confidence Interval), **RR** (Risk Ratio)
- **SAE** (Serious Adverse Event)
- **RTOG** ( Radiation Therapy Oncology Group)
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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</thead>
<tbody>
<tr>
<td>Knisely, 2008(^{15})</td>
<td>Age: WBRT + thalidomide: 58.5 [median] and WBRT alone: 59 [median]</td>
<td>WBRT + Thalidomide 3750 cGy, 15 fractions, qd</td>
<td>Intervention: 90 randomized, 84 analyzed</td>
<td>Intervention vs Comparator: Time of randomization until death</td>
<td>Intervention vs Comparator: Number of events (Grade 4) 8 vs 1</td>
</tr>
<tr>
<td>Corn, 2008(^{18})</td>
<td>Gender: 55% female</td>
<td>200 mg of thalidomide per day and had a weekly dose escalation of 200 mg per day during WBRT</td>
<td>Comparator: 93 randomized, 92 analyzed</td>
<td>HR 1; CI (0.57, 1.76) Median survival was 3.9 months for both arms</td>
<td>Number of adverse events 255 vs 146</td>
</tr>
<tr>
<td>National Cancer Institute, 2006(^{30})</td>
<td>Primary tumor type: Different cancer types; 90% lung, breast, melanoma</td>
<td>WBRT 3750 cGy, 15 fractions, qd</td>
<td>Followup: 2 [median] months</td>
<td>Rate of deaths due to brain metastases RR 0.82; CI (0.51, 1.33)</td>
<td></td>
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<tr>
<td>NCT0033254 RCT</td>
<td>Metastases: Number: WBRT + thalidomide: 82% have &gt; 3 brain metastases, WBRT: 79% have &gt;3 brain metastases</td>
<td></td>
<td></td>
<td>CNS progression The time to progression curves were not different (p = 0.097)</td>
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<tr>
<td>Power calculation: Yes USA</td>
<td>Volume: N/A</td>
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<td>Non industry Journal article</td>
<td>Size: N/A</td>
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<tr>
<td>N: 183</td>
<td>Prognosis: mixture of good and moderate prognosis (75% RPA class 2, 25% RPA class 1)</td>
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<tr>
<td>Kirkpatrick, 2015(^{14})</td>
<td>Age: 61 [median]</td>
<td>SRS 1-mm volume 1-mm uniform expansion of the gross target volume</td>
<td>Intervention: randomized, analyzed</td>
<td>Intervention vs Comparator: Local recurrence at the site of radiosurgery</td>
<td>Intervention vs Comparator: Lesion with radionecrosis 0.028 versus 0.152 (p=0.10)</td>
</tr>
<tr>
<td>Duke University(^{19})</td>
<td>Gender: 67.3% female</td>
<td>SRS 3-mm volume 3-mm uniform expansion of the gross target volume</td>
<td>Comparator: randomized, analyzed</td>
<td>12 month local control 95% vs 91% (p=0.51)</td>
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<tr>
<td>NCT01017497 RCT (other)</td>
<td>Primary tumor type: Different cancer types; 80% lung, breast, melanoma</td>
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<td>Followup: 48 months</td>
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<tr>
<td>Power calculation: No USA</td>
<td>Metastases: Number: 1-3 metastases (mean unclear)</td>
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<tr>
<td>Non industry Journal article</td>
<td>Volume: NA</td>
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<tr>
<td>N: 49</td>
<td>Size: NA</td>
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<tr>
<td>Age: 60 [median]</td>
<td>Intervention: 180 randomized, 180 analyzed</td>
<td>Intervention vs Comparator: Overall survival HR 0.98; CI (0.77, 1.24)</td>
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<tr>
<td>Gender: 35% female</td>
<td>Comparator: 179 randomized, 179 analyzed</td>
<td>Progression-free survival HR 0.74; CI (0.5, 1.09)</td>
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<tr>
<td>Primary tumor type: Different cancer types; 70% lung, breast or melanoma</td>
<td>Followup: 49 [median] (survivors) months</td>
<td>Deaths due to intracranial progression RR 0.64; CI (0.48, 0.85)</td>
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<td>Metastases: Number: 1.25 (mean)</td>
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<td>Progression at both initial sites and new sites</td>
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<tr>
<td>Volume: N/A</td>
<td>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, 0.64-2.80; 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)</td>
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<tr>
<td>Size: unclear</td>
<td></td>
<td>HRQOL SMD -0.51; CI (-0.72, -0.3)</td>
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<td>Prognosis: good to moderate prognosis: WHO performance status 0: 44%, 1: 45%, 2: 11%</td>
<td>Median time to WHO PS more than 2</td>
<td>No difference was found between the two arms (HR 0.96; 95% CI, 0.76 to 1.20; P =.71).</td>
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<tr>
<td>(Surgery or SRS) + WBRT 3000 cGy, 10 fractions, qd</td>
<td>Salvage treatment</td>
<td>Salvage therapies for intracranial relapses were more frequent in patients after observation than in those who received adjuvant WBRT (51% vs. 16%)</td>
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<tr>
<td>Complete surgery or SRS</td>
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<tr>
<td>(Surgery or SRS) + observation</td>
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<tr>
<td>Complete surgery or SRS and observation</td>
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<tr>
<td>NCT00002899</td>
<td>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)</td>
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<td>RCT</td>
<td>Grade 4 late toxicities (number of events): WBRT 41, observation 40</td>
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<tr>
<td>Power calculation: Yes</td>
<td>Number of events (late toxicities)</td>
<td>WBRT 63, observation 70;</td>
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<tr>
<td>Multinational Germany, Italy, Turkey, Spain, France, Netherlands, Israel, Finland, Latvia, Belgium</td>
<td>Number of patients (grade 4 late toxicity): WBRT 22, observation 23</td>
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<tr>
<td>Non industry</td>
<td>Severe acute toxicity - radiation necrosis RR 1.99; CI (0.18, 21.74)</td>
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<tr>
<td>Journal article</td>
<td>Severe acute toxicity - seizure RR 5.97; CI (0.3, 118.26)</td>
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<tr>
<td>N: 359</td>
<td>Number of patients with headaches (grade 4 late toxicity) RR 1.99; CI (0.18, 21.74)</td>
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<td>Number of headaches (grade 2-4 late toxicity): WBRT 85, observation 98</td>
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<tr>
<td>Study</td>
<td>Participants</td>
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<td>Effects</td>
<td>Adverse Events</td>
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<tr>
<td>Kondziolka, 1999[17]</td>
<td>Age: WBRT + SRS: 59 [mean], WBRT: 58 [mean]</td>
<td>WBRT + SRS WMRT: 3000 cGy, 12 fractions, qd, SRS: 1600 cGy, 1 fraction WMRT 3000 cGy, 12 fractions, qd</td>
<td>Intervention: 13 randomized, 13 analyzed</td>
<td>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)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kondziolka, 2000[21]</td>
<td>Gender: 41% female</td>
<td></td>
<td>Comparator: 14 randomized, 14 analyzed</td>
<td>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)</td>
<td></td>
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<tr>
<td>N/A RCT Power calculation: Yes USA Non industry Journal article N: 27</td>
<td>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</td>
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<td>Followup: 11 [median] months</td>
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<tr>
<td>Lanier, 2019[19] N/A Cohort</td>
<td>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 &lt;70, about 90% have DS-GPA between 0-2.5, about 40% with widespread disease, more than 50% with progressive disease</td>
<td>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)]</td>
<td>Intervention: randomized, 101 analyzed Comparator: 170 randomized, 170 analyzed Followup: 29.9 [median] months</td>
<td>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</td>
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<tr>
<td>Study</td>
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<td>Effects</td>
<td>Adverse Events</td>
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</table>
| Lee, 2008[^15] | **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  
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 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. |
<table>
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<tr>
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<th>Effects</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>Lee, 2014&lt;sup&gt;120&lt;/sup&gt; University College London Cancer Research U. K.&lt;sup&gt;261&lt;/sup&gt; NCT00554775 RCT</td>
<td>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% &lt; 3, WBRT+erlotinib: 57.5% &lt; 3 metastases Volume: N/A Size: N/A Prognosis: mostly moderate to good</td>
<td>WBRT + Erlotinib 2000 cGy, 5 fractions, qd Erlotinib 100mg/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</td>
<td>Intervention: 40 randomized, 40 analyzed Comparator: 40 randomized, 40 analyzed Followup: 3 [median] months</td>
<td>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 &lt;.40)</td>
<td>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%)</td>
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<tr>
<td>Study</td>
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<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<td>Lim, 2015[21]</td>
<td>Age: SRS: 58 [mean], Upfront chemotherapy group: 57 [mean]</td>
<td>SRS + Chemotherapy</td>
<td>Intervention: randomized, 49 analyzed</td>
<td>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</td>
<td>Not reported</td>
</tr>
<tr>
<td>Samsung Medical Center</td>
<td>Gender: 28% female</td>
<td>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</td>
<td>Comparator: randomized, 49 analyzed</td>
<td>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</td>
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<tr>
<td>NCT01301560 RCT</td>
<td>Primary tumor type: Lung cancer only; Metastases:</td>
<td></td>
<td>Followup: 43 [median] months</td>
<td>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</td>
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<tr>
<td>Power calculation: Yes</td>
<td>Number: SRS: 2.18 (1.17), Upfront chemo: 1.82 (1.07) Volume: SRS: 1.92 cm³, Upfront chemo: 1.54 cm³</td>
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<td>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</td>
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<td>South Korea</td>
<td>Size: N/A</td>
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<tr>
<td>Non industry</td>
<td>Prognosis: moderate</td>
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<tr>
<td>Journal article N: 105</td>
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<td>Liu, 2017&lt;sup&gt;122&lt;/sup&gt; N/A RCT Power calculation: No China Non industry Journal article N: 72</td>
<td>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</td>
<td>WBRT + temozolomide 4000 cGy, 20 fractions, qd Temozolomide (150-200 mg/m(2)/day WBRT 4000 cGy, 20 fractions, qd</td>
<td>Intervention: 36 randomized, 36 analyzed Comparator: 36 randomized, 36 analyzed Followup: 9 [median] months</td>
<td>Intervention vs Comparator: Overall survival Overall survival 8.5 in WBRQ + temozolomide vs 5 months in WBRT alone (p&lt;0.0001) Progression-free survival Significantly longer progression-free survival (p&lt;0.001) Progressive disease No difference between groups (p=0.2327) KPS increase &gt;=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</td>
<td>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)</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<tr>
<td>Magnuson, 2017[23]</td>
<td>Age: EGFR: 60 (53-70), WBRT: 58 (51-65), SRS: 63 (54-70) [intervention: median (IQR)]</td>
<td>SRS followed by tyrosine kinase inhibitor</td>
<td>Intervention: randomized, 100 analyzed</td>
<td>Intervention vs Comparator: Time to death HR 0.39; CI (0.26, 0.58)</td>
<td>Not reported</td>
</tr>
<tr>
<td>N/A Cohort</td>
<td>Gender: 67%</td>
<td>SRS followed by tyrosine kinase inhibitor (98% patients received erlotinib, dose and duration not specified)</td>
<td>Comparator: randomized, 131 analyzed</td>
<td>Time to intracranial progression HR 0.92; CI (0.66, 1.29)</td>
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</tr>
<tr>
<td>Power calculation: No USA</td>
<td>Primary tumor type: Lung cancer only;</td>
<td>Tyrosine kinase inhibitor alone</td>
<td>Additional comparator: randomized, 120 analyzed</td>
<td>Intervention vs additional comparison: Time to death HR 0.7; CI (0.5, 0.98)</td>
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<tr>
<td>N/A</td>
<td>Metastases: Number: 69 patients with 1 metastasis, 129 patients with 2-4 metastases, 82 patients with 5-10 metastases, 71 patients with &gt;10 metastases</td>
<td>WBRT followed by tyrosine kinase inhibitor</td>
<td>Followup: 22 [median] months</td>
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<tr>
<td>USA</td>
<td>Volume:</td>
<td></td>
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<tr>
<td>Author COI</td>
<td>Size:</td>
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<tr>
<td>Journal article</td>
<td>Prognosis: about 37% with DS-GPA between 2-3.5, &gt;70% with ECOG 0-1</td>
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<td>N: 351</td>
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<tr>
<td>Mahajan, 2017[24]</td>
<td>Age: 59 [median]</td>
<td>Surgery + SRS 1200-1600 cGy, 1 fraction Complete resection of brain metastases</td>
<td>Intervention: 63 randomized, 63 analyzed</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>M.D. Anderson Cancer Center</td>
<td>Gender: 47% female</td>
<td>Surgery only Complete resection of brain metastases</td>
<td>Comparator: 65 randomized, 65 analyzed</td>
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<tr>
<td>NCT00950001 RCT</td>
<td>Primary tumor type: Different cancer types; 60% lung, breast, melanoma</td>
<td></td>
<td>Followup: 11 [median] months</td>
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<tr>
<td>Power calculation: Not relevant outcome USA Non industry Journal article</td>
<td>Metastases: Number: 1.5 (mean) Volume: N/A Size: 3 cm (median) Prognosis: mixed, majority moderate</td>
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<td>N: 132</td>
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<tr>
<td>Martin, 2018[25]</td>
<td>Age: Immunotherapy: 61 (11), No-immunotherapy: 62 (11) Gender: 44% female</td>
<td>SRS + Immunotherapy Tumors &lt;2cm: 1800-2000 cGy, 1 fraction, 2-3cm 1800 cGy, 1 fraction, and &gt;3cm 2500-3000 cGy, 5 fractions Immunotherapy (ipilimumab, pembrolizumab, nivolumab) SRS Tumors &lt;2cm: 1800-2000 cGy, 1 fraction, 2-3cm 1800 cGy, 1 fraction, and &gt;3cm 2500-3000 cGy, 5 fractions</td>
<td>Intervention: randomized, 115 analyzed Comparator: randomized, 365 analyzed Followup: 25 [median] (survivors) months</td>
<td>Intervention vs Comparator: Surviving median followup Median survival was 23.1 (IQR 15.4-42.1) vs 25.1 (15.2-34.3)</td>
<td>Intervention vs Comparator: Symptomatic radiation necrosis RR 2.92; CI (1.73, 4.94)</td>
</tr>
<tr>
<td>Cagney, 2019[33]</td>
<td>(same database, different patients) N/A Cohort Power calculation: No USA Author COI Trial record N: 480</td>
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<td>McPherson, 2010[36]</td>
<td>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% &lt; 3 cm Prognosis: All RPA 1 (48%) or 2 (52%)</td>
<td>Surgery + WBRT 3000 cGy, 10-15 fractions Resection of single brain metastases Surgery alone Resection of single brain metastases</td>
<td>Intervention: randomized, 142 analyzed Comparator: randomized, 216 analyzed Followup: 60 [median] months</td>
<td>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&lt;.001 for distant recurrence , both favoring WBRT; withholding WBRT was an independent predictor of local and distant recurrence</td>
<td>Not reported</td>
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<td>Mehta, 2003&lt;sup&gt;127&lt;/sup&gt; Meyers, 2004&lt;sup&gt;2,25&lt;/sup&gt;, Mehta, 2002&lt;sup&gt;2,22&lt;/sup&gt;</td>
<td>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</td>
<td>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</td>
<td>Intervention: 193 randomized, 193 analyzed Comparator: 208 randomized, 208 analyzed Followup: 5 [median] months</td>
<td>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</td>
<td>Intervention vs Comparator: Number of adverse events 763 vs 155</td>
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<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
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<tr>
<td>Mehta, 2009</td>
<td>Age: 59.3 [mean]</td>
<td>WBRT + motexafin gadolinium 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 279 randomized, 279 analyzed</td>
<td>Intervention vs Comparator: Time to death HR: 1.02</td>
<td>Intervention vs Comparator: Number of adverse events 1012 vs 369</td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: 43% female</td>
<td>Motexafin gadolinium 5 mg/kg/d 2-5 hours before each fraction</td>
<td>Comparator: 275 randomized, 275 analyzed</td>
<td>Progression-free survival No significant difference in progression-free survival</td>
<td>Nausea and vomiting RR 1.65; CI (1.3, 2.1)</td>
</tr>
<tr>
<td>RCT</td>
<td>Primary tumor type: Lung cancer only; Metastases: Number: 81.2% had multiple metastases</td>
<td>WBRT 3000 cGy, 10 fractions, qd</td>
<td>Followup: 24 [median] months</td>
<td>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).</td>
<td>Number of patients RR 1.09; CI (0.84, 1.42)</td>
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<tr>
<td>Power</td>
<td>Metastases: Number: N/A</td>
<td></td>
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<td>Interval to neurocognitive progression</td>
<td>Liver function; asthenia; hypertension</td>
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<tr>
<td>calculation: Yes</td>
<td>Volume: N/A</td>
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<td>The interval to neurocognitive progression (HR 0.78) was in favor of the MGd Group (p=0.057).</td>
<td>The most common MGd-related Grade 3 and above adverse events included liver function abnormalities (5.5%), asthenia (4.0%), and hypertension (4%).</td>
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<tr>
<td>Multinational</td>
<td>Size: N/A</td>
<td></td>
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<td>Salvage treatment</td>
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<tr>
<td>USA, Canada,</td>
<td>Prognosis: moderate</td>
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<td>WBRT patients required significantly more salvage brain surgery or radiosurgery than did the WBRT+MGd patients (54 vs. 25)</td>
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<td>France,</td>
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<td>Journal article</td>
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<td>N: 554</td>
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<tr>
<td>Merck Sharp &amp; Dohme Corp, 2008</td>
<td>N: 35</td>
<td>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</td>
<td>Intervention: 22 randomized, 18 analyzed Comparator: 13 randomized, 13 analyzed Followup: 6 months</td>
<td>Intervention vs Comparator: Progression-free survival at 6 months 8/18 (WBRT + temozolomide) vs 8/13 (WBRT alone)</td>
<td>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)</td>
</tr>
<tr>
<td>Minniti, 2016</td>
<td>N: 289</td>
<td>Single-Fraction SRS 1800 cGy for metastases of 2-3 cm and 1500-1600 cGy for metastases &gt;=3 cm Multifraction SRS 2700 cGy, 3 fractions</td>
<td>Intervention: randomized, 151 analyzed Comparator: randomized, 138 analyzed Followup: 29 [median] months</td>
<td>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%)</td>
<td>Intervention vs Comparator: Radiation necrosis as suggested by MRI and PET-CT RR 2.58; CI (1.35, 4.92)</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
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<tr>
<td>Mintz, 1996</td>
<td>Age: Surgery + WBRT: 58.9 (8.98) and Radiation Alone: 58 (9.86)</td>
<td>WBRT + surgery 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 41 randomized, 41 analyzed</td>
<td>Intervention vs Comparator: Survival HR 1.12; CI (0.42, 2.98) There were no significant differences in the 30-day morbidity between groups</td>
<td>Intervention vs Comparator: Number of events (surgical and radiation-related complications) 11 vs 8</td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: 45% female</td>
<td>Craniotomy to achieve gross total removal of the metastases or lobectomy</td>
<td>Comparator: 43 randomized, 43 analyzed</td>
<td>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 &gt;= 70 SMD 0; CI (-0.43, 0.43)</td>
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<tr>
<td>RCT</td>
<td>Primary tumor type: Different cancer types; 70% lung, breast, melanoma</td>
<td>WBRT 3000 cGy, 10 fractions, qd</td>
<td>Followup: 6 [median] months</td>
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<tr>
<td>Power calculation: No</td>
<td>Metastases: Number: 1 (all had 1 brain metastasis)</td>
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<td>Canada</td>
<td>Volume: N/A</td>
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<td>Non industry</td>
<td>Size: N/A</td>
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<td>Journal article</td>
<td>Prognosis: mixed</td>
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<td>N: 84</td>
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<tr>
<td>Mornex, 2003</td>
<td>Age: Fotemustine alone: 53.1 [mean], fotemustine+WBRT: 49.2 [median]</td>
<td>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)</td>
<td>Intervention: 37 randomized, 37 analyzed Comparator: 39 randomized, 39 analyzed Followup: 4 [median] months</td>
<td>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%).</td>
<td>Intervention vs Comparator: Number of events (hematological and non-hematological toxicities) 122 vs 125 Vomiting RR 0.53; CI (0.1, 2.71)</td>
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<tr>
<td>N/A</td>
<td>RCT</td>
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<tr>
<td>Power</td>
<td>calculation: Underpowered</td>
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<td>France</td>
<td>Non industry</td>
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<td>Journal article</td>
<td>N: 76</td>
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<tr>
<td>Muacevic, 2008</td>
<td>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</td>
<td>Surgery + WBRT 4000 cGy, 20 fractions, qd Complete resection using microsurgery SRS 1400-2700 cGy, 1 fraction</td>
<td>Intervention: 33 randomized, 33 analyzed Comparator: 31 randomized, 31 analyzed Followup: 12 months</td>
<td>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&gt;0.1)</td>
<td>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.</td>
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<td>Study</td>
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| Mulvenna, 2016<sup>11</sup>  | 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) |
| Langley, 2013<sup>12,16</sup>,  
Medical Research Council<sup>212</sup>  
NCT00403065  
RCT  
Power calculation: Yes  
Multinational UK and Australia  
Non industry  
Journal article  
N: 538 | 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%) |  |
| Murray, 1997<sup>124</sup>  
Gaspar, 2000<sup>196</sup>,  
Regine, 2001<sup>240</sup>  
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:  
Number of events (Grade 5)  
1 vs 0  
Number of events (acute and late toxicities)  
275 vs 196 |  |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Institute 2011 NCT01217411</td>
<td>Age: WBR + R04929097: 49 [median], SRS + RO4929097: 49 [median] Gender: WBR + RO4929097: 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</td>
<td>SRS + RO4929097  3000-4000 cGy in 10-20 fractions R04929097 (gamma secretase inhibitor) 5mg WBR + R04929097  2000 cGy for tumors up to 1cm diameter, 1800 cGy for tumors from 1.1-2.5 cm, 1600 cGy for tumors &gt;2.5 cm for patients with 3 or fewer brain lesions R04929097 5mg</td>
<td>Intervention:  2 randomized, 2 analyzed Comparator:  3 randomized, 3 analyzed Followup: 4 months</td>
<td>Not reported</td>
<td>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)</td>
</tr>
<tr>
<td>Noordijk, 1994 N/A</td>
<td>Age: surgery + WBR: 59.2 [mean], WBR: 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</td>
<td>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</td>
<td>Intervention:  32 randomized, 32 analyzed Comparator:  31 randomized, 31 analyzed Followup: 78 months</td>
<td>Intervention vs Comparator: Overall survival HR 1.56; CI (0.92, 2.65) Neurologic deaths RR 0.87; CI (0.41, 1.85)</td>
<td>Intervention vs Comparator: Number of patients with complications of radiotherapy (headache, nausea, and vomiting) RR 1.08; CI (0.51, 2.29)</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
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<tr>
<td>Pesce, 2012137</td>
<td>Age: WBRT + temozolomide: 63 [median], WBRT + gefitinib: 57 [median]</td>
<td>WBRT + temozolomide 3000 cGy, 10 fractions, qd Temozolomide 75 mg/m2 p.o. daily for 21 days every 28 days</td>
<td>Intervention: 43 randomized, 43 analyzed</td>
<td>Intervention vs Comparator: Overall Survival HR 1.29; CI (0.47, 3.55)</td>
<td>Intervention vs Comparator: Number of events (grade 4) 1 vs 1 Number of adverse events 36 vs 11</td>
</tr>
<tr>
<td>Research Swiss Group for Clinical Cancer,</td>
<td>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</td>
<td></td>
<td>Comparator: 16 randomized, 16 analyzed</td>
<td></td>
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<tr>
<td>2009156</td>
<td>Volume: N/A Prognosis: mixed</td>
<td>Followup: 34 [median] (survivors) months</td>
<td></td>
<td>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</td>
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<tr>
<td>NCT00238251 RCT</td>
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<td>Deaths due to CNS progression RR 0.43; CI (0.18, 0.98)</td>
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<tr>
<td>Power calculation: Yes Switzerland</td>
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<td>Industry funded</td>
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<tr>
<td>Journal article N: 59</td>
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<tr>
<td>Phillips, 1995118</td>
<td>Age: WBRT + bromodeoxyuridine: 60.7 [mean], and radiotherapy: 59.5 [mean]</td>
<td>WBRT + bromodeoxyuridine 3750 cGy, 15 fractions, qd Bromodeoxyuridine 0.8 g/m2 per day, continuous 96 h i.v. infusion</td>
<td>Intervention: 35 randomized, 34 analyzed</td>
<td>Intervention vs Comparator: Survival No significant difference between treatment arms (median 4.3 vs 6.12 months for combination vs WBRT alone)</td>
<td>Intervention vs Comparator: Grade 5 SAE RR 6.35; CI (0.33, 122.23) Number of adverse events 30 vs 37</td>
</tr>
<tr>
<td>RTOG 8905 RCT</td>
<td>Gender: 44% female Primary tumor type: Different cancer types; 73% lung or breast</td>
<td>WBRT 3750 cGy, 15 fractions, qd</td>
<td>Comparator: 37 randomized, 36 analyzed</td>
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<tr>
<td>Power calculation: No USA</td>
<td>Metastases: Number: 66% had multiple metastases</td>
<td></td>
<td>Followup: 6 [median] months</td>
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<tr>
<td>Non industry Journal article N: 72</td>
<td>Volume: N/A Prognosis: mixed</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
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<tr>
<td>Pirzkall, 1998</td>
<td>Age: SRS: 57.4 [median], SRS+WBRT: 55.6 [median]</td>
<td>Intervention: randomized, 158 analyzed</td>
<td>Intervention vs Comparator: 1 and 2 year survival rates</td>
<td>Intervention vs Comparator: 1 and 2 year survival rates</td>
<td>Not reported</td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: 32% female</td>
<td>Comparator: 78 randomized, 78 analyzed</td>
<td>Intervention: 1-year survival 30.4%, 2-year survival 13.9%; 1-year survival 19.2%, 2-year survival 8.3%</td>
<td>Comparator: 1-year survival 19.2%, 2-year survival 8.3%</td>
<td></td>
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<tr>
<td>Germany</td>
<td>Primary tumor type: Different cancer types; predominantly lung cancer</td>
<td>Followup: 6 [median] months</td>
<td>Local control rates</td>
<td>Local control rates</td>
<td></td>
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<tr>
<td>Non industry</td>
<td>Metastases: Number: Predominantly solitary brain metastasis</td>
<td></td>
<td>Intervention: 1-year survival 30.4%, 2-year survival 13.9%; 1-year survival 19.2%, 2-year survival 8.3%</td>
<td>Disease control rate</td>
<td></td>
</tr>
<tr>
<td>Journal article</td>
<td>Size: RS: 20 mm median diameter (range 3-38), RS+WBRT: 20 (3-36)</td>
<td></td>
<td>Disease control rates</td>
<td>Disease control rates were not significantly different between the groups</td>
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<tr>
<td>N: 236</td>
<td>Prognosis: Excluded patients with &gt;3 metastases or recurrent metastases</td>
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<td></td>
<td></td>
<td>SRS + WBRT SRS: 1000-2700 cGy; total radiation dose 3000-5000 cGy (median 3600 cGy) SRS: 1000-3000 cGy</td>
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<tr>
<td>Prabhu, 2017</td>
<td>Age: SRS+ surgery: 59.5 (IQR 51-68), SRS alone: 58 (IQR 48-66)</td>
<td>Intervention vs Comparator: Overall survival</td>
<td>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)</td>
<td>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)</td>
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<tr>
<td>N/A</td>
<td>Gender: N/A</td>
<td>One-year local recurrence rate</td>
<td>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.</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>Primary tumor type: Different cancer types; lung, breast, melanoma, renal, other</td>
<td>The local recurrence rate was significantly lower with surgery and SRS (36.7% vs 20.5%)</td>
<td>Leptomeningeal disease</td>
<td>Leptomeningeal disease</td>
<td></td>
</tr>
<tr>
<td>Non industry</td>
<td>Metastases: Number: 66% has 1 metastasis</td>
<td></td>
<td>No significant difference in leptomeningeal disease between groups (p=.13). Adjusted analysis not performed.</td>
<td>No significant difference in leptomeningeal disease between groups (p=.13). Adjusted analysis not performed.</td>
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<tr>
<td>Journal article</td>
<td>Size: SRS+ surgery: 9.6 cm³, SRS: 5.9 cm³</td>
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<tr>
<td>N: 213</td>
<td>Prognosis: mixed</td>
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<td></td>
<td></td>
<td>Surgery + pre- or post-surgery SRS</td>
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<td>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%</td>
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<td>Gross total resection</td>
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<td></td>
<td></td>
<td>SRS: 1800 cGy for lesions 2.1 to 3 cm and 1500 cGy for lesions 3.1 to 4 cm</td>
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<td></td>
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<td>Intervention: randomized, 153 analyzed</td>
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<td>Comparator: randomized, 60 analyzed</td>
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<td>Followup: 13 [median] months</td>
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<td>Study</td>
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</table>
| Priestman, Royal College of Radiologists' Trial, 1996 | 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) |
<table>
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<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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</thead>
<tbody>
<tr>
<td>Quantin, 2010^42</td>
<td>Age: Group A: 59.1(7.8), Group B: 56(9.5)</td>
<td>WBRT + Cisplatin-Vinorelbine-Ifosfomide 5400 cGy, 30 fractions, qd (3600 cGy to whole brain, 1800 cGy boost to metastases)</td>
<td>Intervention: 37 randomized, 37 analyzed Comparator: 33 randomized, 33 analyzed Followup: 21 [minimum] months</td>
<td>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) 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.</td>
<td>Number of events (grade 4 hematological toxicity) 55 vs 38 events Number of events (hematological toxicity) 140 vs 132</td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: 24% female</td>
<td>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</td>
<td></td>
<td>Progression 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%)</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>Primary tumor type: Lung cancer only; Metastases: Number: Group A: 54.05% have one metastases, Group B: 48.48% have one metastases</td>
<td>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 hematopoietic support with r-HuG-CSF day 5 to day 14</td>
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<tr>
<td>Power calculation: Not relevant outcome</td>
<td>Volume: N/A Size: N/A Prognosis: mixed</td>
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<tr>
<td>France</td>
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<tr>
<td>Non industry</td>
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<td>Journal article</td>
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<td>N: 70</td>
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<td>Study</td>
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<tr>
<td>Rades, 2007¹⁴³</td>
<td>Age: Group A: 53% &lt;60, Group B: 52% &lt;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</td>
<td>Surgery + WBRT 3000 cGy, 10 fractions or 4000 cGy, 20 fractions Resection of metastases SRS 1800-2500 cGy, 1 fraction</td>
<td>Intervention: randomized, 112 analyzed Comparator: randomized, 94 analyzed Followup: 9 [median] (survivors) months</td>
<td>Intervention vs Comparator: Overall survival No significantly difference in overall survival between groups. No significantly difference in local or distant intracerebral failure between groups</td>
<td>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.</td>
</tr>
<tr>
<td>Rades, 2017¹⁴⁴</td>
<td>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</td>
<td>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</td>
<td>Intervention: 84 randomized, 84 analyzed Comparator: 168 randomized, 168 analyzed Followup: 11 [median] months</td>
<td>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</td>
<td>Not reported</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
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<td>Adverse Events</td>
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<tr>
<td>Raman, 2020 [45] British Columbia Cancer, 2019 [79] NCT02220491 RCT</td>
<td>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)</td>
<td>SRS 1500 cGy, 1 fraction, qd WBRT 2000 cGy, 5 fractions qd</td>
<td>Intervention: 10 randomized, 10 analyzed Comparator: 10 randomized, 10 analyzed Followup: 7 [median] months</td>
<td>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</td>
<td>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)</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<tr>
<td>Rauschenberg, 2019</td>
<td>Age: 60.1 (26.6-92.7) [median (range)]</td>
<td>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</td>
<td>Intervention: randomized, 87 analyzed</td>
<td>Comparator: randomized, 51 analyzed Followup: 7.3 [median] months</td>
<td>Intervention vs Comparator: Time to death SRS and immunotherapy achieved the highest overall survival rates</td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: 36%</td>
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<td>Intervention vs Comparator: Radiation necrosis RR 4.69; CI (0.25, 86.91)</td>
</tr>
<tr>
<td>Cohort</td>
<td>Primary tumor type: Melanoma only;</td>
<td></td>
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<td>Intervention vs additional comparison: Radiation necrosis RR 2.48; CI (0.14, 45.49)</td>
</tr>
<tr>
<td>Power calculation: No</td>
<td>Metastases: Number: WBRT: 5 (1-100) [median (range)], SRS: 2 (1-7) [median (range)]</td>
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<tr>
<td>Germany</td>
<td>Volume: N/A</td>
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<tr>
<td>Author COI</td>
<td>Prognosis: mixed, 80% ECOG performance of 0-1 (10% unknown, 10% &gt;1), but RPA classification would have been at least RPA class 2 as 84% had extracranial metastases</td>
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<td>Journal article</td>
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<tr>
<td>Regine, 2004&lt;sup&gt;147&lt;/sup&gt;</td>
<td>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</td>
<td>Surgery + WBRT 5040 cGy, 28 fractions, qd Complete surgical resection Surgery Complete surgical resection</td>
<td>Intervention: 49 randomized, 49 analyzed Comparator: 46 randomized, 46 analyzed Followup: 11 [median] months</td>
<td>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</td>
<td>Not reported</td>
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<td>Patchell, 1998&lt;sup&gt;235&lt;/sup&gt;</td>
<td>N/A</td>
<td>RCT</td>
<td>Power calculation: Not relevant outcome USA Non industry Journal article N: 95</td>
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<td>Robinet, 2001&lt;sup&gt;148&lt;/sup&gt;</td>
<td>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</td>
<td>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 nonresponders 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</td>
<td>Intervention: 85 randomized, 85 analyzed Comparator: 86 randomized, 86 analyzed Followup: 6 [median] months</td>
<td>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</td>
<td>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).</td>
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<td>Rojas-Puentes, 2013</td>
<td>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</td>
<td>WBRT + chloroquine 3000 cGy, 10 fractions, qd Chloroquine 150 mg/day 1 hour prior to WBRT for 28 days</td>
<td>Intervention: 40 randomized, 39 analyzed Comparator: 36 randomized, 34 analyzed Followup: 8 [median] months</td>
<td>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%)</td>
<td>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.</td>
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<td>Instituto Nacional de Cancerologia de Mexico</td>
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<td>NCT01894633</td>
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<td>Power calculation: Not relevant outcome</td>
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<td>N: 73</td>
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<th>Adverse Events</th>
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<tr>
<td>Roos, 2006&lt;sup&gt;131&lt;/sup&gt; TROG 98.05 RCT Power calculation: Underpowered Australia Non industry Journal article</td>
<td>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</td>
<td>(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</td>
<td>Intervention: 10 randomized, 10 analyzed Comparator: 9 randomized, 9 analyzed Followup: 74 [median] months</td>
<td>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 &gt;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</td>
<td>Not reported</td>
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<tr>
<td>Roos, 2011</td>
<td>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 metastasis) Volume: N/A Size: SRS + WBRT: 17 mm [median], Surgery + WBRT: 24 mm [median] Prognosis: mixture, majority moderate prognosis</td>
<td>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</td>
<td>Intervention: 11 randomized, 11 analyzed Comparator: 11 randomized, 10 analyzed Followup: 16 [minimum] (survivors) months</td>
<td>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</td>
<td>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)</td>
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<td>Study</td>
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<td>Saha, 2014</td>
<td>Age: Arm A: 50%</td>
<td>50-&lt;60, Arm B: 46.15%</td>
<td>50-&lt;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</td>
<td>WBRT 30Gy 3000 cGy, 10 fractions, qd Dexamethasone 8 mg bid at the beginning and tapered to 4 mg/day; antiemetics, hematinsics and proton pump inhibitors throughout the treatment period; blood transfusions and anti-seizure medications as needed</td>
<td>Intervention: randomized, 30 analyzed Comparator: randomized, 26 analyzed Followup: 7 [median] months</td>
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<td>N/A RCT</td>
<td>Power calculation: No India Non industry Journal article N: 56</td>
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<td>Intervention vs Comparator: Number of events (grade 4) No SAE in either group</td>
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<tr>
<td>Sneed, 2002</td>
<td>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</td>
<td>SRS + WBRT WBRT 3000 cGy in 10 fractions, 3000 cGy in 12 fractions, 3500 cGy in 14 fractions, 3750 cGy in 15 fractions, 4000 cGy in 20 fractions, or 5040 cGy in 28 fractions; SRS no details were collected SRS No details of SRS were collected</td>
<td>Intervention: 301 randomized, 301 analyzed Comparator: 268 randomized, 268 analyzed Followup: 43 [median] (survivors) months</td>
<td>Intervention vs Comparator: Time to death HR 0.99; CI (0.83, 1.18)</td>
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<td>N/A Cohort</td>
<td>Power calculation: No Multinational Brazil and USA Unclear funding source Journal article N: 569</td>
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| Sperduto, 2013<sup>1</sup> | 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) |
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<tr>
<td>Suh, 2006[^155]</td>
<td>Age: Efaproxiral: 72% &lt;65 and Control: 73% &lt;65</td>
<td>WBRT + Efaproxiral 3000 cGy, 10 fractions, qd</td>
<td>Intervention: 265 randomized, 265 analyzed</td>
<td>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</td>
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<td>Scott, 2007[^244], Stea, 2006[^238][^239], Spectrum Pharmaceuticals, 2000[^240], Nabid, 2004[^242], Shaw, 2004[^243], Stea, 2004[^245], Suh, 2004[^246], Suh, 2004[^247]</td>
<td>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</td>
<td>EFAPROXIRAL (radiosensitizer) 75 or 100 mg/kg intravenous, supplemental oxygen</td>
<td>Comparator: 250 randomized, 250 analyzed Followup: 15 [median] months</td>
<td>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)</td>
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<tr>
<td>NCT00005887 RCT Power calculation: Yes USA Non industry Journal article N: 515</td>
<td>WBRT 3000 cGy, 10 fractions, qd Supplemental oxygen</td>
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[^155]: [Suh, 2006](#)
[^244]: [Scott, 2007](#)
[^238]: [Spectrum Pharmaceuticals, 2000](#)
[^240]: [Nabid, 2004](#)
[^242]: [Shaw, 2004](#)
[^243]: [SpectRum Pharmaceuticals, 2000](#)
[^245]: [Suh, 2004](#)
[^246]: [Suh, 2004](#)
[^247]: [Suh, 2004](#)
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<tr>
<td>Suh, 2008&lt;sup&gt;156&lt;/sup&gt;</td>
<td>Spectrum Pharmaceuticals, 2007&lt;sup&gt;249&lt;/sup&gt; NCT00083304 RCT</td>
<td>WBRT + Efaproxial 3000 cGy, 10 fractions, qd Efaproxiral; supplemental oxygen</td>
<td>Intervention: randomized, 182 analyzed</td>
<td>Intervention vs Comparator: Overall survival HR 0.87; CI (0.69, 1.09)</td>
<td>Not reported</td>
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<td>WBRT 3000 cGy, 10 fractions, qd Supplemental oxygen</td>
<td>Comparator: randomized, 183 analyzed</td>
<td>KPS, and neurological signs and symptoms improvement in WBRT+Efaproxiral failed to achieve statistical significance.</td>
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<td>Followup: 13 [median] months</td>
<td>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</td>
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<td>Tetu, 2019&lt;sup&gt;157&lt;/sup&gt;</td>
<td>Assistance Publique - Hopitaux de Paris&lt;sup&gt;34&lt;/sup&gt; NCT02828202 Cohort</td>
<td>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 ps choice Immunotherapy/targeted Targeted therapy (anti-BRAF anti-MEK) or immunotherapy (ipilimumab or anti-PD1), according to investigator ps choice</td>
<td>Intervention: randomized, 93 analyzed</td>
<td>Intervention vs Comparator: Overall survival HR 0.6; CI (0.45, 0.8) Progression-free survival Progressive disease</td>
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<td>Comparator: randomized, 169 analyzed</td>
<td>Additional comparator: randomized, analyzed</td>
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<td>Followup: 7 [median] months</td>
<td>Followup: 7 [median] months</td>
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<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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<tr>
<td><strong>University of Michigan, 2016</strong>&lt;sup&gt;138&lt;/sup&gt; Silk, 2015&lt;sup&gt;346&lt;/sup&gt; NCT02097732 RCT Power calculation: No USA Industry funded Trial record N: 4</td>
<td><strong>Age: 58 [mean] 48-69 [range]</strong>&lt;br&gt;Gender: 25%&lt;br&gt;Primary tumor type: Melanoma only;&lt;br&gt;Metastases: Number: NA&lt;br&gt;Volume: NA&lt;br&gt;Size: NA&lt;br&gt;Prognosis: unclear</td>
<td>Induction ipilimumab + SRS N/A&lt;br&gt;Ipilimumab 3mg/kg given intravenously every 3 weeks, total of 4 doses&lt;br&gt;SRS followed by ipilimumab NA&lt;br&gt;Ipilimumab 3mg/kg given intravenously prior to SRS, every 3 weeks, total of 4 doses</td>
<td>Intervention: 3 randomized, 3 analyzed&lt;br&gt;Comparator: 1 randomized, 1 analyzed&lt;br&gt;Followup: NA months</td>
<td>Not reported</td>
<td>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)</td>
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<td><strong>Ushio, 1991</strong>&lt;sup&gt;159&lt;/sup&gt; N/A RCT Power calculation: No Japan Non industry Journal article N: 100</td>
<td><strong>Age: Group A: 62 [mean], Group B: 56 [mean], Group C: 58 [mean]</strong>&lt;br&gt;Gender: 15% female&lt;br&gt;Primary tumor type: Different cancer types; majority NSCLC (some SCLC)&lt;br&gt;Metastases: Number: 33% had multiple metastases&lt;br&gt;Volume: N/A&lt;br&gt;Size: N/A&lt;br&gt;Prognosis: unclear</td>
<td>WBRT + Methyl-CCNU/ACNU + Tegafur&lt;br&gt;4000 cGy, 20 fractions&lt;br&gt;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&lt;br&gt;WBRT 4000 cGy, 20 fractions&lt;br&gt;Conventional doses of corticosteroids as needed&lt;br&gt;WBRT + Methyl-CCNU/ACNU&lt;br&gt;4000 cGy, 20 fractions&lt;br&gt;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</td>
<td>Intervention: 33 randomized, 29 analyzed&lt;br&gt;Comparator: 31 randomized, 25 analyzed&lt;br&gt;Additional comparator: 36 randomized, 34 analyzed&lt;br&gt;Followup: 82 months</td>
<td>Not reported</td>
<td>Intervention vs Comparator: Time to death&lt;br&gt;Median survival 27 (control), 30.5, (comparator) and 30 (intervention) weeks; 1 long-term survivor (more than 5 years) in the control group, 3 in the comparison group, 1 in the intervention group&lt;br&gt;Progressive disease&lt;br&gt;Patients with progression: 1/19 (intervention) vs 4/14 (control), 2/16 (comparator)&lt;br&gt;Complete resolution of tumor&lt;br&gt;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</td>
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<td>Study</td>
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<tr>
<td>Vecht, 1993</td>
<td>Age: surgery + WBRT: 59.2 (10.3) and WBRT: 59.8 (12)</td>
<td>WBRT + surgery 4000 cGy, 20 fractions, bid Neurosurgical excision, dexamethasone up to 16 mg/day during radiation therapy</td>
<td>Intervention: 33 randomized, 32 analyzed</td>
<td>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 &lt;= 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</td>
<td>Intervention vs Comparator: Number of participants with complications of radiotherapy such as headache, nausea, or vomiting RR 1.08; CI (0.51, 2.29)</td>
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<tr>
<td>N/A</td>
<td>Gender: 48% female</td>
<td></td>
<td>Comparator: 33 randomized, 31 analyzed</td>
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<tr>
<td>RCT</td>
<td>Primary tumor type: Different cancer types; majority lung, breast, melanoma</td>
<td>WBRT 4000 cGy, 20 fractions, bid</td>
<td>Followup: 70 months</td>
<td></td>
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<tr>
<td>Power calculation: No</td>
<td>Metastases: Number: 1 (all patients had 1 brain metastasis)</td>
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<tr>
<td>Netherlands</td>
<td>Volume: N/A</td>
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<tr>
<td>Non industry</td>
<td>Size: N/A</td>
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<tr>
<td>Journal article</td>
<td>Prognosis: unclear</td>
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<tr>
<td>N: 63</td>
<td>Age: surgery + WBRT: 59.2 (10.3) and WBRT: 59.8 (12)</td>
<td>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</td>
<td>Intervention: 41 randomized, 41 analyzed</td>
<td>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</td>
<td>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.</td>
</tr>
<tr>
<td>Verger, 2005</td>
<td>Age: WBRT: 58.3 (11.6), WBRT+TMZ: 57.8 (12.2)</td>
<td>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</td>
<td>Intervention: 41 randomized, 41 analyzed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td>Gender: 65% female</td>
<td></td>
<td>Comparator: 41 randomized, 41 analyzed</td>
<td></td>
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<tr>
<td>RCT</td>
<td>Primary tumor type: Different cancer types; majority lung or breast</td>
<td>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</td>
<td>Followup: 5 [median] months</td>
<td></td>
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<tr>
<td>Power calculation: Yes</td>
<td>Metastases: Number: WBRT: 3 [median], WBRT + TMZ: 2 [median]</td>
<td></td>
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<td>Spain</td>
<td>Volume: N/A</td>
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<td>Non industry</td>
<td>Size: N/A</td>
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<tr>
<td>Journal article N: 82</td>
<td>Prognosis: mixed, majority moderate to poor</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<tr>
<td>Wang, 2015 162 N/A RCT</td>
<td>Age: Gefitinib: 61 [median], VMP chemotherapy: 62 [median]</td>
<td>WBRT + Gefitinib 5000 cGy, 25 fractions, qd</td>
<td>37 randomized</td>
<td>Intervention vs Comparator: Median survival time was 13.3 (gefitinib) vs 12.7 (VMP) (p&lt;0.05)</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Gender: 34% female</td>
<td>Gefitinib 250 mg/day p.o. started at first day of radiation therapy</td>
<td>analyzed</td>
<td>Progressive disease at 2 months 5.4% (gefitinib) vs 5.8% (VMP) of patients with progressive disease</td>
<td></td>
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<tr>
<td></td>
<td>Primary tumor type: Lung cancer only;</td>
<td>WBRT + VMP chemotherapy 5000 cGy, 25 fractions, qd</td>
<td>36 randomized</td>
<td>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</td>
<td></td>
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<tr>
<td></td>
<td>Metastases: Number: N/A Volume: N/A Size: N/A</td>
<td>Intravenous infusion of 100 mg/day VM-26 from day 1 to day 3; intravenous</td>
<td>34 analyzed</td>
<td></td>
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<tr>
<td></td>
<td>Prognosis: unclear</td>
<td>infusion of cisplatin 25 mg/m2 from day 1 to day 3; one cycle was defined</td>
<td>14 [median]</td>
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<td></td>
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<td>as a 21-day therapy duration, with a total of 2 cycles; radiotherapy starting</td>
<td>months</td>
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<tr>
<td></td>
<td></td>
<td>from the first day of chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>Wolfson, 1994 163 RCT</td>
<td>Age: 58 [median]</td>
<td>WBRT + dexamethasone 3000 cGy, 10 fractions, qd</td>
<td>7 randomized</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender: 58% female</td>
<td>dexamethasone 4 mg PO q6h</td>
<td>7 analyzed</td>
<td>Intervention vs Comparator: Side effects (including serious adverse events) RR 0.71; CI (0.02, 30.32)</td>
<td></td>
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<tr>
<td></td>
<td>Primary tumor type: Different cancer types; 92% lung or breast</td>
<td>WBRT alone 3000 cGy, 10 fractions, qd</td>
<td>5 randomized</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Metastases: Number: A third each with 1, 2, or &gt;2 Volume: NA Size: A third</td>
<td></td>
<td>5 analyzed</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>each with &lt;2, 2-4, and &gt;4 cm Prognosis: unclear</td>
<td>Followup: 24 months</td>
<td></td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<tr>
<td>Yang, 2017&lt;sup&gt;164&lt;/sup&gt; Guangdong Association of Clinical Trials, 2015&lt;sup&gt;165&lt;/sup&gt;; Wu, 2017&lt;sup&gt;166&lt;/sup&gt;</td>
<td>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</td>
<td>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</td>
<td>Intervention: 91 randomized, 73 analyzed Comparator: 85 randomized, 85 analyzed Followup: 17 [median] months</td>
<td>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=0.0669)</td>
<td>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.</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<tr>
<td>Yang, 2017</td>
<td>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</td>
<td>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</td>
<td>Intervention: 76 randomized, 76 analyzed Comparator: 75 randomized, 75 analyzed Additional comparator: 77 randomized, 77 analyzed Followup: NA months</td>
<td>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</td>
<td>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)</td>
</tr>
<tr>
<td>CNSDQFSH010</td>
<td>Age: Lung cancer only; Metastases: Number: bevacizumab+gefitinib+WBRT: 36% more than 5 metastases, 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</td>
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<tr>
<td>RCT</td>
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<td>Power calculation: No</td>
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<tr>
<td>Source: China</td>
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<td>Journal article</td>
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<td>N: 218</td>
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<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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</tbody>
</table>
| Yang, 2018<sup>167</sup> Daping Hospital<sup>189</sup> 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). | Not reported |
| Yang, 2019<sup>166</sup> National Taiwan University, 2019<sup>332</sup> 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 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>N and Followup</th>
<th>Effects</th>
<th>Adverse Events</th>
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<tbody>
<tr>
<td>Zeng, 2016&lt;sup&gt;168&lt;/sup&gt;</td>
<td>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</td>
<td>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)</td>
<td>Intervention: 32 randomized, 32 analyzed Comparator: 32 randomized, 32 analyzed Followup: 10 [median] months</td>
<td>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%)</td>
<td>Intervention vs Comparator: Number of adverse events 450 vs 448 events Fatigue 2 vs 1 Vomiting 3 vs 1 Headaches 0 vs 0</td>
</tr>
<tr>
<td>Zhu, 2018&lt;sup&gt;169&lt;/sup&gt;</td>
<td>Age: N/A Gender: N/A Primary tumor type: Lung cancer only; Metastases: Number: N/A Volume: N/A Size: N/A Prognosis: unclear</td>
<td>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</td>
<td>Intervention: 37 randomized, 37 analyzed Comparator: 38 randomized, 38 analyzed Followup: 15 [median] months</td>
<td>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)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>N and Followup</td>
<td>Effects</td>
<td>Adverse Events</td>
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<td>Zhuang, 2020&lt;sup&gt;70&lt;/sup&gt; ChiCTR1900022750 Cohort Power calculation: No China Non industry Journal article N: 361</td>
<td>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</td>
<td>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)</td>
<td>Intervention: randomized, 196 analyzed Comparator: randomized, 165 analyzed Followup: &gt;10 months months</td>
<td>Not reported</td>
<td>Intervention vs Comparator: Radiation necrosis RR 4.8; CI (2.53, 9.09)</td>
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</table>
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 researchers.

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

<table>
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<tr>
<th>Standard Category</th>
<th>Abbrev.</th>
<th>Standard</th>
<th>Is this standard applicable to this SR?</th>
<th>List sections and pages of the SR report where you address this standard</th>
<th>If applicable, describe how and why the SR deviated from this standard?</th>
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<tr>
<td>IR-1</td>
<td>IR-1</td>
<td>A priori, specify plans for quantitative data analysis that correspond to major aims.</td>
<td>Yes</td>
<td>Published protocol</td>
<td></td>
</tr>
<tr>
<td>IR-2</td>
<td>IR-2</td>
<td>Assess data source adequacy.</td>
<td>Yes</td>
<td>Risk of bias assessment</td>
<td></td>
</tr>
<tr>
<td>IR-3</td>
<td>IR-3</td>
<td>Describe data linkage plans, if applicable.</td>
<td>Yes</td>
<td>SRDR</td>
<td></td>
</tr>
<tr>
<td>IR-4</td>
<td>IR-4</td>
<td>Document validated scales and tests.</td>
<td>Yes</td>
<td>Evidence table in appendix</td>
<td></td>
</tr>
<tr>
<td>IR-5</td>
<td>IR-5</td>
<td>Provide sufficient information in reports to allow for assessments of the study’s internal and external validity.</td>
<td>Yes</td>
<td>Methods appendix</td>
<td></td>
</tr>
<tr>
<td>IR-6</td>
<td>IR-6</td>
<td>Masking should be used when feasible.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>IR-7</td>
<td>IR-7</td>
<td>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.</td>
<td>Yes</td>
<td>Published protocol</td>
<td></td>
</tr>
</tbody>
</table>

## Standards for Preventing and Handling Missing Data

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</thead>
<tbody>
<tr>
<td>MD-1</td>
<td>MD-1</td>
<td>Describe methods to prevent and monitor missing data.</td>
<td>Yes</td>
<td>Methods appendix</td>
<td></td>
</tr>
<tr>
<td>MD-2</td>
<td>MD-2</td>
<td>Use valid statistical methods to deal with missing data that properly account for statistical uncertainty due to missingness.</td>
<td>Yes</td>
<td>SoE assessment, result section</td>
<td></td>
</tr>
<tr>
<td>MD-3</td>
<td>MD-3</td>
<td>Record and report all reasons for dropout and missing data, and account for all patients in reports.</td>
<td>Yes</td>
<td>Methods appendix</td>
<td></td>
</tr>
<tr>
<td>MD-4</td>
<td>MD-4</td>
<td>Examine sensitivity of inferences to missing data methods and assumptions, and incorporate into interpretation.</td>
<td>Yes</td>
<td>Result chapter</td>
<td></td>
</tr>
</tbody>
</table>

## Standards for Heterogeneity of Treatment Effect (HTE)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>HT-1</td>
<td>HT-1</td>
<td>State the goals of HTE analyses, including hypotheses and the supporting evidence base.</td>
<td>Yes</td>
<td>Result chapter</td>
<td></td>
</tr>
<tr>
<td>HT-2</td>
<td>HT-2</td>
<td>For all HTE analyses, provide an analysis plan, including the use of appropriate statistical methods.</td>
<td>Yes</td>
<td>Methods appendix</td>
<td></td>
</tr>
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</tr>
<tr>
<td><strong>HT-3</strong></td>
<td></td>
<td>Report all prespecified HTE analyses and, at minimum, the number of post-hoc HTE analyses, including all subgroups and outcomes analyzed.</td>
<td>Yes</td>
<td>Result chapter</td>
<td></td>
</tr>
<tr>
<td><strong>DR-1</strong></td>
<td></td>
<td>Requirements for the design of registries.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DR-2</strong></td>
<td></td>
<td>Documentation and reporting requirements of registry materials, characteristics, and bias.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DR-3</strong></td>
<td></td>
<td>Adapting established registries for PCOR.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DR-4</strong></td>
<td></td>
<td>Documentation requirements when using registry data.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DN-1</strong></td>
<td></td>
<td>Requirements for the design and features of data networks.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DN-2</strong></td>
<td></td>
<td>Selection and use of data networks.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CI-1</strong></td>
<td></td>
<td>Specify the causal model underlying the research question (cross-cutting standard, applies to all PCOR/CER studies).</td>
<td>Yes</td>
<td>Key questions</td>
<td></td>
</tr>
<tr>
<td><strong>CI-2</strong></td>
<td></td>
<td>Define and appropriately characterize the analysis population used to generate effect estimates.</td>
<td>Yes</td>
<td>Result chapter, evidence table</td>
<td></td>
</tr>
<tr>
<td><strong>CI-3</strong></td>
<td></td>
<td>Define with the appropriate precision the timing of the outcome assessment relative to the initiation and duration of exposure.</td>
<td>Yes</td>
<td>Evidence table in appendix</td>
<td></td>
</tr>
<tr>
<td><strong>CI-4</strong></td>
<td></td>
<td>Measure potential confounders before start of exposure and report data on potential confounders with study results.</td>
<td>Yes</td>
<td>Result chapter, meta-regressions</td>
<td></td>
</tr>
<tr>
<td><strong>CI-5</strong></td>
<td></td>
<td>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.</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td><strong>CI-6</strong></td>
<td></td>
<td>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.</td>
<td>N/A</td>
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<tr>
<td>Standards for Adaptive and Bayesian Trial Designs</td>
<td>AT-1</td>
<td>Specify planned adaptations, decisional thresholds, and statistical properties of those adaptations.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AT-2</td>
<td>Specify the structure and analysis plan for Bayesian adaptive randomized clinical trial designs.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AT-3</td>
<td>Ensure that clinical trial infrastructure is adequate to support planned adaptation(s) and independent interim analyses.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AT-4</td>
<td>When reporting adaptive randomized clinical trials, use the CONSORT statement, with modifications.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Standards for Studies of Medical Tests</td>
<td>MT-1</td>
<td>Specify clinical context and key elements of the medical test.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MT-2</td>
<td>Assess the effect of factors known to affect performance and outcomes.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MT-3</td>
<td>Focus studies of medical tests on patient-centered outcomes, using rigorous study designs with a preference for randomized controlled trials.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Standards for Systematic Reviews</td>
<td>SR-1</td>
<td>Adhere to National Academy of Medicine (NAM) standards for systematic reviews of comparative effectiveness research, as appropriate.</td>
<td>Yes</td>
<td>Protocol, report</td>
<td></td>
</tr>
<tr>
<td>Standards on Research Designs Using Clusters</td>
<td>RC-1</td>
<td>Specify whether the study objectives, the interventions, and the primary outcomes pertain to the cluster level or the individual level.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RC-2</td>
<td>Justify the choice of cluster randomization.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RC-3</td>
<td>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.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RC-4</td>
<td>Data analyses must account for the dependence of observations within clusters regardless of its magnitude.</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RC-5</td>
<td>Stratified randomization should be used when feasible.</td>
<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td>Standards for Studies of Complex Interventions</td>
<td>SCI-1</td>
<td>Fully describe the intervention and comparator and define their core functions.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCI-2</td>
<td>Specify the hypothesized causal pathways and their theoretical basis.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCI-3</td>
<td>Specify how adaptations to the form of the intervention and comparator will be allowed and recorded.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCI-4</td>
<td>Plan and describe a process evaluation.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCI-5</td>
<td>Select patient outcomes informed by the causal pathway.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standards for Qualitative Methods</td>
<td>QM-1</td>
<td>State the qualitative approach to research inquiry, design, and conduct.</td>
<td>Yes</td>
<td>Methods appendix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QM-2</td>
<td>Select and justify appropriate qualitative methods sampling strategy.</td>
<td>Yes</td>
<td>Methods appendix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QM-3</td>
<td>Link the qualitative data analysis, interpretations, and conclusions to the study question.</td>
<td>Yes</td>
<td>Result chapter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QM-5</td>
<td>Establish trustworthiness and credibility of qualitative research.</td>
<td>Yes</td>
<td>Result chapter</td>
<td></td>
</tr>
<tr>
<td>Standards for Mixed Methods Research</td>
<td>MM-2</td>
<td>Specify how mixed methods are integrated across design, data sources, and/or data collection phases.</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>MM-3</td>
<td>Integrate data analysis, data interpretation, and conclusions.</td>
<td>N/A</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>IPD-1</td>
<td>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.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>Standards for Individual Participant-Level Data Meta-Analysis (IPD-MA)</td>
<td>IPD-2</td>
<td>Describe the proposed governance structure for the IPD-MA in the protocol and study reports.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD-3</td>
<td></td>
<td>Use systematic, reproducible methods to identify studies for inclusion in the IPD-MA.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPD-4</td>
<td></td>
<td>Specify the design and planned analyses of the IPD-MA in a protocol, document any changes, and report significant amendments and modifications.</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>