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Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases (Review)

Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL

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TABLE OF CONTENTS

[Intervention Review]

Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases

Chirag G Patil[1], Katie Pricola[2], J Manuel Sarmiento[3], Sachin K Garg[4], Andrew Bryant[5], Keith L Black[1]

[1]Department of Neurosurgery, Maxine Dunitz Neurosurgical Institute, Los Angeles, CA, USA. [2]Stanford School of Medicine, Stanford, CA, USA. [3]Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA. [4]Department of General Internal Medicine, University of Pennsylvania, Philadelphia, PA, USA. [5]Institute of Health & Society, Newcastle University, Newcastle upon Tyne, UK

Contact: Chirag G Patil, chiragpatil@gmail.com.

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ABSTRACT

Background

Historically, whole brain radiation therapy (WBRT) has been the main treatment for brain metastases. Stereotactic radiosurgery (SRS) delivers high-dose focused radiation and is being increasingly utilized to treat brain metastases. The benefit of adding SRS to WBRT is unclear. This is an updated version of the original Cochrane Review published in Issue 9, 2012.

Objectives

To assess the efficacy of WBRT plus SRS versus WBRT alone in the treatment of adults with brain metastases.

Search methods

For the original review, in 2009 we searched the following electronic databases: CENTRAL, MEDLINE, Embase, and CancerLit in order to identify trials for inclusion in this review. For the first update the searches were updated in May 2012.

For this update, in May 2017 we searched CENTRAL, MEDLINE, and Embase in order to identify trials for inclusion in the review.

Selection criteria

We restricted the review to randomized controlled trials (RCTs) that compared use of WBRT plus SRS versus WBRT alone for upfront treatment of adults with newly diagnosed metastases (single or multiple) in the brain resulting from any primary, extracranial cancer.

Data collection and analysis

We used the generic inverse variance method, random-effects model in Review Manager 5 for the meta-analysis.

Main results

We identified three studies and one abstract for inclusion but we could only include two studies, with a total of 358 participants in a meta-analysis. This found no difference in overall survival (OS) between the WBRT plus SRS and WBRT alone groups (hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.65 to 1.02; 2 studies, 358 participants; moderate-quality evidence). For participants with one brain metastasis median survival was significantly longer in the WBRT plus SRS group (6.5 months) versus WBRT group (4.9 months; P = 0.04). Participants in the WBRT plus SRS group had decreased local failure compared to participants who received WBRT alone (HR 0.27, 95% CI 0.14 to 0.52; 2 studies, 129 participants; moderate-quality evidence). Furthermore, we observed an improvement in performance status scores and decrease in steroid use in the WBRT plus SRS group (risk ratio (RR) 0.64 CI 0.42 to 0.97; 1 study, 118 participants; low-quality evidence).

Unchanged or improved Karnofsky Performance Scale (KPS) at six months was seen in 43% of participants in the combined therapy group versus only 28% in the WBRT-alone group (RR 0.78 CI 0.61 to 1.00; P value = 0.05; 1 study, 118 participants; low-quality evidence). Overall, risk of bias in the included studies was unclear.

Authors' conclusions

Since the last version of this review we have identified one new study that met the inclusion criteria. However, due to a lack of data from this study we were not able to include it in a meta-analysis. Given the unclear risk of bias in the included studies, the results of this analysis have to be interpreted with caution. In our analysis of all included participants, SRS plus WBRT did not show a survival benefit over WBRT alone. However, performance status and local control were significantly better in the SRS plus WBRT group. Furthermore, significantly longer OS was reported in the combined treatment group for recursive partitioning analysis (RPA) Class I patients as well as patients with single metastasis. Most of our outcomes of interest were graded as moderate-quality evidence according to the GRADE criteria and the risk of bias in the majority of included studies was mostly unclear.

PLAIN LANGUAGE SUMMARY

Is adding focused radiation (radiosurgery) to whole brain radiation therapy beneficial to people with brain metastases?

The issue
The benefit of adding stereotactic radiosurgery (SRS), which is non-surgical targeted radiation therapy, to whole brain radiation therapy (WBRT), where radiation is given to the whole brain when tumours cannot be removed by surgery, for people with brain metastases is unclear.

The aim of the review
We sought to determine whether adding SRS to WBRT is beneficial compared to WBRT alone in the treatment of brain metastases.

What are the main findings?
We identified three randomised controlled trials (RCTs), which are studies that randomly assign participants into different treatment groups, that looked at whether adding focused (targeted) radiation (radiosurgery) to WBRT is beneficial to people with brain metastases. Overall, participants who underwent WBRT and SRS did not survive longer than participants who were treated with WBRT alone. However, participants with high functional status to perform activities of daily life and those with a single metastasis did survive longer after SRS and WBRT. Participants treated with WBRT and SRS did experience improved local control and performance status, as well as decreased steroid use compared to participants treated with WBRT alone.

Quality of the evidence
The overall quality of the evidence was moderate based on the GRADE assessments for our outcomes of interest, and the overall risk of bias was unclear.

What are the conclusions?
Most of our conclusions are based on the results of one large trial with unclear risk of bias and therefore, we cautiously make the following remarks: we found that when radiosurgery was added to WBRT, there was no evidence to suggest that people lived any longer than if they had WBRT alone, except for people with only one brain metastasis (who may live longer if they receive the combination treatment). People having combination treatment also seemed to function better in daily life, their treated tumors were associated with having less chance of growing back, and they had to take less steroid medication. The side effects of combined therapy and WBRT alone were similar.

Summary of findings 1. Whole brain radiation therapy (WBRT) + stereotactic radiosurgery (SRS) versus WBRT for the treatment of brain metastases

Whole brain radiation therapy (WBRT) + stereotactic radiosurgery (SRS) versus WBRT for the treatment of brain metastases

Patient or population: people with brain metastases

Settings: inpatient or outpatient

Intervention: WBRT + SRS versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	WBRT + SRS versus WBRT				
Overall survival Follow-up: 12 months[1]	**Study population**		**HR 0.82** (0.65 to 1.02)	358 (2 studies[2])	⊕⊕⊕⊖ **moderate** [3]	
	762 per 1000	**692 per 1000** (607 to 769)				
	Medium-risk population					
	773 per 1000	**704 per 1000** (619 to 780)				
Disease-specific survival	**Study population**		**RR 0.92** (0.64 to 1.32)	286 (1 study[2])	⊕⊕⊕⊖ **moderate** [3]	
	309 per 1000	**284 per 1000** (198 to 408)				
	Medium-risk population					
	309 per 1000	**284 per 1000** (198 to 408)				
Local tumor control Follow-up: 12 months[1]	**Study population**		**HR 0.27** (0.14 to 0.52)	129 (2 studies[2])	⊕⊕⊕⊖ **moderate** [3]	
	439 per 1000	**145 per 1000** (78 to 260)				
	Medium-risk population					

	644 per 1000	**243 per 1000** (135 to 416)			
Functionally independent survival (KPS) Follow-up: 6 months	**Study population**		**RR 0.78** (0.61 to 1.00)	145 (1 study[2])	⊕⊕⊕⊝ **moderate** [3]
	725 per 1000	**565 per 1000** (442 to 725)			
	Medium-risk population				
	725 per 1000	**565 per 1000** (442 to 725)			
Steroid use Follow-up: 6 months	**Study population**		**RR 0.64** (0.42 to 0.97)	118 (1 study[2])	⊕⊕⊝⊝ **low** [3]
	545 per 1000	**349 per 1000** (229 to 529)			
	Medium-risk population				
	546 per 1000	**349 per 1000** (229 to 530)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; HR: hazard ratio; KPS: Karnofsky Performance Status; RR: risk ratio; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]12 months was used to calculate baseline rates, since we used a HR in the main analysis.
[2]Downgraded to moderate quality of evidence because, "further research is very unlikely to change our confidence in the estimate of effect", may not be true. Evidence from more relevant trials would be welcome.
[3]Estimate is imprecise as there is a fair degree of uncertainty in the pooled estimate as indicated by 95% CI.

BACKGROUND

This review is an update of a previously published review in the Cochrane Library (Issue 6, 2010 and Issue 9, 2012) on whole brain radiation therapy (WBRT) alone versus WBRT plus stereotactic radiosurgery (SRS) for the treatment of brain metastases.

Description of the condition

Approximately 20% to 40% of people with cancer will go on to develop brain metastases (Andrews 2004; Hasegawa 2003). Primary tumor histologies most commonly include non-small cell lung cancer, breast cancer, melanoma, colon cancer, and renal cell carcinoma (Chidel 2000; Flickinger 1994; Hasegawa 2003; Pirzkall 1998). The median survival of people after diagnosis of brain metastases is less than six months (Li 2000).

Description of the intervention

Historically, WBRT has been utilized as the main treatment modality for the management of brain metastases (Hasegawa 2003; Sneed 1999). Before WBRT, survival rates averaged one to two months with the administration of corticosteroids (Andrews 2004; Pirzkall 1998; Tsao 2012). The addition of WBRT to steroids extended median survival to three to six months (Andrews 2004; Flickinger 1994; Hasegawa 2003; Kondziolka 1999; Sneed 1999). However, in the last decade there has been mounting evidence enumerating the toxic effects of WBRT, especially serious neurocognitive impairments (Hasegawa 2003). We identified three randomized controlled trials (RCTs) and one abstract for inclusion in this review. Two of these RCTs of people with solitary brain metastasis showed that combined treatment of surgical resection (craniotomy) with WBRT improved survival rates and led to greater local tumor control than WBRT alone (Flickinger 1994; Pirzkall 1998). It has since been suggested that WBRT and SRS together could produce similar results (Sneed 1999). SRS, developed by Swedish neurosurgeon Lars Leksell in 1951, is a technique that focuses high-dose radiation at precise intracranial targets (Andrews 2004). Radiosurgical procedures are non-invasive, provide excellent local tumor control, and can be used to treat multiple tumors with minimal dose overlapping (Fuller 1992; Kondziolka 1999).

Why it is important to do this review

In the past, WBRT has been the standard treatment for brain metastases; however, SRS is being increasingly used for the management of brain metastases. How and in what situations these two treatments should be combined or used individually remains to be definitively answered. Therefore, defining the role of SRS in the management of people with brain metastases has become critical.

OBJECTIVES

To assess the efficacy of WBRT plus SRS versus WBRT alone in the treatment of adults with brain metastases.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs

Types of participants

We included adults (over 18 years of age), with newly diagnosed metastases (single or multiple) in the brain, resulting from any primary, extracranial cancer. We excluded people who had received previous cranial radiation.

Types of interventions

Intervention:

- WBRT with SRS for upfront treatment of single or multiple brain metastases.

Comparison:

- WBRT alone.

Salvage treatments (i.e. treatments after initial treatment failure) should follow clinical protocol.

Types of outcome measures

Primary outcomes

- Overall survival (OS): death from all causes from time of randomization
- Disease-specific survival (DSS): death from metastases of the brain
- Functionally independent survival (FIS): as measured using a Karnofsky Performance Scale (KPS) (Karnofsky 1949) baseline or some equivalent system of measurement

Secondary outcomes

- Local tumor control: as defined by either a complete response, partial response, or stable response of all metastases known at time of randomization
- Adverse events (radiation necrosis, new neurologic deficit, peritumoral edema)
- Neurologic performance
- Quality of life (QoL), measured using a validated scale
- Steroid requirement

Search methods for identification of studies

We sought papers in all languages and carried out translations where necessary.

Electronic searches

For the original review, in 2009 we searched the following electronic databases in the following order to identify trials for inclusion: Cochrane Central Register of Controlled Trials (CENTRAL; 2009, Issue 2) in the Cochrane Library (Appendix 1), MEDLINE (1966 to 2009) (Appendix 2), Embase (1980 to 2009) (Appendix 3) and CancerLit (1975 to 2003) (Appendix 4)

We searched the following electronic databases in May 2012 for the first update and May 2017 for this update to identify new trials for inclusion: CENTRAL; 2017, Issue 5, in the Cochrane Library (Appendix 5), MEDLINE (Ovid) (May 2012 to May week 1 2017) (Appendix 6), and Embase (Ovid) (May 2012 to 2017 week 20) (Appendix 7). We employed a standard strategy to search each electronic database. We created three separate search 'buckets' using the 'OR' operator, that focused on identifying RCTs, diseases

of interest, and interventions of interest. We then combined all three buckets using the 'AND' operator to yield the final data bucket and eliminated duplicates and non-human applications. Please note: elements of the search strategies have been adopted from those detailed in Hart 2004.

For MEDLINE search strategies, terms one to 10 were originally devised and have been revised by Carol Lefebvre at the UK Cochrane Centre for the identification of all randomized and clinical controlled trials. For further source detail, please see Lefebvre 2011.

We identified all relevant articles that we had found on PubMed and carried out a further search for newly published articles using the 'related articles' feature.

The review author team developed and executed the search strategies for the original review. For this and the previous update, Jane Hayes and Jo Platt, Information Specilaists for Cochrane Gynaecological, Neuro-oncology and Orphan Cancers revised the search strategies and ran the searches.

Searching other resources

Unpublished and grey literature

We searched Meta-Register, Physicians Data Query, www.isrctn.com, www.clinicaltrials.gov, and www.cancer.gov/about-cancer/treatment/clinical-trials for ongoing trials. We contacted the main investigators of any relevant ongoing trials for further information, as well as any major co-operative trials groups active in this area.

Reference lists and correspondence

We checked the citation lists of all included trials and contacted experts in the field to identify further reports of trials.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database EndNote, removed duplicates, and two review authors (KP, CP) independently examined the remaining references. Review authors were not blinded to the authors or affiliations of the studies. We excluded those studies that clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Three review authors (KP, CP, JMS) independently assessed the eligibility of retrieved papers. We resolved disagreements by discussion between the two review authors. We documented reasons for exclusion.

Data extraction and management

For included trials, we abstracted data as recommended in chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). This included data on the following:

- author, year of publication, and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- study population:
  - total number enrolled;
  - participant characteristics;
  - age;
  - sex;
  - comorbidities;
  - previous treatment;
  - neurologic performance;
  - primary cancer type;
- brain metastases details at diagnosis:
  - size of metastases (including largest);
  - number of brain metastases;
  - tumor histology;
- intervention details:
  - details of SRS;
    - type,
    - dose,
    - fractions,
    - maximum radiosurgical dose (Dmax),
    - dose to the tumor margin and isodose line,
    - duration;
  - details of WBRT;
    - type,
    - dose,
    - fractions,
    - duration;
- risk of bias in study (Assessment of risk of bias in included studies);
- duration of follow-up;
- outcomes included OS, FIS, local tumor control, cause of death, steroid requirement, and adverse events:
  - OS:
    - definition: OS was measured from date of randomization until death or last follow-up,
    - unit of measurement: months;
  - FIS;
    - assessed via the KPS. The KPS score runs from 100% to 0%, where 100% is perfect health and 0% is death:
      - 100% - normal, no complaints, no signs of disease;
      - 90% - capable of normal activity, few symptoms or signs of disease;
      - 80% - normal activity with some difficulty, some symptoms or signs;
      - 70% - caring for self, not capable of normal activity or work;
      - 60% - requiring some help, can take care of most personal requirements;
      - 50% - requires help often, requires frequent medical care;
      - 40% - disabled, requires special care and help;
      - 30% - severely disabled, hospital admission indicated but no risk of death;
      - 20% - very ill, urgently requiring admission, requires supportive measures or treatment;

- 10% - moribund, rapidly progressive fatal disease processes;
- 0% - death;

- local tumor control:
  - defined as decrease or no change in tumor size as judged by serial post-treatment magnetic resonance imaging (MRI) scans;
- DSS:
  - definition: death owing to neurologic cause that is because of brain metastasis
- steroid requirement:
  - steroid requirement was measured as unchanged, improved, or worsened;
  - people with brain metastases are often managed with steroids to decrease cerebral edema. Longer steroid use has been implicated in many medical complications including worsened sugar control and increased cardiovascular risk;
- adverse events:
  - treatment toxicities were classified in the trial of Andrews 2004 as:
    - acute (within 90 days of radiation treatment) or
    - late toxicities and included nausea/vomiting, hearing loss, skin, neurologic, and other toxicities. These were graded as per the Radiation Therapy Oncology Group (RTOG) central nervous system (CNS) toxicity criteria (Appendix 8).

Outcome data

We extracted data on outcomes as below.

- For time to event (e.g. OS, DSS, and local tumor control rates) data, we extracted the log of the hazard ratio (log(HR)) and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events or deaths) if it was not possible to use a HR, we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at end point, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we extracted the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at end point in each treatment arm at the end of follow-up, in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardized mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants were analyzed in the groups to which they had been assigned.

We noted the time points at which outcomes were collected and reported.

Two review authors (KP, CP) independently abstracted data onto a data abstraction form specially designed for the review. We resolved differences between review authors by discussion or by appeal to a third review author if necessary.

Assessment of risk of bias in included studies

We assessed risk of bias in included RCTs using the following questions and criteria (see Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2011b):

Sequence generation

Was the allocation sequence adequately generated?

- Yes, for example a computer-generated random sequence or a table of random numbers.
- No, for example date of birth, clinic id number or surname.
- Unclear, for example not reported.

Allocation concealment

Was allocation adequately concealed?

- Yes, for example where the allocation sequence could not be foretold.
- No, for example allocation sequence could be foretold by participants, investigators, or treatment providers.
- Unclear, for example not reported.

Blinding

Assessment of blinding was restricted to blinding of outcome assessors, since it would not be possible to blind participants and treatment providers to the different interventions.

Was knowledge of the allocated interventions adequately prevented during the study?

- Yes
- No
- Unclear

Incomplete reporting of outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the study.

Were incomplete outcome data adequately addressed?

- Yes, if fewer than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
- No, if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
- Unclear if loss to follow-up was not reported.

Selective reporting of outcomes

Are reports of the study free of suggestion of selective outcome reporting?

- Yes, for example if review reported all outcomes specified in the protocol.
- No, otherwise.
- Unclear, if insufficient information available.

Other potential threats to validity

Was the study apparently free of other problems that could put it at a high risk of bias?

- Yes
- No
- Unclear

Three review authors (KP, CP, JMS) independently applied the 'Risk of bias' tool and resolved any differences by discussion. We have presented results in both a 'Risk of bias' graph and a 'Risk of bias' summary. We interpreted the results of meta-analyses in light of the findings with respect to risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- for time-to-event data, we used the HR, where possible;
- for dichotomous outcomes, we used the RR;
- for continuous outcomes (e.g. QoL measures), we used the mean difference between treatment arms.

Dealing with missing data

We did not impute missing outcome data. For the primary outcome, if data were missing or only imputed data were reported, we contacted trial authors to request data on the outcomes among participants who were assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons.

Assessment of reporting biases

We did not assess reporting biases as there was an insufficient number of included trials in which to compute funnel plots to assess the potential for small study effects such as publication bias.

Data synthesis

If sufficient, clinically similar studies were available, we pooled their results in meta-analyses.

- For time-to-event data, we pooled HRs using the generic inverse variance facility of Review Manager 5 (RevMan 5) (RevMan 2014).
- For dichotomous outcomes, we calculated the RR for each study and then pooled them.
- For continuous outcomes, if all trials measured the outcome on the same scale, we pooled the mean differences between the treatment arms at the end of follow-up, otherwise we pooled standardized mean differences.

We used random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

We presented the overall quality of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2103). We created a 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011) and using GRADEpro GDT. We used the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014). We downgraded the evidence from 'high' quality by one level for serious concerns (or by two for very serious) for each limitation:

- **High quality:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low quality:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- **Very low quality:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Subgroup analysis and investigation of heterogeneity

In interpretation of any heterogeneity we considered factors such as age, number of metastases, and length of follow-up.

Sensitivity analysis

We did not perform sensitivity analysis as there was an insufficient number of trials in the review.

RESULTS

Description of studies

Results of the search

The search strategy identified 628 references in MEDLINE including Cancer-Lit, 2347 in Embase and 161 in CENTRAL. Reference lists and correspondence did not produce any additional studies. We retrieved a total of twelve articles in full. The full-text screening of these twelve references excluded eight studies for the reasons described in the table Characteristics of excluded studies. The remaining four RCTs (three full articles and one abstract) met our inclusion criteria and are described in the table Characteristics of included studies, but we only included two in the analysis. Searches of the grey literature did not identify any additional relevant trials.

Included studies

Four RCTs met our inclusion criteria. Chougule 2000 was presented in abstract form only and included 109 participants who were randomized into WBRT-alone, WBRT plus SRS and SRS-alone groups. No difference in overall median survival was reported in the WBRT-alone and WBRT plus SRS groups. Local control was reported as being superior in the WBRT plus SRS group (91%) versus 62% in the WBRT-alone group. No other outcomes were evaluated in this trial. The abstract only reported median survival and local control in the different groups without providing P values or Kaplan-Meier analysis. We could not obtain any further details about the trial from the authors. Hence, we did not include this RCT in the current meta-analysis.

El Gantery 2014 was a single-institution RCT that compared outcomes among participants receiving WBRT plus SRS (n = 21),

WBRT alone (n = 21), and SRS alone (n = 18). This trial included participants aged 70 or less with KPS of 70% or more and with one to three brain metastases less than 4 cm on contrast-enhanced MRI scan. This study evaluated OS, local control and treatment-related morbidity. There was no difference in six-month, 12-month and median OS between the three treatment groups; however, subgroup analysis indicated that WBRT plus SRS (15 months) provided a survival benefit to participants with tumors 3 cm or less in diameter versus WBRT alone (5 months) (P = 0.002). Participants with controlled primary disease who received WBRT plus SRS (12 months) also demonstrated a survival benefit compared to WBRT alone (5.5 months) and SRS alone (8 months) (P = 0.027). Furthermore, El Gantery 2014 showed that the WBRT plus SRS group (42.9%) had better local control at one year compared to the WBRT-alone group (19%) and SRS alone group (22.2%) (P = 0.04). Of note, WBRT plus SRS (12 months) provided the most local control benefit to participants with brain metastasis less than 3 cm in diameter compared to WBRT alone (6 months) and SRS alone (3 months) (P = 0.004). Acute and late toxicities were similar among treatment groups. Unfortunately, we could not include this trial in the meta-analysis due to lack of available data from the original trial team.

Our meta-analysis included two trials (Andrews 2004; Kondziolka 1999) that randomized 358 participants who were assessed at the end of the trials. Andrews 2004 was by far the largest and only Phase III multi-institutional RCT to compare outcomes in participants who received WBRT plus SRS (n = 164) versus WBRT alone (n = 167). This trial included adults with one to three brain metastases with KPS more than 70%. Outcomes reported included OS, local control, KPS, cause of death, steroid requirement, and neurologic performance. OS was stratified for participants with one metastasis and more than one metastasis. In addition Andrews 2004 stratified survival according to recursive partitioning analysis (RPA) class. RPA class prognosticates survival and outcomes in people with brain metastases. RPA Class 1 describes people who have a KPS of 70% or more, controlled primary status, age less than 65 years, and have no extracranial disease. Andrews 2004 analyzed RPA Class I participants separately and reported significantly longer survival in the WBRT-plus-SRS group (11.6 months) versus WBRT (9.6 months) (P = 0.045). No such stratification was available in the other studies.

In the 2017 search we identified Sperduto 2014 (see Andrews 2004 for reference), which was categorized as an additional report because it was a secondary analysis of participants from Andrews 2004, stratified by the Graded Prognostic Assessment (GPA) but not included in the meta analysis.

Kondziolka 1999 was a single-institution RCT that was stopped following an interim analysis of 27 participants that revealed a significant benefit in the rate of local control in the WBRT-plus-SRS group. This trial included participants with two to four brain metastases that were 25 mm or less. Local tumor control was the primary outcome and OS was also evaluated. No other outcomes were assessed. Follow-up MRI scans were read by an independent, blinded observer. This trial found a difference in local control of tumors in the WBRT-plus-SRS group compared to the WBRT-alone group. Survival was similar in both groups.

See Characteristics of included studies for details.

Excluded studies

We obtained the full text for seven additional references, but we excluded all of them from the review for the reasons given in Characteristics of excluded studies.

Feng 2002, Sanghavi 2001, and Sneed 2002 were retrospective studies. Li 2000 and Minniti 2010 were prospective non-RCTs. Rades 2017 was a matched-pair analysis and not an RCT. Sperduto 2013 was an RCT that evaluated WBRT plus SRS versus WBRT plus chemotherapy.

Risk of bias in included studies

All four included trials (Andrews 2004; Chougule 2000; El Gantery 2014; Kondziolka 1999) were at high risk of bias: they satisfied at most only two of the criteria that we used to assess risk of bias. The trial of Chougule 2000 was at extremely high risk of bias as it was only in abstract form and did not satisfy any of the criteria (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

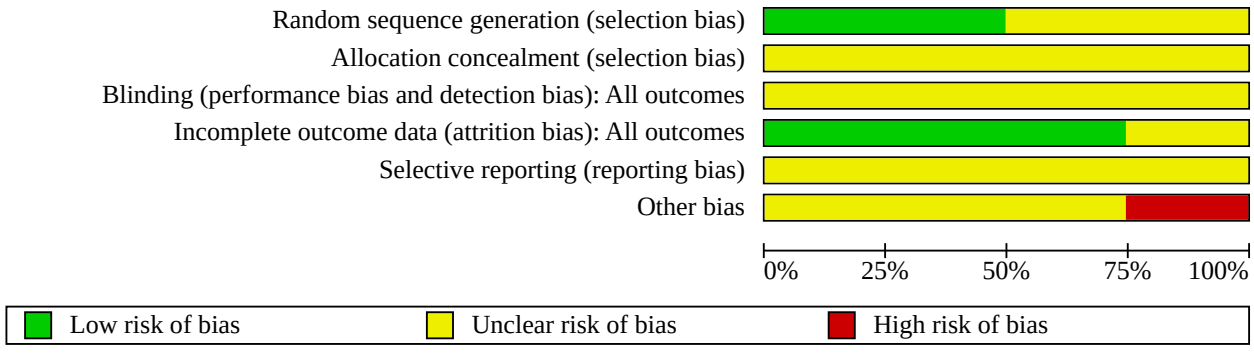
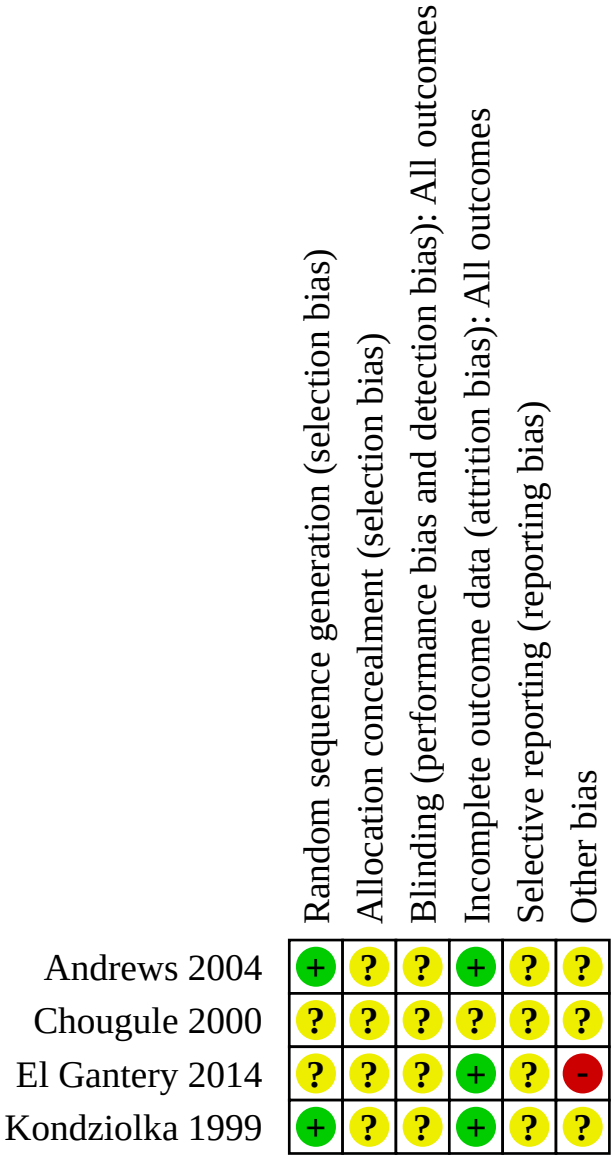


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Two trials (Andrews 2004; Kondziolka 1999) reported the method of generation of the sequence of random numbers used to allocate women to treatment arms, but did not report how they concealed the allocation sequence from participants and healthcare professionals involved in the trial. The El Gantery 2014 trial did not disclose the method of generating the allocation sequence or whether the allocation sequence was concealed from participants and healthcare professionals. In the trial of Chougule 2000 it was unclear whether the method of assigning participants to treatment groups was carried out using an adequate method of sequence generation and it was also unclear whether an attempt to conceal the allocation was made. None of the trials reported whether the outcome assessors were blinded. In three of the trials (Andrews 2004; El Gantery 2014; Kondziolka 1999) 100% of participants who were enrolled were assessed at end point, but this was unclear in the trial of Chougule 2000. There was insufficient information to permit judgment as to whether any of the trials reported all the outcomes that they assessed.

Other potential sources of bias: performance bias

The trials of Andrews 2004 and Kondziolka 1999 both indicated that participants were allowed to pursue further treatment upon tumor recurrence or progression, or both. Kondziolka 1999 presented outcomes of participants initially assigned to WBRT

alone, who later were treated with delayed salvage SRS as a third treatment group. Aside from this discrete cohort, neither trial clearly elaborated the number of participants who required further interventions or the extent of successive interventions. These successive treatments may confound interpretation of survival data. El Gantery 2014 did not indicate whether participants were allowed to pursue further treatment upon tumor recurrence or progression, or both. It was not certain whether any other bias may have been present in any of the four trials.

Effects of interventions

See: **Summary of findings 1** Whole brain radiation therapy (WBRT) + stereotactic radiosurgery (SRS) versus WBRT for the treatment of brain metastases

Overall survival

Using an HR to compare the survival experience of participants in the two treatment groups, a meta-analysis of two trials (Andrews 2004; Kondziolka 1999), assessing 358 participants, found no difference in OS between the WBRT plus SRS and the WBRT-alone groups (HR 0.82, 95% CI 0.65 to 1.02; Analysis 1.1). The percentage of the variability in effect estimates that was because of heterogeneity rather than by chance was not important (I^2 = 0%).

Subgroup analysis for overall survival

El Gantery 2014 reported a survival benefit in participants undergoing WBRT plus SRS (15 months) with tumors 3 cm or less in diameter compared with participants undergoing WBRT alone (5 months) (P = 0.002). Participants with controlled primary disease who received WBRT plus SRS (12 months) also demonstrated a survival benefit compared to WBRT alone (5.5 months) and SRS alone (8 months) (P = 0.027). The trials El Gantery 2014 and Andrews 2004 included and analyzed participants with one brain metastasis, but the El Gantery 2014 trial did not stratify their survival analysis based on treatment modality. For participants with one brain metastasis, Andrews 2004 showed that median survival was significantly longer in the WBRT-plus-SRS group (6.5 months) versus the WBRT-alone group (4.9 months) (P = 0.04). Similarly, Andrews 2004 analyzed RPA Class I participants separately and reported significantly longer survival in the WBRT-plus-SRS group (11.6 months) versus WBRT-alone group (9.6 months) (P = 0.045). El Gantery 2014 evaluated overall survival while adjusting for any previous chemotherapy and the RPA class but these correlations were insignificant. No such stratification was available in the other trials.

Disease-specific survival

Only Andrews 2004 reported data on DSS. Cause of death was ascertained in 149 out of 167 participants in the WBRT-alone group and 137 out of 164 participants in the WBRT-plus-SRS group. They found no significant difference in the risk of death from metastases of the brain in the WBRT-plus-SRS group (28%) compared to the WBRT-alone group (31%) (RR 0.92, 95% CI 0.64 to 1.32 (Analysis 1.2).

Local tumor control/failure

Local control was defined as unchanged or improved post-treatment MRI scans. When a treated tumor increased in size on follow-up MRI scan, it was deemed a local failure. Local control was assessed in all participants in the El Gantery 2014 trial, in 135 participants each in both treatment groups in the trial of Andrews 2004 and in all participants in the Kondziolka 1999 trial. The addition of SRS to WBRT increased local control of tumors in all the included studies. Meta-analysis of two trials (Andrews 2004; Kondziolka 1999), assessing 358 participants, found that participants receiving WBRT plus SRS had less chance of local failure than participants who received WBRT alone (HR 0.27, 95% CI 0.14 to 0.52) (Analysis 1.3). The percentage of the variability in effect estimates that was because of heterogeneity rather than by chance was not important (I^2 = 0%).

Functionally independent survival

Only the trial of Andrews 2004 reported on functional or performance status. This trial compared KPS scores before and six months after treatment (WBRT plus SRS or WBRT alone). At six months 75 participants in the WBRT-alone group and 79 in the WBRT-plus-SRS group were available for outcome assessment. KPS was assessed in 69 out of 75 participants at six months in the WBRT-alone group (six missing) and in 76 out of 79 participants in the WBRT-plus-SRS group (three missing). Participants who received WBRT plus SRS for treatment of brain metastases were associated with significantly (borderline) less chance of a worse KPS score at six months compared to those who received WBRT alone (RR 0.78, 95% CI 0.61 to 1.00; P = 0.05), although statistical significance was only marginally significant at the 5% level (Analysis 1.4).

Quality of life

None of the RCTs assessed or reported a QoL measure.

Steroid requirement

The trial of Andrews 2004 studied the need for steroids six months after treatment in both groups. Steroid requirement was assessed in 55 out of 75 participants at six months in the WBRT-alone group (20 missing) and in 63 out of 79 participants in the WBRT-plus-SRS group (13 missing). This trial found that participants who received WBRT plus SRS for treatment of brain metastases were associated with significantly less chance of prolonged steroid use compared to those who received WBRT alone (RR 0.64, 95% CI 0.42 to 0.97; P = 0.03) (Analysis 1.5).

Adverse events

Two trials (Andrews 2004; El Gantery 2014) reported treatment toxicities after WBRT plus SRS versus WBRT alone. The El Gantery 2014 trial evaluated acute (events that arose within 90 days from start of radiotherapy) and late toxicities (events that occurred three months after start of radiotherapy) in 21 participants in the WBRT plus SRS arm and 21 participants in the WBRT-alone arm. The WBRT-plus-SRS group reported >more than Grade 2 headaches in 9.5% of participants and neurologic worsening without CNS progression in 9.5% of participants. There was a 9.5% rate of greater than Grade 2 headaches and 4.8% rate of neurologic worsening in participants randomized to the WBRT- alone arm. With respect to chronic toxicities, El Gantery 2014 reported incidence of radiation necrosis, brain edema, and neurologic worsening without progression as 4.8%, 4.8% and 9.5% of participants within the WBRT-plus-SRS group. Participants in the WBRT-alone arm were reported to have brain edema and neurologic worsening in 4.8% and 4.8% of cases, respectively. The Andrews 2004 trial assessed acute and late toxicities in 166 and 112 participants, respectively, in the WBRT-alone group and 160 and 113 participants in the WBRT-plus-SRS group. Acute toxicities (within 90 days of treatment)

were similar in the WBRT-plus-SRS group versus WBRT-alone group. They most commonly included skin changes, nausea or vomiting, and CNS deficit or toxicity. In the WBRT-plus-SRS group 43% of participants reported Grade I toxicity, 18% reported Grade 2 toxicity, 2% Grade 3 toxicity and 1% Grade 4 toxicity. In comparison, 36% of participants with WBRT alone reported Grade I toxicity and 26% reported Grade 2 toxicity. Similarly, late toxicities did not differ between treatment groups and most commonly included CNS deficit/toxicity. The study concluded that acute and late toxicities did not increase significantly with the addition of SRS (Appendix 8).

Kondziolka 1999 reported no neurologic or systemic morbidity related to SRS and only commented that WBRT was associated with mild scalp erythema and hair loss.

DISCUSSION

Summary of main results

Overall, WBRT plus SRS did not significantly improve survival in people with brain metastases as compared to WBRT alone. Analysis of all included participants did not show a survival benefit from the addition of SRS to WBRT in either trial but there were survival benefits in subgroup analyses reported by the El Gantery 2014 and Andrews 2004 studies. El Gantery 2014 is a single-center RCT whose subgroup analysis showed that WBRT plus SRS (15 months) provided a survival benefit to participants with tumors 3 cm or less in diameter versus WBRT alone (5 months) (P = 0.002). Participants with controlled primary disease who received WBRT plus SRS (12 months) also demonstrated a survival benefit compared to WBRT alone (5.5 months) and SRS alone (8 months). The large, multicenter cohort in the trial of Andrews 2004 showed that WBRT plus SRS statistically improved median survival in participants with single, unresectable metastatic foci as compared to WBRT alone. Of note, only Andrews 2004 included and analyzed participants with single brain metastases. For participants with one brain metastasis, median survival was significantly longer in the WBRT-plus-SRS group (6.5 months) versus the WBRT-alone group (4.9 months). Additionally, Andrews 2004 analyzed RPA Class I participants separately and reported significantly longer survival in the WBRT-plus-SRS group (11.6 months) versus WBRT-alone (9.6 months). Participants with unresectable lesions (either located in deep gray matter or in areas of eloquent cortex) typically are treated with WBRT alone thereby missing the known advantage conferred by surgical resection plus WBRT. However, the data from this RCT suggests WBRT followed by radiosurgical boost similarly improves median survival in this oncologic niche.

In the analysis of all included participants, combined therapy improved local tumor control. Compared with WBRT alone, addition of SRS to WBRT increased local control of tumors in both studies included studies in the meta-analysis. When a treated tumor increased in size on follow-up MRI scan, it was deemed a local failure. Kondziolka 1999 discontinued their control treatment arm (WBRT alone) after interim analysis performed at the 60% accrual mark showed markedly improved local control in the combined treatment group. El Gantery 2014 showed that the WBRT-plus-SRS group (42.9%) had better local control at one year compared to the WBRT-alone group (19%) and SRS-alone group (22.2%). Similarly, Andrews 2004 reported a 43% greater risk of local recurrence with WBRT alone. Our analysis showed that participants receiving WBRT plus SRS had significantly lower local failures compared to WBRT alone.

One of the most important clinical measures of treatment efficacy is performance status or functional outcome. Andrews 2004 compared KPS scores before and six months after treatment (WBRT plus SRS or WBRT alone). Improvements in KPS scores was reported in the WBRT-plus-SRS group compared to the WBRT-alone group. Forty-three per cent of participants in the WBRT-plus-SRS group had unchanged or improved KPS at six months post-treatment versus only 28% in WBRT group. And although none of the trials indicated participant-reported measures of QoL, Andrews 2004 assessed the need for long-term steroid use after three months status post intervention. They found that 65% of participants in the WBRT-plus-SRS group had decreased steroid use (and most were not taking steroids) compared to 45% with decreased steroid use in the WBRT-alone group. Decreased steroid requirement likely diminishes the associated comorbidities of long-term steroid use including weight gain, poor glycemic control, and successive increase in cardiovascular risk and may contribute to a better QoL or functional status.

Treatment-related morbidity did not change significantly with the addition of SRS to WBRT. El Gantery 2014 reported no significant differences in acute or chronic toxicities between participants in the WBRT-plus-SRS group and participants in the WBRT-alone group. Kondziolka 1999 reported "no neurologic or systemic morbidity related to SRS" and only mild scalp erythema and hair loss associated with WBRT. Andrews 2004, reported similar rates of acute toxicities (within 90 days of treatment) across treatment groups. Most commonly reported side effects included skin changes, nausea/vomiting, and CNS deficit/toxicity. Similarly, late toxicities did not differ between treatment groups and most commonly included CNS deficit/toxicity. Andrews 2004 concluded that neither acute nor late toxicities increase significantly with the addition of SRS, further validating the addition of radiosurgical boost to WBRT without significant risk of harm to the patient.

Overall completeness and applicability of evidence

The Andrews 2004, El Gantery 2014 and Kondziolka 1999, trials were aimed at evaluating the precise question we were trying to answer in this review: is the addition of upfront SRS to WBRT better than WBRT alone? Kondziolka 1999 focused on local control as their primary outcome and their study was stopped because of the benefit seen in the WBRT-plus-SRS group. Therefore, their study was not powered to detect a difference in OS or any other outcomes. They did not assess functional outcome or QoL, which are extremely important primary outcomes in any palliative treatment. Andrews 2004 conducted a large well-designed multicenter RCT and appropriately evaluated many key outcomes including, OS, local control, performance status, steroid requirement, and cause of death. El Gantery 2014 was a single-institution RCT that evaluated OS, local control and treatment-related morbidity among participants receiving WBRT plus SRS, WBRT alone, and SRS alone. Neurocognitive performance and overall QoL was not assessed adequately in any trial and needs to be the focus of future investigations. Since SRS and WBRT may have different effects on cognition, especially in long-term survivors, it is imperative that future trials use neurocognitive performance as one of their primary end points. These results should change current practice of WBRT alone for all people with multiple brain metastases, and SRS should be added as upfront treatment for selected patients.

Quality of the evidence

Three RCTs, one large multicenter RCT (Andrews 2004) and two small single-institution RCTs (El Gantery 2014 and Kondziolka 1999), form the basis of our systematic review and its conclusions. Overall all studies had an unclear risk of bias and they satisfied at most only two of the criteria that we used to assess risk of bias. Given this risk of bias, the results and conclusions of our review have to be interpreted in the context of this uncertainty.

All three trials are consistent in showing that local control is superior in the WBRT-plus-SRS group compared to WBRT-alone group and that survival is similar in the two groups. The trial of Andrews 2004 assessed other outcomes such as performance status, steroid requirement, and cause of death. Conclusions based on these outcome measures are derived solely from this large multicenter RCT and may be prone to bias. For example, performance status was only assessed six months after treatment and hence may not accurately represent the performance status at other time points. Kondziolka 1999 and El Gantery 2014 did not investigate functional outcome, cognitive outcome, or QoL. Furthermore, the study by El Gantery 2014 could not be included in the meta-analysis due to lack of data available from the original trial team. Hence, the majority of the results and conclusions are based on a single large RCT (Andrews 2004), which limits the internal validity of this systematic review.

Potential biases in the review process

We performed a comprehensive search, including a thorough search of the gray literature, and at least two review authors independently sifted all the studies and extracted data. We restricted the included studies to RCTs as they provide the strongest level of evidence available. Hence, we have attempted to reduce bias in the review process. The greatest threat to the validity of the review is likely to be the possibility of publication bias, that is studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as the analyses were restricted to meta-analyses of a small number of trials or single trials.

Despite our best efforts, we were not able to get detailed data on one RCT (Chougule 2000), which was published in abstract form. Therefore, data from this trial were not available for meta-analysis.

Agreements and disagreements with other studies or reviews

Sanghavi 2001 reported improved survival in participants treated with WBRT plus SRS compared to WBRT alone in a large retrospective multi-institutional analysis. Participants with WBRT plus SRS and RPA Class I had median survival of 16.1 months versus 7.1 months ($P < 0.05$). This result is in disagreement with our review and all three RCTs included in this review. It is very likely that there was a strong selection bias in this retrospective analysis. No other outcomes, such as local control, were evaluated.

Li 2000, in a prospective non-RCT, evaluated outcomes in participants with single lung cancer metastasis. Three treatment groups, WBRT alone, SRS alone, and WBRT plus SRS, were compared. Similar to the Sanghavi 2001 study, Li 2000 reported longer median survival in participants who received WBRT plus SRS (10.6 months) versus WBRT alone (5.7 months) ($P < 0.0001$). Li 2000 reports superior local control and KPS along with a lower neurologic death rate in the WBRT-plus-SRS group compared to WBRT alone.

One retrospective study also reported a similar survival and local tumor control advantage in the WBRT-plus-SRS group compared to WBRT alone (Feng 2002).

The OS advantage seen in these retrospective studies is again likely to be because of a strong selection bias in a non-RCT setting. Local control, KPS, and cause of death data appear to agree with the results of the Andrews 2004 trial.

AUTHORS' CONCLUSIONS

Implications for practice

The conclusions we have presented are based on only three randomised controlled trials (RCTs). Since the last version of this review, one new study was found. The risk of bias in all of these trials was unclear. Therefore, our results and conclusions have to be interpreted in the context of unclear study bias. In an analysis of all included participants, whole brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) did not show an overall survival (OS) benefit over WBRT alone. However, local control and functional outcome were significantly better in the WBRT-plus-SRS group. Furthermore, significantly longer OS was reported in the combined treatment group when tumors where less than 3 cm in maximum diameter, in whom primary cancer was controlled, and in recursive partitioning analysis (RPA) Class I participants as well as participants with single metastasis. Finally, there was no increase in treatment toxicity with the addition of SRS to WBRT. Therefore, we conclude the following:

- people with tumors less than 3 cm in maximum diameter and in whom primary cancer is controlled should be treated with WBRT plus SRS;
- people with a single unresectable brain metastasis should be treated with WBRT plus SRS;
- people who are RPA Class I should be treated with WBRT plus SRS;
- people with two to four brain metastases should be treated with WBRT plus SRS on the basis of better functional outcome, local control, and decreased steroid requirement.

Implications for research

Further trials designed to have a low risk of bias and sufficient sample size are needed to affirm the results and conclusions of this systematic review. Future trials should also rigorously compare the QoL and cognitive performance of people undergoing WBRT plus SRS versus WBRT alone. Also, knowing the significant neurocognitive side effects of WBRT in long-term survivors, trials that omit upfront WBRT are being conducted.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andrews 2004

Study characteristics	
Methods	Multi-institutional, RCT Power = 0.8: study was designed to detect a 50% improvement in median survival for participants in the WBRT+SRS group
Participants	Inclusion criteria: patients 18 years of age or older with no previous cranial radiation. MRI confirmed contrast enhancing, 1-3 metastatic brain tumors < 4 cm in diameter Exclusion criteria: KPS < 70%, previous cranial radiation, brain stem metastasis or metastasis within 1 cm of optic apparatus, treatment of systemic cancer within 1 month, platelet count < 50,000 cells/µL, hemoglobin < 80 g/L, and absolute neutrophil count of < 1000 cells/µL This was the largest Phase III, multi-institutional trial with 331 total participants randomized to WBRT plus SRS or WBRT alone. Participants were stratified by number of brain metastases (1 versus 2-3) and extent of extracranial disease (none versus present)
Interventions	All participants received 37.5 Gy in 2.5-Gy daily fractions WBRT plus SRS: 164 participants included in analysis, 31 participants did not receive SRS. SRS dose prescribed per RTOG 90-05 trial WBRT: dose 37.5 Gy and all participants completed treatment
Outcomes	Primary outcome: median OS after randomization Secondary outcomes: 1. local control; 2. adverse events; 3. change in KPS; 4. cause of death; 5. steroid requirement
Notes	15% of participants allocated to the SRS group did not receive SRS (all participants in both groups received WBRT) At 3 months, in the WBRT-alone group (n = 167), 32 participants had died, 57 cases did not have appropriate follow-up scans and hence MRIs for only 78 participants (58%) were reviewed. In the WBRT +SRS group (n = 164), 29 participants had died at 3 months, 60 participants did not have appropriate follow-up scans, leaving 75 MRI (55%) sets for analysis Reporting bias is possible given cause of death and intracranial tumor progression was assessed by the treating physician at each participating institution

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation within strata by permutated blocks was done by use of computerized techniques at RTOG headquarters when member institutions telephoned to enrol eligible patients"
Allocation concealment (selection bias)	Unclear risk	There is no mention of allocation concealment in the manuscript
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported

Andrews 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	% analyzed in primary analyses: 331 out of 331 (100%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Chougule 2000

Study characteristics	
Methods	Single institution, RCT
Participants	Patients with MRI confirmed 1-3 brain metastases, tumor volume < 30 cc and minimum of 3-month life expectancy
Interventions	WBRT alone: 31 participants received 30 Gy in 10 fractions WBRT plus SRS: 37 participants, 30 Gy WBRT in 10 fractions plus GK SRS 20 Gy to the tumor margin
Outcomes	Primary outcome: median OS Secondary outcome: local control
Notes	Abstract form only. No difference in median OS was reported in the WBRT alone and WBRT plus SRS groups. Local control was reported as being superior in the WBRT+SRS group (91%) versus 62% in the WBRT-alone group. No other outcomes were evaluated in this trial. The abstract only reported median survival and local control in the different groups without providing P values or Kaplan-Meier analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgment
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

El Gantery 2014

Study characteristics	
Methods	Single institution, RCT Intention-to-treat analysis
Participants	This study randomized participants into 3 arms, 21 participants received WBRT, 18 participants received SRS, and 21 participants received WBRT plus SRS Inclusion criteria: patients with MRI-confirmed 1-3 brain metastases with a maximum diameter ≤ 4 cm derived from a histologically confirmed systemic cancer. Age ≤ 70 years, KPS ≥ 70%, ensured adequate organ function, no previous treatment for brain metastases Exclusion criteria: Age > 70, KPS < 70%
Interventions	The WBRT dosage schedule was 30 Gy in 10 fractions over 2 weeks The prescribed dose of SRS in the WBRT plus SRS arm ranged from 14 to 20 Gy (mean = 14.6 Gy, median = 14 Gy)
Outcomes	Median OS, local control, and adverse events
Notes	Steroid requirement, functional status, and quality of life were not assessed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants in each of the three treatment arms were analyzed
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	High risk	Small sample sizes in each treatment arm

Kondziolka 1999

Study characteristics	
Methods	Single institution RCT Power = 0.8: study was designed to detect a 40% increase in local control after WBRT plus SRS

Kondziolka 1999 *(Continued)*

Participants	Inclusion criteria: patients with 2-4 MRI-confirmed contrast-enhancing brain metastases with a biopsy-confirmed primary tumor. Tumor size ≤ 25 mm and > 5 mm from the optic chiasm. KPS ≥ 70% Exclusion criteria: KPS < 70%
Interventions	WBRT alone: 14 participants received 30 Gy in 12 fractions WBRT plus SRS: 13 participants received 30-Gy WBRT plus 16-Gy SRS to tumor margin
Outcomes	Primary: local tumor control Secondary: OS
Notes	The study was stopped at 60% accrual at interim evaluation. The interim analysis revealed a "significant benefit in the rate of local tumour control" after WBRT plus SRS. Local control was assessed at 1.5, 3, 6, 9, 12, 15, and 18 months. The rate of local failure was 100% at 1 year in the WBRT-alone group, "but only 8% in surviving patients who had SRS plus WBRT". No difference in OS was noted in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The method of randomization consisted of a coin toss at the initial clinic visit"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The data were collated and reviewed by an investigator independent from each treatment arm." It is unclear if the investigator assessing outcomes was blinded, it only notes that the investigator was independent
Incomplete outcome data (attrition bias) All outcomes	Low risk	% Analyzed in primary analyses: 27/27 (100%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgment
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

GK: Gamma Knife; KPS: Karnofsky Performance Status; MRI: magnetic resonance imaging; OS: overall survival; RCT: randomized controlled trial; RTOG: Radiation Therapy Oncology Group; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Feng 2002	Retrospective study, not an RCT
Li 2000	Prospective non-RCT. Evaluated outcomes in participants with single lung cancer metastasis. 3 treatment groups: WBRT alone, SRS alone, and WBRT plus SRS
Minniti 2010	Prospective non-RCT
Rades 2017	Non-RCT. This is a matched-pair analysis

Study	Reason for exclusion
Sanghavi 2001	Retrospective multi-institutional study, not an RCT
Sneed 2002	Retrospective cohort study, not an RCT. Evaluated SRS alone vs SRS plus WBRT
Sperduto 2013	RCT that evaluated WBRT plus SRS vs WBRT plus chemotherapy

DATA AND ANALYSES

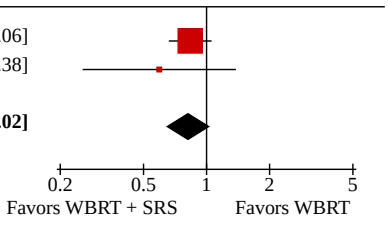
Comparison 1. WBRT plus radiosurgery versus WBRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	2	358	Hazard Ratio (IV, Random, 95% CI)	0.82 [0.65, 1.02]
1.2 Disease-specific survival	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.3 Local tumor control	2	358	Hazard Ratio (IV, Random, 95% CI)	0.27 [0.14, 0.52]
1.4 Functionally independent survival (KPS)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.5 Steroid use	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1: WBRT plus radiosurgery versus WBRT, Outcome 1: Overall survival

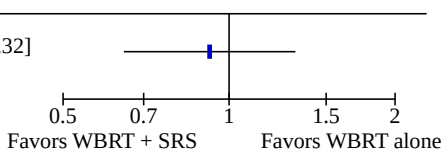
Study or Subgroup	log[Other]	SE	WBRT + SRS Total	WBRT Total	Weight	Other IV, Random, 95% CI
Andrews 2004	-0.18	0.12	164	167	92.8%	0.84 [0.66 , 1.06]
Kondziolka 1999	-0.52	0.43	13	14	7.2%	0.59 [0.26 , 1.38]
Total (95% CI)			**177**	**181**	**100.0%**	**0.82 [0.65 , 1.02]**

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: WBRT plus radiosurgery versus WBRT, Outcome 2: Disease-specific survival

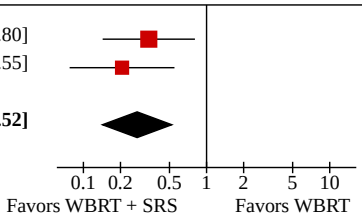
Study or Subgroup	WBRT + SRS Events	WBRT + SRS Total	WBRT Events	WBRT Total	Risk Ratio IV, Random, 95% CI
Andrews 2004	39	137	46	149	0.92 [0.64 , 1.32]



Analysis 1.3. Comparison 1: WBRT plus radiosurgery versus WBRT, Outcome 3: Local tumor control

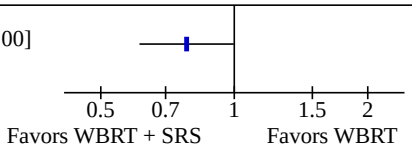
Study or Subgroup	log[Other]	SE	WBRT + SRS Total	WBRT Total	Weight	Other IV, Random, 95% CI
Andrews 2004	-1.08	0.44	164	167	56.4%	0.34 [0.14 , 0.80]
Kondziolka 1999	-1.58	0.5	13	14	43.6%	0.21 [0.08 , 0.55]
Total (95% CI)			**177**	**181**	**100.0%**	**0.27 [0.14 , 0.52]**

Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.93 (P < 0.0001)
Test for subgroup differences: Not applicable



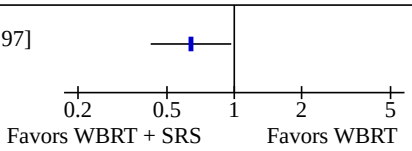
Analysis 1.4. Comparison 1: WBRT plus radiosurgery versus WBRT, Outcome 4: Functionally independent survival (KPS)

Study or Subgroup	WBRT + SRS Events	WBRT + SRS Total	WBRT Events	WBRT Total	Risk Ratio IV, Random, 95% CI
Andrews 2004	43	76	50	69	0.78 [0.61 , 1.00]



Analysis 1.5. Comparison 1: WBRT plus radiosurgery versus WBRT, Outcome 5: Steroid use

Study or Subgroup	WBRT + SRS Events	WBRT + SRS Total	WBRT Events	WBRT Total	Risk Ratio IV, Random, 95% CI
Andrews 2004	22	63	30	55	0.64 [0.42 , 0.97]



APPENDICES

Appendix 1. CENTRAL original search strategy

Cochrane Central Register of Controlled Trials (CENTRAL; 2009, Issue 2) in the Cochrane Library

1. exp central-nervous-system-neoplasms.tw.
2. metastasis.tw.
3. metastases.tw.
4. secondary.tw.
5. secondaries.tw.
6. OR/1-5
7. exp radiosurgery.tw.
8. radiosurg$.tw.
9. Stereotactic surgery.tw.
10. stereotaxic-techniques.tw.
11. stereotactic radiotherapy.tw.

12.OR 7-11
13.exp radiotherapy.tw.
14.radiation therapy.tw.
15.radiotherapy.tw.
16.irradiation.tw.
17.WBRT.tw.
18.OR 13-17
19.6 AND 12
20.18 AND 19

Appendix 2. MEDLINE (Ovid) original search strategy

1966 to 2009

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.animals.sh. not (humans.sh. and animals.sh.)
11.9 NOT 10
12.exp central nervous system neoplasm/
13.exp cerebral cortex/ab,pa,an,cy,su
14.exp Neoplasm Metastasis/
15.brain metastas$.mp.
16.intracranial tumo$.mp.
17.cerebral metastas$.mp.
18.(single adj3 metastas$).mp.
19.(solitary adj3 metastas$).mp.
20.12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
21.radiosurgery/
22.radiosurg$.mp.
23."stereotactic radiotherapy".mp.
24."stereotactic surgery".mp
25."stereotaxic technique$".mp.
26.21 OR 22 OR 23 OR 24 OR 25
27.exp radiotherapy/
28.radiotherapy.mp.
29.radiation therapy.mp.
30.irradiation.mp.
31.WBRT.mp.
32.27 OR 28 OR 29 OR 30 OR 31
33.11 AND 20 AND 26 AND 32

Appendix 3. Embase (Ovid) original search strategy

1980 to 2009

1. clinical trial/
2. controlled clinical trial/
3. multicenter study/

4. phase 2 clinical trial/
5. phase 3 clinical trial/
6. phase 4 clinical trial/
7. randomized controlled trial/
8. controlled study/
9. meta analysis/
10. crossover procedure/
11. double blind procedure/
12. single blind procedure/
13. randomization/
14. clinical study/
15. (clin$ adj25 trial$).tw.
16. ((singl$ or doubl$ or triple$ or treb$) adj25 (blind$ or mask$)).tw.
17. random$.tw
18. control$.tw
19. OR/1-18
20. limit 19 to human
21. brain neoplasm/
22. exp central nervous system tumor/
23. exp brain cortex/di,su
24. brain tumo?r.tw.
25. (metastasis).tw.
26. brain cancer/ or brain stem tumo$/ or brain tumo$/ or intracranial tumo$/ or posterior cranial fossa tumo$/
27. OR/21-26
28. stereotactic radiosurgery/ or stereotaxic surgery/
29. SRT/
30. radiosurgery/
31. gamma knife radiosurgery/
32. radiosurg$.tw
33. stereotactic radiotherapy.tw
34. OR/28-33
35. exp/radiotherapy/
36. irradiation/
37. WBRT/
38. OR/35-37
39. 27 AND 34
40. 38 AND 39
41. 20 AND 40

Appendix 4. CancerLit search strategy

1975 to 2009
This database was searched with the strategy outlined for MEDLINE

Appendix 5. CENTRAL updated search strategies

Cochrane Central Register of Controlled Trials (CENTRAL; 2012, Issue 5 to 2017, Issue 5) in the Cochrane Library

1. MeSH descriptor Central Nervous System Neoplasms explode all trees
2. ((brain* or cerebr* or intracranial or intra-cranial) adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or metasta* or secondar*))
3. (#1 OR #2)
4. MeSH descriptor Radiotherapy explode all trees
5. Any MeSH descriptor with qualifier: RT
6. (radiotherap* or radiat* or irradiat*)
7. WBRT

8. (#4 OR #5 OR #6 OR #7)
9. MeSH descriptor Stereotaxic Techniques explode all trees
10. (radiosurg* or (stereota* and (technique* or surg* or radiotherap*)))
11. (#9 OR #10)
12. (#3 AND #8 AND #11)

Appendix 6. MEDLINE (Ovid) updated search strategy

2009 to May week 1 2017

1. exp Central Nervous System Neoplasms/
2. ((brain* or cerebr* or intracranial or intra-cranial) adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or metasta* or secondar*)).mp.
3. 1 or 2
4. exp Radiotherapy/
5. radiotherapy.fs.
6. (radiotherap* or radiat* or irradiat*).mp.
7. WBRT.mp.
8. 4 or 5 or 6 or 7
9. exp Stereotaxic Techniques/
10. (radiosurg* or (stereota* and (technique* or surg* or radiotherap*))).mp.
11. 9 or 10
12. 3 and 8 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. clinical trials as topic.sh.
18. randomly.ab.
19. trial.ti.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 12 and 20

key:
mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt = publication type
ab = abstract
ti = title

Appendix 7. Embase (Ovid) updated search strategies

2009 to 2017 week 20

1. exp central nervous system tumor/
2. ((brain* or cerebr* or intracranial or intra-cranial) adj5 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or metasta* or secondar*)).mp.
3. 1 or 2
4. exp radiotherapy/
5. rt.fs.
6. (radiotherap* or radiat* or irradiat*).mp.
7. WBRT.mp.
8. 4 or 5 or 6 or 7
9. exp radiosurgery/
10. exp stereotactic procedure/
11. (radiosurg* or (stereota* and (technique* or surg* or radiotherap*))).mp.
12. 9 or 10 or 11
13. 3 and 8 and 12
14. crossover procedure/
15. double-blind procedure/
16. randomized controlled trial/
17. single-blind procedure/
18. random*.mp.
19. factorial*.mp.

20. (crossover* or cross over* or cross-over*).mp.
21. placebo*.mp.
22. (double* adj blind*).mp.
23. (singl* adj blind*).mp.
24. assign*.mp.
25. allocat*.mp.
26. volunteer*.mp.
27. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 13 and 27

key:
[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 8. Central nervous system toxicity grading

	Grade 1	Grade 2	Grade 3	Grade 4
Motor	No weakness or no change	Subjective weakness/no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function
Sensory	None or no change	Mild paresthesias or loss of deep tendon reflexes	Mild to moderate objective sensory loss/paresthesias	Severe objective sensory loss or paresthesias that interfere with function

WHAT'S NEW

Date	Event	Description
10 June 2020	Review declared as stable	No longer updated as research area no longer active. Clinical research trend is now more towards whole brain radiotherapy with or without hippocampal avoidance.

HISTORY

Protocol first published: Issue 3, 2006
Review first published: Issue 6, 2010

Date	Event	Description
18 July 2017	New citation required but conclusions have not changed	One new study met the inclusion criteria but was not included in the meta-analysis due to lack of data from the original trial team.
18 July 2017	New search has been performed	Searches updated in May 2017
7 August 2012	New citation required but conclusions have not changed	1. Since the last version of this review no new studies were found; therefore, changes to this update were minimal. 2. The search was updated to include studies published from 2009 to 2012 from the following electronic databases: CENTRAL, MEDLINE, and EMBASE.

Date	Event	Description
		3. One new excluded study was added in this review: Minniti 2010. This is a prospective, non-RCT and does not meet the current study's inclusion criteria. 4. There are no additional participants that are part of the review. 5. No further analyses were necessary in this review. 6. The updated search has not altered the conclusions from the last publication of this review. Given that no new RCTs were included in this review, we feel that it is low-priority for previous readers of the review to re-read this update.
5 July 2012	New search has been performed	1. Electronic search methods section updated. 2. Added appendices 3 and 4.

CONTRIBUTIONS OF AUTHORS

CP had the original idea for the protocol and helped review initial drafts of the protocol and prepared the final review.
SG designed and wrote the protocol in collaboration with CP and helped prepare the final review.
KP helped with the search and in preparing the final review.
AB helped with the analysis and preparation of the final review.
JMS helped with the search and in preparing the final review.
KB was the senior mentor who helped CP with the initial drafts of the review, gave expert opinion, and helped edit the review.

DECLARATIONS OF INTEREST

Chirag G Patil: None known
Katie Pricola: None known
J Manuel Sarmiento: None known
Sachin K Garg: None known
Andrew Bryant: None known
Keith L Black: Relevant financial activities outside the submitted work include employment with Cedars-Sinai Medical Center, board membership and stock ownership in Neurovision, Black Light Surgical, and Arrogene.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- None, Other

INDEX TERMS

Medical Subject Headings (MeSH)

Brain Neoplasms [mortality] [*radiotherapy] [*secondary]; Combined Modality Therapy [methods] [mortality]; Cranial Irradiation [*methods] [mortality]; Karnofsky Performance Status; Radiosurgery [*methods] [mortality]; Randomized Controlled Trials as Topic; Steroids [therapeutic use]

MeSH check words

Adult; Humans