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

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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

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A B S T R A C T

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 radiosurgery to WBRT is unclear.

Objectives

To assess the efficacy of WBRT plus radiosurgery versus WBRT alone in the treatment of of brain metastases.

Search strategy

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2009), MEDLINE (1966 to 2009), EMBASE (1980 to 2009) and CancerLit (1975 to 2009) in order to identify trials for inclusion in this review.

Selection criteria

The review was restricted to randomised controlled trials (RCTs) that compared use of radiosurgery and WBRT versus WBRT alone for upfront treatment of adult patients with newly diagnosed metastases (single or multiple) in the brain resulting from any primary, extracranial cancer

Data collection and analysis

The Generic Inverse Variance method, random effects model in RevMan 5 was used for the meta-analysis.

Main results

A meta-analysis of two trials with a total of 358 participants, found no statistically significant difference in overall survival (OS) between WBRT plus radiosurgery and WBRT alone groups (HR = 0.82, 95% CI 0.65 to 1.02). For patients with one brain metastasis median survival was significantly longer in WBRT plus SRS group (6.5 months) versus WBRT group (4.9 months, P = 0.04). Patients in the WBRT plus radiosurgery group had decreased local failure compared to patients who received WBRT alone (HR = 0.27, 95% CI 0.14

to 0.52). Furthermore, a statistically significant improvement in performance status scores and decrease in steroid use was seen in the WBRT plus SRS group. Unchanged or improved KPS at 6 months was seen in 43% of patients in the combined therapy group versus only 28% in WBRT group (P = 0.03). Overall, risk of bias in the included studies was unclear.

Authors' conclusions

Given the unclear risk of bias in the included studies, the results of this analysis have to be interpreted with caution. Analysis of all included patients, 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 RPA Class I patients as well as patients with single metastasis.

PLAIN LANGUAGE SUMMARY

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

We identified three RCTs that looked at whether adding focused radiation (radiosurgery) to whole brain radiation therapy (WBRT) is beneficial to patients with brain metastases. Most of our conclusions are based on the results of one large trial with unclear prejudice and therefore, we cautiously make the following remarks: We found that when radiosurgery is added to WBRT, there was no evidence to suggest that patients lived any longer than if they had WBRT alone, except for patients with only one brain metastasis (who may live longer if they receive the combination treatment). Patients in the combination treatment also seemed to function better in daily life, their treated tumours were associated with having less chance of growing back and patients had to take less steroid medication. The side effects of combined therapy and WBRT alone were similar.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

WBRT + Radiosurgery versus WBRT for the treatment of brain metastases

Patient or population: patients with the treatment of brain metastases
Settings: Inpatients or outpatient
Intervention: WBRT + Radiosurgery 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 + Radiosurgery versus WBRT				
Overall Survival Follow-up: 12 months[1]	**Study population**		**HR 0.82** (0.65 to 1.02)	358 (2 studies[3])	⊕⊕⊕○ **moderate**[2]	
	762 per 1000	**692 per 1000** (607 to 769)				
	Medium risk population					
	773 per 1000	**704 per 1000** (619 to 780)				
Overall Survival Follow-up: 24 months[4]	**Study population**		**HR 0.82** (0.65 to 1.02)	358 (2 studies[3])	⊕⊕⊕○ **moderate**[2]	
	912 per 1000	**864 per 1000** (794 to 916)				
	Medium risk population					
	952 per 1000	**917 per 1000** (861 to 955)				
Death due to brain metastasis	**Study population**		**RR 0.92** (0.64 to 1.32)	286 (1 study[3])	⊕⊕⊕○ **moderate**[2]	

	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[3])	⊕⊕⊕○ **moderate**[2]	
	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)	145 (1 study[3])	⊕⊕⊕○ **moderate**[2]	
	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[3])	⊕⊕○○ **low**[2]	
	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; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 12 months was used to calculate baseline rates, since we used a HR in the main analysis.
[2] Estimate is imprecise as there is a fair degree of uncertainty in the pooled estimate as indicated by 95% confidence interval.
[3] 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.
[4] 24 months was used to calculate baseline rates, since we used a HR in the main analysis.

BACKGROUND

Description of the condition

Approximately 20 to 40% of patients with cancer will go on to develop brain metastases (Andrews 2004; Hasegawa 2003). Primary tumour 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 patients 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 2003). 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 neuro-cognitive impairments (Hasegawa 2003). Two RCTs of patients with solitary brain metastasis have shown that combined treatment of surgical resection (craniotomy) with WBRT improved survival rates and led to greater local tumour control than WBRT alone (Flickinger 1994; Pirzkall 1998). It has since been suggested radiosurgery and WBRT together can produce similar results (Sneed 1999). Radiosurgery, 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 tumour control and can be used to treat multiple tumours 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. Today, stereotactic radiosurgery 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 radiosurgery in the management of patients with brain metastases has become critical.

OBJECTIVES

To assess the efficacy of WBRT plus radiosurgery versus WBRT alone in the treatment of adult patients with brain metastases.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised Controlled Trials (RCTs)

Types of participants

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

Types of interventions

Intervention:

- WBRT with radiosurgery 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 randomisation.
- 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 tumour control, as defined by either a complete response, partial response or stable response of all metastases known at time of randomisation
- Adverse events (radiation necrosis, new neurological deficit, peritumoral oedema)
- Neurological performance
- Quality of life (QoL), measured using a validated scale
- Steroid requirement

Search methods for identification of studies

Papers in all languages were sought and translations carried out where necessary.

Electronic searches

The following electronic databases were searched in the following order to identify trials for inclusion in this review: Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2, 2009); MEDLINE (1966 to 2009) including CancerLit (1975 to 2009); EMBASE (1980 to 2009). A standard strategy was employed to search each electronic database. Three separate search buckets were independently created using the 'OR' operator. These buckets focused on identifying RCTs, diseases of interest and interventions of interest. All three buckets were then combined using the 'AND' operator to yield the final data bucket. Duplicates and non-human applications were then eliminated from this bucket. Please Note: Elements of the search strategies have been adopted from those detailed in Hart 2004.
For MEDLINE (1966 to 2009) search strategy see Appendix 1: Terms 1 to 10 were originally devised and have been revised by Carol Lefebvre and Steve McDonald at the UK Cochrane Centre for the identification of all randomised and clinical controlled trials. For further source detail, please reference the Higgins 2009. For databases other than MEDLINE, the search strategy was adapted accordingly. For full list of all electronic databases see Appendix 2.
All relevant articles found were identified on PubMed and using the 'related articles' feature, a further search was carried out for newly published articles.
The search strategies used have been developed and executed by the author team.

Searching other resources

Unpublished and Grey literature

Metaregister (mRCT), Physicians Data Query, www.controlled-trials.com/
rct, www.clinicaltrials.gov and www.cancer.gov/clinicaltrials were searched for ongoing trials. The main investigators of any relevant ongoing trials were contacted for further information, as were any major co-operative trials groups active in this area.

Reference lists and correspondence

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

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference management database Endnote, duplicates were removed and the remaining references were examined by two review authors (KP, CP) independently. Authors were not blinded to the author or affiliations of the studies. Those studies which clearly did not meet the inclusion criteria were excluded and copies of the full text of potentially relevant references were obtained. The eligibility of retrieved papers were assessed independently by two review authors (KP, CP). Disagreements were resolved by discussion between the two review authors. Reasons for exclusion are documented.

Data extraction and management

For included trials, data were abstracted as recommended in Chapter 7 of the Higgins 2009. 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
  - patient characteristics
  - age
  - sex
  - co-morbidities
  - previous treatment
  - neurological performance
  - primary cancer type
- Brain metastases details at diagnosis
  - size of metastases (including largest)
  - number of brain metastases
  - tumour histology
- Intervention details
  - details of SRS
    - type
    - dose
    - fractions
    - maximum radiosurgical dose (Dmax)
    - dose to the tumour 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, functionally independent survival, local tumour control, cause of death, steroid requirement and adverse events.
  - OS
    - definition: OS was measured from date of randomisation 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 tumour control
    - Local tumour control was defined as decrease or no change in tumour size as judged by serial post-treatment MRI scans
  - DSS
    - Definition: Death due to neurological cause i.e., due to brain metastasis
  - steroid requirement
    - Steroid requirement was measured as unchanged, improved or worsened
    - Patients 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, neurological and other toxicities. These were graded as per the RTOG CNS toxicity criteria (Appendix 3).

Data on outcomes were be extracted as below

- For time to event (e.g. OS, DSS and local tumour 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 patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, 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 patients assessed at endpoint 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 standardised 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 analysed in groups to which they were assigned.
The time points at which outcomes were collected and reported was noted.
Data were abstracted independently by two review authors (KP, CP) onto a data abstraction form specially designed for the review. Differences between review authors was resolved by discussion or by appeal to a third review author if necessary.

Assessment of risk of bias in included studies

Risk of bias in included RCTs was assessed using the following questions and criteria (see Chapter 8 of Higgins 2009):

Sequence generation

Was the allocation sequence adequately generated?
- Yes, e.g. a computer-generated random sequence or a table of random numbers
- No, e.g. date of birth, clinic id-number or surname
- Unclear, e.g. not reported

Allocation concealment

Was allocation adequately concealed?
- Yes, e.g. where the allocation sequence could not be foretold
- No, e.g. e.g. allocation sequence could be foretold by patients, investigators or treatment providers
- Unclear, e.g. 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 patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms
- No, if more than 20% of patients 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, e.g., 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

The risk of bias tool was applied independently by two review authors (KP, CP) and differences were resolved by discussion. Results are presented in both a risk of bias graph and a risk of bias summary. Results of meta-analyses were interpreted 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

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot 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, the possible reasons for this were investigated and reported.

Assessment of reporting biases

Reporting biases were not assessed 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 their results were pooled in meta-analyses.

- For time-to-event data, HRs were pooled using the generic inverse variance facility of RevMan 5.
- For dichotomous outcomes, the RR was calculated for each study and these were then pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences were pooled.

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

Subgroup analysis and investigation of heterogeneity

Factors such as age, number of metastases, length of follow-up, were considered in interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analysis was not performed as there were an insufficient number of trials in the review.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search strategy identified 482 references in MEDLINE including Cancer-Lit, 1961 in EMBASE and 38 in CENTRAL. Reference lists and correspondence did not produce any additional studies. A total of seven articles were retrieved in full. The full text screening of these seven references excluded four studies for the reasons described in the table Characteristics of excluded studies. The remaining three RCTs (two full articles and one abstract) met our inclusion criteria and are described in the table Characteristics of included studies, but only two were included in the analysis. Searches of the grey literature did not identify any additional relevant trials.

Included studies

Three RCTs met our inclusion criteria. Chougule 2000 was presented in abstract form only and included 109 patients who were randomised into WBRT only, WBRT plus stereotactic radiosurgery (SRS) and SRS only groups. No difference in overall median survival was reported in the WBRT only and WBRT plus SRS groups. Local control was reported as being superior in the WBRT plus SRS group (91%) versus 62% in the WBRT only 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. Further details about the trial could not be obtained from the authors. Hence, this RCT was not included in the current meta-analysis.

Our meta-analysis included two trials (Andrews 2004; Kondziolka 1999) which randomised a total of 358 participants all of whom 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 patients who received WBRT plus SRS (n = 164) versus WBRT only (n = 167). This trial included adult patients with 1 to 3 brain metastases with KPS > 70. Outcomes reported included OS, local control, KPS, cause of death, steroid requirement and neurological performance. OS was stratified for patients with 1 metastasis and greater than 1 metastasis. In addition Andrews 2004 stratified survival according to recursive partitioning analysis (RPA) class. RPA class prognosticates survival and outcomes in patients with brain metastases. RPA Class 1 patients are those who have a KPS> = 70, controlled primary status, age less than 65, and have no extracranial disease. Andrews 2004 analysed RPA Class I patients 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.

Kondziolka 1999 was a single institution RCT which was stopped following an interim analysis of 27 patients that revealed a significant benefit in the rate of local control in the WBRT plus SRS group. This trial included patients with 2 to 4 brain metastases that were less than or equal to 25mm. Local tumour 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 statistically significant difference in local control of tumours in the WBRT plus SRS group compared to WBRT only group. Survival was similar in both groups.

Please refer to the section Characteristics of included studies below for details.

Excluded studies

The full text was obtained for four additional references, but all were excluded from the review for the reasons given in Characteristics of excluded studies.

None of the four excluded studies were RCTs. Feng 2002, Sanghavi 2001 and Sneed 2002 were retrospective studies and Li 2000 was a prospective non-RCT.

Risk of bias in included studies

All three trials (Andrews 2004; Chougule 2000; 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 didn't satisfy any of the criteria (Figure 1; Figure 2).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

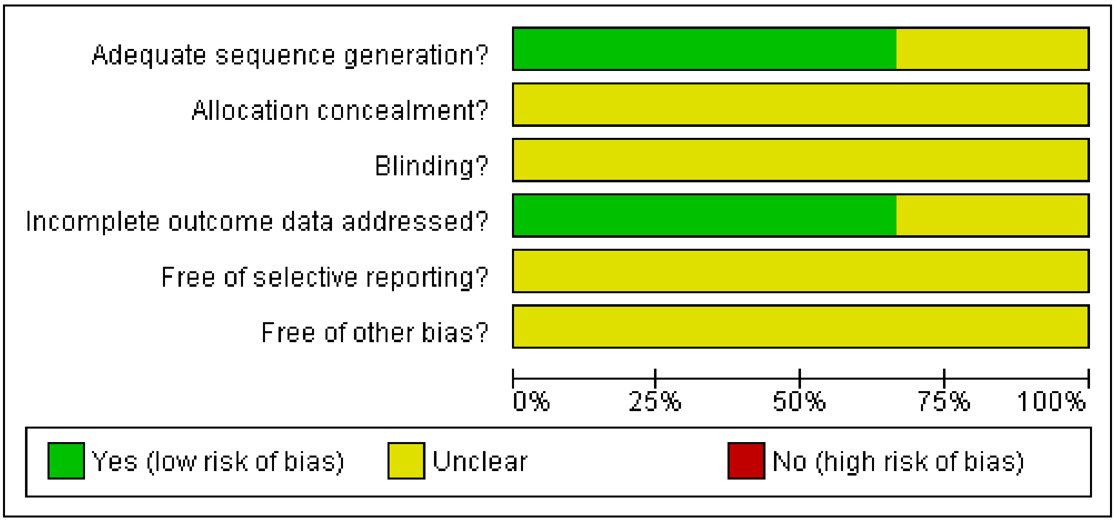
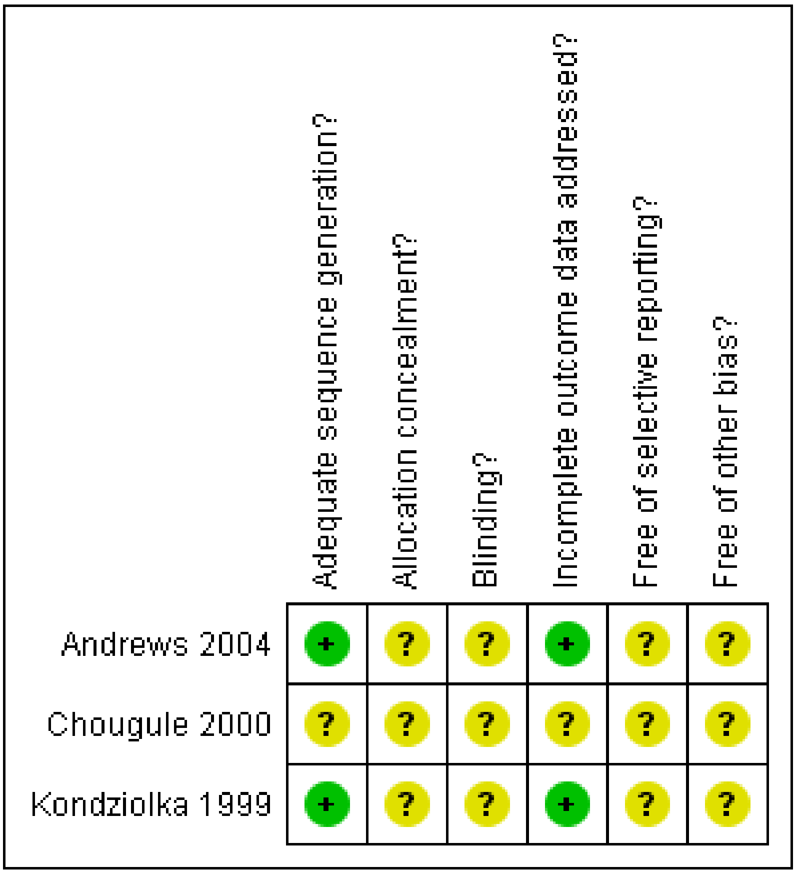


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



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 concealment of this allocation sequence from patients and healthcare professionals involved in the trial was not reported. In the trial of Chougule 2000 it was unclear whether the method of assigning patients 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 two of the trials (Andrews 2004; Kondziolka 1999) 100% of patients who were enrolled were assessed at endpoint, but this was unclear in the trial of Chougule 2000. There was insufficient information to permit judgement 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 indicate that participants were allowed to pursue further treatment upon tumour recurrence and/or progression. Kondziolka 1999 presents outcomes of patients initially assigned to WBRT alone who later were treated with delayed salvage radiosurgery as a third treatment group. Aside from this discreet cohort, neither trial clearly elaborates the number of patients who required further interventions nor the extent of successive interventions. These successive treatments may confound interpretation of survival data. It was not certain whether any other bias may have been present in any of the three trials.

Effects of interventions

See: **Summary of findings for the main comparison** SoF table

Overall Survival

Using a HR to compare the survival experience of women in the two treatment groups, a meta-analysis of two trials (Andrews 2004; Kondziolka 1999), assessing 358 participants, found no statistically significant difference in overall survival between the WBRT plus radiosurgery 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 is due to heterogeneity rather than by chance is not important (I^2 = 0%).

Subgroup Analysis for Overall Survival

Only the trial of Andrews 2004 included and analysed patients with one brain metastasis. For patients with one brain metastasis, median survival was significantly longer in the WBRT plus SRS group (6.5 months) versus the WBRT group (4.9 months), P = 0.04. Similarly, Andrews 2004 analysed RPA Class I patients 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 trials.

Disease-specific Survival

Only Andrews 2004 reported data on disease specific survival. Cause of death was ascertained in 149 out of 167 participants in the WBRT group and 137 out of 164 patients 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 only group (31%) (RR = 0.92 95% CI: 0.64 to1.32, Analysis 1.2).

Local Tumor Control/Failure

Local control was defined as unchanged or improved post treatment MRI scans. When a treated tumour increased in size on follow-up MRI scan, it was deemed a local failure. Local control was assessed 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 tumours in both the included studies. Meta-analysis of two trials (Andrews 2004; Kondziolka 1999), assessing 358 participants, found patients receiving WBRT plus radiosurgery had less chance of local failure than patients 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 is due to heterogeneity rather than by chance is 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 only). At 6 months 75 participants in WBRT group and 79 in WBRT plus SRS were available for outcome assessment. KPS was assessed in 69 out of 75 participants at 6 months in WBRT group (6 missing) and in 76 out of 79 participants in the WBRT plus SRS group (3 missing). Patients who received WBRT plus radiosurgery 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 6 months in WBRT group (20 missing) and in 63 out of 79 participants in the WBRT plus SRS group (13 missing). This trial found that patients who received WBRT plus radiosurgery 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

One trial (Andrews 2004) reported treatment toxicities after WBRT plus SRS versus WBRT only. Acute and late toxicities were assessed in 166 and 112 participants respectively in the WBRT 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 only group. They most commonly included skin changes, nausea or vomiting and central nervous system (CNS) deficit or toxicity. 43% of patients in the WBRT plus SRS group reported Grade I toxicity, 18% reported Grade 2 toxicity, 2% Grade 3 toxicity and 1% Grade 4 toxicity. In comparison, 36% of patients with WBRT only reported Grade I toxicity and 26% reported Grade 2 toxicity. Similary 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 3).

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 radiosurgery did not significantly improve survival in patients with brain metastases as compared to WBRT alone. Analysis of all included patients, neither trial showed a survival benefit from the addition of SRS to WBRT but there was a survival benefit reported by the trial of Andrews 2004 for patients with a single metastasis and for patients that were RPA class I. The large, multicenter cohort in the trial of Andrews 2004 showed that WBRT plus radiosurgery statistically improves median survival in patients with single, unresectable metastatic foci as compared to WBRT alone. Of note, only Andrews 2004 included and analysed patients with single brain metastases. For patients with one brain metastasis, median survival was significantly longer in the WBRT plus SRS group (6.5 months) versus the WBRT group (4.9 months). Additionally, Andrews 2004 analysed RPA Class I patients separately and reported significantly longer survival in the WBRT plus SRS group (11.6 months) versus WBRT (9.6 months). Patients with unresectable lesions- either located in deep grey 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 randomised clinical trial suggests WBRT followed by radiosurgical boost similarly improves median survival in this oncologic niche. Analysis of all included patients, combined therapy improved local tumour control. As compared to WBRT alone, addition of SRS to WBRT increased local control of tumours in both the included studies. When a treated tumour 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. Similarly, Andrews 2004 reported a 43% greater risk of local recurrence with WBRT alone. Our analysis showed that patients receiving WBRT plus SRS were found to have 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 only). Statistically significant improvement in KPS scores was reported in the WBRT plus SRS group compared to the WBRT only group. Fourty-three percent of patients 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 aforementioned clinical trials indicated patient reported measures of QoL, Andrews 2004 assessed the need for long-term steroid three months status post-intervention. They found that 65% of patients 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 group. Decreased steroid requirement likely diminishes the associated co-morbidities of long-term steroid use including weight gain, poor glycaemic 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 radiosurgery to WBRT. 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 central nervous system (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 Kondziolka 1999 and Andrews 2004 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, cause of death. Neurocognitive performance and overall quality of life was not assessed adequately in either 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 point. These results should change current practice of WBRT only for all patients with multiple brain metastases and radiosurgery should be added as upfront treatment for selected patients.

Quality of the evidence

Two RCTs, one large multicenter RCT (Andrews 2004) and a small single institution RCT (Kondziolka 1999) form the basis of our systematic review and its conclusions. Overall both 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.

Both trials are consistent in showing that local control is superior in the WBRT plus SRS group compared to WBRT only group and that survival of all-comers 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 only used local control as their primary end-point in a small RCT and did not investigate functional outcome, cognitive outcome or QoL. 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

A comprehensive search was performed, including a thorough search of the grey literature and all studies were sifted and data extracted by at least two review authors independently. 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 i.e. 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 was not available for meta-analysis.

Agreements and disagreements with other studies or reviews

Sanghavi 2001 reported improved survival in patients treated with WBRT plus SRS compared to WBRT alone in a large retrospective multi-institutional analysis. Patients 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 patients with single lung cancer metastasis. Three treatment groups used WBRT only, SRS only and WBRT plus SRS were compared. Similar to the Sanghavi 2001 study, Li 2000 reported longer median survival in patients who received WBRT plus SRS (10.6 months) versus WBRT only (5.7 months, $P < 0.0001$). Li 2000 reports superior local control and KPS along with a lower neurological death rate in the WBRT plus SRS group compared to WBRT alone.

In a retrospective study also report a similar survival and local tumour control advantage in the WBRT plus SRS group compared to WBRT only (Feng 2002).

The OS advantage seen in these retrospective studies is again likely due to 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 are presenting are based on only two RCTs. The risk of bias in both these trials was unclear. Therefore, our results and conclusions have to be interpreted in the context of unclear study bias. Analysis of all included patients, SRS plus WBRT, did not show a survival benefit over WBRT alone. However, local control and functional outcome were significantly better in the SRS plus WBRT group. Furthermore, significantly longer OS was reported in the combined treatment group for RPA Class I patients as well as patients with single metastasis. Finally, there was no increase in treatment toxicity with the addition of SRS to WBRT. Therefore, we conclude the following:

1. Patients with a single unresectable brain metastases should be treated with SRS plus WBRT.

2. Patients who are RPA class I should be treated with SRS plus WBRT

3. Patients with 2 to 4 brain metastases should be treated with SRS plus WBRT 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 patients undergoing WBRT plus SRS versus WBRT alone. Also, knowing the significant neurocognitive side effects of WBRT in long-term survivors, trials that omit up-front 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

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

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	'Randomisation within strata by permutated blocks was done by use of computerised techniques at RTOG headquarters when member institutions telephoned to enrol eligible patients.'

Andrews 2004 (*Continued)*

Allocation concealment?	Unclear	There is no mention of allocation concealment in the manuscript.
Blinding? All outcomes	Unclear	Not reported
Incomplete outcome data addressed? All outcomes	Yes	% analysed in primary analyses: 331 out of 331 (100%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Chougule 2000

Methods	Single Institution, RCT
Participants	Patients with MRI confirmed 1 to 3 brain metastases, tumour volume less than 30 cc and minimum of 3 month life expectancy.
Interventions	WBRT alone: 31 patients received 30 Gy in 10 fractions. WBRT plus SRS: 37 patients, 30Gy WBRT in 10 fractions plus Gamma Knife (GK) SRS 20 Gy to the tumour margin
Outcomes	Primary: Overall median survival Secondary: Local control
Notes	Abstract form only. No difference in overall median survival was reported in the WBRT only and WBRT plus SRS groups. Local control was reported as being superior in the WBRT plus SRS group (91%) versus 62% in the WBRT only 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information to permit judgement
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? All outcomes	Unclear	Insufficient information to permit judgement

Incomplete outcome data addressed? All outcomes	Unclear	Insufficient information to permit judgement
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Kondziolka 1999

Methods	Single institution RCT Power = 0.8: Study was designed to detect a 40% increase in local control after WBRT plus SRS
Participants	Inclusion criteria: Patients with 2 to 4 MRI confirmed contrast enhancing brain metastases with a biopsy proven primary tumour. Tumor size 25mm or less and > 5mm from the optic chiasm. KPS >= 70 Exclusion criteria: KPS < 70
Interventions	WBRT only: 14 patients received 30 Gy in 12 fractions. WBRT plus SRS: 13 patients received 30 Gy WBRT plus 16 Gy SRS to tumour margin.
Outcomes	Primary: Local Tumor Control Secondary: Overall survival
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 overall survival was noted in both groups.

Risk of bias

Item	Authors’ judgement	Description
Adequate sequence generation?	Yes	“The method of randomization consisted of a coin toss at the initial clinic visit”
Allocation concealment?	Unclear	Insufficient information to permit judgement
Blinding? All outcomes	Unclear	“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.

Kondziolka 1999 (*Continued)*

Incomplete outcome data addressed? All outcomes	Yes	% analysed in primary analyses: 27 out of /27 (100%)
Free of selective reporting?	Unclear	Insufficient information to permit judgement
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

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

Feng 2002	Retrospective study, not an RCT.
Li 2000	Prospective non-RCT. Evaluated outcomes in patients with single lung cancer metastasis. Three treatment groups WBRT only, SRS only and WBRT plus SRS.
Sanghavi 2001	Retrospective multi-institutional study, not an RCT.
Sneed 2002	Retrospective cohort study, not an RCT. Evaluated SRS alone versus SRS plus WBRT.

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 Overall Survival	2	358	Hazard Ratio (Random, 95% CI)	0.82 [0.65, 1.02]
2 Death due to brain metastasis	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3 Local Tumor Control	2	358	Hazard Ratio (Random, 95% CI)	0.27 [0.14, 0.52]
4 Functionally Independent Survival (KPS)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
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.

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

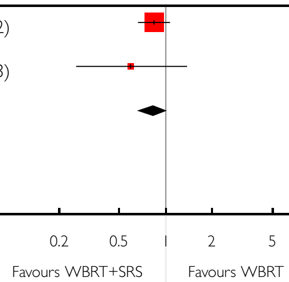
Comparison: 1 WBRT plus Radiosurgery versus WBRT

Outcome: 1 Overall Survival

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

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.58$, df = 1 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 1.77 (P = 0.077)



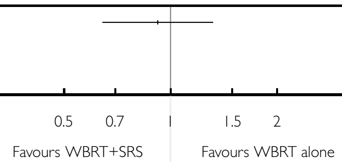
Analysis 1.2. Comparison 1 WBRT plus Radiosurgery versus WBRT, Outcome 2 Death due to brain metastasis.

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

Comparison: 1 WBRT plus Radiosurgery versus WBRT

Outcome: 2 Death due to brain metastasis

Study or subgroup	WBRT + SRS n/N	WBRT n/N	Risk Ratio IV,Random,95% CI	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.

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

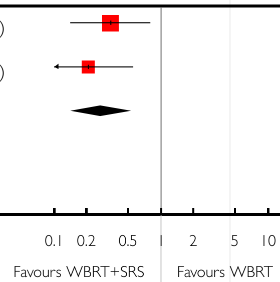
Comparison: 1 WBRT plus Radiosurgery versus WBRT

Outcome: 3 Local Tumor Control

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

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.56$, df = 1 (P = 0.45); I^2 =0.0%

Test for overall effect: Z = 3.93 (P = 0.000085)



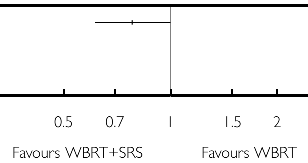
Analysis 1.4. Comparison 1 WBRT plus Radiosurgery versus WBRT, Outcome 4 Functionally Independent Survival (KPS).

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

Comparison: 1 WBRT plus Radiosurgery versus WBRT

Outcome: 4 Functionally Independent Survival (KPS)

Study or subgroup	WBRT + SRS n/N	WBRT n/N	Risk Ratio IV,Random,95% CI	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.

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

Comparison: 1 WBRT plus Radiosurgery versus WBRT

Outcome: 5 Steroid Use

Study or subgroup	WBRT + SRS n/N	WBRT n/N	Risk Ratio IV,Random,95% CI	Risk Ratio IV,Random,95% CI
Andrews 2004	22/63	30/55		0.64 [0.42, 0.97]

APPENDICES

Appendix 1. MEDLINE search strategy

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 2. Search Strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

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

EMBASE (1980 to 2009) search strategy

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

CANCERLIT (1975 to 2009) search strategy

This database was searched with the strategy outlined for MEDLINE

Appendix 3. 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 paraesthesias or loss of deep tendon reflexes	Mild to moderate objective sensory loss/paraesthesias	Severe objective sensory loss or paraesthesias that interfere with function

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 6, 2010

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. 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

None

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.