Cochrane
Library

Cochrane Database of Systematic Reviews

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

Tsao MN, Xu W, Wong RKS, Lloyd N, Laperriere N, Sahgal A, Rakovitch E, Chow E

Tsao MN, Xu W, Wong RKS, Lloyd N, Laperriere N, Sahgal A, Rakovitch E, Chow E.
Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases.
Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD003869.
DOI: [10.1002/14651858.CD003869.pub4](https://doi.org/10.1002/14651858.CD003869.pub4).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	11
OBJECTIVES	11
METHODS	11
Figure 1.	13
Figure 2.	14
RESULTS	16
Figure 3.	17
DISCUSSION	26
AUTHORS' CONCLUSIONS	28
ACKNOWLEDGEMENTS	28
REFERENCES	30
CHARACTERISTICS OF STUDIES	35
DATA AND ANALYSES	79
Analysis 1.1. Comparison 1 Altered WBRT fractionation schedules versus WBRT control, Outcome 1 Overall survival: lower-dose WBRT vs control WBRT (3000 cGy/10 daily fractions).	80
Analysis 1.2. Comparison 1 Altered WBRT fractionation schedules versus WBRT control, Outcome 2 Overall survival: higher-dose WBRT vs control (3000 cGy/10 daily fractions).	80
Analysis 1.3. Comparison 1 Altered WBRT fractionation schedules versus WBRT control, Outcome 3 Overall survival: WBRT 4000 cGy/20 fractions BID vs control WBRT (2000 cGy/4-5 daily fractions).	81
Analysis 2.1. Comparison 2 Altered WBRT fractionation schedules versus WBRT control: neurological function improvement, Outcome 1 Neurological function improvement: lower-dose WBRT vs control dose WBRT (3000 cGy/10 fractions).	81
Analysis 2.2. Comparison 2 Altered WBRT fractionation schedules versus WBRT control: neurological function improvement, Outcome 2 Neurological function improvement: higher-dose WBRT vs control dose WBRT (3000 cGy/10 fractions).	82
Analysis 3.1. Comparison 3 WBRT with radiosensitisers (radiosen) versus WBRT alone, Outcome 1 Overall survival.	82
Analysis 3.2. Comparison 3 WBRT with radiosensitisers (radiosen) versus WBRT alone, Outcome 2 Brain tumour response rates: complete response (CR) and partial response (PR) combined.	83
Analysis 4.1. Comparison 4 WBRT and radiosurgery versus WBRT, Outcome 1 Overall survival.	83
Analysis 4.2. Comparison 4 WBRT and radiosurgery versus WBRT, Outcome 2 1-Year overall brain control rates.	84
Analysis 5.1. Comparison 5 Radiosurgery alone versus WBRT and radiosurgery, Outcome 1 Overall survival.	84
Analysis 5.2. Comparison 5 Radiosurgery alone versus WBRT and radiosurgery, Outcome 2 1-Year radiosurgery-targeted lesion control.	85
Analysis 5.3. Comparison 5 Radiosurgery alone versus WBRT and radiosurgery, Outcome 3 1-Year distant brain control.	85
APPENDICES	85
WHAT'S NEW	87
HISTORY	87
CONTRIBUTIONS OF AUTHORS	87
DECLARATIONS OF INTEREST	88
SOURCES OF SUPPORT	88
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	88
INDEX TERMS	88

[Intervention Review]

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases

May N Tsao¹, Wei Xu², Rebecca KS Wong³, Nancy Lloyd⁴, Normand Laperriere³, Arjun Sahgal⁵, Eileen Rakovitch⁵, Edward Chow⁵

¹Department of Radiation Oncology, University of Toronto, Toronto, Canada. ²Department of Biostatistics, University of Toronto, Toronto, Canada. ³Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Canada. ⁴Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada. ⁵Department of Radiation Oncology, Odette Cancer Centre, Toronto, Canada

Contact address: May N Tsao, Department of Radiation Oncology, University of Toronto, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada. may.tsao@sunnybrook.ca.

Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 1, 2018.

Citation: Tsao MN, Xu W, Wong RKS, Lloyd N, Laperriere N, Sahgal A, Rakovitch E, Chow E. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database of Systematic Reviews* 2018, Issue 1. Art. No.: CD003869. DOI: [10.1002/14651858.CD003869.pub4](https://doi.org/10.1002/14651858.CD003869.pub4).

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

This is an update to the review published in the Cochrane Library (2012, Issue 4).

It is estimated that 20% to 40% of people with cancer will develop brain metastases during the course of their illness. The burden of brain metastases impacts quality and length of survival.

Objectives

To assess the effectiveness and adverse effects of whole brain radiotherapy (WBRT) given alone or in combination with other therapies to adults with newly diagnosed multiple brain metastases.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase to May 2017 and the National Cancer Institute Physicians Data Query for ongoing trials.

Selection criteria

We included phase III randomised controlled trials (RCTs) comparing WBRT versus other treatments for adults with newly diagnosed multiple brain metastases.

Data collection and analysis

Two review authors independently assessed trial quality and abstracted information in accordance with Cochrane methods.

Main results

We added 10 RCTs to this updated review. The review now includes 54 published trials (45 fully published reports, four abstracts, and five subsets of data from previously published RCTs) involving 11,898 participants.

Lower biological WBRT doses versus control

The hazard ratio (HR) for overall survival (OS) with lower biological WBRT doses as compared with control (3000 cGy in 10 daily fractions) was 1.21 (95% confidence interval (CI) 1.04 to 1.40; $P = 0.01$; moderate-certainty evidence) in favour of control. The HR for neurological function improvement (NFI) was 1.74 (95% CI 1.06 to 2.84; $P = 0.03$; moderate-certainty evidence) in favour of control fractionation.

Higher biological WBRT doses versus control

The HR for OS with higher biological WBRT doses as compared with control (3000 cGy in 10 daily fractions) was 0.97 (95% CI 0.83 to 1.12; $P = 0.65$; moderate-certainty evidence). The HR for NFI was 1.14 (95% CI 0.92 to 1.42; $P = 0.23$; moderate-certainty evidence).

WBRT and radiosensitisers

The addition of radiosensitisers to WBRT did not confer additional benefit for OS (HR 1.05, 95% CI 0.99 to 1.12; $P = 0.12$; moderate-certainty evidence) or for brain tumour response rates (odds ratio (OR) 0.84, 95% CI 0.63 to 1.11; $P = 0.22$; high-certainty evidence).

Radiosurgery and WBRT versus WBRT alone

The HR for OS with use of WBRT and radiosurgery boost as compared with WBRT alone for selected participants was 0.61 (95% CI 0.27 to 1.39; $P = 0.24$; moderate-certainty evidence). For overall brain control at one year, the HR was 0.39 (95% CI 0.25 to 0.60; $P < 0.0001$; high-certainty evidence) favouring the WBRT and radiosurgery boost group.

Radiosurgery alone versus radiosurgery and WBRT

The HR for local brain control was 2.73 (95% CI 1.87 to 3.99; $P < 0.00001$; high-certainty evidence) favouring the addition of WBRT to radiosurgery. The HR for distant brain control was 2.34 (95% CI 1.73 to 3.18; $P < 0.00001$; high-certainty evidence) favouring WBRT and radiosurgery. The HR for OS was 1.00 (95% CI 0.80 to 1.25; $P = 0.99$; moderate-certainty evidence). Two trials reported worse neurocognitive outcomes and one trial reported worse quality of life outcomes when WBRT was added to radiosurgery.

We could not pool data from trials related to chemotherapy, optimal supportive care (OSC), molecular targeted agents, neurocognitive protective agents, and hippocampal sparing WBRT. However, one trial reported no differences in quality-adjusted life-years for selected participants with brain metastases from non-small-cell lung cancer randomised to OSC and WBRT versus OSC alone.

Authors' conclusions

None of the trials with altered higher biological WBRT dose-fractionation schemes reported benefit for OS, NFI, or symptom control compared with standard care. However, OS and NFI were worse for lower biological WBRT dose-fractionation schemes than for standard dose schedules.

The addition of WBRT to radiosurgery improved local and distant brain control in selected people with brain metastases, but data show worse neurocognitive outcomes and no differences in OS.

Selected people with multiple brain metastases from non-small-cell lung cancer may show no difference in OS when OSC is given and WBRT is omitted.

Use of radiosensitisers, chemotherapy, or molecular targeted agents in conjunction with WBRT remains experimental.

Further trials are needed to evaluate the use of neurocognitive protective agents and hippocampal sparing with WBRT. As well, future trials should examine homogeneous participants with brain metastases with focus on prognostic features and molecular markers.

PLAIN LANGUAGE SUMMARY

Whole brain radiotherapy for the treatment of multiple brain metastases

The issue

A large proportion of people with cancer will receive a diagnosis of the spread of cancer (metastases) to the brain. Radiotherapy is commonly used to treat brain metastases.

The aim of the review

We conducted this review to determine the effectiveness and adverse effects of whole brain radiotherapy (WBRT) given alone or in combination with other treatments to adults with multiple brain metastases.

What are the main findings?

This review includes 54 published trials involving 11,898 participants.

Data show no apparent additional benefit of altered WBRT dose schedules compared with standard dose schedules.

Use of other treatments such as chemotherapy, radiosensitisers, and molecular targeted agents in conjunction with WBRT has not yet been shown to be of benefit.

Radiosurgery boost with WBRT does not improve survival among selected people with multiple brain metastases. WBRT when added to radiosurgery improves local and distant brain control. However, neurocognitive outcomes are better for selected people treated with radiosurgery alone as compared with WBRT and radiosurgery.

For selected individuals with metastatic non-small-cell lung cancer to brain, survival may not be better with WBRT and optimal supportive care than with optimal supportive care alone.

Quality of the evidence

Studies have provided evidence of moderate to high certainty.

What are the conclusions?

Altered higher biological WBRT dose-fractionation schemes, as reported in randomised trials, did not confer benefit for overall survival, neurological function, or symptom control compared with standard treatment (3000 cGy in 10 daily fractions, or 2000 cGy in 4 or 5 daily fractions). However, overall survival and neurological function were worse for lower biological WBRT dose-fractionation schemes than for standard dose schedules.

The addition of WBRT to radiosurgery improved local and distant brain control (i.e. absence of new intracranial lesions at the site or outside of treated lesions after treatment) among selected people with brain metastases, but investigators reported worse cognitive outcomes and no differences in overall survival.

Selected people with multiple brain metastases from non-small-cell lung cancer may show no difference in overall survival when optimal supportive care is given and WBRT is omitted.

Use of other treatments (radiosensitisers, chemotherapy, or molecular targeted agents) in conjunction with WBRT remains experimental.

Additional trials are needed to evaluate strategies to protect cognitive decline associated with WBRT. As well, future trials should examine people with brain metastases with focus on prognostic features and tumour characteristics.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Altered WBRT fractionation schedules compared with WBRT control for treatment of newly diagnosed multiple brain metastases

Altered WBRT fractionation schedules compared with WBRT control for treatment of newly diagnosed multiple brain metastases

Patient or population: patients with newly diagnosed multiple brain metastases

Setting: hospital

Intervention: altered WBRT fractionation schedules

Comparison: WBRT control

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty (quality) of the evidence (GRADE)	What happens
		Without altered WBRT fractionation schedules	With altered WBRT fractionation schedules	Difference		
Overall survival: lower-dose WBRT vs control WBRT (3000 cGy/10 daily fractions) No. of participants: 705 (3 RCTs)	HR 1.21 (1.04 to 1.40)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		Not estimable as only HR data available	Not estimable as only HR data available	N/A		
Overall survival: higher-dose WBRT vs control (3000 cGy/10 daily fractions) No. of participants: 846 (4 RCTs)	HR 0.97 (0.83 to 1.12)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		Not estimable as only HR data available	Not estimable as only HR data available	N/A		
Overall survival: WBRT 4000 cGy/20 fractions BID vs control WBRT (2000 cGy/4-5 daily fractions) No. of participants: 203 (2 RCTs)	HR 1.18 (0.89 to 1.56)	Study population			⊕⊕⊕⊖ MODERATE ^a	
		Not estimable as only HR data available	Not estimable as only HR data available	N/A		
Adverse effects No. of participants: 1754 (9 RCTs)	not pooled	Study population			⊕⊕⊕⊕ HIGH	
		not pooled	not pooled	not pooled		
Symptom control No. of participants: 2877 (7 RCTs)	not pooled	Study population			⊕⊕⊕⊖ MODERATE ^b	
		not pooled	not pooled	not pooled		
Overall brain control No. of participants: 203 (2 RCTs)	not pooled	Study population			⊕⊕⊕⊖ MODERATE ^c	

not pooled

not pooled

not pooled

***The risk in the intervention group** (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).

BID = twice daily; CI = confidence interval; HR = hazard ratio; N/A = not applicable; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; 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.

^aIncluded population heterogeneous with respect to survival owing to varying primary cancer diagnoses. Molecular subtypes important for prognoses may not have been balanced between groups.

^bOutcome of symptom control subject to attrition and reporting bias.

^cReporting bias.

Summary of findings 2. Altered WBRT fractionation schedules compared with WBRT control: neurological function improvement for treatment of newly diagnosed multiple brain metastases

Altered WBRT fractionation schedules compared with WBRT control: neurological function improvement for treatment of newly diagnosed multiple brain metastases

Patient or population: patients with newly diagnosed multiple brain metastases

Setting: hospital

Intervention: altered WBRT fractionation schedules

Comparison: WBRT control: neurological function improvement

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty (quality) of the evidence (GRADE)	What happens
		Without altered WBRT fractionation schedules	With altered WBRT fractionation schedules	Difference		
Neurological function improvement: lower-dose WBRT vs control dose WBRT (3000 cGy/10 fractions) No. of participants: 1612 (5 RCTs)	OR 1.74 (1.06 to 2.84)	Study population 49.6%	 63.1% (51.0 to 73.6)	 13.5% more	⊕⊕⊕⊖ MODERATE ^a	

				(1.5 more to 24.1 more)	
Neurological function improvement: higher-dose WBRT vs control dose WBRT (3000 cGy/10 fractions) No. of participants: 1480 (4 RCTs)	OR 1.14 (0.92 to 1.42)	Study population			⊕⊕⊕⊖ MODERATE ^a
		49.4%	52.7% (47.3 to 58.1)	3.3% more (2.1 fewer to 8.7 more)	

***The risk in the intervention group** (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; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; WBRT = whole body 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.

^aUnclear whether groups were balanced for steroid use.

Summary of findings 3. WBRT with radiosensitisers (radiosen) compared with WBRT alone for treatment of newly diagnosed multiple brain metastases

WBRT with radiosensitisers (radiosen) compared with WBRT alone for treatment of newly diagnosed multiple brain metastases

Patient or population: patients with newly diagnosed multiple brain metastases

Setting: hospital

Intervention: WBRT with radiosensitisers (radiosen)

Comparison: WBRT alone

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty (quality) of the evidence (GRADE)	What happens
		Without WBRT with radiosensitisers (radiosen)	With WBRT with radiosensitisers (radiosen)	Difference		
Overall survival No. of participants: 2631 (8 RCTs)	HR 1.05 (0.99 to 1.12)	study population			⊕⊕⊕⊖ MODERATE ^a	
		not estimable as only HR data available	not estimable as only HR data available	N/A		

Brain tumour response rates: complete response (CR) and partial response (PR) combined No. of participants: 847 (6 RCTs)	OR 0.84 (0.63 to 1.11)	study population			⊕⊕⊕⊕ HIGH
		62.2%	58.1% (50.9 to 64.6)	4.2% fewer (11.3 fewer to 2.4 more)	
Adverse effects No. of participants: 2631 (8 RCTs)	not pooled	study population			⊕⊕⊕⊕ HIGH
		not pooled	not pooled	not pooled	
Quality of life No. of participants: 966 (3 RCTs)	not pooled	study population			⊕⊕⊕⊕ MODERATE ^b
		not pooled	not pooled	not pooled	
Symptom control No. of participants: 1814 (3 RCTs)	not pooled	study population			⊕⊕⊕⊕ MODERATE ^b
		not pooled	not pooled	not pooled	

***The risk in the intervention group** (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; N/A = not applicable; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; WBRT = whole body 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.

^aHeterogeneous population owing to varying primary cancer histologies, and unclear whether groups were balanced for other prognostic variables such as molecular subtype.

^bAttrition and reporting bias.

Summary of findings 4. WBRT and radiosurgery compared with WBRT for treatment of newly diagnosed multiple brain metastases

WBRT and radiosurgery compared with WBRT for treatment of newly diagnosed multiple brain metastases

Patient or population: patients with newly diagnosed multiple brain metastases

Setting: hospital

Intervention: WBRT and radiosurgery

Comparison: WBRT

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty (quality) of the evidence (GRADE)	What happens
		Without WBRT and radio-surgery	With WBRT and radio-surgery	Difference		
Overall survival No. of participants: 358 (2 RCTs)	HR 0.61 (0.27 to 1.39)	study population			⊕⊕⊕⊖ MODERATE ^a	
		not estimable as only HR data available	not estimable as only HR data available	N/A		
1-Year overall brain control rates No. of participants: 400 (3 RCTs)	HR 0.39 (0.25 to 0.60)	study population			⊕⊕⊕⊕ HIGH	
		not estimable as only HR data available	not estimable as only HR data available	N/A		
Adverse effects No. of participants: 400 (3 RCTs)	not pooled	study population			⊕⊕⊕⊕ HIGH	
		not pooled	not pooled	not pooled		
Intracranial progression-free duration No. of participants: 400 (3 RCTs)	not pooled	study population			⊕⊕⊕⊕ HIGH	
		not pooled	not pooled	not pooled		

***The risk in the intervention group** (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; OR = odds ratio; RCT = randomised controlled trial; RR = risk ratio; WBRT = whole body 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.

^aHeterogeneous population with varying primary cancer types; unclear whether groups were balanced by molecular subtype important for survival.

Summary of findings 5. Radiosurgery alone compared with WBRT and radiosurgery for treatment of newly diagnosed multiple brain metastases

Radiosurgery alone compared with WBRT and radiosurgery for treatment of newly diagnosed multiple brain metastases

Patient or population: patients with newly diagnosed multiple brain metastases

Setting: hospital
Intervention: radiosurgery alone
Comparison: WBRT and radiosurgery

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty (quality) of the evidence (GRADE)	What happens
		Without radiosurgery alone	With radiosurgery alone	Difference		
Overall survival No. of participants: 403 (3 RCTs)	HR 1.00 (0.80 to 1.25)	study population			⊕⊕⊕⊖ MODERATE ^a	
		not estimable as only HR data available	not estimable as only HR data available	N/A		
1-Year radiosurgery-targeted lesion control No. of participants: 602 (4 RCTs)	HR 2.73 (1.87 to 3.99)	study population			⊕⊕⊕⊕ HIGH	
		not estimable as only HR data available	not estimable as only HR data available	N/A		
1-Year distant brain control No. of participants: 602 (4 RCTs)	HR 2.34 (1.73 to 3.18)	study population			⊕⊕⊕⊕ HIGH	
		not estimable as only HR data available	not estimable as only HR data available	N/A		
Adverse effects No. of participants: 602 (4 RCTs)	not pooled	study population			⊕⊕⊕⊕ HIGH	
		not pooled	not pooled	not pooled		
Neurocognition No. of participants: 403 (3 RCTs)	not pooled	study population			⊕⊕⊕⊖ MODERATE ^b	
		not pooled	not pooled	not pooled		
Neurological function No. of participants: 544 (3 RCTs)	not pooled	study population			⊕⊕⊕⊖ MODERATE ^b	
		not pooled	not pooled	not pooled		
Quality of life No. of participants: 271 (2 RCTs)	not pooled	study population			⊕⊕⊕⊖ MODERATE ^b	
		not pooled	not pooled	not pooled		

***The risk in the intervention group** (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; N/A = not applicable; OR = odds ratio; RCT = randomised controlled trial; RR: risk ratio; WBRT = whole body 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.

^aHeterogeneous population with respect to survival. Prognostic variables such as primary cancer histologies and molecular cancer features may not have been balanced between groups.

^bAttrition bias.

BACKGROUND

This review is an update of a review previously published in the *Cochrane Database of Systematic Reviews* (Tsao 2012b).

Description of the condition

Brain metastases represent a significant healthcare problem. It is estimated that 20% to 40% of people with cancer will develop metastatic cancer to the brain during the course of their illness (Loeffler 1997). The burden of brain metastases impacts quality and length of survival. Presenting symptoms include headache (49%), focal weakness (30%), mental disturbances (32%), gait ataxia (21%), seizures (18%), speech difficulty (12%), visual disturbance (6%), sensory disturbance (6%), and limb ataxia (6%) (Posner 1995).

Brain metastases may spread from any primary site. The most common primary site is the lung, followed by the breast, then gastrointestinal sites (Walker 1985). Eighty-five per cent of brain metastases are found in the cerebral hemispheres, 10% to 15% in the cerebellum, and 1% to 3% in the brainstem (Arbit 1995).

Description of the intervention

The mainstay of treatment for brain metastases has been corticosteroids for treatment of peritumoural oedema, antiepileptic medication for treatment of seizures, whole brain radiotherapy (WBRT), and radiosurgery and surgery provided alone or in combination.

How the intervention might work

WBRT has been shown to improve neurological symptoms and function with minimal morbidity (Chao 1954; Posner 1977). Non-randomised studies suggest that WBRT increases median survival up to three to six months (Chao 1954; Katz 1981; Posner 1977; Zimm 1981). Median survival of participants with symptomatic brain metastases was approximately one month without treatment and two months with corticosteroid use. The overall response rate to WBRT, which is dependent on the symptoms reported, ranged from 64% to 85% (Borgelt 1980a; Katz 1981; Sneed 1996). However, on the whole, studies have vaguely defined symptom response. In one study, 74% of participants showed improvement in neurological symptoms and 65% maintained this improvement for at least nine months (Cairncross 1980).

Why it is important to do this review

Even with treatment, brain metastases cause significant morbidity and mortality. Despite WBRT, up to one-half of patients will die from intracranial progression (Borgelt 1980a; Chao 1954; Gelber 1981; Katz 1981; Noordijk 1994). As such, review authors evaluated strategies to improve outcomes involving WBRT.

In an attempt to improve outcomes, investigators have examined use of WBRT combined with systemic treatment (cytotoxic chemotherapy), molecular targeted therapy (agents that block growth of cancer cells by inhibiting specific molecules needed for carcinogenesis or tumour growth), or radiosensitisers (agents that enhance the radiation effect) and altered dose-fractionation schedules.

Investigators have also studied neurocognitive protective strategies (such as drugs) and radiation strategies (such as

hippocampal sparing methods) in an attempt to reduce the neurocognitive decline associated with WBRT.

Investigators have combined surgery with WBRT for single metastasis (Grant 2001) and with radiosurgery (a specialised, focused radiation technique) for selected people with brain metastases.

We have excluded from this review studies that examined use of surgery or WBRT, or both, for single brain metastases, as this was the topic of another Cochrane systematic review (Hart 2004).

OBJECTIVES

To assess the effectiveness and adverse effects of WBRT given alone or in combination with other therapies to adults with newly diagnosed multiple brain metastases.

METHODS

Criteria for considering studies for this review

Types of studies

We included fully published phase 3 trials of adults with newly diagnosed multiple metastases to the brain who were randomised to treatment with WBRT or with other therapies discussed in this review.

Types of participants

We included adult participants (18 years and older) receiving WBRT for newly diagnosed multiple metastases to the brain from any primary cancer.

Types of interventions

Trials that compared the following interventions were eligible for inclusion.

1. Altered WBRT dose-fractionation schedules versus conventional WBRT fractionation schedules (*3000 cGy in 10 fractions, or 2000 cGy in 4 or 5 daily fractions).
2. WBRT* and systemic therapy.
3. WBRT plus radiosensitisers versus WBRT*.
4. WBRT plus radiosurgery versus WBRT*.
5. Radiosurgery alone versus radiosurgery and WBRT*.
6. Steroids alone versus WBRT and steroids*.

We added three new categories to this updated review.

1. WBRT* and molecular targeted agents.
2. WBRT* and neurocognitive protective agents.
3. Hippocampal sparing WBRT versus WBRT*.

*Designated as a control arm in the trial.

We excluded trials of prophylactic WBRT in which WBRT was used without evidence of existing brain metastases. We also excluded studies that examined use of surgery or WBRT, or both, for single brain metastases, as this is the topic of another Cochrane systematic review (Hart 2004). We excluded intervention trials for people with recurrent brain metastases, as well as phase II randomised trials.

Types of outcome measures

We sought data for the following outcome measures.

1. Overall survival.
2. Intracranial progression-free duration (defined as time from randomisation or entry into the trial until diagnosis of progressive brain disease (i.e. enlarging brain metastases or identification of new brain metastases based on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scan)).
3. Brain response (reported as the percentage of participants achieving complete response (CR) or partial response (PR) of existing brain metastases to treatment). Complete response was defined as complete radiographic disappearance of brain metastases. Partial response was defined as a greater than 50% decrease in the size of brain metastases on CT or MRI.
4. Local brain control (reported as the percentage of participants with unchanged or improved serial post-treatment CT or MRI scans judged as showing CR, PR, or stable disease (SD), with improving or stable neurological symptoms or neurological examination. SD was defined as a 0% to 50% decrease in the size of all lesions, with stabilisation of neurological symptoms or neurological examination and stable dexamethasone dose. Progressive disease was defined as an increase in the size of any lesion.
5. Distant brain control (defined as CR, PR, or SD of brain metastases not treated with focal therapy such as radiosurgery).
6. Quality of life assessed by any scale.
7. Symptom control.
8. Neurological function.
9. Proportion of participants who were able to reduce their daily dexamethasone dose and duration of reduced dexamethasone requirements.
10. Adverse effects.

Search methods for identification of studies

Electronic searches

Review update

We updated the searches in May 2017 - Cochrane Central Register of Controlled Trials, CENTRAL Issue 4 May 2017, MEDLINE (Ovid) April week 4 2017, and Embase (Ovid) 2017 week 19. Refer to [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#), respectively.

Searching other resources

We handsearched the references of included studies to identify additional studies. We searched the National Cancer Institute [Physicians Data Query](#) (PDQ) for ongoing trials.

Data collection and analysis

Selection of studies

Two radiation oncologists (MNT and EC) assessed titles and abstracts retrieved by the search strategy. We obtained full published reports for all references deemed to meet the inclusion criteria. We retrieved articles if we believed that we should review article reference lists to look for additional relevant studies.

Assessment of full reports enabled identification of studies for inclusion in the review. We listed in the [Characteristics of excluded studies](#) table trials excluded at this stage along with reasons for exclusion.

Assessors were not blinded to author, institution, journal of publication, or trial results, as the review authors were familiar with most studies and with the typographical layout of journals.

Data extraction and management

Two review authors (MNT and EC) independently extracted data using standard data extraction forms. A third assessor (RW) resolved disagreements or discrepancies.

We extracted the following data items.

1. Study characteristics.
2. Participant characteristics.
3. Interventions.
4. Outcome data ([Types of outcome measures](#)).

We also extracted from trial reports participant characteristics based on age, Karnofsky Performance Status (KPS), and status of extracranial disease, along with treatment characteristics.

Assessment of risk of bias in included studies

Since the last update was published, we assessed risk of bias in included studies using the Cochrane tool for assessing bias ([Higgins 2011](#)). As none of the radiation trials were blinded, we excluded domains related to blinding and used the following domains.

1. Selection bias: random sequence generation and allocation concealment.
2. Attrition bias: incomplete outcome data.
3. Reporting bias: selective reporting of outcomes.

We summarised assessment results using the 'Risk of bias' graph ([Figure 1](#)) and the 'Risk of bias' summary ([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.

	Random sequence generation (selection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Andrews 2004	+	?	+
Antonadou 2002	?	?	?
Antonadou 2003	?	?	?
Aoyama 2006	+	+	+
Aoyama 2015	+	-	+
Borgelt 1980a	?	?	?
Borgelt 1980b	?	?	?
Borgelt 1981a	?	?	?
Borgelt 1981b	?	?	?
Brown 2013	+	+	+
Brown 2016	+	-	+
Chang 2009	+	+	+
Chatani 1985	?	?	?
Chatani 1994	?	+	?
Chougule 2000	?	?	?
Davey 2008	+	+	+
DeAngelis 1989	?	?	?
El Gantery 2014	?	?	?
El-Hamamsy 2016	?	?	?
Eyre 1984	?	?	?
Fogarty 2015	?	-	?
Graham 2010	+	?	?

Figure 2. (Continued)

Graham 2010	+	?	?
Guerrieri 2004	?	-	?
Harwood 1977	?	?	?
Horton 1971	?	?	?
Knisely 2008	+	?	?
Kocher 2011	+	+	?
Komarnicky 1991	?	?	?
Kondziolka 1999	-	-	?
Kurtz 1981	?	?	?
Lee 2008	?	?	?
Mehta 2003	?	?	?
Mehta 2009	+	?	?
Meyers 2004	+	?	+
Mornex 2003	?	?	?
Mulvenna 2016	+	+	?
Murray 1997	?	?	?
Neuhaus 2009	?	?	?
Phillips 1995	?	?	?
Postmus 2000	?	?	?
Priestman 1996	?	-	?
Puthiyottil 2016	?	?	?
Ramlau 2013	?	?	?
Rapp 2015	+	+	+
Robinet 2001	?	?	?
Scott 2007	?	-	?
Sperduto 2013	?	-	?
Sperduto 2014	?	-	?
Stea 2006	?	?	?
Sturm 2015	?	?	?
Suh 2006	+	?	?
Suh 2008	?	?	?

Figure 2. (Continued)

Suh 2008	?	?	?
Ushio 1991	?	?	?
Zeng 2016	?	?	?

Since the last update, we have presented the overall certainty of evidence for each outcome in the meta-analysis according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account issues related not only to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity, such as directness of results. We used [GRADEpro GDT \(GRADEpro GDT 2015\)](#) to prepare 'Summary of findings' tables, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

We abstracted study withdrawals, deaths, and losses to follow-up. We performed all analyses on an intention-to-treat basis.

Assessment of heterogeneity

The Radiation Therapy Oncology Group (RTOG) analysed the database of 1200 participants from three consecutive RTOG trials that examined several dose-fractionation schemes of WBRT and use of radiosensitisers with WBRT ([Gaspar 1997](#)). Using recursive partitioning analysis (RPA), we generated three prognostic classes based on survival: Class 1: KPS ≥ 70 , < 65 years of age with controlled primary and no extracranial metastases; Class 3: KPS < 70; and Class 2: all others. These classes enable the classification of brain metastasis populations separated into homogeneous patient groups on the basis of survival.

Since the last Cochrane update, researchers have refined the prognostic classification of brain metastases (the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA)) ([Sperduto 2012](#)). Many trials pre-dated the DS-GPA publication. In addition, many trials pre-dated the recognition of molecular cancer subtypes important for prognoses. As such, it is unclear whether study groups in these older trials were balanced for prognostic variables based on the DS-GPA, which also takes into account the molecular profile of certain cancers.

Patient characteristics predicting other outcomes of interest (intracranial progression-free survival, quality of life, symptom control, neurological function, ability to taper down on dexamethasone dose) have not been defined.

Data synthesis

If pooling of data was deemed appropriate, we used the statistical package [RevMan 5.3 \(Review Manager 2014\)](#). In this updated review, we reported hazard ratios (HRs) with 95% confidence intervals (CIs) for overall survival, one-year overall brain control, one-year radiosurgery-targeted lesion control, and one-year distant brain control. We reported odds ratios (ORs) with 95% CIs using the random-effects model for neurological function improvement (NFI) and brain tumour response.

We extracted data from full published trials. Data from abstracts as these reports lacked the detail to permit pooling of outcomes. We did not contact authors of abstracts to request further information.

This updated review includes the following statistical analyses.

1. For the pooled analysis of overall survival, we estimated one-year overall brain control, one-year radiosurgery-targeted lesion control, and one-year distant brain control by using hazard ratios (HRs) derived from the Hazard Ratio Meta-analysis Box ([Parmar 1998](#)). We pooled HRs using the generic inverse variance method and the fixed-effect model provided in RevMan 5.3
2. For the pooled analysis of brain tumour response, we abstracted from tables, figures, or text of published reports the proportion of participants with a complete or partial response. We determined tumour response using the proportion of participants achieving complete response (CR) or partial response (PR). We treated these data as dichotomous outcome measures. We pooled odds ratios (ORs) for brain tumour response using a random-effects model.
3. We described neurological function improvement (NFI) as the proportion of participants with improved neurological function and treated this as a dichotomous outcome. We pooled ORs for NFI using random effects.
4. Owing to the heterogeneity of instruments used and differences in reporting, we described and did not pool quality of life, symptom control, and adverse effects outcomes.

Subgroup analysis and investigation of heterogeneity

We planned no subgroup analyses.

Sensitivity analysis

We performed no sensitivity analyses.

RESULTS

Description of studies

Results of the search

We added to this updated review 10 new fully published randomised controlled trials (RCTs) involving 2457 participants ([Brown 2013](#); [Brown 2016](#); [El Gantery 2014](#); [El-Hamamsy 2016](#); [Fogarty 2015](#); [Mehta 2009](#); [Mulvenna 2016](#); [Rapp 2015](#); [Sperduto 2013](#); [Zeng 2016](#)). This updated review now includes a total of 45 fully published trials involving 11,152 participants (see [Included studies](#)). We identified four additional trials consisting of 746 participants that were published in abstract form ([Antonadou 2003](#); [Puthiyottil 2016](#); [Ramlau 2013](#); [Sturm 2015](#)). Five additional publications described secondary outcomes, prognostic factors, or subgroup analyses for a subset of 1385 trial participants ([Figure 3](#)) ([Aoyama 2015](#); [Meyers 2004](#); [Scott 2007](#); [Sperduto 2014](#); [Stea 2006](#)).

Figure 3. Study flow diagram.

Included studies

Altered WBRT schedules

We identified a total of 10 published reports involved 4056 participants randomised to altered WBRT dose-fractionation schedules compared with standard 3000 cGy in 10 daily fractions, or 2000 cGy in 4 or 5 daily fractions ([Borgelt 1980a](#); [Borgelt 1981a](#); [Chatani 1985](#); [Chatani 1994](#); [Davey 2008](#); [Graham 2010](#); [Harwood 1977](#); [Kurtz 1981](#); [Murray 1997](#); [Priestman 1996](#)).

The published reports [Borgelt 1980a](#) and [Borgelt 1980b](#) presented the results of two sequential trials (Study 1: [Borgelt 1980a](#); and Study 2: [Borgelt 1980b](#)). Investigators randomised participants to one of five WBRT schedules ranging from 4000 cGy/4 weeks to 2000 cGy/1 week. Study 1 randomised participants to one of four regimens (3000 cGy/2 weeks, 3000 cGy/3 weeks, 4000 cGy/3

weeks, or 4000 cGy/4 weeks) ([Borgelt 1980a](#)). Study 2 randomised participants to one of three regimens (2000 cGy/1 week, 3000 cGy/2 weeks, or 4000 cGy/3 weeks) ([Borgelt 1980b](#)).

[Borgelt 1981a](#) reported on participants randomised to 1000 cGy/1 fraction in Study 1, and [Borgelt 1981b](#) reported on participants randomised to 1200 cGy/2 fractions in Study 2, as compared with participants treated on one of five schedules ranging from 4000 cGy/4 weeks to 2000 cGy/1 week. Thus, duplicate reports describe participants treated on one of five WBRT schedules ranging from 4000 cGy/4 weeks to 2000 cGy/1 week ([Borgelt 1980a](#); [Borgelt 1980b](#); [Borgelt 1981a](#); [Borgelt 1981b](#)). It was not possible to separate the subgroup of participants duplicated in the comparison group treated on one of five schedules ranging from 4000 cGy/4 weeks to 2000 cGy/1 week. As such, we entered data from these reports to show completely separate groups of participants.

Chatani 1985 and Chatani 1994 reported on separate groups of participants who were enrolled sequentially into these trials. The other trials reported no duplication of participant data (Harwood 1977; Kurtz 1981; Murray 1997; Priestman 1996).

Regine 2001 subsequently reported neurocognitive outcomes in trial participants from Murray 1997.

Two RCTs examined the use of 4000 cGy in 20 twice-daily fractions of WBRT versus 2000 cGy in 4 or 5 daily fractions of WBRT (Davey 2008; Graham 2010).

WBRT with or without radiosensitisers

Radiosensitisers are drugs that make cancer cells more sensitive to the treatment effects of radiation therapy. A total of nine fully published trials examined use of radiosensitisers in addition to WBRT (2712 participants) (DeAngelis 1989; El-Hamamsy 2016; Eyre 1984; Komarnicky 1991; Mehta 2003; Mehta 2009; Phillips 1995; Suh 2006; Zeng 2016). Mehta 2009, El-Hamamsy 2016, and Zeng 2016 are new to this update. Suh 2008, which included 368 participants, was published in abstract form.

The radiosensitisers used were metronidazole (Eyre 1984), lonidamine (DeAngelis 1989), misonidazole (Komarnicky 1991), bromodeoxyuridine (BrdU) (Phillips 1995), motexafin gadolinium (Mehta 2003; Mehta 2009), efaproxiral (Suh 2006), simvastatin (El-Hamamsy 2016), and sodium glycididazole (Zeng 2016).

Suh 2006 reported on survival as the primary endpoint with response rate as the secondary endpoint among participants randomised to WBRT and efaproxiral versus WBRT alone. Stea 2006 explored prognostic significance based on radiographic response among participants in Suh 2006.

A published post hoc subgroup analysis examined participants with breast cancer treated with the radiosensitiser efaproxiral and WBRT versus WBRT (Scott 2007). Subsequently, Suh 2008 reported in abstract form a trial that included a priori only participants with breast cancer randomised to WBRT plus efaproxiral versus WBRT alone.

Mehta 2003 reported on survival and neurological outcomes in participants with a variety of primary cancers metastatic to brain who were randomised to WBRT and motexafin gadolinium as compared with WBRT alone. In a follow-up report, Meyers 2004 reported specifically on neurocognitive outcomes among the same group of participants randomised in the motexafin gadolinium trial (Mehta 2003).

Subsequently, Mehta 2009 reported on a new group of participants with non-small-cell lung cancer brain metastases randomised to WBRT and motexafin gadolinium as compared with WBRT alone.

WBRT and chemotherapy

A total of nine fully published trials (1130 participants) reported on the use of WBRT and chemotherapy (Guerrieri 2004; Knisely 2008; Lee 2008; Mornex 2003; Neuhaus 2009; Postmus 2000; Robinet 2001; Sperduto 2013; Ushio 1991).

Four trials were reported in abstract form (Antonadou 2002; Antonadou 2003; Puthiyottil 2016; Ramlau 2013).

The Antonadou 2002 trial randomised participants to WBRT with or without temozolomide chemotherapy. Eighty-two per cent of 134 eligible participants in Antonadou 2002 had lung primaries. These participants with lung cancer brain metastases were reported subsequently in abstract form (Antonadou 2003).

The Ramlau 2013 abstract reported on participants with non-small-cell lung cancer with brain metastases randomised to WBRT with or without oral topotecan.

Puthiyottil 2016 reported, in abstract form, on participants with non-small-cell lung cancer brain metastases who were randomised to WBRT with or without temozolomide chemotherapy.

The remaining fully published randomised trials studied a variety of other chemotherapy agents.

1. Guerrieri 2004 randomised participants with non-small-cell lung cancer metastatic to brain to WBRT with or without carboplatin chemotherapy.
2. Knisely 2008 examined use of WBRT with or without thalidomide in participants with brain metastases from a variety of primary cancers.
3. Lee 2008 randomised participants with metastatic non-small-cell lung cancer with brain metastases to WBRT with or without gemcitabine and vinorelbine chemotherapy.
4. Mornex 2003 randomised participants with metastatic malignant melanoma to brain to fotemustine and WBRT versus fotemustine alone.
5. Neuhaus 2009 randomised participants with brain metastases from non-small-cell and small-cell lung cancer to WBRT with or without topotecan chemotherapy.
6. Postmus 2000 examined participants with metastatic small-cell lung cancer to brain and randomised these participants to teniposide versus teniposide and WBRT.
7. Robinet 2001 reported on participants with non-small-cell lung cancer metastatic to brain randomised to early versus delayed WBRT with concurrent cisplatin and vinorelbine chemotherapy.
8. Sperduto 2013 reported on participants with metastatic non-small-cell lung cancer to brain randomised to one of three groups: WBRT and radiosurgery; WBRT, radiosurgery, and temozolomide chemotherapy; or WBRT, radiosurgery, and the targeted agent, erlotinib.
9. Ushio 1991 randomised participants with metastatic lung cancer to brain to one of three groups: WBRT alone; WBRT and chloroethyl nitrosoureas; or WBRT, chloroethyl nitrosoureas, and tegafur.

WBRT with or without radiosurgery boost

Three trials examined use of WBRT with or without radiosurgery boost for up to four brain metastases (464 participants in total) (Andrews 2004; Chougule 2000; Kondziolka 1999). Two trials have been fully published (Andrews 2004; Kondziolka 1999). Kondziolka 1999 included participants with two to four brain metastases (all $\leq$ 25 mm in diameter). Andrews 2004 reported on participants with one to three brain metastases, with a maximum diameter of 4 cm for the largest lesion and additional lesions not exceeding 3 cm in diameter. Chougule 2000 has been published in abstract form. This trial included participants with one to three brain metastases, tumour volume of 30 cc or less, and minimum life expectancy of three months.

We added to this update one new fully published trial ([El Gantery 2014](#)), which examined use of WBRT alone versus WBRT and radiosurgery versus radiosurgery alone. This trial included 60 participants, each with one to three brain metastases.

Since the last published Cochrane Review, [Sperduto PW 2014](#) has reported a secondary analysis of the [Andrews 2004](#) trial, stratifying overall survival by the Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) ([Sperduto 2012](#)),

Radiosurgery alone versus radiosurgery and WBRT

[Aoyama 2006](#) randomised 160 participants, each with one to four brain metastases (≤ 3 cm) to radiosurgery alone or radiosurgery and WBRT. A secondary analysis of [Aoyama 2006](#) trial data explored overall survival and control rates of brain metastases based on the DS-GPA (determined by significant prognostic factors such as primary cancer type, performance status, age, presence of extracranial disease, and number of brain metastases) ([Aoyama 2015](#)).

[Chang 2009](#) randomised 58 participants, each with one to three brain metastases, to radiosurgery alone versus WBRT and radiosurgery.

[Kocher 2011](#) randomised 359 participants, each with one to three brain metastases, to one of the following groups: radiosurgery alone, surgery alone, radiosurgery and WBRT, or surgery and WBRT.

Since the last update, three additional RCTs have been fully published ([Brown 2016](#); [El Gantery 2014](#); [Fogarty 2015](#)).

1. [El Gantery 2014](#) randomised 60 participants, each with one to three brain metastases, to radiosurgery alone versus WBRT versus both.
2. [Fogarty 2015](#) reported on an interim analysis of 100 metastatic melanoma participants, each with one to three brain metastases treated with radiosurgery or surgery, who were then randomised to adjuvant WBRT or observation.
3. [Brown 2016](#) randomised 213 participants, each with one to three brain metastases, to radiosurgery alone versus radiosurgery and WBRT.

Steroids with or without WBRT

One trial (48 participants) reported on use of oral prednisone with or without WBRT ([Horton 1971](#)).

Since the last update, one RCT (538 participants) has reported on use of WBRT and optimal supportive care versus optimal supportive care alone in participants with multiple brain metastases from non-small-cell lung cancer ([Mulvenna 2016](#)).

We added the following three categories since the last update.

WBRT and molecular targeted agents

[Sperduto 2013](#) examined both chemotherapy and molecular targeted therapy. Investigators randomised participants with metastatic non-small-cell lung cancer to brain to one of three groups: WBRT and radiosurgery versus WBRT; radiosurgery and temozolomide chemotherapy versus WBRT; or radiosurgery and the targeted agent, erlotinib.

WBRT with or without neurocognitive sparing agents

[Brown 2013](#) randomised participants with brain metastases to memantine versus placebo. Memantine is a potentially neurocognitive protective agent.

[Rapp 2015](#) randomised participants with brain metastases and primary brain tumour who had undergone partial brain radiotherapy or WBRT to donepezil (also a potential neurocognitive protective agent) versus placebo.

Hippocampal sparing WBRT versus WBRT

No fully published phase III randomised trials have examined use of hippocampal sparing WBRT versus WBRT. However, phase 3 trials are ongoing ([NRG-CC001](#); [Sturm 2015](#)). It is hypothesised that minimising radiation dose to the hippocampus might be associated with less cognitive decline after WBRT.

Excluded studies

We excluded one study because the trial design did not include a standard WBRT dose-fractionation group (3000 cGy in 10 fractions, or 2000 cGy in 5 fractions) ([Haie-Meder 1993](#)).

We excluded another trial as the radiotherapy group used three-dimensional conformal radiation therapy (3D CRT) rather than WBRT ([Wang 2015](#)).

Risk of bias in included studies

See [Figure 1](#) and [Figure 2](#).

Allocation

We assessed the method used to generate the allocation sequence as conferring low risk of bias when investigators used any truly random process, and when treatment allocation was protected before and until assignment.

Incomplete outcome data

We defined risk as low when less than 10% of participants did not complete the outcome assessment. Not all studies described the percentage of missing data in sufficient detail to allow a judgement (classified as unclear risk).

Selective reporting

We deemed overall survival as not subject to reporting bias. We determined that other outcomes reported in included trials such as progression-free survival, quality of life, and adverse effects may have been subject to possible selective outcomes reporting bias.

Effects of interventions

See: [Summary of findings for the main comparison](#) Altered WBRT fractionation schedules compared with WBRT control for treatment of newly diagnosed multiple brain metastases; [Summary of findings 2](#) Altered WBRT fractionation schedules compared with WBRT control: neurological function improvement for treatment of newly diagnosed multiple brain metastases; [Summary of findings 3](#) WBRT with radiosensitisers (radiosen) compared with WBRT alone for treatment of newly diagnosed multiple brain metastases; [Summary of findings 4](#) WBRT and radiosurgery compared with WBRT for treatment of newly diagnosed multiple brain metastases; [Summary of findings 5](#) Radiosurgery alone compared with WBRT

and radiosurgery for treatment of newly diagnosed multiple brain metastases

1. Altered WBRT dose-fractionation schedules versus conventional WBRT fractionation schedule (control: 3000 cGy in 10 daily fractions, or 2000 cGy in 4 or 5 daily fractions)

Ten reports examining the effectiveness of different dose-fractionation schedules of WBRT provided data for statistical analysis (Borgelt 1980a; Borgelt 1981a; Chatani 1985; Chatani 1994; Davey 2008; Graham 2010; Harwood 1977; Kurtz 1981; Murray 1997; Priestman 1996).

Regine 2001 reported on neurocognitive outcomes in participants with brain metastases treated in the Murray 1997 trial of accelerated fractionation versus accelerated hyperfractionated WBRT.

Dose response was the primary outcome for this comparison. To evaluate dose response, investigators compared many different dose-fractionation schedules. The most commonly employed 'control' regimen was 3000 cGy in 10 daily fractions. Investigators used the concept of 'biological equivalent dose' (BED) to facilitate comparison between different dose-fractionation regimens.

BED can be calculated using the equation $BED = nd [1 + d/(\alpha/\beta)]$, where n = number of fractions, d = dose per fraction, and α/β = 10 for tumour (Hall 2000). For the purpose of assessing dose response, review authors divided studies into those comparing lower biological doses versus 3000 cGy in 10 daily fractions and those comparing higher biological doses versus 3000 cGy in 10 daily fractions. To explore whether a dose response relationship was present, we used relative biological effectiveness (RBE) = 39 Gy for the fractionation scheme of 3000 cGy in 10 daily fractions as a control. We compared outcomes between RBE < 39 Gy versus 39 Gy and 39 Gy versus > 39 Gy.

With regard to the outcomes of interest, none of the included trials reported on:

1. intracranial progression-free duration;
2. local brain control (CR + PR + SD);
3. local brain tumour response (CR + PR);
4. quality of life; or
5. the proportion of participants able to reduce their dexamethasone dose.

Overall survival

Data for this outcome were available from eight trials (Chatani 1985; Chatani 1994; Davey 2008; Graham 2010; Harwood 1977; Kurtz 1981; Murray 1997; Priestman 1996).

Three trials compared lower-dose radiation with RBE < 39 Gy (2000 cGy in 5 fractions, 1000 cGy in a single fraction, or 1200 cGy in 2 fractions) versus standard-dose WBRT with RBE = 39 Gy (3000 cGy in 10 fractions) (Chatani 1994; Harwood 1977; Priestman 1996). Combining these data in a meta-analysis revealed an HR of 1.21 (95% CI 1.04 to 1.40; $P = 0.01$, favouring 3000 cGy in 10 fractions; moderate-certainty evidence) (Analysis 1.1; Summary of findings for the main comparison).

Of note, Chatani 1994 reported median and one-year survival as 3.4 months versus 2.4 months and 6% versus 4% ($P = 0.943$) for

participants treated with 3000 cGy in 10 daily fractions versus 2000 cGy in 5 daily fractions of WBRT, respectively.

Four trials compared higher-dose WBRT with RBE > 39 Gy (5000 cGy in 20 fractions, or 5440 cGy in 34 fractions twice daily) versus standard-dose WBRT with RBE = 39 Gy (3000 cGy in 10 fractions) (Chatani 1985; Chatani 1994; Kurtz 1981; Murray 1997). Pooling of data from these four trials revealed an HR for survival of 0.97 (95% CI 0.83 to 1.12; $P = 0.65$; moderate-certainty evidence) (Analysis 1.2; Summary of findings for the main comparison).

We could not obtain overall survival data from published reports of Borgelt 1980a, Borgelt 1980b, Borgelt 1981a, and Borgelt 1981b.

Two published RCTs examined participants treated with WBRT 4000 cGy in 20 fractions twice daily (BID) versus standard WBRT 2000 cGy in 4 or 5 daily fractions. Davey 2008 randomised participants to 4000 cGy in 20 fractions BID WBRT versus 2000 cGy in 5 daily fractions WBRT. Graham 2010 randomised participants to 4000 cGy in 20 fractions BID WBRT versus 2000 cGy in 4 daily fractions WBRT. Pooling of data from these two trials revealed an HR for survival of 1.18 (95% CI 0.89 to 1.56; $P = 0.25$; moderate-certainty evidence) (Analysis 1.3; Summary of findings for the main comparison).

Symptom control

Seven published reports assessed symptom control (Borgelt 1980a; Borgelt 1981a; Chatani 1985; Chatani 1994; Harwood 1977; Kurtz 1981; Priestman 1996). However, investigators used a variety of scales (e.g. neurological symptom relief, palliative index, performance status), making statistical pooling of data not meaningful. Considered individually, none of these trials showed a difference in symptom control with altered dose-fractionation schedules as compared with control (3000 cGy in 10 fractions).

Overall brain control

A post hoc subset analysis from the Davey 2008 trial showed that time to retreatment for intracranial relapse was 14 weeks in the control WBRT group (2000 cGy in 5 daily fractions) as compared with 32 weeks in the 4000 cGy in 20 BID (twice-daily) fractions group ($P = 0.03$). The primary endpoint for Graham 2010 was the proportion of participants with overall brain progression. Brain progression was worse for participants treated with 2000 cGy in 4 fractions as compared with those given 4000 cGy in 20 BID fractions (64% vs 44%; $P = 0.03$, respectively).

Neurological function

We pooled neurological function outcomes from seven reports (Borgelt 1980a; Borgelt 1981a; Chatani 1985; Chatani 1994; Harwood 1977; Kurtz 1981; Priestman 1996). Neurological function grading scales utilised were similar across trials and typically ranged from one (minimal interference) to four (comatose or requiring constant nursing care).

Three trials reported NFI only for participants with a baseline neurological function of grade 2 or 3 (Borgelt 1980a; Borgelt 1981a; Kurtz 1981). Within this limitation, the OR was 1.14 (95% CI 0.92 to 1.42; $P = 0.23$; moderate-certainty evidence) for those treated with a biologically higher dose versus those given the control dose (Analysis 2.2).

The OR was 1.74 (95% CI 1.06 to 2.84; $P = 0.027$; moderate-certainty evidence) for NFI, favouring the control WBRT dose of 3000 cGy

in 10 daily fractions as compared with a lower dose ([Analysis 2.1; Summary of findings 2](#)). The duration of any improvement was not consistently reported.

[Regine 2001](#) reported on neurocognitive outcomes in participants with brain metastases treated in the [Murray 1997](#) trial of accelerated fractionation versus accelerated hyperfractionated WBRT. Mini-Mental State Examination (MMSE) scores showed that neurocognitive function outcomes between the two treatment groups of the trial were similar. However, at three months, participants with uncontrolled brain metastases showed a significant drop in MMSE scores as compared with participants with radiographically controlled brain metastases.

Adverse effects

Included trials inconsistently reported adverse effects among participants in terms of incidence and grade. [Borgelt 1981a](#) described no differences in treatment morbidity (defined as worsening of neurological symptoms or the appearance of new symptoms) among treatment groups.

[Chatani 1994](#) reported that no participant experienced grade 3 or higher acute toxicity. [Chatani 1985](#) did not report adverse effects.

In the [Harwood 1977](#) study, 40% (of 51 participants) treated with a single dose of WBRT developed acute complications (increased headache, nausea and vomiting, neurological deficit; or a fall in the level of consciousness) compared with 27% (of 50 participants) treated with the fractionated course. This difference did not reach statistical significance ($P = 0.254$).

Murray's study of accelerated hyperfractionation versus 3000 cGy in 10 fractions over 10 days resulted in one grade 4 ototoxicity and one grade 5 toxicity (death) due to cerebral oedema in the accelerated hyperfractionation group ($N = 216$ participants) ([Murray 1997](#)). Data show no differences in the incidence of acute grade 3 toxicity nor in the incidence of grade 3 or 4 late toxicity.

In [Priestman 1996](#), 22 (of 274) participants treated with 1200 cGy in 2 fractions of WBRT developed drowsiness or lethargy, headache, nausea or vomiting, dizziness or ataxia, cerebral haemorrhage, blurred vision, or fits, as compared with 13 (of 270) participants treated with 3000 cGy in 10 fractions.

[Davey 2008](#) reported similar central nervous system late effects of normal tissues (LENT)/subjective, objective, management, analytical (SOMA) scores between the two groups.

In the [Graham 2010](#) trial, late significant toxicity was uncommon. Grade 2 or higher toxicity occurred in one participant in each group.

2. WBRT plus radiosensitisers versus WBRT

We did not pool results from [Scott 2007](#), as this report described a post hoc subset analysis of participants with breast cancer randomised to WBRT and efaproxiral versus WBRT alone ([Suh 2006](#)). A larger confirmatory trial, which included participants with breast cancer only (a priori), was subsequently published in abstract form ([Suh 2008](#)). We could not pool results from [Suh 2008](#) as the abstract provided insufficient details.

[Mehta 2003](#) reported on 401 participants with a variety of primary cancers metastatic to brain randomised to WBRT with or without motexafin gadolinium.

[Mehta 2009](#) reported on 554 participants with non-small-cell lung cancer as primary cancer metastatic to brain randomised between December 2002 and March 2005 to WBRT with or without motexafin gadolinium.

These publications did not describe whether duplicate participants may have been reported by [Mehta 2003](#) and [Mehta 2009](#).

Nine fully published RCTs examined use of radiosensitisers in addition to WBRT ([DeAngelis 1989](#); [El-Hamamsy 2016](#); [Eyre 1984](#); [Komarnicky 1991](#); [Mehta 2003](#); [Mehta 2009](#); [Phillips 1995](#); [Suh 2006](#); [Zeng 2016](#)).

With regard to the following outcomes of interest, none of the included trials reported on:

1. neurological function; or
2. proportions of participants who were able to reduce their daily dexamethasone dose and the duration of reduced dexamethasone requirements.

Overall survival

We pooled data on survival from eight trials ([El-Hamamsy 2016](#); [Eyre 1984](#); [Komarnicky 1991](#); [Mehta 2003](#); [Mehta 2009](#); [Phillips 1995](#); [Suh 2006](#); [Zeng 2016](#)). When these data were combined, the HR was 1.05 (95% CI 0.99 to 1.12; $P = 0.12$; moderate-certainty evidence) for overall survival ([Summary of findings 3](#)).

[DeAngelis 1989](#) examined use of WBRT with or without lonidamine. Median survival was 165 days for the WBRT group versus 120 days for the lonidamine group ($P = 0.42$). Details were insufficient to generate a hazard ratio for survival from this study, and as such we could not pool survival data.

Local brain tumour response

Six trials reported on local brain tumour response rates - complete response (CR) or partial response (PR) ([DeAngelis 1989](#); [El-Hamamsy 2016](#); [Eyre 1984](#); [Phillips 1995](#); [Suh 2006](#); [Zeng 2016](#)). The OR was 0.84 (95% CI 0.63 to 1.11; $P = 0.22$; high-certainty evidence) for response rate between participants receiving only WBRT and those receiving treatment with WBRT and radiosensitisers ([Analysis 3.2](#); [Summary of findings 3](#)).

Quality of life

[Mehta 2003](#) reported quality of life outcomes for 401 participants with lung cancer, breast cancer, melanoma, and other cancers randomised to motexafin gadolinium and WBRT or WBRT alone. Data show similar time to progression for brain-specific quality of life assessment (Functional Assessment of Cancer Therapy-Brain (FACT-BR)) in both treatment groups.

[Mehta 2009](#) did not report quality of life outcomes using validated quality of life instruments.

[Suh 2006](#) reported on Spitzer Quality of Life Index and KPS outcomes for participants randomised to efaproxiral and WBRT versus WBRT alone. A higher proportion of participants in the efaproxiral group had stable or improving quality of life scores and KPS ratings (OR 1.21 and 1.38, respectively; $P = 0.008$) as compared with participants treated with WBRT alone.

El-Hamamsy 2016 reported on quality of life using European Organization for Research and Treatment of Cancer core quality of life questionnaires (EORTC QLQ-C30). However, the number of participants (N = 29) at four weeks was too small to allow any meaningful comparisons.

Symptom control

For participants receiving WBRT with or without the radiosensitiser misonidazole (Komarnicky 1991), data show no differences between treatment groups in the percentage of total survival time spent in an improved or stable KPS, nor in median time to deterioration of KPS. The percentage of participants who spent 90% to 100% of their survival time in an improved or stable neurological state was also similar among treatment and control groups.

Meyers 2004 reported on participants in the Mehta 2003 trial of WBRT with or without motexafin gadolinium. The HR for all eight neurocognitive tests was 0.66 (P = 0.114). Participants with lung cancer (but not other types of cancer) who were treated with motexafin gadolinium in addition to WBRT tended to have improved memory and executive function (P = 0.062) along with improved neurological function as assessed by a blinded events review committee (P = 0.048).

In Mehta 2009, the interval to neurological progression (based on symptoms and radiographic findings) for participants treated with WBRT and motexafin gadolinium as compared with those treated with WBRT alone was 15 months versus 10 months (HR 0.78; P = 0.12). We concluded that motexafin gadolinium did not confer an overall advantage in survival or time to neurological progression for the entire cohort. Subgroup analyses suggest that participants with lung cancer may benefit (in the light of improved neurological function, memory, and executive function). A randomised trial examining this specific subgroup has been published (Mehta 2009).

Adverse effects

All nine fully published trials that assessed the addition of radiosensitisers to WBRT reported serious adverse effects.

Participants who received WBRT and metronidazole in the Eyre 1984 study reported a 51% (of 57 participants) incidence of nausea and vomiting compared with 3.2% (of 54 participants) in the WBRT-alone group.

DeAngelis 1989 found that the most common side effects of lonidamine and WBRT were myalgia (68%, or 21/31), testicular pain (42%, or 8/19 of men), anorexia (26%, or 8/31), ototoxicity (26%, or 8/31), malaise or fatigue (26%, or 8/31), and nausea and vomiting (19%, or 6/31). Investigators noted no acute or subacute radiation-related neurotoxicity in either treatment group.

Komarnicky 1991 reported that misonidazole administration with WBRT was well tolerated and produced no grade 3 neurotoxicity or ototoxicity. However, investigators noted several (number not reported) grade 3 symptoms of nausea and vomiting (defined as occurring one to three times daily).

Phillips 1995 reported three fatal toxicities in 34 participants randomised to WBRT with administration of the radiosensitiser BrdU. One death resulted from a severe Stevens-Johnson skin reaction (a rare and severe adverse reaction to sulphonamides involving skin and mucous membranes of the eyes, mouth, nose,

and genitals with ulceration and loss of epithelium) and two other deaths were due to neutropenia and infection. Trial authors noted no increase in rate of radiation skin reactions or central nervous system injuries in the BrdU group of this study.

Mehta 2003 reported grade 3 and 4 adverse events - hypotension (5.8%), asthaenia (2.6%), hyponatraemia (2.1%), leukopaenia (2.1%), hyperglycaemia (1.6%), and vomiting (1.6%) - among 193 participants randomised to the WBRT and motexafin gadolinium group.

In the Suh 2006 trial, 28% of participants in the efaproxiral group experienced grade 3 or 4 treatment-emergent adverse events. The most common efaproxiral severe adverse effect was hypoxaemia (11%; 29 of 266 participants).

Mehta 2009 reported that the most frequent motexafin gadolinium side effects (all grades) were green discolouration (68%), chromaturia (35%), asthaenic conditions (51%), nausea/vomiting (44%), pain and paraesthesia (28%), finger blisters (20%), hypertension (20%), diarrhoea (22%), headache (30%), liver function abnormalities (11%), dizziness (14%), rash (10%), arthralgia (10%), and gastrointestinal and abdominal pain (9%).

El-Hamamsy 2016 reported that use of simvastatin added to WBRT was tolerated. Data show a significant difference within the simvastatin group with respect to serum alanine aminotransferase (ALT) at baseline median 24 IU/L (95% CI 16 to 29) and after WBRT 36 IU/L (95% CI 17 to 59) (P = 0.035).

Zeng 2016 reported no significant differences in toxicity between WBRT with or without sodium gycididazole and no grade 4 or 5 toxicities.

3. WBRT and systemic therapy

A total of nine fully published trials have provided information on comparison of the effectiveness of WBRT and systemic therapy (Guerrieri 2004; Knisely 2008; Lee 2008; Mornex 2003; Neuhaus 2009; Postmus 2000; Robinet 2001; Sperduto 2013; Ushio 1991). However, we could not pool results from the trials of systemic therapy and WBRT owing to the heterogeneity of study interventions. Therefore, we report the results for each trial separately.

In the randomised controlled trial by Ushio 1991, investigators randomised 100 participants to one of three treatment groups and reported brain tumour regression (more than 50%) as follows.

1. WBRT alone (36%, or 5/14).
2. WBRT plus chloroethyl nitrosoureas (methyl-CCNU or ACNU) (69%, or 11/16).
3. WBRT plus chloroethyl nitrosoureas plus tegafur (74%, or 14/19).

Response rates were 36% (5/14) for WBRT alone and 74% (14/19) for WBRT + chloroethyl nitrosoureas + tegafur (P < 0.05). For median survival times, however, three groups reported P > 0.05.

1. WBRT alone, 27 weeks.
2. WBRT plus chloroethyl nitrosoureas (methyl-CCNU or ACNU), 29 weeks.
3. WBRT plus chloroethyl nitrosoureas plus tegafur, 30.5 weeks.

Investigators did not provide information regarding intracranial progression-free duration, quality of life, symptom control, neurological function, and ability to taper down on dexamethasone dose. Two participants died of probable adverse effects of chemotherapy.

Postmus 2000 conducted an RCT on use of teniposide chemotherapy with or without WBRT in participants with small-cell lung cancer metastatic to brain. Data show a 57% response rate in the combined modality group and a 22% response rate in the teniposide-alone group ($P < 0.001$). Time to brain progression was longer in the combined group ($P = 0.005$). Response outside the brain was no different. Median survival was 3.5 months for the combined group versus 3.2 months for the teniposide-only group ($P = 0.87$). Forty-five teniposide-only participants and 43 combined modality participants had a neurological function score both at baseline and after cycle two. Among participants in the teniposide-only group, eight improved and 34 remained stable compared with 12 and 23, respectively, in the combined modality group. Trial authors did not report quality of life outcomes and did not report the proportions of participants able to reduce their dexamethasone dose. Toxicities were mild, and the most common toxicity was haematological, resulting in dose delays in 45 participants and dose reductions in eight participants. Non-haematological toxicities occurred infrequently, for example, World Health Organization (WHO) grade 3 or 4 nausea and vomiting occurred in 11% of 60 participants treated with combined modality, and in 5% of 60 participants treated with teniposide only. WHO grade 3 or 4 infection occurred in 4% of 60 participants treated with combined modality and in 6% of 60 participants treated with teniposide only. Less than 3% of 60 participants in each group experienced mucositis, headache, or cutaneous reactions not exceeding WHO grade 3 toxicity.

Robinet 2001 examined early versus delayed WBRT with concurrent cisplatin and vinorelbine chemotherapy in participants with metastatic non-small-cell lung cancer. WBRT was given on a delayed (after two to six cycles of chemotherapy for intracranial non-responders) or early basis (on days 1 to 12 during the first cycle of chemotherapy). Median survival duration was 24 weeks in the delayed radiotherapy group and 21 weeks in the early radiotherapy group ($P = 0.12$). Investigators did not report intracranial progression-free duration, quality of life, symptom control, neurological function, or ability to reduce dexamethasone dose but did report a high number of deaths:

- as a result of toxicity - 13 participants (six in the delayed radiotherapy group (6.9%) and seven in the early radiotherapy group (8.2%));
- as a result of sepsis during severe neutropenia - 10 participants;
- from pneumonia (without neutropaenia) - one participant in each study group following the second cycle of chemotherapy; and
- from renal failure - one participant in the delayed chemotherapy group after the first cycle.

Mornex 2003 reported on use of fotemustine combined with WBRT (37 participants) versus fotemustine alone (39 participants) for metastatic melanoma to brain. Median survival was 86 days in the fotemustine-alone group versus 105 days in the combined treatment group ($P = 0.73$). Objective cerebral response at day 50 was 7.4% in the fotemustine-alone group versus 10% in the

combined treatment group ($P = 0.73$). Investigators did not report quality of life, symptom control, neurological function, or ability to reduce dexamethasone dose. Myelosuppression was the most severe adverse event. Delayed grade 3 to 4 neutropaenia occurred in 46% of 39 participants in the fotemustine-alone group and in 35% of 37 participants in the combined treatment group. Delayed grade 3 to 4 thrombocytopenia occurred in 44% of 39 participants in the fotemustine-alone group and in 38% of 37 participants in the combined treatment group. Severe anaemia occurred in 5% of 39 participants in the fotemustine-alone group and in 11% of 37 participants in the combined treatment group. One participant suffered a cerebral haemorrhage, and three participants died of pneumonia.

Guerrieri 2004 randomised participants with brain metastases from non-small-cell lung cancer to WBRT alone versus WBRT and carboplatin chemotherapy. The planned accrual target was 300 participants. However, the study was closed early owing to poor accrual, and investigators reported the results of 42 participants entered into the study. As such, no firm conclusions could be drawn. From this small sample, median survival was 4.4 months in the WBRT group versus 3.7 months in the combined group ($P = 0.64$). Objective brain response rates were 10% in the WBRT group and 29% in the combined treatment group ($P = 0.24$).

Knisely 2008 compared WBRT versus WBRT and thalidomide. Median survival was 3.9 months for both groups. Trialists noted no novel toxicities but reported that thalidomide was not tolerated. Forty-eight per cent of participants discontinued thalidomide because of side effects. Time to brain progression curves was similar ($P = 0.097$) between the two treatment groups.

Lee 2008 included participants with metastatic non-small-cell lung cancer to the brain treated with primary chemotherapy (gemcitabine and vinorelbine) followed by WBRT versus WBRT first then followed by the same chemotherapy. Progression-free survival was 3.6 months versus 4.4 months ($P = 0.62$), and overall survival was 9.1 months versus 9.9 months ($P = 0.61$), for primary chemotherapy versus WBRT first groups, respectively. In the WBRT first group, grade 3 or 4 neutropaenia was more frequent (79% vs 40%) during chemotherapy.

Neuhaus 2009 randomised participants with brain metastases from lung cancer (small-cell lung cancer or non-small-cell lung cancer) to WBRT and topotecan chemotherapy versus WBRT alone. The trial was stopped early because of poor accrual (total of 96 participants compared with a planned 320 participants). Data show no significant differences in overall survival (HR 1.32, 95% CI 0.83 to 2.10; $P = 0.43$) or progression-free survival (HR 1.28, 95% CI 0.73 to 2.43; $P = 0.89$). Haematological events occurred mainly in the combined treatment group.

Sperduto 2013 randomised participants with brain metastases with non-small-cell lung cancer to WBRT and radiosurgery versus WBRT and radiosurgery plus temozolomide chemotherapy or the molecular targeted agent erlotinib. The trial was stopped early owing to poor accrual (total 126 participants enrolled of a planned 381 participants). The addition of temozolomide or erlotinib to WBRT and radiosurgery was associated with worse survival and toxicity. Median survivals for WBRT and radiosurgery versus WBRT and radiosurgery and temozolomide versus WBRT and radiosurgery and erlotinib were 13.4 (95% CI 6.5 to 20.8), 6.3 (95% CI 3.4 to 10.1),

and 6.1 (95% CI 3.6 to 12.1) months, respectively. Grade 3 to 5 toxicities were 11%, 41%, and 49%, respectively ($P < 0.001$).

4. WBRT plus radiosurgery versus WBRT

Four trials provided information on the effectiveness of WBRT alone compared with WBRT plus radiosurgery (Andrews 2004; Chougule 2000; El Gantery 2014; Kondziolka 1999). The Chougule 2000 trial was published in abstract form and the full report has never been published.

No trials reported the following outcomes of interest.

1. Quality of life.
2. Symptom control.

Overall survival

(See comparison Analysis 4.1.)

We pooled results of the two fully published reports (Andrews 2004; Kondziolka 1999). The HR for overall survival was 0.61 (95% CI 0.27 to 1.39; $P = 0.24$; moderate-certainty evidence) (Summary of findings 4) between participants with multiple brain metastases treated with WBRT and radiosurgery boost as compared with WBRT alone.

Andrews 2004 reported improved survival ($P = 0.0393$) for the subset of participants with surgically unresectable single brain metastasis treated with WBRT and radiosurgery boost as compared with WBRT alone (median survival 6.5 months vs 4.9 months).

We could not pool survival data from the El Gantery 2014 trial as an HR could not be calculated owing to lack of detail in the publication. Chougule 2000 (reported in abstract form) also did not find median survival differences (P value not stated) among the randomised groups (radiosurgery alone: seven months; radiosurgery and WBRT: five months; WBRT alone: nine months). We could not pool results of the Chougule 2000 trial as insufficient detail was available from the published abstract.

One-year overall brain tumour control

(See comparison Analysis 4.2.)

Local control was defined as unchanged or improved serial post-treatment MRI scans judged as showing complete response, partial response, or stable disease. Progressive disease was defined as an increase in size of any brain lesion, development of new brain lesions, or stable disease with neurological deterioration. We pooled data for one-year overall brain control provided by the Kondziolka 1999, Andrews 2004, and El Gantery 2014 trials, and found that overall, the HR was 0.39 (95% CI 0.25 to 0.60; $P < 0.0001$; high-certainty evidence) for local brain control favouring the WBRT and radiosurgery boost group (Summary of findings 4). Data on one-year local brain control were not provided in the Chougule 2000 abstract.

Intracranial progression-free duration

In the Kondziolka 1999 trial, median time to local brain failure was six months after WBRT alone (95% CI 3.5 to 8.5) in comparison with 36 months after WBRT and radiosurgery boost (95% CI 15.6 to 57). In the Andrews 2004 trial, the P value was 0.1278 with respect to overall time to intracranial tumour progression or neurological death rates between those treated with WBRT and radiosurgery

boost as compared with WBRT alone. The Chougule 2000 abstract and the El Gantery 2014 report did not describe intracranial progression-free duration. We could not pool these results owing to differences in reporting of this outcome.

Neurological function

Kondziolka 1999, Chougule 2000, and El Gantery 2014 did not report neurological function outcomes. Andrews 2004 reported that the KPS was improved at six months in 10/79 or 13% of participants treated with WBRT and radiosurgery boost as compared with 3/75 or 4% of participants treated with WBRT alone ($P = 0.0331$). However, mental status as measured by the MMSE was similar between the two groups.

Proportion of participants who were able to reduce their daily dexamethasone dose and duration

Andrews 2004 reported that a higher proportion of participants (41/79) in the WBRT and radiosurgery group had decreased steroid requirements at six months as compared with 25/75 participants in the WBRT-alone arm ($P = 0.0158$). The other trials did not report dexamethasone use.

Adverse effects

Kondziolka 1999 reported no neurological or systemic morbidity related to stereotactic radiosurgery. After WBRT, participants expectedly developed mild scalp erythema and hair loss. In the Andrews 2004 trial, early and late toxicities did not differ greatly between the two treatment arms. However, investigators included more participants with acute grade 3 and 4 toxicity in the WBRT and radiosurgery boost arm (4/160 participants) than in the WBRT-alone arm (0/166 participants). Also, they reported more late grade 3 and 4 toxicity in the combined arm (6/160 participants) than in the WBRT-alone arm (3/166 participants). El Gantery 2014 reported no differences in acute nor late toxicities among randomised groups.

5. Radiosurgery alone versus radiosurgery and WBRT

For this updated review, we identified two new fully published trials (on radiosurgery alone versus radiosurgery and WBRT (Brown 2016; Fogarty 2015).

Fogarty 2015 randomised participants with metastatic melanoma brain metastases to local therapy (neurosurgical resection or radiosurgery) followed by WBRT or observation.

None of the trials examining use of radiosurgery alone versus radiosurgery and WBRT reported on response rates of brain metastases (CR + PR) nor on the percentage of participants able to reduce the dexamethasone dose or the duration of a reduced dexamethasone dose (Aoyama 2006; Brown 2016; Chang 2009; Fogarty 2015; Kocher 2011).

Overall survival

The HR for the pooled overall survival analysis for three RCTs (Aoyama 2006; Brown 2016; Chang 2009) was 1.0 (95% CI 0.80 to 1.25, $P = 0.99$; moderate-certainty evidence) (Analysis 5.1; Summary of findings 5).

Fogarty 2015 did not report on survival outcomes.

In the Kocher 2011 trial, overall survival for radiosurgery alone versus WBRT and radiosurgery boost could not be

isolated. Nevertheless, median survival was 10.9 months (among participants treated with combined therapy) versus 10.7 months (in those treated with surgery or radiosurgery alone) ($P = 0.89$).

One-year radiosurgery-targeted lesion control

Data from four trials show an HR of 2.73 (95% CI 1.87 to 3.99; $P < 0.00001$) for one-year radiosurgery-targeted lesion control (Analysis 5.2), with high-certainty evidence favouring WBRT and radiosurgery versus radiosurgery alone (Summary of findings 5) (Aoyama 2006; Brown 2016; Chang 2009; Kocher 2011).

Fogarty 2015 did not report local brain control outcomes by randomised study group.

One-year distant brain control

The HR from four trials was 2.34 (95% CI 1.73 to 3.18; $P < 0.00001$) for one-year distant brain control (Analysis 5.3), with high-certainty evidence favouring WBRT and radiosurgery versus radiosurgery alone (Summary of findings 5) (Aoyama 2006; Brown 2016; Chang 2009; Kocher 2011).

Fogarty 2015 did not report distant brain control outcomes by randomised study group.

Neurological function

Aoyama 2006 reported systemic functional preservation rates (KPS ≥ 70) at 12 months of 33.9% in the WBRT and radiosurgery arm as compared with 26.9% in the radiosurgery-alone arm ($P = 0.53$). The neurological preservation rate at 12 months was 72.1% in the WBRT and radiosurgery arm, similar to 70.3% in the radiosurgery alone arm ($P = 0.99$).

Chang 2009 did not describe neurological function outcomes.

In Kocher 2011, the duration of functional independence was the primary endpoint (defined as the date of randomisations to the first report of WHO performance status decline > 2). Median time to WHO performance status greater than 2 (survival with functional independence) was 10 months in the surgery or radiosurgery-alone arm versus 9.5 months in the surgery and WBRT or radiosurgery and WBRT arms ($P = 0.71$).

Brown 2016 reported that Barthel activity of daily living scores were not significantly different between the two randomised groups.

Fogarty 2015 did not report neurological function outcomes.

Neurocognition

The Aoyama 2006 trial used a crude measure of neurocognition - the MMSE. Aoyama 2006 reported that average duration until MMSE deterioration was 16.5 months in the WBRT and radiosurgery group versus 7.6 months in the radiosurgery-alone group ($P = 0.05$).

Neurocognition was the primary outcome in Chang 2009, which used a formal battery of neurocognitive tests. After 58 participants were entered, the trial was stopped early based on early stopping rules indicating the high probability (96%) that participants randomised to radiosurgery and WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at four months compared with participants treated with radiosurgery alone (mean posterior probability of decline 24%).

Kocher 2011 did not report neurocognitive outcomes.

The primary endpoint in the Brown 2016 trial was cognitive deterioration, which was less frequent in the radiosurgery-alone group than in the radiosurgery plus WBRT group (63.5% vs 91.7%; $P < 0.001$).

Fogarty 2015 did not report neurocognitive outcomes.

Quality of life

Aoyama 2006 did not report quality of life outcomes.

The Chang 2009 trial used the validated quality of life instrument FACT-BR. The FACT-BR mean difference between randomised groups at four months compared with baseline was 2.8 (95% CI -26 to 21; $P = 0.76$). Trial authors indicated, however, that the wide confidence interval implied that the quality of life results were inconclusive.

Kocher 2011 indicated that quality of life was a secondary endpoint but has not yet reported trial results related to quality of life.

Brown 2016 reported better overall quality of life at three months among participants randomised to radiosurgery alone compared with radiosurgery and WBRT ($P = 0.001$).

Fogarty 2015 did not report quality of life outcomes.

Side effects

Aoyama 2006 observed symptomatic acute neurological toxicity in four (of 65) participants receiving WBRT and radiosurgery and in eight (of 67) participants receiving radiosurgery alone ($P = 0.36$). Investigators noted symptomatic late neurological toxic effects in seven participants in the WBRT and radiosurgery group versus three participants in the radiosurgery-alone group ($P = 0.20$).

Chang 2009 reported one case of grade 3 toxicity in the radiosurgery and WBRT group and one case of grade 3 toxicity in the radiosurgery-alone group that were attributable to radiation. Data also show two cases of grade 4 toxicity (pathologically proven radiation necrosis) in the radiosurgery-alone group.

Kocher 2011 reported 16 serious acute toxicities (13 participants in the surgery and WBRT or radiosurgery and WBRT group and three participants in the surgery or radiosurgery-alone group). Trialists noted symptomatic radionecrosis in 8% (7/90 participants) after radiosurgery alone and in 13% (12/95 participants) after treatment with radiosurgery and WBRT.

Brown 2016 reported no differences in grade 3 or higher adverse effects between the two randomised groups.

Fogarty 2015 reported minimal adverse events and no serious adverse events related to the trial.

6. Steroids alone versus steroids and WBRT

One randomised trial examined use of prednisone with or without WBRT (Horton 1971). This small trial (48 recruited participants) was conducted at a time when computed tomography (CT) scanning was not available. Participants were enrolled in the study if they had a histologically proven cancer and clinical symptoms and signs of brain metastases, such as abnormalities identified by radioisotope brain scans, electroencephalograms

(EEGs), angiograms, and spinal fluid chemistry and cytology. The proportion of participants with improved performance status was similar in the prednisone-alone and WBRT plus prednisone groups (63% of 19 participants and 61% of 28 participants, respectively). Median survival time in the prednisone-alone group was 10 weeks as compared with 14 weeks in the combined treatment group (P value not stated). Participants were not stratified for other known prognostic factors such as age, performance status, and extent of extracranial disease. Investigators did not report other outcomes such as intracranial progression-free duration, quality of life, symptom control, neurological function, toxicities, and ability to taper steroid doses.

[Mulvenna 2016](#) published a multi-centre randomised controlled trial of optimal supportive care (including use of dexamethasone) and WBRT versus optimal supportive care alone in 538 non-small-cell lung cancer participants with brain metastases not eligible for surgery or radiosurgery. The HR for overall survival was 1.06 (95% CI 0.90 to 1.26; $P = 0.8084$) between the two randomised groups. As well, overall quality of life and dexamethasone use were similar between the two groups. The primary endpoint was quality-adjusted life-years, which was 46.4 days, with a standard deviation (SD) of 3.66 days for those assigned to optimal supportive care and WBRT versus 41.7 days (SD 3.23) for participants randomised to optimal supportive care alone. The mean difference was only 4.7 days in favour of optimal supportive care and WBRT. Trial authors reported no differences in symptoms or side effects and no performance status changes in both groups. They did not report brain control and response.

We could not pool data from [Horton 1971](#) and [Mulvenna 2016](#), as [Horton 1971](#) did not publish results in sufficient detail.

7. WBRT alone or with molecular targeted agents

[Sperduto 2013](#) examined both chemotherapy and molecular targeted therapy. Investigators randomised participants with metastatic non-small-cell lung cancer to brain to one of three groups: WBRT and radiosurgery; WBRT, radiosurgery, and temozolomide chemotherapy; or WBRT, radiosurgery, and the targeted agent, erlotinib. The trial was stopped early owing to poor accrual (total 126 participants enrolled of a planned 381 participants). The addition of temozolomide or erlotinib to WBRT and radiosurgery was associated with worse survival and toxicity. Median survival for WBRT and radiosurgery versus WBRT and radiosurgery and temozolomide versus WBRT and radiosurgery and erlotinib was 13.4 (95% CI 6.5 to 20.8), 6.3 (95% CI 3.4 to 10.1), and 6.1 (95% CI 3.6 to 12.1) months, respectively. Grade 3 to 5 toxicities were 11%, 41%, and 49%, respectively ($P < 0.001$).

[Yang 2015](#) outlined in abstract form an ongoing phase 3 randomised trial of WBRT with or without erlotinib for metastatic non-small-cell lung cancer to brain. Trialists did not report results in this abstract.

8. WBRT alone or with neurocognitive protective agents

The [Brown 2013](#) double-blind trial randomised participants with brain metastases to memantine versus placebo. The primary outcome was median decline in delayed recall at 24 weeks, which was 0 in the memantine group and -0.90 in the placebo group ($P = 0.059$). However, owing to attrition, Investigators analysed only 149 (of 554 randomised) participants at that time point. For the secondary endpoint - time to cognitive failure - trial authors reported that participants in the memantine group had longer time

to cognitive decline (HR 0.78, 95% CI 0.62 to 0.99; $P = 0.01$). The memantine group was favoured for executive function at 8 weeks ($P = 0.008$) and at 16 weeks ($P = 0.0041$). In addition, the memantine group was better for processing speed ($P = 0.0137$) and delayed recognition ($P = 0.0149$) at 24 weeks. Grade 3 and 4 side effects were the same (28%) in both groups. The most common side effects were fatigue, alopecia, nausea, and headache, with no differences reported between the two groups. Investigators did not report quality of life.

[Rapp 2015](#) was a double-blind trial that randomised participants with brain metastases and primary brain tumour who had received partial brain radiotherapy or WBRT to donepezil versus placebo. At 24 weeks, mean composite cognitive score was 0.22 versus 0.19 in donepezil and control groups, respectively ($P = 0.484$). For the subset analysis of memory recognition ($P = 0.027$), memory discrimination ($P = 0.007$), and motor speed/dexterity ($P = 0.016$), use of donepezil was favoured. Trial authors did not report survival, progression-free survival, quality of life, dexamethasone use, neurological function, or side effects.

Owing to the heterogeneity of included participants (brain metastasis and primary brain tumour) in the [Rapp 2015](#) trial, we did not pool these results. The subset of participants with brain metastases could not be separated in the [Rapp 2015](#) publication.

9. Hippocampal sparing WBRT versus WBRT

No fully published phase 3 randomised trials have examined use of hippocampal sparing WBRT versus WBRT. However, phase 3 trials are ongoing ([NRG-CC001](#); [Sturm 2015](#)). The [Sturm 2015](#) abstract described the planned hippocampal sparing trial but presented no results.

DISCUSSION

Summary of main results

Altered whole body radiation therapy (WBRT) dose-fractionation schedules versus conventional WBRT fractionation schedule

In summary, none of the included randomised controlled trials (RCTs) found benefit (in terms of overall survival, neurological function, or symptom control) with **higher** biological altered dose-fractionation schedules as compared with standard doses (3000 cGy in 10 fractions, or 2000 cGy in 4 or 5 daily fractions). Two studies provided data on comparison of two fractionation schedules commonly employed in Canada (2000 cGy in 5 fractions, or 3000 cGy in 10 fractions) ([Borgelt 1980a](#); [Chatani 1994](#)). Overall survival and neurological function were similar between these two fractionation schemes.

However, trials with **lower** biological altered dose-fractionation schedules reported worse survival and neurological function improvement (NFI) as compared with standard care.

Two trials reported on 4000 cGy in 20 twice-daily (BID) fractions WBRT versus 2000 cGy in 4 or 5 daily fractions WBRT ([Davey 2008](#); [Graham 2010](#)). The hazard ratio (HR) for overall survival was 1.18 (95% confidence interval (CI) 0.89 to 1.56; $P = 0.25$; moderate-certainty evidence).

A post hoc subset analysis in the [Davey 2008](#) trial showed that time to retreatment for intracranial relapse was 14 weeks in the

control WBRT group (2000 cGy in 5 daily fractions) as compared with 32 weeks in the 4000 cGy in 20 BID (twice-daily) fractions group ($P = 0.03$). The primary endpoint for the [Graham 2010](#) trial was proportion of participants with overall brain progression. Brain progression was worse for participants treated with 2000 cGy in 4 fractions as compared with 4000 cGy in 20 BID fractions (64% vs 44%; $P = 0.03$).

WBRT plus radiosensitisers versus WBRT

In an attempt to improve local brain control, clinicians have added radiosensitisers to WBRT. However, none of the included RCTs showed benefit in terms of overall survival or brain response (complete response (CR) + partial response (PR)). Use of radiosensitisers in these trials (lonidamine, metronidazole, misonidazole, bromodeoxyuridine (BrdU), motexafin gadolinium, efaproxiral) was associated with toxicity. Use of radiosensitisers with WBRT remains experimental.

WBRT and systemic therapy

All fully published phase 3 trials examining use of WBRT and chemotherapy versus WBRT alone reported no survival benefit with the addition of chemotherapy to WBRT. These trials showed an increase in toxicity when chemotherapy was added to WBRT.

Use of chemotherapy with WBRT remains experimental.

WBRT plus radiosurgery versus WBRT

We pooled results of the two fully published reports ([Andrews 2004](#); [Kondziolka 1999](#)). The HR for overall survival was 0.61 (95% CI 0.27 to 1.39; $P = 0.24$) between participants with multiple brain metastases treated with WBRT and radiosurgery boost as compared with those given WBRT alone. The [Kondziolka 1999](#) trial was methodologically weaker (small trial size and early trial closure) as compared with the [Andrews 2004](#) trial. [Andrews 2004](#) included participants with one to three brain metastases. Although overall there was no improvement in survival with the addition of radiosurgery boost in the [Andrews 2004](#) trial, survival was improved among participants with surgically unresectable single brain metastasis. This trial was designed with an a priori sample size calculation to test the hypothesis of improved survival in participants with single brain metastasis. Median survival time was 6.5 months for those with single brain metastasis treated with WBRT and radiosurgery boost versus 4.9 months for those treated with WBRT alone ($P = 0.0393$). The [Kondziolka 1999](#) trial excluded participants with single brain metastasis (two to four brain metastases included).

We pooled data for one-year overall brain control in the [Kondziolka 1999](#), [Andrews 2004](#), and [El Gantery 2014](#) trials. Overall, the HR was 0.39 (95% CI 0.25 to 0.60; $P < 0.0001$; high-certainty evidence) for local brain control, favouring the WBRT and radiosurgery boost group.

Thus, although overall brain control favours the addition of radiosurgery boost, radiosurgery boost added to WBRT did not improve survival among participants with two to four brain metastases. One trial reported that survival was increased among selected participants with surgically unresectable single brain metastasis treated with WBRT and radiosurgery boost as compared with WBRT alone.

Radiosurgery alone versus WBRT and radiosurgery

The HR for the pooled overall survival analysis for the three randomised controlled trials comparing radiosurgery alone versus WBRT and radiosurgery was 1.0 (95% CI 0.80 to 1.25; $P = 0.99$) ([Aoyama 2006](#); [Chang 2009](#); [Brown 2016](#)).

Again, these trials pre-dated the recognition of significant prognostic factors identified by the Diagnosis-Specific Graded Prognostic Assessment. As well, molecular markers are now recognised as important for survival of certain cancers. It is unclear whether specific groups of participants with brain metastases may derive survival benefit with WBRT and radiosurgery as compared with radiosurgery alone, as trials evaluated heterogeneous participants with brain metastases.

Although local and distant control of brain metastases is favoured with WBRT and radiosurgery as compared with radiosurgery alone, two trials reported worse neurocognitive function after WBRT and radiosurgery as compared with radiosurgery alone ([Brown 2016](#); [Chang 2009](#)). [Brown 2016](#) reported better quality of life outcomes at three months among participants randomised to radiosurgery alone versus WBRT and radiosurgery.

Although overall survival is not different among the strategies of radiosurgery alone, radiosurgery and WBRT, and WBRT alone for selected patients with brain metastases, the strategy of radiosurgery alone spares neurocognitive decline associated with WBRT and has been associated with better quality of life as compared with WBRT.

Steroids versus steroids and WBRT

The older [Horton 1971](#) trial could not be interpreted as the study was small, diagnostic criteria used for brain metastases were outdated, and no statistical analysis was performed.

The modern multi-centre trial of [Mulvenna 2016](#) reported no differences in quality-adjusted life-years for participants with brain metastases from non-small-cell lung cancer randomised to optimal supportive care and WBRT versus WBRT alone. However [Mulvenna 2016](#) spanned the time from March 2007 to August 2014. During this time, molecular drivers for non-small-cell lung cancer such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and programmed death-ligand 1 (PD-L1) were becoming increasingly important for prognostic classification and molecular targeted therapy. It is not known whether the two randomised groups were balanced for molecular features. Furthermore, survival was notably short, with a median survival of 9.2 weeks (95% CI 7.2 to 11.1) for those who received optimal supportive care and WBRT versus 8.5 weeks (95% CI 7.1 to 9.9) for those who received optimal supportive care alone. Participants in this trial were not suitable for resection or radiosurgery and likely were selected for enrolment in this trial on the basis of estimated poor prognoses.

More RCTs are needed to help guide practitioners as to which subsets of patients with brain metastases may benefit (in terms of survival, symptom control, or quality of life) from WBRT, and which subsets may not.

WBRT and molecular targeted agents

[Sperduto 2013](#), which was closed early owing to poor accrual, reported worse survival and increased toxicity in participants with

non-small-cell lung cancer with brain metastases randomised to WBRT and radiosurgery and erlotinib as compared with WBRT and radiosurgery. However, participants were not tested for EGFR mutation; thus any possible beneficial effect of erlotinib may have been diluted by participants with non-EGFR mutated non-small-cell lung cancer. Additional trials are needed to assess use of molecular targeted agents in subsets of patients with brain metastases, based on molecular cancer profiles.

WBRT and neurocognitive protective agents

Although the [Brown 2013](#) and [Rapp 2015](#) trials were negative for the primary outcome of delayed recall or composite cognitive scores with use of neuroprotective agents (memantine and donepezil, respectively), certain subsets of cognitive function may be improved with use of neuroprotective agents combined with WBRT for brain metastases.

Hippocampal sparing WBRT versus WBRT

Full reports from phase III randomised trials are awaited to determine whether hippocampal sparing WBRT preserves cognitive function as compared with WBRT.

Overall completeness and applicability of evidence

These trials pre-date the recognition of significant prognostic factors identified by the Diagnosis-Specific Graded Prognostic Assessment ([Sperduto 2012](#)). As well, molecular markers are increasingly important for therapeutic intervention and for prognoses in certain cancers. It is unclear whether groups in these older trials were balanced for these prognostic variables.

In addition, results of these RCTs may not be applicable to certain subgroups of patients with brain metastases (e.g. based on molecular tumour subtypes, or the Diagnosis-Specific Graded Prognostic Assessment), as trials evaluated heterogeneous patients with brain metastases. Most participants in these studies had lung, breast, or colorectal cancer primaries. Participants with small-cell lung cancer, germ cell tumours, and haematological malignancies were often excluded from trials.

Many of these trials lacked quality of life outcomes, neurocognitive outcomes, and information regarding the proportion of participants in each group who were able to reduce steroid dose. In cases in which overall survival was similar among trial groups, palliative endpoints such as quality of life, neurocognition, and steroid use are important.

Quality of the evidence

Evidence ranged from moderate to high certainty. Depending on the comparisons, downgrading of evidence was based on one or more of the following factors.

1. The included population was heterogeneous with respect to survival owing to varying primary cancer diagnoses and varying molecular subtypes.
2. Attrition bias
3. Reporting bias
4. Trial groups may not have been balanced for steroid use.

Potential biases in the review process

This meta-analysis is biased toward older trials, which are flawed by the inclusion of heterogeneous populations with brain metastases. Older trials are also limited by the lack of neurocognitive outcomes, which have become increasingly important in later trials examining radiosurgery and neurocognitive protective strategies.

Agreements and disagreements with other studies or reviews

Findings of this meta-analysis are consistent with those of other published meta-analyses examining interventions using WBRT ([Patil 2017](#); [Tsao 2012a](#)).

AUTHORS' CONCLUSIONS

Implications for practice

This updated review did not result in changes to original conclusions or new implications for practice.

None of the randomised controlled trials (RCTs) with altered higher biological whole body radiation therapy (WBRT) dose-fractionation schemes reported benefit in terms of overall survival, neurological function, or symptom control compared with standard treatment (3000 cGy in 10 daily fractions, or 2000 cGy in 4 or 5 daily fractions). However, survival and neurological function improvement (NFI) were worse for lower biological WBRT dose-fractionation schemes as compared with standard fractionation. The addition of WBRT to radiosurgery improves local and distant brain control but is associated with worse neurocognitive outcomes and no differences in overall survival. Among selected people with multiple brain metastases from non-small-cell lung cancer, data show that no differences in overall survival may occur when optimal supportive care is undertaken with omission of WBRT.

Implications for research

Future trials should examine homogeneous patients with brain metastases by using the Diagnosis-Specific Graded Prognostic Assessment and molecular markers. Investigators should elucidate the optimal number or volume of brain metastases best suited for radiosurgery as compared with WBRT for outcomes of neurocognitive function, quality of life, and survival. With the aim of ameliorating the neurocognitive side effects of WBRT, further trials must evaluate use of neurocognitive protective agents and hippocampal sparing WBRT. Use of radiosensitisers, chemotherapy, or molecular targeted agents in conjunction with WBRT remains experimental.

ACKNOWLEDGEMENTS

The review authors thank Dr. A Ohlsson for his guidance in developing and reviewing the original Cochrane Review. We note that the Cancer Care Ontario Program in Evidence-based Care's Supportive Care Guidelines Group and the Neuro-oncology Disease Site Group also contributed to development of the original Cochrane Review. Please see the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) website (http://www.cancercare.on.ca/access_PEBG.htm) for a complete list of current members of the Supportive Care Guidelines Group and the Neuro-oncology Disease Site Group.

The review authors thank Gail Quinn and Clare Jess for their contributions to the editorial process as well as Joanne Platt for designing and running the literature searches. We would also like to thank all of our external peer reviewers.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

References to studies included in this review

Andrews 2004 {published data only}

Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;**363**:1665-72.

Antonadou 2002 {published data only}

Antonadou D, Coliarakis N, Paraskevaidis M, Athansiou H, Sarris G, Synodinou M, et al. Whole brain radiotherapy alone or in combination with temozolomide for brain metastases. A phase III study (abstract). *International Journal of Radiation Oncology, Biology, Physics* 2002;**54**:93.

Antonadou 2003 {published data only}

Antonadou DCN, Coliarakis N, Paraskevaidis M, Athanasiou H, Sarris G, Synodinou M, et al. A multi-institutional trial comparing survival of patients with brain metastases from lung cancer treated with temozolomide plus radiotherapy versus radiotherapy alone (abstract). *Lung Cancer* 2003;**41**:S22-3.

Aoyama 2006 {published data only}

Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases. A randomised controlled trial. *JAMA* 2006;**295**(21):2483-91.

Aoyama 2015 {published data only}

Aoyama H, Tago M, Shirato H, the Japanese Radiation Oncology Study Group 99-1 (JROSG 99-1) Investigators. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases. Secondary analysis of the JROSG 99-1 randomised clinical trial. *JAMA Oncology* 2015;**1**(4):457-64.

Borgelt 1980a {published data only}

Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 1980;**6**:1-9.

Borgelt 1980b {published data only}

Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 1980;**6**:1-9.

Borgelt 1981a {published data only}

Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:1633-8.

Borgelt 1981b {published data only}

Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:1633-8.

Brown 2013 {published data only}

Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomised, double-blind, placebo-controlled trial. *Neuro-Oncology* 2013;**15**(10):1429-37.

Brown 2016 {published data only}

Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson K, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases. A randomised clinical trial. *JAMA* 2016;**316**(4):401-9.

Chang 2009 {published data only}

Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncology* 2009;**10**:1037-44.

Chatani 1985 {published data only}

Chatani M, Teshima T, Hata K, Inoue T, Suzuki T. Whole brain irradiation for metastases from lung carcinoma. A clinical investigation. *Acta Radiological Oncology* 1985;**24**:311-4.

Chatani 1994 {published data only}

Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to level of lactate dehydrogenase. *Strahlentherapie Onkologie* 1994;**170**:155-61.

Chougule 2000 {published data only}

Chougule PB, Burton-Williams M, Saris S, Zheng Z, Ponte B, Noren G, et al. Randomized treatment of brain metastases with gamma knife radiosurgery, whole brain radiotherapy or both (abstract). *International Journal of Radiation Oncology, Biology, Physics* 2000;**48**:114.

Davey 2008 {published data only}

Davey P, Hoegler D, Ennis M, Smith J. A phase III study of accelerated versus conventional hypofractionated whole brain irradiation in patients of good performance status with brain metastases not suitable for surgical excision. *Radiotherapy and Oncology* 2008;**88**:173-6.

DeAngelis 1989 {published data only}

DeAngelis LM, Currie VE, Kim J-H, Krol G, O'Hehir MA, Farag FM, et al. The combined use of radiation therapy and lonidamide in the treatment of brain metastases. *Journal of Neuro-oncology* 1989;**7**:241-7.

El Gantery 2014 {published data only}

El Gantery MM, Abd El Baky HM, El Hossieny HA, Mahmoud M, Youssef O. Management of brain metastases with stereotactic radiosurgery alone versus whole brain irradiation alone versus both. *Radiation Oncology* 2014;**9**:116.

El-Hamamsy 2016 {published data only}

El-Hamamsy M, Elwakil H, Saad AS, Shawki MA. A randomized controlled open-label pilot study of simvastatin in addition to whole-brain radiation therapy in patients with brain metastases. *Oncology Research* 2016;**24**:521-8.

Eyre 1984 {published data only}

Eyre HJ, Ohlsen JD, Frank J, LoBuglio AF, McCracken JD, Weatherall TJ, et al. Randomized trial of radiotherapy versus radiotherapy plus metronidazole for the treatment of metastatic cancer to brain. *Journal of Neuro-oncology* 1984;**2**:325-30.

Fogarty 2015 {published data only}

Fogarty GB, Hong A, Dolven-Jacobsen K, Reisse CH, Burmeister B, Haydu LH, et al. First interim analysis of a randomised trial of whole brain radiotherapy in melanoma brain metastases confirms high data quality. *BMC Research Notes* 2015;**8**:192.

Graham 2010 {published data only}

Graham PH, Bucci J, Browne L. Randomized comparison of whole brain radiotherapy, 20 Gy in four daily fractions versus 40 Gy in 20 twice-daily fractions, for brain metastases. *International Journal of Radiation Oncology, Biology, Physics* 2010;**77**(3):648-54.

Guerrieri 2004 {published data only}

Guerrieri M, Wong K, Ryan G, Millward M, Quong G, Ball DL. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of lung. *Lung Cancer* 2004;**46**:107-11.

Harwood 1977 {published data only}

Harwood AR, Simpson WJ. Radiation therapy of cerebral metastases: a randomized prospective clinical trial. *International Journal of Radiation Oncology, Biology, Physics* 1977;**2**:1091-4.

Horton 1971 {published data only}

Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* 1971;**3**:334-6.

Knisely 2008 {published data only}

Knisely J, Berkey B, Chakravarti A, Yung AWK, Curran WJ, Robins HI, et al. A phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases (RTOG 0118). *International Journal of Radiation Oncology, Biology, Physics* 2008;**71**(1):79-86.

Kocher 2011 {published data only}

Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy versus

observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *Journal of Clinical Oncology* 2011;**29**(2):134-41.

Komarnicky 1991 {published data only}

Komarnicky LT, Phillips TL, Martz K, Asbell S, Isaacson S, Urtasun R. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). *International Journal of Radiation Oncology, Biology, Physics* 1991;**20**:53-8.

Kondziolka 1999 {published data only}

Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *International Journal of Radiation Oncology, Biology, Physics* 1999;**45**(2):427-34.

Kurtz 1981 {published data only}

Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favourable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:891-5.

Lee 2008 {published data only}

Lee DH, Han J-Y, Kim HT, Yoon SJ, Pyo HR, Cho KH, et al. Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first. Results of a randomized pilot study. *Cancer* 2008;**113**:143-9.

Mehta 2003 {published data only}

* Mehta MP, Rodrigus P, Terhaard CHJ, Rao A, Suh J, Roa W, et al. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *Journal of Clinical Oncology* 2003;**21**:2529-36.

Mehta 2009 {published data only}

Mehta MP, Shapiro WR, Phan SC, Gervais R, Carrie C, Chabot P, et al. Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small cell lung cancer patients with brain metastases: results of a phase III trial. *International Journal of Radiation Oncology, Biology, Physics* 2009;**73**(4):1069-76.

Meyers 2004 {published data only}

Meyers CA, Smith JA, Bezjak A, Mehta MP, Liebmann J, Illidge T, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *Journal of Clinical Oncology* 2004;**22**(1):157-65.

Mornex 2003 {published data only}

Mornex F, Thomas L, Mohr P, Hauschild A, Delaunay MM, Lesimple T. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Research* 2003;**13**(1):97-103.

Mulvenna 2016 {published data only}

Mulvenna P, Nankivell M, Barton R, Faivre-Finn C, Wilson P, McColl E, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016;**388**(10055):2004-14.

Murray 1997 {published data only}

Murray KJ, Scott C, Greenberg HM, Emami B, Seider M, Vora NL, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. *International Journal of Radiation Oncology, Biology, Physics* 1997;**39**:571-4.

Neuhaus 2009 {published data only}

Neuhaus T, Ko Y, Muller RP, Grabenbauer GG, Hedde JP, Schueller H, et al. A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. *British Journal of Cancer* 2009;**100**:291-7.

Phillips 1995 {published data only}

Phillips TL, Scott CB, Leibel SA, Rotman M, Weigensberg IJ. Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *International Journal of Radiation Oncology, Biology, Physics* 1995;**33**:339-48.

Postmus 2000 {published data only}

Postmus PE, Haaxma-Reiche H, Smit EF, Groen HJM, Karnicka H, Lewinski T, et al. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy - a phase III study of the European Organization for the Research and Treatment of Lung Cancer Cooperative Group. *Journal of Clinical Oncology* 2000;**18**(19):3400-8.

Priestman 1996 {published data only}

Priestman TJ, Dunn J, Brada M, Rampling R, Baker PG. Final results of the Royal College of Radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases. *Clinical Oncology* 1996;**8**:308-15.

Puthiyottil 2016 {published data only}

Puthiyottil SSV, Mathew BS, Jayaprakash PG, Sivanandan CD, Ratheesan K. Whole brain radiotherapy with concurrent temozolomide for brain metastasis in non-small cell lung cancer: a single institution, open labelled randomized clinical study from South India (abstract). *Journal of Thoracic Oncology* 2016;**9**(4 Suppl 1):S46-7.

Ramlau 2013 {published data only}

Ramlau R, Jassem J, Papai-Szekely Z, Chabot P, Lagenne P, Levin J, et al. Whole brain radiation therapy (WBRT) with or without oral topotecan (TPT) in patients with non-small cell lung cancer (NSCLC) with brain metastases: final analysis of an open-label phase III study (abstract). *Journal of Clinical Oncology* 2013;**31**(15 Suppl 1):2031.

Rapp 2015 {published data only}

Rapp SR, Case LD, Peiffer A, Naughton MM, Chan MD, Stieber VW, et al. Donepezil for irradiated brain tumor survivors: a phase III randomized placebo-controlled clinical trial. *Journal of Clinical Oncology* 2015;**33**(15):1653-9.

Robinet 2001 {published data only}

Robinet G, Thomas P, Breton JL, Lena H, Gouva S, Dabouis G, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small cell lung cancer: Groupe Francaise de Pneumo-Cancerologie (GFPC) protocol 95-1. *Annals of Oncology* 2001;**12**:59-67.

Scott 2007 {published data only}

Scott C, Suh J, Stea B, Nabid A, Hackman J. Improved survival, quality of life, and quality-adjusted survival in breast cancer patients treated with efaproxiral (Efaproxyn) plus whole-brain radiation therapy for brain metastases. *American Journal of Clinical Oncology* 2007;**30**:580-7.

Sperduto 2013 {published data only}

Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, et al. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *International Journal of Radiation Oncology, Biology, Physics* 2013;**85**(5):1312-8.

Sperduto 2014 {published data only}

Sperduto PW, Shanley R, Luo X, Andrews D, Werner-Wasik M, Valicenti R, et al. Patients with 1-3 brain metastases; post stratified by the Graded Prognostic Assessment (GPA). *International Journal of Radiation Oncology, Biology, Physics* 2014;**90**(3):526-31.

Stea 2006 {published data only}

Stea B, Suh JH, Boyd AP, Cagnoni PJ, Shaw E, REACH Study Group. Whole-brain radiotherapy with or without efaproxiral for the treatment of brain metastases: determinants of response and its prognostic value for subsequent survival. *International Journal of Radiation Oncology, Biology, Physics* 2006;**64**(4):1023-30.

Sturm 2015 {published data only}

Sturm D, Frings L, Oehlke O, Grosu AL. Whole brain irradiation with hippocampal sparing and dose escalation on metastases: memory, performance, depression and quality of life (abstract). *Strahlentherapie und Onkologie* 2015;**191**:S59.

Suh 2006 {published data only}

Suh JH, Stea B, Nabid A, Kresl JJ, Fortin A, Mercier J-P, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *Journal of Clinical Oncology* 2006;**24**:106-14.

Suh 2008 {published data only}

Suh JH, Stea B, Tankel K, Marsiglia H, Belkacemi Y, Gomez H, et al. Results of the Phase III ENRICH (RT-016) study of Efaproxiral administered concurrent with whole brain radiation therapy

(WBRT) in women with brain metastases from breast cancer (abstract). *International Journal of Radiation Oncology Biology Physics* 2008;**72**:S50-1.

Ushio 1991 {published data only}

Ushio Y, Arita N, Hayakawa T, Mogami H, Hasegawa H, Bitoh S, et al. Chemotherapy of brain metastases from lung carcinoma: a controlled randomized study. *Neurosurgery* 1991;**28**:201-5.

Zeng 2016 {published data only}

Zeng YC, Wu R, Xing R, Chi F, Wang SL, Chen XD, et al. Radiation-enhancing effect of sodium glycididazole in patients suffering from non-small cell lung cancer with multiple brain metastases: a randomized, placebo-controlled study. *Cancer Radiotherapy* 2016;**20**(3):187-92.

References to studies excluded from this review

Haie-Meder 1993 {published data only}

Haie-Meder C, Pellae-Cosset B, Laplanche A, Lagrange JL, Tuchais C, Nogues C, et al. Results of a randomized clinical trial comparing two radiation schedules in the palliative treatment of brain metastases. *Radiotherapy and Oncology* 1993;**26**:111-6.

Wang 2015 {published data only}

Wang F, Ning F, Liu C, Hao Y, Li L, Yu Z, et al. Comparison of gefitinib versus VMP in combination with radiotherapy for multiple brain metastases from non-small cell lung cancer. *Cell Biochemistry and Biophysics* 2015;**71**:1261-5.

References to ongoing studies

CCCWFU-97600 {published data only (unpublished sought but not used)}

Shaw EG. Phase 3 randomised study of d-methylphenidate to improve quality of life in patients receiving radiotherapy for primary or metastatic brain tumours. www.clinicaltrials.gov/ct2/show/record/NCT00031798.

EORTC-18981 {published data only (unpublished sought but not used)}

EORTC Melanoma Group. Phase III randomised study of temozolomide with or without WBRT in patients with stage IV melanoma with asymptomatic brain metastases. www.clinicaltrials.gov/ct/show/NCT00020839.

NCT00075166 {published data only (unpublished sought but not used)}

Surgery versus radiosurgery to treat metastatic brain tumours. clinicaltrials.gov/ct2/show/record/NCT00075166.

NCT00076856 {published data only (unpublished sought but not used)}

Temozolomide for treatment of brain metastases from non-small-cell lung cancer. www.clinicaltrials.gov/ct2/show/NCT00076856.

NRG-CC001 {published data only}

A randomized phase III trial of memantine and whole brain radiotherapy with or without hippocampal avoidance in

patients with brain metastases. <https://clinicaltrials.gov/ct2/show/NCT02360215>.

RTOG-BR0118/ DEV1006 {published data only (unpublished sought but not used)}

Knisely J. A Phase III study of conventional radiation therapy plus thalidomide versus conventional radiation therapy for multiple brain metastases. www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0118.

Yang 2015 {published data only}

Yang ZZ, Li RQ, Zhu B. Phase III study of WBRT with or without erlotinib for brain metastasis NSCLC. *Journal of Thoracic Oncology* 2015:S426-S427.

Additional references

Arbit 1995

Arbit E, Wronski M. The treatment of brain metastases. *Neurosurgery Quarterly* 1995;**5**:1.

Cairncross 1980

Cairncross JG, Kim JH, Posner JB. Radiation therapy for brain metastases. *Annals of Neurology* 1980;**7**:529-41.

Chao 1954

Chao JH, Philips R, Nickson JJ. Roentgen ray therapy for cerebral metastases. *Cancer* 1954;**7**:682-9.

Detsky 1989

Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbe KA. Incorporating variations in the quality of individual randomized trials in meta-analysis. *Journal of Clinical Epidemiology* 1992;**45**:255-65.

Gaspar 1997

Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *International Journal of Radiation Oncology, Biology, Physics* 1997;**37**:745-51.

Gelber 1981

Gelber RD, Larson M, Borgelt BB, Kramer S. Equivalence of radiation schedules for the palliative treatment of brain metastases in patients with favorable prognosis. *Cancer* 1981;**48**:1749-53.

GRADEpro GDT 2015

GRADEproGDT [Computer program]. McMaster University, Hamilton (ON) (developed by Evidence Prime), 2015. Available from gradeprg.org (accessed May 2017).

Grant 2001

Grant R, Walker M. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy for solitary brain metastases. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: [10.1002/14651858.CD003292.pub2](https://doi.org/10.1002/14651858.CD003292.pub2)]

Hall 2000

Hall EJ. Time, dose and fractionation in radiotherapy. In: John JR, Pamela Sutton P, Deirdre Marino D editor(s). *Radiobiology for the Radiologist*. 5th Edition. Philadelphia: Lippincott Williams and Wilkins, 2000:412.

Hart 2004

Hart MG, Grant R, Walker M, Dickinson H. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: [10.1002/14651858.CD003292.pub2](https://doi.org/10.1002/14651858.CD003292.pub2)]

Higgins 2011

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jadad 1996

Jadad AR, Moore RA, Carroll D. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

Katz 1981

Katz HR. The relative effectiveness of radiation therapy, corticosteroids and surgery in the management of melanoma metastatic to the central nervous system. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**:897-906.

Loeffler 1997

Loeffler JS, Patchell RA, Sawaya R. Treatment of metastatic cancer. In: Devita VT, Hellman S, Rosenberg SA editor(s). *Cancer: Principles and Practice of Oncology*. Fifth. Philadelphia: Lippincott-Raven, 1997:2523.

Noordijk 1994

Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JHC, Hoekstra FH, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *International Journal of Radiation Oncology, Biology, Physics* 1994;**29**:711-7.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Patil 2017

Patil CG, Pricola K, Sarmiento JM, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database of Systematic Reviews* 2017, Issue 9. [DOI: [10.1002/14651858.CD006121.pub4](https://doi.org/10.1002/14651858.CD006121.pub4)]

Posner 1977

Posner JB. Management of central nervous system metastases. *Seminars in Oncology* 1977;**4**:81-91.

Posner 1995

Posner JB. *Neurologic Complications of Cancer*. Vol. **37**, Philadelphia: FA Davis, 1995:311.

Regine 2001

Regine WF, Scott C, Murray K, Curran W. Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation vs accelerated-hyperfractionated radiotherapy: an analysis from Radiation Therapy Oncology Group study 91-04. *International Journal of Radiation Oncology, Biology, Physics* 2001;**51**(3):711-7.

Review Manager 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5) [Computer program]. Version 5.3. Copenhagen. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sneed 1996

Sneed PK, Larson DA, Wara WM. Radiotherapy for cerebral metastases. *Neurosurgery Clinics of North America* 1996;**7**:505-16.

Sperduto 2012

Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *Journal of Clinical Oncology* 2012;**30**(4):419-25.

Sperduto PW 2014

Sperduto PW, Shanley R, Luo X, Andrews D, Werner-Wasik M, Valicenti R, et al. Secondary analysis of RTOG 9508, a phase 3 randomized trial of whole-brain radiation therapy versus WBRT plus stereotactic radiosurgery in patients with 1-3 brain metastases; post stratified by the Graded Prognostic Assessment (GPA). *International Journal of Radiation Oncology, Biology, Physics* 2014;**90**(3):526-31.

Tsao 2012a

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

Walker 1985

Walker AE, Robins M, Weinfield FD. Epidemiology of brain tumors: the national survey of intracranial neoplasms. *Neurology* 1985;**35**:219-26.

Zimm 1981

Zimm S, Wampler GL, Stablein D. Intracerebral metastases in solid tumor patients: natural history and results of treatment. *Cancer* 1981;**48**:384-94.

References to other published versions of this review

Tsao 2002

Tsao MN, Chow E, Wong R, Rakovitch E, Laperriere N. Whole brain radiotherapy for the treatment of multiple brain

metastases. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: [10.1002/14651858.CD003869](https://doi.org/10.1002/14651858.CD003869)]

newly diagnosed multiple brain metastases. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: [10.1002/14651858.CD003869.pub3](https://doi.org/10.1002/14651858.CD003869.pub3)]

Tsao 2012b

Tsao MN, Lloyd N, Wong RKS, Chow E, Rakovitch E, Laperriere N, et al. Whole brain radiotherapy for the treatment of

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Andrews 2004

Methods	RCT; study period 31 January 1996 to 15 June 2001: enrolled: 333 evaluated: 331
Participants	Inclusion: 1. 1 to 3 brain metastases 2. maximum size 4 cm (largest lesion); others not more than 3 cm Exclusion: 1. KPS < 70 2. brainstem metastasis 3. metastasis < 1 cm from optic apparatus 4. active extracranial disease judged by systemic treatment given within 1 month of enrolment
Interventions	WBRT and radiosurgery boost vs WBRT
Outcomes	1. overall survival 2. local control, overall intracranial recurrence rates 3. cause of death 4. performance status 5. steroid usage
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised within strata by permuted blocks
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Low risk	Primary outcome (survival) unlikely to be affected by selective reporting. Secondary outcome consisted of overall time to intracranial tumour progression at risk of selective reporting; only 153 MRI sets were assessed at 3 months and 117 MRI sets were deficient.

Antonadou 2002

Methods	RCT (abstract); study period not reported: enrolled: 134 evaluated: not reported
---------	--

Antonadou 2002 (Continued)

Participants	Inclusion: 1. previously untreated brain metastases
Interventions	WBRT with or without temozolomide chemotherapy
Outcomes	1. response rates 2. neurological response 3. overall survival
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient detail in abstract

Antonadou 2003

Methods	RCT (abstract); study period not reported: evaluated: 108
Participants	Inclusion: histologically or cytologically proven lung cancer
Interventions	WBRT with or without temozolomide chemotherapy
Outcomes	1. response rates 2. survival 3. toxicity
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract

Antonadou 2003 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	Insufficient detail in abstract
---	--------------	---------------------------------

Aoyama 2006

Methods	RCT; study period October 1999 to December 2003 enrolled: 160 evaluated: 132
Participants	Inclusion: 1. 1 to 4 brain metastases 2. ≤ 3 cm 3. pathologically confirmed systemic cancer Exclusion: 1. history of brain irradiation or surgery 2. small-cell cancer, lymphoma, germinoma, myeloma, non-melanomatous skin cancer
Interventions	Radiosurgery alone vs WBRT and radiosurgery
Outcomes	1. overall survival 2. cause of death 3. proportion with KPS ≥ 70 4. neurological functional preservation rate 5. freedom from metachronous brain metastases 6. freedom from new brain metastases 7. salvage treatment for new/recurrent brain metastases 8. local tumour control rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A permuted-block randomisation algorithm was used with block size 4.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was described, with 0 lost to follow-up.
Selective reporting (re-reporting bias)	Low risk	Primary endpoint, overall survival at low risk of bias. Secondary endpoints consisting of brain tumour recurrence, functional preservation, toxic radiation effects, and cause of death may be at risk of reporting bias.

Aoyama 2015

Methods	RCT; secondary analysis of Aoyama 2006 : 88 participants
Participants	Inclusion: 1. non-small-cell lung cancer

Aoyama 2015 (Continued)

2. 1 to 4 brain metastases
 3. ≤ 3 cm
- Exclusion:
1. history of brain irradiation or surgery

Interventions	Radiosurgery alone vs WBRT and radiosurgery
Outcomes	Stratified by Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) scores: <ol style="list-style-type: none">1. overall survival2. brain tumour recurrence rates3. toxic effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A permuted-block randomisation algorithm was used with block size of 4.
Incomplete outcome data (attrition bias) All outcomes	High risk	This was a secondary analysis of Aoyama 2006 . This publication consisted of 88 participants of a total of 160 participants enrolled in Aoyama 2006 .
Selective reporting (reporting bias)	Low risk	Primary endpoint, overall survival at low risk of bias. Secondary endpoints consisting of brain tumour recurrence, functional preservation, toxic radiation effects, and cause of death may be at risk of reporting bias.

Borgelt 1980a

Methods	Publication consisted of 2 RCTs. RCT 1; study period January 1971 to November 1973: enrolled: 993 evaluated: 910
Participants	Inclusion: <ol style="list-style-type: none">1. brain metastases by clinical symptoms, EEG, radioisotope brain scans, arteriogram, pneumoencephalogram, biopsy Exclusion: <ol style="list-style-type: none">1. general medical or neoplastic status prohibiting adequate assessment2. other cancer treatment within 2 weeks of entry3. lesions too numerous or symptoms too vague for followup
Interventions	RCT 1: 4000 cGy/20 fr (227 participants) vs 4000 cGy/15 fr (233 participants) vs 3000 cGy/15 fr

Borgelt 1980a (Continued)

(217 participants)
vs
3000 cGy/10 fr
(233 participants)

Outcomes	1. survival 2. palliative index
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Multi-centre trial, randomised centrally but randomisation process not described. Trial included an "optional" group, in which participants were randomised to 1000 cGy in 1 fraction or 1200 cGy in 2 fractions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Endpoints consisting of neurological function status and maintenance of improved or stable neurological function may be prone to selective reporting.

Borgelt 1980b

Methods	Publication consisted of 2 RCTs. RCT 2; study period November 1973 to February 1976: enrolled: 1001 evaluated: 902
Participants	Inclusion: 1. brain metastases by clinical symptoms, EEG, radioisotope brain scans, arteriogram, pneumoencephalogram, biopsy Exclusion: 1. general medical or neoplastic status prohibiting adequate assessment 2. other cancer treatment within 2 weeks of entry 3. lesions too numerous or symptoms too vague for follow-up
Interventions	RCT 2: 4000 cGy/15 fr (227 participants) vs 3000 cGy/10 fr (228 participants) vs 2000 cGy/5 fr (447 participants)
Outcomes	1. survival 2. palliative index
Notes	

Borgelt 1980b (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Multi-centre trial, randomised centrally but randomisation process not described. Trial included an "optional" group, in which participants were randomised to 1000 cGy in 1 fraction or 1200 cGy in 2 fractions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Endpoints consisting of neurological function status and maintenance of improved or stable neurological function may be prone to selective reporting.

Borgelt 1981a

Methods	Publication consisted of 2 RCTs; study period January 1971 to February 1976 RCT 1 enrolled: 155 evaluated: 138
Participants	Inclusion: 1. brain metastases diagnosed by clinical symptoms and EEG, radioisotope brain scans, arteriograms, pneumoencephalograms, or biopsy Exclusion: 1. medical condition precluding adequate follow-up 2. new anticancer treatment within 2 weeks 3. lesions too numerous 4. symptoms too vague for adequate assessment
Interventions	RCT 1: 1000 cGy/1 fr 3000 cGy to 4000 cGy/10 to 20 fr
Outcomes	1. survival 2. improvement in neurological function 3. treatment morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Multi-centre trial, randomised centrally but randomisation process not described. Trial included an "optional" group, in which participants were randomised to 1000 cGy in 1 fraction or 1200 cGy in 2 fractions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described

Borgelt 1981a (Continued)

Selective reporting (reporting bias)	Unclear risk	Endpoints consisting of neurological function status and maintenance of improved or stable neurological function may be prone to selective reporting.
--------------------------------------	--------------	---

Borgelt 1981b

Methods	Publication consisted of 2 RCTs (study period January 1971 to February 1976) RCT 2: enrolled: 78 evaluated: 64
Participants	Inclusion: 1. brain metastases diagnosed by clinical symptoms and EEG, radioisotope brain scans, arteriograms, pneumoencephalograms, or biopsy Exclusion: 1. medical condition precluding adequate follow-up 2. new anticancer treatment within 2 weeks 3. lesions too numerous 4. symptoms too vague for adequate assessment
Interventions	RCT 2: 1200 cGy/ 2 fr 2000 cGy/5 fr
Outcomes	1. survival 2. improvement in neurological function 3. treatment morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Multi-centre trial, randomised centrally but randomisation process not described. Trial included an "optional" group, in which participants were randomised to 1000 cGy in 1 fraction or 1200 cGy in 2 fractions.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Endpoints consisting of neurological function status and maintenance of improved or stable neurological function may be prone to selective reporting.

Brown 2013

Methods	RCT; study period March 2008 to July 2010: enrolled: 554 eligible: 508
---------	--

Brown 2013 (Continued)

evaluated: 473

Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. pathologically proven solid malignancy within 5 years of registration 2. brain metastases on contrast-enhanced CT or MRI 3. Karnofsky Performance Status ≥ 70 4. stable systemic disease in the 3 months before study entry 5. Mini-Mental State Examination (MMSE) score > 18 <p>Exclusion:</p> <ol style="list-style-type: none"> 1. memantine allergy 2. current alcohol or drug abuse 3. chronic benzodiazepine use
Interventions	WBRT plus memantine vs WBRT plus placebo
Outcomes	<ol style="list-style-type: none"> 1. cognitive function (primary endpoint) 2. time to cognitive failure 3. overall survival 4. progression-free survival 5. adverse effects

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multi-centre trial using the Zelen treatment allocation scheme to stratify participants. Within each stratum, participants were randomised in a 1:1 ratio.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition completely described. 235/278 randomised to memantine analysed and 238/276 randomised to placebo analysed for the primary endpoint, memory measured by HVLT-R DR.
Selective reporting (reporting bias)	Low risk	Formal neurocognitive test HVLT-R DR (primary endpoint) unlikely to be subject to selective reporting

Brown 2016

Methods	<p>RCT; study period February 2002 to December 2013:</p> <p>enrolled: 213</p> <p>evaluated: 111</p>
Participants	Inclusion:

Brown 2016 (Continued)

1. 1 to 3 brain metastases all smaller than 3 cm
 2. pathological confirmation extracerebral tumour site
- Exclusion:
1. prior resection of cerebral metastasis
 2. chemotherapy within 7 days of preregistration or during radiation
 3. prior cranial radiation
 4. leptomeningeal metastases
 5. lesion located within 5 mm of the optic chiasm or within the brainstem
 6. primary germ cell tumour, small cell carcinoma, or lymphoma

Interventions	SRS alone vs SRS and WBRT
Outcomes	<ol style="list-style-type: none"> 1. cognitive deterioration (primary endpoint) 2. time to intracranial failure 3. quality of life 4. toxic effects 5. functional independence 6. overall survival

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multi-centre trial randomised centrally by a dynamic minimisation strategy with stratification
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition completely described. 63/111 in the radiosurgery-alone group and 48/102 in the radiosurgery plus WBRT group included in the primary endpoint analysis (cognitive deterioration). As attrition was significant for the primary endpoint, outcome data for many randomised participants were incomplete.
Selective reporting (reporting bias)	Low risk	Primary endpoint of cognitive deterioration unlikely to be associated with selective outcome reporting

Chang 2009

Methods	<p>RCT; study period 2001 January 2 to 14 September 2007:</p> <p>enrolled: 58</p> <p>evaluated: 58</p>
Participants	<p>older than 18 years of age</p> <p>recursive partitioning analysis (RPA) class 1 or 2</p>

Chang 2009 (Continued)

	Karnofsky Performance Status ≥ 70 1 to 3 newly diagnosed brain metastases eligible for radiosurgery excluded if leukaemia, lymphoma, germ cell, or small-cell cancer; leptomeningeal disease or unknown primary tumour
Interventions	radiosurgery and WBRT vs radiosurgery alone
Outcomes	Primary: neurocognitive endpoint of total recall
Notes	The trial was stopped early (based on early stopping rules) on the basis of a high probability (96%) that participants randomised to radiosurgery and WBRT were more likely to show a decline in learning and memory.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1 randomisation using permuted block algorithm (block sizes randomly chosen from 2, 4, 6, or 8)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition described; only 1 participant lost to follow-up
Selective reporting (reporting bias)	Low risk	Formal neurocognitive test for learning and memory (primary endpoint) unlikely to be subject to reporting bias

Chatani 1985

Methods	RCT; study period September 1980 to October 1983; evaluated: 69
Participants	Inclusion: 1. brain metastases from lung cancer 2. diagnosed with clinical symptoms and CT Exclusion: not specified
Interventions	5000 cGy/20 fr vs 3000 cGy/10 fr
Outcomes	1. survival 2. neurological improvement
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Chatani 1985 (Continued)

Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival outcome unlikely to be associated with selective reporting. Neurological function improvement may have been associated with selective reporting.

Chatani 1994

Methods	RCT; study period January 1985 to April 1992: evaluated: 162
Participants	Inclusion: 1. brain metastases from lung cancer 2. diagnosed with clinical symptoms and CT
Interventions	Normal LDH: 5000 cGy/20 fr vs 3000 cGy/10 fr Elevated LDH: 3000 cGy/10 fr vs 2000 cGy/5 fr
Outcomes	1. survival 2. neurological improvement 3. acute side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Survival not prone to selective reporting. The outcome of neurological improvement may have been subject to selective reporting.

Chougule 2000

Methods	RCT; study period not reported: evaluated: 104
---------	--

Chougule 2000 (Continued)

Participants	Inclusion: 1. ≤ 3 lesions 2. tumour volume ≤ 30 cc 3. minimum life expectancy 3 months
Interventions	radiosurgery vs radiosurgery and WBRT (3000 cGy/10 fr) vs WBRT (3000 cGy/10 fr)
Outcomes	1. survival 2. brain local control
Notes	Abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient detail in abstract

Davey 2008

Methods	RCT; study period 1996 to 2003: evaluated: 90
Participants	Inclusion: confirmed malignant disease brain metastases ECOG performance status 0 to 2 Exclusion: patients with complete excision of a single brain metastasis and life expectancy < 6 weeks
Interventions	WBRT 40 Gy in 20 fractions twice daily vs WBRT 20 Gy in 5 fractions once daily
Outcomes	1. overall survival (primary)
Notes	

Davey 2008 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed via an allocation table of random numbers
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the primary analysis (survival).
Selective reporting (reporting bias)	Low risk	Primary endpoint of survival was unlikely to be associated with selective reporting.

DeAngelis 1989

Methods	RCT; study period January 1985 to January 1987: evaluated: 58	
Participants	Inclusion: 1. histologically confirmed cancer and brain mets (CT) Exclusion: 1. prior WBRT	
Interventions	3000 cGy/10 fr and lonidamine vs 3000 cGy/10 fr	
Outcomes	1. survival 2. response rates (CR + PR)	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7/27 participants in the WBRT group could not be evaluated and 12/31 participants in the WBRT and lonidamine group could not be evaluated.
Selective reporting (reporting bias)	Unclear risk	Survival not likely to be associated with selective reporting. However, response rate may have been subject to selective reporting.

El Gantery 2014

Methods	RCT; study period January 2008 to March 2011: 60 participants	
Participants	Inclusion:	

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

El Gantery 2014 (Continued)

1. 1 to 3 brain metastases
2. each no larger than 4 cm on contrast-enhanced MRI
3. histologically confirmed systemic cancer

Interventions	WBRT and radiosurgery vs radiosurgery alone vs WBRT alone
Outcomes	<ol style="list-style-type: none"> 1. overall survival 2. brain local control 3. performance status 4. treatment-related morbidity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival not likely associated with selective reporting. Local brain control may have been subject to selective reporting.

El-Hamamsy 2016

Methods	<p>RCT; study period April 2014 to October 2015:</p> <p>50 participants</p>
Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. measurable intracranial brain metastases on MRI 2. planned 30 Gy WBRT <p>Exclusion:</p> <ol style="list-style-type: none"> 1. statin therapy 2. haematological central nervous system infiltration 3. renal, hepatic dysfunction 4. hypersensitivity to simvastatin 5. non-compliance
Interventions	WBRT with or without simvastatin
Outcomes	1. radiological response at 4 weeks post WBRT

El-Hamamsy 2016 (Continued)

2. 1-year progression-free survival
3. 1-year overall survival
4. adverse effects

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition described. 3/25 in the WBRT alone and 1/25 in the WBRT and simvastatin group lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Primary outcome of radiological response at 4 weeks may have been subject to selective reporting. Secondary outcome of survival not likely to be associated with selective reporting. However secondary outcomes consisting of 1-year progression-free survival and quality of life may have been subject to selective reporting.

Eyre 1984

Methods	RCT; study period July 1978 to May 1982: enrolled: 116 evaluated: 111
Participants	Inclusion: <ol style="list-style-type: none"> 1. histological proof of malignancy 2. clinical documentation of brain mets (isotope or CT) 3. neurological symptoms 4. no prior cranial radiation 5. expected survival longer than 4 weeks 6. adults Exclusion: <ol style="list-style-type: none"> 1. systemic chemotherapy with agents that cross blood-brain barrier
Interventions	3000 cGy/10 fr and metronidazole vs 3000 cGy/10 fr
Outcomes	<ol style="list-style-type: none"> 1. survival 2. response rates (CR + PR)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described

Eyre 1984 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	111/116 fully or partially evaluable. Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	Response rates subject to possible selective reporting. Survival not likely to be associated with selective reporting

Fogarty 2015

Methods	RCT (interim analysis); study period December 2008 to December 2012: 100 participants	
Participants	Inclusion: <ol style="list-style-type: none"> 1 to 3 brain metastases from metastatic melanoma treated with local therapy (surgery and/or radiosurgery) life expectancy ≥ 6 months ECOG performance status of 0, 1, or 2 at randomisation Exclusion: <ol style="list-style-type: none"> untreated gross intracranial disease previous brain treatment leptomeningeal disease 	
Interventions	Local treatment for brain metastases (surgery and/or radiosurgery) alone vs local treatment with post-local treatment WBRT	
Outcomes	<ol style="list-style-type: none"> proportion of participants with distant intracranial failure (primary outcome) time to distant intracranial failure time to local intracranial failure deterioration in neurocognitive function time to deterioration in health-related quality of life time to deterioration in performance status overall survival 	

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Incomplete outcome data (attrition bias)	High risk	Incomplete randomised trial. First 100 participants reported.

Fogarty 2015 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Primary outcome consisting of proportion of participants with distant intracranial failure may be subject to reporting bias. All listed secondary outcomes (with the exception of overall survival) may also be subject to reporting bias.
--------------------------------------	--------------	--

Graham 2010

Methods	RCT; study period February 1996 to March 2006: evaluated: 113	
Participants	ECOG performance status < 3 life expectancy > 2 months extracranial disease (stable for 2 months, or absent or concurrent with brain metastases at time of initial cancer diagnosis)	
Interventions	WBRT 40 Gy in 20 twice-daily fractions vs WBRT 20 Gy in 4 daily fractions	
Outcomes	1. intracranial control and quality of life (primary) 2. interval to CNS progression 3. overall survival	

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random block sequences used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Intracranial control, quality of life, interval to CNS progression may be subject to selective reporting. Overall survival not likely to be associated with selective reporting

Guerrieri 2004

Methods	RCT; study period June 1993 to December 1996: planned sample: 300 closed owing to poor accrual: 42	
Participants	Inclusion:	

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

Guerrieri 2004 (Continued)

1. metastatic NSCLC to brain
2. inoperable CNS disease or refusal of surgery
3. WHO performance status 0 to 2
4. adequate blood counts
5. urinary creatinine $\geq$ 50 mL/min

Exclusion:

1. prior chemotherapy
2. prior brain radiotherapy

Interventions	2000 cGy/5 fr vs 2000 cGy/5 fr and carboplatin
Outcomes	<ol style="list-style-type: none"> 1. overall survival 2. radiographic brain response 3. symptom control 4. toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Trial terminated early and 42 participants reported of a planned 300 target size
Selective reporting (reporting bias)	Unclear risk	Overall survival not likely to be at risk of selective reporting. Radiographic brain response, symptom control may be at risk of selective reporting.

Harwood 1977

Methods	RCT; study period not reported enrolled: 108 evaluated: 101
Participants	Inclusion: <ol style="list-style-type: none"> 1. brain metastases Exclusion: <ol style="list-style-type: none"> 1. previous WBRT 2. chemotherapy given 3 weeks prior
Interventions	1000 cGy/1 fr vs 3000 cGy/10 fr
Outcomes	<ol style="list-style-type: none"> 1. survival 2. local control 3. response frequency 4. complication rate
Notes	

Harwood 1977 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting. Local control and response may have been subject to selective reporting.

Horton 1971

Methods	RCT; study period not reported evaluated: 48	
Participants	Inclusion: 1. histologically proven cancer 2. parenchymal brain metastases (radioisotope brain scans, EEG, echoencephalograms, angiograms, spinal fluid cytology and chemistry) Exclusion: 1. all gross brain tumours surgically excised	
Interventions	Supportive care (oral prednisone) vs Supportive care (oral prednisone) and WBRT	
Outcomes	1. survival 2. improvement in performance status	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants assigned by "closed envelope" technique but randomisation method not fully described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival not likely to be associated with reporting bias. Improvement in performance status may have been subject to selective reporting.

Knisely 2008

Methods	RCT; study period February 2002 to July 2004:	
---------	---	--

Knisely 2008 (Continued)

	enrolled: 332
	evaluated: 183
Participants	18 years of age or older anticipated survival longer than 8 weeks Zubrod performance status of 0 to 1 MRI-documented brain metastases histologically proven extracranial solid tumour not eligible for radiosurgery (> 4 cm, > 3 tumours, or location e.g. midbrain)
Interventions	WBRT vs WBRT and thalidomide
Outcomes	Primary: survival Secondary: CNS progression rates toxicity

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multi-centre trial randomised centrally via a permuted block design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	Primary outcome (survival) not likely to be associated with selective reporting. Central nervous system progression rates may be associated with selective reporting.

Kocher 2011

Methods	RCT; study period November 1996 to November 2007: enrolled: 359 evaluated: 359
Participants	1. age 18 years or older 2. WHO performance status ≤ 2

Kocher 2011 (Continued)

	3. 1 to 3 brain metastases 4. radiosurgery: single metastasis ≤ 3.5 cm, multiple metastases ≤ 2.5 cm 5. surgery: complete surgical resection 6. stable systemic cancer for 3 months or longer and/or asymptomatic synchronous primary tumour without metastases outside the CNS or unknown primary tumour 7. excluded small-cell lung cancer, lymphoma, leukaemia, myeloma, germ cell tumours, brainstem metastases, leptomeningeal metastases, recurrent brain metastases
Interventions	1. radiosurgery alone 2. radiosurgery and WBRT 1. surgery alone 2. surgery and WBRT
Outcomes	Primary outcome: duration of functional independence (measured from day of random assignment to first report of deterioration of a WHO PS > 2) Secondary outcomes: frequency of intracranial relapse at initially treated sites and at new sites progression-free survival overall survival late toxicities quality of life
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multi-centre trial randomised centrally via minimisation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	All outcomes except survival may be at risk of selective reporting.

Komarnicky 1991

Methods	RCT; study period 1979 to July 1983: enrolled: 859 evaluated: 779
Participants	Inclusion: 1. brain metastases with measurable disease

Komarnicky 1991 (Continued)

2. 18 to 75 years of age
3. KPS $\geq$ 40
4. Neurological function class (NFC) 1, 2, 3
5. If on chemo must not have had change in drugs within 2 weeks before randomisation, during RT/misonidazole or 2 weeks after completion of RT

Interventions	WBRT with or without misonidazole
Outcomes	1. survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	Survival outcome unlikely to be associated with selective reporting

Kondziolka 1999

Methods	RCT; study period not reported: evaluated: 27
Participants	Inclusion: 1. histological confirmation of cancer 2. $\leq$ 25 mm 3. $>$ 5 mm from the optic chiasm 4. 2 to 4 brain metastases Exclusion: participants unable to undergo an MRI
Interventions	WBRT (3000 cGy/10 fr) vs WBRT (3000 cGy/10 fr) and radiosurgery
Outcomes	1. survival 2. local brain control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation described as a "coin toss" at the initial clinic visit

Kondziolka 1999 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Trial stopped early and only a total of 27 (60% accrual) participants reported
Selective reporting (reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting. Local brain control may have been subject to selective reporting.

Kurtz 1981

Methods	RCT; study period May 1976 to August 1979: enrolled: 309 evaluated: 255	
Participants	Inclusion: 1. patients with cancer with positive isotope brain scans 2. no evidence of disseminated disease Exclusion: 1. NFC IV 2. anticancer treatment within previous 2 weeks 3. progressive untreated primary	
Interventions	5000 cGy/20 fr vs 3000 cGy/10 fr	
Outcomes	1. survival 2. median time to progression 3. palliation of symptoms 4. improvement rate 5. cause of death	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	Survival not likely to be subject to selective reporting. Median time to progression, palliation of symptoms may have been associated with selective reporting.

Lee 2008

Methods	RCT; study period August 2002 to November 2005: enrolled: 48	
---------	---	--

Lee 2008 (Continued)

evaluated: 48

Participants	<p>pathologically confirmed non-small-cell lung cancer</p> <p>clinically silent brain metastases (not surgically resectable)</p> <p>age 18 to 75 years</p> <p>ECOG performance status 0 to 3</p> <p>adequate bone marrow, hepatic, renal functions</p> <p>no prior chemotherapy nor molecular targeted therapy</p>
Interventions	<p>chemotherapy first followed by WBRT</p> <p>vs</p> <p>WBRT followed by chemotherapy</p>
Outcomes	<p>progression-free survival</p> <p>tumour response</p> <p>quality of life</p> <p>toxicity</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Progression-free survival, tumour response, and quality of life outcomes may have been subject to selective reporting.

Mehta 2003

Methods	RCT; study period not reported: evaluated: 401
Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. MRI-demonstrated brain metastases 2. histologically proven solid tumours 3. required WBRT 4. KPS $\geq$ 70 <p>Exclusion:</p> <ol style="list-style-type: none"> 1. small-cell lung cancer, lymphoma, or germ cell tumours 2. brain metastases partially or completely resected 3. received prior cranial irradiation

Mehta 2003 (Continued)

4. leptomeningeal metastases
5. ≥ 2 sites of extracranial metastases except when breast was the primary cancer
6. chemotherapy planned during WBRT

Interventions	WBRT with or without motexafin gadolinium
Outcomes	1. survival 2. neurological progression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival not likely to be subject to selective reporting. Neurological progression may have been subject to selective reporting.

Mehta 2009

Methods	RCT; study period December 2002 to March 2005: enrolled: 554 evaluated: 554
Participants	Inclusion: 1. metastatic non-small-cell lung cancer to brain 2. Karnofsky Performance Status ≥ 70 Exclusion: 1. liver metastases 2. ≥ 2 sites of extracranial metastases 3. leptomeningeal metastases 4. previous resection single brain metastasis 5. previous WBRT 6. previous radiosurgery
Interventions	WBRT with or without motexafin gadolinium
Outcomes	1. events review committee-determined interval to neurological progression or death with evidence of neurological progression (primary endpoint) 2. investigator-determined neurological progression

Mehta 2009 (Continued)

3. interval to neurocognitive progression
4. survival
5. safety

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned according to the urn randomisation method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	Neurological progression and neurocognitive progression at unclear risk of selective reporting

Meyers 2004

Methods	RCT; study period not reported: enrolled: not reported evaluated: 401
Participants	See Mehta 2003 .
Interventions	WBRT (3000 cGy/10 fr) and motexafin gadolinium vs WBRT (3000 cGy/ 10 fr)
Outcomes	1. neurocognitive function and progression
Notes	same trial as Mehta 2003

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned according to the urn randomisation method
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not completely described
Selective reporting (reporting bias)	Low risk	Neurocognitive function and progression measured by formal neurocognitive testing unlikely to be associated with selective reporting

Mornex 2003

Methods	RCT; study period May 1991 to July 1997:
---------	--

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Mornex 2003 (Continued)

enrolled: 76

evaluated: 76

Participants	Inclusion: <ol style="list-style-type: none"> 1. histologically confirmed malignant melanoma 2. ≥ 1 measurable, non-resectable cerebral lesion 3. age 18 to 70 years 4. life expectancy > 3 months 5. adequate blood counts 6. satisfactory liver and renal function 7. no previous chemotherapy within last 4 weeks 8. no previous cranial irradiation 9. informed consent
Interventions	fotemustine vs fotemustine and WBRT
Outcomes	<ol style="list-style-type: none"> 1. cerebral response rates (complete and partial) and control rate (complete, partial and stable disease) and time to cerebral progression on day 50 2. overall response rate, time to overall progression, overall survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Brain response rate, time to overall progression may be at risk of selective reporting. Survival unlikely to be associated with selective reporting

Mulvenna 2016

Methods	RCT; study period 2 March 2007 to 29 August 2014: enrolled: 538 evaluated: 538
Participants	Inclusion: <ol style="list-style-type: none"> 1. metastatic non-small-cell lung cancer brain metastases in patients unsuitable for surgery or radio-surgery 2. ability to respond to questions regarding quality of life, symptoms, side effects Exclusion: <ol style="list-style-type: none"> 1. previous brain irradiation

Mulvenna 2016 (Continued)

Interventions	WBRT vs optimal supportive care
Outcomes	1. quality-adjusted life-years (primary outcome) 2. symptoms 3. side effects 4. quality of life 5. Karnofsky Performance Status changes 6. overall survival 7. dexamethasone use
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multi-centre trial centrally randomised via minimisation and stratified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition described. More than 90% follow-up forms received, 80% expected quality of life forms completely filled in, only 1 participant lost to follow-up
Selective reporting (reporting bias)	Unclear risk	All outcomes may be associated with selective reporting except for overall survival.

Murray 1997

Methods	RCT; study period 1991 to 1995: enrolled:445 evaluated: 429
Participants	Inclusion: 1. proof of underlying primary 2. measurable brain lesion(s) on CT/MRI 3. KPS $\geq$ 70 4. NFC 1 or 2 Exclusion: 1. primary site haematopoietic origin 2. metastatic lymphoma involving meninges
Interventions	5440 cGy/34 fr (BID over 17 days) vs 3000 cGy/10 fr (over 10 days)
Outcomes	1. survival 2. acute toxicity
Notes	

Murray 1997 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting

Neuhaus 2009

Methods	RCT; study period October 2001 to 6 August 2004: enrolled: 96 evaluated: 96	
Participants	histologically proven lung cancer (small-cell or non-small-cell) 18 to 75 years of age ≥ 1 measurable lesion in the brain sufficient bone marrow reserve, renal function tests ECOG performance status 0 to 2 excluded leptomeningeal metastases	
Interventions	WBRT with or without topotecan	
Outcomes	response rate progression-free survival overall survival quality of life	

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not fully described

Neuhaus 2009 (Continued)

Selective reporting (reporting bias)	Unclear risk	All outcomes except overall survival associated with unclear risk of selective reporting
--------------------------------------	--------------	--

Phillips 1995

Methods	RCT; study period October 1989 to March 1993: evaluated: 72	
Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. metastatic cancer to brain (based on neurodiagnostic tests, biopsy of primary, biopsy of brain lesion) 2. KPS $\geq$ 70 3. age > 18 4. measurable lesion(s) 5. WBC > 4000/mm³ 6. platelets > 125,000/mm³ 7. NFC 1, 2 <p>Exclusion:</p> <ol style="list-style-type: none"> 1. prior brain RT 2. complete surgical excision 3. CNS primary, leukaemia, lymphoma 4. concurrent chemotherapy 5. primary absent or controlled or under RT 	
Interventions	WBRT with or without BrdU	
Outcomes	<ol style="list-style-type: none"> 1. survival 2. response (CR + PR) 	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting. Response associated with unclear risk of selective reporting

Postmus 2000

Methods	RCT; study period 1989 to 1995: enrolled: 134 evaluated: 120	
Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. metastatic small-cell lung cancer 	

Postmus 2000 (Continued)

2. brain metastases (CT)
 3. extracranial tumour
 4. no previous treatment with chemotherapy or radiation for brain metastases
 5. no prior teniposide
 6. younger than 76 years
- Exclusion:
1. uncontrolled infection
 2. serious non-malignant disease

Interventions	teniposide chemotherapy with or without WBRT
Outcomes	<ol style="list-style-type: none"> 1. survival 2. time to progression 3. duration of response
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Time to progression and duration of response associated with unclear risk of selective reporting. Survival unlikely to be associated with selective reporting

Priestman 1996

Methods	RCT; study period February 1990 to February 1993: enrolled: 533 evaluated: 352
Participants	<p>Inclusion:</p> <ol style="list-style-type: none"> 1. symptomatic cerebral metastases confirmed on CT/radioisotope scans/biopsy 2. histological confirmation of primary 3. if no obvious primary, biopsy brain metastases 4. presence of symptoms related to brain metastases 5. stable dose of decadron 1 week before randomisation 6. 16 years of age and older 7. WHO performance status 0 to 3 <p>NFC < 4 (MRC)</p> <p>Exclusion:</p> <ol style="list-style-type: none"> 1. cytotoxic chemotherapy in prior 4 weeks
Interventions	1200 cGy/2 fr vs 3000 cGy/10 fr
Outcomes	<ol style="list-style-type: none"> 1. survival 2. neurological symptom response 3. cause of death

Priestman 1996 (Continued)

4. morbidity

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was by phone call. However, randomisation method was not completely described.
Incomplete outcome data (attrition bias) All outcomes	High risk	Of 533 eligible participants, only 66% were evaluable for neurological symptom response.
Selective reporting (reporting bias)	Unclear risk	Survival not likely to be associated with selective reporting. Neurological symptom response may be associated with selective reporting.

Puthiyottil 2016

Methods	RCT (abstract); study period December 2011 to August 2013: enrolled: 82
Participants	1. non-small-cell lung cancer 2. multiple brain metastases
Interventions	WBRT with or without concurrent temozolomide chemotherapy
Outcomes	1. progression-free survival
Notes	abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient detail in abstract

Ramlau 2013

Methods	RCT (abstract); study period not reported: evaluated: 468
---------	--

Ramlau 2013 (Continued)

Participants	1. non-small-cell lung cancer 2. ≥ 1 measurable brain metastasis
Interventions	WBRT with or without topotecan
Outcomes	1. overall survival 2. complete response 3. overall response 4. time to response 5. neurological signs and symptoms 6. adverse events
Notes	abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient detail in abstract

Rapp 2015

Methods	RCT; study period not reported: enrolled and evaluated: 198
Participants	1. primary or metastatic brain tumour 2. completed partial brain or WBRT of ≥ 30 Gy ≥ 6 months before enrolment 3. no imaging progression within 3 months before enrolment 4. life expectancy > 6 months 5. Eastern Cooperative Oncology Group score ≥ 2 6. no concurrent use of cognition-enhancing medications nor anticancer treatment, except hormonal or herceptin allowed
Interventions	donepezil vs placebo
Outcomes	cognitive composite score
Notes	

Rapp 2015 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified; permuted block randomisation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition fully described. 27/99 in the donepezil group and 25/99 in the placebo group dropped out of the trial between 0 and 24 weeks.
Selective reporting (reporting bias)	Low risk	Cognitive composite score measured by formal neurocognitive testing; unlikely to be at risk of selective reporting

Robinet 2001

Methods	RCT; study period July 1995 to October 1997: enrolled: 176 evaluated: 171	
Participants	Inclusion: 1. metastatic non-small-cell lung cancer 2. ≥ 1 measurable brain metastasis 3. ECOG performance ≤ 2 4. good renal and haematological function Exclusion: 1. recent myocardial infarction, congestive heart failure, or arrhythmia 3. prior chemotherapy or brain radiotherapy 4. previous cancer (non-melanoma skin cancer or in situ cervical cancer allowed)	
Interventions	early vs delayed WBRT and concurrent cisplatin and vinorelbine chemotherapy	
Outcomes	1. survival 2. progression-free survival 3. response	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not completely described
Selective reporting (reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting. Progression-free survival and response associated with unclear reporting bias

Scott 2007

Methods	RCT; study period February 2000 to August 2002: enrolled: 538 (non-small-cell lung cancer, breast cancer, and other primaries) evaluated: 106 (subgroup of breast cancer)
Participants	brain metastases RTOG recursive partitioning analysis (class I or II) no prior treatment of brain metastases (except partial resection allowed) chemotherapy discontinued ≥ 7 days before the start of whole brain radiotherapy and not to be restarted until ≥ 1 month after whole brain radiotherapy excluded small-cell lung cancer, germ cell tumours, and lymphomas
Interventions	WBRT with or without efaproxiral
Outcomes	Primary: overall survival Secondary: quality of life
Notes	subgroup analysis (not a priori)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Subgroup analysis 106 of 538 enrolled
Selective reporting (reporting bias)	Unclear risk	Survival not likely to be at risk of selective reporting. Quality of life at unclear risk

Sperduto 2013

Methods	RCT; study period October 2004 to August 2009
Participants	126 of 381 planned participants reported (trial closed early owing to poor accrual) Inclusion: 1. NSCLC 2. 1 to 3 brain metastases Exclusion: 1. brain stem metastases

Sperduto 2013 (Continued)

2. prior cranial irradiation
3. leptomeningeal disease

Interventions	WBRT and radiosurgery vs WBRT and radiosurgery and temozolomide chemotherapy vs WBRT and radiosurgery and erlotinib
Outcomes	<ol style="list-style-type: none"> 1. survival (primary) 2. time to central nervous system progression 3. performance status 4. toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Multi-centre trial centrally randomised via Zelen permuted block design
Incomplete outcome data (attrition bias) All outcomes	High risk	126 of 381 planned participants reported (trial closed early owing to poor accrual)
Selective reporting (reporting bias)	Unclear risk	All outcomes at unclear risk of selective reporting except for survival

Sperduto 2014

Methods	RCT (secondary analysis Andrews et al 2004): evaluated: 252
Participants	See Andrews 2004 .
Interventions	WBRT and radiosurgery vs WBRT
Outcomes	survival by graded prognostic assessment (GPA)
Notes	secondary analysis of RCT reported by Andrews et al 2004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Centrally randomised within strata by permuted blocks
Incomplete outcome data (attrition bias) All outcomes	High risk	Secondary analysis of the larger trial (Andres 2004); 252 evaluated of 333 enrolled .

Sperduto 2014 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting
---	--------------	---

Stea 2006

Methods	RCT; study period not reported: randomised: 538 evaluated: 515
Participants	1. brain metastases 2. Karnofsky Performance Status ≥ 70
Interventions	WBRT and supplemental oxygen vs WBRT and supplemental oxygen and efaproxiral
Outcomes	1. response 2. survival

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation process not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (re-reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting. Response associated with unclear reporting bias

Sturm 2015

Methods	RCT (abstract); study period not reported: randomised: 96
Participants	1. multiple brain metastases
Interventions	hippocampal avoidance WBRT vs WBRT
Outcomes	1. verbal learning and memory test
Notes	no results reported

Risk of bias

Bias	Authors' judgement	Support for judgement
------	--------------------	-----------------------

Sturm 2015 (Continued)

Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient detail in abstract

Suh 2006

Methods	RCT; study period ended January 31, 2003; start date not specified: enrolled: 538 evaluated: 515	
Participants	Inclusion: 1. RPA class I or II 2. no prior treatment for brain metastases 3. age ≥ 18 years 4. adequate haematological, hepatic, renal function 5. no other concurrent active malignancy 6. no planned therapy for brain metastases 1 month post follow-up visit 7. pulse oximetry $\geq 90\%$ Exclusion: 1. small-cell lung cancer, germ cell, or lymphoma 2. pregnant or breastfeeding 3. prior exposure to efaproxiral 4. chemotherapy within 7 days or investigational agents within 28 days of whole brain radiotherapy	
Interventions	3000 cGy/10 fr vs 3000 cGy/10 fr plus efaproxiral	
Outcomes	1. survival 2. radiographic brain response 3. radiological and clinical brain progression 4. cause of death 5. quality of life	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted blocks within strata
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	All outcomes except survival associated with unclear risk of reporting bias

Suh 2008

Methods	RCT (abstract); study period February 2004 to September 2006: randomised: 368 evaluated: 365
Participants	1. breast cancer 2. brain metastases
Interventions	WBRT with or without efaproxiral
Outcomes	1. overall survival 2. brain response rate at 3 months
Notes	abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient detail in abstract
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient detail in abstract
Selective reporting (reporting bias)	Unclear risk	Insufficient detail in abstract

Ushio 1991

Methods	RCT; study period not reported: enrolled: 100 evaluated: 88
Participants	Inclusion: 1. brain metastases from lung cancer 2. extracranial cancer relatively well controlled 3. good general condition
Interventions	WBRT vs WBRT + chloroethyl nitrosoureas vs WBRT + chloroethyl nitrosoureas + tegafur
Outcomes	1. response rates 2. survival
Notes	

Risk of bias

Ushio 1991 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised "by telephone call" but details of randomisation process not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described
Selective reporting (reporting bias)	Unclear risk	Survival unlikely to be associated with selective reporting. Unclear reporting bias with response rates

Zeng 2016

Methods	RCT; study period not reported: randomised and analysed: 64	
Participants	Inclusion: 1. non-small-cell lung cancer 2. brain metastases 3. ECOG performance status ≥ 3 Exclusion: 1. previous craniotomy 2. previous radiosurgery 3. single brain metastasis suitable for radiosurgery or surgery 4. miliary brain metastases	
Interventions	WBRT with or without sodium glycididazole	
Outcomes	1. CNS disease control rate 2. CNS progression-free survival 3. overall survival 4. toxicity	

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A random number list found in a statistics book was used for the randomisation process. Investigators did not have access to the randomisation list.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described

Zeng 2016 (Continued)

Selective reporting (re-reporting bias)	Unclear risk	All outcomes except survival associated with unclear reporting bias
---	--------------	---

CNS = central nervous system.
 CR = complete response.
 CT = computed tomography.
 DS-GPA = Diagnosis-Specific Graded Prognostic Assessment.
 ECOG = Eastern Cooperative Oncology Group.
 EEG = electroencephalography.
 GPA = graded prognostic assessment.
 HVLT-R DR = Hopkins Verbal Learning Test-Revised Delayed Recall.
 KPS = Karnofsky Performance Status.
 MMSE = Mini-Mental State Examination.
 MRC = Medical Research Council.
 MRI = magnetic resonance imaging.
 NFC = neurological function classification.
 NSCLC = non-small-cell lung cancer.
 PR = partial response.
 PS = performance status.
 RCT = randomised controlled trial.
 RPA = recursive partitioning analysis.
 RT = radiotherapy.
 SRS = stereotactic radiosurgery.

WBC = white blood cell count.
 WBRT = whole brain radiotherapy.
 WHO = World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Haie-Meder 1993	This RCT examined altered dose-fractionation schedules and was excluded based on inclusion of no standard group (3000 cGy/10 fr, or 2000 cGy/5 fr). Randomisations included: 1. 1 course of WBRT: 1800 cGy/3 fr/3 d vs 2. 2 courses of WBRT: 1800 cGy/3 fr/3 d, followed 1 month later by another 1800 cGy/3 fr/3 d or 3. 1800 cGy/3 fr/3 d, followed 1 month later by another 2500 cGy/10 fr/2 weeks
Wang 2015	This RCT was excluded as the radiotherapy used 3-dimensional conformal radiation therapy (3D CRT) rather than WBRT.

3D CRT = three-dimensional conformal radiation therapy.
 RCT = randomised controlled trial.
 WBRT = whole brain radiotherapy.

Characteristics of ongoing studies [ordered by study ID]

CCCWFU-97600

Trial name or title	NCI-P02-0211; NCT00031798 Phase 3 randomised study of d-methylphenidate to improve quality of life in patients receiving radiotherapy for primary or metastatic brain tumours
Methods	RCT

Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases (Review)

CCCWFU-97600 (Continued)

Participants	1. histologically confirmed metastatic cancer to brain or primary brain tumour 2. planned cranial irradiation (partial or whole brain) with a total dose $\geq$ 25 Gy
Interventions	d-methylphenidate (oral) vs placebo
Outcomes	1. fatigue score 2. quality of life 3. depression 4. neurocognitive function
Starting date	
Contact information	
Notes	Reference: Protocol Alert. Oncology Times. May 2002. Volume 24 (Issue 5)- p 36

EORTC-18981

Trial name or title	Phase III randomised study of temozolomide with or without WBRT in patients with stage IV melanoma with asymptomatic brain metastases
Methods	RCT
Participants	1. histologically confirmed unresectable metastatic melanoma 2. concurrent visceral/soft tissue metastases 3. $\geq$ 1 site of measurable disease 4. documented evidence of disease progression 5. no neurological symptoms
Interventions	temozolomide chemotherapy vs temozolomide chemotherapy and WBRT
Outcomes	1. survival 2. time to appearance of neurological symptoms 3. progression-free survival 4. quality of life and quality-adjusted survival 5. toxicity
Starting date	closed
Contact information	
Notes	Reference: http://www.eortc.org/research_field/clinical-detail/18981/

NCT00075166

Trial name or title	Protocol ID: 040066 Surgery vs radiosurgery to treat metastatic brain tumours
Methods	RCT

NCT00075166 (Continued)

Participants	<p>Eligibility:</p> <ol style="list-style-type: none"> 1. histologically confirmed cancer 2. 1 to 3 brain metastases 3. ≤ 4 cm <p>Exclusion:</p> <ol style="list-style-type: none"> 1. brainstem lesions 2. tumours within 10 mm from optic apparatus 3. poor operative candidates 4. leptomeningeal disease 5. psychiatric impairments 6. infection 7. germ cell tumour, lymphoma, small-cell lung cancer
Interventions	<p>surgery vs radiosurgery</p>
Outcomes	<ol style="list-style-type: none"> 1. survival 2. tumour recurrence or progression 3. neurological sign or symptom development 4. functional independence 5. steroid and anticonvulsant use 6. quality of life
Starting date	
Contact information	
Notes	Reference: https://clinicaltrials.gov/ct2/show/NCT00075166

NCT00076856

Trial name or title	<p>Protocol ID: P03247 Temozolomide for treatment of brain metastases from non-small-cell lung cancer</p>
Methods	RCT
Participants	<ol style="list-style-type: none"> 1. histologically confirmed non-small-cell lung cancer 2. ≥ 1 brain metastases 3. no previous WBRT or radiosurgery 4. no more than 2 sites of extracranial disease 5. KPS > 70
Interventions	<p>WBRT plus temozolomide vs WBRT plus placebo</p>
Outcomes	<ol style="list-style-type: none"> 1. survival 2. improvement in time to radiological CNS progression
Starting date	
Contact information	

NCT00076856 (Continued)

Notes

Reference: <https://clinicaltrials.gov/ct2/show/NCT00076856>
NRG-CC001

Trial name or title	A randomized phase III trial of memantine and whole brain radiotherapy with or without hippocampal avoidance in patients with brain metastases
Methods	RCT
Participants	Brain metastases outside a 5-mm margin around either hippocampus
Interventions	WBRT 30 Gy in 10 daily fractions and memantine vs WBRT with hippocampal avoidance and memantine
Outcomes	1. time to neurocognitive decline 2. health outcomes (EQ-5D-5L) 3. adverse events 4. intracranial progression 5. overall survival 6. symptom burden
Starting date	
Contact information	
Notes	Reference: https://clinicaltrials.gov/ct2/show/NCT02360215

RTOG-BR0118/ DEV1006

Trial name or title	Phase III randomised study of radiotherapy with or without thalidomide in patients with multiple brain metastases
Methods	RCT
Participants	1. histologically confirmed cancer 2. multiple brain metastases 3. ≥ 1 measurable brain metastasis by MRI > 4 cm or located in brainstem
Interventions	WBRT vs WBRT and thalidomide
Outcomes	1. survival 2. time to tumour progression 3. time to neurocognitive progression 4. cause of death 5. toxic effects 6. quality of life

RTOG-BR0118/ DEV1006 (Continued)

Starting date

Contact information

Notes Reference: <https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0118>
Yang 2015

Trial name or title Phase III study of WBRT with or without erlotinib for brain metastases in NSCLC

Methods RCT

Participants EGFR mutated NSCLC brain metastases

Interventions WBRT and erlotinib vs WBRT alone

Outcomes
1. time to neurological progression (primary)
2. overall survival
3. overall brain response rate
4. quality of life

Starting date August 2013

Contact information

Notes Reference: Yang ZZ, Li RQ, Zhu B. Phase III study of WBRT with or without erlotinib for brain metastasis NSCLC. J Thor Oncol 2015. S 426-S427

CNS = central nervous system.

EGFR = epidermal growth factor receptor.

EQ-5D-5L = EuroQoL Group Quality of Life Questionnaire based on five-level scale.

KPS = Karnofsky Performance Status.

MRI = magnetic resonance imaging.

NSCLC = non-small-cell lung cancer.

RCT = randomised controlled trial.

RSR 13 = efaproxiral.

WBRT = whole brain radiotherapy.

HVL-T-R DR = Hopkins Verbal Learning Test-Revised Delayed Recall.

DATA AND ANALYSES
Comparison 1. Altered WBRT fractionation schedules versus WBRT control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival: lower-dose WBRT vs control WBRT (3000 cGy/10 daily fractions)	3		Hazard Ratio (Fixed, 95% CI)	1.21 [1.04, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Overall survival: higher-dose WBRT vs control (3000 cGy/10 daily fractions)	4		Hazard Ratio (Fixed, 95% CI)	0.97 [0.83, 1.12]
3 Overall survival: WBRT 4000 cGy/20 fractions BID vs control WBRT (2000 cGy/4-5 daily fractions)	2		Hazard Ratio (Fixed, 95% CI)	1.18 [0.89, 1.56]

Analysis 1.1. Comparison 1 Altered WBRT fractionation schedules versus WBRT control, Outcome 1 Overall survival: lower-dose WBRT vs control WBRT (3000 cGy/10 daily fractions).

Analysis 1.2. Comparison 1 Altered WBRT fractionation schedules versus WBRT control, Outcome 2 Overall survival: higher-dose WBRT vs control (3000 cGy/10 daily fractions).

Analysis 1.3. Comparison 1 Altered WBRT fractionation schedules versus WBRT control, Outcome 3 Overall survival: WBRT 4000 cGy/20 fractions BID vs control WBRT (2000 cGy/4-5 daily fractions).

Comparison 2. Altered WBRT fractionation schedules versus WBRT control: neurological function improvement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neurological function improvement: lower-dose WBRT vs control dose WBRT (3000 cGy/10 fractions)	5	1612	Odds Ratio (M-H, Random, 95% CI)	1.74 [1.06, 2.84]
2 Neurological function improvement: higher-dose WBRT vs control dose WBRT (3000 cGy/10 fractions)	4	1480	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.92, 1.42]

Analysis 2.1. Comparison 2 Altered WBRT fractionation schedules versus WBRT control: neurological function improvement, Outcome 1 Neurological function improvement: lower-dose WBRT vs control dose WBRT (3000 cGy/10 fractions).

Analysis 2.2. Comparison 2 Altered WBRT fractionation schedules versus WBRT control: neurological function improvement, Outcome 2 Neurological function improvement: higher-dose WBRT vs control dose WBRT (3000 cGy/10 fractions). **Comparison 3. WBRT with radiosensitisers (radiosen) versus WBRT alone**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	8		Hazard Ratio (Fixed, 95% CI)	1.05 [0.99, 1.12]
2 Brain tumour response rates: complete response (CR) and partial response (PR) combined	6	847	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.63, 1.11]

Analysis 3.1. Comparison 3 WBRT with radiosensitisers (radiosen) versus WBRT alone, Outcome 1 Overall survival.

Analysis 3.2. Comparison 3 WBRT with radiosensitisers (radiosen) versus WBRT alone, Outcome 2 Brain tumour response rates: complete response (CR) and partial response (PR) combined.

Comparison 4. WBRT and radiosurgery versus WBRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	2		Hazard Ratio (Fixed, 95% CI)	0.61 [0.27, 1.39]
2 1-Year overall brain control rates	3		Hazard Ratio (Fixed, 95% CI)	0.39 [0.25, 0.60]

Analysis 4.1. Comparison 4 WBRT and radiosurgery versus WBRT, Outcome 1 Overall survival.

Analysis 4.2. Comparison 4 WBRT and radiosurgery versus WBRT, Outcome 2 1-Year overall brain control rates.

Comparison 5. Radiosurgery alone versus WBRT and radiosurgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	3		Hazard Ratio (Fixed, 95% CI)	1.00 [0.80, 1.25]
2 1-Year radiosurgery-targeted lesion control	4		Hazard Ratio (Fixed, 95% CI)	2.73 [1.87, 3.99]
3 1-Year distant brain control	4		Hazard Ratio (Fixed, 95% CI)	2.34 [1.73, 3.18]

Analysis 5.1. Comparison 5 Radiosurgery alone versus WBRT and radiosurgery, Outcome 1 Overall survival.

Analysis 5.2. Comparison 5 Radiosurgery alone versus WBRT and radiosurgery, Outcome 2 1-Year radiosurgery-targeted lesion control.

Analysis 5.3. Comparison 5 Radiosurgery alone versus WBRT and radiosurgery, Outcome 3 1-Year distant brain control.

APPENDICES

Appendix 1. MEDLINE search strategy

- 1 exp Brain Neoplasms/
- 2 ((brain or brainstem or intracranial or posterior fossa) adj3 (cancer* or carcinom* or tumor* or tumour* or neoplasm*)).mp.
- 3 1 or 2
- 4 exp Neoplasm Metastasis/ or metastas*.mp.
- 5 Radiotherapy/
- 6 Radiotherapy, Adjuvant/
- 7 (radiotherapy or radiat* or radiosurg*).mp.
- 8 Combined Modality Therapy/
- 9 Radiosurgery/
- 10 gamma knife.mp.
- 11 or/5-10
- 12 3 and 4 and 11
- 13 randomized controlled trial.pt.
- 14 controlled clinical trial.pt.
- 15 randomized.ab.

16 placebo.ab.
17 radiotherapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 or/13-20
22 12 and 21

key: mp=title, original title, abstract, name of substance word, subject heading word, unique identifier, pt=publication type, ab=abstract, fs=floating subheading, sh=subject heading

Appendix 2. Embase search strategy

1 exp Central Nervous System Tumor/
2 exp brain cortex/
3 ((brain or brainstem or intracranial or posterior fossa) adj3 (neoplasm* or cancer* or carcinoma* or tumor* or tumour*)).mp.
4 or/1-3
5 Brain Metastasis/ or metastas*.mp.
6 4 and 5
7 exp radiosurgery/
8 multimodality cancer therapy/
9 Radiotherapy/
10 Cancer radiotherapy/
11 (radiotherap* or radiosurg*).mp.
12 gamma knife.mp.
13 radiat*.mp.
14 or/7-13
15 6 and 14
16 random*.ti,ab.
17 factorial*.ti,ab.
18 (crossover* or cross over* or cross-over*).ti,ab.
19 placebo*.ti,ab.
20 (doubl* adj blind*).ti,ab.
21 (singl* adj blind*).ti,ab.
22 assign*.ti,ab.
23 allocat*.ti,ab.
24 volunteer*.ti,ab.
25 crossover procedure/
26 double blind procedure/
27 randomized controlled trial/
28 single blind procedure/
29 or/16-28
30 15 and 29

key:; mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name, ti=title, ab=abstract

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor Brain Neoplasms explode all trees
#2 brain* near/3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)
#3 brainstem near/3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)
#4 intracranial near/3 (cancer* or carcinoma* or tumor* or tumour* or neoplasm*)
#5 posterior fossa near/3 (cancer* or carcinoma* tumor* or tumour* or neoplasm*)
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Neoplasm Metastasis explode all trees
#8 metastas*
#9 (#7 OR #8)
#10 MeSH descriptor Radiotherapy explode all trees
#11 MeSH descriptor Radiotherapy, Adjuvant explode all trees
#12 radiotherapy or radiat* or radiosurg*
#13 MeSH descriptor Combined Modality Therapy explode all trees
#14 MeSH descriptor Radiosurgery explode all trees

#15 gamma knife
#16 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#6 AND #9 AND #16)

WHAT'S NEW

Date	Event	Description
18 January 2018	New citation required but conclusions have not changed	Ten new fully published randomised controlled trials involving 2457 participants were added to the review, including the following categories: whole brain radiotherapy (WBRT) with molecular targeted agents, WBRT with neurocognitive protective agents, and hippocampal sparing WBRT.
9 May 2017	New search has been performed	Literature searches were updated in May 2017. Risk of bias for included studies and overall certainty of evidence for each outcome are based on the GRADE approach has been included.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 3, 2006

Date	Event	Description
8 March 2012	New search has been performed	A new search was conducted on 19 July 2011.
6 March 2012	New citation required but conclusions have not changed	This update does not provide substantive changes to the original review. The title has been amended to: "Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases". The descriptor 'newly diagnosed' was added to clarify that the review deals only with upfront management rather than management at relapse. The literature search was updated in July 2011. Nine new trials involving 1420 participants were added. This updated review now includes a total of 39 trials involving 10,835 participants. Statistical analyses have been revised, and hazard ratios (rather than odds ratios) provided for the outcomes of overall survival, local control, and distant brain control. Risk ratios with 95% confidence intervals were recalculated with formal statistical input for the outcomes of neurological function improvement and brain tumour response. In terms of implications for practice, the option of radiosurgery alone (without whole brain radiotherapy (WBRT)) for selected patients with newly diagnosed brain metastases has been added.

CONTRIBUTIONS OF AUTHORS

MNT: literature search and identification of trials for inclusion; evaluation of methodological quality of included trials; abstraction of data; writing of the review. Main responsibility for updating the review.

WX: statistical analysis.

RW: assistance in writing the review; abstraction of data for the original review.

NLloyd: literature search and identification of trials for inclusion; abstraction of data; assistance in writing the original review.

NLap: assistance in writing the review.

AS: assistance in writing the review.

ER: assistance in writing the original review.

EC: literature search and identification of trials for inclusion; evaluation of methodological quality of included trials; abstraction of data.

DECLARATIONS OF INTEREST

MNT: none known.

WX: none known.

RW: none known.

NLloyd: none known.

NLap: none known.

AS: A Sahgal has conducted educational seminars for Medtronic, Elekta AB, Accuray Inc., and Varian Medical Systems; received a research grant from Elekta AB; received travel accommodations/expenses from Medtronic, Elekta, and Varian; and serves as a member of the Elekta MR Linac Research Consortium.

ER: none.

SOURCES OF SUPPORT

Internal sources

- University of Toronto, Odette Cancer Centre, Toronto, ON, Canada.

External sources

- Cancer Care Ontario Program in Evidence-based Care's Supportive Care Guidelines Group and Neuro-oncology Disease Site Group, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added to this update three new categories: WBRT with molecular targeted agents, WBRT with neurocognitive protective agents, and hippocampal sparing WBRT. As well, the risk of bias for included studies and the overall certainty of evidence for each outcome (based on the GRADE approach) have replaced the Oxford Quality Scale ([Jadad 1996](#)), along with Detsky quality scores ([Detsky 1989](#)).

INDEX TERMS

Medical Subject Headings (MeSH)

Brain Neoplasms [mortality] [*radiotherapy] [secondary] [*surgery]; Combined Modality Therapy; Cranial Irradiation [methods] [mortality]; Dose Fractionation, Radiation; Radiation-Sensitizing Agents [therapeutic use]; Radiosurgery [adverse effects] [methods]; Randomized Controlled Trials as Topic; Survival Analysis

MeSH check words

Adult; Humans