National Institute for Health and Care Excellence

Final

Brain tumours (primary) and brain metastases in adults

Evidence reviews for the investigation, management and follow-up of brain metastases

NICE guideline NG99

Evidence Report C

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Final

These evidence reviews were developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Investigation, management and follow-up of brain metastases

This Evidence Report contains information on 5 reviews relating to the investigation, management and follow-up of brain metastases. The Evidence Report is split into 3 sections:

- investigation of suspected brain metastases, which contains 1 review on imaging for suspected brain metastases
- management of confirmed brain metastases, which contains 3 reviews:
  - management of single metastases
  - management of multiple metastases
  - management of metastases with a mixed population
- follow-up for brain metastases, which contains 1 review on follow-up for brain metastases.

Investigation of suspected brain metastases

Investigation of suspected brain metastases

Review question

What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?

Introduction

Based on their clinical knowledge, the committee described how there has been substantial progress in the systemic treatment of primary cancers related to brain metastases such as lung, breast and melanoma. As a result of these improvements to treatment of primary cancer, there are expected to be increasing numbers of long-term survivors of these cancers, and therefore a corresponding increase in the number of people living with brain metastases as a result of their primary cancer. The committee believes that a major determinant of treatment is the number of metastases, and therefore it is important to review the evidence on what techniques best identify the number of metastases, in order that people are better treated as a result. This review question will focus on what is the most appropriate imaging strategy for patients being considered for focal treatment of their brain metastases, focusing primarily on advanced magnetic resonance imaging (MRI) and on studies published since the year 2000, as this is when MRI technology changed significantly.

PICO table

Table 1: Summary of the protocol

Population	Adults with a radiologically (by CT scan or MRI) suspected brain metastases
Intervention	Advanced MRI: • double dose or triple dose gadolinium contrast agent • PET-CT (including FDG: FET, MET, Choline-PET) • PET-MRI (including FDG: FET, MET, Choline-PET)
Comparison	Standard structural MRI (core protocol) +/- contrast (T1 pre and post contrast and T2)
Outcome	Critical: • number of metastases If the critical outcome is reported, the following outcomes will be also considered:

	Critical:
	• overall survival.
	• progression-free survival:
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life
	
	Important:
	• cognitive function:
	  ○ neurological function
	  ○ Karnofsky Performance Status (or WHO or ECOG)
	• Neurological Function Scale
	• treatment-related morbidity:
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke

CT computer tomography; ECOG Eastern Cooperative Oncology Group; FDG 2-deoxy-2-(18)fluoro-D-glucose; FET (18)F-fluoro-ethyl-l-tyrosine; MET (11)C-methionine; MRI magnetic resonance imaging; PET-CT Positron emission tomography–computed tomography; PET-MRI positron emission tomography - magnetic resonance imaging; WHO world health organization. T1 and T2 are not abbreviations but the name of techniques used in MRI.

Note that while this is classified as a diagnostic review, the outcomes to be evaluated are not typical of a diagnostic review. This is because the typical approach of evaluating diagnostic test accuracy against a reference standard (using sensitivity and specificity versus pathology, for example) would not be appropriate for a small metastasis, since a scan can identify a real tumour which either moves or disappears before it is biopsied. In these circumstances a negative biopsy result would not represent the gold standard, and therefore the purpose of including a list of clinical outcomes is to examine how the outcomes vary with the number of tumours detected, thus providing indirect evidence of the accuracy of the index test

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

No evidence was identified.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the major challenge with the diagnostic imaging of brain metastases was accurately identifying the disease burden. Since this is done through knowing the exact number of metastases, the number of metastases was considered a critical outcome.

If the number of metastases was given, the committee would consider overall survival, progression-free survival and health-related quality of life as additional critical outcomes as these directly relate to the effectiveness of subsequent treatment (they are not relevant if the number of metastases is not known, as they would not add any clinical information). In addition, treatment-related morbidity, cognitive and neurological function would be considered important outcomes in the case where the number of metastases was known, as these are indirect evidence of subsequent treatment effectiveness. As before, these outcomes are not relevant if the number of metastases is not known.

The quality of the evidence

The clinical evidence search identified no studies that met the inclusion criteria for this review.

The committee believed it would be appropriate to make recommendations regardless. This is because while using MRI to investigate tumours is standard practice, the suggested imaging schedule (extracranial and completed before multidisciplinary team meetings) is not uniformly conducted at every treatment centre, and the committee believed consensus recommendations to standardise practice in this area would greatly improve patient outcomes.

The committee decided not to make a research recommendation, as they believed that research was too impossible to ethically conduct, owing to the absence of a reference standard against which to judge results.

Benefits and harms

The benefits of more standardised scanning are that improved knowledge of the number of metastases can lead to different, more effective management and consequently a reduction in unnecessary or ineffective treatments. In any given diagnostic test, there is normally a trade-off between identifying all metastases (sensitivity) and not identifying too many cases of non-metastases (specificity). The committee believed that these considerations did not apply to this review on brain metastases; since a small tumour could show up on imaging but then shrink and disappear by the time of a biopsy, sensitivity and specificity cannot be estimated reliably. However in the experience of the committee, most tumours which show up on an MRI scan are clinically significant, and it would be very rare to offer radical intervention on the basis of an imaging result of uncertain significance. Consequently the committee believed the balance of benefits and harms greatly favoured recommending imaging.

For people with radiologically suspected brain metastases, the use of standard structural MRI was recommended on the basis of clinical experience, since it was the current standard of care. The committee described how the risk of not offering MRI would be an inability to correctly assess how many metastases were in the skull, and that clinicians might recommend harmful treatments on the basis of inadequate information. Therefore the committee justified a stronger 'offer' recommendation on the basis of the potential for large harms to patients if MRI was not conducted.

For people with radiologically confirmed brain metastases, the committee recommended that extracranial imaging appropriate to tumour type should be performed before treatment begins. This recommendation was made on the basis of the committee's experience. This is so people do not have inappropriate therapy or treatment that will not work for them because of their primary tumour. The committee justified the stronger 'offer' recommendation on the basis that not conducting extracranial imaging before treatment begins risks an inappropriate treatment being selected, which could potentially harm the patient.

Based on their experience, the committee recommended that people should have all imaging done before referral to neuro-oncology multidisciplinary team meetings, and relevant biopsies of the extracranial disease taken if this will help determine management. This will make the multidisciplinary team meeting process more efficient and reduce delays for people with brain metastases. This was on the basis of the committee's expertise. The committee justified the stronger 'offer' recommendation on the basis that the multidisciplinary team would not be able to make any treatment decisions about a person until they have the results of imaging to base these decisions on. This does not risk harming the patient, but scheduling the multidisciplinary team meeting before imaging is done would waste clinician time and NHS resources for no benefit.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

The recommendations will reinforce current best practice and what is already happening across most centres. The recommendations reinforce the need to complete diagnostic imaging prior to any neuro-oncology multidisciplinary team meetings which will result in

imaging being performed in a more standardised way without any overall increase in the number of imaging procedures. While the committee considered that these recommendations would be cost neutral it was noted that they could be cost saving through better treatment planning at the multidisciplinary team stage and a consequent reduction in unnecessary or ineffective treatments.

Other factors the committee took into account

The committee noted the lack of evidence for more advanced MRI techniques and the increased cost associated with these. The committee decided not to recommend routine additional imaging sequences as there is currently no evidence that they improve the diagnosis of brain metastases and introducing new imaging will create delays for people with brain metastases accessing treatment.

References

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Management of confirmed brain metastases

Management of single brain metastases

Review question

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these) for a single brain metastasis?

Introduction

Brain metastases are the most common intracranial tumours in adults and arise as a consequence of cancer elsewhere in the body. Uncontrolled brain metastases may cause headache, neurocognitive dysfunction, seizures and eventually death. Decisions regarding the most effective treatment for brain metastases require important consideration between optimising local control, the potential side-effects, overall survival and cost. The number of people diagnosed with brain metastases is likely to continue to rise as a consequence of the improvement of systemic treatments for a number of common cancers.

Those diagnosed with a solitary brain metastasis are considered to be in an advantageous position compared to those with multiple brain metastases, with potential longer survival. However the optimal treatment strategy is not clear, particularly regarding the balance between intracranial disease control and neurocognitive sequelae of both the disease and the treatment. Traditionally single brain metastases were treated with surgical resection with adjuvant whole brain radiotherapy (WBRT), but in more recent years stereotactic radiosurgery (SRS) has become the favoured treatment unless, for example, the histology is uncertain. However, the role of adjuvant WBRT remains controversial, the decision to offer SRS or surgery is centre dependant, the more novel concept of surgery and then SRS to the cavity is becoming more common, and the interplay with systemic therapies is unclear. The development of new guidance regarding the optimal treatment of a solitary metastasis will help provide clarity and consistency in this area.

PICO table

Table 2: Summary of the protocol (PICO table)

Population	People with a single brain metastasis

Intervention	• Surgery
	• Radiotherapy:
	  ○ radiosurgery (1 fraction)
	  ○ stereotactic radiotherapy (2-5 fractions)
	  ○ whole brain radiotherapy
	• Combined therapy (any combination of the above)
	• Combination of radiation and drug therapy

Comparison	• Each other

	• Combinations of treatments

Outcome	Critical:
	• overall survival.
	• progression-free survival
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life
	
	Important:
	• cognitive function.
	• neurological function
	  ○ Karnofsky performance status (or WHO or ECOG)
	  ○ Neurological Function Scale
	• treatment-related morbidity.
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke
	
	Limited:
	steroid (for example dexamethasone) use (duration and dose)

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Seven randomised control trials (N=563) with people with single brain metastases were included in this review (Brown 2017; Kepka 2016; Mintz 1996; Muacevic 2008; Patchell 1990; Patchell 1998; Roos 2006). Data reported in a secondary publication from 1 of these trials were also included (Kepka 2017). Two additional randomised control trials provided a post-hoc analyses of single brain metastases from a pool of multiple metastases (Andrews 2004, Mulvenna 2016). A summary of these trials is provided in Table 3.

Two studies compared whole brain radiation therapy (WBRT) with WBRT combined with surgery. One study compared WBRT combined with surgery to radiosurgery alone. Four of the studies assessed adjuvant treatment after resection of a single brain metastasis: 2 compared stereotactic radiosurgery with WBRT and 2 compared WBRT with observation. One study included a minority (23%) of participants with multiple metastases (2-4) (Brown 2017), whilst the remaining 6 studies specifically included participants with a single metastasis. No participants had a history of cranial radiation before entry to the trials.

A summary of these studies is provided in Table 3, and the results along with the quality of the evidence for each outcome are listed Table 4 - Table 12 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K. Note that there was a single search conducted for all 3 populations considered in the management brain metastases, therefore the excluded studies list is common for these 3 reviews.

Summary of clinical studies included in the evidence review

Table 3: Summary of included studies

Study	Age	N	Single metastases	Previous treatment	Intervention	Comparison	Duration Follow up
Andrews 2004	Mean (range)= 58.8 (19-82) in the WBRT+SRS groups and 59.9 (24-90) in the WBRT alone group	186 (only a subgroup of patients [56%] with a single brain metastasis were included)	Post-hoc analysis 100%	No previous cranial radiation.	WBRT	WBRT+SRS	6 months
Brown 2017	Median 61 years in SRS group, 62 years in WBRT group	194	77% (23% had 2-4 metastases)	All participants had surgical resection of the metastasis prior to trial entry. No previous cranial radiation. Prior treatment with systemic therapies (e.g. chemotherapy) was permitted.	Stereotactic radiosurgery to the tumour bed	WBRT	Median follow up 11.1 months for entire population; 22.6 months for those who had not died.

Study	Age	N	Single metastases	Previous treatment	Intervention	Comparison	Duration Follow up
Kepka 2016, Kepka 2017	Median 59.5 years	59	100%	All participants had surgical resection of the metastasis prior to trial entry. No previous brain irradiation.	Stereotactic radiosurgery to the tumour bed	WBRT	Median follow up 29 months for those who had not died.
Mintz 1996	Man (SD)= 58 (9.86) in the WBRT group and 58.9 (8.98) in the WBRT + surgery group	84	100%	No previous cranial irradiation. Some patients received other treatments for their primary tumour, e.g., chemotherapy after treatment of the brain metastasis	WBRT	WBRT + Surgery	18 months
Muacevic 2008	Mean (SD)= 58.3 (9.6) in the WBRT + surgery group and 54.3 (11.7) radiosurgery group	64	100%	No history of previous cranial radiotherapy	Radiosurgery	WBRT + Surgery	12 months
Mulvenna 2016	Median (range) = 58 (38.80) in the best care group and 60 (42-78) in the	162 (only a subgroup of patients [30%] with a single brain	Post-hoc analysis 100%	Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine	WBRT+Best care	Best care (included oral dexamethasone; support from a specialist nurse and access to specialised	11 months

Study	Age	N	Single metastases	Previous treatment	Intervention	Comparison	Duration / Follow up
	WBRT+ best care group	metastasis were included)		kinase inhibitors [TKI]) was permitted (with predefined washout periods of 4 weeks for chemotherapy and 1 week for TKIs)		clinical and palliative care)	
Patchell 1990	Median (range) in the surgery +WBRT =59 (44-74) and in the WBRT only = 60 (49-73)	48	100%	No history of previous cranial radiotherapy. Some had previous treatment for primary tumour	WBRT	WBRT + Surgery	15-40 weeks
Patchell 1998	Median 60 years in radiotherapy group, 58 years in observation group	95	100%	All participants had surgical resection of the metastasis prior to trial entry. No previous brain irradiation.	WBRT	Observation	Median 127 and 132 weeks for each group
Roos 2006	Median 51.5 years in radiotherapy group, 65 years in observation group	19	100%	All participants had undergone surgery or radiosurgery to remove the metastasis prior to trial entry. No previous	WBRT	Observation	Median potential follow up 6.2 years (range 5.6 – 7.3)

Study	Age	N	Single metastases	Previous treatment	Intervention	Comparison	Duration / Follow up
				cranial irradiation.			

SD standard deviation; SRS stereotactic radiosurgery; WBRT whole brain radiation therapy.

Quality assessment of clinical studies included in the evidence review

Table 4: Summary clinical evidence profile for WBRT and surgery versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+Surgery			
Deaths within 30 days of surgery	76 per 1000	77 per 1000 (70 to 84)	RR 1.02 (0.93 to 1.11)	132 (2 studies)	⊕⊕⊕⊖ moderate[1]
Deaths within 1 year of treatment	698 per 1000	879 per 1000 (698 to 1000)	RR 1.26 (1 to 1.58)	84 (1 study)	⊕⊕⊖⊖ low[1,2]
Death due to systemic causes	478 per 1000	598 per 1000 (354 to 1000)	RR 1.25 (0.74 to 2.14)	48 (1 study)	⊕⊖⊖⊖ very low[1,3]
Risk of death[a]	Not estimable	Not estimable	RR 2.2 (1.21 to 4)	48 (1 study)	⊕⊕⊖⊖ low[1,2]
Morbidity rate 30 days	174 per 1000	377 per 1000 (77 to 1000)	RR 2.17 (0.44 to 10.77)	48 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Quality of life (Spitzer score) 3 months	Not applicable	The mean quality of life (spitzer score) 3 months in the intervention groups was 1.02 higher (0.02 lower to 2.06 higher)	Not applicable	84 (1 study)	⊕⊖⊖⊖ very low[1,4,5]
Quality of life (Spitzer	Not applicable	The mean quality of life (spitzer score) 4-6 months in the	Not applicable	84 (1 study)	⊕⊖⊖⊖ very low[1,4,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
score) 4-6 months		intervention groups was 0.17 higher (0.67 lower to 1.01 higher)			
Recurrence original only	435 per 1000	78 per 1000 (17 to 326)	RR 0.18 (0.04 to 0.75)	48 (1 study)	⊕⊕⊖⊖ low[1,4]
Recurrence original and distant	87 per 1000	111 per 1000 (22 to 655)	RR 1.28 (0.25 to 7.53)	48 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Recurrence original all types	522 per 1000	198 per 1000 (83 to 480)	RR 0.38 (0.16 to 0.92)	48 (1 study)	⊕⊖⊖⊖ very low[1,4,7]

CI: confidence interval; RR: relative risk; WBRT whole brain radiation therapy.
[a]Risk of death was defined as those who died after the beginning of the intervention as compared to those who were still alive.
1 It was unclear how randomisation was performed and unclear in both studies if allocation concealment was performed.
2 95% CI crossed 1 MID (1.25)
3 95% CI crossed 2 MIDs (0.8 and 1.25)
4 It was unclear if either the participants, assessors or investigators were blinded.
5 95% CI crossed 1 MID (0.5x2.19=1.10)
6 95% CI crossed 1 MID (0.5x1.9=1.0)
7 95% CI crossed 1 MID (0.8)

Table 5: Summary clinical evidence profile of surgery and WBRT versus radiosurgery

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Radiosurgery	Surgery+WBRT			
Death at 1 year follow up	613 per 1000	515 per 1000 (331 to 797)	RR 0.84 (0.54 to 1.30)	64 (1 study)	⊕⊖⊖⊖ very low[1,2]
Complete response (complete resolution)	290 per 1000	6 per 1000 (0 to 96)	RR 0.02 (0.00 to 0.33)	64 (1 study)	⊕⊕⊖⊖ low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Partial response (tumour volume reduction >50%)	484 per 1000	924 per 1000 (658 to 1000)	RR 1.91 (1.36 to 2.68)	64 (1 study)	⊕⊕⊖⊖ low[1,3]
Stable disease (tumour control)	194 per 1000	240 per 1000 (199 to 286)	RR 1.24 (1.03 to 1.48)	64 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Progressive disease (any tumour V increase >25%)	32 per 1000	10 per 1000 (0 to 239)	RR 0.31 (0.01 to 7.42)	64 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Freedom from local recurrence - 1 year	968 per 1000	1000 per 1000 (697 to 1000)	RR 5.64 (0.72 to 44.20)	64 (1 study)	⊕⊖⊖⊖ very low[1,2]
Steroid use	710 per 1000	852 per 1000 (653 to 1000)	RR 1.20 (0.92 to 1.56)	64 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Acute toxicity (<90 days)	516 per 1000	970 per 1000 (686 to 1000)	RR 1.88 (1.33 to 2.66)	64 (1 study)	⊕⊕⊖⊖ low[1,3]

CI: confidence interval; RR: relative risk; WBRT whole brain radiation therapy.
1 It was unclear how randomisation was performed and insufficient detail was given on allocation concealment
2 95% CI crossed 2 MIDs (0.8 and 1.25)
3 It was unclear if either the participants, assessors or investigators were blinded.
4 95% CI crossed 1 MID (1.25)

Table 6: Summary clinical evidence profile of WBRT and best supportive care versus best supportive care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Best supportive care	WBRT + best supportive care			
Overall survival	Not applicable	Not applicable	HR 1 (0.73 to 1.36)	162 (1 study)	⊕⊕⊖⊖ low[1]

CI confidence interval; HR hazard ratio; WBRT whole brain radiotherapy
[1] Unclear method of allocation concealment. Stratification was not done by number of metastases

Table 7: Summary clinical evidence profile of WBRT + SRS versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+SRS			
Mean overall survival (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[3]	186 (1 study)	⊕⊖⊖⊖ very low[1,2]

CI confidence interval; SRS stereotactic radiosurgery; WBRT whole brain radiotherapy
1 Selective reporting of outcomes
2 Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
3 Not calculated as SDs were not reported. Mean overall survival in WBRT = 4.9 (n=94); mean overall survival in WBRT+SRS= 6.5 (n=92), p=0.0390.

Table 8: Clinical evidence profile of Stereotactic radiosurgery versus WBRT for resected metastasis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	Stereotactic radiosurgery			
Overall survival (median follow up 22-29 months)	Not applicable	Not applicable	HR 1.31 (0.80 to 2.15)	253 (2 studies)	⊕⊖⊖⊖ very low[1,6]
Median survival (median follow-up 22.6 months)	12.2 months	11.6 months (9.9 to 18.0)	HR 1.07 (0.76 to 1.50)	194 (1 study)	⊕⊕⊖⊖ low[1]
Cumulative incidence of neurological/ cognitive failure by 2 years	633 per 1000	722 per 1000 (506 to 1000)	RR 1.14 (0.80 to 1.63)	59 (1 study)	⊕⊖⊖⊖ very low[1,2]
Toxicity events (any grade)	707 per 1000	509 per 1000 (396 to 643)	RR 0.72 (0.56 to 0.91)	185 (1 study)	⊕⊕⊖⊖ very low[2,4]
Total intracranial progression	357 per 1000	578 per 1000 (311 to 1000)	RR 1.62 (0.87 to 3.04)	47 (1 study)	⊕⊕⊖⊖ very low[2,3]
Relapse in the tumour bed	250 per 1000	262 per 1000 (97 to 707)	RR 1.05 (0.39 to 2.83)	47 (1 study)	⊕⊖⊖⊖ very low[1,2]
Progression at new sites in the brain	214 per 1000	420 per 1000 (173 to 1000)	RR 1.96 (0.81 to 4.76)	47 (1 study)	⊕⊕⊖⊖ low[2,3]
Time to intracranial tumour progression	27.5 months	6.4 months (5.16 to 8.90)	HR 2.45 (1.62 to 3.72)	194 (1 study)	⊕⊕⊕⊖ moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Median duration of stable or better functional independence[c]	14.0 months	median not yet reach (17-6 months to not yet reached)	HR 0.56 (0.32 to 0.96)	194 (1 study)	⊕⊕⊖⊖ low[2,4]
Stable/improved LASA (QOL) score at 6 months	391 per 1000	539 per 1000 (368 to 789)	RR 1.38 (0.94 to 2.02)	129 (1 study)	⊕⊕⊖⊖ low[2,3]
Stable/improved FACT-Br total score at 6 months	438 per 1000	600 per 1000 (425 to 845)	RR 1.37 (0.97 to 1.93)	129 (1 study)	⊕⊕⊖⊖ low[2,3]
Global quality of life score at 2 months	Not applicable	The mean quality of life score was 4.5 points higher in the SRS group (from 8.6 points lower to 17.6 points higher)	Not applicable	58 (1 study)	⊕⊕⊖⊖ low[1,5]
Global quality of life score at 5 months	Not applicable	The mean quality of life score was 11.4 points lower in the SRS group (from 24.79 points lower to 1.99 points higher)	Not applicable	58 (1 study)	⊕⊕⊖⊖ low[1,5]

CI confidence interval; FACT-Br Functional Assessment of Cancer Therapy-Brain; HR Hazard ratio; LASA (QOL) Linear Analog Scale Assessment of Quality of Life; RR relative risk; SRS stereotactic radiosurgery; WBRT whole brain radiotherapy

[1] 95% CI crossed 2 default MIDs (0.80 and 1.25)

[2] It was unclear whether blinding was performed.

[3] 95% CI crossed 1 default MID (1.25)

[4] 95% CI crossed 1 default MID (0.80)

[5] 95% CI crossed 1 default MID (±33.4 x ±0.5= ±16.7)

[6] Serious inconsistency (I^2>50%)

a Defined as the time from randomisation to a drop of greater than 1 SD from baseline in at least 1 of the 6 cognitive tests

c assessed by the Barthel ADL Index as a score that fell by at least 10% below the baseline level.

Table 9: Clinical evidence profile of WBRT versus observation for resected metastasis

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Observation	WBRT			
Overall survival Follow-up: median 127-132 weeks	152 per 1000	122 per 1000 (44 to 338)	RR 0.80 (0.29 to 2.22)	95 (1 study)	⊕⊖⊖⊖ low[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Progression free survival	Not applicable	Not applicable	HR 1.27 (0.46 to 3.54)	19 (1 study)	⊕⊖⊖⊖ very low[1,2]
Median CNS failure-free survival[a]	Not applicable	Not applicable	HR 1.18 (0.45 to 3.09)	19 (1 study)	⊕⊖⊖⊖ very low[1,2]
CNS relapse[b]	778 per 1000	303 per 1000 (109 to 824)	RR 0.39 (0.14 to 1.06)	19 (1 study)	⊕⊕⊖⊖ low[1,3]
CNS toxicity[c]	Not estimable	Not estimable	RR 4.55 (0.25 to 83.70)	19 (1 study)	⊕⊖⊖⊖ very low[1,2]
No brain recurrence	304 per 1000	816 per 1000 (517 to 1000)	RR 2.68 (1.70 to 4.23)	95 (1 study)	⊕⊕⊕⊖ moderate[2]
Recurrence at site of original metastasis	326 per 1000	42 per 1000 (10 to 170)	RR 0.13 (0.03 to 0.52)	95 (1 study)	⊕⊕⊕⊖ moderate[2]
Recurrence at original metastasis site and distant brain recurrence	130 per 1000	61 per 1000 (16 to 231)	RR 0.47 (0.12 to 1.77)	95 (1 study)	⊕⊖⊖⊖ very low[1,2]
Recurrence at distant brain site(s) only	239 per 1000	81 per 1000 (29 to 239)	RR 0.34 (0.12 to 1.00)	95 (1 study)	⊕⊕⊖⊖ low2[,3]
Radiation toxicity ≥ grade 3	Not estimable	Not estimable	RR 4.55 (0.25 to 83.7)	19 (1 study)	⊕⊖⊖⊖ very low[1,2]

CI confidence interval; CNS central nervous system; HR Hazard ratio; RR relative risk; WBRT whole brain radiation therapy;
[1] 95% CI crosses 2 default MIDs (0.80 and 1.25)
[2] Unclear method of allocation concealment. Stratification was not done by number of metastases
[3] 95% CI crossed 1 default MID (0.80)
a CNS failure-free survival defined as time to CNS relapse (either radiological or symptomatic, see below), or CNS toxicity (see below) or death from any cause.
b CNS relapse defined as either radiological (≥25% increase in the product of diameters of an enhancing lesion at the index site and/or new enhancing lesions on brain imaging) or symptomatic (new or progressive symptoms of intracranial disease associated with radiological relapse or treated with surgery or radiosurgery despite a lack of diagnostic radiological changes or occurring in the terminal phase).
c CNS toxicity defined as new or worsening cognitive dysfunction with new/progressive generalised atrophy and/or diffuse white matter change on CT/MRI. Radiological evidence of CNS relapse had to be absent, and no intercurrent cause of cognitive dysfunction could be present. Focal CNS toxicity was identified in the presence of a new/persistent neurological deficit clinically compatible with a focal area of atrophy, a negative thallium/SPECT scan in the presence of an enhancing lesion, or an excised solitary mass lesion of necrotic tissue.

See Appendix F for the full GRADE tables.

Economic evidence

Included studies

The search identified 438 possibly relevant papers. Of these, 15 full papers relating to this topic were obtained for appraisal. 2 papers (Kimmell 2015 and Kim 2017) were included in the current review of published economic evidence for this topic.

Health economic evidence profile

Table 10: Health economic evidence profile

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Study 1										
Kimmell 2015 USA	People with a single brain metastasis	Whole Brain Radiotherapy (WBRT)	$32,140	0.69 QALYs	Reference			No sensitivity analysis performed	Partially Applicable	Very Serious Limitations.
		Stereotactic Radiosurgery (SRS)	$33,043	0.82 QALYs	$903	0.13 QALYs	$7,377 per QALY			
		Surgery	$36,786	0.88 QALYs	$4,646	0.19 QALYs	$25,514 per QALY			
		SRS+WBRT	$40,884	0.92 QALYs	$8,744	0.23 QALYs	$39,117 per QALY			
		Surgery+WBRT	$47,603	0.88 QALYs	$15,463	0.19 QALYs	$82,769 per QALY			
		Surgery+SRS	$58,728	0.98 QALYs	$26,588	0.29 QALYs	$91,856 per QALY			
	Comments: The study acknowledges that the patient groups for each intervention were not homogenous in terms of characteristics likely to predict the efficacy of treatment and no attempt was made to account for this.									
Study 2										

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Kim 2017 USA	Hypothetical cohort of patients with brain metastases from oligometastatic disease	SRS+WBRT	Not reported	Not reported	Reference			Deterministic Sensitivity Analysis: The cost effectiveness of SRS was sensitive to probability of cognitive decline with it being dominated for probabilities of cognitive decline >60%. The preferred intervention was robust to changes to other parameters. Probabilistic Sensitivity Analysis:	Partially Applicable	Potentially Serious Limitations
		SRS	Not reported	Not reported	$1,027	0.1 QALYs	$9,917			

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
								Probability that SRS was the preferred choice at a cost per QALY threshold of $10,000 and $50,000 was 82% and 92% respectively.		
	Comments: No distinction, or reporting of the percentage, of single and multiple metastases.									

Summary of studies included in the economic evidence review

Kimmell 2015 is a cost utility study comparing stereotactic radiosurgery (SRS), surgery and whole brain radiotherapy (WBRT) and combinations of these to each other in people with a single brain metastasis. The study took a US healthcare payer perspective and reported outcomes in terms of cost per QALY. Effectiveness data were taken from a systematic review of the literature. Utility data were informed by clinician opinion. Costs were taken from publically available US pharmacy costs.

Kim 2017 is a cost utility study comparing SRS to SRS and WBRT in patients with brain metastases (single and multiple). The study took a US healthcare payer perspective and reported outcomes in terms of cost per QALY. Effectiveness data were taken from four RCTs comparing SRS with and without adjuvant WBRT. Utility data were estimated using the standard gamble technique, from a survey of patients with brain metastases and nurses involved in their care before and after treatment with either SRS or WBRT. Cost data were obtained from Medicare reimbursement rates.

Both studies were deemed partially applicable to the decision problem. This is because they did not take a NHS and PSS perspective.

Kimmell 2015 was considered to have very serious limitations in terms of methodological quality. Amongst the limitations were that patient groups which were not necessarily comparable and no exploration of uncertainty was undertaken.

Kim 2017 was considered to have potentially serious limitations. This was because there was a lack of clarity around how some model parameters were estimated and incorporated and because of limited exploration around uncertainty in the model.

In Kimmell 2015 the base-case analysis estimated that surgery and SRS was the most cost effective treatment option if a cost per QALY threshold of $100,000 was assumed. Surgery and WBRT was dominated (less effective, more costly) in the analysis. No exploration of uncertainty was reported for this study.

In Kim 2017 the base-case analysis estimated that SRS alone was cost effective compared to SRS and WBRT with an incremental cost-effectiveness ratio (ICER) of $9,917 per QALY. This result was robust during probabilistic sensitivity analysis with the 92% probability that SRS was the preferred choice at a cost per QALY threshold of $50,000. The preferred choice was sensitive to the effectiveness (probability of cognitive decline) with SRS alone being dominated for probabilities above 60%, within the range reported in the RCTs used to inform the model.

The results of both published economic studies are not strictly comparable given the different interventions considered by each. Only SRS versus SRS and WBRT was considered by both studies although in slightly different patient groups. Despite having almost identical perspectives they reported opposite results. Kimmel 2015 reported SRS and WBRT as both cost increasing and health improving compared to SRS, while Kim 2017 had SRS alone as both cost increasing and health improving. A hypothesised explanation for this contradiction, in the absence of sensitivity analysis by Kimmell 2015 was that Kim 2017 included follow-up and surveillance costs, increasing costs for the more effective intervention. Kimmell 2017 did not include these costs.

For full economic evidence tables see Appendix H.

Economic model

A full report of the economic model is available in Appendix I.

Overview of methods

Two decision analytical models in the form of a partitioned survival analysis were developed to evaluate the relative cost effectiveness of the addition of different adjuncts following the treatment of a single brain metastasis with either surgery or stereotactic radiosurgery. The adjuncts considered were whole brain radiotherapy (WBRT) following either initial treatment or SRS following surgery. The model did not compare the cost effectiveness of initial treatment with surgery and initial treatment with SRS as whether to initially receive surgery or SRS would be based on factors such as the size of the metastasis, the location, and the presence of any comorbidities. The patient group initially receiving SRS would therefore differ from that of the group receiving surgery and there would be little validity in comparing their cost effectiveness. The main outcome of the economic model was incremental cost per QALY of each adjunct compared to the base-case strategy of initial treatment only. A NHS

and PSS perspective was taken. The model had a time horizon of 5 years which was deemed sufficient to capture the lifetime of the majority of the cohort as life expectancy in this group is limited.

Clinical data were derived entirely from 3 RCTs identified in the accompanying systematic review of clinical evidence. All costs were taken from NHS Reference Costs estimating a unit cost of the addition of WBRT and SRS as £1,702 and £3,556 respectively. Adverse event costs were not included in the base-case analysis as these were reasonably common and it was assumed their treatment cost would be included in NHS Reference Costs. Further or repeated interventions upon progression of disease were not costed in the base-case analysis as there were concerns that any cost savings would be through the contraindication of subsequent effective treatments. A secondary analysis was performed where these costs were included.

Quality of life weights for unprogressed disease was taken from 1 US study of 67 patients who received SRS following diagnosis of brain metastases using the EQ-5D-3L quality of life instrument. From this study a weight of 0.752 was estimated for unprogressed disease. Quality of life weights for the other disease states were estimated from 1 US study in 24 patients and 31 nurses involved with treatment of brain metastases using the standard gamble technique. This estimated a quality of life weight of 0.54 and 0.42 for intracranial and extracranial progression respectively.

All health and cost outcomes were discounted at a rate of 3.5% per annum.

Results of the economic models

The addition of WBRT to either surgery or SRS led to a reduction in life months of 0.27 and a reduction in QALYs of 0.0156 when compared to surgery or SRS alone. (Table 64 and Table 65) Consequently both interventions are dominated by (are more expensive and less effective than) the reference case of surgery or SRS alone. The addition of SRS to surgery also led to greater costs and decreased QALYs. These conclusions were consistent when salvage therapy costs were used.

Table 11: Initial treatment surgery primary base-case analysis results excluding salvage treatment costs

Intervention	Life Months	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
Surgery	17.80	0.7675	£ 8,901	Reference	Reference	Reference	Reference
Surgery+WBRT	17.53	0.7516	£ 10,572	-0.0159	£1,672	-£ 1,989	Dominated
Surgery+SRS	14.10	0.5267	£ 12,044	-0.2408	£3,144	£3144	Dominated

ICER incremental cost-effectiveness ratio; QALY quality-adjusted life year; SRS Stereotactic radiosurgery; WBRT whole brain radiation therapy.

Table 12: Initial treatment SRS primary base-case analysis results excluding salvage treatment costs

Intervention	Life Months	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
SRS	17.80	0.7742	£ 5,424	Reference	Reference	Reference	Reference
SRS+WBRT	17.53	0.7516	£ 7,096	-0.0226	£1,672	-£ 2,124	Dominated

ICER incremental cost-effectiveness ratio; QALY quality-adjusted life year; SRS Stereotactic radiosurgery; WBRT whole brain radiation therapy.

The results were sensitive to the overall survival for the surgery and SRS group with that intervention becoming the most cost-effective for values of overall survival within the 95% confidence interval reported by the pooled estimate of effectiveness reported in the clinical evidence review. Extensive sensitivity analyses were carried out around quality of life given the low quality evidence used to inform this important parameter with a large difference needed between quality of life weights for progressed and unprogressed disease for the addition of WBRT to become cost effective. These results were robust when probabilistic sensitivity analysis was carried out with an 82% and 88% probability of surgery alone and SRS alone being cost effective when a £20,000 per QALY threshold was assumed.

Conclusions

Using either WBRT or SRS as an adjunct to the initial treatment of people with a single brain metastases does not appear to be a cost effective use of NHS resources in the base-cases of the 2 models. Surgery and SRS is also the preferred option when overall survival is within the range of the 95% confidence interval reported by the pooled estimate. This suggest there may be considerable uncertainty in the model for deciding between surgery alone and surgery and SRS.

The 2 economic models were largely based around 3 RCTs which did not match the patient group considered by the model perfectly. The committee thought this would not significantly impact upon the results or conclusions. No high quality or directly applicable evidence was identified during a search for quality of life evidence to inform the economic models although conclusions were robust to sensitivity analyses around these parameters.

It is not possible to compare the results of the guideline economic analysis with that of the previously identified economic evidence given the different interventions considered, perspectives and methodologies of the models. However, 1 common comparator was found between the bespoke guideline models and the published evidence which concurred with the bespoke guideline model that the addition of WBRT to SRS would not be cost effective.

Resource Impact

Unit costs and resource use was presented to the committee as part of the de-novo economic model.

Evidence statements

WBRT and surgery versus WBRT

- Two randomised control trials (N=132) provided moderate quality evidence that showed no differences in mortality within 30 days of surgery (relative risk (RR) = 1.02, 95% confidence interval (CI) 0.93-1.11) between WBRT, and WBRT and surgery.
- One randomised control trial (N=84) provided low quality evidence that showed no differences in mortality 1 year after treatment with WBRT compared to WBRT and surgery (RR= 1.26 95% CI 1-1.58).
- One randomised control trial (N=48) provided very low quality evidence that showed no differences in death due to systemic causes between WBRT compared to WBRT and surgery (RR 1.25, 95% CI 0.74-2.14). This same trial showed that those who received WBRT had smaller risk of death (RR 2.2, 95% CI 1.21-4.00) and found no differences in the morbidity rate at 30 days between the treatment arms (RR= 2.17, 95% CI 0.44-10.77, very low quality).
- One randomised controlled trial (N=84) provided very low quality evidence to show no differences in quality of life at 3 months (mean in the WBRT and surgery= 1.02 higher, 95% CI 0.02 to 2.06) and at 4 to 6 months (mean in the WBRT and surgery = 0.17 higher, 95% CI -0.67 to 01.01).
- One randomised controlled trial (N=48) provided very low to low quality evidence to show that treatment with WBRT and surgery is more effective at reducing the number of recurrences at the original site (RR= 0.18, 95% CI 0.04 – 0.75) and at original (all site types) (RR= 0.38, 95% CI 0.16-0.92). However, no difference was found between the 2 treatment arms for the number of brain tumours appearing at distant sites only (RR= 1.28, 95% CI 0.25-7.83).

WBRT and surgery versus radiosurgery

- One randomised control trial (N=64) provided very low to moderate quality evidence that showed that surgery and WBRT are more effective at achieving a complete response (RR=0.02, 95% CI 0.00-0.33) compared with radiosurgery alone whereas radiosurgery was associated with more patients who showed a partial response (RR= 1.91, 95% CI 1.36-2.68) and stable disease (RR=1.24, 95% CI 1.03-1.48) compared with surgery and WBRT and with less acute toxicity (RR= 1.88, 95% CI 1.33-2.66) compared with the WBRT and surgery.
- The treatments did not differ in terms of death at 1 year (RR= 0.84, 95% CI 0.54-1.30), freedom from local recurrence at 1 year (RR= 5.64, 95% CI 0.72-44.20), progressive disease (RR= 0.31, 95% CI 0.01-7.42, or in the number of patients treated with steroids (RR= 1.20, 95% CI 0.92-1.56).

WBRT and best supportive care versus best supportive care

- One randomised control trial (N=162) provided low quality evidence in a post-hoc analysis that showed no difference in overall survival between WBRT and best supportive care, and best supportive care alone (HR=1, 95% CI 0.73-1.36).

WBRT and SRS versus WBRT

- One randomised control trial (N=186) provided very low quality evidence in a post-hoc analysis that showed WBRT and SRS is more effective at prolonging overall survival than WBRT alone (mean overall survival in the WBRT and SRS group= 6.5 months and mean overall survival in the WBRT = 4.9 months).

SRS versus WBRT for resected metastasis

- Two randomised controlled trials (N = 253) provided very low quality evidence that showed no difference in overall survival between SRS and WBRT following resection of a single brain metastasis (HR=1.31, 95% CI 0.80-2.15). One of these trials (N = 194) also showed no difference in median survival between the groups (low quality evidence) (HR= 1.07, 95% CI 0.76-1.50).
- Very low quality evidence from 1 randomised controlled trial (N = 59) showed no difference in the cumulative incidence of neurological/cognitive failure by 2 years follow-up (RR=1.14, 95% CI 0.80-1.63).
- Very low quality evidence from 1 trial (N = 185) showed a significant decrease in the risk of any radiation toxicity events for those who received SRS as compared with WBRT (RR=0.72, 95% CI 0.56-0.91).
- Very low to low quality evidence from 1 randomised controlled trial (N = 47) showed no significant differences in total intracranial progression (RR=1.62, 95% CI 0.87-3.04), relapse in the tumour bed (RR=1.05, 95% CI 0.39-2.83) or progression at new sites in the brain (RR=1.96, 95% CI 0.81-4.76). Moderate quality evidence from 1 trial showed that the time to intracranial tumour progression was significantly shorter for those who received SRS compared with WBRT (HR=2.45, 95% CI 1.62-3.72).
- Low quality evidence from 1 randomised controlled trial showed a significant increase in the duration of stable or better functional independence for those who received SRS compared to WBRT (HR=0.56, 95% CI 0.32-0.96). Low quality evidence from 1 trial showed no differences between the treatment groups in quality of life at 6 months as measured by both LASA (RR 1.38, 95% CI 0.94-2.02) and FACT-Br (RR= 1.37, 95% CI 0.97-1.93), and a second study provided low quality evidence which showed no significant difference between the treatment groups at 2 months (mean quality of life in the SRS arm = 4.5 higher, 95% CI 8.60 to 17.60) or 5 months either (mean quality of life in the SRS arm = 11.4 lower, 95% CI -24.79 to 1.99), using different scoring systems (European Organisation for Research and Treatment of Cancer quality of life questionnaire C30 and BN20 questionnaires [EORTC-QLQ-C30 and QLQ-BN20 questionnaires]).

WBRT versus observation for resected metastasis

- One randomised controlled trial (N = 95) provided low quality evidence that showed no significant difference in overall survival between those who received WBRT and those who were simply observed following resection of a single brain metastasis (RR=0.8, 95% CI 0.29-2.22). Very low to low quality evidence from 1 randomised controlled trial (N=19) showed no difference in progression free survival (HR= 1.27, 95% CI 0.46-3.54), in median CNS failure-free survival (HR = 1.18, 95% CI 0.45-3.09), in CNS relapse rate (RR=0.39, 95% CI 0.14-1.06),CNS toxicity (RR=4.55, 95% CI 0.25-83.7) or radiation toxicity events grade 3 or above (RR = 4.55, 95% CI 0.25-83.7) between the treatment

groups. Moderate quality evidence 1 randomised controlled trial (N = 95) showed a significantly higher proportion of people without any brain recurrence in the group who received WBRT compared to those who were observed (RR= 2.68, 95% CI 1.70-4.23). Recurrence at the site of the original metastasis (RR=0.13, 95% CI 0.03-0.52) was reduced in the group who received WBRT compared to observation. No difference was seen for recurrence at both the original site and distant sites (RR=0.47, 95% CI 0.12-1.77) or for recurrence at distant brain sites (RR=0.34, 95% CI 0.12-1.00).

The committee's discussion of the evidence

See the committee's discussion of the evidence in the management of brain metastases with a mixed population section.

References

See the references in the management of brain metastases with a mixed population section.

Management of multiple brain metastases

Review question

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these) for multiple brain metastases?

Introduction

Until recently whole brain radiotherapy (WBRT) was the standard treatment for multiple brain metastases (as the brain has special protection against foreign substances called the 'blood-brain barrier' this prevents systemic treatments alone). WBRT can provide some local control of intracranial metastases but can cause significant neurocognitive toxicity. This led to the concept of using single fraction stereotactic radiosurgery (SRS) for multiple lesions which may reduce the neurocognitive risks but does not treat areas of potential microscopic disease. Some patients may also have neurosurgery for brain metastases that are causing significant symptoms or if a tissue diagnosis is needed and these patients may then require any of the radiotherapy techniques described. For some patients, where overall prognosis is poor, the optimum management may be best supportive care (BSC) and none of the interventions described.

PICO table

Table 13: Summary of the protocol (PICO table)

Population	People with multiple brain metastases (≥2 metastases)

Intervention	• Neurosurgery
	• Radiotherapy:
	  ○ radiosurgery SRS (1 fraction)
	  ○ stereotactic radiotherapy SRT (2-5 fractions)
	  ○ whole brain radiotherapy (WBRT)
	  ○ hippocampal avoidance WBRT
	• Chemotherapy or systemic anti-cancer therapy/ treatment
	• Combined therapy (any combination of the above)
	• Best supportive care

Comparison	• Each other

Outcome	<u>Critical:</u>
	• overall survival.
	• progression-free survival
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life
	
	<u>Important:</u>
	• cognitive function.

	• neurological function
	  ○ Karnofsky performance status (or WHO or ECOG)
	  ○ Neurological Function Scale
	• treatment-related morbidity.
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke
	
	<u>Limited:</u>
	• steroid (for example dexamethasone) use (duration and dose)

ECOG Eastern Cooperative Oncology Group scale; SRS Stereotactic radiosurgery; SRT stereotactic radiotherapy; WBRT whole brain radiation therapy; WHO World Health Organization.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Six RCTs (N=1191) reported in 7 publications were included in the review (Cao 2015; Chabot 2016; Corn 2008; Knisely 2008; Kondziolka 2000; Pesce 2012; Suh 2006).

In all included studies, WBRT was offered to patients with or without an additional treatment, including chemotherapy (temozolomide [TMZ]), a radiation sensitizer (verliparib, parp inhibitor), an EGFR inhibitor (gefitinib [GFB]), cholesterol pathway modifier (efaproxiral), an immunomodulatory modifier (thalidomide) or radiosurgery.

Five studies included patients with a single metastasis (4 to 19%), but were included in this review because the number of people with a single metastasis was low (less than 25%, as described in the protocol). The studies by Cao 2015 and Pesce 2012 included patients who previously had chemotherapy but not necessarily the type delivered in the study. Suh 2006 included patients (9%) who previously had brain tumour resection. The same data were published in 2 papers by Kondzioka in 1999 and 2000, the results from 2000 were included in this review.

A summary of these studies is provided in Table 14, and the results along with the quality of the evidence for each outcome are listed Table 15 - Table 20 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K. Note that there was a single search conducted for all 3 populations considered in the management brain metastases, therefore the excluded studies list is common for these 3 reviews.

Summary of clinical studies included in the evidence review

Table 14: Summary of included studies

Study	N	Single metastases	Previous treatment	Intervention	Comparison	Duration of treatment
Cao 2015	100	15%	Mean number of prior chemotherapy regimens WBRT: 2.5 WBRT + TMZ 2.9	WBRT + Temozolomide (75 mg/m^2/day)	WBRT	14 days
Chabot 2016	307	19%	No prior cranial radiation or resection for brain metastases. About 32% currently taking EGFR	WBRT + Veliparib 50mg WBRT + Veliparib 200mg	WBRT	45 days
Knisely 2008, Corn 2008	183	4%	No prior radiotherapy or radiosurgery, no prior thalidomide	WBRT + Thalidomide	WBRT	2 years
Kondziolka 2000/Kondziolka 1999	27	0%	Unclear	WBRT + Radiosurgery	WBRT	Not reported
Pesce 2012	59	14%	No prior irradiation to brain, yes prior chemotherapy (except GFT or TMZ)	WBRT + Gefitinib (250 mg p.o. daily)	WBRT + TMZ (75 mg/m^2 p.o. daily)	28 days
Suh 2006	515	18.5%	9% had prior brain tumour resection. No other prior brain treatment for brain metastases, no chemo in past 7 days or prior efaproxiral treatment	WBRT+ efaproxiral	WBRT	2 weeks

EGFR epidermal growth factor receptor; GFT Gefitinib; TMZ temozolomide; WBRT whole brain radiotherapy; p.o. 'per orem' or 'by mouth'.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question are presented in Table 15 to Table 20.

Table 15: Summary clinical evidence profile for WBRT+ gefitinib versus WBRT + temozolomide

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT+TMZ	WBRT +gefitinib			
Median overall survival (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[6]	59 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Median time to progression (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[7]	59 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]
1 year survival rates	209 per 1000	375 per 1000 (159 to 885)	RR 1.79 (0.76 to 4.23)	59 (1 study)	⊕⊖⊖⊖ very low[1,2,5]
Withdrew due to toxicity	70 per 1000	188 per 1000 (42 to 835)	RR 2.69 (0.60 to 11.97)	59 (1 study)	⊕⊖⊖⊖ very low[1,2,4,5]

CI: confidence interval; RR: risk ratio; TMZ temozolomide, WBRT whole brain radiotherapy.
[1] It was unclear how participants were randomised or if allocation concealment was performed. Drop outs >20% were detected in 1 arm.
[2] 14% of patients had a single metastases.
[3] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
[4] Neither the participants, investigators nor assessors were blinded
[5] 95% CI crossed 2 MIDs (0.8 and 1.25)
[6] Not calculated as only descriptive data have been reported. Median overall survival in WBRT + gefitinib = 6.3 (2.1-14.6); median overall survival in WBRT + TMZ = 4.9 (2.3-5.6)
[7] Not calculated as only descriptive data have been reported. Median time to progression in WBRT + gefitinib =1.8 (1.1-3.9); median time to progression in WBRT + TMZ = 1.8 (1.5-1.8)

Table 16: Summary clinical evidence profile for WBRT+veliparib versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+veliparib			
Median overall survival, days	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[6]	307 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Objective response rate	395 per 1000	411 per 1000 (308 to 549)	RR 1.04 (0.78 to 1.39)	307 (1 study)	⊕⊖⊖⊖ very low[1,2,4,5]
Any adverse event	874 per 1000	891 per 1000 (821 to 970)	RR 1.02 (0.94 to 1.11)	308 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
Brain oedema	5 per 1000	1 per 1000 (0 to 3)	RR 0.12 (0.02 to 0.67)	307 (1 study)	⊕⊖⊖⊖ very low[1,2,4]

CI: confidence interval; RR: risk ratio; WBRT whole brain radiotherapy.
[1] Unclear how randomisation was performed or if allocation concealment was performed.
[2] 19% of patients had a single metastases
[3] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
[4] Patients were not blinded and it was unclear if investigators or assessors were blinded.
[5] 95% CI crossed 2 default MIDs (0.8 and 1.25)
6 Not calculated as only medians have been reported. Median overall survival in days for the WBRT group= 185 (137-251); median overall survival in days for the WBRT + veliparib 50g group= 209 (169-264); veliparib 200g + WBRT = 209 (138-255)

Table 17: Summary clinical evidence profile for WBRT +thalidomide versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+Thalidomide			
Death due to brain metastases	337 per 1000	273 per 1000 (175 to 431)	RR 0.81 (0.52 to 1.28)	176 (1 study)	⊕⊖⊖⊖ very low[1,2]
3 month rates of CNS progression	185 per 1000	131 per 1000 (65 to 262)	RR 0.71 (0.35 to 1.42)	176 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Grade 3-4 treatment related AE	120 per 1000	464 per 1000 (255 to 847)	RR 3.88 (2.13 to 7.08)	176 (1 study)	⊕⊕⊖⊖ low[1,3]
Cardiovascular-related AE	Not estimable	Not estimable	RR 5.47 (0.27 to 112.33)	176 (1 study)	⊕⊖⊖⊖ very low[1,2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Infection (not necessarily post-op)	Not estimable[6]	Not estimable[6]	Not estimable	176 (1 study)	⊕⊕⊖⊖ low[1,3]
Quality of life	Data reported insufficient to allow calculation	Data reported insufficient to allow calculation	Not estimable[5]	176 (1 study)	⊕⊖⊖⊖ very low[1,3,4]

AE adverse events; CI: confidence interval; CNS central nervous system; RR: risk ratio; WBRT whole brain radiotherapy.
[1] Unclear how participants were randomised or if allocation concealment was performed
[2] 95% CI crossed 2 MIDs (0.80 and 1.25)
[3] Participants were not blinded but it was unclear if assessors or investigators were blinded.
[4] Not calculated as standard deviation of the outcomes were not reported. Mean change from baseline to endpoint in WBRT arm= -0.53; mean change from baseline in the WNRT + thalidomide arm= 0.33
[5] Only descriptive data were reported, insufficient details to assess MID thresholds and imprecision
[6] The event rate was 0 in both groups

Table 18: Summary clinical evidence profile for WBRT and radiosurgery versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+ radiosurgery			
Median overall survival (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[4]	27 (1 study)	⊕⊖⊖⊖ very low[1,2]
Rate of local failure (including patients who died)	77 per 1000	8 per 1000 (2 to 38)	RR 0.11 (0.02 to 0.50)	27 (1 study)	⊕⊕⊖⊖ low[1,3]

CI: confidence interval; RR: risk ratio; WBRT whole brain radiotherapy.
[1] It was unclear if allocation concealment was performed.
[2] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
[3] Participants were not blinded, however, investigators and assessors were blinded
[4]Not calculable as only medians have been reported. Median overall survival in WBRT = 7.5 (4.6-10.4) and median time of survival in WBRT + radiosurgery = 11 (3.8-18.2).

Table 19: Summary clinical evidence profile for WBRT+temozolomide versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+temozolomide			
Median overall survival (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable [5]	100 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Median progression free survival (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable [8]	100 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]
Complete response	Not estimable[10]	Not estimable[10]	Not estimable	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4]
Partial response	300 per 1000	249 per 1000 (144 to 438)	RR 0.83 (0.48 to 1.46)	66 (1 study)	⊕⊖⊖⊖ very low[1,2,4,6]
Stable disease	520 per 1000	359 per 1000 (229 to 567)	RR 0.69 (0.44 to 1.09)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4,9]
Progressive disease	60 per 1000	80 per 1000 (19 to 2339)	RR 1.33 (0.31 to 5.65)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4,6]
Neurological symptoms (6 weeks)	240 per 1000	132 per 1000 (72 to 235)	RR 0.55 (0.30 to 0.98)	100 (1 study)	⊕⊖⊖⊖ very low[1,2,4,9]

CI: confidence interval; RR: risk ratio; WBRT whole brain radiotherapy.

[1] *It was unclear how randomisation was performed or if allocation concealment was conducted.*

[2] *15% of patients had a single metastases.*

[3] *Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision*

[4] *Participants were not blinded, assessors were blinded but it was unclear if investigators were blinded.*

[5] *Not calculable as only medians were reported. Median overall survival in the WBRT group = 11.1 months (8.3-15.3); median overall survival in the WBRT + TMZ arm= 9.4 months (7.3-13.4)*

[6] *95% CI crossed 1 MID (0.8 and 1.25)*

[7] *95% CI crossed 1 MID (1.25)*

[8] *Not calculable as only medians were reported. Median progression free survival in the WBRT group = 7.4 months (5.3-13.1); median progression free survival in the WBRT + TMZ arm= 6.8 months (4.6-8.6)*

[9] *95% CI crossed 1 default MID (0.8)*

[10] *The event rate was 0 in both groups*

Table 20: Summary clinical evidence profile for WBRT +efaproxiral versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WRBT	WBRT+Efaproxiral			
Overall survival	Not applicable	Not applicable	HR 0.87 (0.71-1.05)	515 (1 study)	⊕⊕⊖⊖ low[1,2]
Death at 30 days	64 per 1000	49 per 1000 (24 to 100)	RR 0.77 (0.38 to 1.56)	515 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Death at 6 months	604 per 1000	538 per 1000 (459 to 622)	RR 0.89 (0.76 to 1.03)	515 (1 study)	⊕⊖⊖⊖ very low[1,3,5]
Death at 30 months	824 per 1000	808 per 1000 (750 to 882)	RR 0.98 (0.91 to 1.07)	515 (1 study)	⊕⊕⊖⊖ low[1,3]
Radiographic progression at 1 year	180 per 1000	207 per 1000 (146 to 295)	RR 1.15 (0.81 to 1.64)	515 (1 study)	⊕⊖⊖⊖ very low[1,2,3,6]
Clinical progression at 1 year	512 per 1000	492 per 1000 (415 to 584)	RR 0.96 (0.81 to 1.14)	515 (1 study)	⊕⊖⊖⊖ very low[1,2,3]
Complete response	56 per 1000	106 per 1000 (57 to 196)	RR 1.89 (1.02 to 3.50)	515 (1 study)	⊕⊖⊖⊖ very low[1,2,3,6]
Partial response	328 per 1000	351 per 1000 (276 to 446)	RR 1.07 (0.84 to 1.36)	515 (1 study)	⊕⊖⊖⊖ very low[1,2,3,6]
Stable or improving QoL	152 per 1000	163 per 1000 (109 to 242)	RR 1.07 (0.72 to 1.59)	515 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]
Stable or improving KPS	104 per 1000	131 per 1000 (88 to 194)	RR 1.26 (0.85 to 1.87)	515 (1 study)	⊕⊖⊖⊖ very low[1,2,3,6]
Grade 4 (severe) adverse events	106 per 1000	125 per 1000 (78 to 199)	RR 1.17 (0.73 to 1.87)	529 (1 study)	⊕⊖⊖⊖ very low[1,2,3,4]

CI Confidence interval; KPS Karnofsky Performance Status; RR Risk ratio; WBRT whole brain radiotherapy.
1 It was unclear how randomisation was performed or if allocation concealment was performed.
2 It is unlikely the participants were blinded, assessors were blinded but it was unclear if investigators were blinded.
3 18.5% of patients had a single metastases.
4 95% CI crossed 2 MIDs (0.8 and 1.25)
5 95% CI crossed 1 MID (0.8)
6 95% CI crossed 1 MID (1.25)

See also Appendix F for the full GRADE tables.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

WBRT and gefitinib versus WBRT and temozolomide

- One randomised controlled trials (N=59) provided very low quality evidence that showed no differences between those who received WBRT in combination with gefitinib and WBRT in combination with temozolomide in median overall survival (median overall survival in WBRT + gefitinib = 6.3 [2.1-14.6]; median overall survival in WBRT + TMZ = 4.9 [2.3-5.6]) or time to progression (median time to progression in WBRT + gefitinib =1.8 [1.1-3.9]; median time to progression in WBRT + TMZ = 1.8 [1.5-1.8]).
- One randomised controlled trial (N=59) provided very low quality evidence that showed no differences in 1 year survival rates (relative risk (RR) =1.79, 95% CI 0.76-4.23), or the number of those who withdrew due to toxicity (RR= 2.69, 95% CI 2.69, 95% CI 0.60 - 11.97) in those who received WBRT in combination with gefinitib as compared to those who received WBRT and temozolomide.

WBRT and veliparib versus WBRT

- One randomised controlled trial (N=307) provided very low quality evidence that showed no differences between WBRT alone and WBRT in combination with veliparib in median overall survival (median overall survival in days for the WBRT group= 185 [137-251]; median overall survival in days for the WBRT + veliparib 50g group= 209 (169-264); veliparib 200g + WBRT = 209 [138-255]), objective response rate (RR= 1.04, 95% CI 0.78-1.39) and any adverse event rate (RR= 1.02, 95% CI 0.94-1.11) in people with multiple brain metastases. The incidence of brain oedema was however higher in the WBRT alone group compared to the WBRT in combination with veliparib group (RR= 0.12, 95% CI 0.02-0.67).

WBRT and thalidomide versus WBRT

- One randomised controlled trial (N=176) provided very low to low quality evidence that showed no differences between WBRT alone and WBRT in combination with thalidomide in death due to brain metastases (RR= 0.81, 95% CI 0.52-1.28), CNS progression at 3 months (RR= 0.71, 95% CI 0.35-1.42), cardiovascular-related adverse events (RR=5.47, 95% CI 0.27-112.23) in people with multiple brain metastases. A higher number of participants treated with WBRT in combination with thalidomide had grade 3-4 treated related adverse events compared with WBRT alone (RR= 3.88, 95% CI 2.13-7.08). Very low quality evidence showed no differences in quality of life scores between both treatment arms.

WBRT and radiosurgery versus WBRT

- One randomised controlled trial (N=27) provided very low quality evidence that showed no differences in median overall survival (median in the WBRT in combination with

radiosurgery group =11 (3.8-18.2) and median overall survival in WBRT = 7.5 (4.6-10.4) between WBRT alone and WBRT in combination with radiosurgery in people with multiple brain metastases. One randomised controlled trial (N=27) provided low quality evidence that showed that those who received WBRT in combination with radiosurgery had a reduced rate of local failure compared to those who received WBRT only RR 0.11 (0.02 to 0.50)

WBRT and temozolomide versus WBRT

- One randomised controlled trial (N=100) provided very low quality evidence that showed no differences between treatment with WBRT and with WBRT in combination with temozolomide in median overall survival (median overall survival in the WBRT group = 11.1 months [8.3-15.3]; median overall survival in the WBRT + TMZ arm= 9.4 months [7.3-13.4]), median progression free survival (median progression free survival in the WBRT group = 7.4 months [5.3-13.1]; median progression free survival in the WBRT + TMZ arm= 6.8 months [4.6-8.6]), complete response rate (0/50 in both treatment groups), partial response rate (RR=0.83, 95% CI 0.48-1.46), stable disease rate (RR=0.69, 95% CI 0.44-1.09), and progressive disease rate (RR= 1.33, 95% CI 0.31-5.65), however a higher number of neurological symptoms were reported in those who received WBRT with temozolomide compared to WBRT alone (RR=0.55, 95% CI 0.30-0.98).

WBRT and efaproxiral versus WBRT

- One randomised controlled trial (N=515) provided very low to low quality evidence that showed no differences between WBRT alone and WBRT in combination with efaproxiral in death at 30 days (RR= 0.77, 95% CI 0.38-1.56), death at 6 months (RR=0.89, 95% CI 0.976-1.03), death at 30 months (RR= 0.98, 95% CI 0.91-1.07), overall survival (HR = 0.87, 95% CI 0.71 to 1.05), radiographic progression at 1 year (RR= 1.15, 95% CI 0.81-1.64), clinical progression at 1 year (RR= 0.96, 95% CI 0.81-1.14), partial response (RR= 1.07, 95% CI 0.84-1.36), stable or improving quality of life (RR= 1.07, 95% CI 0.72-1.59), stable or improving KPS scores (RR= 1.26, 95% CI 0.85-1.84) and the number of grade 4 adverse events (RR= 1.17, 95% CI 0.73-1.87) in people with multiple brain metastases. However, the complete response rate in the WBRT in combination with efaproxiral group was higher than in the WRT alone group (RR=1.89, 95% CI 1.02-3.50).

The committee's discussion of the evidence

See the committee's discussion of the evidence in the management of brain metastases with a mixed population section.

References

See the references in the management of brain metastases with a mixed population section.

Management of brain metastases with a mixed population

Review question

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these) for a mixed population of single and multiple brain metastases?

Introduction

This review was developed by the committee to account for the fact that clinical studies evaluating intracranial treatment for brain metastases were not restricted to those in which all participants had a single metastasis (as discussed in the section on the management of single metastases) or multiple metastases (as discussed in the section on the management of multiple metastases). The evidence contributed through this review was derived from studies involving mixed populations (the participants might have a single metastasis or multiple metastases).

PICO table

Table 21: Summary of the protocol (PICO table)

Population	People with any number of brain metastases not otherwise covered by review on single or multiple metastases (that is, populations of people with an unknown mix of single and multiple metastases will be reported)

Intervention	• Neurosurgery
	• Radiotherapy:
	  ○ radiosurgery SRS (1 fraction)
	  ○ stereotactic radiotherapy SRT (2-5 fractions)
	  ○ whole brain radiotherapy (WBRT)
	  ○ hippocampal avoidance WBRT
	• Chemotherapy or systemic anti-cancer therapy/ treatment
	• Combined therapy (any combination of the above)
	• Best supportive care

Comparison	• Each other

Outcome	Outcomes are the same as for the review on multiple metastases, since some outcomes of importance in multiple metastases are not covered by the outcomes for the single metastasis review.
	
	<u>Critical:</u>
	• overall survival.
	• progression-free survival
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life

	Important:
	• cognitive function.
	• neurological function
	  ○ Karnofsky performance status (or WHO or ECOG)
	  ○ Neurological Function Scale
	
	• treatment-related morbidity.
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke
	
	Limited:
	• steroid (for example dexamethasone) use (duration and dose)

ECOG Eastern Cooperative Oncology Group scale; SRS Stereotactic radiosurgery; SRT stereotactic radiotherapy; WBRT whole brain radiation therapy; WHO World Health Organization.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

Sixteen RCTs reported in 17 articles (N=2913) on people with mixed brain metastases were included in the review (Antonadou 2002; Andrews 2004; Verger 2005; Aoyama 2006; Chang 2009; Chua 2010; Kocher 2010/Soffietti 2013; El Gamboa-Vignolle 2012; Sperduto 2012; Brown 2013; Gantery 2014; Lee 2014; Lim 2015; Brown 2016; Mulvenna 2016; Mahajan 2017). Studies included a population with a mixed number of brain metastases (between 25 and 75% single) or studies of people with brain metastases which was not identified as either single or multiple. People included in the studies may or may not have received previous treatment (that is to say, radiosurgery and surgical resection or previous chemotherapy) and were followed-up between 21 and 66 months, although some trials follow people up until they died.

A summary of these studies is provided in Table 22 and the results along with the quality of the evidence for each outcome are listed Table 23 to Table 33 below.

For further details, see also the study selection flow chart in Appendix C, the evidence tables for the individual studies in Supplementary Material D and the full GRADE tables in Appendix F.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K. Note that there was a single search conducted for all 3 populations considered in the management brain metastases, therefore the excluded studies list is common for these 3 reviews.

Summary of clinical studies included in the evidence review

Table 22: Summary of included studies

Study	N	Single metastases	Previous treatment	Intervention	Comparison	Treatment duration	Follow-up
Andrews 2004	331	56%	No previous cranial radiation. Postoperative patients with either residual or distal brain metastases remained 3 or fewer.	WBRT	WBRT + radiosurgery	4 weeks	24 months
Antonadou 2002	55	27%	No prior chemotherapy or radiotherapy for brain metastases	WBRT	WBRT+TMZ	4 weeks WBRT; TMZ 6 months	21 months
Aoyama 2006	67	49%	Unclear	WBRT+SRS	SRS	2.5 months	60 months
Brown 2016	213	52%	No prior resection, cranial radiotherapy, no chemo <7 days	WBRT+SRS	SRS	2 weeks	62 months
Brown 2013	554	Unclear	Patients could have received prior therapy for brain metastasis, including radiosurgery and surgical resection (but no prior cranial external beam radiotherapy).	WBRT	WBRT + Memantine	24 weeks	52 weeks
Chang 2009	58	57%	Yes, received systemic therapy. SRS+WBRT:	SRS+WBRT	SRS	4 weeks	66 months

Study	N	Single metastases	Previous treatment	Intervention	Comparison	Treatment duration	Follow-up
			21 (75%) patients SRS: 21 (70%) patients				
Chua 2010	95	Unclear	Yes, previous chemotherapy (81% in the WBRT + temozolomide arm versus. 58% in the WBRT)	WBRT + oral chemotherapy	WBRT	WBRT 1-14 days; TMZ 1-28 days	Until death
El Gantery 2014	60	70%	No previous treatment for brain metastases.	WBRT+SRS WBRT alone	SRS	2-4 weeks	34 months
Gamboa-Vignolle 2012	55	Unclear	Excluded if received radiotherapy or surgery for brain metastases	TMZ + WBI	WBI	2 weeks	Until death, at least 15 months
Kocher 2010/Soffietti 2013	359	Unclear	Had surgery or radiosurgery	Radiosurgery /Surgery +WBRT	Radiosurgery/ Surgery + observation	WBRT 2 weeks	The median follow-up time of the surviving patients was 49 months in the WBRT arm and 40 months in the OBS arm (P .17).
Lee 2014	80	unclear <3 versus. >3	No previous cranial radiotherapy; at least 28 days since any	WBRT + epidermal growth factor receptor (EGFR).	WBRT	WBRT= 5 days/ erlotinib - until disease	Until death

Study	N	Single metastases	Previous treatment	Intervention	Comparison	Treatment duration	Follow-up
			chemotherapy			progression	
Lim 2015	98	47%	None of patients had prior surgical treatment or radiotherapy for brain metastases and leptomeningeal metastases by MRI or cerebrospinal fluid evaluation	SRS + Chemotherapy	SRS		Median follow up duration 43 months (0.8 to 56.2)
Mahajan 2017	128	62%	No participants had a history of previous radiotherapy to the brain, or of resection of metastases (prior to those required for the trial).	SRS to the surgical cavity (following resection of metastases)	Observation following resection of metastases	SRS was administered in a single session	Median follow-up 11.1 months (IQR 4.8 to 20.4)
Mulvenna 2016	538	30%	Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted (with predefined washout periods of 4 weeks for chemotherapy and 1 week for TKIs)	WBRT+BSC	BSC	5 to 8 days WBRT	Up to 11 months

Study	N	Single metastases	Previous treatment	Intervention	Comparison	Treatment duration	Follow-up
Sperduto 2012	125	41%	Prior resection of a brain metastasis was allowed if the patient had a separate brain metastasis that would be treated with SRS	WBRT + SRS + receptor tyrosine kinase inhibitor	WBRT +SRS +chemotherapy (TMZ)	WBRT - 3 weeks. TMZ - 21 days up to 6 months (up to investigators discretion)	33.6 months
Verger 2005	82	unclear	No prior RT	RT+ Chemotherapy (TMZ)	RT	Was delivered 5 times weekly, in 10 doses of 3-Gy, to a total dose of 30-Gy. TMZ was given for 2 weeks, followed by 5 days, every 28 days. Between the end of concurrent treatment and the 5-day cycles of TMZ, there was a 4-week interval.	30 weeks(unclear)

BSC best supportive care; EGFR epidermal growth factor receptor; WBRT whole brain radiotherapy; WBI whole brain imaging; RT radiotherapy; SRS stereotactic radiosurgery; TMZ temozolomide.

See Supplementary Material D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question are presented in Table 23 to Table 33.

Table 23: Summary of clinical evidence profile for WBRT + BSC versus BSC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Best supportive care	WBRT+BSC			
Overall survival	Not applicable	Not applicable	HR 1.10 (0.93 to 1.31)	97 (1 study)	⊕⊕⊖⊖ low[1,2]
Quality of life (EQ-5D) improved or maintained 12 weeks	488 per 1000	444 per 1000 (288 to 684)	RR 0.91 (0.59 to 1.4)	97 (1 study)	⊕⊖⊖⊖ very low[1,3]
KPS change 12 weeks	Not Applicable	The mean KPS change 12 weeks in the intervention groups was 4.6 higher (2.13 to 7.07 higher)	Not applicable	538 (1 study)	⊕⊕⊖⊖ low[1,4]
Any serious adverse event	305 per 1000	332 per 1000 (259 to 424)	RR 1.09 (0.85 to 1.39)	538 (1 study)	⊕⊕⊖⊖ low[1,2]
Infection	59 per 1000	63 per 1000 (33 to 123)	RR 1.06 (0.55 to 2.06)	538 (1 study)	⊕⊖⊖⊖ very low[1,3]
Cardiac AE	4 per 1000	7 per 1000 (1 to 82)	RR 2 (0.18 to 21.93)	538 (1 study)	⊕⊖⊖⊖ very low[1,3]
Use of dexamethasone 8 weeks	103 per 1000	123 per 1000 (74 to 203)	RR 1.19 (0.72 to 1.97)	478 (1 study)	⊕⊖⊖⊖ very low[1,3]

AE adverse events; CI confidence interval; BSC best supportive care ; KPS Karnofsky Performance Status; HR hazard ratio; RR risk ratio; WBRT whole brain radiosurgery.
1 Adequate randomisation and allocation concealment. Participants and investigators were not blinded, it was unclear if assessors were. Unclear reporting bias. Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted
2 95% CI crossed 1 MID 1.25
3 95% CI crossed 2 MIDs 0.8 and 1.25
*4 95% CI crossed1 MID 6.8 (0.5*13.66)*

Table 24: Summary of clinical evidence profile for WBRT + SRS versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT + SRS			

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Overall survival	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[6]	331 (1 study)	⊕⊖⊖⊖ very low[1,5]
Lesions complete response 3 months	77 per 1000	160 per 1000 (63 to 404)	RR 2.08 (0.82 to 5.25)	153 (1 study)	⊕⊕⊖⊖ low[2,3]
Partial response 3 months	538 per 1000	571 per 1000 (431 to 759)	RR 1.06 (0.80 to 1.41)	153 (1 study)	⊕⊖⊖⊖ very low[2,4]
Stable lesions 3 months	218 per 1000	146 per 1000 (74 to 292)	RR 0.67 (0.34 to 1.34)	153 (1 study)	⊕⊖⊖⊖ very low[2,4]
Progression lesions 3 months	167 per 1000	107 per 1000 (47 to 243)	RR 0.64 (0.28 to 1.46)	153 (1 study)	⊕⊖⊖⊖ very low[2,4]
Control of treated lesion 1 year	586 per 1000	720 per 1000 (574 to 908)	RR 1.23 (0.98 to 1.55)	141 (2 studies)	⊕⊕⊖⊖ low[2,3]
KPS Improved	40 per 1000	126 per 1000 (36 to 442)	RR 3.16 (0.91 to 11.06)	154 (1 study)	⊕⊕⊖⊖ low[2,3]
Steroid use increased	80 per 1000	92 per 1000 (33 to 262)	RR 1.15 (0.41 to 3.27)	151 (1 study)	⊕⊖⊖⊖ very low[2,4]
Acute toxicity GRADE 3-4 (<90 days)	0 per 1000	0 per 1000 (0 to 0)	RR 11.41 (0.64 to 204.68)	326 (1 study)	⊕⊕⊖⊖ low[2,4]
Death due to brain metastases	309 per 1000	284 per 1000 (198 to 408)	RR 0.92 (0.64 to 1.32)	286 (1 study)	⊕⊖⊖⊖ very low[2,4]
Late necrosis	0 per 1000	0 per 1000 (0 to 0)	RR 2.59 (0.11 to 59.93)	39 (1 study)	⊕⊖⊖⊖ very low[2,4]
Brain oedema	56 per 1000	56 per 1000 (48 to 65)	RR 1.01 (0.87 to 1.17)	39 (1 study)	⊕⊕⊕⊖ moderate[2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Neurological progression >3 months	111 per 1000	113 per 1000 (91 to 140)	RR 1.02 (0.82 to 1.26)	39 (1 study)	⊕⊕⊖⊖ low[2,3]

CI confidence interval; HR hazard ratio; KPS Karnofsky performance status; RR risk ratio; WBRT whole brain radiosurgery.
1 Unclear reporting bias
2 It was unclear if participants, investigators or assessors were blinded. Unclear reporting bias. No previous cranial radiation.
3 95% CI crossed 1 MID 1.25
4 95% CI crossed 2 MIDs 0.8 and 1.25
5 Not SDs were reported to assess the MID thresholds and imprecision
6 Not calculable as no SDs have been provided. Mean overall survival in the WBRT+SRS group=5.7 months and mean overall survival in the WBRT group = 6.5 months.

Table 25: Summary of clinical evidence profile for WBRT versus SRS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	SRS	WBRT			
Local control	222 per 1000	191 per 1000 (56 to 656)	RR 0.86 (0.25 to 2.95)	39 (1 study)	⊕⊖⊖⊖ very low[1,2]
Late radiation necrosis	56 per 1000	59 per 1000 (51 to 68)	RR 1.06 (0.92 to 1.23)	39 (1 study)	⊕⊕⊖⊖ low[1]
Brain oedema	48 per 1000	56 per 1000 (4 to 826)	RR 1.17 (0.08 to 17.35)	39 (1 study)	⊕⊖⊖⊖ very low[1,2]
Neurological progression >3 months	111 per 1000	119 per 1000 (99 to 143)	RR 1.07 (0.89 to 1.29)	39 (1 study)	⊕⊖⊖⊖ very low[1,3]

CI confidence interval; RR risk ratio; SRS Stereotactic radiosurgery; WBRT whole brain radiosurgery
1 Unclear how randomisation was performed; unclear allocation concealment; unclear blinding; reporting bias
2 95% CI crossed 2 default MIDs (0.8 and 1.25)
3 95% CI crossed 1 default MID (1.25)

Table 26: Summary of clinical evidence profile for WBRT + TMZ versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT+TMZ			

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Overall survival[a]	Not applicable	Not applicable	HR 1.14 (0.71 to 1.83)	95 (1 study)	⊕⊖⊖⊖ very low[1,2]
Median overall survival[b]	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[1,2]	55 (1 study)	⊕⊖⊖⊖ very low[3,6]
Progression free survival	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable[1,3]	55 (1 study)	⊕⊖⊖⊖ very low[5,6]
Complete response 4 weeks - 3 months	79 per 1000	124 per 1000 (59 to 260)	RR 1.58 (0.75 to 3.31)	182 (3 studies)	⊕⊖⊖⊖ very low[2,8]
Partial response 4 wk -3 months	3444 per 1000	1000 per 1000 (1000 to 1000)	RR 1.38 (0.98 to 1.94)	102 (3 studies)	⊕⊖⊖⊖ very low[7,8]
Stable disease 4 wk - 3 months	326 per 1000	192 per 1000 (59 to 622)	RR 0.59 (0.18 to 1.91)	182 (3 studies)	⊕⊖⊖⊖ very low[2,8,9]
Progressive disease 4 weeks - 3months	112 per 1000	67 per 1000 (27 to 171)	RR 0.60 (0.24 to 1.52)	182 (3 studies)	⊕⊖⊖⊖ very low[2,8]
Neurological fully functional or improved	560 per 1000	722 per 1000 (549 to 946)	RR 1.29 (0.98 to 1.69)	103 (2 studies)	⊕⊖⊖⊖ very low[7,10]
Required corticosteroids	913 per 1000	676 per 1000 (502 to 913)	RR 0.74 (0.55 to 1.00)	48 (1 study)	⊕⊖⊖⊖ very low[4,5]
Died from systemic disease 21mo	905 per 1000	832 per 1000 (660 to 1000)	RR 0.92 (0.73 to 1.16)	45 (1 study)	⊕⊖⊖⊖ very low[4,5]
Adverse events >=3	93 per 1000	367 per 1000 (190 to 707)	RR 3.93 (2.04 to 7.58)	140 (2 studies)	⊕⊖⊖⊖ very low[7,11]

CI confidence interval; HR hazard ratio; RR risk ratio; WBRT whole brain radiosurgery
[a]Chua 2010 ,[b]Gamboa-Vignolle 2012
[1] Unclear randomisation
[2] 95% CI crossed 2 default MIDs (0.8 and 1.25)
[3] Unclear randomisation, no blinding (participants, assessors and investigators)
[4] 95% CI crossed 1 default MID (0.8)
[5] Unclear randomisation, unclear allocation concealment, open trial
[6] Only descriptive data have been reported, insufficient details provided to assess the MID threshold and imprecision

[7] 95% CI crossed 1 default MID (1.25)
[8] The three trials presented with unclear randomisation and allocation concealment. Two trials presented with unclear blinding, one with unclear reporting bias and one was an open trial
[9] I-square> 50%
[10] Both trials presented with unclear randomisation and allocation concealment. One of the trials presented with unclear patient and investigator blinding and unclear reporting bias. The second was an open trial
[11] Both were open trials presented with unclear randomisation. One trial presented with unclear allocation concealment
[12] Not calculable as only medians have been reported. The median overall survival in the intervention arm= 8 months (4.9 to 11.1) and the median overall survival in the control arm=8.1 months (5.9 to 10.1)
[13] Not calculable as only medians have been reported. The median progression free survival in the intervention arm= 11.8 months (4.7 to 18.9) and the median progression free survival in the control arm = 5.6 months (4.9 to 6.2)

Table 27: Summary of clinical evidence profile for SRS + WBRT versus SRS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	SRS	SRS+ WBRT			
Survival time (median months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable [13]	132 (1 study)	⊕⊖⊖⊖ very low[1,2]
Overall survival	Not applicable	Not applicable	HR 1.02 (0.75 to 1.38)[a]	167 (1 study)	⊕⊕⊖⊖ low[3,7]
	Not applicable	Not applicable	HR 2.47 (1.34 to 4.55)[b]	58 (1 study)	⊕⊕⊕⊕ high
Brain tumour recurrence at distal sites (median months)	Data not reported to allow calculation	Data not reported to allow calculation	Not estimable [14]	62 (1 study)	⊕⊕⊖⊖ low[1,2]
Time to intracranial failure	Not applicable	Not applicable	HR 3.60 (2.21 to 5.86)	213 (1 study)	⊕⊕⊖⊖ low[5]
Actuarial brain tumour recurrence rate 12 months	753 per 1000	429 per 1000 (331 to 557)	RR 0.57 (0.44 to 0.74)	190 (2 studies)	⊕⊕⊖⊖ low[1,5]
New brain metastases at distal sites 12 months	507 per 1000	325 per 1000 (213 to 492)	RR 0.64 (0.42 to 0.97)	132 (1 study)	⊕⊖⊖⊖ very low[1,3]
Actuarial new brain tumour metastases 12 months	642 per 1000	417 per 1000 (295 to 584)	RR 0.65 (0.46 to 0.91)	132 (1 study)	⊕⊖⊖⊖ very low[1,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Local tumour control rate (actuarial) 12 months	670 per 1000	864 per 1000 (784 to 958)	RR 1.29 (1.17 to 1.43)	426 (4 studies)	⊕⊖⊖⊖ very low[4,6]
Distal brain tumour control 12 months	647 per 1000	879 per 1000 (763 to 1000)	RR 1.36 (1.18 to 1.56)	252 (2 studies)	⊕⊖⊖⊖ very low[4,5]
KPS score >=70	269 per 1000	339 per 1000 (201 to 570)	RR 1.26 (0.75 to 2.12)	132 (1 study)	⊕⊖⊖⊖ very low[1,3,4]
Quality of life	Not applicable	The mean quality of life in the intervention groups was 11.9 lower (17.71 to 6.09 lower)	Not applicable	115 (1 study)	⊕⊖⊖⊖ very low[7,8]
Cognitive deterioration	635 per 1000	457 per 1000 (95 to 1000)	RR 0.72 (0.15 to 3.53)	142 (2 studies)	⊕⊖⊖⊖ very low[3,4,6,9]
Neurological preservation	761 per 1000	769 per 1000 (655 to 898)	RR 1.01 (0.86 to 1.18)	174 (2 studies)	⊕⊕⊖⊖ low[10]
Late toxic effects GRADE 3-4	270 per 1000	262 per 1000 (232 to 294)	RR 0.97 (0.86 to 1.09)	345 (2 studies)	⊕⊕⊖⊖ low[1,11]
Edema limbs	0 per 1000	0 per 1000 (0 to 0)	RR 0.99 (0.96 to 1.02)	213 (1 study)	⊕⊕⊕⊖ moderate[7]
Late oedema	48 per 1000	48 per 1000 (41 to 54)	RR 1 (0.87 to 1.14)	42 (1 study)	⊕⊕⊖⊖ low[12]

CI confidence interval; KPS Karnofsky performance status; HR hazard ratio; RR risk ratio; WBRT whole brain radiosurgery
A Brown 2016
b Chang 2009
1 Unclear allocation concealment and patient blinding. Outcome assessors and investigators were not blinded
2 Only descriptive data reported, insufficient details given to assess the MID threshold and imprecision
3 95% CI crossed 1 default MID (0.8)
4 95% CI crossed 1 default MID (1.25)
5 Not blinded
6 Unclear or not blinding (participants, assessors and investigators) in any of the 4 trials included, unclear randomisation in 1 trial and unclear allocation concealment in 2
7 No patient or outcome assessor blinding
8 95% CI crossed 1 default MID (± 0.5 x 24= ± 12)
9 I-square > 80%
10 Both trials had unclear/no assessor blinding and unclear allocation concealment. One trial presented with unclear randomisation and reporting bias
11 Unclear/not blinding (participants, assessors and investigators) in 2 trials
12 Unclear randomisation, unclear allocation concealment, unclear patient allocation, unclear blinding and high reporting bias
13 Not calculable as only medians have been reported. The median survival time in the SRS + WBRT group was 7.5 months (0.8-58.7) and the median survival time in the SRS group was 8 months (0.5-57)

14 Not calculable as only medians have been reported. The median months brain tumour recurrence in distal sites in the WBRT+ SRS group was 16.2 and the median months in the SRS group was 5.5

Table 28: Summary of clinical evidence profile for SRS + cisplatin or carboplatin versus SRS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	SRS	SRS + cisplatin or carboplatin			
Overall survival	Not applicable	Not applicable	HR 1.2 (0.77 to 1.89)	98 (1 study)	⊕⊖⊖⊖ very low[1,2]
Progression free survival	Not applicable	Not applicable	HR 1.44 (0.87 to 2.35)	98 (1 study)	⊕⊕⊖⊖ low[3,4]

CI confidence interval; SRS stereotactic radiosurgery.
[1] Unclear randomisation methods and unclear allocation concealment
[2] 95% crossed 2 default MIDs (0.8 and 1.25)
[3] Unclear randomisation methods, unclear allocation concealment and unclear blinding
[4] 95% CI crossed 1 default MID (1.25)

Table 29: Summary of clinical evidence profile for WBRT + erlotinib versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT + erlotinib			
Overall survival	Not applicable	Not applicable	HR 0.94 (0.58 to 1.53)	80 (1 study)	⊕⊖⊖⊖ very low[1,2]
Grade 3-4 adverse events	700 per 1000	700 per 1000 (525 to 931)	RR 1.00 (0.75 to 1.33)	80 (1 study)	⊕⊖⊖⊖ very low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Quality of life	Not applicable	The mean quality of life in the intervention group was 0.05 higher (0.34 lower to 0.44 higher)	Not applicable	80 (1 study)	⊕⊕⊕⊖ moderate[1]
Infection	50 per 1000	125 per 1000 (25 to 607)	RR 1.13 (0.92 to 1.38)	80 (1 study)	⊕⊕⊖⊖ low[1,3]

CI confidence interval; HR hazard ratio; RR risk ratio; WBRT whole brain radiosurgery
1 Unclear sequence generation and high risk of reporting bias
2 95% CI crossed 2 default MIDs (0.80 and 1.25)
3 95% CI crossed 1 default MID (1.25)

Table 30: Summary of clinical evidence profile for Surgery/SRS/WBRT versus Surgery/SRS/observation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Surgery/SRS/Observation	Surgery/SRS/WBRT			
Median progression-free survival (months)	Data not reported to allow calculation	Data not reported to allow calculation	Not calculable[7]	359 (1 study)	⊕⊖⊖⊖ very low[1,6]
Intracranial progression	777 per 1000	481 per 1000 (404 to 575)	RR 0.62 (0.52 to 0.74)	359 (1 study)	⊕⊕⊖⊖ low[1]
Overall survival	Not applicable	Not applicable	HR 0.98 (0.78 to 1.23)	359 (1 study)	⊕⊖⊖⊖ very low[2,3]
Serious side effects	72 per 1000	17 per 1000 (5 to 758)	RR 0.23 (0.07 to 0.80)	359 (1 study)	⊕⊕⊖⊖ low[1,4]
Serious infection	11 per 1000	2 per 1000 (0 to 46)	RR 0.20 (0.01 to 4.16)	359 (1 study)	⊕⊕⊖⊖ low[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Serious radionecrosis	11 per 1000	6 per 1000 (1 to 61)	RR 0.50 (0.05 to 5.50)	369 (1 study)	⊕⊕⊖⊖ low[1]
Quality of life 12 months	Not applicable	The mean quality of life at 12 months in the surgery/SRS/WBRT group was 1.9 lower (3.72 lower to 0.08 lower)	Not applicable	65 (1 study)	⊕⊖⊖⊖ very low[1,5]

CI confidence interval; HR hazard ratio; RR risk ratio; SRS stereotactic radiosurgery; WBRT whole brain radiosurgery
[1] Unclear how randomisation was performed, not blinded trial
[2] Unclear how randomisation was performed
[3] 95% CI crossed 2 default MIDs (0.8 and 1.25)
[4] 95% CI crossed 1 default MID
[5] 95% CI crossed 1 default MID (1.8 x 0.5= ± 0.9)
6 Only descriptive data has been reported, insufficient details given to assess the MID threshold and imprecision
7 Not calculable as only medians have been reported median progression-free survival was slightly longer in patients receiving WBRT (4.6 months; 95% CI, 3.9 to 6.1 months) compared with those on OBS alone (3.4 months; 95% CI, 3.1 to 3.9 months).

Table 31: Summary of clinical evidence profile for WBRT+SRS+TMZ versus WBRT+SRS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT+SRS	WBRT+SRS+TMZ			
Overall survival	Not applicable	Not applicable	HR 1.43 (0.89 to 2.31)	84 (1 study)	⊕⊕⊖⊖ low[1,2]
CNS progression rate 6 months	159 per 1000	301 per 1000 (130 to 687)	RR 1.89 (0.82 to 4.32)	84 (1 study)	⊕⊖⊖⊖ very low[2,3]
New metastases 6 months	91 per 1000	200 per 1000 (65 to 614)	RR 2.20 (0.72 to 6.75)	84 (1 study)	⊕⊖⊖⊖ very low[3,5]
Steroid use at 6 months	545 per 1000	447 per 1000 (289 to 698)	RR 0.82 (0.53 to 1.28)	84 (1 study)	⊕⊖⊖⊖ very low[3,5]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Serious grade 3-5 toxicity	114 per 1000	400 per 1000 (161 to 992)	RR 3.52 (1.42 to 8.73)	84 (1 study)	⊕⊕⊖⊖ low[3]
Brain necrosis grade 4	Not estimable [6]	Not estimable[6]	Not estimable	84 (1 study)	⊕⊕⊖⊖ low[3]

CI confidence interval; RR risk ratio; SRS stereotactic radiosurgery; TMZ temozolomide; WBRT whole brain radiosurgery.
[1] Unclear allocation concealment
[2] 95% CI crossed 1 default MID (1.25)
[3] Unclear allocation concealment and unclear blinding of participants assessors and investigators
[4] 95% CI crossed 1 default MID (0.8)
[5] 95% CI crossed 2 default MIDs (0.8 and 1.25)
[6] The event rate was 0 in both groups

Table 32: Summary of clinical evidence profile for WBRT+SRS+erlotinib versus WBRT+SRS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT+SRS	WBRT+SRS+erlotinib			
Overall survival	Not applicable	Not applicable	HR 1.47 (0.92 to 2.36)	85 (1 study)	⊕⊕⊖⊖ low[1,2]
CNS progression rates 6 months	159 per 1000	1293 per 1000 (127 to 671)	RR 1.84 (0.80 to 4.22)	85 (1 study)	⊕⊖⊖⊖ very low[3,4]
Deterioration in performance 6 months	523 per 1000	852 per 1000 (627 to 1000)	RR 1.63 (1.20 to 2.23)	85 (1 study)	⊕⊖⊖⊖ very low[2,3]
Steroid use at 6 months	545 per 1000	415 per 1000 (262 to 655)	RR 0.76 (0.48 to 1.20)	85 (1 study)	⊕⊖⊖⊖ very low[3,5]
Serious grade 3-5 toxicity	114 per 1000	487 per 1000 (202 to 1000)	RR 4.29 (1.78 to 10.38	85 (1 study)	⊕⊕⊖⊖ low[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Brain necrosis grade 4	0 per 1000	0 per 1000 (0 to 0)	RR 3.21 (0.13 to 76.74)	85 (1 study)	⊕⊖⊖⊖ very low[3,4]

CI confidence interval; RR risk ratio; SRS stereotactic radiosurgery; WBRT whole brain radiosurgery.
[1] Unclear allocation concealment
[2] 95% CI crossed 1 default MID (0.18) (0.37 x ± 0.5= ± 0.18)
[3] Unclear allocation concealment and unclear blinding
[4] 95% CI crossed 2 default MIDs (0.8 and 1.25)
[5] 95% CI crossed 1 default MID (0.80)
[6] 95% CI crossed 1 default MID (1.25)

Table 33: Summary clinical evidence profile for SRS versus observation following resection of metastases

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Observation	SRS			
Median overall survival	18 months	17 months (95% CI 13 – 22)	HR 1.29 (0.84 to 1.98)	128 (1 study)	⊕⊕⊖⊖ low[1]
Local recurrence at 12 months	569 per 1000	321 per 1000 (95% CI 183 to 523)	HR 0.46 (0.24 to 0.88)	128 (1 study)	⊕⊕⊖⊖ low[1]
Median time to local recurrence	7.6 months	median not reached (95% CI 15.6 months to not reached)	HR 0.41 (0.21 to 0.80)	128 (1 study)	⊕⊕⊕⊖ moderate[2]
Distant brain recurrence at 12 months	662 per 1000	585 per 1000 (95% CI 425 to 748)	HR 0.81 (0.51 to 1.27)	128 (1 study)	⊕⊖⊖⊖ very low[3]

CI confidence interval; HR hazard ratio; RR risk ratio; SRS stereotactic radiosurgery.
[1] Serious risk of bias (no blinding) and serious imprecision
[2] Serious risk of bias (no blinding)
[3] Serious risk of bias (no blinding) and very serious imprecision

Table 34: Summary clinical evidence profile for WBRT + receptor antagonist (memantine) versus WBRT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	WBRT	WBRT + receptor antagonist (Memantine)			

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
Overall survival	Not applicable	Not applicable	HR 1.06 (0.86 to 1.31)	508 (1 study)	⊕⊕⊖⊖ low[1,2]
Progression free survival	Not applicable	Not applicable	HR 1.06 (0.87 to 1.30)	508 (1 study)	⊕⊖⊖⊖ very low[2,3]
Time to cognitive failure	Not applicable	Not applicable	HR 0.78 (0.62 to 0.99)	141 (1 study)	⊕⊖⊖⊖ very low[3,4]
Cognitive function failure 3 months	515 per 1000	438 per 1000 (309 to 623)	RR 0.85 (0.60 to 1.21)	141 (1 study)	⊕⊖⊖⊖ very low[2,3]
Cognitive function failure 15 months	667 per 1000	553 per 1000 (267 to 973)	RR 0.83 (0.40 to 1.46)	18 (1 study)	⊕⊖⊖⊖ very low[3,5]
Grade 3-4 adverse events	139 per 1000	140 per 1000 (92 to 217)	RR 1.01 (0.66 to 1.56)	508 (1 study)	⊕⊖⊖⊖ very low[3,5]

CI confidence interval, HR hazard ratio, WBRT whole brain radiotherapy
1 Unclear randomisation method
2 95% CI crossed 1 default MID (1.25)
3 Unclear randomisation method; unclear whether outcome assessors were blinded to treatment allocation
4 95% CI crossed 1 default MID (0.8)
5 95% CI crossed 2 default MIDs (0.8 and 1.25)

See Appendix F for the full GRADE tables.

Economic evidence

The search identified 438 possibly relevant papers. Of these, 15 full papers relating to this topic were obtained for appraisal. 1 paper (Wernicke 2016) was included in the current review of published economic evidence for this topic..

Health economic evidence profile

Table 35: Health economic evidence profile

Study	Population	Comparators	Costs	Effects	Incr costs			Incr effects	ICER	Uncertainty
Wernicke 2016 USA	People with 1-3 Brains metastases for which surgery was clinically	Surgery+ Cs-131	$19,271	A:0.78 B:0.67	Reference			No sensitivity analysis performed	Partially Applicable	Very Serious Limitations.
		Surgery+ SRS	$44,219	A:0.47 B:0.45	$24,948	A:-0.31 B:-0.22	A:Surgery +Cs-131 dominant B:Surgery +Cs-131 dominant			

	identifie d									
	Comments:									

Summary of studies included in the economic evidence review

Wernicke 2016 is a cost utility study comparing surgery with Cs-131 stranded implanted seeds with surgery and SRS in patients with 1-3 brain metastases. The study took a US hospital perspective and reported outcomes in terms of cost per QALY. Effectiveness data were taken from 1 prospective Phase I/II trial at 1 US centre for the Cs-131. For the SRS cohort, effectiveness evidence was derived from patient records at the same single centre who did not participate in the trial. Utility data were either estimated for use in the study or converted from Karnofsky performance status scores. Cost data were taken directly from hospital receipts.

This study was deemed partially applicable to the decision problem. This is because they did not take a NHS and PSS perspective.

Wernicke 2016 was considered to have very serious limitations in terms of methodological quality. Amongst the limitations the patient groups which were not necessarily comparable and no exploration of uncertainty was performed. The methods for obtaining parameter estimates for the model were also not clear.

In Wernicke 2016 the base-case analysis estimated surgery and Cs-131 was both cost saving and health improving compared to surgery and SRS. No exploration of uncertainty was reported for this study.

For full economic evidence tables see Appendix H.

Resource Impact

No unit costs were presented to the committee as these were not prioritised for decision making purposes.

Evidence statements

WBRT and BSC versus BSC

- One randomised controlled trial (N=97) provided very low to moderate quality evidence that showed no significant differences between those who received WBRT and BSC compared to those who received BSC only in overall survival (hazard ratio (HR)=1.10, 95% confidence interval (CI) 0.93-1.31), any serious adverse events (relative risk (RR)=1.09, 95% CI 0.85-1.39); infection (RR= 1.06, 95% CI 0.55-2.06); cardiac adverse events (RR=2.00, 95% CI 0.18-21.93); or use of dexamethasone (RR= 1.19, 95% CI 0.72-1.97)
- One randomised controlled trial (N=97) provided very low quality evidence that showed no significant differences in quality of life (improved or maintained) (RR= 0.91, 95% CI 0.59-1.4). KPS change at 12 weeks appeared to be higher in those who received whole brain radiotherapy in combination with best supportive care compared to those who received

best supportive care only (mean change in the WBRT and BSC group = 4.60 higher, 95% CI 2.13-7.07).

WBRT and SRS versus WBRT

- One randomised controlled trial (N=331) provided moderate quality evidence to show no significant differences in overall survival in those who received WBRT compared to those who received WBRT and SRS (mean overall survival in the WBRT+SRS group=5.7 months and mean overall survival in the WBRT group = 6.5 months).
- Very low to low quality evidence from 1 or 2 randomised controlled trials (N=39-326) showed no differences between the treatment groups in complete response rate (RR= 2.08, 95% CI 0.82-5.25); partial response rate (RR= 1.06, 95% CI 0.80-1.41); stable lesion rate (RR= 0.67, 95% CI 0.34-1.34); progression lesion rate (RR=0.64, 95% CI 0.28-3.51.465); control of treated lesions (RR= 1.23, 95% CI 0.98-1.55); improvement in KPS (RR= 3.16, 95% CI 0.91-11.06); increase in steroid use (RR= 1.15, 95% CI 0.41-3.27); acute toxicity (RR= 11.41, 95% CI 0.64-204.68); death due to brain metastases (RR= 0.92, 95% CI 0.64-1.532); late necrosis (RR= 2.59, 95% CI 0.11-59.93); brain oedema (RR= 1.01, 95% CI 0.87-1.17) or neurological progression (RR= 1.02, 95% CI 0.82-1.26).

WBRT versus SRS

- One randomised controlled trial (N=39) provided very low to low quality evidence that showed no significant differences between those who received WBRT compared to those who received SRS in local control (RR= 0.86, 95% CI 0.25-2.95); late radiation necrosis (RR=1.06, 95% CI 0.92-1.23); brain oedema (RR= 1.17, 95% CI 0.08-17.35) and neurological progression (RR=1.07, 95% CI 0.89-1.29).

WBRT and TMZ versus WBRT

- One randomised controlled trial (N=55) provided very low to moderate quality evidence that showed no differences in overall survival (HR= 1.14, 95% CI 0.71-1.83); median overall survival (median overall survival in the intervention arm= 8 months [4.9 to 11.1] and the median overall survival in the control arm=8.1 months [5.9 to 10.1]), or progression free survival (median progression free survival in the intervention arm= 11.8 months [4.7 to 18.9] and the median progression free survival in the control arm = 5.6 months [4.9 to 6.2]) between those who received WBRT compared to those who received WBRT and TMZ.
- Three randomised controlled trials (N=102) provided very low to low quality evidence that showed no significant differences in complete response rate (RR= 1.58, 95% CI 0.75-3.31); partial response rate (RR= 1.38, 95% CI 0.98-1. 94); stable disease rate (RR= 0.59, 95% CI 0.18-1. 91) and progressive disease rate (RR= 0.60, 95% CI 0.24-1. 52) between those who received WBRT compared to those who received WBRT and TMZ.
- Two randomised controlled trials (N=103) provided very low quality evidence that showed no significant differences in neurological outcomes between those who received WBRT compared to those who received WBRT and TMZ (RR= 1.29, 95% CI 0.98-1.69).
- One randomised controlled trial (N=48) provided very low quality evidence that showed no differences in between those who received WBRT as compared to those who received WBRT and TMZ in corticosteroids use (RR=0.74, 95% CI 0.55-1.00). There were not differences in death because of systemic disease (RR=0.92, 95% CI 0.73-1.16).

- Two randomised controlled trials (N=150) provided very low quality evidence that showed that those who received WBRT experienced fewer grade ≥ 3 adverse events compared to those who received WBRT and TMZ (RR=3.93, 95% CI 2.04-7.58).

SRS and WBRT versus SRS

- One randomised controlled trial provided low to very low quality evidence showing no significant differences in the median survival time or brain tumour recurrence at distal sited between those who received SRS in combination with WBRT and SRS alone (median survival time in the SRS + WBRT group was 7.5 months [0.8-58.7] and the median survival time in the SRS group was 8 months [0.5-57] and median months brain tumour recurrence in distal sites in the WBRT+ SRS group was 16.2 and the median months in the SRS group was 5.5)
- One randomised randomised controlled trial (N=167) provided low quality evidence showing no significant difference in overall survival between those who received SRS and WBRT compared to those who received SRS (HR 1.02, 95% CI 0.75-1.38).Conversely, 1 of these trials (N=58) provided high quality evidence to show that those who received SRS only experienced longer overall survival compared to those who received SRS and WBRT (HR=2.47, 95% CI 1.34-4.55).
- One randomised controlled trial (N=213) provided low quality evidence that showed that those who received WBRT and SRS experienced a longer time to intracranial failure (HR= 3.60, 95% CI 2.21-5.86) compared to those who received SRS only.
- One randomised controlled trial (N=132) provided very low quality evidence that showed that those who received WBRT and SRS had a lower rate of new brain metastases at distal sites (RR= 0.64, 95% CI 0.42-0.97) or actuarial new brain tumour metastases (RR= 0.65, 95% CI 0.46-0.91) compared to those who received SRS only.
- Four randomised controlled trials (N=426) provided very low quality evidence to show that those who received WBRT and SRS had a higher local control rate (RR=1.29, 95% CI 1.17-1.43) and distant brain tumour control (RR=1.36, 95% CI 1.18-1.56) compared to those who received SRS only.
- One randomised controlled trial (N=132) provided very low quality evidence that showed no differences in KPS score (≥70) between those who received WBRT and SRS and those who received SRS only (RR=1.26, 95% CI 0.75-2.12).
- One randomised controlled trial (N=115) provided very low quality evidence that showed that quality of life was higher at 3 months for those who received SRS compared to those who received WBRT and SRS (mean quality of life in the WBRT and SRS= 11.9 lower, 95% CI -17.71 to -6.09).
- One or 2 randomised controlled trials provided low to moderate quality evidence that showed no significant differences in the following adverse events between those who received WBRT and SRS compared to those who received SRS only: cognitive deterioration (RR=0.72, 95% CI 0.15-3.53); neurological preservation (RR=1.01, 95% CI 0.86-1.18); grade 3 and 4 late toxic effects (RR= 0.97, 95%CI 0.86-1.09); oedema limbs (RR= 0.99, 95%CI 0.96-1.02) and late oedema (RR=1, 95% CI 0.87-1.14).

SRS and cisplatin or carboplatin versus SRS

- One randomised controlled trial (N=98) provided very low quality evidence that showed no difference in overall survival (HR 1.2, 95% CI 0.77 to 1.89) or progression free survival

(HR = 1.44, 95% CI 0.87 to 2.35) between those who received SRS combined with cisplatin or carboplatin compared to those who received SRS only

WBRT and erlotinib versus WBRT

- One randomised controlled trial (N=80) provided very low to moderate quality evidence that showed no difference in overall survival (HR = 0.94, 95% CI 0.58-1.53); grade 3 to 4 adverse events (RR= 1, 95% CI 0.75-1.33); quality of life (mean quality of life in the WBRT and erlotinib= 0.05 higher, 95% CI 0.34 to 0.344) or infection (RR=1.13, 95% CI 0.92 to 1.38) between those who received WBRT and erlotinib compared to those who received WBRT only.

Surgery, SRS and WBRT versus surgery, SRS and observation

- One randomised controlled trial (N=369) provided very low to low quality evidence that showed slightly shorter median progression free survival (4.6 months; 95% CI, 3.9 to 6.1 months) in the surgery/SRS/WBRT group relative to the surgery/SRS/observation group (3.4 months; 95% CI, 3.1 to 3.9 months), whereas the groups did not differ in terms of overall survival (HR = 0.98, 95% CI 0.78-1.23).
- One randomised controlled trial (n=369) provided very low quality evidence that showed that those who received Surgery/SRS/ observation experienced fewer serious side effects (RR= 0.23, 95% CI 0.07-0.80) that those who received surgery/ SRS/WBRT, but those who received Surgery/SRS/ observation presented with a higher risk of intracranial progression (RR= 0.62, 95% CI 0.52-0.74) as compared to those who received surgery/ SRS/WBRT. There were no differences between the treatment groups in serious infection rate (RR= 0.20, 95% CI 0.01-4.16), serious radionecrosis rate (RR=0.50, 95% CI 0.05-5.50), but quality of life was lower in the surgery/SRS/WBRT group compared to the surgery/SRS/Observation group (mean quality of life in surgery/SRS/WBRT = 1.90 lower, 95% CI 3.72-0.08)

WBRT, SRS and TMZ versus WBRT and SRS

- One randomised controlled trial (N=84) provided very low to low quality evidence that showed no differences in overall survival (HR 1.43, 95% CI 0.89 to 2.31), CNS progression rate (RR= 1.89, 95% CI 0.82-4.32), new metastases (RR= 2.20, 95% CI 0.72 to 6.75); steroid use (RR= 0.82, 95% CI 0.53-1.28) or grade 4 brain necrosis (there were no events in either treatment group) between those who received WBRT/SRS/TMZ and those who received WBRT and SRS. Those who received WBRT and SRS experienced less grade 3-5 toxicity (RR= 3.52, 95% CI 1.42-8.73) compared to those who received WBRT/SRS/TMZ.

WBRT, SRS and erlotinib versus WBRT and SRS

- One randomised controlled trial (N=85) provided very low to low quality evidence that showed no differences in overall survival (HR=1.47, 95% CI 0.92 to 2.36); CNS progression rate (RR=1.84, 95% CI 0.80-4.22); steroid use (RR= 0.76, 95% CI 0.48-1.20) and grade 4 brain necrosis rate (RR= 3.21, 95% CI 0.13-76.74) between those who received WBRT and SRS compared to those who received WBRT/SRS/erlotinib.
- Those who received WBRT and SRS experienced less deterioration in performance (RR= 1.63, 95% CI 1.20-2.23) and grade 3-5 toxicity (RR= 4.29, 95% CI 1.78-10.38).

SRS versus observation following resection of metastases

- One randomised controlled trial (N = 128) provided very low to low quality evidence that showed no significant differences in median overall survival time (HR= 1.29, 95% CI 0.84-1.98) or in distant recurrence rates (HR= 0.81, 95% CI 0.51-1.27) between those who received SRS and those who were observed after resection of brain metastases. The same trial did show a significant reduction in local recurrence rates (low quality evidence) (HR= 0.46, 95% CI 0.24 to 0.88), and a longer time to local recurrence (moderate quality evidence) (HR= 0.41, 95% CI 0.21-0.80) for those who received SRS as compared with those who were observed.

WBRT and memantine versus WBRT

- One randomised controlled trial (n=508) provided low to very low quality evidence that showed no significant differences in overall survival (HR=1.06, 95% CI 0.86-1.31) or progression free survival (HR=1.06, 95% CI 0.87-1.30).
- One randomised controlled trial provided very low quality evidence that showed longer time to cognitive failure in those who received WBRT in combination with memantine compared to those who received WBRT alone (HR=0.78, 95% CI 0.62-0.99).
- One randomised controlled trial provided very low quality evidence that showed no differences in cognitive function failure at three months (RR=0.85, 95% CI 0.60 to 1.21); cognitive failure at 15 months (RR=0.83, 95% CI 0.40 to 1.46) or grade 3 to 4 adverse events (RR=1.01, 95% CI 0.66 to 1.56) between those who received WBRT in combination with memantine or WBRT alone.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee selected 3 outcomes as being critical: overall survival, 2 measures of progression-free survival (local control and intracranial control) and health-related quality of life. These outcomes were prioritised because they were either related to length of life or a direct measure of quality of life.

The committee selected 3 outcomes as being important: cognitive function, 2 measures of neurological function (Karnofsky Performance Status and Neurological Function Scale) and several measures of treatment-related morbidity including postoperative infection and radionecrosis. These outcomes were considered important, as they were indirect measures of quality of life, as well as representing areas of particular concern for patients. The committee added steroid use as an outcome of limited importance, as this was a common response to WBRT.

The quality of the evidence

The evidence consisted of a very large number of studies reporting outcomes rated as low quality, with no consistent intervention and comparator. The question on single brain metastases consisted of 5 studies, of which all but 1 outcome for 1 study was ranked as low

quality evidence. The study which produced outcomes graded moderate showed a difference in overall survival favouring whole brain radiotherapy and stereotactic radiosurgery over whole brain radiotherapy alone. The combined mixed-population and multiple brain metastases review consisted of 22 studies, comparing 18 different sets of interventions and comparisons. The quality of outcomes reported by these studies was generally low or very low. The main quality issues noted in these studies were very small sample sizes, no clear consensus on a 'gold standard' comparator and multiple conflicting outcome measures.

The committee discussed how the trial entry criteria for the main study on whole brain radiotherapy was quite specific; a population of patients with a poor prognosis whose oncologist was unclear about the efficacy of WBRT. This limited its wider applicability.

The committee agreed that the quality of evidence was high enough to support strong recommendations. Although evidence for each outcome was generally low or very low quality, the committee considered that the evidence was consistent with itself, with their clinical experience and with trials in similar areas, and consequently they believed the evidence was largely reliable.

The committee chose not to make a research recommendation, as the evidence for answering this question was robust.

Benefits and harms

The committee agreed that the benefit of these recommendations would be fewer people receiving harmful and unnecessary treatment. There may also be an effect whereby clinicians are prompted to consider the most appropriate treatment for groups they might previously have put on a palliative care plan but who nevertheless may benefit from treatment (especially in groups of people with <4 metastases). The committee added that the emphasis on discussing treatment options would likely help to reassure people with brain tumours, in particular the recognition that treatment has to be individualised.

The harms of offering any intervention are the side effects of treatment. In particular for brain tumours the harm of offering too much radiation is side effects, and the harm of offering too little is (lesser) side effects and tumour recurrence. Therefore the committee drafted their recommendations to try and limit the amount of radiation given to healthy brain tissue, where possible. In this way the benefit was maximised for the person with a tumour compared to the risk.

Based on their clinical experience, the committee recommended that when choosing treatment, clinicians and people with a tumour should take various factors into account, which they listed. The list was generated using the committee's knowledge and indirect evidence from the review – for example the primary tumour site was seen to lead to a different outcome and therefore it might be appropriate to treat tumours arising from a different primary site differently. The committee described how leptomeningeal disease and the preferences of the person with the tumour were extremely important to take into account because they could substantially alter treatment, but that these considerations could not be indirectly based on the evidence and were therefore entirely based on the experience of the committee.

On the basis of their clinical experience the committee described how systematic anti-cancer therapies might be expected to work for brain tumours. The committee described how systematic anti-cancer therapies could have very severe side-effects, and therefore the committee recommended them only if the metastasis was likely to respond and therapy was

likely to be beneficial. The committee described how germ cell tumours or small cell lung cancer were examples of primaries which were especially likely to respond.

For people with a single metastasis, the committee recommended treatment with surgery,stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT). This was based on trials that showed that whole brain radiotherapy (WBRT) plus one of either surgery or SRS/SRT led to fewer recurrences at the original site and improved overall survival respectively, and additionally on evidence that WBRT was no better than observation only. From this the committee concluded that there was indirect evidence that SRS/SRT and surgery was superior to WBRT or observation.

The committee described how SRS and SRT were techniques which should be selected between on the basis of which number of fractions was more appropriate. The committee discussed how there were other radiotherapy modalities on which no evidence was found, and therefore no recommendation could be made on these modalities.

The committee did not have evidence of when SRS/SRT or surgery should be preferred for people with a single brain metastasis, and so recommended additional factors to consider before making the decision on the basis of their experience. Although the committee did not have any evidence, they discussed how these considerations should be standard practice and so a weak recommendation to base the decision on a variety of factors was appropriate.

The committee recommended against whole brain radiotherapy following local treatment of a single metastasis. This was based on evidence that showed that neurological death rate was improved by withholding whole brain radiotherapy, and health economic analysis. This was consistent with the committee's clinical experience.

The committee recommended considering adjuvant stereotactic radiosurgery/radiotherapy to the surgical cavities for people with 1-3 brain metastases that have been resected. This was based on evidence showing people who received SRS/SRT had reduced local recurrence rates and an increase in the time to local recurrence compared with those who were observed. The committee agreed this evidence was mixed, but argued that there were plausible reasons to believe irradiation of the surgical cavity should prevent recurrence and so were persuaded by it. The committee noted that there was no overall increase in survival in the group that did not receive SRS/SRT. While it was unclear if this finding was clinically meaningful, the committee argued that lengthening the time to local recurrence would likely improve quality of life even if it did not extend length of life.

The committee recommended stereotactic radiosurgery/radiotherapy should be considered in patients with a reasonable prognosis, controlled extracranial disease and a low number of brain metastases. This was based on evidence for improvement in overall survival and quality of life. The committee added on the basis of their experience that they only expected this benefit to be seen if the number and total volume of metastases were taken into account.

The committee made a recommendation to avoid offering whole brain radiotherapy to people with brain metastases from non-small cell lung cancer who had a poor performance status and were therefore unlikely to be candidates for additional systemic treatments for their primary cancer (such as immunotherapy). This was based on a large trial which only included this group of patients and found no benefit to whole brain radiotherapy versus best supportive care. The committee discussed how it might be possible to consider whole-brain radiotherapy in other groups, but determined on the basis of the available evidence that they could not make this recommendation. As this is considered to be a very specific population,

the committee did not think it was appropriate to extend this recommendation to other people with metastases originating from different tumour sites or an improved performance status.

The evidence for the use of whole brain radiotherapy in people with brain metastases from cancers other than lung cancer and who are not suitable for SRS was mixed. Overall, the evidence neither favoured nor did not favour whole brain radiotherapy alone. Whole brain radiotherapy has not been demonstrated to improve survival, and may harm cognition. However, it can reduce the development of new brain metastases. Therefore the committee recommended that both WRBT and no WBRT be considered, with the choice of treatment made after discussion with the person about the potential risks and benefits.

Based on evidence of no statistically significant effect, the committee recommended memantine should not be offered in addition to whole brain radiotherapy to people with multiple brain metastases outside clinical trials. The committee also noted that memantine is not currently licensed for this indication in the UK.

Based on evidence of both benefits and harms, the committee did not believe that the evidence for a benefit was robust enough to justify the risks of recommending concurrent systematic therapy. Therefore the committee recommended these treatments only be given in a research context. However, the committee added that this did not mean systematic therapy could not be given following treatment, only that the evidence did not support it being given concurrently. Therefore, such drugs should not be stopped if they are part of the treatment of the primary tumour site (that is to say, if they would have been given regardless of the brain metastases).

Cost effectiveness and resource use

Three previously published economic evaluations were identified for this topic. Given they were not deemed directly applicable to the decision problem, had methodological problems and came to conflicting conclusions with each other the committee did not think it would be useful to use this evidence to inform their recommendations.

Two bespoke economic models were developed looking at adjuncts to surgery and SRS in the treatment of a single brain metastasis to help inform recommendations. The base-case analysis found that the addition of WBRT to either initial treatment with surgery or SRS would lead to an increase in costs of approximately £2000 per patient and a small decrease in QALYs. These results were robust to a range of deterministic and probabilistic sensitivity analyses, with the addition of WBRT only becoming cost effective for a difference in quality of life weights between a case where the tumour progressed and a case where it remained unprogressed that the committee considered to be implausibly large.

Given that WBRT would very likely increase costs and decrease health the committee made a recommendation not to use WBRT as an adjunct to SRS and surgery. Given there is currently variation across the NHS in England and numerous centres are using WBRT in this context, there would likely be reasonable cost savings from this recommendation.

The committee acknowledged that in the base-case analysis that the addition of SRS to initial surgery would lead to both cost increases and health decreases. It was noted that during deterministic sensitivity analysis, surgery with SRS became the preferred option for values of overall survival within the 95% confidence intervals reported in the clinical evidence review. Using the lower, more favourable, estimate for the hazard ratio of the addition of SRS to surgery led to an ICER of £22,841 per QALY. Given the uncertainty around this important

parameter, the reasonable probability that it may be cost effective and the relative newness of this technique it was agreed that it was reasonable to consider its use.

The committee acknowledged that this recommendation, if followed, would almost certainly increase resource use with all iterations in the probabilistic sensitivity analysis leading to increased costs. However, given the arguments above there was a reasonable probability it would be an efficient use of NHS resources.

All other recommendations for this topic were concerned with the reduction of unnecessary and harmful interventions in people they would not clinically benefit. These recommendations would lead to cost savings from the reduction in use of these interventions. It was thought that with the exception of the addition of SRS to surgery all the recommendations would be either cost neutral or cost saving with the recommendations as a whole being cost saving.

Other factors the committee took into account

The committee noted that there was a widespread and firmly held belief in patient support groups (especially online) that whole brain radiotherapy was harmful in metastatic lung and breast cancer; clinicians should expect to be challenged if they offer it to people with tumour. The committee reiterated that due to mixed evidence, the role of whole brain radiotherapy in people with a Karnofsky performance status of 70 or greater was an area of significant clinical debate. Therefore the committee did not make a recommendation on groups with a good performance status.

The committee described how for most people, their radiation would be given in a single dose (stereotactic radiosurgery). However the committee emphasised that there would be very rare occasions when this would be unsuitable, for example with large metastases that require hypofractionated stereotactic radiotherapy Although this was consistent with the evidence, the point at which the switch should be made was impossible to define so the committee chose not to make a recommendation on this topic.

The committee discussed the evidence regarding whether there was a cut off or threshold number of brain metastases above which stereotactic radiosurgery should not be offered. The committee noted that the study on which the recommendation is based had an upper limit of 3 or 4 metastases, but that there was no clear biological rational for that number. There is also no clear survival difference between incremental increases in number of metastases so it is difficult to set an arbitrary maximum. The committee noted that some centres are able to treat >10 metastases safely and with good outcome. The committee therefore decided not to make a recommendation regarding the maximum number of metastases to be treated with stereotactic radiosurgery.

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Follow-up for brain metastases

Follow-up for brain metastases

Review question

What is the most effective follow-up protocol (including duration, frequency and tests) to detect intracranial recurrence after treatment for brain metastases?

Introduction

People with brain metastases have a substantial risk of developing either local recurrence of the brain tumour or further brain metastases (distant recurrence) in the first few years after initial treatment. Detection of asymptomatic recurrence may allow earlier treatment of recurrence, when there are more treatment options and overall neurological outcome may be better. However, options will vary depending on the initial treatment used and the overall prognosis of the person. Follow-up imaging is also helpful to see if treatment has been effective, and to distinguish between changes due to treatment and tumour regrowth. The optimal timing and method of monitoring has not been established, which has resulted in variation in the frequency and content of follow-up programmes. Without evidence of benefit, scanning should be avoided as there are costs to healthcare resources, people with tumour's time and potentially their psychological health and excess radiation if CT scans are used.

PICO table

Table 36: Summary of the protocol (PICO table)

Population	People treated for brain metastases
Intervention	Follow-up protocol including duration, and frequency of tests (e.g., MRI/CT scans)
Comparison	• Any other follow-up protocol • No follow up (wait until patient reports symptoms of recurrence)

Outcome	Critical:
	• treatment for recurrence
	• overall survival.
	• cognition
	• symptomatic versus asymptomatic presentation
	Important:
	• health-related quality of life
	  ○ neurological outcomes
	  ○ seizures

CT computerised tomography; MRI magnetic resonance imaging.

For further details see the full review protocol in Appendix A.

Clinical evidence

Included studies

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Excluded studies

Full-text studies not included in this review with reasons for their exclusions are provided in Appendix K.

Economic evidence

The economic evidence search identified no studies that met the inclusion criteria for this review.

Resource impact

Table 37: Resource impact and unit costs associated with follow-up for brain metastases

Resource	Unit costs	Source
Follow-Up Appointment	£188	NHS reference costs 2015-16 (WF01A)
MRI Scan	£145	NHS reference costs 2015-16 (RD01A)

Evidence statements

No evidence was identified.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee designated 4 outcomes as critical. These were cognitive function, treatment for recurrence, overall survival and the numbers of patients with symptomatic versus asymptomatic presentation. As the committee was unsure whether identifying early progression of a tumour would be clinically beneficial, they identified these outcomes as the easiest to interpret, so that the benefit or harm of treatment would be most obvious on review.

Health related quality of life was also important, although not critical as the committee agreed the link between recurrence and health-related quality of life was not as direct.

The quality of the evidence

The clinical evidence search identified no studies that met the inclusion criteria for this review.

The committee decided that since the question was so important and the evidence so limited they would make weak recommendations to provide guidance for clinicians based on their clinical knowledge.

The committee determined that further research into the most effective follow-up of people with brain metastases could help to standardise practice. However, they determined that the major outstanding clinical question was how valuable early detection of recurrence was compared to later detection. This was true for all 3 questions on follow-up the committee looked at (for glioma, meningioma and brain metastases). The committee elected to prioritise glioma as treatment options for recurrence of glioma had significant evidence, so it was more likely that findings would influence clinical practice. Therefore the committee did not make a research recommendation on the follow-up of brain metastases.

See Evidence Report A for details of this research recommendation.

Benefits and harms

The committee agreed that the overall benefits of the recommendations would be that more people who have been treated for brain metastases will have better quality of life because more recurrences will be picked up while they are still asymptomatic - which is when recurrences are easiest to treat. However, the committee also recognised that scanning is associated with psychological stress and anxiety for some people. The committee discussed whether more frequent scanning would provoke or reduce anxiety in people with brain tumours, but reached no consensus as it might be different for different people – for example reassurance of regular contact versus anxiety induction of worrying results (especially false positives). While there was no absolute balance to be struck – the actual balance in all cases should depend on individual factors to do with the person – the committee believe their suggested follow-up schedule is a useful guide to balancing these benefits and harms.

Based on their experience and judgement, the committee recommended clinical review of a person with brain metastases as this would be useful to detect recurrence, based on changes in the person's symptoms and function. Clinical assessment can also lead to intervention or onward referral, if indicated. This may improve a person's quality of life by alleviating symptoms or helping the person develop adaptive strategies. Although the committee identified no evidence that early detection of changes in clinical status could improve outcomes, they agreed that failing to detect a change had happened at all could have severely negative consequences for the person with a tumour. Consequently they made a strong recommendation for offering a review that could detect recurrence or other changes in clinical condition, but weaker recommendations on what should be in that review.

The committee identified no direct evidence on which to make recommendations about when to arrange regular clinical review. However, the committee had indirect evidence from reviews on the management of the tumour about factors that would make a recurrence more dangerous. Consequently they made a weak recommendation to consider the factors that could alter the urgency of the review. The recommendation on taking into account the person's preferences was made on the basis of the committee's experience.

While there was no evidence for or against the use of MRI or other scans to detect recurrence, the committee recommended that MRI scanning could be useful to detect recurrence on the basis that it is standard practice to do this already and that unstandardised MRI is not as useful as standard structural MRI. As this recommendation was made on the basis of the committee's experience it was a weak recommendation. The committee explained how under certain circumstances not all of the sequence would be necessary, for example if the tumour had very well-defined characteristics which could be adequately monitored with only some of the suggested sequence. Consequently they made a weaker recommendation than for the equivalent sequence in the investigation of the tumour, because in the investigation of the tumour it is not yet known what characteristics the tumour will have and therefore clinicians cannot determine if there are any aspects of the sequence which can be left out whereas in the follow up there is more scope for the use of clinical judgement in determining which steps were necessary.

The committee recommended advanced MRI techniques for situations where, in their clinical judgement, it might be helpful to distinguish between recurrence of metastases and the after effects of treatment. As this recommendation was made on the basis of the committee's experience it was a weak recommendation.

Based on their experience, the committee recommended that clinicians be aware that routine imaging (and waiting for the result) may cause anxiety. In addition, the committee recommended that the possibility of uncertain results (such as ambiguous growth) be explained. The committee made these recommendations because in their experience the potential harms of scanning very frequently were sometimes not appreciated by all clinicians.

The committee recommended clinical review (outside the usual schedule of scans) in response to new or changing neurological symptoms. This was based on the fact that the purpose of routine follow-up is to identify changes to the tumour in order to treat these before they become symptomatic (if this is possible). In addition, the review would represent an opportunity for the clinician to discuss how the change might affect the risk of negative effects (such as infection and swelling). The committee discussed how they had not reviewed the evidence for how long a clinical review could be delayed in the case of new or changing symptoms and therefore could not specifically recommend a timeframe for review, but discussed how similar clinical considerations would apply in the case of a changing symptom as a new cancer referral and that therefore the timing might be related to that in practice. New or changing symptoms likely mean that the tumour has grown between scans, and therefore waiting until the next routine scan could limit treatment options. The committee justified the stronger 'offer' recommendation on the basis that changes to neurological condition could require immediate treatment to prevent death, and so assessment of the change in order to assess risk could be life saving.

The committee suggested a schedule of scans for a person with brain metastases as a possible guide to discuss with the person with the tumour. Although there was no evidence for the most effective follow-up schedule the committee agreed that consensus recommendations would be valuable to try to help standardise practice and reduce inequity from clinical variation. The committee based the schedule of scans on a large clinical trial which was conducted, their clinical experience and a discussion about the likely rate of recurrence following a long period of no recurrence. In the committee's experience, most people with brain metastases treated with stereotactic radiosurgery or surgical treatment relapse in the first 2 years. Therefore frequent scanning during this period to identify relapse is recommended, with annual scans until 5 years to identify late relapse.

The committee discussed whether or not to make recommendations for people who had been treated with whole brain radiotherapy (WBRT). As this is a diverse group with widely varying management options it was not possible to make a single recommendation. For example, in a person who has had WBRT and is now receiving immunotherapy, routine MRI scanning is appropriate to ensure continuing this therapy is appropriate, whereas for a frail person with no other options, routine MRI is unlikely to be helpful and may cause distress.

Cost effectiveness and resource use

A literature review of published cost effectiveness analyses did not identify any relevant studies for this topic.

The committee believed these recommendations to be in line with current practice nationally and therefore did not think they would lead to any significant change in practice. The committee acknowledge that a small number of centres may not be using a follow up protocol similar or identical to the schedule they suggest, and in these centres increased follow-up imaging and some service reconfiguration may be needed if the centre wishes to implement this schedule. This would lead to increased costs and resource use although given the small number of centres this is unlikely to be significant. These additional costs may also be somewhat offset by quicker identification of recurrence and resultantly more effective treatment leading to reduced costs of treating adverse events.

Other factors the committee took into account

The committee also discussed that people with physical disabilities might find it difficult to attend very frequent scanning, and that consideration should therefore be given to alternative modalities of assessment for these people. They did not make a specific recommendation on this point as the types of physical disability experienced by people with brain tumours were very variable, and in not referring specifically to disability the committee believed they would make it clear that all people with tumours should be followed up in an appropriate way, regardless of the presence of a disability.

References

The clinical evidence search identified no studies that met the inclusion criteria for this review.

Appendices

Appendix A – Review protocols

Review protocol for review 1b - imaging strategy for brain metastases

Field (based on PRISMA-P)	Content
Key area in the scope	Diagnosing radiologically identified glioma, meningioma and brain metastases
Actual review question	1b What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?
Type of review question	Diagnostic Note that while this is classified as a diagnostic review, the outcomes to be evaluated are not typical of a diagnostic review; this is because the typical approach of evaluating diagnostic test accuracy against a reference standard (using sensitivity and specificity versus pathology, for example) would not be appropriate for a small metastasis; a scan can identify a real tumour which either moves or disappears before it is biopsied, and in these circumstances a negative biopsy result would not represent the gold standard; the purpose of including a list of clinical outcomes is to examine how the outcomes vary with the number of tumours detected, thus providing indirect evidence of the accuracy of the index test
Objective of the review	This protocol explores the evidence for imaging strategies for patients with radiologically suspected brain metastases. Under consideration are the imaging techniques, or combination of techniques, that provide the information necessary to make a putative diagnosis and plan appropriate treatment.

Field (based on PRISMA-P)	Content
Eligibility criteria – **population**/disease/condition/issue/domain	Adults with a radiologically (by CT scan or MRI scan) suspected brain metastasis
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Advanced MRI: ○ double dose or triple dose Gadolinium contrast agent ○ PET-CT (including FDG: FET, MET, Choline-PET) ○ PET-MRI (including FDG: FET, MET, Choline-PET)
Eligibility criteria – **comparator(s)/**control or reference (gold) standard	Standard structural MRI (core protocol) +/- contrast (T1 pre and post contrast and T2)
Outcomes and prioritisation	• Number of metastases It is recognised that this outcome will be challenging to interpret, but the committee points out that a more typical reference standard (pathology, for example) would usually not be appropriate for a small metastasis as a scan can identify a real tumour which either moves or disappears before it is biopsied, and therefore a negative biopsy result would not be gold standard. Therefore other outcomes will only be considered in papers containing information on the number of metastases: <u>Critical:</u> • overall survival. • progression-free survival: ○ local control (site of metastasis) ○ intracranial control (recurrence elsewhere in the brain) • health-related quality of life

Field (based on PRISMA-P)	Content

	Important:
	• cognitive function:
	  ○ neurological function
	  ○ Karnofsky Performance Status (or WHO or ECOG)
	• Neurological Function Scale
	• treatment-related morbidity:
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke
	
	Limited:
	Steroid (for example dexamethasone) use (duration and dose)

Eligibility criteria – **study design**	Only published full-text English language papers Studies published from the year 2000 when MRI technology changed significantly **Study design:** RCTs Cross-sectional studies (>20) Observational studies (>20)
Other inclusion **exclusion criteria**	Recurrent meningioma, low grade glioma or high-grade glioma Children and young people (under 16 years old) The following list of tumour types:

Field (based on PRISMA-P)	Content
	• neuronal and mixed neuronal-glial tumours • tumours of the pineal region • embryonal tumours • tumours of the cranial and paraspinal nerves • melanocytic tumours • lymphomas • mesenchymal, histiocytic, germ cell, sellar originating and choroid plexus tumours.
Proposed stratified, sensitivity/**sub-group analysis**, or meta-regression	Type of gadolinium contrast agent Type of PET tracer agent
Selection process – duplicate screening/selection/analysis	Double sifting, data extraction and methodological quality assessment will not be done.
Data management (software)	STAR will be used for generating bibliographies/citations, study sifting, data extraction, and quality assessment/critical appraisal.
Information sources – databases and dates	See Appendix B for full list of databases. Sources to be searched: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limit to studies published from the year 2000 when MRI technology changed significantly. Limit to English language only where possible (Medline and Embase). Limit to RCTs and systematic reviews unless overall return is small Supplementary search techniques: No supplementary search techniques were used
Identify if an update	Not an update.

Field (based on PRISMA-P)	Content
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk)
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see Appendix B of the evidence report.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D (clinical evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	The quality of the evidence for an outcome (i.e. across studies) will be assessed using QUADAS –II. Synthesis of data: Meta-analysis will be conducted where appropriate.

Field (based on PRISMA-P)	Content
	Minimally important differences: Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature. Data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will be performed when capacity allows.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from [add name of developer] undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	[add name of developer] is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	[add name of developer] is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Field (based on PRISMA-P)	Content
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO

Review protocol for review 4a – management of single metastases

Field (based on PRISMA-P)	Content
Key area in the scope	Managing brain metastases
Actual review question	4a What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these) for a single brain metastasis?
Type of review question	Intervention
Objective of the review	Single brain metastases were traditionally treated with surgery, but new therapies mean that optimal treatment is now uncertain. A review in this area will help establish what the optimal treatment for a single metastasis is.
Eligibility criteria – **population**/disease/condition/issue/domain	People with a single brain metastasis

Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Surgery
	• Radiotherapy:
	  ○ radiosurgery (1 fraction)
	  ○ stereotactic radiotherapy (2-5 fractions)
	  ○ whole brain radiotherapy
	  ○ combined therapy (any combination of the above)
	  ○ combination of radiation and drug therapy

Field (based on PRISMA-P)	Content
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	• Each other

Outcomes and prioritisation	Critical:
	• overall survival.
	• progression-free survival
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life
	
	Important:
	• cognitive function.
	• neurological function
	  ○ Karnofsky performance status (or WHO or ECOG)
	  ○ Neurological Function Scale
	• treatment-related morbidity.
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke
	
	Limited:
	• steroid (for example dexamethasone) use (duration and dose)

Eligibility criteria – **study design**	Only published full text papers in English language

Field (based on PRISMA-P)	Content
	Systematic reviews RCTs Cohort or observational studies where RCTs are not available
Other inclusion **exclusion criteria**	Populations including children <16 included will be considered if the number of children is low (<10%) or the average age of the cohort is high (>40) or results are reported separately for children and adults Populations with mixed single / multiple metastases will be extracted separately if possible. If results are not reported by single / multiple subgroup they will be included if they are more than 75% single, included in the sister review of multiple metastases if they are less than 25% single and included in a 'mixed' review if more than 10% of the population has a metastasis which is not described as either single or multiple or if the population is between 25% and 75% single. The following type of cancers are excluded: • small cell lung cancers • germ cell tumours • secondary lymphoma • metastasis from brain tumours or CNS As above, studies reporting these tumours will be excluded unless the total number of these types of cancers is small (<10% in total) or outcomes for included and excluded cancers are reported separately Studies with an unclear number of metastases will be treated as 'multiple' and so excluded from this review
Proposed sensitivity/**sub-group analysis**, or meta-regression	• Size/volume of metastasis <10 v >=10cc • Site of primary tumour: breast v non-small cell lung v other • brainstem v elsewhere in brain
Selection process – duplicate screening/selection/analysis	Double sifting, data extraction and methodological quality will not be done. In order to ensure accuracy, all results are checked by a Senior Systematic Reviewer and the excluded study list is checked by the committee prior to making recommendations.

Field (based on PRISMA-P)	Content
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B full list of databases. No date limit. A single search will be conducted for management of single, multiple and mixed brain metastases.
Identify if an update	Not an update.
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk).
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see Appendix B of the evidence report.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D (clinical evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
	The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists

Field (based on PRISMA-P)	Content
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO.

Review protocol for review 4b – management of multiple metastases

Field (based on PRISMA-P)	Content
Key area in the scope	Managing brain metastases
Actual review question	4b What is the most effective intracranial treatment - surgery stereotactic radiotherapy, whole brain radiotherapy, combinations of these, or best supportive care) for multiple brain metastases?
Type of review question	Intervention
Objective of the review	Until recently whole brain radiotherapy (WBRT) was the mainstay of treatment of multiple brain metastases. WBRT can offset the morbidity of intracranial metastases but can cause significant neurocognitive toxicity. This led to the concept of using single fraction stereotactic radiosurgery (SRS) for multiple lesions which may reduce the neurocognitive risks but does not treat areas of potential microscopic disease. This review will identify which therapy is most appropriate for people with multiple brain metastases.
Eligibility criteria – **population**/disease/condition/issue/domain	People with multiple brain metastases (≥2 metastases)

Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Neurosurgery
	• Radiotherapy:
	  ○ radiosurgery SRS (1 fraction)
	  ○ stereotactic radiotherapy SRT (2-5 fractions)
	  ○ whole brain radiotherapy (WBRT)
	  ○ hippocampal avoidance WBRT

Field (based on PRISMA-P)	Content
	• Chemotherapy or systemic anti-cancer therapy/ treatment • Combined therapy (any combination of the above) • Best supportive care
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	Any intervention compared to any other intervention

Outcomes and prioritisation	Critical:
	• overall survival.
	• progression-free survival
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life
	
	Important:
	• cognitive function.
	• neurological function
	  ○ Karnofsky performance status (or WHO or ECOG)
	  ○ Neurological Function Scale
	
	• treatment-related morbidity.
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke

Field (based on PRISMA-P)	Content
	Limited: • steroid (for example dexamethasone) use (duration and dose)
Eligibility criteria – **study design**	Only published full text papers Systematic reviews RCTs Cohort or observational studies where RCTs are not available No date or size limit
Other **exclusion criteria**	Populations including children <16 included will be considered if the number of children is low (<10%) or the average age of the cohort is high (>40) or results are reported separately for children and adults Populations with mixed single / multiple metastases will be extracted separately if possible. If results are not reported by single / multiple subgroup they will be included if they are more than 75% single, included in the sister review of multiple metastases if they are less than 25% single and included in a 'mixed' review if more than 10% of the population has a metastasis which is not described as either single or multiple or if the population is between 25% and 75% single. The following type of cancers are excluded: • small cell lung cancers • germ cell tumours • secondary lymphoma • metastasis from brain tumours or CNS

Field (based on PRISMA-P)	Content
	As above, studies reporting these tumours will be excluded unless the total number of these types of cancers is small (<10% in total) or outcomes for included and excluded cancers are reported separately
Proposed sensitivity/**sub-group analysis**, or meta-regression	• Number of metastases: 2-4 versus >4 • Total volume of metastases: ≤/20 ml > 20 ml (cm^3) • Primary tumour types: ○ non-small cell lung ○ breast ○ melanoma ○ renal ○ other
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be done. In order to ensure accuracy, all results are checked by a Senior Systematic Reviewer and the excluded study list is checked by the committee prior to making recommendations.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. No date limit. A single search will be conducted for management of single, multiple and mixed brain metastases.

Field (based on PRISMA-P)	Content
Identify if an update	Not an update.
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk).
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see Appendix B of the evidence report.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D (clinical evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences

Field (based on PRISMA-P)	Content
	Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO.

Review protocol for review 4c – management of brain metastases with a mixed population

Note that this protocol was not initially included in the scope, however the committee determined that limiting their evidence search to only populations of single or multiple metastases (that is, no populations where some people have a single metastasis and some have multiple

metastases) was too limiting. Therefore this protocol was drafted to give the committee more evidence on which to base their recommendations.

Field (based on PRISMA-P)	Content
Key area in the scope	Managing brain metastases
Actual review question	What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these) for a mixed population of single and multiple brain metastases?
Type of review question	Intervention
Objective of the review	This review question was not included in the scope, but added by the committee during development. The reason for this is that the committee found the evidence on those with only one kind of metastasis (single or multiple) to be limited, but they knew of a number of good quality studies which addressed a population with a mix of single and multiple metastases. Therefore in making their recommendations, the committee were able to make more robust judgements, and make judgements on populations with a number of metastases different from 1 or >1 (for example, 1-3). This should lead to clearer and more applicable recommendations.
Eligibility criteria – **population**/disease/condition/issue/domain	People with an unknown number of brain metastases
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	• Neurosurgery • Radiotherapy: ○ radiosurgery SRS (1 fraction) ○ stereotactic radiotherapy SRT (2-5 fractions) ○ whole brain radiotherapy (WBRT) ○ Hippocampal avoidance WBRT • Chemotherapy or systemic anti-cancer therapy/ treatment

Field (based on PRISMA-P)	Content
	• Combined therapy (any combination of the above) • Best supportive care
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	Any intervention compared to any other intervention

Outcomes and prioritisation	Critical:
	• overall survival.
	• progression-free survival
	  ○ local control (site of metastasis)
	  ○ intracranial control (recurrence elsewhere in the brain)
	• health-related quality of life
	
	Important:
	• cognitive function.
	• neurological function
	  ○ Karnofsky performance status (or WHO or ECOG)
	  ○ Neurological Function Scale
	
	• treatment-related morbidity.
	  ○ radionecrosis
	  ○ oedema
	  ○ postoperative infection
	  ○ stroke
	
	Limited:

Field (based on PRISMA-P)	Content
	• steroid (for example dexamethasone) use (duration and dose)
Eligibility criteria – **study design**	Only published full text papers Systematic reviews RCTs Cohort or observational studies where RCTs are not available No date or size limit
Other **exclusion criteria**	Populations including children <16 included will be considered if the number of children is low (<10%) or the average age of the cohort is high (>40) or results are reported separately for children and adults. Populations with mixed single / multiple metastases will be extracted separately if possible. If results are not reported by single / multiple subgroup they will be included if they are more than 75% single, included in the sister review of multiple metastases if they are less than 25% single and included in a 'mixed' review if more than 10% of the population has a metastasis which is not described as either single or multiple or if the population is between 25% and 75% single. The following type of cancers are excluded: • Small cell lung cancers • Germ cell tumours • Secondary Lymphoma • Metastasis from brain tumours or CNS As above, studies reporting these tumours will be excluded unless the total number of these types of cancers is small (<10% in total) or outcomes for included and excluded cancers are reported separately

Field (based on PRISMA-P)	Content
Proposed sensitivity/**sub-group analysis**, or meta-regression	• Number of metastases: 2-4 versus >4 • Total volume of metastases: ≤/20 ml > 20 ml (cm^3) • Primary tumour types: ○ non-small cell lung ○ breast ○ melanoma ○ renal ○ other
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis was undertaken for this review will not be done. In order to ensure accuracy, all results are checked by a Senior Systematic Reviewer and the excluded study list is checked by the committee prior to making recommendations.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. No date limit A single search will be conducted for management of single, multiple and mixed brain metastases.
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk).
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see Appendix B of the evidence report.

Field (based on PRISMA-P)	Content
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D (clinical evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO.

Review protocol for review 5c – follow-up of metastases

Field (based on PRISMA-P)	Content
Key area in the scope	Follow-up care after treatment for glioma, meningioma or brain metastases
Actual review question	5c What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?
Type of review question	Intervention

Field (based on PRISMA-P)	Content
Objective of the review	To determine what is the most effective follow-up to detect recurrence after treatment of brain metastases
Eligibility criteria – **population**/disease/condition/issue/domain	Adults treated for brain metastases
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Any follow-up protocol including duration and frequency of any tests (e.g., MRI/CT scans)
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	Any other follow-up protocol No follow up (wait until patient reports symptoms of recurrence)
Outcomes and prioritisation	Critical: • cognitive function, • treatment for recurrence • overall survival, • numbers of patients with symptomatic versus asymptomatic presentation Important: • health-related quality of life
Eligibility criteria – **study design**	Only published full text papers Systematic reviews RCTs Comparative observational studies
Other inclusion **exclusion criteria**	We will include papers that have more than 90% of patients who have been treated for brain metastases

Field (based on PRISMA-P)	Content
Proposed sensitivity/**sub-group analysis**, or meta-regression	Adults with: • metastases arising from lung cancer versus breast cancer versus melanoma versus other cancers (for lung cancer: non-small cell versus small cell) • less than or equal to 3 metastases versus more than 3 metastases • surgery versus stereotactic radiosurgery versus whole brain radiotherapy versus combination of these
Selection process – duplicate screening/selection/analysis	Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Dual sifting, quality assessment and data extraction will not be done.
Data management (software)	If pairwise meta-analyses undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	See Appendix B for full list of databases. Date limit: 1990 (CT/MRI not available/comparable to present time before 1990)
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance (NGA-enquiries@rcog.org.uk).
Highlight if amendment to previous protocol	Not applicable.
Search strategy – for one database	For details please see Appendix B of the evidence report
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Supplementary Material D (clinical evidence tables).

Field (based on PRISMA-P)	Content
Data items – define all variables to be collected	For details please see evidence tables in Supplementary Material D.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for randomised studies • Cochrane risk of bias tool for non-randomised studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences Default values will be used of: 0.8 and 1.2 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. No evidence was identified. No explorations of publication bias were therefore undertaken.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale/context – what is known	For details please see the introduction to the evidence review in the full evidence review/guideline.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by [add name of developer] and membership is given in Supplementary Material B in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplementary Material C.
Sources of funding/support	[add name of developer] is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	[add name of developer] is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds [add name of developer] to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered in PROSPERO.

Appendix B – Literature search strategies

Literature search strategy for review 1b - imaging strategy for brain metastases

Systematic reviews and RCTs

Date of initial search: 05/07/2017

Database: Embase 1980 to 2017 Week 27, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 05/09/2017

Database(s): Embase 1980 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Brain Neoplasms/ use ppez
2	exp brain tumor/ use emez
3	exp Cerebral Cortex/ use ppez
4	exp brain cortex/ use emez
5	exp Brain/ use ppez
6	exp brain/ use emez
7	exp Meninges/ use ppez
8	meninx/ use emez
9	or/1-8
10	exp Neoplasm Metastasis/ use ppez
11	metastasis/ use emez
12	10 or 11
13	9 and 12
14	exp Brain Neoplasms/sc use ppez
15	brain metastasis/ use emez
16	meningeal metastasis/ use emez
17	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
18	or/13-17
19	Diagnostic Imaging/ use ppez
20	diagnostic imaging/ use emez
21	exp Neuroimaging/ use ppez
22	exp neuroimaging/ use emez
23	Multimodal Imaging/ use ppez
24	multimodal imaging/ use emez
25	Radionuclide Imaging/ use ppez
26	exp brain scintiscanning/ use emez
27	exp Magnetic Resonance Imaging/ use ppez
28	exp nuclear magnetic resonance imaging/ use emez
29	exp Magnetic Resonance Spectroscopy/ use ppez
30	proton nuclear magnetic resonance/ use emez
31	magnetic resonance.tw.
32	(MRI or MR*1 or NMR*1).tw.

#	Searches
33	(MR adj2 (imag* or neuroimag* or scan* or spectroscop* or elastogra* or examination)).tw.
34	(magnet* adj2 (imag* or neuroimag* or spectroscop* or scan* or elastogra* or examination)).tw.
35	(magneti?ation adj2 imaging).tw.
36	exp Positron-Emission Tomography/ use ppez
37	positron emission tomography/ use emez
38	computer assisted emission tomography/ use emez
39	(PET adj (scan* or imag* or examination)).tw.
40	positron emission tomogra*.tw.
41	(PET or PET-CT or PET MR*1).tw.
42	(advanced adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
43	(structural adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
44	(functional adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
45	exp nuclear magnetic resonance imaging agent/ use emez
46	dynamic contrast.tw.
47	Fluorodeoxyglucose F18/ use ppez
48	fluorodeoxyglucose f 18/ use emez
49	("18F fluorodeoxyglucose" or FDG).tw.
50	Tyrosine/ use ppez
51	"18F fluoro ethyl tyrosine".tw.
52	18F FET.tw.
53	Methionine/ use ppez
54	methionine c 11/ use emez
55	((11C or "carbon 11") adj methionine).tw.
56	MET PET.tw.
57	Gadolinium DTPA/ use ppez
58	gadolinium pentetate/ use emez
59	gadolinium.tw.
60	or/19-59
61	18 and 60
62	limit 61 to english language
63	limit 62 to yr="2000 -Current"
64	Letter/ use ppez
65	letter.pt. or letter/ use emez
66	note.pt.
67	editorial.pt.
68	Editorial/ use ppez
69	News/ use ppez
70	exp Historical Article/ use ppez
71	Anecdotes as Topic/ use ppez
72	Comment/ use ppez
73	Case Report/ use ppez
74	case report/ or case study/ use emez
75	(letter or comment*).ti.
76	or/64-75
77	randomized controlled trial/ use ppez
78	randomized controlled trial/ use emez
79	random*.ti,ab.
80	or/77-79
81	76 not 80
82	animals/ not humans/ use ppez
83	animal/ not human/ use emez
84	nonhuman/ use emez
85	exp Animals, Laboratory/ use ppez
86	exp Animal Experimentation/ use ppez
87	exp Animal Experiment/ use emez
88	exp Experimental Animal/ use emez
89	exp Models, Animal/ use ppez
90	animal model/ use emez
91	exp Rodentia/ use ppez
92	exp Rodent/ use emez
93	(rat or rats or mouse or mice).ti.

#	Searches
94	or/81-93
95	63 not 94
96	Meta-Analysis/
97	Meta-Analysis as Topic/
98	systematic review/
99	meta-analysis/
100	(meta analy* or metanaly* or metaanaly*).ti,ab.
101	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
102	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
103	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
104	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
105	(search* adj4 literature).ab.
106	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
107	cochrane.jw.
108	((pool* or combined) adj2 (data or trials or studies or results)).ab.
109	or/96-97,100,102-107 use ppez
110	or/98-101,103-108 use emez
111	or/109-110
112	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
113	112 use ppez
114	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
115	114 use ppez
116	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
117	116 use emez
118	113 or 115
119	117 or 118
120	111 or 119
121	95 and 120
122	remove duplicates from 121

Observational Studies

Date of initial search: 05/07/2017

Database: Embase 1980 to 2017 Week 27, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 05/09/2017

Database(s): Embase 1980 to 2017 Week 35, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Brain Neoplasms/ use ppez
2	exp brain tumor/ use emez
3	exp Cerebral Cortex/ use ppez
4	exp brain cortex/ use emez
5	exp Brain/ use ppez
6	exp brain/ use emez
7	exp Meninges/ use ppez
8	meninx/ use emez
9	or/1-8

#	Searches
10	exp Neoplasm Metastasis/ use ppez
11	metastasis/ use emez
12	10 or 11
13	9 and 12
14	exp Brain Neoplasms/sc use ppez
15	brain metastasis/ use emez
16	meningeal metastasis/ use emez
17	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
18	or/13-17
19	Diagnostic Imaging/ use ppez
20	diagnostic imaging/ use emez
21	exp Neuroimaging/ use ppez
22	exp neuroimaging/ use emez
23	Multimodal Imaging/ use ppez
24	multimodal imaging/ use emez
25	Radionuclide Imaging/ use ppez
26	exp brain scintiscanning/ use emez
27	exp Magnetic Resonance Imaging/ use ppez
28	exp nuclear magnetic resonance imaging/ use emez
29	exp Magnetic Resonance Spectroscopy/ use ppez
30	proton nuclear magnetic resonance/ use emez
31	magnetic resonance.tw.
32	(MRI or MR*1 or NMR*1).tw.
33	(MR adj2 (imag* or neuroimag* or scan* or spectroscop* or elastogra* or examination)).tw.
34	(magnet* adj2 (imag* or neuroimag* or spectroscop* or scan* or elastogra* or examination)).tw.
35	(magneti?ation adj2 imaging).tw.
36	exp Positron-Emission Tomography/ use ppez
37	positron emission tomography/ use emez
38	computer assisted emission tomography/ use emez
39	(PET adj (scan* or imag* or examination)).tw.
40	positron emission tomogra*.tw.
41	(PET or PET-CT or PET MR*1).tw.
42	(advanced adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
43	(structural adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
44	(functional adj2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*)).tw.
45	exp nuclear magnetic resonance imaging agent/ use emez
46	dynamic contrast.tw.
47	Fluorodeoxyglucose F18/ use ppez
48	fluorodeoxyglucose f 18/ use emez
49	("18F fluorodeoxyglucose" or FDG).tw.
50	Tyrosine/ use ppez
51	"18F fluoro ethyl tyrosine".tw.
52	18F FET.tw.
53	Methionine/ use ppez
54	methionine c 11/ use emez
55	((11C or "carbon 11") adj methionine).tw.
56	MET PET.tw.
57	Gadolinium DTPA/ use ppez
58	gadolinium pentetate/ use emez
59	gadolinium.tw.
60	or/19-59
61	18 and 60
62	limit 61 to english language
63	limit 62 to yr="2000 -Current"
64	Letter/ use ppez
65	letter.pt. or letter/ use emez
66	note.pt.
67	editorial.pt.
68	Editorial/ use ppez

#	Searches
69	News/ use ppez
70	exp Historical Article/ use ppez
71	Anecdotes as Topic/ use ppez
72	Comment/ use ppez
73	Case Report/ use ppez
74	case report/ or case study/ use emez
75	(letter or comment*).ti.
76	or/64-75
77	randomized controlled trial/ use ppez
78	randomized controlled trial/ use emez
79	random*.ti,ab.
80	or/77-79
81	76 not 80
82	animals/ not humans/ use ppez
83	animal/ not human/ use emez
84	nonhuman/ use emez
85	exp Animals, Laboratory/ use ppez
86	exp Animal Experimentation/ use ppez
87	exp Animal Experiment/ use emez
88	exp Experimental Animal/ use emez
89	exp Models, Animal/ use ppez
90	animal model/ use emez
91	exp Rodentia/ use ppez
92	exp Rodent/ use emez
93	(rat or rats or mouse or mice).ti.
94	or/81-93
95	63 not 94
96	Epidemiologic Studies/
97	Case Control Studies/
98	Retrospective Studies/
99	Cohort Studies/
100	Longitudinal Studies/
101	Follow-Up Studies/
102	Prospective Studies/
103	Cross-Sectional Studies/
104	or/96-103 use ppez
105	clinical study/
106	case control study/
107	family study/
108	longitudinal study/
109	retrospective study/
110	prospective study/
111	cohort analysis/
112	or/105-111 use emez
113	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
114	104 or 112 or 113
115	95 and 114
116	remove duplicates from 115

Date of initial search: 05/07/2017

Database: The Cochrane Library, Issue 7 of 12, July 2017

Date of re-run: 7th September 2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Brain Neoplasms] explode all trees
#2	MeSH descriptor: [Cerebral Cortex] explode all trees
#3	MeSH descriptor: [Brain] explode all trees
#4	MeSH descriptor: [Meninges] explode all trees
#5	{or #1-#4}
#6	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#7	#5 and #6
#8	MeSH descriptor: [Brain Neoplasms] explode all trees and with qualifier(s): [Secondary - SC]
#9	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) near/3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*))
#10	{or #7-#9}
#11	MeSH descriptor: [Diagnostic Imaging] this term only
#12	MeSH descriptor: [Neuroimaging] explode all trees
#13	MeSH descriptor: [Multimodal Imaging] explode all trees
#14	MeSH descriptor: [Radionuclide Imaging] this term only
#15	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#16	MeSH descriptor: [Magnetic Resonance Spectroscopy] explode all trees
#17	(MRI or MR*1 or NMR*1)
#18	(MR near/2 (imag* or neuroimag* or scan* or spectroscop* or elastogra* or examination))
#19	(magnet* near/2 (imag* or neuroimag* or spectroscop* or scan* or elastogra* or examination))
#20	(magneti?ation near/2 imaging)
#21	MeSH descriptor: [Positron-Emission Tomography] explode all trees
#22	(PET near (scan* or imag* or examination))
#23	positron emission tomogra*
#24	(PET or PET-CT or PETCT or PET MR*1)
#25	(advanced near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#26	(structural near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#27	(functional near/2 (imag* or spectroscop* or neuroimag* or scan* or MR* or NMR*))
#28	dynamic contrast
#29	MeSH descriptor: [Fluorodeoxyglucose F18] explode all trees
#30	("18F fluorodeoxyglucose" or FDG)
#31	MeSH descriptor: [Tyrosine] this term only
#32	"18F fluoro ethyl tyrosine"
#33	18F FET
#34	MeSH descriptor: [Methionine] this term only
#35	((11C or "carbon 11") and methionine)
#36	MET PET
#37	MeSH descriptor: [Gadolinium DTPA] this term only
#38	gadolinium
#39	{or #11-#38}
#40	#10 and #39 Publication Year from 2000 to 2017

Literature search strategy for review 4a – management of single metastases

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations.

Systematic reviews and RCTs

Date of initial search: 04/10/2016

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Brain Neoplasms/
2	exp Cerebral Cortex/
3	exp Brain/
4	exp Meninges/
5	or/1-4
6	exp Neoplasm Metastasis/
7	5 and 6
8	exp Brain Neoplasms/sc
9	7 or 8
10	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
11	9 or 10
12	Neurosurgery/
13	exp Neurosurgical Procedures/
14	Surgical Procedures, Operative/
15	Metastasectomy/
16	exp Stereotaxic Techniques/
17	((brain or neuro* or intracereb* or intracrani* or crani*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops*)).tw.
18	(neurosurg* or craniotom* or craniectom* or metastasectom*).tw.
19	((intra-operat* or intraoperat*) adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
20	or/12-19
21	exp Radiotherapy/
22	radiotherapy.fs.
23	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap*).tw.
24	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT).tw.
25	Radiation Oncology/
26	(chemoradiotherap* or chemo-radiat* or chemo-irradiat*).tw.
27	or/21-26
28	exp Antineoplastic Agents/
29	antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/
30	exp Antibodies, Monoclonal/ad, tu
31	Cancer Vaccines/ad, tu
32	drug therapy.fs.
33	chemotherap*.tw.
34	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
35	Bevacizumab/
36	(bevacizumab or avastin).tw.
37	Carboplatin/
38	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
39	Carmustine/
40	(bcnu or bicnu or carmustine or fivb or gliadel wafer? or nitrosurea or nitrumon).tw.
41	cilengitide.tw.
42	(DCVAX or (dentric cell? adj (vaccin* or immnuotherap*))).tw.
43	Ifosfamide/
44	(holoxan or ifosamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.

#	Searches
45	(Ipilimumab or yervoy).tw.
46	(irinotecan or campto or camptosar).tw.
47	Lomustine/
48	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
49	Methotrexate/
50	(amethopterin or methotrexate or mexate).tw.
51	(nivolumab or opdivo).tw.
52	Procarbazine/
53	(matulan or natulan or procarbazine).tw.
54	(rindopepimut or rintega).tw.
55	Tamoxifen/
56	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
57	(temozolomide or temodal or temodar).tw.
58	Vinblastine/
59	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
60	Vincristine/
61	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
62	or/28-61
63	exp Combined Modality Therapy/
64	((combin* or concomitant) adj2 (therap* or treatment* or regimen* or protocol*)).tw.
65	63 or 64
66	Watchful Waiting/
67	Observation/
68	watchful wait*.tw.
69	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
70	(best supportive care or BSC).tw.
71	or/66-70
72	20 or 27 or 62 or 65 or 71
73	11 and 72
74	limit 73 to yr="1990 -Current"
75	limit 74 to english language
76	Meta-Analysis/
77	Meta-Analysis as Topic/
78	(meta analy* or metanaly* or metaanaly*).ti,ab.
79	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
80	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
81	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
82	(search* adj4 literature).ab.
83	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
84	cochrane.jw.
85	or/76-84
86	randomized controlled trial.pt.
87	controlled clinical trial.pt.
88	pragmatic clinical trial.pt.
89	randomi#ed.ab.
90	placebo.ab.
91	drug therapy.fs.
92	randomly.ab.
93	trial.ab.
94	groups.ab.
95	or/86-94
96	Clinical Trials as topic.sh.
97	trial.ti.
98	or/86-90,92,96-97
99	85 or 98
100	75 and 99
101	Letter/
102	Editorial/
103	News/
104	exp Historical Article/

#	Searches
105	Anecdotes as Topic/
106	Comment/
107	Case Report/
108	(letter or comment* or abstracts).ti.
109	or/101-108
110	Randomized Controlled Trial/ or random*.ti,ab.
111	109 not 110
112	Animals/ not Humans/
113	exp Animals, Laboratory/
114	exp Animal Experimentation/
115	exp Models, Animal/
116	exp Rodentia/
117	(rat or rats or mouse or mice).ti.
118	or/111-117
119	100 not 118

Systematic reviews and RCTs

Date of initial search: 04/10/2016

Database: Embase 1980 to 2016 Week 40

Date of re-run: 07/09/2017
Database: Embase 1980 to 2016 Week 35

#	Searches
1	exp brain tumor/
2	exp brain cortex/
3	exp brain/
4	meninx/
5	or/1-4
6	metastasis/
7	5 and 6
8	brain metastasis/
9	meningeal metastasis/
10	8 or 9
11	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
12	7 or 10 or 11
13	exp neurosurgery/
14	exp cancer surgery/
15	metastasis resection/
16	exp stereotactic procedure/
17	((brain or neuro* or intracereb* or intracrani* or crani*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops*)).tw.
18	(neurosurg* or craniotom* or craniectom* or metastasectom*).tw.
19	((intra-operat* or intraoperat*) adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
20	or/13-19
21	exp radiotherapy/
22	radiotherapy.fs.
23	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap*).tw.
24	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT).tw.
25	(chemoradiotherap* or chemo-radiat* or chemo-irradiat*).tw.
26	or/21-25
27	exp antineoplastic agent/

#	Searches
28	exp chemotherapy/
29	monoclonal antibody/ad, dt [Drug Administration, Drug Therapy]
30	cancer vaccine/ad, dt [Drug Administration, Drug Therapy]
31	drug therapy.fs.
32	chemotherap*.tw.
33	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
34	bevacizumab/
35	(bevacizumab or avastin or altusan).tw.
36	carboplatin/
37	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
38	carmustine/
39	(bcnu or bicnu or carmustine or fivb or gliadel wafer? or nitrosurea or nitrumon).tw.
40	cilengitide/
41	cilengitide.tw.
42	dendritic cell vaccine/
43	(DCVAX or (dentri* cell? adj (vaccin* or immnuotherap*))).tw.
44	ifosfamide/
45	(holoxan or ifosamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
46	ipilimumab/
47	(Ipilimumab or yervoy).tw.
48	irinotecan/
49	(Irinotecan or campto or camptosar).tw.
50	lomustine/
51	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
52	methotrexate/
53	(amethopterin or methotrexate or mexate).tw.
54	nivolumab/
55	(Nivolumab or opdivo).tw.
56	procarbazine/
57	(matulan or natulan or procarbazine).tw.
58	rindopepimut/
59	(rindopepimut or rintega).tw.
60	tamoxifen/
61	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
62	temozolomide/
63	(temozolomide or temodal or temodar).tw.
64	vinblastine/
65	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
66	vincristine/
67	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
68	or/27-67
69	multimodality cancer therapy/
70	((combin* or concomitant) adj2 (therap* or treatment* or regimen* or protocol*)).tw.
71	69 or 70
72	watchful waiting/
73	conservative treatment/
74	clinical observation/
75	watchful wait*.tw.
76	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
77	(best supportive care or BSC).tw.
78	or/72-77
79	20 or 26 or 68 or 71 or 78
80	12 and 79
81	limit 80 to yr="1990 -Current"
82	limit 81 to english language
83	random*.ti,ab.
84	factorial*.ti,ab.
85	(crossover* or cross over*).ti,ab.
86	((doubl* or singl*) adj blind*).ti,ab.

#	Searches
87	(assign* or allocat* or volunteer* or placebo*).ti,ab.
88	crossover procedure/
89	single blind procedure/
90	randomized controlled trial/
91	double blind procedure/
92	or/83-91
93	systematic review/
94	meta-analysis/
95	(meta analy* or metanaly* or metaanaly*).ti,ab.
96	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
97	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
98	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
99	(search* adj4 literature).ab.
100	or/93-99
101	92 or 100
102	82 and 101
103	letter.pt. or letter/
104	note.pt.
105	editorial.pt.
106	case report/ or case study/
107	(letter or comment*).ti.
108	or/103-107
109	randomized controlled trial/ or random*.ti,ab.
110	108 not 109
111	animal/ not human/
112	nonhuman/
113	exp Animal Experiment/
114	exp Experimental Animal/
115	animal model/
116	exp Rodent/
117	(rat or rats or mouse or mice).ti.
118	or/110-117
119	102 not 118

Observational studies

Date of initial search: 04/10/2016

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Brain Neoplasms/
2	exp Cerebral Cortex/
3	exp Brain/
4	exp Meninges/
5	or/1-4
6	exp Neoplasm Metastasis/
7	5 and 6
8	exp Brain Neoplasms/sc
9	7 or 8

#	Searches
10	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
11	9 or 10
12	Neurosurgery/
13	exp Neurosurgical Procedures/
14	Surgical Procedures, Operative/
15	Metastasectomy/
16	exp Stereotaxic Techniques/
17	((brain or neuro* or intracereb* or intracrani* or crani*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops*)).tw.
18	(neurosurg* or craniotom* or craniectom* or metastasectom*).tw.
19	((intra-operat* or intraoperat*) adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
20	or/12-19
21	exp Radiotherapy/
22	radiotherapy.fs.
23	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap*).tw.
24	(WBRT or WBI-IMRT or HA-WBRT or IMRT or LINAC or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT).tw.
25	Radiation Oncology/
26	(chemoradiotherap* or chemo-radiat* or chemo-irradiat*).tw.
27	or/21-26
28	exp Antineoplastic Agents/
29	antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/
30	exp Antibodies, Monoclonal/ad, tu
31	Cancer Vaccines/ad, tu
32	drug therapy.fs.
33	chemotherap*.tw.
34	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
35	Bevacizumab/
36	(bevacizumab or avastin).tw.
37	Carboplatin/
38	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
39	Carmustine/
40	(bcnu or bicnu or carmustine or fivb or gliadel wafer? or nitrosurea or nitrumon).tw.
41	cilengitide.tw.
42	(DCVAX or (dentric cell? adj (vaccin* or immnuotherap*))).tw.
43	Ifosfamide/
44	(holoxan or ifosamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
45	(Ipilimumab or yervoy).tw.
46	(irinotecan or campto or camptosar).tw.
47	Lomustine/
48	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
49	Methotrexate/
50	(amethopterin or methotrexate or mexate).tw.
51	(nivolumab or opdivo).tw.
52	Procarbazine/
53	(matulan or natulan or procarbazine).tw.
54	(rindopepimut or rintega).tw.
55	Tamoxifen/
56	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
57	(temozolomide or temodal or temodar).tw.
58	Vinblastine/
59	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
60	Vincristine/
61	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
62	or/28-61
63	exp Combined Modality Therapy/

#	Searches
64	((combin* or concomitant) adj2 (therap* or treatment* or regimen* or protocol*)).tw.
65	63 or 64
66	Watchful Waiting/
67	Observation/
68	watchful wait*.tw.
69	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
70	(best supportive care or BSC).tw.
71	or/66-70
72	20 or 27 or 62 or 65 or 71
73	11 and 72
74	limit 73 to yr="1990 -Current"
75	limit 74 to english language
76	Epidemiologic Studies/
77	Case Control Studies/
78	Retrospective Studies/
79	Cohort Studies/
80	Longitudinal Studies/
81	Follow-Up Studies/
82	Prospective Studies/
83	Cross-Sectional Studies/
84	((retrospective$ or cohort$ or longitudinal or follow?up or prospective or cross section$) adj3 (stud$ or research or analys$)).ti.
85	or/76-84
86	75 and 85
87	Letter/
88	Editorial/
89	News/
90	exp Historical Article/
91	Anecdotes as Topic/
92	Comment/
93	Case Report/
94	(letter or comment* or abstracts).ti.
95	or/87-94
96	Randomized Controlled Trial/ or random*.ti,ab.
97	95 not 96
98	Animals/ not Humans/
99	exp Animals, Laboratory/
100	exp Animal Experimentation/
101	exp Models, Animal/
102	exp Rodentia/
103	(rat or rats or mouse or mice).ti.
104	or/97-103
105	86 not 104

Observational studies

Date of initial search: 04/10/2016

Database: Embase 1980 to 2016 Week 40

Date of re-run: 07/09/2017
Database: Embase 1980 to 2016 Week 35

#	Searches
1	exp brain tumor/
2	exp brain cortex/
3	exp brain/
4	meninx/

#	Searches
5	or/1-4
6	metastasis/
7	5 and 6
8	brain metastasis/
9	meningeal metastasis/
10	8 or 9
11	((brain or cereb* or intracereb* or intracrani* or mening* or brainstem*) adj3 (metasta* or micromet* or macromet* or oligomet* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
12	7 or 10 or 11
13	exp neurosurgery/
14	exp cancer surgery/
15	metastasis resection/
16	exp stereotactic procedure/
17	((brain or neuro* or intracereb* or intracrani* or crani*) adj2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis* or ablat* or biops*)).tw.
18	(neurosurg* or craniotom* or craniectom* or metastasectom*).tw.
19	((intra-operat* or intraoperat*) adj3 (technolog* or modalit* or procedur* or technique* or method*)).tw.
20	or/13-19
21	exp radiotherapy/
22	radiotherapy.fs.
23	(radiotherap* or radiat* or irradiat* or tomotherap* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap*).tw.
24	(WBRT or WBI-IMRT or HA-WBRT or LINAC or IMRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT).tw.
25	(chemoradiotherap* or chemo-radiat* or chemo-irradiat*).tw.
26	or/21-25
27	exp antineoplastic agent/
28	exp chemotherapy/
29	monoclonal antibody/ad, dt [Drug Administration, Drug Therapy]
30	cancer vaccine/ad, dt [Drug Administration, Drug Therapy]
31	drug therapy.fs.
32	chemotherap*.tw.
33	((anti cancer or systemic or anti neoplas* or cytotoxi*) adj2 (therap* or treatment* or regimen* or protocol* or drug* or agent*)).tw.
34	bevacizumab/
35	(bevacizumab or avastin or altusan).tw.
36	carboplatin/
37	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo).tw.
38	carmustine/
39	(bcnu or bicnu or carmustine or fivb or gliadel wafer? or nitrosurea or nitrumon).tw.
40	cilengitide/
41	cilengitide.tw.
42	dendritic cell vaccine/
43	(DCVAX or (dentri* cell? adj (vaccin* or immnuotherap*))).tw.
44	ifosfamide/
45	(holoxan or ifosamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide).tw.
46	ipilimumab/
47	(Ipilimumab or yervoy).tw.
48	irinotecan/
49	(Irinotecan or campto or camptosar).tw.
50	lomustine/
51	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037).tw.
52	methotrexate/
53	(amethopterin or methotrexate or mexate).tw.
54	nivolumab/
55	(Nivolumab or opdivo).tw.
56	procarbazine/
57	(matulan or natulan or procarbazine).tw.
58	rindopepimut/

#	Searches
59	(rindopepimut or rintega).tw.
60	tamoxifen/
61	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium).tw.
62	temozolomide/
63	(temozolomide or temodal or temodar).tw.
64	vinblastine/
65	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine).tw.
66	vincristine/
67	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec).tw.
68	or/27-67
69	multimodality cancer therapy/
70	((combin* or concomitant) adj2 (therap* or treatment* or regimen* or protocol*)).tw.
71	69 or 70
72	watchful waiting/
73	conservative treatment/
74	clinical observation/
75	watchful wait*.tw.
76	((active or expect* or symptom* or watch*) adj2 (manag* or monitor* or surveill* or observ* or control*)).tw.
77	(best supportive care or BSC).tw.
78	or/72-77
79	20 or 26 or 68 or 71 or 78
80	12 and 79
81	limit 80 to yr="1990 -Current"
82	limit 81 to english language
83	Clinical study/
84	Case control study/
85	family study/
86	longitudinal study/
87	retrospective study/
88	prospective study/
89	cohort analysis/
90	((retrospective* or cohort* or longitudinal or follow?up or prospective or cross section* or observation* or epidemiolog*) adj3 (stud* or research or analys*)).ti.
91	or/83-90
92	82 and 91
93	letter.pt. or letter/
94	note.pt.
95	editorial.pt.
96	case report/ or case study/
97	(letter or comment*).ti.
98	or/93-97
99	randomized controlled trial/ or random*.ti,ab.
100	98 not 99
101	animal/ not human/
102	nonhuman/
103	exp Animal Experiment/
104	exp Experimental Animal/
105	animal model/
106	exp Rodent/
107	(rat or rats or mouse or mice).ti.
108	or/100-107
109	92 not 108

Date of initial search: 04/10/2016

Database: The Cochrane Library, Issue 10 of 12, October 2016

Date of re-run: 07/09/2017

Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Brain Neoplasms] explode all trees
#2	MeSH descriptor: [Cerebral Cortex] explode all trees
#3	MeSH descriptor: [Brain] explode all trees
#4	MeSH descriptor: [Meninges] explode all trees
#5	{or #1-#4}
#6	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#7	#5 and #6
#8	MeSH descriptor: [Brain Neoplasms] this term only and with qualifier(s): [Secondary - SC]
#9	#7 or #8
#10	((brain or cereb* or intracranial or mening* or brainstem*) near/3 (metasta* or micrometa* or macrometa* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*))
#11	#9 or #10
#12	MeSH descriptor: [Neurosurgery] explode all trees
#13	MeSH descriptor: [Neurosurgical Procedures] explode all trees
#14	MeSH descriptor: [Surgical Procedures, Operative] explode all trees
#15	MeSH descriptor: [Metastasectomy] explode all trees
#16	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#17	((brain or neuro* or intracranial or crani*) near/2 (surg* or microsurg* or manipulat* or procedur* or operat* or resect* or debulk* or excis*))
#18	(neurosurg* or craniotom* or metastasectom*)
#19	((intra-operat* or intraoperat*) near/3 (technolog* or modalit* or procedur* or technique* or method?))
#20	{or #12-#19}
#21	MeSH descriptor: [Radiotherapy] explode all trees
#22	(radiotherap* or radiat* or irradiat* or radiosurg* or brachytherap* or fractionat* or hyperfraction* or hypofraction* or gamma knife or cyber knife or cyberknife or xknife or arc therap*)
#23	(WBRT or WBI-IMRT or HA-WBRT or IMRT or XRT or XBT or SRS or SRT or VMAT or 3DCRT or 3D CRT or CRT)
#24	MeSH descriptor: [Radiation Oncology] explode all trees
#25	(chemoradiotherap* or chemo-radiat* or chemo-irradiat*)
#26	{or #21-#25}
#27	MeSH descriptor: [Antineoplastic Agents] explode all trees
#28	MeSH descriptor: [Antineoplastic Protocols] explode all trees
#29	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
#30	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#31	MeSH descriptor: [Cancer Vaccines] explode all trees
#32	chemotherap*
#33	((anti cancer or systemic or anti neoplas* or cytotoxi*) near/2 (therap* or treatment* or regimen* or protocol* or drug* or agent*))
#34	MeSH descriptor: [Bevacizumab] explode all trees
#35	(bevacizumab or avastin)
#36	MeSH descriptor: [Carboplatin] explode all trees
#37	(blastocarb or carboplatin or carbosin or carbotec or cbdca or ercar or jm8 or nealorin or neocarbo or nsc24120 or paraplatin* or platinwas or ribocarbo)
#38	MeSH descriptor: [Carmustine] explode all trees
#39	(bcnu or bicnu or carmustine or fivb or gliadel wafer? or nitrosurea or nitrumon)
#40	cilengitide
#41	(DCVAX or (dentri* cell? next (vaccin* or immnuotherap*)))
#42	MeSH descriptor: [Ifosfamide] explode all trees
#43	(holoxan or ifosamide or ifosphamide or iso-endoxan or isofosfamide or isophosphamide)
#44	(Ipilimumab or yervoy)
#45	(irinotecan or campto or camptosar)
#46	MeSH descriptor: [Lomustine] explode all trees
#47	(belustine or ccnu or cecenu or ceenu or lomustine or nsc79037)
#48	MeSH descriptor: [Methotrexate] explode all trees
#49	(amethopterin or methotrexate or mexate)
#50	(nivolumab or opdivo)
#51	MeSH descriptor: [Procarbazine] explode all trees
#52	(matulan or natulan or procarbazine)
#53	(rindopepimut or rintega)
#54	MeSH descriptor: [Tamoxifen] explode all trees

ID	Search
#55	(nolvadex or novaldex or soltamox or tamoxifen or tomaxithen or zitazonium)
#56	(temozolomide or temodal or temodar)
#57	MeSH descriptor: [Vinblastine] explode all trees
#58	(lemblastine or velban or velbe or vinblastin* or vincaleukoblastine)
#59	MeSH descriptor: [Vincristine] explode all trees
#60	(citomid or farmistin or leucocristine or oncovin? or onkocristin or vincasar or vincristin? or vincrisul or vintec)
#61	{or #27-#60}
#62	MeSH descriptor: [Combined Modality Therapy] explode all trees
#63	((combin* or concomitant) near/2 (therap* or treatment* or regimen* or protocol*))
#64	#62 or #63
#65	MeSH descriptor: [Watchful Waiting] explode all trees
#66	MeSH descriptor: [Observation] explode all trees
#67	watchful wait*
#68	((active or expect* or symptom* or watch*) near/2 (manag* or monitor* or surveill* or observ* or control*))
#69	(best supportive care or BSC)
#70	{or #65-#69}
#71	{or #20, #26, #61, #64, #70}
#72	#11 and #71 Publication Year from 1990 to 2016

Literature search strategy for review 4b – management of multiple metastases

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations.

Literature search strategy for review 4c – management of brain metastases with a mixed population

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations.

Literature search strategy for review 5c – follow-up of metastases

Date of initial search: 22/03/2017

Database: Embase 1974 to 2017 March 21, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of re-run: 07/09/2017

Database: Embase 1980 to 2017 Week 36, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	exp Glioma/ use ppez
2	exp Glioma/ use oemezd
3	exp Astrocytoma/ use ppez
4	exp Astrocytoma/ use oemezd
5	Oligodendroglioma/ use ppez
6	exp Glioblastoma/ use ppez
7	(glioma* or glioblastoma* or GBM or gliosarcoma* or astrocytoma* or oligoastrocytoma* or oligodendroglioma* or oligo?astrocytoma* or xanthoastrocytoma*).tw.
8	or/1-7
9	Meningioma/ use ppez
10	Meningeal Neoplasms/ use ppez
11	exp Meningioma/ use oemezd
12	meningioma*.tw.
13	(mening* adj3 (neoplas* or cancer* or carcin* or tumo* or malign* or h?emangiopericytoma* or h?emangioblastoma*)).tw.
14	or/9-13
15	exp Brain Neoplasms/ use ppez
16	exp Brain Tumor/ use oemezd
17	exp Cerebral Cortex/ use ppez
18	exp Brain Cortex/ use oemezd
19	exp Brain/ use ppez
20	exp Brain/ use oemezd
21	exp Meninges/ use ppez
22	Meninx/ use oemezd
23	or/15-22

#	Searches
24	exp Neoplasm Metastasis/ use ppez
25	metastasis/ use oemezd
26	24 or 25
27	23 and 26
28	exp Brain Neoplasms/sc use ppez
29	Brain Metastasis/ use oemezd
30	Meningeal Metastasis/ use oemezd
31	or/28-30
32	27 or 31
33	((brain or cereb* or intracranial or mening* or brainstem*) adj3 (metasta* or micrometa* or macrometa* or spread* or carcinomatosis or carcinosis or secondar* or seeding or seeded or disseminat* or migrat*)).tw.
34	32 or 33
35	8 or 14 or 34
36	exp Recurrence/ use ppez
37	Neoplasm Recurrence, Local/ use ppez
38	Disease Progression/ use ppez
39	cancer recurrence/ use oemezd
40	recurrent disease/ use oemezd
41	tumor recurrence/ use oemezd
42	recurr*.ti.
43	or/36-42
44	35 and 43
45	exp Aftercare/ use ppez
46	exp aftercare/ use oemezd
47	(aftercare or "after care" or after-care or follow-up or "follow up" or followup or surveillance).tw.
48	(after treatment or after-treatment or posttreatment or post treatment or post-treatment or post-therap* or post therap*).ti,ab.
49	((post-surg* or post surg* or post-operat* or postoperat* or post operat*) adj1 (evaluat* or monitor* or care)).tw.
50	(post-hospital* or post hospital* or posthospital* or after hospital* or follow* hospital*).ti,ab.
51	disease surveillance/ use oemezd
52	periodic medical examination/ use oemezd
53	"medical record review"/ use oemezd
54	exp patient monitoring/ use oemezd
55	(re-examin* or reexamin or monitor* or periodic examin* or regular examin* or checkup* or check-up* or check up*).ti,ab.
56	follow*.ti.
57	or/45-56
58	44 and 57
59	limit 58 to english language
60	limit 59 to yr="1990 -Current"
61	Letter/ use ppez
62	letter.pt. or letter/ use oemezd
63	note.pt.
64	editorial.pt.
65	Editorial/ use ppez
66	News/ use ppez
67	exp Historical Article/ use ppez
68	Anecdotes as Topic/ use ppez
69	Comment/ use ppez
70	Case Report/ use ppez
71	case report/ or case study/ use oemezd
72	(letter or comment*).ti.
73	or/61-72
74	randomized controlled trial/ use ppez
75	randomized controlled trial/ use oemezd
76	random*.ti,ab.
77	or/74-76
78	73 not 77
79	animals/ not humans/ use ppez
80	animal/ not human/ use oemezd
81	nonhuman/ use oemezd

#	Searches
82	exp Animals, Laboratory/ use ppez
83	exp Animal Experimentation/ use ppez
84	exp Animal Experiment/ use oemezd
85	exp Experimental Animal/ use oemezd
86	exp Models, Animal/ use ppez
87	animal model/ use oemezd
88	exp Rodentia/ use ppez
89	exp Rodent/ use oemezd
90	(rat or rats or mouse or mice).ti.
91	or/78-90
92	60 not 91
93	Meta-Analysis/
94	Meta-Analysis as Topic/
95	systematic review/
96	meta-analysis/
97	(meta analy* or metanaly* or metaanaly*).ti,ab.
98	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
99	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
100	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
101	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
102	(search* adj4 literature).ab.
103	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
104	cochrane.jw.
105	((pool* or combined) adj2 (data or trials or studies or results)).ab.
106	or/93-94,97,99-104 use ppez
107	or/95-98,100-105 use oemezd
108	or/106-107
109	clinical Trials as topic.sh. or (controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or (placebo or randomi#ed or randomly).ab. or trial.ti.
110	109 use ppez
111	(controlled clinical trial or pragmatic clinical trial or randomized controlled trial).pt. or drug therapy.fs. or (groups or placebo or randomi#ed or randomly or trial).ab.
112	111 use ppez
113	crossover procedure/ or double blind procedure/ or randomized controlled trial/ or single blind procedure/ or (assign* or allocat* or crossover* or cross over* or ((doubl* or singl*) adj blind*) or factorial* or placebo* or random* or volunteer*).ti,ab.
114	113 use oemezd
115	110 or 112
116	112 or 114
117	Cohort Studies/ or Longitudinal Studies/ or Follow-Up Studies/ or Prospective Studies/ or Comparative Study/
118	117 use ppez
119	cohort analysis/ or longitudinal study/ or follow up/ or prospective study/ or comparative study/
120	119 use oemezd
121	((cohort* or follow-up or follow?up or inciden* or longitudinal or prospective) adj1 (stud* or research or analys*)).tw.
122	118 or 120 or 121
123	108 or 115 or 122
124	92 and 123
125	remove duplicates from 124

Date of initial search: 22/03/2017

Database: The Cochrane Library, Issue 3 of 12, March 2017

Date of re-run: 07/09/2017

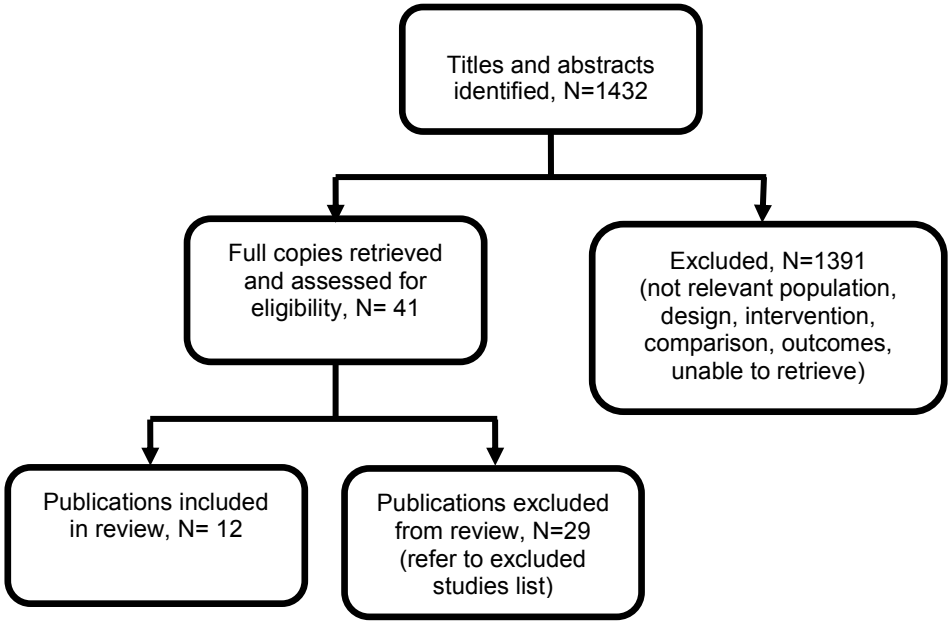
Database: The Cochrane Library, Issue 9 of 12, September 2017

ID	Search
#1	MeSH descriptor: [Glioma] explode all trees
#2	(glioma* or glioblastoma* or gliosarcoma* or astrocytoma* or astroblastoma* or oligodendroglioma* or oligodendrocytoma* or oligoastrocytoma* or GBM)
#3	(glial near/3 (neoplas* or cancer* or tumo* or carcin* or malign* or metasta*))
#4	{or #1-#3}
#5	MeSH descriptor: [Meningioma] explode all trees
#6	MeSH descriptor: [Meningeal Neoplasms] explode all trees
#7	meningioma*
#8	(mening* near/3 (neoplas* or cancer* or carcin* or tumo* or malign* or metasta*))
#9	{or #5-#8}
#10	MeSH descriptor: [Neoplasm Metastasis] explode all trees
#11	MeSH descriptor: [Brain Neoplasms] explode all trees
#12	MeSH descriptor: [Brain] explode all trees
#13	#11 or #12
#14	#10 and #13
#15	((brain or cereb* or intracranial or mening*) near/3 (metasta* or micometasta* or spread* or involvement or carcinosis or secondar*))
#16	#14 or #15
#17	#4 or #9 or #16
#18	MeSH descriptor: [Recurrence] explode all trees
#19	MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
#20	recurr*
#21	{or #18-#20}
#22	#17 and #21
#23	MeSH descriptor: [Aftercare] explode all trees
#24	(aftercare or "after care" or after-care or follow-up or "follow up" or followup or surveillance)
#25	("after treatment*" or after-treatment* or posttreatment* or "post treatment*" or post-treatment* or post-therap* or "post therap*")
#26	((post-surg* or "post surg*" or post-operat* or postoperat* or "post operat*") adj1 (evaluat* or monitor* or care))
#27	(post-hospital* or "post hospital*" or posthospital* or "after hospital*" or "follow* hospital*")
#28	{or #23-#27}
#29	#22 and #28 Publication Year from 1990 to 2017

Appendix C – Clinical evidence study selection

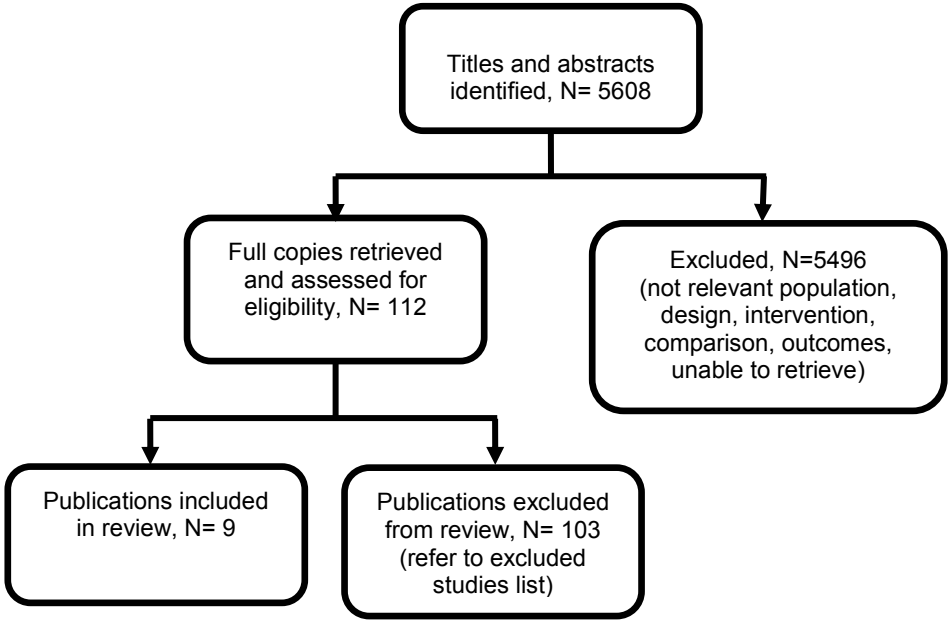
PRISMA diagram for review 1b - imaging strategy for brain metastases

Figure 1: Flow diagram of clinical article selection for review 1b - imaging strategy for brain metastases



PRISMA diagram for review 4a – management of single metastases

Figure 2: Flow diagram of clinical article selection for reviews 4a, 4b and 4c – management of any number of metastases (these questions were searched together before being reviewed separately)


Titles and abstracts identified, N= 5608
Full copies retrieved and assessed for eligibility, N= 112
Excluded, N=5496 (not relevant population, design, intervention, comparison, outcomes, unable to retrieve)
Publications included in review, N= 9
Publications excluded from review, N= 103 (refer to excluded studies list)

PRISMA diagram for review 4b – management of multiple metastases

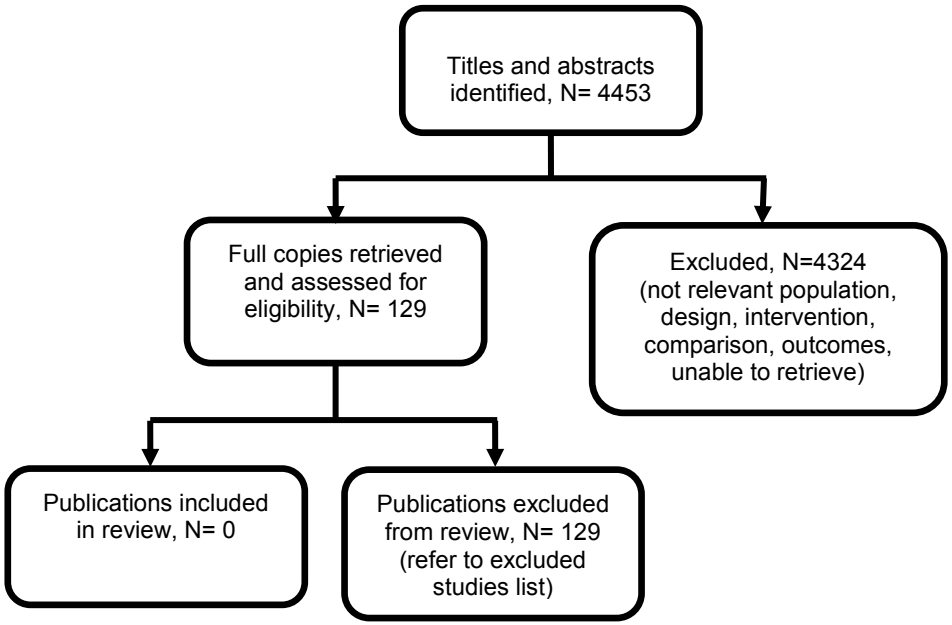
A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations..

PRISMA diagram for review 4c – management of brain metastases with a mixed population

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations.

PRISMA diagram for review 5c – follow-up of metastases

Figure 3: Flow diagram of clinical article selection for follow up after treatment for glioma, meningioma and brain metastases reviews (the searches for all three reviews were conducted as one search)


Titles and abstracts identified, N= 4453
Full copies retrieved and assessed for eligibility, N= 129
Excluded, N=4324 (not relevant population, design, intervention, comparison, outcomes, unable to retrieve)
Publications included in review, N= 0
Publications excluded from review, N= 129 (refer to excluded studies list)

Appendix D – Clinical evidence tables

See Supplementary Material D.

Appendix E – Forest plots

Forest plots for review 1b - imaging strategy for brain metastases

Not applicable - no evidence was identified.

Forest plots for review 4a – management of single metastases

Figure 4: WBRT+ surgery versus WBRT: deaths within 30 days of surgery

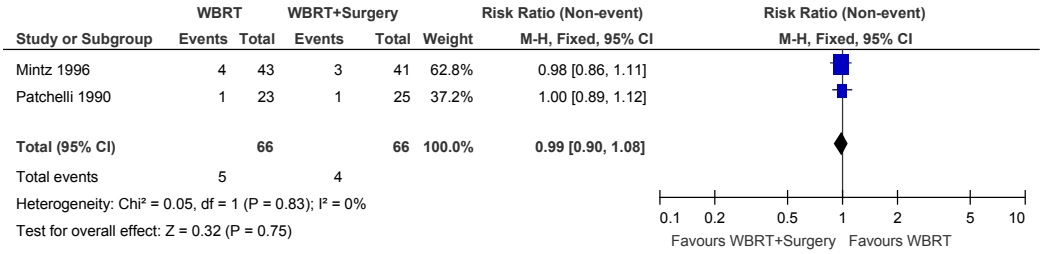


Figure 5: Stereotactic radiosurgery versus WBRT for resected metastasis: overall survival

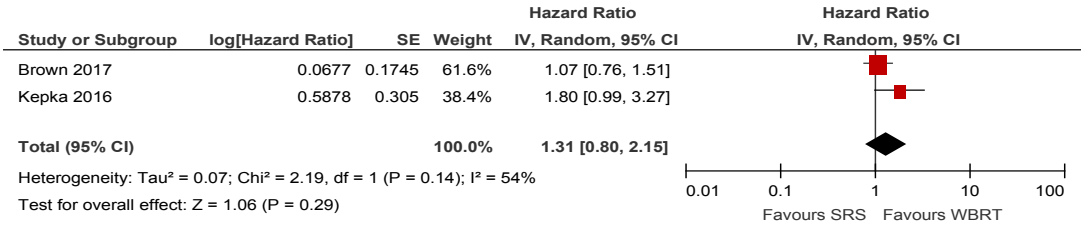
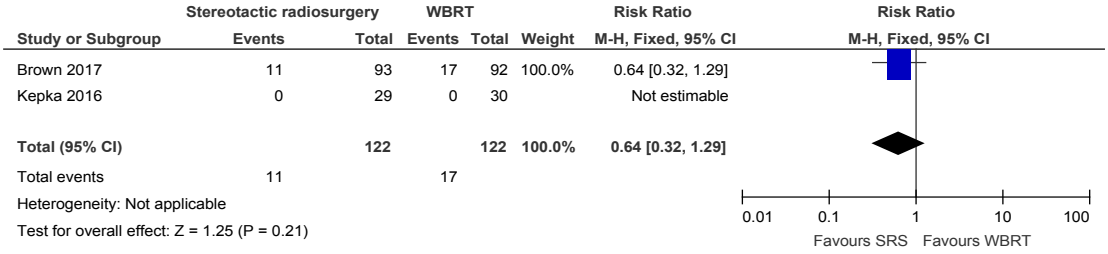


Figure 6: Stereotactic radiosurgery versus WBRT for resected metastasis: toxicity events grade 3 or higher



Forest plots for review 4b – management of multiple metastases

Not applicable.

Forest plots for review 4c – management of brain metastases with a mixed population

Figure 7: WBRT + SRS versus WBRT: control of treated lesion at 1 year

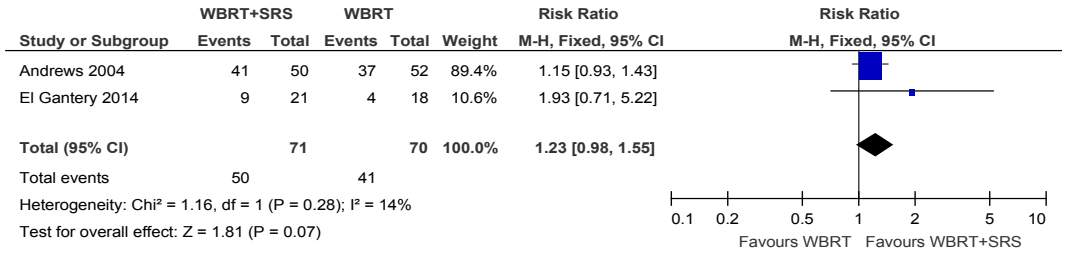


Figure 8: WBRT + TMZ versus WBRT: complete response 4 weeks- 3 months

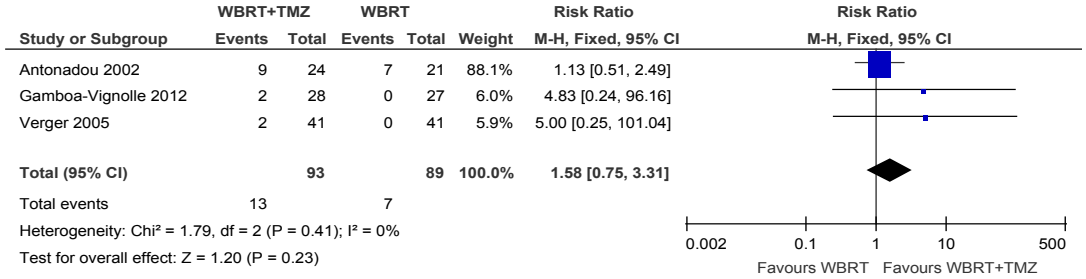


Figure 9: WBRT + TMZ versus WBRT: partial response 4 weeks- 3 months

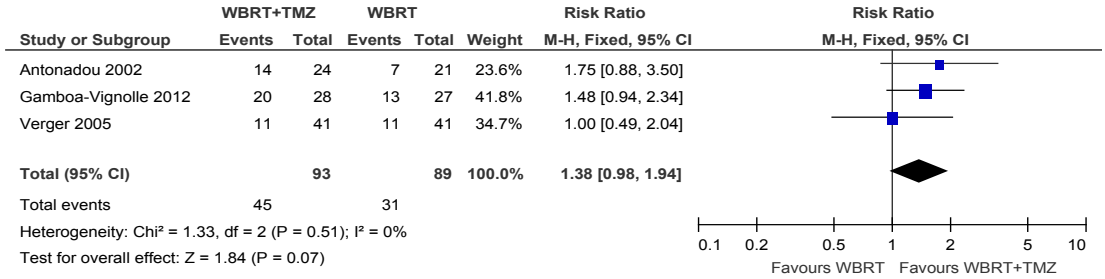


Figure 10: WBRT + TMZ versus WBRT: stable disease 4 weeks- 3 months

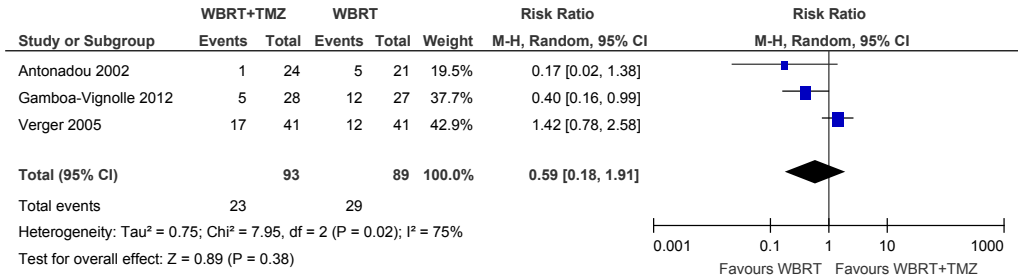


Figure 11: WBRT +TMZ versus WBRT: progressive disease 4 weeks- 3 months

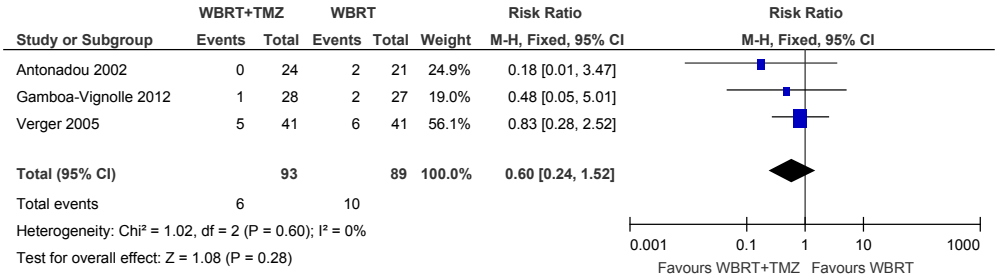


Figure 12: WBRT+TMZ versus WBRT: neurological fully functional or improved

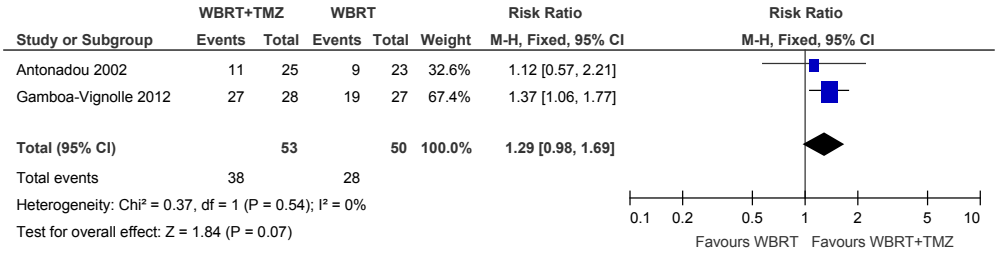


Figure 13: WBRT+ TMZ versus WBRT: adverse events ≥3

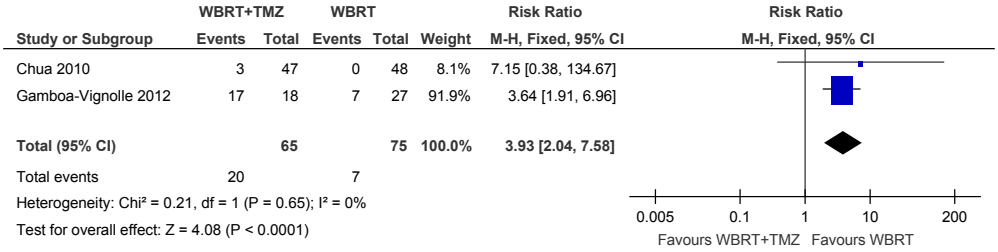


Figure 14: SRS + WBRT versus SRS: overall survival

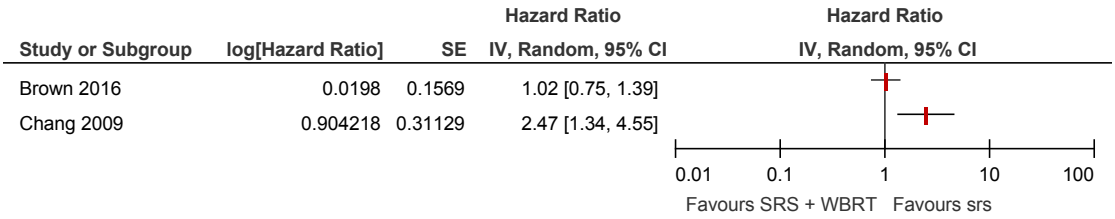


Figure 15: SRS+ WBRT versus SRS: local tumour control rate (actuarial) at 12 months

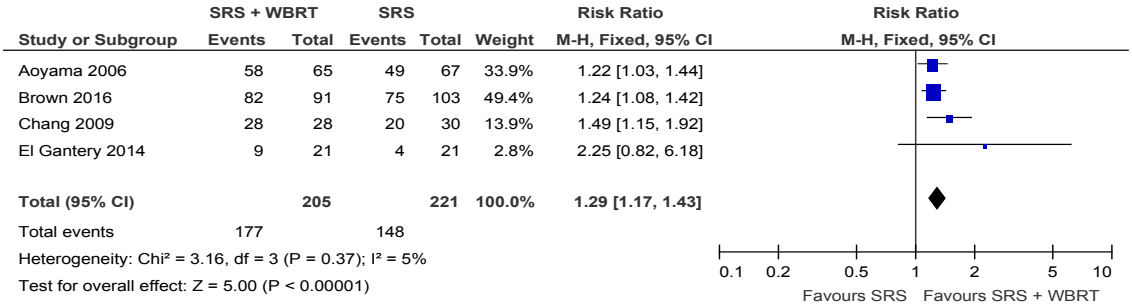


Figure 16: SRS+ WBRT versus SRS: distant brain tumour control at 12 months

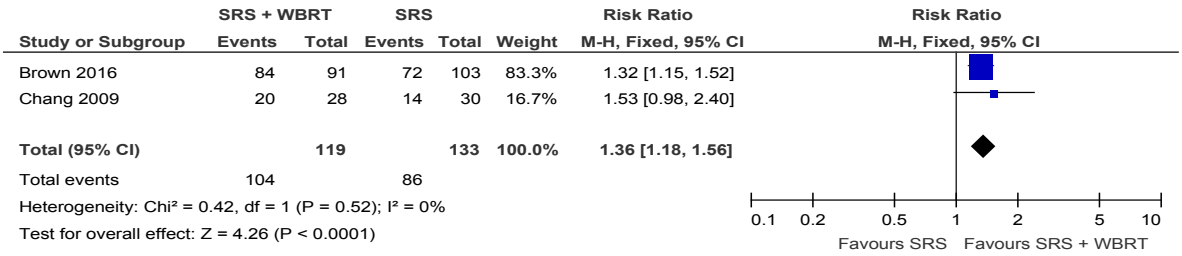


Figure 17: SRS+ WBRT versus SRS: cognitive deterioration

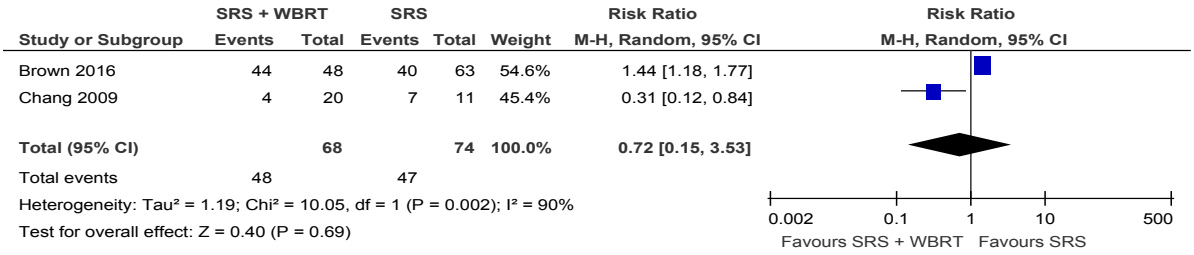


Figure 18: SRS+ WBRT versus SRS: neurological preservation

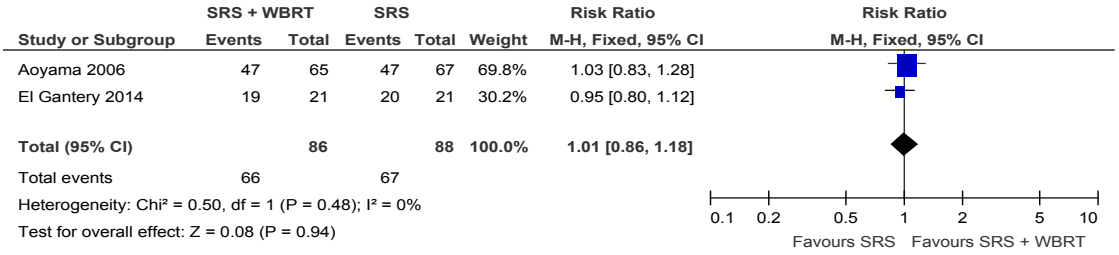
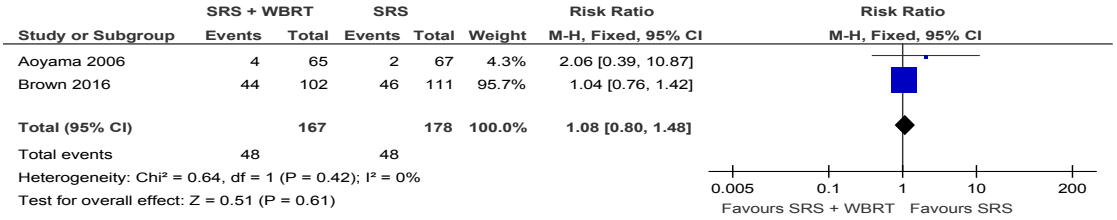


Figure 19: SRS+ WBRT versus SRS: late toxic effects grade 3-4



Forest plots for review 5c – follow-up of metastases

Not applicable - no evidence was identified.

Appendix F – GRADE tables

GRADE tables for review 1b - imaging strategy for brain metastases

Not applicable - no evidence was identified.

GRADE tables for review 4a – management of single metastases

Table 38: Clinical evidence profile for WBRT and surgery versus WBRT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Surgery	WBRT	Relative (95% CI)	Absolute	Quality	Importance
Deaths within 30 days of surgery												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/66 (6.1%)	5/66 (7.6%)	RR 1.02 (0.93 to 1.11)	2 more per 1000 (from 5 fewer to 8 more)	MODERATE	CRITICAL
Deaths within 1 year of treatment												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT+Surgery**	**WBRT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/41 (87.8%)	30/43 (69.8%)	RR 1.26 (1 to 1.58)	181 more per 1000 (from 0 more to 405 more)	LOW	CRITICAL
Death due to systemic causes												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/25 (60%)	11/23 (47.8%)	RR 1.25 (0.74 to 2.14)	120 more per 1000 (from 124 fewer to 545 more)	VERY LOW	
Risk of death												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/25 (8%)	0/23 (0%)	RR 2.2 (1.21 to 4)	-	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Surgery	WBRT	Relative (95% CI)	Absolute		
Morbidity rate 30 days												
1	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/25 (8%)	4/23 (17.4%)	RR 2.17 (0.44 to 10.77)	203 more per 1000 (from 97 fewer to 1000 more)	VERY LOW	CRITICAL
Quality of life (Spitzer score) 3 months (Better indicated by higher values)												
1	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	serious[5]	none	41	43	-	MD 1.02 higher (0.02 lower to 2.06 higher)	VERY LOW	CRITICAL
Quality of life (Spitzer score) 4-6 months (Better indicated by higher values)												
1	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	serious[6]	none	41	43	-	MD 0.17 higher	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Surgery	WBRT	Relative (95% CI)	Absolute		
										(0.67 lower to 1.01 higher)		
Recurrence original only												
1	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/25 (8%)	10/23 (43.5%)	RR 0.18 (0.04 to 0.75)	357 fewer per 1000 (from 109 fewer to 417 fewer)	LOW	CRITICAL
Recurrence original and distant												
1	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	serious[3]	none	3/25 (12%)	2/23 (8.7%)	RR 1.28 (0.25 to 7.53)	24 more per 1000 (from 65 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Surgery	WBRT	Relative (95% CI)	Absolute		
										to 568 more)		
Recurrence original all types												
1	randomised trials	very serious[1, 4]	no serious inconsistency	no serious indirectness	serious[7]	none	5/25 (20%)	12/23 (52.2%)	RR 0.38 (0.16 to 0.92)	323 fewer per 1000 (from 42 fewer to 438 fewer)	VERY LOW	CRITICAL

[1] *It was unclear how randomisation was performed and unclear in both studies if allocation concealment was performed.*
[2] *95% CI crossed 1 MID (1.25)*
[3] *95% CI crossed 2 MIDs (0.8 and 1.25)*
[4] *It was unclear if either the participants, assessors or investigators were blinded.*
[5] *95% CI crossed 1 MID (0.5x2.19=1.10)*
[6] *95% CI crossed 1 MID (0.5x1.9=1.0)*
[7] *95% CI crossed 1 MID (0.8)*

Table 39: Clinical evidence profile for surgery and WBRT versus radiosurgery

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery+ WBRT	Radiosurgery	Relative (95% CI)	Absolute	Quality	Importance
Death at 1 year follow up												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/33 (51.5%)	19/31 (61.3%)	RR 0.84 (0.54 to 1.30)	98 fewer per 1000 (from 282 fewer to 184 more)	VERY LOW	CRITICAL
Complete response (complete resolution)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	33/33 (100%)	9/31 (29%)	RR 0.02 (0.00 to 0.33)	285 fewer per 1000 (from 195 fewer to 290 fewer)	LOW	CRITICAL
Partial response (tumour volume reduction >50%)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery+ WBRT	Radiosurgery	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/33 (0%)	15/31 (48.4%)	RR 1.91 (1.36 to 2.68)	440 more per 1000 (from 174 more to 813 more)	LOW	CRITICAL
Stable disease (tumour control)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[4]	none	0/33 (0%)	6/31 (19.4%)	RR 1.24 (1.03 to 1.48)	46 more per 1000 (from 6 more to 93 more)	VERY LOW	CRITICAL
Progressive disease (any tumour V increase >25%)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/33 (0%)	1/31 (3.2%)	RR 0.31 (0.01	22 fewer per	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery+ WBRT	Radiosurgery	Relative (95% CI)	Absolute		
									to 7.42)	1000 (from 32 fewer to 207 more)		
Freedom from local recurrence - 1 year												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	27/33 (81.8%)	30/31 (96.8%)	RR 5.64 (0.72 to 44.20)	1000 more per 1000 (from 271 fewer to 1000 more)	VERY LOW	CRITICAL
Steroid use												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[4]	none	28/33 (84.8%)	22/31 (71%)	RR 1.20 (0.92 to 1.56)	142 more per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery+ WBRT	Radiosurgery	Relative (95% CI)	Absolute		
										57 fewer to 397 more)		
Acute toxicity (<90 days)												
1	randomised trials	very serious[1, 3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/33 (97%)	16/31 (51.6%)	RR 1.88 (1.33 to 2.66)	454 more per 1000 (from 170 more to 857 more)	LOW	IMPORTANT

1 It was unclear how randomisation was performed and insufficient detail was given on allocation concealment
2 95% CI crossed 2 MIDs (0.8 and 1.25)
3 It was unclear if either the participants, assessors or investigators were blinded.
4 95% CI crossed 1 MID (1.25)

Table 40: Clinical evidence profile for WBRT and best supportive care versus best supportive care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + best care	Best care	Relative (95% CI)	Absolute		
Overall survival												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	80	82	-	HR 1 (0.76 to 1.36)	LOW	CRITICAL

1 Unclear method of allocation concealment. Stratification was not done by number of metastases.

Table 41: Clinical evidence profile for WBRT+SRS versus WBRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+SRS	WBRT	Relative (95% CI)	Absolute		
Overall survival (Better indicated by lower values)												
1	randomised trials	serious risk of bias[1]	no serious inconsistency	no serious indirectness	very serious imprecision [2]	none	94	92	Not estimable[3]	-	VERY LOW	CRITICAL

1 Selective reporting of outcomes
2 Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
3 Not calculated as SDs were not reported. Mean overall survival in WBRT = 4.9 (n=94); mean overall survival in WBRT+SRS= 6.5 (n=92)

Table 42: Clinical evidence profile for Stereotactic radiosurgery versus WBRT for resected metastasis

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Stereotactic radiosurgery**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival (follow-up median 22-29 months)												
2	randomised trials	no serious risk of bias	serious inconsistency[6]	no serious indirectness	very serious imprecision [1]	none	-	-	HR 1.31 (0.80 to 2.15)	-	LOW	CRITICAL
Median survival (follow-up median 22.6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision [1]	none	12.2 months (95% CI 9.7 to 16.0)	11.6 months (95% CI 9.9 to 18.0)	HR 1.07 (0.76 to 1.50)	-	LOW	CRITICAL
Cumulative incidence of neurological/cognitive failure by 2 years												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stereotactic radiosurgery	WBRT	Relative (95% CI)	Absolute		
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious imprecision[1]	none	21/29 (72.4%)	19/30 (63.3%)	RR 1.14 (0.8 to 1.63)	89 more per 1000 (from 127 fewer to 399 more)	VERY LOW	IMPORTANT
Median cognitive-deterioration free survival												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3.7 months (95% CI 3.45 to 5.06)	3.0 months (95% CI 2.86 to 3.25)	HR 0.47 (95% CI 0.35 to 0.63)	-	MODERATE	IMPORTANT
Toxicity events (any grade)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	47/93 (50.5%)	65/92 (70.7%)	RR 0.64 (0.32 to 1.29)	198 fewer per 1000 (from	LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stereotactic radiosurgery	WBRT	Relative (95% CI)	Absolute	Quality	Importance
										64 fewer to 311 fewer)		
Total intracranial progression												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	11/19 (57.9%)	10/28 (35.7%)	RR 1.62 (0.87 to 3.04)	221 more per 1000 (from 46 fewer to 729 more)	LOW	CRITICAL
Relapse in the tumour bed												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	5/19 (26.3%)	7/28 (25%)	RR 1.05 (0.39 to 2.83)	12 more per 1000 (from 153 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stereotactic radiosurgery	WBRT	Relative (95% CI)	Absolute		
										to 457 more)		
Progression at new sites in the brain												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	8/19 (42.1%)	6/28 (21.4%)	RR 1.96 (0.81 to 4.76)	206 more per 1000 (from 41 fewer to 806 more)	LOW	CRITICAL
Time to intracranial tumour progression												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6.4 months (95% CI 5.16 to 8.90)	27.5 months (95% CI 14.85 – not reached)	HR 2.45 (95% CI 1.62 to 3.72)	-	MODERATE	CRITICAL
Median duration of stable or better functional independence												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stereotactic radiosurgery	WBRT	Relative (95% CI)	Absolute		
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	median not yet reached (95% CI 17.6 months to not yet reached)	14.0 months (95% CI 8.4 to 27.0)	HR 0.56 (95% CI 0.32 to 0.96)	-	LOW	CRITICAL
Stable/improved LASA (QOL) score at 6 months												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	35/65 (53.8%)	25/64 (39.1%)	RR 1.38 (0.94 to 2.02)	148 more per 1000 (from 23 fewer to 398 more)	LOW	CRITICAL
Stable/improved FACT-Br total score at 6 months												
1	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	39/65 (60%)	28/64 (43.8%)	RR 1.37 (0.97	162 more per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Stereotactic radiosurgery	WBRT	Relative (95% CI)	Absolute		
									to 1.93)	(from 13 fewer to 407 more)		
Global quality of life score at 2 months (measured with: EORTC-QLQC30 and QLQ-BN20 questionnaires; Better indicated by higher values)												
1	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	Serious[5]	none	24	34	-	MD 4.5 higher (8.6 lower to 17.6 higher)	LOW	CRITICAL
Global quality of life score at 5 months (measured with: EORTC-QLQC30 and QLQ-BN20 questionnaires; Better indicated by higher values)												
1	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	Serious[5]	none	24	34	-	MD 11.4 lower (24.79 lower to 1.99 higher)	LOW	CRITICAL

1 95% CI crossed 2 default MIDs (0.8 and 1.25)
2 It was unclear whether blinding was performed.
3 95% CI crossed 1 default MID (1.25)
4 95% CI crossed 1 default MID (0.8)

5 95% CI crossed 1 default MID (±33.4 x ±0.5= ±16.7)
6 Serious inconsistency (>50%)

Table 43: Clinical evidence profile for WBRT versus observation for resected metastasis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	Observation	Relative (95% CI)	Absolute		
Overall survival (follow-up median 127-132 weeks)												
1	randomised trials	No serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	6/49 (12.2%)	7/46 (15.2%)	RR 0.8 (0.29 to 2.22)	30 fewer per 1000 (from 108 fewer to 186 more)	LOW	CRITICAL
Progression free survival												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	-	HR 1.27 (0.46-3.54)	-	VERY LOW	CRITICAL
Median CNS failure-free survival												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	Observation	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	-	- (95% CI not reported)	HR 1.18 (0.45 to 3.09)	-	VERY LOW	IMPORTANT
CNS relapse												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	3/10 (30%)	7/9 (77.8%)	RR 0.39 (0.14 to 1.06)	474 fewer per 1000 (from 669 fewer to 47 more)	LOW	IMPORTANT
CNS toxicity												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/10 (20%)	0/9 (0%)	RR 4.55 (0.25 to 83.7)	-	VERY LOW	IMPORTANT
No brain recurrence												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/49 (81.6%)	14/46 (30.4%)	RR 2.68 (1.7 to 4.23)	511 more per 1000	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	Observation	Relative (95% CI)	Absolute	Quality	Importance
										(from 213 more to 983 more)		
Recurrence at site of original metastasis												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/49 (4.1%)	15/46 (32.6%)	RR 0.13 (0.03 to 0.52)	284 fewer per 1000 (from 157 fewer to 316 fewer)	MODERATE	CRITICAL
Recurrence at original metastasis site and distant brain recurrence												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/49 (6.1%)	6/46 (13%)	RR 0.47 (0.12 to 1.77)	69 fewer per 1000 (from 115 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	Observation	Relative (95% CI)	Absolute	Quality	Importance
										to 100 more)		
Recurrence at distant brain site(s) only												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	4/49 (8.2%)	11/46 (23.9%)	RR 0.34 (0.12 to 1)	158 fewer per 1000 (from 210 fewer to 0 more)	LOW	CRITICAL
Median time to deterioration in WHO score (>1)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	not reported	not reported	HR 1.16 (95% CI 0.38 to 3.48)	-	VERY LOW	CRITICAL
Radiation toxicity ≥ grade 3												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	2/10 (20%)	0/9 (0%)	RR 4.55 (0.25 to 83.7)	-	VERY LOW	IMPORTANT

1 95% CI crosses 2 default MIDs (0.8 and 1.25)
2 Unclear method of allocation concealment. Stratification was not done by number of metastases
3 95% CI crossed 1 default MID (0.8)

GRADE tables for review 4b – management of multiple metastases

Table 44: Clinical evidence profile for WBRT and gefitinib versus WBRT and temozolomide

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT +gefitinib	WBRT + TMZ	Relative (95% CI)	Absolute	Quality	Importance
Median overall survival (months) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	16	43	-	Not estimable[6]	VERY LOW	CRITICAL
Median time to progression (months) (Better indicated by higher values)												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	serious[3]	none	16	43	-	Not estimable[7]	VERY LOW	CRITICAL
1 year survival rates												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious5	none	6/16 (37.5 %)	9/43 (20.9%)	RR 1.79 (0.76 to 4.23)	165 more per 1000 (from 50	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT +gefitinib	WBRT + TMZ	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 676 more)		
Withdrew due to toxicity												
1	randomised trials	very serious[1, 4]	no serious inconsistency	serious[2]	very serious[5]	none	3/16 (18.8 %)	3/43 (7%)	RR 2.69 (0.6 to 11.97)	118 more per 1000 (from 28 fewer to 765 more)	VERY LOW	IMPORTANT

[1] It was unclear how participants were randomised or if allocation concealment was performed. Drop outs >20% were detected in 1 arm.
[2] 14% of patients had a single metastases.
[3] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision
[4] Neither the participants, investigators nor assessors were blinded
[5] 95% CI crossed 2 MIDs (0.8 and 1.25)
6 Not calculated as only descriptive data have been reported. Median overall survival in WBRT + gefitinib = 6.3 (2.1-14.6); median overall survival in WBRT + TMZ = 4.9 (2.3-5.6)

7 Not calculated as only descriptive data have been reported. Median overall survival in WBRT + gefitinib =1.8 (1.1-3.9); median overall survival in WBRT + TMZ = 1.8 (1.5-1.8)

Table 45: Clinical evidence profile for WBRT and biological agent (Veliparib) versus WBRT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT + Veliparib**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Median overall survival, days (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	205	102	-	Not estimable [6]	VERY LOW	CRITICAL
Objective response rate												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	very serious[5]	none	42/102 (41.2%)	81/205 (39.5%)	RR 1.04 (0.78 to 1.39)	16 more per 1000 (from 87 fewer to 154 more)	VERY LOW	CRITICAL
Any adverse event												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT + Veliparib**	**WBRT**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	no serious imprecision	none	91/102 (89.2%)	180/206 (87.4%)	RR 1.02 (0.94 to 1.11)	17 more per 1000 (from 52 fewer to 96 more)	VERY LOW	IMPORTANT
Brain Oedema												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	no serious imprecision	none	6/102 (5.9%)	1/205 (0.49%)	RR 0.12 (0.02 to 0.67)	4 fewer per 1000 (from 2 fewer to 5 fewer)	VERY LOW	IMPORTANT

[1] Unclear how randomisation was performed or if allocation concealment was performed.
[2] 19% of patients had a single metastases
[3] Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision 4 Patients were not blinded and it was unclear if investigators or assessors were blinded.
[4] Patients were not blinded and it was unclear if investigators or assessors were blinded.
[5] 95% CI crossed 2 default MIDs (0.8 and 1.25)
6 Not calculated as only medians have been reported. Median overall survival in WBRT = 185 (137-251); median overall survival in veliparib 50 + WBRT= 209 (169-264); veliparib 200g + WBRT = 209 (138-255)

Table 46: Clinical evidence profile for WBRT and thalidomide versus WBRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Thalidomide	WBRT	Relative (95% CI)	Absolute		
Death due to brain metastases												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/84 (27.4%)	31/92 (33.7%)	RR 0.81 (0.52 to 1.28)	64 fewer per 1000 (from 162 fewer to 94 more)	VERY LOW	CRITICAL
3 month rates of CNS progression												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/84 (13.1%)	17/92 (18.5%)	RR 0.71 (0.35 to 1.42)	54 fewer per 1000 (from 120 fewer to 78 more)	VERY LOW	CRITICAL
Grade 3-4 treatment related AE												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Thalidomide	WBRT	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39/84 (46.4%)	11/92 (12%)	RR 3.88 (2.13 to 7.08)	344 more per 1000 (from 135 more to 727 more)	LOW	IMPORTANT
Cardiovascular-related AE												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/84 (2.4%)	0/92 (0%)	RR 5.47 (0.27 to 112.23)	-	VERY LOW	IMPORTANT
Infection (not necessarily post-op)												
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/84 (0%)	0/92 (0%)	Not estimable	-	LOW	IMPORTANT
Quality of life												
1	Randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious	none	73	83	Not estimable[5]	-	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Thalidomide	WBRT	Relative (95% CI)	Absolute	Quality	Importance
					imprecision[4]							

1 Unclear how participants were randomised or if allocation concealment was performed
2 95% CI crossed 2 MIDs (0.80 and 1.25)
3 Participants were not blinded but it was unclear if assessors or investigators were blinded.
4 Not calculated as standard deviation of the outcomes were not reported. Mean change from baseline to endpoint in WBRT arm= -0.53; mean change from baseline in the WNRT + thalidomide arm= 0.33
5 Only descriptive data were reported, insufficient details to assess MID thresholds and imprecision

Table 47: Clinical evidence profile for WBRT and radiosurgery versus WBRT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+ Radiosurgery	WBRT	Relative (95% CI)	Absolute	Quality	Importance
Median time of survival (months) (Better indicated by higher values)												
1	randomised trials	serious[1]	serious inconsistency[4]	no serious indirectness	very serious[2]	none	14	13	-	Not estimable4	VERY LOW	CRITICAL
Rate of local failure (including patients who died)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+ Radiosurgery	WBRT	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	14/14 (100%)	1/13 (7.7%)	RR 0.11 (0.02 to 0.50)	68 fewer per 1000 (from 38 fewer to 75 fewer)	LOW	CRITICAL

1 It was unclear if allocation concealment was performed.

2 Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision

3 Participants were not blinded, however, investigators and assessors were blinded

4Not calculable as only medians have been reported. Median overall survival in WBRT = 7.5 (4.6-10.4) and median time of survival in WBRT + radiosurgery = 11 (3.8-18.2).

Table 48: Clinical evidence profile for WBRT and temozolomide versus WBRT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+ TMZ	WBRT	Relative (95% CI)	Absolute	Quality	Importance
Median time overall survival (months) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	50	50	-	Not estimable[5]	VERY LOW	CRITICAL
Median progression free survival (months) (Better indicated by higher values)												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	very serious[5]	none	50	50	-	Not estimable[8]	VERY LOW	CRITICAL
Complete response												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	no serious imprecision	none	0/50 (0%)	0/50 (0%)	Not estimable	-	VERY LOW	CRITICAL
Partial response												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	very serious6	none	18/50 (50%)	15/50 (30%)	RR 0.83 (0.48 to 1.46)	51 fewer per 1000 (from 156 fewer to 138 fewer)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+ TMZ	WBRT	Relative (95% CI)	Absolute		
Stable disease												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	Serious[9]	none	26/50 (52%)	18/50 (36%)	RR 0.69 (0.44 to 1.09)	161 fewer per 1000 (from 291 fewer to 47 more)	VERY LOW	CRITICAL
Progressive disease												
1	randomised trials	very serious[1,4]	no serious inconsistency	serious2	very serious[6]	none	4/50 (8%)	3/50 (6%)	RR 1.33 (0.31 to 5.65)	20 more per 1000 (from 41 fewer to 279 more)	VERY LOW	CRITICAL
Neurological symptoms (6 weeks)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+ TMZ	WBRT	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,4]	no serious inconsistency	serious[2]	Serious[9]	none	22/50 (44%)	12/50 (24%)	RR 0.55 (0.30 to 0.98)	108 fewer per 1000 (from 5 fewer to 168 fewer)	VERY LOW	IMPORTANT

[1] *It was unclear how randomisation was performed or if allocation concealment was conducted.*
[2] *15% of patients had a single metastases.*
[3] *Only descriptive data reported, insufficient details given to assess the MID thresholds and imprecision*
[4] *Participants were not blinded, assessors were blinded but it was unclear if investigators were blinded.*
[5] *Not estimable as only medians were reported. Median overall survival in the WBRT group = 11.1 months (8.3-15.3); median overall survival in the WBRT + TMZ arm= 9.4 months (7.3-13.4)*
[6] *95% CI crossed 1 MID (0.8 and 1.25)*
[7] *95% CI crossed 1 MID (1.25)*
8 Not estimable as only medians were reported. Median progression free survival in the WBRT group = 7.4 months (5.3-13.1); median progression free survival in the WBRT + TMZ arm= 6.8 months (4.6-8.6)
9 95% CI crossed 1 default MID (0.8)

Table 49: Clinical evidence profile for WBRT and Efaproxiral versus WBRT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Efaproxiral	WRBT	Relative (95% CI)	Absolute		
Overall survival (Better indicated by lower values)												
1	randomised trials	very serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	250	265	-	HR 0.87 (0.71 to 1.05)	LOW	CRITICAL
Death at 30 days												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	13/265 (4.9%)	16/250 (6.4%)	RR 0.77 (0.38 to 1.56)	15 fewer per 1000 (from 40 fewer to 36 more)	VERY LOW	CRITICAL
Death at 6 months												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[5]	none	142/265 (53.6%)	151/250 (60.4%)	RR 0.89 (0.76 to 1.03)	66 fewer per 1000 (from	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Efaproxiral	WRBT	Relative (95% CI)	Absolute		
										145 fewer to 18 more)		
Death at 30 months												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	215/265 (81.1%)	206/250 (82.4%)	RR 0.98 (0.91 to 1.07)	16 fewer per 1000 (from 74 fewer to 58 more)	LOW	CRITICAL
Radiographic progression at 1 year												
1	randomised trials	very serious[1,2]	no serious inconsistency	serious[3]	serious[6]	none	55/265 (20.8%)	45/250 (18%)	RR 1.15 (0.81 to 1.64)	27 more per 1000 (from 34 fewer	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Efaproxiral	WRBT	Relative (95% CI)	Absolute		
										to 115 more)		
Clinical progression at 1 year												
1	randomised trials	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	130/265 (49.1%)	128/250 (51.2%)	RR 0.96 (0.81 to 1.14)	20 fewer per 1000 (from 97 fewer to 72 more)	VERY LOW	CRITICAL
Complete response												
1	randomised trials	very serious[1,2]	no serious inconsistency	serious[3]	serious[6]	none	28/265 (10.6%)	14/250 (5.6%)	RR 1.89 (1.02 to 3.50)	50 more per 1000 (from 1 more to 140 more)	VERY LOW	CRITICAL
Partial response												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Efaproxiral	WRBT	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1,2]	no serious inconsistency	serious[3]	serious[6]	none	93/265 (35.1%)	82/250 (32.8%)	RR 1.07 (0.84 to 1.36)	23 more per 1000 (from 52 fewer to 118 more)	VERY LOW	CRITICAL
Stable or improving QoL												
1	randomised trials	very serious[1,2]	no serious inconsistency	serious[3]	very serious[4]	none	43/265 (16.2%)	38/250 (15.2%)	RR 1.07 (0.72 to 1.59)	11 more per 1000 (from 43 fewer to 90 more)	VERY LOW	IMPORTANT
Stable or improving KPS												
1	randomised trials	very serious[1,2]	no serious inconsistency	serious[3]	serious[6]	none	48/265 (18.1%)	26/250	RR 1.26 (0.85	27 more per	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+Efaproxiral	WRBT	Relative (95% CI)	Absolute		
								(10.4 %)	to 1.87)	1000 (from 16 fewer to 90 more)		
Grade 4 (severe) adverse events												
1	randomised trials	very serious[1, 2]	no serious inconsistency	serious[3]	very serious[4]	none	33/266 (12.4%)	28/263 (10.6 %)	RR 1.17 (0.73 to 1.87)	18 more per 1000 (from 29 fewer to 93 more)	VERY LOW	IMPORTANT

[1] *It was unclear how randomisation was performed or if allocation concealment was performed.*
[2] *It is unlikely the participants were blinded, assessors were blinded but it was unclear if investigators were blinded.*
[3] *18.5% of patients had a single metastases.*
[4] *95% CI crossed 2 MIDs (0.8 and 1.25)*
[5] *95% CI crossed 1 MID (0.8)*
[6] *95% CI crossed 1 MID (1.25)*

GRADE tables for review 4c – management of brain metastases with a mixed population

Table 50: Clinical evidence profile for WBRT +BSC versus BSC

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+BSC	Best supportive care	Relative (95% CI)	Absolute	Quality	Importance
HR Overall survival												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	43	-	HR 1.1 (0.93 to 1.3)	LOW	CRITICAL
Quality of life (EQ-5D) improved or maintained 12 weeks												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/54 (44.4 %)	21/43 (48.8%)	RR 0.91 (0.59 to 1.4)	44 fewer per 1000 (from 200 fewer to 195 more)	VERY LOW	CRITICAL
KPS change 12 weeks (Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT+BSC**	**Best supportive care**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	269	269	-	MD 4.6 higher (2.13 to 7.07 higher)	LOW	IMPORTANT
Any serious adverse event												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	89/269 (33.1%)	82/269 (30.5%)	RR 1.09 (0.85 to 1.39)	27 more per 1000 (from 46 fewer to 119 more)	LOW	IMPORTANT
Infection												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious3	none	17/269 (6.3%)	16/269 (5.9%)	RR 1.06 (0.55 to 2.06)	4 more per 1000 (from 27 fewer to 63 more)	VERY LOW	IMPORTANT
Cardiac AE												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT+BSC**	**Best supportive care**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	2/269 (0.74 %)	1/269 (0.37%)	RR 2 (0.18 to 21.93)	4 more per 1000 (from 3 fewer to 78 more)	VERY LOW	IMPORTANT
Use of dexamethasone 8 wks												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[3]	none	30/245 (12.2 %)	24/233 (10.3%)	RR 1.19 (0.72 to 1.97)	20 more per 1000 (from 29 fewer to 100 more)	VERY LOW	IMPORTANT

1 Adequate randomisation and allocation concealment. Particvpants and investigators were not blinded, it was unclear if assessos were. Unclear reporting bias.Previous treatment with systemic anticancer treatment (chemo therapy or tyrosine kinase inhibitors [TKI]) was permitted
2 95% CI crossed 1 MID 1.25
3 95% CI crossed 2 MIDs 0.8 and 1.25
*4 95% CI crossed1 MID 6.8 (0.5*13.66)*

Table 51: WBRT +SRS versus WBRT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + SRS	WBRT	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (Better indicated by lower values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision [5]	none	164	167	-	Not calculable6	VERY LOW	CRITICAL
Lesions complete response 3mo												
1	randomised trials	serious [2]	no serious inconsistency	no serious indirectness	serious [3]	none	12/75 (16%)	6/78 (7.7%)	RR 2.08 (0.82 to 5.25)	83 more per 1000 (from 14 fewer to 327 more)	LOW	CRITICAL
Partial response 3 mo												
1	randomised trials	serious [2]	no serious inconsistency	no serious indirectness	very serious [4]	none	43/75 (57.3 %)	42/78 (53.8 %)	RR 1.06 (0.80 to 1.41)	32 more per 1000 (from 108	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + SRS	WBRT	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 221 more)		
Stable lesions 3 mo												
1	randomised trials	serious [2]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/75 (14.7 %)	17/78 (21.8 %)	RR 0.67 (0.34 to 1.34)	72 fewer per 1000 (from 144 fewer to 74 more)	VERY LOW	CRITICAL
Progression lesions 3 mo												
1	randomised trials	serious [2]	no serious inconsistency	no serious indirectness	very serious[4]	none	8/75 (10.7 %)	13/78 (16.7 %)	RR 0.64 (0.28 to 1.46)	60 fewer per 1000 (from 120 fewer to 77 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT + SRS**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Control of treated lesion 1 yr												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50/71 (70.4 %)	41/70 (58.6 %)	RR 1.23 (0.98 to 1.55)	135 more per 1000 (from 12 fewer to 322 more)	LOW	CRITICAL
KPS Improved												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	10/79 (12.7 %)	3/75 (4%)	RR 3.16 (0.91 to 11.06)	86 more per 1000 (from 4 fewer to 402 more)	LOW	IMPORTANT
Steriod use increased												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/76 (9.2%)	6/75 (8%)	RR 1.15 (0.41	12 more per	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + SRS	WBRT	Relative (95% CI)	Absolute	Quality	Importance
									to 3.27)	1000 (from 47 fewer to 182 more)		
Acute toxicity GRADE 3-4 (<90 days)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	5/160 (3.1%)	0/166 (0%)	RR 11.41 (0.64 to 204.68)	-	LOW	IMPORTANT
Death due to brain metastases												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	39/137 (28.5%)	46/149 (30.9%)	RR 0.92 (0.64 to 1.32)	25 fewer per 1000 (from 111 fewer to 99 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + SRS	WBRT	Relative (95% CI)	Absolute	Quality	Importance
Late necrosis												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/21 (4.8%)	0/18 (0%)	RR 2.59 (0.11 to 59.93)	-	VERY LOW	IMPORTANT
Brain oedema												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/21 (4.8%)	1/18 (5.6%)	RR 1.01 (0.87 to 1.17)	1 more per 1000 (from 7 fewer to 9 more)	MODERATE	IMPORTANT
Neurological progression >3 mo												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	2/21 (9.5%)	2/18 (11.1%)	RR 1.02 (0.82 to 1.26)	2 more per 1000 (from 20 fewer to 29 more)	LOW	IMPORTANT

1 Unclear reporting bias
2 It was unclear if participants, investigators or assessors were blind. Unclear reporting bias. No previous cranial radiation.
3 95% CI crossed 1 MID 1.25
4 95% CI crossed 2 MIDs 0.8 and 1.25
5 Not SDs were reported to assess the MID thresholds and imprecision
6 Not calculable as no SDs were provided

Table 52: Clinical evidence profile for WBRT versus SRS

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT**	**SRS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Local control												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/21 (19 %)	4/18 (22.2 %)	RR 0.86 (0.25 to 2.95)	31 fewer per 1000 (from 167 fewer to 433 more)	VERY LOW	CRITICAL
Late radiation necrosis												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/21 (0%)	1/18 (5.6%)	RR 1.06	3 more per 1000 (from 4	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT	SRS	Relative (95% CI)	Absolute		
									(0.92 to 1.23)	fewer to 13 more)		
Brain oedema												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/18 (5.6 %)	1/21 (4.8%)	RR 1.17 (0.08 to 17.35)	8 more per 1000 (from 44 fewer to 779 more)	VERY LOW	IMPORTANT
Neurological progression >3 mo												
1	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	1/21 (4.8 %)	2/18 (11.1 %)	RR 1.07 (0.89 to 1.29)	8 more per 1000 (from 12 fewer to 32 more)	VERY LOW	IMPORTANT

1 Unclear how randomisation was performed; unclear allocation concealment; unclear blinding; reporting bias
2 95% CI crossed 2 default MIDs (0.8 and 1.25)
3 95% CI crossed 1 default MID (1.25)

Table 53: Clinical evidence profile for WBRT+ TMZ versus WBRT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT+TMZ**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival[a]												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	47	48	HR = 1.14 (0.71-1.83)	-	VERY LOW	CRITICAL
Median overall survival[b]												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	27	28	Not estimable[12]	-	VERY LOW	CRITICAL
Median progression free survival												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	27	28	Not estimable[13]	-	VERY LOW	CRITICAL
Complete response 4 wk - 3 mo												
3	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/93 (14%)	7/89 (7.9%)	RR 1.58 (0.75 to 3.31)	46 more per 1000 (from 20 fewer to 182 more)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+TMZ	WBRT	Relative (95% CI)	Absolute	Quality	Importance
Partial response 4 wk -3 mo												
3	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	45/93 (48.4%)	31/9 (344.4 %)	RR 1.38 (0.98 to 1.94)	1000 more per 1000 (from 69 fewer to 1000 more)	VERY LOW	CRITICAL
Stable disease 4 wk - 3 mo												
3	randomised trials	very serious[8]	serious9	no serious indirectness	serious[2]	none	23/93 (24.7%)	29/89 (32.6%)	RR 0.59 (0.18 to 1.91)	134 fewer per 1000 (from 267 fewer to 297 more)	VERY LOW	CRITICAL
Progressive disease 4 wk - 3mo												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+TMZ	WBRT	Relative (95% CI)	Absolute	Quality	Importance
3	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/93 (6.5%)	10/89 (11.2%)	RR 0.60 (0.24 to 1.52)	45 fewer per 1000 (from 85 fewer to 58 more)	VERY LOW	CRITICAL
Neurological fully functional or improved												
2	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	serious[7]	none	38/53 (71.7%)	28/50 (56%)	RR 1.29 (0.98 to 1.69)	162 more per 1000 (from 11 fewer to 386 more)	VERY LOW	IMPORTANT
Required corticosteroids												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	17/25 (68%)	21/23 (91.3%)	RR 0.74 (0.55 to 1.00)	237 fewer per	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+TMZ	WBRT	Relative (95% CI)	Absolute	Quality	Importance
										1000 (from 411 fewer to 0 more)		
Died from systemic disease 21mo												
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	20/24 (83.3%)	19/21 (90.5%)	RR 0.92 (0.73 to 1.16)	72 fewer per 1000 (from 244 fewer to 145 more)	VERY LOW	IMPORTANT
Adverse events >=3												
2	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	serious[7]	none	20/65 (30.8%)	7/75 (9.3%)	RR 3.93 (2.04 to 7.58)	273 more per 1000 (from 97	VERY LOW	

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+TMZ	WBRT	Relative (95% CI)	Absolute	Quality	Importance
										more to 614 more)		

aChua 2010 ,bGamboa-Vignolle
1 Unclear randomisation
2 95% CI crossed 2 default MIDs (0.8 and 1.25)
3 Unclear randomisation, no blinding (participants, asessors and investigators)
4 95% CI crossed 1 default MID (0.8)
5 Unclear randomisation, unclear allocation concealment, open trial
6 Only descriptive data have been reported, insuficcient details provided to assess the MID threshold and imprecision
7 95% CI crossed 1 default MID (1.25)
8 The three trials presented with unclear randomisation and allocation concealment. Two trials presented with unclear blinding, one with unclear reporting bias and one was an open trial
9 I-square> 50%
10 Both trials presented with unclear randomisation and allocation concealemnt. One of the trials presented with unclear patient and investigatior blinding and unclear reporting bias. The second was an open trial
11 Both were open trials presented with unclear randomisation. One trial presented with unclear allocation concealment
12 Not calculable as only medians have been reported. The median overall survival in the intervention arm= 8 months (4.9 to 11.1) and the median overall survival in the control arm=8.1 months (5.9 to 10.1)
13 Not calculable as only medians have been reported. The median progression free survival in the intervention arm= 11.8 onths (4.7 to 18.9) and the median progression free survival in the control arm = 5.6 months (4.9 to 6.2)

Table 54: Clinical evidence profile for SRS+WBRT versus SRS

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SRS+WBRT**	**SRS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Survival time (median months)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	195	208	-	Data not reported to allow calculation 13	VERY LOW	CRITICAL
Overall survival												
1	randomised trials	serious risk of bias[7]	no serious inconsistency	no serious indirectness	very serious[3]	none	111	102	HR 1.02(0.75-1.38)[a]	-	LOW	CRITICAL
1	randomised trials	No serious risk of bias	no serious inconsistency	no serious indirectness	no serious risk of bias	none	28	30	HR 2.47 (1.34-4.55)[b]	-	HIGH	CRITICAL
Brain tumour recurrence at distal sites (median months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31	31	-	Data not reported to allow calculation	LOW	IMPORTANT
Time to intracranial failure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SRS+ WBRT**	**SRS**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	-		HR (3.60 2.21-5.86)	-	LOW	CRITICAL
Actuarial brain tumour recurrence rate 12 months												
2	randomised trials	very serious[1,5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40/93 (43%)	73/97 (75.3 %)	RR 0.57 (0.44 to 0.74)	324 fewer per 1000 (from 196 fewer to 421 fewer)	LOW	CRITICAL
New brain mets at distal sites 12 monthsnt												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	21/65 (32.3 %)	34/67 (50.7 %)	RR 0.64 (0.42 to 0.97)	183 fewer per 1000 (from 15 fewer to 294 fewer)	VERY LOW	CRITICAL
Actuarial new brain tumour metastases 12 months												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	27/65 (41.5 %)	43/67 (64.2 %)	RR 0.65 (0.46 to 0.91)	225 fewer per 1000 (from 58 fewer to 347 fewer)	VERY LOW	CRITICAL
Local tumour control rate (actuarial) 12 months												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRS+ WBRT	SRS	Relative (95% CI)	Absolute		
4	randomised trials	very serious[6]	no serious inconsistency	no serious indirectness	serious[4]	none	177/205 (86.3%)	148/221 (67%)	RR 1.29 (1.17 to 1.43)	194 more per 1000 (from 114 more to 288 more)	VERY LOW	CRITICAL
Distal brain tumour control 12 months												
2	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	104/119 (87.4%)	86/133 (64.7%)	RR 1.36 (1.18 to 1.56)	233 more per 1000 (from 116 more to 362 more)	VERY LOW	CRITICAL
KPS score ≥70												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3,4]	none	22/65 (33.8%)	18/67 (26.9%)	RR 1.26 (0.75 to 2.12)	70 more per 1000 (from 67 fewer to 301 more)	VERY LOW	IMPORTANT
Quality of life (Better indicated by higher values)												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	very serious[8]	none	50	65	-	MD 11.9 lower (17.71 to 6.09 lower)	VERY LOW	IMPORTANT
Cognitive deterioration												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRS+ WBRT	SRS	Relative (95% CI)	Absolute		
2	randomised trials	very serious[6]	very serious[9]	no serious indirectness	very serious[3,4]	none	48/68 (70.6 %)	47/74 (63.5 %)	RR 0.72 (0.15 to 3.53)	178 fewer per 1000 (from 540 fewer to 1000 more)	VERY LOW	IMPORTANT
Neurological preservation												
2	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66/86 (76.7 %)	67/88 (76.1 %)	RR 1.01 (0.86 to 1.18)	8 more per 1000 (from 107 fewer to 137 more)	LOW	IMPORTANT
Late toxic effects GRADE 3-4												
2	randomised trials	very serious[1,11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/167 (28.7 %)	48/178 (27%)	RR 0.97 (0.86 to 1.09)	8 fewer per 1000 (from 38 fewer to 24 more)	LOW	IMPORTANT
Edema limbs												
1	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/102 (0.98 %)	0/111 (0%)	RR 0.99 (0.96 to 1.02)	-	MODERATE	IMPORTANT
Late oedema												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRS+ WBRT	SRS	Relative (95% CI)	Absolute		
1	randomised trials	very serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/21 (4.8%)	1/21 (4.8%)	RR 1 (0.87 to 1.14)	0 fewer per 1000 (from 6 fewer to 7 more)	LOW	IMPORTANT

a Brown 2016
b Chang 2009
1 Unclear allocation concealment and patient blinding. Outcome assessors and investigators were not blinded
2 Only descriptive data reported, insufficient details given to assess the MID threshold and imprecision
3 95% CI crossed 1 default MID (0.8)
4 95% CI crossed 1 default MID (1.25)
5 Not blinded
6 Unclear or not blinding (participants, assessors and investigators) in any of the 4 trials included, unclear randomisation in 1 trial and unclear allocation concealment in 2
7 No patient or outcome assessor blinding
8 95% CI crossed 1 default MID (± 0.5 x 24= ± 12)
9 I-square > 80%
10 Both trials had unclear/no assessor blinding and unclear allocation concealment. One trial presented with unclear randomisation and reporting bias
11 Unclear/not blinding (participants, assessors and investigators) in 2 trials
12 Unclear randomisation, unclear allocation concealment, unclear patient allocation, unclear blinding and high reporting bias
13 Not calculable as only medians have been reported. The median survival time in the SRS + WBRT group was 7.5 months (0.8-58.7) and the median survival time in the SRS group was 8 months (0.5-57)
14 Not calculable as only medians have been reported. The median months brain tumour recurrence in distal sites in the WBRT+ SRS group was 16.2 and the median months in the SRS group was 5.5

Table 55: Clinical evidence profile for SRS + cisplatin or carboplatin versus SRS

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRS + cisplatin or carboplatin	SRS	Relative (95% CI)	Absolute	Quality	Importance
Overall survival months												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	49	49	-	HR 1.2 (0.77 – 1.89)	VERY LOW	CRITICAL
Progression free survival months												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[4]	none	49	49	-	HR 1.44 (0.87-2.35)	LOW	

1 Unclear randomisation methods and unclear allocation concealment
2 95% crossed 2 default MIDs (0.8 and 1.25)
3 Unclear randomisation methods, unclear allocation concealment and unclear blinding
4 95% CI crossed 1 default MID (1.25)

Table 56: Clinical evidence profile for WBRT + Erlotinib versus WBRT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT versus WBRT + Erlotinib**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Median overall survival (months)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	-	-	HR 0.94 (0.58-1.53)	-	VERY LOW	CRITICAL
Grade 3-4 AE												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/40 (70%)	28/40 (70%)	RR 1.00 (0.75 to 1.33)	0 fewer per 1000 (from 175 fewer to 231 more)	VERY LOW	IMPORTANT
Quality of life (Better indicated by higher values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	40	40	-	MD 0.05 higher (0.34 lower to 0.44 higher)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT versus WBRT + Erlotinib**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Infection												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[3]	none	2/40 (5%)	5/40 (12.5 %)	RR 1.13 (0.92 to 1.38)	75 more per 1000 (from 25 fewer to 557 more)	LOW	IMPORTANT

1 Unclear random sequence generation and high reporting bias
2 95% CI crossed 2 default MIDs (0.8 and 1.25)
3 95% CI crossed 1 default MID (1.25)

Table 57: Clinical evidence profile for Surgery/SRS/WBRT versus Surgery/SRS/Observation

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/SRS/WBRT**	**Surgery/SRS/ Observation**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Median progression-free survival (months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[6]	none	179	180	-	Not calculable[7]	VERY LOW	CRITICAL
Intracranial progression												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87/180 (48.3%)	139/179 (77.7%)	RR 0.62 (0.52 to 0.74)	295 fewer per 1000 (from 202 fewer to 373 fewer)	LOW	CRITICAL
Overall survival												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	HR 0.98 (0.78-1.23)	-	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Surgery/SRS/WBRT**	**Surgery/SRS/ Observation**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Serious side effects												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[4]	none	3/179 (1.7%)	13/180 (7.2%)	RR 0.23 (0.07 to 0.80)	56 Fewer per 1000 (from 14 fewer to 67 fewer)	LOW	IMPORTANT
Serious infection												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/179 (0%)	2/180 (1.1%)	RR 0.20 (0.01 to 4.16)	9 fewer per 1000 (from 11 fewer to 35 more)	LOW	IMPORTANT
Serious radionecrosis												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery/SRS/WBRT	Surgery/SRS/ Observation	Relative (95% CI)	Absolute		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/179 (0.56%)	2/180 (1.1%)	RR 0.50 (0.05 to 5.50)	6 fewer per 1000 (from 11 fewer to 50 more)	LOW	IMPORTANT
Quality of life 12 months (Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	36	29	-	MD 1.9 lower (3.72 lower to 0.08 lower)	VERY LOW	

[1] Unclear how randomisation was performed, not blinded trial
[2] Unclear how randomisation was performed
[3] 95% CI crossed 2 default MIDs (0.8 and 1.25)
[4] 95% CI crossed 1 default MID
[5] 95% CI crossed 1 default MID (1.8 x 0.5= ± 0.9)
6 Only descriptive data has been reported, insufficient details given to assess the MID threshold and imprecission

7 Not calculable as only medians have been reported median progression-free survival was slightly longer in patients receiving WBRT (4.6 months; 95% CI, 3.9 to 6.1 months) compared with those on OBS alone (3.4 months; 95% CI, 3.1 to 3.9 months.

Table 58: Summary clinical evidence profile for WBRT+ SRS +TMZ versus WBRT+SRS

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT + SRS + TMZ**	**WBRT + SRS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	40	-	HR 1.43 (0.89-2.31)	LOW	CRITICAL
CNS progression rates 6 months												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	12/40 (30%)	7/44 (15.9 %)	RR 1.89 (0.82 to 4.32)	142 more per 1000 (from 29 fewer to 528	VERY LOW	CRITICAL
New metastases 6 months												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[5]	none	8/40 (20%)	4/44 (9.1 %)	RR 2.20 (0.72 to 6.75)	109 more per 1000 (from 25 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + SRS + TMZ	WBRT + SRS	Relative (95% CI)	Absolute		
										523 more)		
Steroid use at 6 months												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[5]	none	18/40 (45%)	24/44 (54.5 %)	RR 0.82 (0.53 to 1.28)	98 fewer per 1000 (from 256 fewer to 153 more)	VERY LOW	IMPORTANT
Serious grade 3-5 toxicity												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/40 (40%)	5/44 (11.4 %)	RR 3.52 (1.42 to 8.73)	286 more per 1000 (from 48 more to 878 more)	LOW	IMPORTANT
Brain necrosis grade 4												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/40 (0%)	0/44 (0%)	-	-	LOW	IMPORTANT

1 Unclear allocation concealment
2 95% CI crossed 1 default MID (1.25)

3 Unclear allocation concealment and unclear blinding of participants assessors and investigators
4 95% CI crossed 1 default MID (0.8)
5 95% CI crossed 2 default MIDs (0.8 and 1.25)

Table 59: Clinical evidence profile for WBRT + SRS + erlotinib versus WBRT+ SRS

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT+SRS +Erlotinib**	**WBRT+SRS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44	41	HR 1.47 (0.92-2.36)	-	LOW	CRITICAL
CNS progression rates 6 months												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	12/41 (29.3%)	7/44 (15.9%)	RR 1.84 (0.80 to 4.22)	134 more per 1000 (from 32 fewer to 512 more)	VERY LOW	CRITICAL
Deterioration in performance 6 months												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT+SRS +Erlotinib**	**WBRT+SRS**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	35/41 (85.4%)	23/44 (52.3%)	RR 1.63 (1.20 to 2.23)	329 more per 1000 (from 105 more to 643 more)	VERY LOW	IMPORTANT
Steroid use at 6 months												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	17/41 (41.5%)	24/44 (54.5%)	RR 0.76 (0.48 to 1.20)	131 fewer per 1000 (from 284 fewer to 109 more)	VERY LOW	IMPORTANT
Serious grade 3-5 toxicity												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious	none	20/41 (48.8%)	5/44 (11.4%)	RR 4.29 (1.78	374 more per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT+SRS +Erlotinib	WBRT+SRS	Relative (95% CI)	Absolute		
					imprecision				to 10.38)	1000 (from 89 more to 1000 more)		
Brain necrosis grade 4												
1	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious imprecision4	none	1/41 (2.4%)	1/41 (2.4%)	RR 3.21 (0.13 to 76.74)	-	VERY LOW	IMPORTANT

1 Unclear allocation concealment
2 95% CI crossed 1 default MID (1.25)
3 Unclear allocation concealment and unclear blinding
4 95% CI crossed 2 default MIDs (0.8 and 1.25)
5 95% CI crossed 1 default MID (0.8)

Table 60: Clinical evidence profile for SRS versus observation following resection of metastases

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRS	Observation	Relative (95% CI)	Absolute	Quality	Importance
Median overall survival												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/63 Median survival 17 months (95% CI 13 – 22)	26/65 Median survival 18 months (95% CI 13 to not reached)	HR 1.29 (0.84 to 1.98)	-	LOW	CRITICAL
Local recurrence (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	18/63 (28%)	37/65 (57%)	HR 0.46 (0.24 to 0.88)	248 fewer per 1000 (from 46 fewer to 386 fewer)	LOW	CRITICAL
Time to local recurrence												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63 Median not reached (95%	65 Median 7.6 months (95% CI	HR 0.41 (0.21 to 0.80)	-	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SRS	Observation	Relative (95% CI)	Absolute	Quality	Importance
							CI 15.6 months to not reached)	5.3 to not reached)				
Distant brain recurrence (follow-up 12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	35/63 (55.6%)	43/65 (66.2%)	HR 0.81 (0.51 to 1.27)	77 fewer per 1000 (from 237 fewer to 86 more)	VERY LOW	CRITICAL

[1] *Participants, outcome assessors and investigators were not blinded to group allocation.*
[2] *Confidence interval crosses 1.25 (MID threshold)*
[3] *Confidence interval crosses 0.80 (MID threshold)*

Table 61: WBRT + receptor antagonist (memantine) versus WBRT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**WBRT + receptor antagonist (Memantine)**	**WBRT**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Overall survival HR												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.06 (0.86-1.31)	-	LOW	CRITICAL
Progression free survival												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	-	-	HR 1.06 (0.87-1.30)	-	VERY LOW	CRITICAL
Time to cognitive failure												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	serious[4]	none	-	-	HR 0.78 (0.62-0.99)	-	VERY LOW	IMPORTANT
Cognitive function failure 3 months												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	serious[2]	none	33/75 (44%)	34/66 (51.5 %)	RR 0.85 (0.60 to 1.21)	77 fewer per 1000 (from	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + receptor antagonist (Memantine)	WBRT	Relative (95% CI)	Absolute		
										206 fewer to 108 more)		
Cognitive function failure 15 months												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[5]	none	5/9 (55.6%)	6/9 (66.7%)	RR 0.83 (0.40 to 1.46)	113 fewer per 1000 (from 400 fewer to 307 more)	VERY LOW	IMPORTANT
Grade 3-4 adverse events												
1	randomised trials	very serious [3]	no serious inconsistency	no serious indirectness	very serious[5]	none	36/256 (14.1%)	35/252 (13.9%)	RR 1.01 (0.66 to 1.56)	1 more per 1000 (from 47 fewer to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	WBRT + receptor antagonist (Memantine)	WBRT	Relative (95% CI)	Absolute	Quality	Importance
										78 more)		

1 Unclear randomisation method
2 95% CI crossed 1 default MID (1.25)
3 Unclear randomisation method; unclear whether outcome assessors were blinded to treatment allocation
4 95% CI crossed 1 default MID (0.8)
5 95% CI crossed 2 default MIDs (0.8 and 1.25)

GRADE tables for review 5c – follow-up of metastases

Not applicable - no evidence was identified.

Appendix G – Economic evidence study selection

Economic evidence study selection for review 1b - imaging strategy for brain metastases

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 4a – management of single metastases

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 4b – management of multiple metastases

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 4c – management of brain metastases with a mixed population

Economic study selection flowcharts are in Supplementary Material D.

Economic evidence study selection for review 5c – follow-up of metastases

Economic study selection flowcharts are in Supplementary Material D.

Appendix H – Economic evidence tables

Economic evidence tables for review 1b - imaging strategy for brain metastases

Not applicable – no economic evidence was identified.

Economic evidence tables for review 4a – management of single metastases

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Study 1						
Author: Kimmell Year: 2015 Country: USA	Type of analysis: Cost utility Model structure: Decision Tree Cycle length: N/A Time horizon: Lifetime Perspective: US Healthcare Payer Perspective	Base-case (population): People with a single brain metastasis. No baseline or population demographics were reported. Subgroup analysis: None performed	1)Whole Brain Radiotherapy (WBRT) 2)Stereotactic Radiosurgery (SRS) 3)Surgery 4)SRS+WBRT 5)Surgery+WBRT 6)Surgery+SRS	Effectiveness (QALYs): WBRT SRS Surgery SRS+WBRT Surgery+WBRT Surgery+SRS Total costs (per patient): WBRT SRS Surgery SRS+WBRT Surgery+WBRT Surgery+SRS ICER (cost per QALY versus WBRT):	 0.69 0.82 0.88 0.92 0.88 0.98 $32,140 $33,043 $36,786 $40,884 $47,603 $58,728	Funding: The authors declared no conflicts of interest. No funding source reported. Comments The study

	Source of base-line data: No baseline characteristics reported for this model Source of effectiveness data: A systematic review was performed of studies published after 1990 and listed on PubMed. The date the search was run was not reported. Studies with greater 5 patients, included solitary brain metastases and reported survival outcomes. The studies identified ranged from randomised prospective studies to retrospective case series Source of utility data: Utility values were based on the authors' clinical experience and informed by Karnofsky performance status. The relationship between KPS and utility score was not made clear.			SRS Surgery SRS+WBRT Surgery+WBRT Surgery+SRS Uncertainty: No investigations around uncertainty were reported.	$7,377 $25,514 $39,117 $82,769 $91,856	acknowledges that the patient groups for each intervention were not homogenous in terms of characteristics likely to predict the efficacy of treatment and no attempt was made to account for this. No sensitivity analyses were

	Source of cost data: Drug costs were taken from online pharmacy data. Intervention costs were taken from the Agency for Healthcare Research and Quality's HCUPnet data. Other costs (surveillance and follow-up) were not considered in the analysis Currency unit: US Dollars ($) Cost year: Not reported Discounting: Costs and outcomes were not discounted.					performed
Study 2						
Author: Kim Year: 2017 Country: USA	Type of analysis: Cost Utility Model structure: Markov Model Cycle length: 1 Month	Base-case (population): Hypothetical cohort of patients with brain metastases from oligometastatic disease. No distinction was made between	Stereotactic Radiosurgery (SRS) Upfront Whole Brain Radiotherapy with Stereotactic Radiosurgery (SRS+WBRT)	Effectiveness (QALY)1: Additional QALYs SRS Total costs (per patient)1: Additional Cost SRS ICER (cost per QALY): SRS versus SRS+WBRT	0.1 $1,027 $9,917	Funding: Not reported Comments No distinction, or reporting of the

[1] Disaggregated results not reported

	Time horizon: 5 years Perspective: US Healthcare Payer Source of base-line data: Baseline characteristics were taken from four RCTs comparing SRS with and without WBRT in patients with 1-3 brain metastases. Given the mix of single and multiple metastases in the patient populations none of these studies were included in the accompanying clinical evidence review. Source of effectiveness data: All transition probabilities in the Markov Model were taken from the four RCTs described above. Methods of synthesis of evidence were not reported. Survival	those with single or multiple metastases or percentage reported. The age at baseline of the cohort was assumed to be 60 years. Subgroup analysis: None performed		Uncertainty: Deterministic Sensitivity Analysis(Cost per QALY) Probability cognitive decline for SRS=0.64 Probability cognitive decline for SRS=0.19 Probability cognitive decline for SRS+WBRT=0.92 Probability cognitive decline for SRS+WBRT=0.46 Overall Survival=7 months Overall Survival=11 months Only 12 month survivors included analysis Only 24 month survivors included analysis Threshold Analysis Values for probability cognitive decline for SRS for which it is dominated Probabilistic Sensitivity Analysis Probability SRS Cost Effective at a cost per QALY threshold of $10,000. Probability SRS Cost Effective at a cost per QALY threshold of $50,000.	$81,866 SRS Dominant $4,526 $80,870 $5,061 $29,084 $15,360 $33,530 >60% 82% 92%	percentage, of single and multiple metastases.

	was assumed equal between both interventions Source of utility data: All utility values, other than for progression-free survival, were taken from Lester-Coll (2016). This was a prospective survey of 24 patients with brain metastases and 31 nurses concerned with the care of patients with brain metastases before and after WBRT or SRS. The questionnaire was administered between December 2013 and May 2015 at 1 US centre. A standard gamble technique was used to estimate utility scores. No adjustment was made for baseline or demographic information. Source of cost data:					

	All cost data were taken from unadjusted national rates for Medicare reimbursement for the year 2016. Currency unit: US Dollars ($) Cost year: 2016 Discounting: QALYs: 3% per Annum Costs: 3% per Annum					

Economic evidence tables for review 4b – management of multiple metastases

Not applicable – no economic evidence was identified.

Economic evidence tables for review 4c – management of brain metastases with a mixed population

Primary details	Design	Patient characteristics	Interventions	Outcome measures	Results	Comments
Author: Wernicke	Type of analysis: Cost Utility	Base-case (population):	1.Surgery with Cs-131 stranded seeds implanted to 5mm	Effectiveness (QALY): Method A		Funding: None declared

Year: 2016 Country: USA	Model structure: N/A Cycle length: N/A Time horizon: Not clear, median survival of cohorts were 15.5 months and 11.3 months for the Cs-131 and SRS cohorts respectively. Perspective: US Hospital Perspective Source of base-line data: Base-line data for the Cs-131 cohort was taken from prospective phase I/II trial of Cs-131 in addition to surgery at 1 US Centre. (Wernicke, 2014) The trial enrolled 24 patients with newly diagnosed metastases of the brain.	Patients with 1-3 newly diagnosed brain metastases >2.5cm (63% had a single metastasis) and ECOG performance status of 0,1 or 2 and expected survival of at least 6 months, who required surgery for relief of mass effect or for diagnosis. The cohort was taken from 1 phase I/II trial of intraoperative Cs-131 at 1 US centre between 2010 and 2012 formed the Surgery and Cs-131 cohort. The Surgery+SRS was made up of patient who chose not to enrol in the Cs-131 trial, needed surgery	from the surface of the resection cavity with an activity of 3-5 mCi with a dose of 80 GY. 2.Surgery and Stereotactic Radiosurgery (SRS) following the RTOG protocol 90-05.	Surgery+Cs-131 Surgery+SRS Method B Surgery+Cs-131 Surgery+SRS Total costs (per patient): Surgery+Cs-131 Surgery+SRS ICER (cost per QALY): Method A Method B Uncertainty: No investigations around uncertainty were reported.	0.78 0.47 0.67 0.45 $19,271 $44,219 Surgery+Cs-131 Dominant Surgery+Cs-131 Dominant	Comments Author AGW supported by funds from the National Institute of Health CTSC KL2 Comparative Effectiveness Research Award UL1-TR000457

	Baseline data for the SRS cohort were taken from 25 patients from the same centre chose not to enrol in the Cs-131 trial, needed surgery urgently before Cs-131 could be ordered or were treated between 2008 and 2010 before commencement of the trial at the same centre. Source of effectiveness data: Effectiveness data were taken from the same trials described above. Overall survival, Karnofsky performance status (KPS) and disability status were taken from the above phase I/II trial. The median survival of cohorts were 15.5 months and 11.3 months for the Cs-131 and SRS cohorts respectively. The values for Karnofsky Performance Score and disability status were not reported in this paper or in	urgently before Cs-131 could be ordered or were treated between 2008 and 2010 before commencement of the trial. 92% of the cohort had a single brain metastasis. Average age of the cohort was 63 years old and was 51% male. The Cs-131 group had a higher Karnofsky performance status than the SRS cohort. Subgroup analysis: None performed				

	the paper for the above trial. Other effectiveness data, such as surgery complications were not directly considered by the study despite being considered by the trial. Source of utility data: 2 methods of quantifying quality of life were used by the authors in separate analyses. Method A assumed a quality of life score of 1 for normal life, 0.8 for mild disability, 0.5 for moderate disability, 0.3 for severe disability and 0.2 for vegetative state. How these health states are defined and scored is not reported. Method B converts the KPS score into a QALY. Again how these have					

	been converted is not reported. Source of cost data: Cost were taken from the receipts of direct hospital related costs of patients during the trial. The study excluded administrative and overhead costs. They also excluded reimbursement costs as these varied widely by type of medical insurance the patient had. Costs related to length of stay were excluded from the analysis as these were heavily correlated with the health insurance the patient had and consequently with socio-economic issues. Currency unit: US Dollar ($) Cost year: Not reported Discounting:					

	No discounting performed					

Economic evidence tables for review 5c – follow-up of metastases

Not applicable – no economic evidence was identified.

Appendix I – Health economic profiles

Economic evidence profiles for review 1b - imaging strategy for brain metastases

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 4a – management of single metastases

See evidence review for management of single metastases for health economic evidence profiles.

Economic evidence profiles for review 4b – management of multiple metastases

Not applicable – no economic evidence was identified.

Economic evidence profiles for review 4c – management of multiple metastases

See evidence review for management of multiple metastases for health economic evidence profiles.

Economic evidence profiles for review 5c – follow-up of metastases

Not applicable – no economic evidence was identified.

Appendix J – Health economic analysis

Economic analysis for review 4a – management of single metastases

Background

People with a single brain metastasis potentially have longer life expectancy, quality of life and are suitable for a wider range of interventions than people with multiple brain metastases. Certainty around the optimal treatment for such patients is lacking with a careful balance needed between disease control and the adverse events of treatment. This is especially true in the face of the improved effectiveness of systemic therapy leading to greater survival in more patients which may increase the importance of achieving local control in people with a single brain metastasis.

Traditionally, single brain metastases have been treated with surgical resection followed by a course of whole brain radiotherapy (WBRT). Over recent years the popularity of stereotactic radiosurgery (SRS) has increased again followed by WBRT. Even more recently the use of surgical resection followed by SRS to the cavity has increased with associated additional costs. Which treatment a patient receives is largely dependent upon the centre at which they are being treated.

Doubts also remain about the use of WBRT following initial treatment with uncertainty around whether better local control associated with WBRT lead to sufficient improvements in quality of life to outweigh the additional costs and adverse events. This economic analysis will compare different adjuncts to initial treatment (surgery or SRS), if any are cost effective.

Methods

Interventions considered

Two economic models were built each with a different initial treatment with no adjuncts for a single brain metastasis and compared this to the same initial treatment but with treatment adjuncts. The comparator and interventions and the considered adjuncts are summarised in Table 62.

Table 62: Comparators and interventions considered by the economic models

	Initial treatment surgery	Initial treatment SRS
Comparator	• Complete surgical resection of the brain metastasis (surgery)	• Stereotactic radiosurgery (SRS)
Intervention(s)	• Surgery and whole brain radiotherapy administered within 6	• SRS and whole brain radiotherapy administered within 6

	weeks of surgery (surgery and WBRT). • Surgery followed by postoperative SRS to the resected tumour bed (surgery and SRS)	weeks of surgery (SRS and WBRT).

Interventions and comparators were compared in terms of health outcomes, costs and cost effectiveness.

Two models were built as whether to initially receive surgery or SRS would be based on factors such as the size of the metastasis, the location, the presence of oedema and any other comorbidities. The patient group initially receiving SRS would therefore differ from that initially receiving surgery and there would be little validity in comparing their cost effectiveness. An analysis comparing all 5 potential interventions was therefore not performed.

For ease of modelling WBRT was assumed to consist of 30 Gy of radiation in 10 fractions targeted at the brain although this was likely to differ by patient based on patient preference and clinical considerations (size and location of the metastasis, performance score etc).

WBRT alone is now largely used in groups for which other targeted treatments are unlikely to be effective or as a palliative treatment but rarely in the patient group considered by these models. While it was hypothesised by the committee that treatment with WBRT alone would lead to a reduction in resource use it would also likely be associated with a significant decrease in both quality of life and life expectancy compared to current treatment. For this reason it was not deemed an appropriate treatment for the patient population considered in this analysis and thus was not modelled.

Model structure

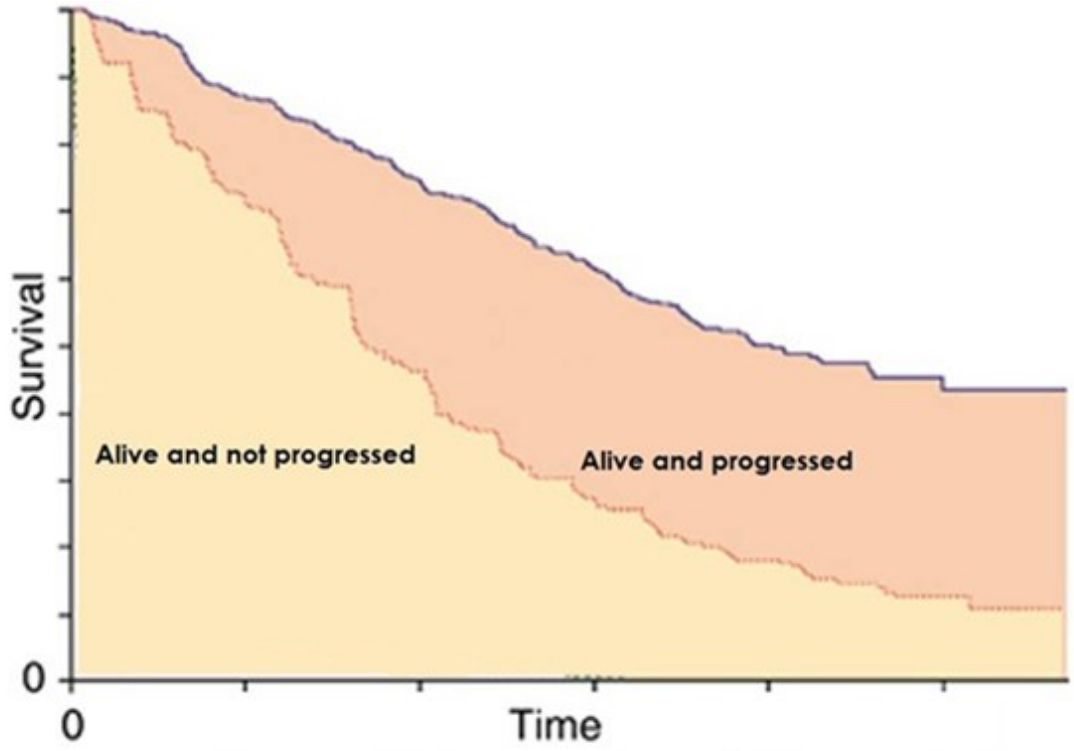
Both models followed an identical model structure. A partitioned survival analysis was developed to estimate the expected life time quality adjusted life years (QALYs) and costs associated with the interventions considered for this patient population. A partitioned survival analysis divides the model cohort between different health states based on survival curves derived for OS and PFS (discussed below). The expected OS and PFS are then calculated from the area under the respective curves. For our model 5 mutually exclusive health states were derived for the cohort to be partitioned into:

- alive without progressed disease (equal to the area under the PFS curve)
- alive with progressed disease (equal to the area between the PFS curve and OS curve).
- death (area above the OS curve)

The alive with progressed disease state includes intracranial progression at the initial site, intracranial progression at a new site and extracranial progression. For simplicity of illustration and as model assumptions mean that individuals could not transit between these states it was included as 1 state in the example but treated as 3 in the model.

An illustrative example of the structure of the partitioned survival analysis is shown in Figure 20.

Figure 20: Illustrative example of partitioned survival analysis



The model has 3 forms of disease progression which feed into the PFS curve; local progression at the initial site, local progression intracranially at a new site and extracranial progression. All these types of progression are regarded as progressed disease in the model and treated identically. While these types of progression are not mutually exclusive (i.e. you can progress at the initial site and extracranially) they were treated as such in the economic models. As the OS and PFS evidence to inform the model would allow for these non-mutually exclusive events in their

reported data (that is to say, patients could appear in both the locally progressed and extracranially progressed counts) it was incorporated in to the model as uncensored data (not accounting for being in other states). The model would then apply the probability of transition from 1 state to another in the following order: death, local progression at initial site, local progression new site, and extracranial progression. This would allow for only 1 transition at a time and prevent the mutual exclusivity assumption being broken. The model assumed that people could progress from the 'not progressed' state directly to any other; people in the 'progressed state' could only transition to death and not other progressed states. As discussed above, while this is not realistic, given the assumptions made by the model it would have no effect on results in terms of costs and outcomes.

A partitioned survival analysis approach was chosen over other modelling approaches, for example a state transition model. However, given the assumptions made the model would approximate to a Markov model with time dependent probabilities. A partitioned survival analysis approach is widely used in economic models of the cost effectiveness of oncology interventions. A review of recent oncology NICE Technology Appraisals found that this approach was used in 73% of submissions (Woods 2017). Given the modelling assumptions made about other events in the model, such as adverse events and receiving further or salvage treatment, do no impact upon OS and PFS, the curves do not need to account for these factors. Such events are a potential source of bias in partitioned survival analysis although given how evidence used to populate the model is reported it would be difficult to account for this bias in any modelling approach.

While not a consideration in choosing the most appropriate modelling approach, a partitioned survival analysis is a more intuitive modelling approach for brain metastases than state transition models. Evidence from clinical trials and observational studies where survival is a key outcome are almost exclusively reported as median overall and progression-free survival with accompanying hazard ratio and Kaplan Meier survival curves. As these are the primary inputs for partitioned survival analysis the outputs of the model can be easily compared with those observed in the included trials and other external sources.

A partitioned survival analysis was performed for each intervention considered in the economic evaluation and total time spent in each health state for the model cohort was recorded. Each health state was assigned a quality of life weighting so that QALYs could be calculated.

A proportion of the cohort will have some form of salvage treatment following disease progression. This will incur costs associated with the treatment received. Salvage therapy will have no impact upon health outcomes in the model as any benefit of such treatment would have been picked up in the OS and PFS of the studies included to populate the model and thus any inclusion in the economic model will lead to double counting and overestimation of the costs and effectiveness of treatments. Independently of the partitioned survival analysis the model cohort also has a probability of having treatment-related adverse events.

More detailed discussion of the definition of these states and how they are informed in the model is discussed below.

The models were built and run in Microsoft Excel 2013. The model had a cycle length of 1 month and a time horizon of 5 years, the longest follow up identified by the accompanying clinical evidence review. The study suggested that over 98% of the cohort would be dead at this time horizon. (Kocher 2011)

Population

The hypothetical cohort considered in the model were adults with a single brain metastasis who had not previously received intracranial treatment for cancer. The metastasis had to be less than or equal to 3cm in diameter and be in an operable site (suitable for both surgery and SRS). Members of the cohort had a Karnofsky performance status (KPS) of at least 70. None of the cohort had progressive systemic disease. This hypothetical patient cohort were clinically suitable for all interventions considered by the 2 models. It was also similar to the patient cohorts in the studies used to parametrise the economic model increasing both the applicability and the validity of the inputs used.

The models did not explicitly consider multiple brain metastases although the results of this economic evaluation may be gerneralisable to people with a limited number of metastases and good performance score who show similar prognosis to that of people with a single metastatsis. This patient group was also included in some of the evidence used to inform the model (see below). The committee were reluctant to explicitly consider multiple metastases in the economic model given they are likely to show greater heterogeneity than single metastases and that greater consideration would be needed to the disease characteristics (number of metastases, total volume, location, comorbidities etc) and patient preference when planning treatment options.

Model Parameters

Overall Survival

Two studies were identified by the accompanying clinical evidence review which compared overall survival between 2 interventions considered in the economic evaluation in patient group similar to that considered by the economic model, both comparing surgery and WBRT to surgery and SRS. (Brown 2017, Kepka 2016) Two studies were identified which reported overall survival (Mulvenna 2016, Andrews 2004). Mulvenna 2016 compared dexamethasone and supportive care with or without WBRT in patients unsuitable for surgery or SRS. As both this patient group and treatments were not considered by the economic evaluation it could not be used to inform the economic model. Similarly Andrews 2004 compared WBRT to SRS and WBRT, although again it was in patients who were unsuitable for surgery (metastasis was located in deep grey matter or in eloquent cortex). As the patient group differed significantly from the 1 considered by the economic model it was again deemed inappropriate to use overall survival estimates from this study.

As no studies were identified in the accompanying clinical evidence review which would adequately populate this variable for surgery, SRS or SRS and WBRT the ‘not included’ studies and multiple metastases and mixed metastases evidence was searched to identify studies comparing overall survival in this group. Only 1 randomised controlled trial was identified that considered all the interventions

considered by the primary economic analysis. (Kocher 2011). The study was an RCT of patients with either a single (n=279, 81%) or multiple [2-3] (n=68, 19%) brain metastases who were in good condition without progressive systemic disease. Patients were randomised to receive WBRT or not after being treated with surgery or before being treated with SRS at multiple European centres. Treatment with surgery or SRS was not randomised. This study was used to inform overall survival for surgery with or without WBRT and SRS with or without WBRT in the economic models.

Kocher 2011 reported a median survival of 10.9 months for those receiving surgery or SRS without WBRT and 10.7 months for those who received WBRT although the results were not statistically significant. The reported hazard ratio for the surgery and SRS alone group compared to the WBRT group was 0.98 (95%CI 0.78 to 1.24). Disaggregated overall survival was not reported for either type of initial treatment or for whether the patient had single or multiple metastases. No robust evidence was identified for overall survival for surgery or SRS alone in this patient group and the committee considered that survival between the 2 groups was unlikely to differ. Therefore, in the base-cases overall survival was assumed identical between SRS and surgery and also identical between SRS and WBRT and surgery and WBRT.

Conversely, survival was likely to differ between patients with single and multiple metastases given the differences in the extent of their disease. The multiple metastases group in this study however had limited additional metastases (maximum 3) and good performance score, therefore this difference was likely to be minimal. Furthermore this patient group made up less than 20% of the study population. Given these considerations as well as the paucity of evidence comparing survival in single and multiple metastases, no adjustments were made to the survival reported in this study. As the overall survival reported in this study was likely to be an underestimate of true overall survival, sensitivity analysis explored the impact of increasing overall survival in the model.

For the base-case analysis an identical survival curve was fitted for both surgery and SRS based on the Kaplan Meier curve for overall survival reported in Kocher 2011. The survival curves were fitted in R Statistical Package using methods reported by Hoyle 2011 using code made publicly available by the authors. The shape and scale parameters were taken directly from the R package results and added to the Excel model. The covariance for these parameters were also calculated in the form of a Cholesky Decomposition Matrix and used to inform the probabilistic sensitivity analysis (PSA). Weibull and exponential models were considered using Akaike Information Criteria (AIC) with Weibull distribution estimated to be the best fit for overall survival (AIC range 1618.5-1627.3 for Weibull function versus 1633.4-1646.4 for Exponential function). The study reported survival up to 5 years post intervention, identical to the time horizon of the model, so no extrapolation was needed beyond this point. These parameters are summarised in Table 63.

The identical survival curves for surgery and WBRT and SRS and WBRT were calculated from the reported hazard ratio relative to the overall survival curves for surgery and SRS. The usual proportional hazard assumptions were made about the

hazard ratio for overall survival. The Hazard ratio was varied using a log-normal distribution during PSA.

OS for surgery and SRS was taken from the clinical evidence review which estimated a pooled which estimated a hazard ratio of 1.31 (95%CI 0.80-2.15). OS in the economic model for surgery and SRS was calculated from the OS curve for surgery and WBRT adjusted using the reported hazard ratio following the usual proportional hazard assumptions. The hazard ratio was varied using a log-normal distribution during PSA using the reported ranges.

The pooled estimate was calculated from two studies Brown 2017 and Kepka 2016. identified by the accompanying review of the clinical evidence. Brown 2017 compared surgery and WBRT (n=96) to surgery and SRS (n=98) in patients with a single brain metastasis at 48 institutions in the United States and Canada. Brown 2017 reported median survival was 12.2 months and 11.6 months for the surgery and SRS and surgery and WBRT groups respectively with a corresponding hazard ratio of 1.07 (95%CI 0.76-1.50). The 11.6 months is similar to the 10.7 months median survival reported for surgery and WBRT by Kocher 2011 and used to inform the economic model. Kepka 2016 compared surgery and WBRT (n=30) to surgery and SRS (n=29) in patients with a single brain metastasis in Poland. Kepka 2016 reported a hazard ratio for OS of 1.80 (95%CI 0.99-3.27). Both studies are discussed in detail in the accompanying clinical evidence review.

Local progression

Local control in terms of intracranial progression at initial site (that treated by surgery or SRS) and intracranial progression at new sites not previously treated were taken from Kocher 2011 for surgery with or without WBRT and SRS with or without WBRT. The study reported intracranial progression for both the initial and new sites was significantly higher in the Surgery and SRS arms compared to the surgery and WBRT and SRS and WBRT arms (78% versus 48% p<.001, Gray test). Time to intracranial progression for both initial and new sites were taken from the time to event curves reported in Kocher 2011. These were reported for all 4 interventions considered in the primary analysis and therefore were different between interventions. As with overall survival these curves were fitted using identical methods as for overall survival up to 2 years. After that the curves plateaued for all interventions and progression was assumed not to occur after this point. While this assumption could only underestimate progression, given the shape of the time to progression curves and the less than 30% survival in this patient group at that time point any underestimate was likely to be very small and unlikely to significantly impact upon results. These shape of the curves were varied during the PSA using a uniform distribution of ±25% on the shape parameters. It would have been inappropriate to use the Cholesky decomposition matrices in this instance given that these estimates are not independent of overall survival.

Local progression at the initial site for surgery and SRS was taken from Brown 2017. The study reported a time to local progression at the initial site of 27.5 months and 6.4 months respectively for surgery and WBRT and surgery and SRS respectively (Hazard ratio=2.45[95%CI 1.62-3.72]). This hazard ratio was used to adjust the surgery and WBRT curve for progression at the initial site following the usual

proportional hazards assumptions. The hazard ratio was varied along its confidence interval using a log-normal distribution during PSA.

Local progression at a new site was not reported by Brown 2017. There was no clinical reason why this would differ from that of surgery alone and was therefore assumed to be identical to that of surgery alone. This assumption was not varied during sensitivity analysis.

Extracranial progression

Extracranial progression, progression of disease that occurs anywhere outside of the cranium, was again taken from Kocher 2011 for the 4 relevant interventions. Extracranial progression was reported in 37% of patients in the surgery and SRS arms and 38% in the surgery and WBRT and SRS and WBRT after 6 months of follow up. This increased to 63% and 65% respectively at 2 years. As time to event or Kaplan Meier curves were not reported for these values an exponential distribution was assumed between the time points for purposes of modelling. As values were only reported up to 2 years extracranial progression was assumed not to occur after 2 years. Again this will be a certain underestimate of the true number of extracranial progressions although the number of missed progressions was likely to be very small.

Extracranial progression was not reported by Brown 2017. As extracranial progression was almost identical for all 4 other interventions and there was no identified clinical reason for why extracranial progression rates would be different for surgery and SRS than for surgery or SRS alone they were given identical values in the model. The percentage values for 6 months and 2 years were varied using a beta distribution during PSA.

As the model assumed no progression either intracranially or extracranially after 2 years no partitioning into these states occurred after this time. Death continued to occur in line with the survival functions estimated above until the time horizon of the model.

Adverse events

The proportion of adverse events associated with each intervention were taken from Kocher 2011 for all interventions other than surgery and SRS. Only Grade 3 (severe) and Grade 4 (life threatening) adverse events were included as these were the ones deemed most likely to significantly impact upon costs and quality of life. Adverse events and proportions are reported in Table 63.

Serious rare adverse events reported by Kocher 2011 (epileptic seizures, radionecrosis, haemorrhage, stroke, erythema multiforme, leukoencephalopathy and hydrocephalus) were excluded from the model as these occurred only in very small number of cases.

The proportion of adverse events were varied using a beta distribution during probabilistic sensitivity analysis. The study did report that grade III and grade IV adverse events were fewer (11 out of 93 people) in the surgery and SRS compared to the surgery and WBRT group (17 out of 92 people). As the model has been

configured so that the type of adverse event does not alter either quality of life or costs we assumed that every category of adverse event for surgery and WBRT was reduced by the proportion reported in Brown 2017 (approximately a decrease of 1/3) to estimate the adverse events for surgery and SRS. Deterministic sensitivity analysis was performed to investigate the impact of this assumption on the conclusions of the model.

The proportion of adverse events were varied using a beta distribution during probabilistic sensitivity analysis.

Resource Use

Interventions

All patients were assumed to receive the intervention relevant to their arm at the start point of the model. While WBRT was assumed to be received within the first 6 weeks following the initial intervention it was still assumed to occur at time 0. It was assumed that no patients died in the surgery and WBRT and SRS and WBRT arms between initial intervention and WBRT and that WBRT would be received by all patients. While in reality some patients may die during that period costs are still likely to be incurred through scheduling of the treatment.

Follow up

Patients were assumed to receive a MRI scan and consultant led follow up for every 3 months they are alive in the model.

Salvage therapy

Patients in the model could receive any salvage therapy if their initial treatment fails and the patient has intracranial progression. Patients in the model could receive either WBRT, SRS or surgery or some combination of them following intracranial progression. The proportion of patients receiving some form of salvage therapy and the type received are taken from Kocher 2011 for all interventions other than surgery and SRS which were taken from Brown 2017. In Kocher 51% of patients in the surgery and SRS arms received some form of salvage therapy following intracranial progression compared to 16% in the surgery and WBRT and SRS and WBRT arms. The main reason for this difference is through the ability to receive WBRT as a salvage therapy in groups that did not receive it as an initial treatment. Approximately 30-40% of patients will receive WBRT as a salvage therapy if they have not received it during initial treatment. (Kocher 2011) It is difficult to give patients who received WBRT at initial treatment WBRT as salvage therapy in these numbers without causing serious irreversible neurological deterioration. In Brown 2017 20 out of 98 patients in the surgery and WBRT group went on to receive WBRT as salvage therapy following disease progression. No other type of salvage therapy was received by this group.

The proportion of patients receiving each type of salvage therapy is reported in Table 63.

Other resource use

Other resource use are likely to be incurred by the patient cohort that have not been considered by the models (e.g. systemic therapy, rehabilitation etc.). This resource use could potentially be significant and account for a large proportion of the total costs. However, no evidence was identified for how such resource use would differ between the different interventions considered and the committee found it difficult to speculate on the direction or size of any potential differences. Given these difficulties this resource use was not included in the economic models.

Costs

Interventions

All interventions were costed using NHS Reference Costs 2015-2016. Costs for WBRT were assumed to be on an outpatient basis assuming 10 fractions of radiation (£105 per fraction) delivered with a megavoltage machine and a one-off cost for preparation of £655. The addition of WBRT to treatment added £1,702 to the cost of treatment. Costs for all other treatments were assumed to be given on an elective inpatient basis and assumed a clinical complication score of between 0-3 where appropriate. The total bed days for this cohort was assumed to be within the trim points of the Reference Costs and thus no additional bed days were added to the costings. Both of these assumptions appeared reasonable given the relatively good performance score, solitary metastasis and suitability for all interventions would not lead to excessive complications in the majority of cases. Where multiple treatments were received this was simply the sum of the combined treatments. In the base-case the cost of surgery was £7,032 while SRS was £3,556.

Follow up

Follow-up was costed as 1 non-admitted face to face follow up in neurosurgery and 1 MRI scan of the brain. The combined cost of 1 follow-up session was £333.

Adverse events

Adverse events were not costed in the baseline model. It was assumed that the costs of treating these adverse events would be picked up by the NHS Reference Costs especially as all included adverse events were common in all the arms of the model. A scenario analysis was performed where these adverse events were costed as 1 non-admitted face to face follow up in neurosurgery.

Salvage therapy

The cost of salvage therapy were not costed in the base-case analysis despite there being significant resource use and costs associated with it. This was because any cost savings from the reduction in salvage therapy in the surgery and WBRT and SRS and WBRT arms would come about through the contraindication of potentially effective subsequent therapies. If this was the key driver of the cost-effectiveness of any interventions of the model it came about through the prevention of widely used current treatments. The committee thought that they could not ethically make a recommendation based on cost effectiveness if this was being driven by the

prevention of people receiving interventions which were standard of care and thus these costs were excluded from the base-case analysis. These costs were included as part of a scenario analysis and were costed identically to those for the primary interventions.

Probabilistic sensitivity analysis

All NHS Reference Costs were varied along their reported ranges during PSA using a gamma distribution. Full costs and ranges are reported in Table 63.

C*ost year*

All costs in the model were taken from 2015-2016 NHS Reference Costs the latest year available. Consequently it was not necessary to perform any inflation of costs.

Health related quality of life

The accompanying clinical evidence review looked for papers considering quality of life amongst the papers that met the inclusion criteria. Three studies identified and matched the inclusion criteria reported on quality of life. Mintz 1996 reported Spitzer Score for quality of life at both 3 months and 4-6 months for patients with a single brain metastasis receiving either surgery and WBRT or WBRT alone. The study showed no difference in quality of life between WBRT and surgery and WBRT at 4-6 months but there was a trend towards higher quality of life at 3 months for people receiving WBRT compared to surgery and WBRT. The Spitzer quality of life index has 5 domains (health, activity, daily living, outlook and support) and is completed by a medical professional. The resulting score is on a scale of 0 to 10. This measure of quality of life is not patient reported, is not scored using population preferences and it is unclear how the score compares to more widely used measures of quality of life. The study is also of considerable age and both techniques have advanced significantly in that time improving effectiveness and decreasing adverse events. Therefore, any historic measures of quality of life are unlikely to be reflective of quality of life following such interventions received today. Therefore, despite having similar interventions and patient population to that considered by this economic analysis, it was not used to inform the model.

The second study identified compared SRS to surgery and WBRT in patients with a single brain metastasis (Muacevic 2008). Quality of life data for this study was collected for both interventions at 6 weeks using the European Organization for Research and Treatment of Cancer Quality of Life and brain cancer module 20. The study reported a difference in score for ‘role functioning’ and ‘QOL’ at 6 weeks favouring SRS but these differences were lost 6 months after treatment. As no absolute values were reported (only a p-value of the difference) it was not possible to use this study to inform the model.

The third study (Mulvenna 2016) compared standard of care with and without WBRT in patients unsuitable for either surgery or SRS. While the study used the EQ-5D to report quality of life, NICE’s preferred instrument, the patient group did not match closely that considered in this economic analysis as patients were ineligible for 2 of the interventions considered. It was likely that quality of life would be much lower in

this patient group compared to that considered by the economic model and would not be generalisable. This was supported by the fact that over 40% of patients in this study had a KPS of less than 70. Again this study was not used to inform quality of life in the economic model.

As none of the evidence around quality of life identified in the accompanying evidence review was appropriate for use in the analysis, we considered evidence from the multiple brain metastases topic, the CEA (Cost-Effectiveness Analysis) registry website, excluded studies from the evidence review and discussion with the committee. This approach identified 2 studies potentially relevant for informing the economic model.

Miller 2017 investigated the quality of life of patients with both single and multiple brain metastases following treatment with SRS. The study prospectively collected health utility data from 67 patients who received SRS following diagnosis of brain metastases at 1 single US tertiary centre between 2008 and 2015. Patients were given the EQ-5D-3L and Patient Health Questionnaire 9 immediately before outpatient visits roughly every 2-3 months. In the whole population (45% single brain metastases) EQ-5D score reported a pre-SRS quality of life weight of 0.752 which deteriorated expectedly to 0.673 at the last follow up with a median of 6 follow ups and follow up of 12 months.

The EQ-5D-3L is NICE's preferred method for the elicitation of quality of life values. The EQ-5D-3L is a non-disease specific survey assessing health related quality of life across 5 health domains (mobility, self-care, daily activities, pain and anxiety/depression) with the severity rated on 1 of 3 levels (No Problems, Moderate Problems, Extreme Problems). This is given alongside a visual analogue scale ranging from 'worst imaginable health' and 'best imaginable health' with a 0 to 100 scale on which responders can rate their current health. These responses were amalgamated into a health profile and given a quality of life score, between 0 and 1 based upon the US general population sample. NICE prefer EQ-5D scores valued using the UK general population sample but no quality of life data were identified using this measure. Quality of life scores are likely to differ between countries through a differing national way of valuing health and through differing demographics leading to sampling differences. These US population values may therefore differ from UK ratings. The patient group pre-SRS in this study was likely to be similar to the patient cohort prior to treatment in our model. The pre-SRS value of 0.752 was used as the baseline health state (Alive with controlled disease) for the patient cohort in the model. The study however only considered 1 intervention investigated by the economic model (SRS) and was not reported in such a way that it could be used to inform quality of life in the economic model. Therefore, values post treatment were not considered by the economic model

Lester-Coll 2016 prospectively measured quality of life utilities for hypothetical health states associated with brain metastases in people with metastases before and after either WBRT or SRS at 1 US tertiary centre. Health status was measured using a standard gamble technique in 24 patients and 31 nurses involved with treatment of brain metastases. The proportion of the patient cohort that had single metastases was not reported. Utilities were estimated for 7 health states: post SRS, post WBRT,

post salvage WBRT, progression after WBRT, neurological dying, radionecrosis and cognitive decline. Despite not considering all interventions considered by the economic model, the different health states somewhat matched those considered by the economic model. Therefore, these values were used to inform health state utilities in the economic model post treatment. Combined values were used (over patient reported and nurse reported) to increase the precision of the estimates. The reported mean values were used over the median values as mean values of costs and QALYs are the appropriate way to report outcomes from an economic evaluation. Local progression at either the initial site or another intracranial site was scored as identical to 'Salvage WBRT' in Lester-Coll 2016 as a large proportion of these patients would receive some form of salvage therapy. Extracranial progression was scored identically to 'Progression after WBRT' in Lester-Coll 2016. This state represents patients who would be receiving only palliative care for their disease which would be the case for the majority of this cohort. These values were varied widely along their interquartile ranges using a uniform distribution to reflect the large uncertainty around these utility values.

No utility data were identified around the quality of life impact of adverse events considered in the model. Therefore, in the base-case, it was assumed that each adverse event had a 'one-off' quality of life detriment equal to 1 month in perfect health. For ease of modelling this detriment was added at the start of the model.

As there was low quality evidence around quality of life both in terms of actual value and interactions between different adverse events (i.e. there would likely be correlation between memory and intellectual deficit) extensive sensitivity analysis was carried out around quality of life. A scenario analysis was also run where no QALY detriment was assigned to the adverse events to see if this would impact upon the preferred intervention. During PSA QALY detriments were given a uniform distribution between no detriment and 1 month.

Discounting

All health and cost outcomes were discounted at a rate of 3.5% per annum in line with the NICE guidelines manual. This was not varied during sensitivity analyses.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base-case are replaced with values drawn randomly from the distributions around the mean values. This done over 10,000 iterations to and the different outcomes of these iterations presented to both diagrammatically and in terms of mean results to reflect the uncertainty around the outcomes of the model. The distributions used are presented in Table 63.

Net monetary benefit

All results are presented as incremental net monetary benefit (INMB). INMB is a representation of cost effectiveness where incremental QALY gains, compared to the comparator intervention, are converted into a monetary value by multiplying by a cost

per QALY threshold. For example if an intervention had a QALY gain of 0.5 compared to the comparator and the cost per QALY threshold was £20,000, the monetary value of the QALY gain would equal £10,000. INMB is then calculated by subtracting total incremental cost from this incremental monetary value of the QALYs gained. For our analysis the threshold per QALY is set equal to £20,000 the cost per QALY below which NICE conventionally recommends interventions and £50,000, a higher threshold which NICE consider for interventions which increase life expectancy by at least 3 months in people in their final 24 months of life relative to current treatment. Interventions which report a positive INMB are cost effective compared to the comparator with those reporting a negative value not being cost effective. The 'preferred' intervention would be the one which reports the highest INMB.

Table 63 List of parameters used in the economic model and PSA distribution

	Value	Source	PSA Distribution
Overall Survival (Weibull Function)			
Surgery/SRS Intercept	2.99	Kocher 2011	Cholesky
Surgery/SRS Log Scale	-0.21	Kocher 2011	Cholesky
HR Addition WBRT	1.02	Kocher 2011	Log Normal(1.02,0.12)
HR Addition SRS	1.30	Clinical Evidence Review	Log Normal(1.30,0.17)
Local Control Initial Site (Weibull Function)			
Surgery Intercept	3.54	Kocher 2011	Uniform (-25%,+25%)
Surgery Log Scale	1.21	Kocher 2011	Uniform (-25%,+25%)
SRS Intercept	5.63	Kocher 2011	Uniform (-25%,+25%)
SRS Log Scale	0.94	Kocher 2011	Uniform (-25%,+25%)
Surgery+WBRT Intercept	5.90	Kocher 2011	Uniform (-25%,+25%)
Surgery+WBRT Log Scale	0.85	Kocher 2011	Uniform (-25%,+25%)
SRS+WBRT Intercept	6.67	Kocher 2011	Uniform (-25%,+25%)
SRS+WBRT Log Scale	0.81	Kocher 2011	Uniform (-25%,+25%)
HR Addition SRS	2.45	Brown 2017	Log Normal(2.45,0.21)
Local Control New Site (Weibull Function)			
Surgery Intercept	4.53	Kocher 2011	Uniform (-25%,+25%)
Surgery Log Scale	0.77	Kocher 2011	Uniform (-25%,+25%)
SRS Intercept	4.00	Kocher 2011	Uniform (-25%,+25%)
SRS Log Scale	0.73	Kocher 2011	Uniform (-25%,+25%)
Surgery+WBRT Intercept	5.48	Kocher 2011	Uniform (-25%,+25%)
Surgery+WBRT Log Scale	0.56	Kocher 2011	Uniform (-25%,+25%)
SRS+WBRT Intercept	4.65	Kocher 2011	Uniform (-25%,+25%)
SRS+WBRT Log Scale	0.54	Kocher 2011	Uniform (-25%,+25%)

	Value	Source	PSA Distribution
HR Addition SRS	1	Assumption	Not Varied
Extracranial Progression (6 Month Cumulative Probability)			
Surgery	0.37	Kocher 2011	Beta(32,46)
SRS	0.37	Kocher 2011	Beta(37,63)
Surgery+WBRT	0.38	Kocher 2011	Beta(25,56)
SRS+WBRT	0.38	Kocher 2011	Beta(30,67)
Surgery+SRS	0.38	Assumption	Beta(30,67)
Extracranial Progression (24 Month Cumulative Probability)			
Surgery	0.63	Kocher 2011	Beta(44,34)
SRS	0.63	Kocher 2011	Beta(56,44)
Surgery+WBRT	0.65	Kocher 2011	Beta(47,34)
SRS+WBRT	0.65	Kocher 2011	Beta(56,41)
Surgery+SRS	0.65	Assumption	Beta(56,41)
Probability Receiving Salvage Therapy			
Following Surgery/SRS			
WBRT	0.31	Kocher 2011	Beta(31,69)†
SRS	0.12	Kocher 2011	Beta(12,88)
Surgery	0.06	Kocher 2011	Beta(6,94)
SRS+WBRT	0.01	Kocher 2011	Beta(1,99)
Surgery+WBRT	0.02	Kocher 2011	Beta(2,98)
Following Surgery+WBRT/SRS+WBRT			
WBRT	0.03	Kocher 2011	Beta(44,34)‡
SRS	0.11	Kocher 2011	Beta(56,44)
Surgery	0.02	Kocher 2011	Beta(47,34)
SRS+WBRT	0.00	Kocher 2011	Not Varied
Surgery+WBRT	0.00	Kocher 2011	Not Varied
Following Surgery+SRS			
WBRT	0.20	Brown 2017	Beta(20,78)
SRS	0.00	Brown 2017	Not Varied
Surgery	0.00	Brown 2017	Not Varied
SRS+WBRT	0.00	Brown 2017	Not Varied
Surgery+WBRT	0.00	Brown 2017	Not Varied
Grade 3/4 Adverse Events			
Following Surgery/SRS			
Neurologic deficit	0.18	Kocher 2011	Beta(18,82)†
Cognitive functions	0.05	Kocher 2011	Beta(5,95)

	Value	Source	PSA Distribution
Mood and personality	0.04	Kocher 2011	Beta(4,96)
Seizures	0.19	Kocher 2011	Beta(19,81)
Headache	0.07	Kocher 2011	Beta(7,93)
Somnolence	0.08	Kocher 2011	Beta(8,92)
Intellectual deficit	0.07	Kocher 2011	Beta(7,93)
Functional competence	0.11	Kocher 2011	Beta(11,89)
Memory	0.05	Kocher 2011	Beta(5,95)
Following Surgery+WBRT/SRS+WBRT			
Neurologic deficit	0.17	Kocher 2011	Beta(16,81)‡
Cognitive functions	0.09	Kocher 2011	Beta(9,88)
Mood and personality	0.10	Kocher 2011	Beta(10,87)
Seizures	0.20	Kocher 2011	Beta(19,78)
Headache	0.05	Kocher 2011	Beta(5,92)
Somnolence	0.11	Kocher 2011	Beta(11,86)
Intellectual deficit	0.09	Kocher 2011	Beta(9,88)
Functional competence	0.14	Kocher 2011	Beta(14,83)
Memory	0.09	Kocher 2011	Beta(9,88)
Following Surgery+SRS			
Neurologic deficit	0.11	Brown 2017	Beta(9,72)
Cognitive functions	0.06	Brown 2017	Beta(5,76)
Mood and personality	0.06	Brown 2017	Beta(5,76)
Seizures	0.04	Brown 2017	Beta(4,77)
Headache	0.02	Brown 2017	Beta(2,79)
Somnolence	0.11	Brown 2017	Beta(9,72)
Intellectual deficit	0.06	Brown 2017	Beta(5,76)
Functional competence	0.10	Brown 2017	Beta(8,73)
Memory	0.06	Brown 2017	Beta(5,76)
Quality of Life Weights			
Alive not progressed	0.752	Miller 2017	Triangular(0.569,0.935)
Local Progression	0.540	Lester-Coll 2016	Triangular(0.45,0.65)
Distant Progression	0.420	Lester-Coll 2016	Triangular(0.30,0.50)
Death	0		Not Varied
Costs			
Surgery	£7,032	NHS Reference Costs (AA53D)	Gamma(7032,18.51)
SRS	£3,556	NHS Reference Costs (AA71B)	Gamma(3556,224.67)

	Value	Source	PSA Distribution
WBRT (one off preparation cost)	£655	NHS Reference Costs (SC51Z)	Gamma(655,0.00)
WBRT (per fraction)	£105	NHS Reference Costs (SC23Z)	Gamma(126,11.90)
Follow-Up Appointment	£188	NHS Reference Costs (WF01A)	Gamma(188,5.15)
MRI Scan	£145	NHS Reference Costs (RD01A)	Gamma(145,10.55)
Discount (per annum)			
Costs	3.5%	NICE 2016	Not varied
QALYs	3.5%	NICE 2016	Not varied
†Reported PSA values are for SRS, Surgery has a distribution with differing values but directly proportionate α and β values in line with the differing number of observations. ‡ Reported PSA values are for SRS+WBRT, Surgery+WBRT has a distribution with differing values but directly proportionate α and β values in line with the differing number of observations.			

Results

Deterministic base-case results

Table 64 and Table 65 show the base-case results for all interventions considered compared to surgery alone and SRS alone when salvage treatment costs are not included. The addition of WBRT to either surgery or SRS led to a reduction in life months of 0.27 and a reduction in QALYs of 0.0156 when compared to surgery or SRS alone. Consequently both interventions are dominated (are more expensive and less effective) by the reference case of surgery or SRS alone. The addition of WBRT led to increased costs and reduced QALYs, regardless of initial treatment, driven by additional costs of WBRT and treatment of the higher number of adverse events. The addition of SRS to surgery led to an decrease in overall survival (3.7 months), QALYs and an increase in costs. Again this intervention was dominated by surgery alone.

Table 64: Initial treatment surgery primary base-case analysis results excluding salvage treatment costs

Intervention	Life Months	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
Surgery	17.80	0.7675	£ 8,901	Reference	Reference	Reference	Reference
Surgery+WBRT	17.53	0.7516	£ 10,572	-0.0159	£1,672	-£ 1,989	Dominated
Surgery+SRS	14.10	0.5267	£ 12,044	-0.2408	£3,144	£3144	Dominated

Table 65: Initial treatment SRS primary base-case analysis results excluding salvage treatment costs

Intervention	Life Months	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
SRS	17.80	0.7742	£ 5,424	Reference	Reference	Reference	Reference
SRS+WBRT	17.53	0.7516	£ 7,096	-0.0226	£1,672	-£ 2,124	Dominated

When salvage therapy costs are considered (Table 66, Table 67) the addition of WBRT to either intervention is related again to an increase in costs as well as QALYs although at a smaller magnitude. This is driven through the significantly fewer interventions received (as salvage therapy) by the non-WBRT group, through the contraindication of these future, potentially effective, interventions. Again the addition of WBRT to initial treatment is dominated by the reference cases.

When salvage therapy costs are included the addition of SRS to surgery remains dominated. Given the assumptions of the model, QALYs and incremental QALYs remain identical to that of the 'excluded salvage therapy costs' analysis.

Table 66: Initial treatment surgery primary base-case analysis results including salvage treatment costs

Intervention	Life Months	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
Surgery	17.80	0.7675	£ 10,504	Reference	Reference	Reference	Reference
Surgery+WBRT	17.53	0.7516	£ 11,155	-0.0159	£651	-£ 1,989	Dominated
Surgery+SRS	14.10	0.5267	£ 12,391	-0.2408	£1,887	£ 6,703	Dominated £12,674

Table 67: Initial treatment SRS primary base-case analysis results including salvage treatment costs

Intervention	Life Months	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
SRS	17.80	0.7742	£ 7,028	Reference	Reference	Reference	Reference
SRS+WBRT	17.53	0.7516	£ 7,679	-0.0226	£651	-£ 1,103	Dominated

Stochastic base-case results

The stochastic base-case results compare the same interventions as for the deterministic results but using the mean values from the iterations from the PSA. The stochastic base-case results (Table 68 & Table 69) are broadly similar to those of the

deterministic base-case results but with a slight increase in QALYs of between 0.02 and 0.05 QALYs for all interventions the equivalent of less than 1 month in a non-progressed state. This is caused by the non-symmetry of the probabilistic outputs of the Cholesky Decomposition matrices during the PSA giving a mean overall survival greater than the point estimate. The estimates remain well within the confidence intervals reported for overall survival by Kocher 2011 and Brown 2017. As this non-symmetry is similar for all interventions the impact upon the incremental results has been small.

When salvage therapy costs are considered (Table 70 & Table 71) surgery and WBRT is now health improving albeit minimally and cost increasing although the ICER of over £1 million per ICER is well above any conventionally held cost per QALY thresholds. SRS and WBRT remains dominated compared to SRS alone.

Table 68: Initial treatment surgery primary base-case analysis stochastic results excluding salvage treatment costs

Intervention	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
Surgery	0.8018	£ 8,983	Reference	Reference	Reference	Reference
Surgery+WBRT	0.8028	£ 10,677	0.0010	£1,694	-£ 1,674	£1,694,266
Surgery+SRS	0.5934	£ 12,171	-0.2130	£3,187	£ 7,447	Dominated

Table 69: Initial treatment SRS primary base-case analysis stochastic results excluding salvage treatment costs

Intervention	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
SRS	0.8318	£ 5,508	Reference	Reference	Reference	Reference
SRS+WBRT	0.8240	£ 7,203	-0.0077	£1,695	-£ 1,850	Dominated

Table 70: Initial treatment surgery primary base-case analysis stochastic results including salvage treatment costs

Intervention	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
Surgery	0.8032	£ 10,649	Reference	Reference	Reference	Reference
Surgery+WBRT	0.8068	£ 11,210	0.0037	£560	-£ 487	£153,260
Surgery+SRS	0.5876	£ 12,521	0.2160	£1,860	£ 6,180	£Dominated

Table 71: Initial treatment SRS primary base-case analysis stochastic results including salvage treatment costs

Intervention	QALY	Cost	I.QALY	I.COST	NMB(£20,000)	ICER
SRS	0.8335	£ 7,112	Reference	Reference	Reference	Reference
SRS+WBRT	0.8272	£ 7,805	-0.0006	£693	-£ 819	Dominated

Deterministic sensitivity analysis results

During one way deterministic sensitivity analysis all but 2 scenarios favoured surgery or SRS alone. Surgery and SRS has an ICER of £22,841 per QALY when compared to surgery alone when the lower estimate of the overall survival hazard ratio (greater overall survival) is assumed. Surgery and SRS has an ICER below £20,000 per QALY for all hazard ratio values below 0.78. This is well within the 95%CI reported by Brown 2017 and used to inform the pooled estimate in the clinical evidence review and subsequently the model.

Deterministic sensitivity analysis was carried out around quality of life given the paucity of high quality evidence to inform this parameter. Given the importance of the difference in quality of life between unprogressed and progressed disease to the conclusions of the model wide variation was carried out around this parameter. Even then, large decreases in quality of life was needed between our base-case best estimates and lower estimates, favouring the addition of WBRT, for surgery and SRS alone to not be the preferred option. Surgery and WBRT became the preferred option when the quality of life weight for progressed disease was below 0.16. SRS and WBRT did not become the preferred option for any positive value of quality of life for progressed disease.

Table 72: Deterministic sensitivity analysis

Parameter	Value	Preferred Option (Surgery Initial Treatment)	Preferred Option (Surgery Initial Treatment)
Overall Survival	Equal for all interventions	Surgery Alone	SRS Alone
Overall Survival HR addition WBRT	L95=0.81	Surgery Alone	SRS Alone
	U95=1.28	Surgery Alone	SRS Alone
Overall Survival HR addition SRS	L95=0.80	Surgery+SRS (ICER=£22,841)	N/A

Parameter	Value	Preferred Option (Surgery Initial Treatment)	Preferred Option (Surgery Initial Treatment)
	U95=2.15	Surgery Alone	N/A
Local Control HR addition SRS	L95=1.62	Surgery Alone	N/A
	U95=3.72	Surgery Alone	N/A
Cost Adverse Events	=£188	Surgery Alone	SRS Alone
Cost Surgery	IQRL=£5,696	Surgery Alone	SRS Alone
	IQRU=£7,901	Surgery Alone	SRS Alone
Cost SRS	IQRL=£3,396	Surgery Alone	SRS Alone
	IQRU=£3,716	Surgery Alone	SRS Alone
Cost WBRT (Total)	IQRL=£1,168	Surgery Alone	SRS Alone
	IQRU=£2,122	Surgery Alone	SRS Alone
Cost Follow-up appointment	IQRL=£127	Surgery Alone	SRS Alone
	IQRU=£328	Surgery Alone	SRS Alone
Quality of Life	All non-dead health states=1	Surgery Alone	SRS Alone
	No QoL Detriments for Adverse Events	Surgery Alone	SRS Alone
	Local Progression Halved=0.027	Surgery Alone	SRS Alone
	Local Progression 25%=0.014	Surgery+WBRT (ICER=£7,689)	SRS Alone
L95=Lower 95% Confidence Interval, U95=Upper 95% Confidence Interval, IQRL=Lower Interquartile Range, IQRU=Upper Interquartile Range			

Cost effectiveness planes

Figure 21 shows the cost effectiveness plane for surgery and WBRT compared to surgery. The iterations show a linear correlation with an increase in incremental costs of the addition of WBRT as incremental QALYs increase. This is as a result as the only non-initial treatment costs in this model are through MRI scans and follow-up. As patients live longer and experience more QALYs they will also have a greater number of follow-ups and MRI scans and consequently incur greater costs. The same linear relationship for the same reasons occurs for SRS and WBRT compared to SRS (Figure 23) for the exact same reasons. Assuming a £20,000 threshold only 9% and 13% of iterations are cost effective with only 48% and 44% of iterations being health improving for surgery and WBRT and surgery and SRS respectively. All iterations in the PSA were cost increasing.

Figure 23 shows surgery and SRS compared to surgery alone. Again all iterations are cost increasing with 16% being health improving. Again assuming a £20,000 threshold less than 5% of iterations were cost effective.

Figure 21: Cost effectiveness plane excluding salvage therapy costs (surgery and WBRT versus surgery)

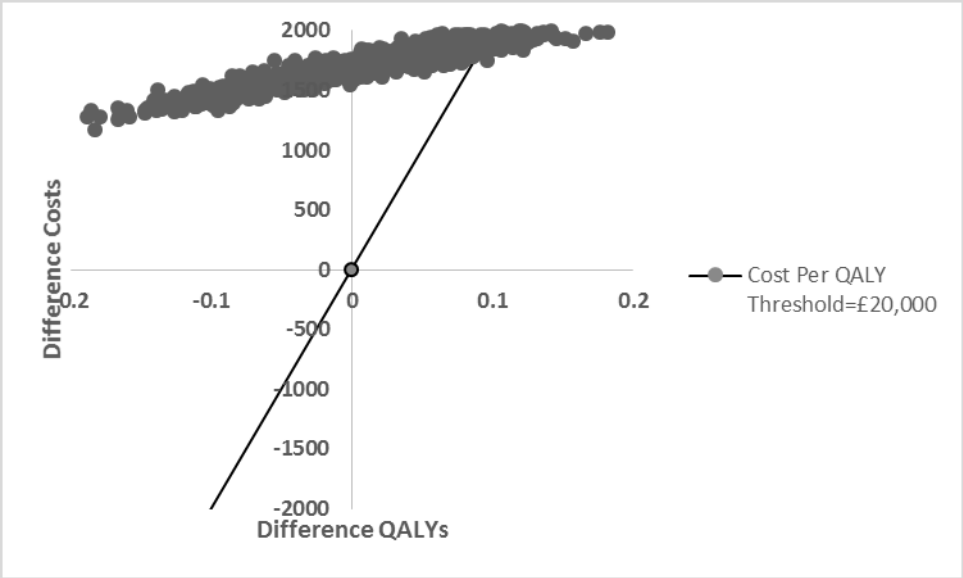


Figure 22: Cost effectiveness plane excluding salvage therapy costs (surgery and SRS versus surgery)

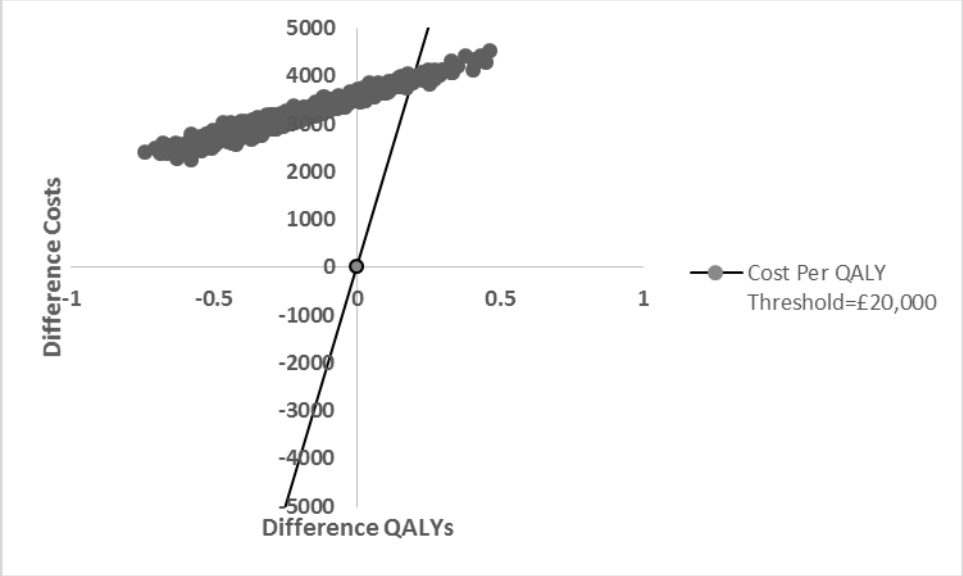


Figure 23: Cost effectiveness plane excluding salvage therapy costs (SRS and WBRT versus SRS)

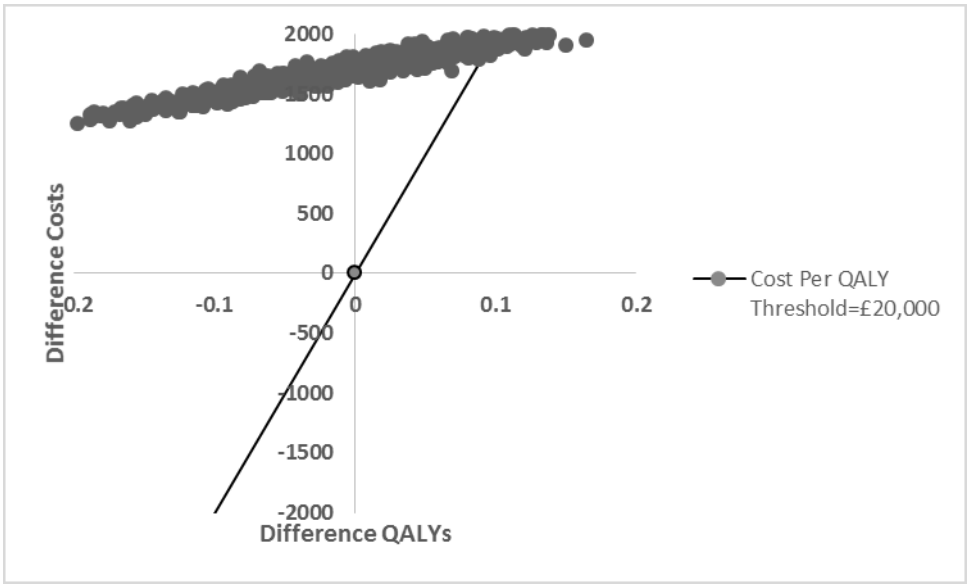


Figure 24, Figure 25 and Figure 26 show the impact of including salvage therapy costs. While the difference in QALYs are very similar between the analyses (given assumptions made) the addition of these costs has dropped some iterations of the PSA into the south (cost saving) quadrants of the cost effectiveness planes. For the surgery and SRS interventions with the addition of WBRT now leading to cost savings in 8% and 2% of iterations respectively. This is almost entirely driven by the greater use of salvage therapy in patients not receiving WBRT as an adjunct. The addition of SRS to surgery still always leads to a cross increase despite again having lower salvage therapy costs compared to surgery alone. When salvage therapy costs are included all non-reference interventions have a greater probability of being cost effective with a probability of the WBRT as an adjunct having a 25% and 30% probability of being the preferred option for an initial treatment of surgery and SRS respectively again assuming a £20,000 threshold. The probability of the addition of SRS to surgery being cost effective remains low.

Figure 24: Cost effectiveness plane including salvage therapy costs (surgery and WBRT versus WBRT)

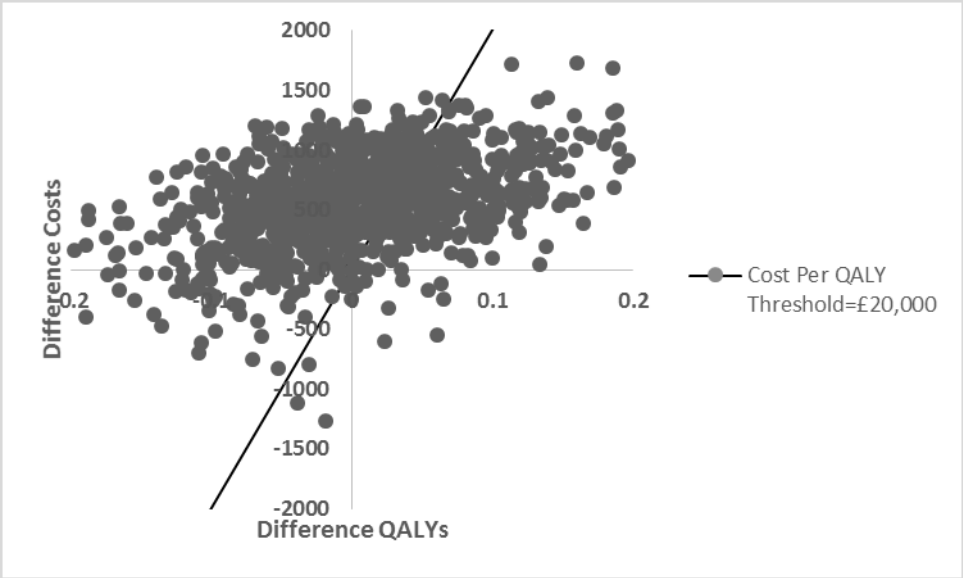


Figure 25: Cost effectiveness plane including salvage therapy costs (surgery and SRS versus surgery)

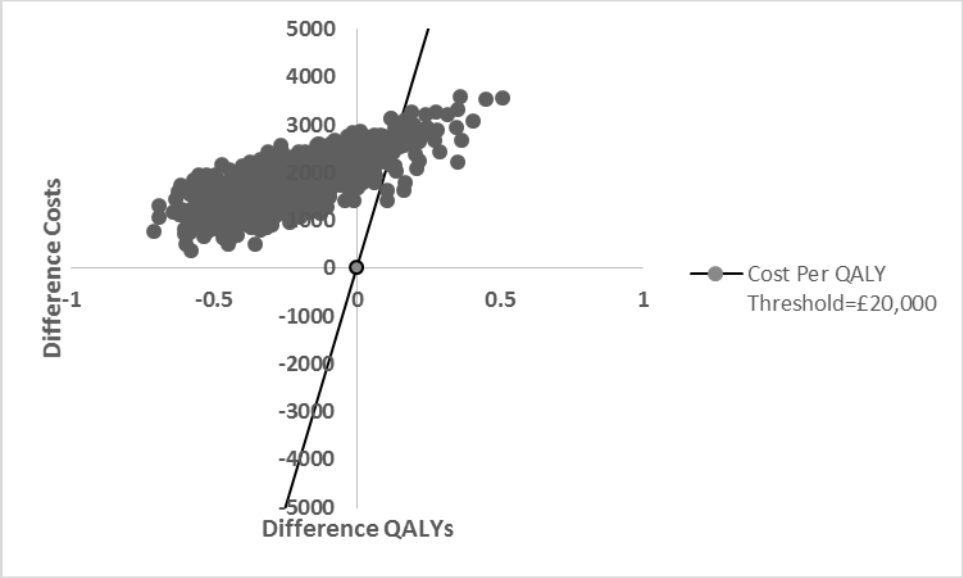
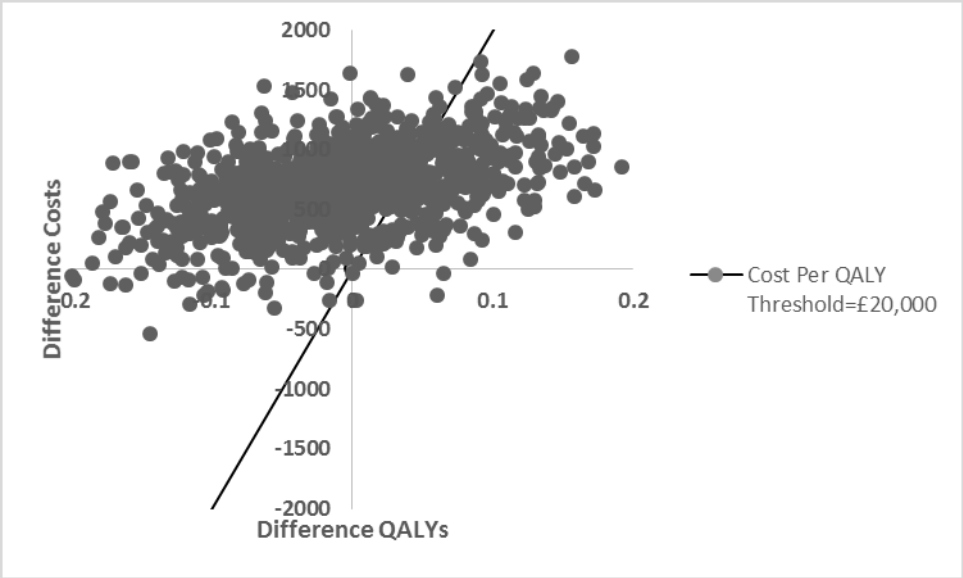


Figure 26: Cost effectiveness plane including salvage therapy costs (SRS and WBRT versus SRS)



Cost effectiveness acceptability curves

Figure 27 shows the cost effectiveness acceptability curve (CEAC) for all intervention compared to surgery alone. At a cost per QALY threshold of £0 i.e. the preferred intervention is the least costly there is a 94% probability surgery is the preferred option. This decreases as the threshold increases with a 82% probability of surgery being the preferred option at the NICE threshold of £20,000 per QALY. At £20,000 surgery and WBRT and surgery and SRS have an 13% and 5% probability of being the preferred option respectively. Surgery remains the most likely cost effective intervention at thresholds beyond £100,000 per QALY greater than any conventionally held thresholds.

Figure 27: Cost effectiveness acceptability curve excluding salvage therapy costs (surgery initial treatment)

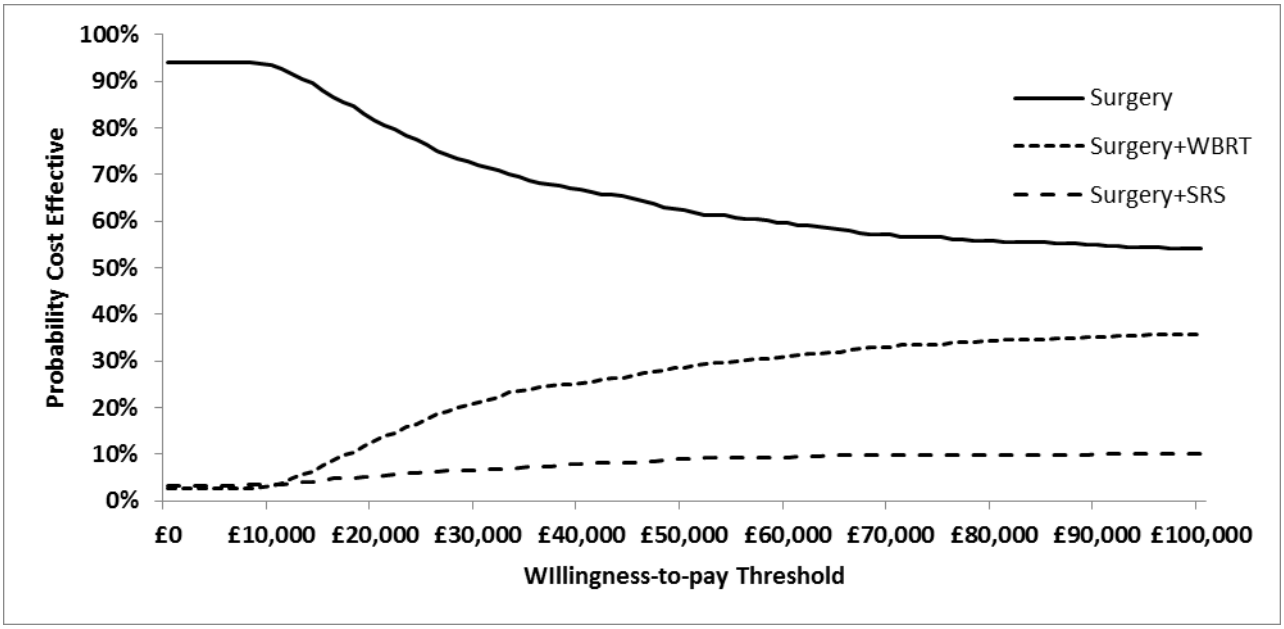


Figure 28 shows the CEAC for SRS versus SRS and WBRT. SRS remains the preferred option for all cost per QALY thresholds. At a £20,000 per QALY there is an 88% probability that SRS alone is the preferred option.

Figure 28: Cost effectiveness acceptability curve excluding salvage therapy costs (SRS initial treatment)

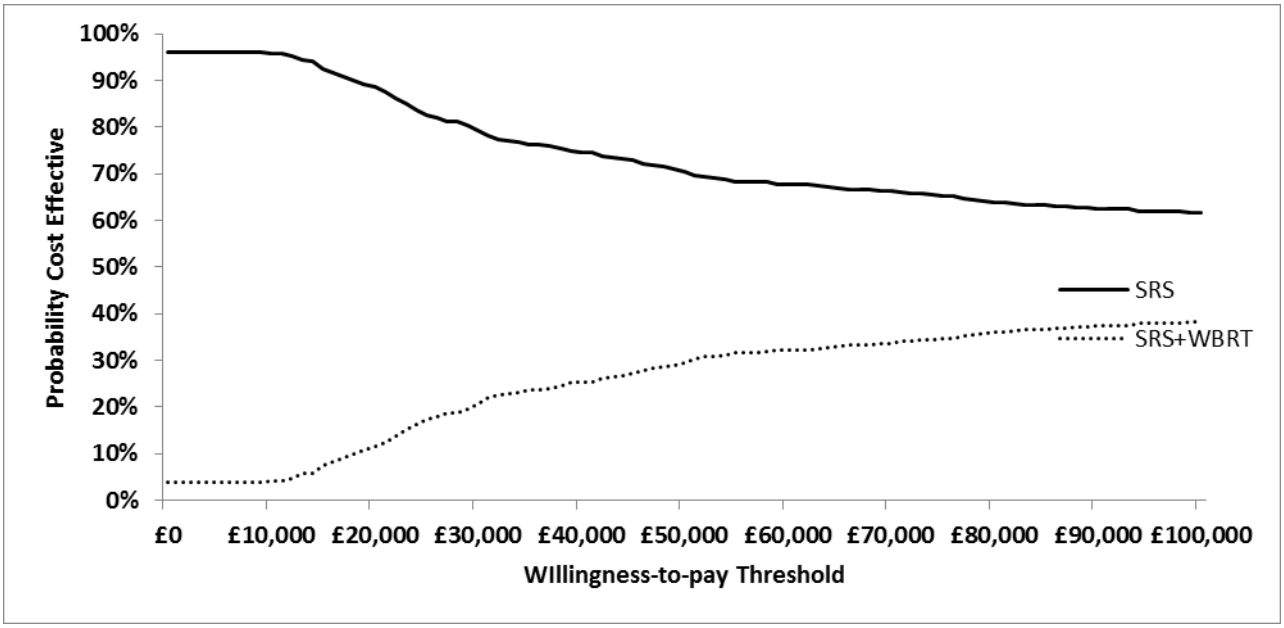


Figure 29 and Figure 30 show the same CEACs as above but with salvage therapy costs now included. When salvage therapy costs are included the case for adjuncts is stronger. Surgery now has a 61% probability of being the preferred option at the NICE threshold of £20,000 per QALY. SRS remains strongly the preferred intervention with 72% of iterations being cost effective at the £20,000 per QALY threshold. Again SRS always remains the preferred option for all cost per QALY thresholds. Surgery and SRS never becomes the preferred option.

Figure 29: Cost effectiveness acceptability curve including salvage therapy costs (surgery initial treatment)

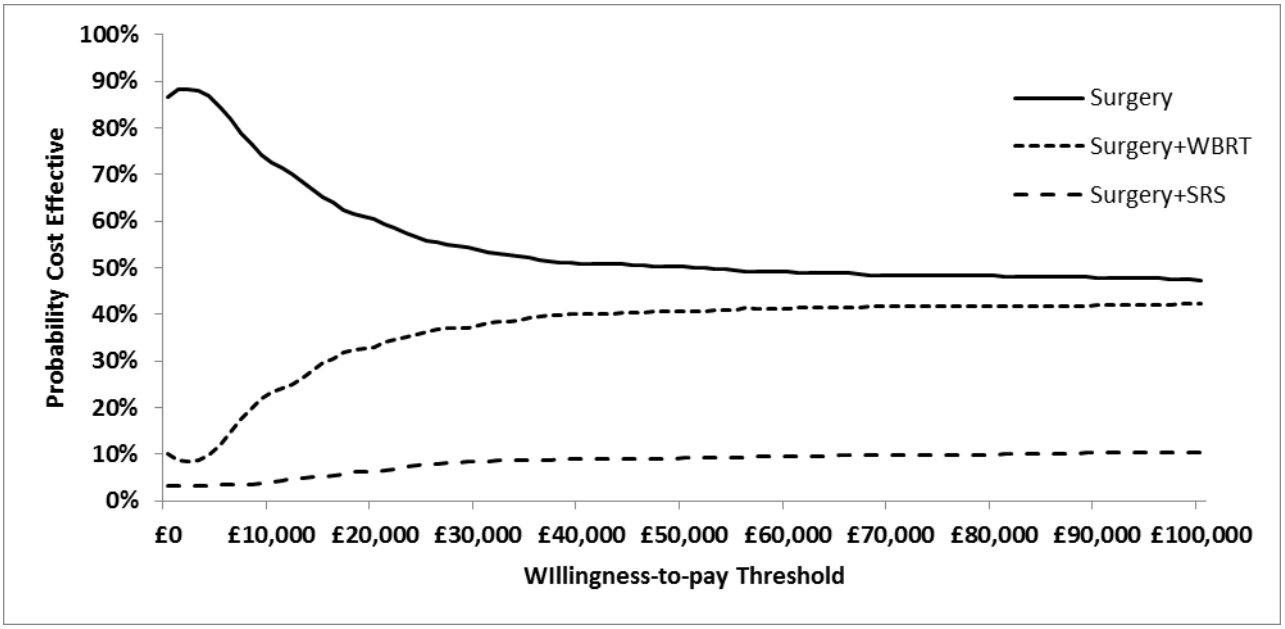
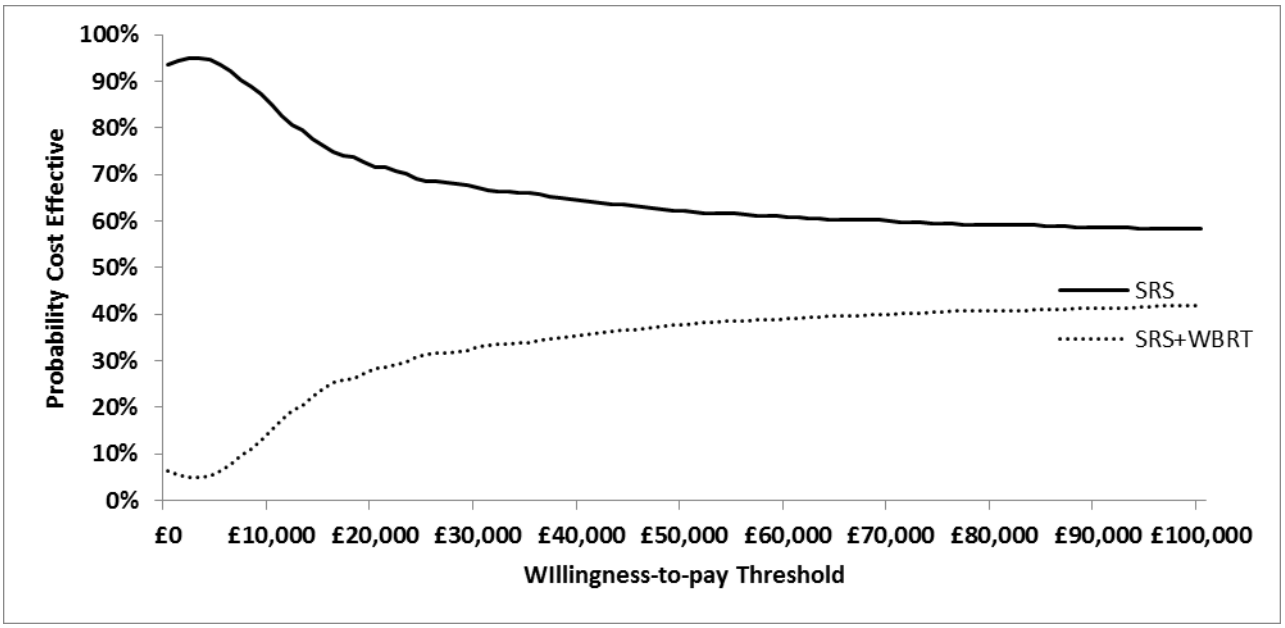


Figure 30: Cost effectiveness acceptability curve including salvage therapy costs (surgery initial treatment)



Discussion

Using either WBRT or SRS as an adjunct to surgery or WBRT as an adjunct to initial treatment with SRS in people with a single brain metastasis does not appear to be a cost effective use of NHS resources in the base-cases of the 2 models. The base-case estimate that the addition of WBRT to either surgery or SRS would lead to both increased costs and a reduction in QALYs. The addition of WBRT only becomes cost effective at a £20,000 per QALY threshold when there are large differences in quality of life between progressed and unprogressed disease. This is supported by the PSA where there is a less than 20% probability of the addition of WBRT to surgery and SRS being cost effective. Even with the addition of salvage therapy costs Surgery alone and SRS alone remain the preferred option in the majority of cases. Surgery and SRS is the preferred option when overall survival is well within the range of the 95% confidence interval reported by the pooled estimate and used to inform this parameter in the model. This suggest there may be considerable uncertainty in the model for deciding between surgery alone and surgery and SRS. Given that surgery and SRS is a relatively new way of treating brain metastases the evidence around it is still immature and this particular comparison could be answered with more certainty as the evidence matures.

The 2 economic models were largely based around 2 RCTs (Kocher 2011, Brown 2017). Kocher did not match the patient group exactly with some patients having multiple metastases. The committee, given the limited number of metastases and that the majority of the cohort had single metastases did not think it would impact significantly on the outcomes of the trial. The cohort in Brown which again broadly matched our patient cohort allowed patients with a metastasis up to 5cm, larger than the cut off in our hypothetical cohort. Again the committee did not think this would significantly impact upon our results but any likely bias would of using this evidence would favour surgery alone again increasing uncertainty around the preferred option between this intervention and surgery and SRS.

No good evidence was identified around quality of life for the economic model despite a comprehensive search and therefore estimates had to be taken from sources other than the cohort considered by this model. Despite this the conclusions of the model were robust to all but the most extreme sensitivity analysis around quality of life weights. This suggests that the addition of better quality of life evidence would not have changed the conclusions of the model.

It is not possible to compare the results with that of the previously identified economic evidence (Kim 2012, Kimmell 2015, Wernicke 2016) given the different intervention considered, different perspectives and different methodologies of informing the input to the economic models. Only 1 common comparator was found between our bespoke models and the previous evidence. Kim 2012, taking a US health care payer perspective and assuming equal overall survival between the groups found that SRS alone was cost increasing and but cost effective when compared with SRS and WBRT, concurring with our sensitivity analysis where we held overall survival equal. Our model however found SRS alone cost decreasing. However, as alluded to above caution should be used when comparing results between studies taking different perspectives and using different modelling approaches and inputs.

Appendix K – Excluded studies

Excluded studies for review 1b - imaging strategy for brain metastases

Clinical

1b- What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?	
Study	**Reason for Exclusion**
Aukema, T. S., Olmos, R. A., Korse, C. M., Kroon, B. B., Wouters, M. W., Vogel, W. V., Bonfrer, J. M., Nieweg, O. E., Utility of FDG PET/CT and brain MRI in melanoma patients with increased serum S-100B level during follow-up, Annals of Surgical Oncology, 17, 1657-61, 2010	Some of the adults included in the study presented with recurrence; not all of them were assessed with the same imaging strategies
Cohen-Inbar, O., Xu, Z., Dodson, B., Rizvi, T., Durst, C. R., Mukherjee, S., Sheehan, J. P., Time-delayed contrast-enhanced MRI improves detection of brain metastases: a prospective validation of diagnostic yield, Journal of Neuro-Oncology, 130, 485-494, 2016	No comparison of interest; no number of metastases have been reported
Colosimo, C., Ruscalleda, J., Korves, M., La Ferla, R., Wool, C., Pianezzola, P., Kirchin, M. A., Detection of intracranial metastases: A multicenter, intrapatient comparison of gadobenate dimeglumine-enhanced MRI with routinely used contrast agents at equal dosage, Investigative Radiology, 36, 72-81, 2001	This study assessed the number of metastases for different dosages of gandolinum, but the only imaging strategy used was spin-echo T1-weighted and spin-echo or fast spin-echo T-2 weighted pre and post gadobenate
Dawoud, M. A. E., Sherif, M. F., Eltomey, M. A., Apparent diffusion coefficient and Magnetic resonance spectroscopy in grading of malignant brain neoplasms, Egyptian Journal of Radiology and Nuclear Medicine, 45, 1215-1222, 2014	Study's objective was to assess the role of the combined application of ADC and MRS. Did not provide the number of metastases, but showed the MRS ratios of benign, malignant and metastatic tumours
Kitajima, K., Nakamoto, Y., Okizuka, H., Onishi, Y., Senda, M., Suganuma, N., Sugimura, K., Accuracy of whole-body FDG-PET/CT for detecting brain	Adults underwent whole-body PET/CT and MRI, however the results of the MRI were patient-based rather than lesion-based

1b- What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?	
Study	**Reason for Exclusion**
metastases from non-central nervous system tumors, Annals of Nuclear Medicine, 22, 595-602, 2008	
Kruger, S., Mottaghy, F. M., Buck, A. K., Maschke, S., Kley, H., Frechen, D., Wibmer, T., Reske, S. N., Pauls, S., Brain metastasis in lung cancer: Comparison of cerebral MRI and ¹⁸F-FDG-PET/CT for diagnosis in the initial staging, NuklearMedizin, 50, 101-106, 2011	Standard MRI results were patient-based rather than lesion-based
Kwak, H. S., Hwang, S., Chung, G. H., Song, J. S., Choi, E. J., Detection of small brain metastases at 3 T: Comparing the diagnostic performances of contrast-enhanced T1-weighted SPACE, MPRAGE, and 2D FLASH imaging, Clinical Imaging, 39, 571-575, 2015	The study compared the diagnostic performance of T1 weighted sampling perfection with different contrasts using different images (SPAE, MPRAGE, and 2D FLASH imaging)
Kwee, S. A., Ko, J. P., Jiang, C. S., Watters, M. R., Coel, M. N., Solitary brain lesions enhancing at MR imaging: evaluation with fluorine 18 fluorocholine PET, RadiologyRadiology, 244, 557-65, 2007	Fluorocholine uptake was not compared with standard structural MRI; other types of malignant tumours apart from brain metastases have been included; the study did not report the number of metastases
Li, Y., Jin, G., Su, D., Comparison of Gadolinium-enhanced MRI and 18FDG PET/PET-CT for the diagnosis of brain metastases in lung cancer patients: A meta-analysis of 5 prospective studies, OncotargetOncotarget, 8, 35743-35749, 2017	This meta-analysis included studies using whole-body MRI as the comparison with advanced MRI techniques. For the included studies, only sensitivity and specificity was reported
Niikura, N., Costelloe, C. M., Madewell, J. E., Hayashi, N., Tse-Kuan, Y., Liu, J., Palla, S. L., Tokuda, Y., Theriault, R. L., Hortobagyi, G. N., Ueno, N. T., FDG-PET/CT compared with conventional imaging in the detection of distant metastases of primary breast cancer, OncologistOncologist, 16, 1111-1119, 2011	The study did not include a comparison of interest (i.e. FDG PET-CT was compared with CT, ultrasonography, radiography, and skeletal scintigraphy)
Rundo, L., Stefano, A., Militello, C., Russo, G., Sabini, M. G., D'Arrigo, C., Marletta, F., Ippolito, M., Mauri, G., Vitabile, S., Gilardi, M. C., A fully automatic approach for multimodal PET and MR image segmentation in gamma knife	MRI and PET imaging was used to assess the absolute volume difference and centroid distanced to segment BTV and GTV, but not to calculate the number of metastasis that adults presented with

1b- What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?	
Study	**Reason for Exclusion**
treatment planning, Computer Methods and Programs in Biomedicine, 144, 77-96, 2017	
Sanderson, A., Bonington, S. C., Carrington, B. M., Alison, D. L., Spencer, J. A., Cerebral metastasis and other cerebral events in women with ovarian cancer, Clinical RadiologyClin Radiol, 57, 815-819, 2002	Not a comparative study - adults underwent CT or MRI
Strobel, K., Dummer, R., Steinert, H. C., Conzett, K. B., Schad, K., Lago, M. P., Soyka, J. D., Veit-Haibach, P., Seifert, B., Kalff, V., Chemotherapy response assessment in stage IV melanoma patients - Comparison of ¹⁸F-FDG-PET/CT, CT, brain MRI, and tumormarker S-100B, European Journal of Nuclear Medicine and Molecular Imaging, 35, 1786-1795, 2008	Adults were assessed after being treated with chemotherapy
Wever, W., Ceyssens, S., Mortelmans, L., Stroobants, S., Marchal, G., Bogaert, J., Verschakelen, J. A., Additional value of PET-CT in the staging of lung cancer: Comparison with CT alone, PET alone and visual correlation of PET and CT, European Radiology, 17, 23-32, 2007	Not comparison of interest (PET-CT was compared with CT alone); the study did not report the number of metastases that each person present with according to the different imaging strategies
Yi, C. A., Shin, K. M., Lee, K. S., Kim, B. T., Kim, H., Kwon, O. J., Choi, J. Y., Chung, M. J., Non-small cell lung cancer staging: efficacy comparison of integrated PET/CT versus 3.0-T whole-body MR imaging, Radiology, 248, 632-42, 2008	The study included adults with metastases located elsewhere than in the brain (i.e. hepatic, lymph node and soft tissue)
Anzalone, N., Gerevini, S., Scotti, R., Vezzulli, P., Picozzi, P., Detection of cerebral metastases on magnetic resonance imaging: intraindividual comparison of gadobutrol with gadopentetate dimeglumine, Acta radiologica (Stockholm, Sweden : 1987), 50, 933-940, 2009	No comparison of interest
Balériaux, D, Colosimo, C, Ruscalleda, J, Korves, M, Schneider, G, Bohndorf, K, Bongartz, G, Buchem, Ma, Reiser, M, Sartor, K, Bourne, Mw, Parizel, Pm, Cherryman, Gr, Salerio, I, Noce, A, Pirovano, G, Kirchin, Ma, Spinazzi, A,	Study did not present with any comparison of interest

1b- What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?	
Study	**Reason for Exclusion**
Magnetic resonance imaging of metastatic disease to the brain with gadobenate dimeglumine, Neuroradiology, 44, 191-203, 2002	
Cohen-Inbar, O, Xu, Z, Dodson, B, Rizvi, T, Durst, Cr, Mukherjee, S, Sheehan, Jp, Time-delayed contrast-enhanced MRI improves detection of brain metastases: a prospective validation of diagnostic yield, Journal of Neuro-Oncology, 130, 485-494, 2016	No comparison of interest
Colosimo, C., Ruscalleda, J., Korves, M., La Ferla, R., Wool, C., Pianezzola, P., Kirchin, M. A., Detection of intracranial metastases: A multicenter, intrapatient comparison of gadobenate dimeglumine-enhanced MRI with routinely used contrast agents at equal dosage, Applied Radiology, 32, 60-70, 2003	No comparison of interest
Kammer, N. N., Coppenrath, E., Treitl, K. M., Kooijman, H., Dietrich, O., Saam, T., Comparison of contrast-enhanced modified T1-weighted 3D TSE black-blood and 3D MP-RAGE sequences for the detection of cerebral metastases and brain tumours, European Radiology, 26, 1818-1825, 2016	No comparison of interest, the study also included other types of cerebral malignomas
Nakajo, M, Jinguji, M, Tani, A, Kajiya, Y, Tanabe, H, Fukukura, Y, Nakabeppu, Y, Koriyama, C, Diagnosis of metastases from postoperative differentiated thyroid cancer: Comparison between FDG and FLT PET/CT studies, Radiology, 267, 891-901, 2013	The comparator was not standard Structural MRI (core protocol) /- contrast (T1 pre and post contrast and T2)
Ochi, T., Taoka, T., Matsuda, R., Sakamoto, M., Akashi, T., Tamamoto, T., Sugimoto, T., Sakaguchi, H., Hasegawa, M., Nakase, H., Kichikawa, K., Comparison between two separate injections and a single injection of double-dose contrast medium for contrast-enhanced MR imaging of metastatic brain tumors, Magnetic Resonance in Medical SciencesMagn, 13, 221-9, 2014	Standard The comparator was not structural MRI (core protocol) /- contrast (T1 pre and post contrast and T2)

1b- What is the most appropriate diagnostic imaging for patients being considered for focal treatment of their brain metastases?	
Study	**Reason for Exclusion**
Sepulveda, F., Yanez, P., Carnevale, M. D., Romero, C., Castillo, M., MIP improves detection of brain metastases, Journal of Computer Assisted Tomography, 40, 997-1000, 2016	MIP-3DT1 is not one of the imaging strategies of interest
Suzuki, K., Yamamoto, M., Hasegawa, Y., Ando, M., Shima, K., Sako, C., Ito, G., Shimokata, K., Magnetic resonance imaging and computed tomography in the diagnoses of brain metastases of lung cancer, Lung Cancer, 46, 357-360, 2004	Contrast-enhanced CT is not one of the imaging strategies of interest
Wu, Y., Li, P., Zhang, H., Shi, Y., Wu, H., Zhang, J., Qian, Y., Li, C., Yang, J., Diagnostic value of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography for the detection of metastases in non-small-cell lung cancer patients, International Journal of Cancer, 132, E37-E47, 2013	The comparison was not standard Structural MRI (core protocol) /- contrast (T1 pre and post contrast and T2)

Economic

Not applicable – health economic inclusion / exclusion detailed in Supplementary Material D

Excluded studies for review 4a – management of single metastases

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations.

Clinical

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Study	**Reason for Exclusion**
Aoyama, H., Tago, M., Kato, N., Toyoda, T., Kenjyo, M., Hirota, S., Shioura, H., Inomata, T., Kunieda, E., Hayakawa, K., Nakagawa, K., Kobashi, G., Shirato, H., Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 68, 1388-95, 2007	Further analysis of the data published in 2006. No new data to add
Aoyama, H., Tago, M., Shirato, H., Japanese Radiation Oncology Study Group, Investigators, Stereotactic Radiosurgery With or Without Whole brain Radiotherapy for Brain Metastases: Secondary Analysis of the JROSG 99-1 Randomized Clinical Trial, JAMA OncologyJAMA Oncol, 1, 457-64, 2015	Further analysis of the data presented in 2006. Examined outcomes in those with different prognosis
Bai, G. R., An, J. B., Chu, Y., Wang, X. Y., Li, S. M., Yan, K. J., Lu, F. R., Gu, N., Griffin, A. N., Sun, B. Y., Li, W., Wang, G. C., Zhou, S. P., Sun, H., Liu, C. X., Comparison of the effectiveness of whole brain radiotherapy plus temozolomide versus whole brain radiotherapy in treating brain metastases based on a systematic review of randomized controlled trials, Anti-Cancer DrugsAnticancer Drugs, 27, 1-8, 2016	This systematic review and meta- analysis included observational studies. The included RCTs have already been included in this review
Barlesi, F., Gervais, R., Lena, H., Hureaux, J., Berard, H., Paillotin, D., Bota, S., Monnet, I., Chajara, A., Robinet, G., Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01), Annals of OncologyAnn Oncol, 22, 2466-70, 2011	Not an RCT
Barrett, T. F., Sarkiss, C. A., Dyvorne, H. A., Lee, J., Balchandani, P., Shrivastava, R. K., Application of Ultrahigh Field Magnetic Resonance Imaging in the Treatment of Brain Tumors: A Meta-Analysis, World NeurosurgeryWorld Neurosurg, 86, 450-465, 2016	Not metastases

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Brower, Jv, Robins, Hi, Erlotinib for the treatment of brain metastases in non-small cell lung cancer, Expert Opinion on Pharmacotherapy, 17, 1013-21, 2016	Narrative review with observational studies included
Brown, P. D., Asher, A. L., Ballman, K. V., Farace, E., Cerhan, J. H., Anderson, S. K., Carrero, X. W., Barker, F. G., Deming, R. L., Burri, S., Menard, C., Chung, C., Stieber, V. W., Pollock, B. E., Galanis, E., Buckner, J. C., Jaeckle, K. A., NCCTG N0574 (Alliance): A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases, Journal of Clinical Oncology. Conference, 33, 2015	Conference abstract
Ceribelli, A., Gridelli, C., De Marinis, F., Fabi, A., Gamucci, T., Cortesi, E., Barduagni, M., Antimi, M., Maione, P., Migliorino, M. R., Giannarelli, D., Cognetti, F., Prolonged gemcitabine infusion in advanced non-small cell lung carcinoma: a randomized phase II study of two different schedules in combination with cisplatin, CancerCancer, 98, 337-43, 2003	No BM subgroup
Chen, B., Zhou, L., He, J., Xiong, W., Liu, Y., Deng, L., Xiang, J., Yu, Q., Liang, M., Zhou, X., Ding, Z., Huang, M., Ren, L., Zhu, J., Li, L., Hou, M., Lu, Y., Neurocognitive Function and Quality of Life in EGFR-Mutated Non-Small Cell Lung Cancer Patients With Brain Metastases Treated With Icotinib and Whole brain Radiation: Results of a Phase 1 Trial, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 96, S171, 2016	Abstract only
Chougule, P. B., Burton-Williams, M., Saris, S., Zheng, Z., Ponte, B., Noren, G., Randomized treatment of brain metastasis with gamma knife radiosurgery, whole brain radiotherapy or both, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 48, 114, 2000	Abstract only
Cortes, J., Dieras, V., Ro, J., Barriere, J., Bachelot, T., Hurvitz, S., Le Rhun, E., Espie, M., Kim, S. B., Schneeweiss, A., Sohn, J. H., Nabholtz, J. M.,	Chemotherapy type not included in the protocol

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Kellokumpu-Lehtinen, P. L., Taguchi, J., Piacentini, F., Ciruelos, E., Bono, P., Ould-Kaci, M., Roux, F., Joensuu, H., Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial, Lancet OncologyLancet Oncol, 16, 1700-10, 2015	
Cortes, J., Rugo, H. S., Awada, A., Twelves, C., Perez, E. A., Im, S. A., Gomez-Pardo, P., Schwartzberg, L. S., Dieras, V., Yardley, D. A., Potter, D. A., Mailliez, A., Moreno-Aspitia, A., Ahn, J. S., Zhao, C., Hoch, U., Tagliaferri, M., Hannah, A. L., O'Shaughnessy, J., Prolonged survival in patients with breast cancer and a history of brain metastases: results of a preplanned subgroup analysis from the randomized phase III BEACON trial, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 165, 329-341, 2017	This study used a varied range of interventions (eribulin, vinorelbine, gemcitabine, nab-paclitaxel, paclitaxel, ixabepilone, or docetaxel). Not all these interventions are part of the ones listed in the protocol
Cortot, A. B., Geriniere, L., Robinet, G., Breton, J. L., Corre, R., Falchero, L., Berard, H., Gimenez, C., Chavaillon, J. M., Perol, M., Bombaron, P., Mercier, C., Souquet, P. J., Groupe Lyon-Saint-Etienne d'Oncologie, Thoracique, Groupe Francais de, Pneumo-Cancerologie, Phase II trial of temozolomide and cisplatin followed by whole brain radiotherapy in non-small-cell lung cancer patients with brain metastases: a GLOT-GFPC study, Annals of OncologyAnn Oncol, 17, 1412-7, 2006	Not an RCT
Dae, H. L., Han, J. Y., Heung, T. K., Sung, J. Y., Hong, R. P., Kwan, H. C., Shin, S. H., Yoo, H., Lee, S. H., Jin, S. L., Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole brain radiotherapy administered first: Result of a randomized pilot study, CancerCancer, 113, 143-149, 2008	Chemotherapy type not included in the protocol
Davey, P., Smith, J., Ennis, M., Randomized Comparison of Whole Brain Radiotherapy, 20 Gy in Four Daily Fractions Versus 40 Gy in 20 Twice-Daily Fractions, for Brain Metastases. in Regard to Graham et al. (Int J Radiat Oncol	Comparing two radiotherapy regimens

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Biol Phys 2010;77(3):648-54.), International Journal of Radiation Oncology Biology Physics, 78, 1605-1606, 2010	
Duan, L., Zeng, R., Yang, K. H., Tian, J. H., Wu, X. L., Dai, Q., Niu, X. D., Ma, D. W., Whole brain radiotherapy combined with stereotactic radiotherapy versus stereotactic radiotherapy alone for brain metastases: a meta-analysis, Asian Pacific Journal of Cancer Prevention: ApjcpAsian Pac J Cancer Prev, 15, 911-5, 2014	This systematic review and meta-analysis included observational studies. The included RCTs have already been included in this review
Feng, Y. Y., Wang, X. S., Yang, R. J., Yang, J. Q., Hu, X. C., Wang, W., Liu, Y. X., Kong, D. J., Zhang, L., Zhang, G. P., A meta-analysis evaluating stereotactic radiotherapy combined with WBRT versus SRT alone for the NSCLC patients with brain metastases, International Journal of Clinical and Experimental Medicine, 10, 675-683, 2017	This meta-analysis included observational studies. The included RCTs have already been included in this review
Fenske, D. C., Price, G. L., Hess, L. M., John, W. J., Kim, E. S., Systematic Review of Brain Metastases in Patients With Non-Small-Cell Lung Cancer in the United States, European Union, and Japan, Clinical Lung CancerClin Lung Cancer, 26, 26, 2017	This systematic review included observational studies. The included RCTs have already been included in this review
Fogarty, G., Morton, R. L., Vardy, J., Nowak, A. K., Mandel, C., Forder, P. M., Hong, A., Hruby, G., Burmeister, B., Shivalingam, B., Dhillon, H., Thompson, J. F., Whole brain radiotherapy after local treatment of brain metastases in melanoma patients - a randomised phase III trial, BMC CancerBMC Cancer, 11 (no pagination), 2011	Protocol
Graham, P. H., 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, PhysicsInt J Radiat Oncol Biol Phys, 77, 648-54, 2010	Comparing two different radiotherapy regimens
Haie-Meder, C., Pellae-Cosset, B., Laplanche, A., Lagrange, J. L., Tuchais, C., Nogues, C., Arriagada, R., Results of a randomized clinical trial comparing two	Subsequent line therapy

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
radiation schedules in the palliative treatment of brain metastases, Radiotherapy & OncologyRadiother Oncol, 26, 111-6, 1993	
Hart, M. G., 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 ReviewsCochrane Database Syst Rev, CD003292, 2005	Cochrane review on single metastases
Hauswald, H., Habl, G., Krug, D., Kehle, D., Combs, S. E., Bermejo, J. L., Debus, J., Sterzing, F., Whole brain helical Tomotherapy with integrated boost for brain metastases in patients with malignant melanoma-a randomized trial, Radiation OncologyRadiat, 8, 234, 2013	Protocol
Jiang, T., Min, W., Li, Y., Yue, Z., Wu, C., Zhou, C., Radiotherapy plus EGFR TKIs in non-small cell lung cancer patients with brain metastases: an update meta-analysis, Cancer MedicineCancer Med, 5, 1055-65, 2016	This systematic review and meta- analysis included observational studies. The included RCTs have already been included in this review
Jiang, X., Ding, M., Qiao, Y., Liu, Y., Liu, L., Recombinant human endostatin combined with radiotherapy in the treatment of brain metastases of non-small cell lung cancer, Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societes & of the National Cancer Institute of MexicoClin Transl Oncol, 16, 630-6, 2014	Chemotherapy type not included in the protocol
Jones, B., Dale, R. G., Final results of the Royal College of Radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases, Clinical oncology (Royal College of Radiologists (Great Britain)), 9, 134-5, 1997	Comparing two different radiotherapy schedules
Khan, M., Lin, J., Liao, G., Li, R., Wang, B., Xie, G., Zheng, J., Yuan, Y., Comparison of WBRT alone, SRS alone, and their combination in the treatment of one or more brain metastases: Review and meta-analysis, Tumor Biology, 39, 1-14, 2017	This meta-analysis included observational studies. The included RCTs have already been included in this review
Lalondrelle, S., Khoo, V., Brain metastases, Clinical EvidenceClin Evid (Online), 2009	Narrative review

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Lam, T. C., Sahgal, A., Chang, E. L., Lo, S. S., Stereotactic radiosurgery for multiple brain metastases, Expert Review of Anticancer TherapyExpert Rev Anticancer Ther, 14, 1153-72, 2014	Review
Lamba, N., Muskens, I. S., DiRisio, A. C., Meijer, L., Briceno, V., Edrees, H., Aslam, B., Minhas, S., Verhoeff, J. J. C., Kleynen, C. E., Smith, T. R., Mekary, R. A., Broekman, M. L., Stereotactic radiosurgery versus whole brain radiotherapy after intracranial metastasis resection: a systematic review and meta-analysis, Radiation OncologyRadiat, 12, 106, 2017	This systematic review and meta- analysis included observational studies. The included RCTs have already been included in this review
Larsen, P. B., Kumler, I., Nielsen, D. L., A systematic review of trastuzumab and lapatinib in the treatment of women with brain metastases from HER2-positive breast cancer, Cancer Treatment ReviewsCancer Treat Rev, 39, 720-7, 2013	Included cohort studies only?
Lee, D. H., Han, J. Y., Kim, H. T., Yoon, S. J., Pyo, H. R., Cho, K. H., Shin, S. H., Yoo, H., Lee, S. H., Lee, J. S., Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole brain radiotherapy administered first : result of a randomized pilot study, CancerCancer, 113, 143-9, 2008	Duplicate of Dae 2008, which was excluded because the chemotherapy type used in the study was not included in this review protocol
Lee, W. Y., Cho, D. Y., Lee, H. C., Chuang, H. C., Chen, C. C., Liu, J. L., Yang, S. N., Liang, J. A., Ho, L. H., Outcomes and cost-effectiveness of gamma knife radiosurgery and whole brain radiotherapy for multiple metastatic brain tumors, Journal of Clinical NeuroscienceJ Clin Neurosci, 16, 630-634, 2009	Study not randomised
Li, B., Yu, J., Suntharalingam, M., Kennedy, A. S., Amin, P. P., Chen, Z., Yin, R., Guo, S., Han, T., Wang, Y., Yu, N., Song, G., Wang, L., Comparison of three treatment options for single brain metastasis from lung cancer, International Journal of CancerInt J Cancer, 90, 37-45, 2000	Not an RCT
Linskey, M. E., Andrews, D. W., Asher, A. L., Burri, S. H., Kondziolka, D., Robinson, P. D., Ammirati, M., Cobbs, C. S., Gaspar, L. E., Loeffler, J. S.,	This systematic review and meta-analysis included observational studies. The included RCTs have already been included in this review

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
McDermott, M., Mehta, M. P., Mikkelsen, T., Olson, J. J., Paleologos, N. A., Patchell, R. A., Ryken, T. C., Kalkanis, S. N., The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline, Journal of Neuro-OncologyJ Neurooncol, 96, 45-68, 2010	
Liu, M., Zhou, Y., Han, Q., Gao, T., Luo, Z., Wang, W., Whole brain radiotherapy concomitant or sequential Vm26/DDP in treating small cell lung cancer patients with brain metastases, Chinese-German Journal of Clinical Oncology, 9, 17-21, 2010	Vm26/DDP not included in the protocol
Liu, R., Wang, X., Ma, B., Yang, K., Zhang, Q., Tian, J., Concomitant or adjuvant temozolomide with whole brain irradiation for brain metastases: a meta-analysis, Anti-Cancer DrugsAnticancer Drugs, 21, 120-8, 2010	This systematic review and meta-analysis included observational studies. The included RCTs have already been included in this review
Liu, W. J., Zeng, X. T., Qin, H. F., Gao, H. J., Bi, W. J., Liu, X. Q., Whole brain radiotherapy plus chemotherapy in the treatment of brain metastases from lung cancer: A metaanalysis of 19 randomized controlled trails, Asian Pacific Journal of Cancer Prevention, 13, 3253-3258, 2012	The included RCTs have already been included in this review
Luo, S., Chen, L., Chen, X., Xie, X., Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases, OncotargetOncotarget, 6, 16725-34, 2015	Tyrosine kinase inhibitors not in PICO
Ma, W., Li, N., An, Y., Zhou, C., Bo, C., Zhang, G., Effects of Temozolomide and Radiotherapy on Brain Metastatic Tumor: A Systematic Review and Meta-Analysis, World NeurosurgeryWorld Neurosurg, 92, 197-205, 2016	Analysis includes small cell lung cancer, which is excluded from the protocol
Meng, F. L., Zhou, Q. H., Zhang, L. L., Ma, Q., Shao, Y., Ren, Y. Y., Antineoplastic therapy combined with whole brain radiation compared with whole brain radiation alone for brain metastases: a systematic review and meta-analysis, European Review for Medical & Pharmacological SciencesEur Rev Med Pharmacol Sci, 17, 777-87, 2013	Antineoplastic therapy not in PICO

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Mornex, F., Thomas, L., Mohr, P., Delaunay, M., Hauschild, A., Lesimple, T., Brain metastases of melanoma: Fotemustine compared with its combination to whole brain radiation, European Journal of CancerEur J Cancer, 35, 370, 1999	Abstract only
Mornex, F., Thomas, L., Mohr, P., Hauschild, A., Delaunay, M. M., Lesimple, T., Tilgen, W., Bui, B. N., Guillot, B., Ulrich, J., Bourdin, S., Mousseau, M., Cupissol, D., Bonneterre, M. E., De Gislain, C., Bensadoun, R. J., Clavel, M., A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma, Melanoma ResearchMelanoma Res, 13, 97-103, 2003	Chemotherapy agent not included in the protocol
Mornex, F., Thomas, L., Mohr, P., Hauschild, A., Delaunay, M. M., Lesimple, T., Tilgen, W., Nguyen, B. B., Guillot, B., Ulrich, J., Bourdin, S., Mousseau, M., Cupissol, D., Bonneterre, J., Gislain, C., Bensadoun, J. R., Clavel, M., [Randomised phase III trial of fotemustine versus fotemustine plus whole brain irradiation in cerebral metastases of melanoma], Cancer radiothérapie : journal de la Société française de radiothérapie oncologique, 7, 1-8, 2003	Study in French
Muller-Riemenschneider, F., Bockelbrink, A., Ernst, I., Schwarzbach, C., Vauth, C., von der Schulenburg, J. M. G., Willich, S. N., Stereotactic radiosurgery for the treatment of brain metastases, Radiotherapy and Oncology, 91, 67-74, 2009	Not an RCT
Murray, K. J., Scott, C., Greenberg, H. M., Emami, B., Seider, M., Vora, N. L., Olson, C., Whitton, A., Moversusas, B., Curran, W., 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, 39, 571-574, 1997	Comparing different radiation regimens (accelerated hyperfractionated versus. accelerated hyperfractionation)
Neuhaus, T., Ko, Y., Muller, R. P., Grabenbauer, G. G., Hedde, J. P., Schueller, H., Kocher, M., Stier, S., Fietkau, R., A phase III trial of topotecan	Chemotherapy type not included in the protocol

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
and whole brain radiation therapy for patients with CNS-metastases due to lung cancer, British Journal of CancerBr J Cancer, 100, 291-7, 2009	
Nieder, C., Norum, J., Dalhaug, A., Aandahl, G., Pawinski, A., Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors, Clinical & Experimental MetastasisClin Exp Metastasis, 30, 723-9, 2013	Not an RCT
Padovani, L., Muracciole, X., Regis, J., gamma knife radiosurgery of brain metastasis from breast cancer, Progress in Neurological SurgeryProg, 25, 156-62, 2012	Narrative review
Patil, C. G., Pricola, K., Garg, S. K., Bryant, A., Black, K. L., Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD006121, 2010	The included RCTs have already been included in this review
Pease, N. J., Edwards, A., Moss, L. J., Effectiveness of whole brain radiotherapy in the treatment of brain metastases: A systematic review, Palliative MedicinePalliat Med, 19, 288-299, 2005	SR includes non-randomised studies. Relevant RCTs have been considered for inclusion
Phillips, T. L., Scott, C. B., Leibel, S. A., Rotman, M., Weigensberg, I. J., 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, 33, 339-348, 1995	Chemotherapy type not included in the protocol
Qin, H., Pan, F., Li, J., Zhang, X., Liang, H., Ruan, Z., Whole brain radiotherapy plus concurrent chemotherapy in non-small cell lung cancer patients with brain metastases: a meta-analysis, PLoS ONE [Electronic Resource]PLoS ONE, 9, e111475, 2014	The included RCTs have already been included in this review
Qin, H., Wang, C., Jiang, Y., Zhang, X., Zhang, Y., Ruan, Z., Patients with single brain metastasis from non-small cell lung cancer equally benefit from	Systematic review. All non-RCTs

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
stereotactic radiosurgery and surgery: a systematic review, Medical Science MonitorMed Sci Monit, 21, 144-52, 2015	
Quantin, X., Bozonnat, M. C., Pujol, J. L., Recursive Partitioning Analysis Groups II-III brain metastases of non-small cell lung cancer: a phase II randomized study comparing two concurrent chemoradiotherapy regimens, Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung CancerJ Thorac Oncol, 5, 846-51, 2010	Chemotherapy type not included in the protocol
Regine, W. F., Scott, C., Murray, K., Curran, W., Neurocognitive outcome in brain metastases patients treated with accelerated-fractionation versus. accelerated-hyperfractionated radiotherapy: An analysis from Radiation Therapy Oncology Group Study 91-04, International Journal of Radiation Oncology Biology Physics, 51, 711-717, 2001	Comparing different radiation regimens
Robinet, G., Thomas, P., Breton, J. L., Lena, H., Gouva, S., Dabouis, G., Bennouna, J., Souquet, P. J., Balmes, P., Thiberville, L., Fournel, P., Quoix, E., Riou, R., Rebattu, P., Perol, M., Paillotin, D., Mornex, F., 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 Francais de Pneumo-Cancerologie (GFPC) protocol 95-1, Annals of OncologyAnn Oncol, 12, 59-67, 2001	Step-wise programme for responders; did not include relevant outcomes for the review protocol
Sahgal, A., Aoyama, H., Kocher, M., Neupane, B., Collette, S., Tago, M., Shaw, P., Beyene, J., Chang, E. L., Phase 3 trials of stereotactic radiosurgery with or without whole brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 91, 710-7, 2015	The included RCTs have already been included in this review
Scoccianti, S., Ricardi, U., Treatment of brain metastases: review of phase III randomized controlled trials, Radiotherapy & OncologyRadiother Oncol, 102, 168-79, 2012	The included RCTs have already been included in this review

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Soon Yu, Yang, Tham Ivan Weng, Keong, Lim Keith, H., Koh Wee, Yao, Lu Jiade, J., Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 2014	The included RCTs have already been included in this review
Soon, Y. Y., Leong, C. N., Koh, W. Y., Tham, I. W. K., EGFR tyrosine kinase inhibitors versus cranial radiation therapy for EGFR mutant non-small cell lung cancer with brain metastases: A systematic review and meta-analysis, Radiotherapy and Oncology, 114, 167-172, 2015	The included RCTs have already been included in this review
Stafinski, T., Jhangri, G. S., Yan, E., Menon, D., Effectiveness of stereotactic radiosurgery alone or in combination with whole brain radiotherapy compared to conventional surgery and/or whole brain radiotherapy for the treatment of one or more brain metastases: A systematic review and meta-analysis, Cancer Treatment ReviewsCancer Treat Rev, 32, 203-213, 2006	Includes non-randomised studies.
Thomas, P., Robinet, G., Breton, J. L., Rebattu, P., Ruffie, P., Debieuvre, D., A randomized study of timing for whole brain radiotherapy (WBRT) with concurrent chemotherapy (CT) in inoperable brain metastasis (BM) of non-small cell lung cancer (NSCLC), Ann-Oncol, 9, 83, 1998	Abstract only
Tian, J., Luo, Y., Xiang, J., Tang, J., Combined treatment for non-small cell lung cancer and breast cancer patients with brain metastases with whole brain radiotherapy and temozolomide: a systematic review and meta-analysis, Journal of Neuro-OncologyJ Neurooncol, 1-11, 2017	This systematic review and meta- analysis included observational studies. The included RCTs have already been included in this review
Treat, J. A., Gonin, R., Socinski, M. A., Edelman, M. J., Catalano, R. B., Marinucci, D. M., Ansari, R., Gillenwater, H. H., Rowland, K. M., Comis, R. L., Obasaju, C. K., Belani, C. P., A randomized, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer, Annals of OncologyAnn Oncol, 21, 540-547, 2010	Chemotherapy agent not in protocol

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Tsao, M. N., Lloyd, N. S., Wong, R. K. S., Rakovitch, E., Chow, E., Laperriere, N., Radiotherapeutic management of brain metastases: A systematic review and meta-analysis, Cancer Treatment ReviewsCancer Treat Rev, 31, 256-273, 2005	Includes small cell lung cancer patients, which are excluded from the review
Tsao, M. N., Lloyd, N., Wong, R. K., Chow, E., Rakovitch, E., Laperriere, N., Xu, W., Sahgal, A., Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD003869, 2012	Abstract
Tsao, M. N., Lloyd, N., Wong, R., Chow, E., Rakovitch, E., Laperriere, N., Whole brain radiotherapy for the treatment of multiple brain metastases, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, CD003869, 2006	The included RCTs have already been included in this review
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, CancerCancer, 118, 2486-93, 2012	The trials included in this systematic review have already been considered for inclusion
Ushio, Y., Arita, N., Hayakawa, T., Mogami, H., Hasegawa, H., Bitoh, S., Oku, Y., Ikeda, H., Kanai, N., Kanoh, M., Akagi, K., Nakagawa, H., Chemotherapy of brain metastases from lung carcinoma: A controlled randomized study, NeurosurgeryNeurosurgery, 28, 201-205, 1991	Chemotherapy type not included in the protocol
Viani, G. A., Manta, G. B., Fonseca, E. C., De Fendi, L. I., Afonso, S. L., Stefano, E. J., Whole brain radiotherapy with radiosensitizer for brain metastases, Journal of Experimental & Clinical Cancer ResearchJ Exp Clin Cancer Res, 28, 1, 2009	The included RCTs have already been included in this review
Weinberg, U, Farber, O, Bomzon, Z, Giladi, M, Kirson, Ed, METIS: a phase III study of radiosurgery with TTFields for 1-10 brain metastases from NSCLC, Journal of thoracic oncology. Conference: 6th european lung cancer conference, ELCC 2016. Geneva switzerland. Conference start: 20160413.	Protocol/abstract

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
Conference end: 20160416. Conference publication: (var.pagings), 11, S146, 2016	
Wronski, M., Ledermann, G., Levine, M., A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis [1] (multiple letters), CancerCancer, 80, 1002-1004, 1997	Letter to editor about Mintz study
Yamamoto, N., Goto, K., Nishio, M., Chikamori, K., Hida, T., Maemondo, M., Katakami, N., Kozuki, T., Yoshioka, H., Seto, T., Tajima, K., Tamura, T., Final overall survival in JO22903, a phase II, open-label study of first-line erlotinib for Japanese patients with EGFR mutation-positive non-small-cell lung cancer, International Journal of Clinical OncologyInt J Clin Oncol, 22, 1-9, 2016	Only 21 of a total of 81 patients had brain metastases
Zeng, Y. C., Wu, R., Xing, R., Chi, F., Wang, S. L., Chen, X. D., Xuan, Y., Wu, L. N., Duan, Q. Y., Tang, M. Y., Niu, N., Sun, Y. N., Fan, G. L., Wang, H. M., 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/Radiotherapie, 20, 187-192, 2016	Includes patients who have received previous therapy for brain metastases
Zhang, W., Jiang, W., Luan, L., Wang, L., Zheng, X., Wang, G., Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis, BMC CancerBMC Cancer, 14, 793, 2014	Population not in PICO
Zhao, Q., Qin, Q., Sun, J., Han, D., Wang, Z., Teng, J., Li, B., Brain Radiotherapy plus Concurrent Temozolomide versus Radiotherapy Alone for Patients with Brain Metastases: A Meta-Analysis, PLoS ONE [Electronic Resource]PLoS ONE, 11, e0150419, 2016	The included RCTs have already been included in this review
Zheng, M. H., Sun, H. T., Xu, J. G., Yang, G., Huo, L. M., Zhang, P., Tian, J. H., Yang, K. H., Combining Whole brain Radiotherapy with Gefitinib/Erlotinib for Brain Metastases from Non-Small-Cell Lung Cancer: A Meta-Analysis, BioMed Research InternationalBiomed Res Int, 2016, 5807346, 2016	The included RCTs have already been included in this review
Larsen, P. B., Kumler, I., Nielsen, D. L., A systematic review of trastuzumab and lapatinib in the treatment of women with brain metastases from HER2-	The chemotherapy agents included in this review are not in the protocol

What is the most effective intracranial treatment (surgery, stereotactic radiotherapy, whole brain radiotherapy or combinations of these, or no treatment) for single, mixed and multiple brain metastases?	
positive breast cancer, Cancer Treatment ReviewsCancer Treat Rev, 39, 720-7, 2013	
Viani, G., Godoi Da Silva, L., Viana, B., Rossi, B., Suguikawa, E., Zuliani, G., Whole brain radiotherapy and stereotactic radiosurgery for patients with recursive partitioning analysis i and lesions <5 cm³: A matched pair analysis, Journal of Cancer Research and Therapeutics, 12, 770-774, 2016	This is a quasi-randomised trial

Economic

Not applicable – health economic inclusion / exclusion detailed in Supplementary Material D.

Excluded studies for review 4b – management of multiple metastases

Clinical

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations, therefore the clinical excluded studies list is the same as for 4a – management of single metastases.

Economic

Not applicable – health economic inclusion / exclusion detailed in Supplementary Material D.

Excluded studies for review 4c – management of brain metastases with a mixed population

Clinical

A single search was conducted for the review questions related to management of single metastases, multiple metastases and brain metastases with mixed populations, therefore the clinical excluded studies list is the same as for 4a – management of single metastases.

Economic

Not applicable – health economic inclusion / exclusion detailed in Supplementary Material D

Excluded studies for review 5c – follow-up of metastases

Clinical

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Study	**Reason for Exclusion**
Albert, F. K., Forsting, M., Sartor, K., Adams, H. P., Kunze, S., Salcman, M., Wilson, C. B., Early postoperative magnetic resonance imaging after resection of malignant glioma: Objective evaluation of residual tumor and its influence on regrowth and prognosis, Neurosurgery, 34, 45-61, 1994	Not follow up protocol
Aukema, T. S., Valdes Olmos, R. A., Korse, C. M., Kroon, B. B. R., Wouters, M. W. J. M., Vogel, W. V., Bonfrer, J. M. G., Nieweg, O. E., Utility of fDG PET/CT and brain MRI in melanoma patients with increased serum S-100B level during follow-up, Annals of Surgical Oncology, 17, 1657-1661, 2010	Population not in PICO (melanoma patients without symptoms and signs of recurrent disease were referred for total body PET/CT and MRI of the brain because of an increased S-100B); not follow up protocol

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Aukema, T. S., Valdes Olmos, R. A., Korse, T. M., Kroon, B. B., Wouters, M. W., Vogel, W. V., Bonfrer, J. M., Nieweg, O. E., Increased serum S-100B level in melanoma patients during followup and utility of FDG PET/CT and brain MRI, Annals of Surgical Oncology, 17, S114-S115, 2010	Abstract only. Same study as excluded Aukema (2010)
Baker, J. J., Meyers, M. O., Frank, J., Amos, K. D., Stitzenberg, K. B., Ollila, D. W., Routine restaging PET/CT and detection of initial recurrence in sentinel lymph node positive stage III melanoma, American Journal of SurgeryAm J Surg, 207, 549-554, 2014	Population not in PICO
Baker, J. J., Meyers, M. O., Yeh, J. J., Frank, J., Amos, K. D., Stitzenberg, K. B., Long, P., Ollila, D. W., Routine restaging PET/CT and detection of recurrence in sentinel lymph node positive stage III melanoma, Annals of Surgical Oncology, 18, S114, 2011	Population not in PICO
Becker, G., Hofmann, E., Woydt, M., Hulsmann, U., Maurer, M., Lindner, A., Becker, T., Krone, A., Postoperative neuroimaging of high-grade gliomas: Comparison of transcranial sonography, magnetic resonance imaging, and computed tomography, Neurosurgery, 44, 469-478, 1999	Outcomes not in PICO and non-comparative study
Becker, G., Krone, A., Schmitt, K., Woydt, M., Hofmann, E., Lindner, A., Bogdahn, U., Gahnl, G., Roosen, K., Preoperative and postoperative follow-up in high-grade gliomas: Comparison of transcranial color-coded real-time sonography and computed tomography findings, Ultrasound in Medicine and Biology, 21, 1123-1135, 1995	Outcomes not in PICO, unclear follow up protocol (“Contrast CT scans, TCCS and neurological follow-up examinations were performed at the same time within a time interval of 6 weeks to 3 months, coinciding with the protocol of adjuvant tumor therapy”.), N = 20

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Belohlavek, O., Simonova, G., Kantorova, I., Novotny Jr, J., Liscak, R., Brain metastases after stereotactic radiosurgery using the Leksell gamma knife: Can FDG PET help to differentiate radionecrosis from tumour progression?, European Journal of Nuclear Medicine and Molecular Imaging, 30, 96-100, 2003	Outcomes not in PICO
Caresia, A. P., Castell-Conesa, J., Negre, M., Mestre, A., Cuberas, G., Manes, A., Maldonado, X., Thallium-201SPECT assessment in the detection of recurrences of treated gliomas and ependymomas, Clinical and Translational Oncology, 8, 750-754, 2006	Population not in PICO (patients received SPECT if they had equivocal CT or RM images)
Casalino, D. D., Remer, E. M., Bishoff, J. T., Coursey, C. A., Dighe, M., Harvin, H. J., Heilbrun, M. E., Majd, M., Nikolaidis, P., Preminger, G. M., Raman, S. S., Sheth, S., Vikram, R., Weinfeld, R. M., ACR appropriateness criteria post-treatment follow-Up of renal cell carcinoma, Journal of the American College of Radiology, 11, 443-449, 2014	Guideline for asymptomatic patients who have been treated for renal cell carcinoma (RCC) by radical nephrectomy or nephron-sparing surgery.
Chabert, I., Belladjou, I., Poisson, F., Dhermain, F., Martin, V., Ammari, S., Vauclin, S., Pineau, P., Buvat, I., Deutsch, E., Robert, C., Correlation between MRI-based hyper-perfused areas and tumor recurrence in high-grade gliomas, Radiotherapy and Oncology, 119, S885, 2016	Published as abstract only, not enough information available to ascertain relevance although it appears to not be relevant
Chang, J. H., Kim, C. Y., Choi, B. S., Kim, Y. J., Kim, J. S., Kim, I. A., Pseudoprogression and pseudoresponse in the management of high-grade glioma: Optimal decision timing according to the response assessment of the neuro-oncology working group, Journal of Korean Neurosurgical Society, 55, 5-11, 2014	Non-comparative study
Chang, P. D., Chow, D. S., Yang, P. H., Filippi, C. G., Lignelli, A., Predicting glioblastoma recurrence by early changes in the apparent diffusion coefficient value and signal intensity on FLAIR images, American Journal of Roentgenology, 208, 57-65, 2017	Population not in PICO ("Only patients for whom follow-up MRI examinations performed at Columbia University Medical Center showed definitive contrast-enhancing recurrent tumor were included in the study.")

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Chow, D. S., Qi, J., Guo, X., Miloushev, V. Z., Iwamoto, F. M., Bruce, J. N., Lassman, A. B., Schwartz, L. H., Lignelli, A., Zhao, B., Filippi, C. G., Semiautomated volumetric measurement on postcontrast MR imaging for analysis of recurrent and residual disease in glioblastoma multiforme, American Journal of Neuroradiology, 35, 498-503, 2014	Not follow up protocol; outcomes not in PICO
Christensen, M., Kamson, D. O., Snyder, M., Kim, H., Robinette, N. L., Mittal, S., Juhasz, C., Tryptophan PET-defined gross tumor volume offers better coverage of initial progression than standard MRI-based planning in glioblastoma patients, Journal of Radiation Oncology, 3, 131-138, 2014	Non-comparative study, N = 11
Darcourt, J., Dufour, M., Mondot, L., Bourg, V., Bondiau, P., Almairac, F., Saada, E., Fontaine, D., Fauchon, F., Vandenbos, F., Ouvrier, M., Sapin, N., Role of 18F-DOPA in the management of patients suspected of brain tumour recurrence, European Journal of Nuclear Medicine and Molecular Imaging, 41, S312, 2014	Published as abstract only, with not enough information to ascertain relevance
Datta, Niloy Ranjan, Pasricha, Rajesh, Gambhir, Sanjay, Prasad, Shambhu Nath, Phadke, Rajendra Vishnu, Comparative evaluation of 201Tl SPECT and CT in the follow-up of irradiated brain tumors, International Journal of Clinical Oncology, 9, 51-8, 2004	Unclear follow up protocol; outcomes/analyses not in PICO
De Paepe, A., Vandeneede, N., Strens, D., Specenier, P., The economics of the treatment and follow-up of patients with glioblastoma, Value in Health, 18 (7), A448, 2015	Published as abstract only, with not enough information to ascertain relevance
Deng, S. M., Zhang, B., Wu, Y. W., Zhang, W., Chen, Y. Y., Detection of glioma recurrence by 11C-methionine positron emission tomography and dynamic susceptibility contrast-enhanced magnetic resonance imaging: A meta-analysis, Nuclear Medicine Communications, 34, 758-766, 2013	Outcomes (and possibly population) not in PICO

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Dong, Y., Hou, H., Wang, C., Li, J., Yao, Q., Amer, S., Tian, M., The diagnostic value of 18F-FDG PET/CT in association with serum tumor marker assays in breast cancer recurrence and metastasis, BioMed Research International, 2015, no pagination, 2015	Population not in PICO (Breast cancer patients who have received modified radical mastectomy and "The patients were diagnosed as suspicion of recurrence and referred to for whole-body 18F-FDG PET/CT scanning at the PET Center fromJuly 2013 to January 2014."
D'Souza, M. M., Sharma, R., Jaimini, A., Panwar, P., Saw, S., Kaur, P., Mondal, A., Mishra, A., Tripathi, R. P., 11C-MET PET/CT and advanced MRI in the evaluation of tumor recurrence in high-grade gliomas, Clinical Nuclear Medicine, 39, 791-798, 2014	Not follow up protocol; outcomes not in PICO
Ekinci, G., Akpinar, I. N., Baltacioglu, F., Erzen, C., Kilic, T., Elmaci, I., Pamir, N., Early-postoperative magnetic resonance imaging in glial tumors: Prediction of tumor regrowth and recurrence, European Journal of Radiology, 45, 99-107, 2003	Not follow up protocol (only pre-operative scan and early-postoperative magnetic resonance scan)
Ellingson, B. M., Cloughesy, T. F., Lai, A., Nghiemphu, P. L., Pope, W. B., Nonlinear registration of diffusion-weighted images improves clinical sensitivity of functional diffusion maps in recurrent glioblastoma treated with bevacizumab, Magnetic Resonance in Medicine, 67, 237-245, 2012	Not follow up protocol ("Baseline scans were obtained approximately 1.5 weeks before treatment, and follow-up scans were obtained at approximately 6 weeks after the initiation of bevacizumab.")
Fields, R. C., Coit, D. G., Evidence-based follow-up for the patient with melanoma, Surgical Oncology Clinics of North America, 20, 181-200, 2011	Guideline/narrative review

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Fink, J. R., Carr, R. B., Matsusue, E., Iyer, R. S., Rockhill, J. K., Haynor, D. R., Maravilla, K. R., Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects, Journal of Magnetic Resonance Imaging, 35, 56-63, 2012	Not follow up protocol; Population not in PICO ("All patients who underwent advanced physiologic 3T MRI, including MRS, DSC, and DWI, for evaluation of suspected malignant glioma recurrence at our institution between October 2006 and December 2008 were identified.")
Forsting, M., Albert, F. K., Kunze, S., Adams, H. P., Zenner, D., Sartor, K., Extirpation of glioblastomas: MR and CT follow-up of residual tumor and regrowth patterns, American Journal of Neuroradiology, 14, 77-87, 1993	Non-comparative study
Fouke, S. J., Benzinger, T., Gibson, D., Ryken, T. C., Kalkanis, S. N., Olson, J. J., The role of imaging in the management of adults with diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline, Journal of Neuro-Oncology, 125, 457-479, 2015	Outcomes not in PICO
Gietema, J. A., Meinardi, M. T., Sleijfer, D. T., Hoekstra, H. J., van der Graaf, W. T. A., Routine chest X-rays have no additional value in the detection of relapse during routine follow-up of patients treated with chemotherapy for disseminated non-seminomatous testicular cancer, Annals of Oncology, 13, 1616-1620, 2002	Non-comparative study; unclear population (not reported how many patients had had brain metastases at study entry)
Goenka, A., Kumar, A., Sharma, R., Seith, A., Kumar, R., Julka, P., Differentiation of glioma progression or recurrence from treatment-induced changes using a combination of diffusion, perfusion and 3D-MR spectroscopy: A prospective study, Journal of Neuroimaging, 20, 99-100, 2010	Published as abstract only, so little information available to use to ascertain relevance; but population appears to not be in PICO

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Gomez-Rio, M., Del Valle Torres, D. M., Rodriguez-Fernandez, A., Llamas-Elvira, J. M., Lozano, S. O., Font, C. R., Ramirez, E. L., Katati, M., 201Tl-SPECT in low-grade gliomas: Diagnostic accuracy in differential diagnosis between tumour recurrence and radionecrosis, European Journal of Nuclear Medicine and Molecular Imaging, 31, 1237-1243, 2004	Not follow up protocol/population not in PICO (patients with suspected tumour recurrence)/outcomes not in PICO
Gourcerol, D., Scherpereel, A., Debeugny, S., Porte, H., Cortot, A. B., Lafitte, J. J., Relevance of an extensive follow-up after surgery for nonsmall cell lung cancer, European Respiratory JournalEur Respir J, 42, 1357-1364, 2013	Population not in PICO (only 2 patients had stage 4 lung cancer)
Grigolato, D., Locantore, L., Cucca, M., Zuffante, M., Ferdeghini, M., 18F-DOPA PET/CT imaging in brain tumors, European Journal of Nuclear Medicine and Molecular Imaging, 43, S264, 2016	Published as abstract only, not enough information available to ascertain relevance, but population appears not to be in PICO
Grosu, A. L., Astner, S. T., Riedel, E., Nieder, C., Wiedenmann, N., Heinemann, F., Schwaiger, M., Molls, M., Wester, H. J., Weber, W. A., An interindividual comparison of O-(2-[18F]fluoroethyl)-L- tyrosine (FET)- and L-[methyl-11C]methionine (MET)-PET in patients with brain gliomas and metastases, International Journal of Radiation Oncology Biology Physics, 81, 1049-1058, 2011	Population not in PICO (All patients had previously been treated for gliomas or brain metastases and now presented with MRI findings suggesting the presence of residual or recurrent tumor tissue)
Hamdan, A., Kane, P., Uncertainty and variability in surveillance imaging after completion of primary treatment in glioblastoma multiforme, Neuro-Oncology, 16, ii80, 2014	Published as abstract only, not enough information available to ascertain relevance
Hamdan, A., Kane, P., Variability in follow up imaging guidelines after the completion of primary therapy in glioblastoma multiforme, Neuro-Oncology, 16, vi1-vi2, 2014	Published as abstract only, not enough information available to ascertain relevance

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Hawighorst, H., Essig, M., Debus, J., Knopp, M. V., Engenhart-Cabilic, R., Schonberg, S. O., Brix, G., Zuna, I., van Kaick, G., Serial MR imaging of intracranial metastases after radiosurgery, Magnetic Resonance ImagingMagn Reson Imaging, 15, 1121-32, 1997	Non-comparative study
Hodgson, T. J., Kingsley, D. P. E., Moseley, I. F., The role of imaging in the follow up of meningiomas, Journal of Neurology Neurosurgery and Psychiatry, 59, 545-547, 1995	Not follow up protocol/unclear when/what the patients had (as) follow up
Hojer, C., Hildebrandt, G., Lanfermann, H., Schroder, R., Haupt, W. F., Pilocytic astrocytomas of the posterior fossa - A follow-up study in 33 patients, Acta Neurochirurgica, 129, 131-139, 1994	Not follow up protocol/unclear which patients received what follow up
Hu, X., Ma, L., Li, W., Sun, X., Sun, J., Yu, J., 11C-choline PET/CT detecting tumour recurrence and predicting survival in post-treatment patients with high-grade Glioma, European Journal of Nuclear Medicine and Molecular Imaging, 40, S351, 2013	Published as abstract only, not enough information available to ascertain relevance
Hu, X., Wong, K. K., Young, G. S., Guo, L., Wong, S. T., Support vector machine multiparametric MRI identification of pseudoprogression from tumor recurrence in patients with resected glioblastoma, Journal of Magnetic Resonance Imaging, 33, 296-305, 2011	Population not in PICO (patients with confirmed radiation necrosis or recurrence)
Huber, P. E., Hawighorst, H., Fuss, M., van Kaick, G., Wannenmacher, M. F., Debus, J., Transient enlargement of contrast uptake on MRI after linear accelerator (linac) stereotactic radiosurgery for brain metastases, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 49, 1339-49, 2001	Not follow up protocol
Ikeda, H., Tsuyuguchi, N., Kunihiro, N., Ishibashi, K., Goto, T., Ohata, K., Analysis of progression and recurrence of meningioma using 11C-methionine PET, Annals of Nuclear Medicine, 27, 772-780, 2013	Not follow up protocol

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Ion-Margineanu, A., Van Cauter, S., Sima, D. M., Maes, F., Van Gool, S. W., Sunaert, S., Himmelreich, U., Van Huffel, S., Tumour Relapse Prediction Using Multiparametric MR Data Recorded during Follow-Up of GBM Patients, BioMed Research InternationalBiomed Res Int, 2015 (no pagination), 2015	Not follow up protocol
Jansen, N., Suchorska, B., Graute, V., Lutz, J., Schwarz, S., Bartenstein, P., Kreth, F. W., La Fougere, C., [18F]FET-PET based therapy monitoring after stereotactic 125iodine brachytherapy in patients with recurrent high grade glioma, NuklearMedizin, 51, A14, 2012	Published as abstract only, with not enough information reported to ascertain relevance
Jora, C., Mattakarottu, J. J., Aniruddha, P. G., Mudalsha, R., Singh, D. K., Pathak, H. C., Sharma, N., Sarin, A., Prince, A., Singh, G., Comparative evaluation of 18F-FDOPA, 13N-AMMONIA, 18F-FDG PET/CT and MRI in primary brain tumors - A pilot study, Indian Journal of Nuclear Medicine, 26, 78-81, 2011	Population not in PICO (15/23 were postoperative cases with suspected recurrence or residual tumor tissue)
Jostel, A., Mukherjee, A., Hulse, P. A., Shalet, S. M., Adult growth hormone replacement therapy and neuroimaging surveillance in brain tumour survivors, Clinical EndocrinologyClin Endocrinol (Oxf), 62, 698-705, 2005	Population not in PICO/mixed population
Juhasz, C., Mittal, S., Muzik, O., Chugani, D. C., Chakraborty, P. K., Bahl, G., Barger, G. R., Accurate identification of recurrent gliomas by kinetic analysis of alpha-methyl-l-tryptophan unidirectional uptake on PET, Neuro-Oncology, 12, iv113, 2010	Published as abstract only, not enough information reported to ascertain relevance, but it seems that population/outcomes not in PICO
Jung, B. H., Hwang, S., Moon, D. B., Ahn, C. S., Kim, K. H., Ha, T. Y., Song, G. W., Jung, D. H., Lee, S. G., Surveillance protocol for hepatocellular carcinoma recurrence after living donor liver transplantation, HPB, 16, 578-579, 2014	Published as abstract only, not enough information reported to ascertain relevance, but it seems that population not in PICO

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Kaplan, M. A., Inal, A., Kucukoner, M., Urakci, Z., Ekici, F., Firat, U., Zincircioglu, S. B., Isikdogan, A., Cranial magnetic resonance imaging in the staging of HER2-positive breast cancer patients, Onkologie, 36, 176-181, 2013	Population not in PICO
Kelly, J, Does the addition of positron emission tomography/computed tomography (PET/CT) to the routine investigation and assessment of patients with melanoma yield clinical and economic benefits? (Structured abstract), Health Technology Assessment Database, 2013	Unavailable/we cannot source paper
Klesse, L., Bezner, S., Gargan, L., Leonard, D., Bowers, D., Utility of long term neuro-imaging in patients with cerebellar pilocytic astrocytomas, Pediatric Blood and Cancer, 56, 963, 2011	Population not in PICO (mean age at diagnosis < 10 years)
Klutmann, S., Bohuslavizki, K. H., Brenner, W., Behnke, A., Tietje, N., Kroger, S., Hugo, H. H., Mehdorn, H. M., Clausen, M., Henze, E., Somatostatin receptor scintigraphy in postsurgical follow-up examinations of meningioma, Journal of Nuclear MedicineJ Nucl Med, 39, 1913-7, 1998	Not follow up protocol
Lagman, C, Bhatt, N, Pelargos, P, Lee, S, Mukherjee, D, Yang, I, A meta-analysis of published literature on adjuvant radiosurgery and surveillance following subtotal resection of atypical meningioma, Neuro-oncology. Conference: 21st annual scientific meeting and education day of the society for neuro-oncology. United states. Conference start: 20161117. Conference end: 20161120, 18, vi101, 2017	Duplicate
Lagman, C., Bhatt, N., Pelargos, P., Lee, S., Mukherjee, D., Yang, I., A meta-analysis of published literature on adjuvant radiosurgery and surveillance following subtotal resection of atypical meningioma, Neuro-Oncology, 18, vi101, 2016	Published as abstract only, not enough information available to ascertain relevance (checked for topic 3a)
Lagman, Carlito, Bhatt, Nikhilesh S., Lee, Seung J., Bui, Timothy T., Chung, Lawrance K., Voth, Brittany L., Barnette, Natalie E., Pouratian, Nader, Lee, Percy, Selch, Michael, Kaprealian, Tania, Chin, Robert, McArthur,	Checked for topic 3a; all included studies checked for relevance for topic 3a

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
David L., Mukherjee, Debraj, Patil, Chirag G., Yang, Isaac, Adjuvant Radiosurgery Versus Serial Surveillance Following Subtotal Resection of Atypical Meningioma: A Systematic Analysis, World Neurosurgery, 98, 339-346, 2017	
Law, A., Loh, N., Francis, R., Bynevelt, M., McCarthy, M., Segard, T., Morandeau, L., Maton, P., Nowak, A., Atkinson, J., 11C-Methionine and 18F-fluorothymidine PET-CT imaging in suspected residual or recurrent glioma, Journal of Medical Imaging and Radiation Oncology, 56, 32, 2012	Published as abstract only and not enough information is reported to ascertain relevance, although it appears not to be a follow up protocol
Le Jeune, F. P., Dubois, F., Blond, S., Steinling, M., Sestamibi technetium-99m brain single-photon emission computed tomography to identify recurrent glioma in adults: 201 studies, Journal of Neuro-Oncology, 77, 177-183, 2006	Outcomes not in PICO
Lee, J. W., Kang, K. W., Park, S. H., Lee, S. M., Paeng, J. C., Chung, J. K., Lee, M. C., Lee, D. S., 18F-FDG PET in the assessment of tumor grade and prediction of tumor recurrence in intracranial meningioma, European Journal of Nuclear Medicine and Molecular Imaging, 36, 1574-1582, 2009	Not follow up protocol
Leimgruber, Antoine, Ostermann, Sandrine, Yeon, Eun Jo, Buff, Evelyn, Maeder, Philippe P., Stupp, Roger, Meuli, Reto A., Perfusion and diffusion MRI of glioblastoma progression in a four-year prospective temozolomide clinical trial, International journal of radiation oncology, biology, physics, 64, 869-75, 2006	Not follow up protocol
Lemasson, B., Chenevert, T. L., Mikkelsen, T., Boes, J. L., Johnson, T. D., Galban, S., Rehemtulla, A., Galban, C., Ross, B. D., Novel MRI-based biomarker for early assessment of glioma recurrence, Cancer Research, 72, no pagination, 2012	Published as an abstract only, not enough information reported to ascertain relevance. N = 14.
Li, Wanhu, Ma, Li, Wang, Xiaoyue, Sun, Jujie, Wang, Suzhen, Hu, Xudong, (11)C-choline PET/CT tumor recurrence detection and survival prediction in post-treatment patients with high-grade gliomas, Tumour	Population not in PICO (suspicion of recurrence)

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
biology : the journal of the International Society for Oncodevelopmental Biology and Medicine, 35, 12353-60, 2014	
Lorberboym, D., Baram, J., Feibel, M., Hercbergs, A., Lieberman, L., A prospective evaluation of thallium-201 single photon emission computerized tomography for brain tumor burden, International Journal of Radiation Oncology Biology Physics, 32, 249-254, 1995	Unclear follow up protocol/outcomes not in PICO
Loreti, F., Trippa, F., Costa, M., Conti, S., Francesconi, E., Giorgi, C., Carletti, S., Maranzano, E., 99mTc-MIBI SPECT/CT in brain metastases treated with stereotactic radiosurgery (SRS): Experience of the Terni Hospital neuro-oncology group, Clinical and Translational Imaging, 1, S40, 2013	Published as an abstract only. Not enough information reported to ascertain relevance.
Madhavi, T., Raunak, V., Rajnish, S., Jaspriya, B., Abhinav, J., Maria, S. M. D., Pandey Santosh, K., Jyotika, J., Puja, P., Mishra Anil, K., Anupam, M., Comparative evaluation of C-11 methionine (METPET) and F-18 flurodeoxyglucose (FDG) PET/CT for detection of recurrent brain tumors, Indian Journal of Nuclear Medicine, 25, 90, 2010	Published as abstract only, not enough information reported to ascertain relevance, but study does not seem to be follow up protocol
Makita, Masujiro, Sakai, Takehiko, Ogiya, Akiko, Kitagawa, Dai, Morizono, Hidetomo, Miyagi, Yumi, Iijima, Kotaro, Iwase, Takuji, Optimal surveillance for postoperative metastasis in breast cancer patients, Breast cancer (Tokyo, Japan), 23, 286-94, 2016	Population not in PICO
Massager, N., De Smedt, F., Devriendt, D., Long-term tumor control of benign intracranial tumors after Gamma Knife radiosurgery in 280 patients followed more than 5 years, Acta Neurologica Belgica, 113, 463-467, 2013	Not follow up protocol
Matsuo, M., Miwa, K., Shinoda, J., Tanaka, O., Krishna, M., Impact Of C11-methionine positron emission tomography (PET) for malignant glioma in radiation therapy: Is C11-methionine PET a superior to magnetic resonance imaging?, International Journal of Radiation Oncology Biology Physics, 81, S182, 2011	Published as abstract only, not enough information reported to ascertain relevance

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Menoux, I., Armspach, J. P., Noel, G., Antoni, D., Imaging methods used in the differential diagnosis between brain tumour relapse and radiation necrosis after stereotactic radiosurgery of brain metastases: Literature review, Cancer/Radiotherapie, 20, 837-845, 2016	Narrative review
Meyers, S. P., Wildenhain, S., Chess, M. A., Tarr, R. W., Postoperative evaluation for intracranial recurrence of medulloblastoma: MR findings with gadopentetate dimeglumine, AJNR. American journal of neuroradiology, 15, 1425-34, 1994	Not follow up protocol/population not in PICO (mean age 8.3 years, range 1-42 years; no further details)
Mori, H., Kunimatsu, A., Abe, O., Sasaki, H., Takao, H., Nojo, T., Kawai, K., Saito, N., Ohtomo, K., Diagnostic ability of fluid-attenuated inversion recovery MR imaging to detect remnant or recurrent meningiomas after resection, Neuroradiology Journal, 25, 163-171, 2012	Not follow up protocol
Mori, H., Kunimatsu, A., Abe, O., Sasaki, H., Takao, H., Nojo, T., Ohtomo, K., Resected meningiomas: Diagnostic performance of fluid-attenuated inversion recovery MR imaging for detection of remnant or recurrence, Neuroradiology Journal, 23, 419-420, 2010	Published as abstract only, not enough information reported to ascertain relevance, but study does not seem to be follow up protocol
Nayeri, A., Prablek, M. A., Brinson, P. R., Weaver, K. D., Thompson, R. C., Chambless, L. B., Short-term postoperative surveillance imaging may be unnecessary in elderly patients with resected WHO Grade i meningiomas, Journal of Clinical NeuroscienceJ Clin Neurosci, 26, 101-104, 2016	Not follow up protocol
Nesbitt, D., Hendry, G., Scoones, D., Kane, P., Routine follow-up imaging after treatment for glioblastoma: How useful is it?, Neuro-Oncology, 12, iii34, 2010	Published as abstract only; non-comparative study
Nihashi, T., Dahabreh, I. J., Terasawa, T., PET in the clinical management of glioma: Evidence map, American Journal of Roentgenology, 200, W654-W660, 2013	Outcomes not in PICO

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Niyazi, M., Schnell, O., Suchorska, B., Schwarz, S. B., Ganswindt, U., Geisler, J., Bartenstein, P., Kreth, F. W., Tonn, J. C., Eigenbrod, S., Belka, C., La Fougere, C., FET-PET assessed recurrence pattern after radio-chemotherapy in newly diagnosed patients with glioblastoma is influenced by MGMT methylation status, Radiotherapy and Oncology, 104, 78-82, 2012	Not follow up protocol
Nowosielski, M., Hutterer, M., Tinkhauser, G., Irschick, R., Waitz, D., Putzer, D., Stockhammer, G., Recheis, W., Jaschke, W., Gotwald, T., Bevacizumab/irinotecan in recurrent malignant glioma: A retrospective analysis of MRI, FET-PET, and clinical performance, Journal of Clinical Oncology, 28, no pagination, 2010	Published as abstract only, not enough information reported to ascertain relevance
Nozawa, A, Rivandi, Ah, Kanematsu, M, Hoshi, H, Piccioni, D, Kesari, S, Hoh, Ck, Glucose-corrected standardized uptake value in the differentiation of high-grade glioma versus post-treatment changes, Nuclear Medicine CommunicationsNucl Med Commun, 36, 573-81, 2015	Not follow up protocol
Nozawa, Asae, Rivandi, Ali Hosseini, Kanematsu, Masayuki, Hoshi, Hiroaki, Piccioni, David, Kesari, Santosh, Hoh, Carl K., Glucose-corrected standardized uptake value in the differentiation of high-grade glioma versus post-treatment changes, Nuclear Medicine Communications, 36, 573-81, 2015	Duplicate
Nuutinen, J., Sonninen, P., Lehikoinen, P., Sutinen, E., Valavaara, R., Eronen, E., Norrgard, S., Kulmala, J., Teras, M., Minn, H., Radiotherapy treatment planning and long-term follow-up with [11C]methionine PET in patients with low-grade astrocytoma, International Journal of Radiation Oncology Biology Physics, 48, 43-52, 2000	Outcomes/analyses not in PICO
Park, Ji Eun, Kim, Ho Sung, Park, Kye Jin, Kim, Sang Joon, Kim, Jeong Hoon, Smith, Seth A., Pre- and Posttreatment Glioma: Comparison of Amide Proton Transfer Imaging with MR Spectroscopy for Biomarkers of Tumor Proliferation, Radiology, 278, 514-23, 2016	Not follow up protocol

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Patel, P., Baradaran, H., Delgado, D., Askin, G., Christos, P., Tsiouris, A. J., Gupta, A., MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: A systematic review and meta-analysis, Neuro-Oncology, 19, 118-127, 2017	Population and outcomes not in PICO
Patel, S. H., Robbins, J. R., Gore, E. M., Bradley, J. D., Gaspar, L. E., Germano, I., Ghafoori, P., Henderson, M. A., Lutz, S. T., McDermott, M. W., Patchell, R. A., Robins, H. I., Vassil, A. D., Wippold, F. J., Videtic, G. M., ACR appropriateness criteria follow-up and retreatment of brain metastases, American Journal of Clinical Oncology: Cancer Clinical Trials, 35, 302-306, 2012	Narrative review/guideline
Pavlicek, R., Garcia, J. R., Baquero, M., Soler, M., Fernandez, Y., Fuertes, S., Carrio, I., Lomena, F., Contribution of 11C-methionine PET to MRI in the differentiation of recurrent brain tumor from radiation necrosis, European Journal of Nuclear Medicine and Molecular Imaging, 38, S342, 2011	Published as abstract only, not enough information reported to ascertain relevance, but study does not seem to be follow up protocol, appears to be non-comparative with N = 14
Potzi, C., Becherer, A., Marosi, C., Karanikas, G., Szabo, M., Dudczak, R., Kletter, K., Asenbaum, S., [11C] methionine and [18F] fluorodeoxyglucose PET in the follow-up of glioblastoma multiforme, Journal of Neuro-Oncology, 84, 305-314, 2007	Outcomes or analyses not in PICO
Prat, R., Galeano, I., Lucas, A., Martinez, J. C., Martin, M., Amador, R., Reynes, G., Relative value of magnetic resonance spectroscopy, magnetic resonance perfusion, and 2-(18F) fluoro-2-deoxy-D-glucose positron emission tomography for detection of recurrence or grade increase in gliomas, Journal of Clinical Neuroscience, 17, 50-53, 2010	Population not in PICO; outcomes not in PICO

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Prigent-Le Jeune, F., Dubois, F., Perez, S., Blond, S., Steinling, M., Technetium-99m sestamibi brain SPECT in the follow-up of glioma for evaluation of response to chemotherapy: First results, European Journal of Nuclear Medicine and Molecular Imaging, 31, 714-719, 2004	Not follow up protocol
Pronin, I., Dolgushin, M., Fadeeva, L., Podoprigora, A., Serkov, S., Golanov, A., Nikitin, K., Kornienko, V., CT perfusion in diagnosis of Radiation Necrosis, Neuroradiology Journal, 23, 354, 2010	Published as abstract only, not enough information reported to ascertain relevance, but outcomes do not appear to be in PICO
Pungavkar, S., Gupta, T., Moiyadi, A., Shetty, P., Shridhar, E., Chinnaswamy, G., Godashastri, J., Jalali, R., 3D arterial spin labeling - A novel, non-invasive technique to assess perfusion in brain tumors - Experience of over 200 cases, European Journal of Cancer, 54, S38, 2016	Published as abstract only, not enough information reported to ascertain relevance
Rachinger, W., Goetz, C., Popperl, G., Gildehaus, F. J., Kreth, F. W., Holtmannspotter, M., Herms, J., Koch, W., Tatsch, K., Tonn, J. C., Positron emission tomography with O-(2-[18F]flouroethyl)-L- tyrosine versus magnetic resonance imaging in the diagnosis of recurrent gliomas, Neurosurgery, 57, 505-511, 2005	Outcomes not in PICO
Radbruch, Alexander, Lutz, Kira, Wiestler, Benedikt, Baumer, Philipp, Heiland, Sabine, Wick, Wolfgang, Bendszus, Martin, Relevance of T2 signal changes in the assessment of progression of glioblastoma according to the Response Assessment in Neurooncology criteria, Neuro-Oncology, 14, 222-9, 2012	Not follow up protocol; unclear when patients had scans
Reiche, W., Schaefer, A., Schmidt, S., Moringlane, J. R., Feiden, W., Kirsch, C. M., Piepgras, U., 18FDG-SPECT imaging of brain tumours: Results in 41 patients, Rivista di Neuroradiologia, 11, 149-160, 1998	Not follow up protocol
Reijneveld, J. C., van der Grond, J., Ramos, L. M. P., Bromberg, J. E. C., Taphoorn, M. J. B., Proton MRS imaging in the follow-up of patients with suspected low-grade gliomas, Neuroradiology, 47, 887-91, 2005	Population not in PICO; non-comparative study with N = 14

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Roberts, S., Jones, L., Exley, C., CT follow up after surgery for lung cancer-should the availability of radio-surgery prompt a change in screening protocol to detect early intracerebral recurrence?, Thorax, 70, A159, 2015	Population not in PICO
Rodriguez-Bel, L., Gamez-Cenzano, C., Garciagarzon, J., Sabate-Llobera, A., Vercher-Conejero, J., Gracia-Sanchez, L., Linares-Tello, E. L., Majos-Torro, C., Lucas-Calduch, A., Macia-garau, M., Bruna-Escuer, J., Diagnostic accuracy for F18-FDG-PET/CT and C11-METHIONINEPET/ CT Co-registered with MRI for differentiation of recurrent brain tumor from radiation injury, European Journal of Nuclear Medicine and Molecular Imaging, 43, S260, 2016	Published as abstract only, not enough information reported to ascertain relevance, but population and outcomes appear not to be in PICO
Rottenburger, C., Hentschel, M., Kelly, T., Trippel, M., Brink, I., Reithmeier, T., Tobias Meyer, P., Nikkhah, G., Comparison of C-11 methionine and C-11 choline for PET imaging of brain metastases: A prospective pilot study, Clinical Nuclear Medicine, 36, 639-642, 2011	Not follow up protocol (N = 8)
Rubinstein, R., Karger, H., Pietrzyk, U., Siegal, T., Gomori, J. M., Chisin, R., Use of 201Thallium brain SPECT, image registration, and semi-quantitative analysis in the follow-up of brain tumors, European Journal of Radiology, 21, 188-95, 1996	Outcomes not in PICO
Sadeghi, N., Lebrun, J. C., Absil, J., Metens, T., Goldman, S., Dynamic susceptibility contrast enhanced (DSC) MR based perfusion imaging to differentiate recurrence from stable disease in brain gliomas, Neuroradiology, 56, 233, 2014	Published as abstract only, not enough information reported to ascertain relevance, but outcomes appear not to be in PICO
Samnick, S., Bader, J. B., Hellwig, D., Moringlane, J. R., Alexander, C., Romeike, B. F. M., Feiden, W., Kirsch, C. M., Clinical value of iodine-123-alpha-methyl-L-tyrosine single-photon emission tomography in the differential diagnosis of recurrent brain tumor in patients pretreated for glioma at follow-up, Journal of Clinical Oncology, 20, 396-404, 2002	Population not in PICO, not follow up protocol

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Santoni, M., Berardi, R., Bittoni, A., Paccapelo, A., Nanni, C., Fanti, S., Burattini, L., Cascinu, S., Clinical impact of [11C]-methionine positron emission tomography on the treatment of primary and recurrent gliomas, Annals of Oncology, 23, ix148, 2012	Published as abstract only, not enough information reported to ascertain relevance
Santoni, M., Nanni, C., Bittoni, A., Polonara, G., Paccapelo, A., Trignani, R., De Lisa, M., Rychlicki, F., Burattini, L., Berardi, R., Fanti, S., Cascinu, S., [11C]-Methionine positron emission tomography in the postoperative imaging and followup of patients with primary and recurrent gliomas, ISRN Oncology, 2014, no pagination, 2014	Not follow up protocol/outcomes not in PICO
Seeger, A., Braun, C., Skardelly, M., Paulsen, F., Schittenhelm, J., Ernemann, U., Bisdas, S., Comparison of Three Different MR Perfusion Techniques and MR Spectroscopy for Multiparametric Assessment in Distinguishing Recurrent High-Grade Gliomas from Stable Disease, Academic Radiology, 20, 1557-1565, 2013	Population not in PICO (patients with the presence of new enhancing lesions after chemoradiotherapy)
Shan, Y., Chen, X., Lin, Y., Wang, Y., Zhong, S., Gong, Y., Value of magnetic resonance spectroscopy and perfusion-weighted imaging in distinguishing glioma recurrence from PTRE: A meta-analysis, International Journal of Clinical and Experimental Medicine, 9, 10006-10017, 2016	Unavailable/we cannot source paper
Sharma, R., D'Souza, M., Jaimini, A., Hazari, P. P., Saw, S., Pandey, S., Singh, D., Solanki, Y., Kumar, N., Mishra, A. K., Mondal, A., A comparison study of 11 C-methionine and 18 F-fluorodeoxyglucose positron emission tomography-computed tomography scans in evaluation of patients with recurrent brain tumors, Indian Journal of Nuclear Medicine, 31, 93-102, 2016	Not follow up protocol (one scan); outcomes not in PICO
Shin, K. E., Ahn, K. J., Choi, H. S., Jung, S. L., Kim, B. S., Jeon, S. S., Hong, Y. G., DCE and DSC MR perfusion imaging in the differentiation of recurrent tumour from treatment-related changes in patients with glioma, Clinical Radiology, 69, e264-e272, 2014	Population not in PICO (“patients who subsequently developed new enhancing

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
	lesions on follow-up contrast-enhanced MRI")
Simpson, J. R., Mendenhall, W. M., Schupak, K. D., Larson, D., Bloomer, W. D., Buckley, J. A., Gaspar, L. E., Gibbs, F. A., Lewin, A. A., Loeffler, J. S., Malcolm, A. W., Schneider, J. F., Shaw, E. G., Wharam Jr, M. D., Gutin, P. H., Rogers, L., Leibel, S., Follow-up and retreatment of brain metastasis. American College of Radiology. ACR Appropriateness Criteria, Radiology, 215 Suppl, 1129-1135, 2000	Unavailable/we cannot source paper
Skvortsova, T., Savintseva, Z., Brodskaya, Z., Medvedev, S. V., Bechtereva, N. P., Direct comparison of [11C]methionine PET with perfusion magnetic resonance imaging for detection of recurrent brain tumors, European Journal of Nuclear Medicine and Molecular Imaging, 39, S381, 2012	Published as abstract only, not enough information reported to ascertain relevance, but population does not appear to be in PICO
Smets, T., Lawson, T. M., Grandin, C., Jankoversuski, A., Raftopoulos, C., Immediate post-operative MRI suggestive of the site and timing of glioblastoma recurrence after gross total resection: A retrospective longitudinal preliminary study, European Radiology, 23, 1467-1477, 2013	Population not in PICO (22/24 were selected to have/had recurrence)
Smith, J. S., Cha, S., Mayo, M. C., McDermott, M. W., Parsa, A. T., Chang, S. M., Dillon, W. P., Berger, M. S., Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury, Journal of Neurosurgery, 103, 428-438, 2005	Not follow up protocol; outcomes not in PICO
Steele, J., Sibtain, A., Brada, M., The content and efficacy of conventional methods of follow-up in neuro-oncology: The need for new strategies, Clinical Oncology, 9, 168-171, 1997	Unclear follow up protocol, non-comparative study, outcomes not in PICO
Stenberg, L., Englund, E., Wirestam, R., Siesjo, P., Salford, L. G., Larsson, E. M., Dynamic susceptibility contrast-enhanced perfusion magnetic resonance (MR) imaging combined with contrast-enhanced MR	Unclear follow up protocol, non-comparative study, N = 8

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
imaging in the follow-up of immunogene-treated glioblastoma multiforme, Acta radiologica (Stockholm, Sweden : 1987), 47, 852-861, 2006	
Stupp, R., Brada, M., van den Bent, M. J., Tonn, J. C., Pentheroudakis, G., High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Annals of Oncology, 25, 93-101, 2014	Guideline/narrative review
Thapa, P. K., Tripathi, M., Jaimini, A., D'Souza, M., Chouttani, K., Pandey, S., Sehar, R., Rawat, H., Mishra, A. K., Sharma, R., Mondal, A., Comparative study between Tc-99m labelled Methionine and C-11 Methionine in detection of low grade astrocytoma, Indian Journal of Nuclear Medicine, 26, S29, 2011	Published as abstract only, not enough information reported to ascertain relevance, but population/outcomes do not appear to be in PICO
Tripathi, M., Sharma, R., Varshney, R., Jaimini, A., Jain, J., Souza, M. M. D., Bal, J., Pandey, S., Kumar, N., Mishra, A. K., Mondal, A., Comparison of F-18 FDG and C-11 methionine PET/CT for the evaluation of recurrent primary brain tumors, Clinical Nuclear Medicine, 37, 158-163, 2012	Population no in PICO (patients referred for evaluation of recurrence); not follow up protocol
Ueki, K., Higuchi, F., Ohtani, R., Udzuka, T., Sakamoto, S., Kim, P., 11C-methionin-pet enables early detection and subsequent intervention of recurrence in 1p/ 19q co-deleted gliomas, Neuro-Oncology, 17, v169, 2015	Published as abstract only, not enough information reported to ascertain relevance, but study appears to be non-comparative
Unterrainer, M., Schweisthal, F., Suchorska, B., Wenter, V., Schmid-Tannwald, C., Fendler, W. P., Schuller, U., Bartenstein, P., Tonn, J. C., Albert, N. L., Serial 18F-FET PET imaging of primarily 18F-FET-negative glioma: Does it make sense?, Journal of Nuclear Medicine, 57, 1177-1182, 2016	Outcomes not in PICO
Van Laere, K., Ceyssens, S., Van Calenbergh, F., De Groot, T., Menten, J., Flamen, P., Bormans, G., Mortelmans, L., Direct comparison of 18F-FDG and 11C-methionine PET in suspected recurrence of glioma: Sensitivity, inter-observer variability and prognostic value, European Journal of Nuclear Medicine and Molecular Imaging, 32, 39-51, 2005	Not follow up protocol: Data obtained in a single session in patients with a history of previously treated primary brain tumours were referred to the PET centre to

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
	differentiate between radiation necrosis and recurrence/progression
Vassilyadi, M., Shamji, M. F., Tataryn, Z., Keene, D., Ventureyra, E., Postoperative surveillance magnetic resonance imaging for cerebellar astrocytoma, Canadian Journal of Neurological Sciences, 36, 707-712, 2009	Population not in PICO (children)
Verburg, N., Hoefnagels, F., Pouwels, P., Boellaard, R., Barkhof, F., Hoekstra, O., Wesseling, P., Reijneveld, J., Heimans, J., Vandertop, P., Zwinderman, K., De Witt Hamer, H., The diagnostic accuracy of neuro-imaging to detect infiltrative glioma within the brain: A meta-analysis based on 1598 patients in 58 publications, Neuro-Oncology, 15, iii194, 2013	Published as abstract only, not enough information available to ascertain relevance, although it appears not to be follow up protocol and outcomes not in PICO
Vigil, C., Caicedo, C., Hernandez, M., Rodriguez-ruiz, M., Olarte, A., Valtuena, G., Moreno-jimenez, M., Penuelas, I., Aristu, J., Arbizu, J., 11C-Methionine-Positron Emission Tomography as prognostic factor of recurrence in glioblastoma, Reports of Practical Oncology and Radiotherapy, 18, S186, 2013	Published as abstract only, not enough information reported to ascertain relevance, but does not appear to be follow up
Vos, M J, Tony, B N, Hoekstra, O S, Postma, T J, Heimans, J J, Hooft, L, Systematic review of the diagnostic accuracy of 201-Tl single photon emission computed tomography in the detection of recurrent glioma (Structured abstract), Nuclear Medicine Communications, 28, 431-439, 2007	Population not in PICO (patients who were clinically suspected of recurrent tumour growth); outcomes not in PICO
Vos, M. J., Hoekstra, O. S., Barkhof, F., Berkhof, J., Heimans, J. J., Van Groeningen, C. J., Vandertop, W. P., Slotman, B. J., Postma, T. J., Thallium-201 single-photon emission computed tomography as an early predictor of outcome in recurrent glioma, Journal of Clinical Oncology, 21, 3559-3565, 2003	Not follow up protocol/analyses not in PICO
Vos, Mj, Berkhof, J, Hoekstra, Os, Bosma, I, Sizoo, Em, Heimans, Jj, Reijneveld, Jc, Sanchez, E, Lagerwaard, Fj, Buter, J, Noske, Dp, Postma, Tj, MRI and thallium-201 SPECT in the prediction of survival in glioma, Neuroradiology, 54, 539-46, 2012	Not follow up protocol/analyses not in PICO

Excluded studies (search conducted together for all three follow up questions): **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma?** **- What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?**	
Vrabec, M., Van Cauter, S., Himmelreich, U., Van Gool, S. W., Sunaert, S., De Vleeschouwer, S., Suput, D., Demaerel, P., MR perfusion and diffusion imaging in the follow-up of recurrent glioblastoma treated with dendritic cell immunotherapy: A pilot study, Neuroradiology, 53, 721-731, 2011	N = 8, outcomes not in PICO, not follow up protocol
Wang, X, Hu, X, Xie, P, Li, W, Li, X, Ma, L, Comparison of magnetic resonance spectroscopy and positron emission tomography in detection of tumor recurrence in posttreatment of glioma: a diagnostic meta-analysis (Provisional abstract), Database of Abstracts of Reviews of Effects, epub, 2014	Unavailable/we cannot source paper
Weber, M. A., Lichy, M. P., Gunther, M., Delorme, S., Thilmann, C., Bachert, P., Schad, L., Debus, J., Schlemmer, H. P., Monitoring of Irradiated Brain Metastases Using Arterial Spin-Labeling MR-Perfusion Imaging and 1H MR Spectroscopy, Rivista di Neuroradiologia, 16, 1118-1122, 2003	Outcomes not in PICO
Weizman, Lior, Sira, Liat Ben, Joskowicz, Leo, Rubin, Daniel L., Yeom, Kristen W., Constantini, Shlomi, Shofty, Ben, Bashat, Dafna Ben, Semiautomatic segmentation and follow-up of multicomponent low-grade tumors in longitudinal brain MRI studies, Medical physics, 41, 052303, 2014	Population not in PICO (children)
Winterstein, Marianne, Munter, Marc W., Burkholder, Iris, Essig, Marco, Kauczor, Hans-Ulrich, Weber, Marc-Andre, Partially resected gliomas: diagnostic performance of fluid-attenuated inversion recovery MR imaging for detection of progression, Radiology, 254, 907-16, 2010	Outcomes not in PICO
Yokoi, K., Miyazawa, N., Arai, T., Brain metastasis in resected lung cancer: value of intensive follow-up with computed tomography, The Annals of thoracic surgery, 61, 546-551, 1996	Population not in PICO (patients treated for lung cancer without brain metastasis)
Yondorf, M. Z., Wernicke, A. G., Parashar, B., Schwartz, T. H., Boockvar, J. A., Stieg, P., Pannullo, S., Nori, D., Chao, K. S. C., Kovanlikaya, I., Impact of Serial DWI and ADC Measurements in Assessment of Brain Metastases Treated With Neurosurgical Resection and Intraoperative Cesium- 131 Brachytherapy: Results of	Published as abstract only, not enough information reported to ascertain relevance, but does not appear to be follow up

Excluded studies (search conducted together for all three follow up questions): - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for glioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for meningioma? - What is the most effective follow-up protocol (including duration, frequency and tests) to detect recurrence after treatment for brain metastases?	
a Prospective Trial, Oncology. Conference: 96th Annual Meeting of the American Radium Society, ARS, 28, 2014	

Economic

Not applicable – health economic inclusion / exclusion detailed in Supplementary Material D.

Appendix L – Research Recommendations

Not applicable – no research recommendations were made for the review questions presented in this report.