ClinicalEvidence

Brain metastases

Search date June 2007

Susan Lalondrelle and Vincent Khoo

ABSTRACT

INTRODUCTION: Metastases to the central nervous system may occur with tumours of any primary origin. Brain (cerebral) metastases may be either single or multiple, with or without disseminated disease elsewhere. Brain metastases may present with focal or generalised symptoms, although up to a third of patients may be asymptomatic. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of interventions for managing brain metastases in adults? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare Regulatory Agency (MHRA). RESULTS: We identified 18 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: corticosteroids; cytotoxic chemotherapy (systemic); radiation sensitisers plus whole-brain radiotherapy (external beam); surgery; radiosurgery; surgery plus radiosurgery; surgery plus radiosurgery plus whole-brain radiotherapy (external beam); surgery plus whole-brain radiotherapy (external beam); whole-brain radiotherapy (external beam); and whole-brain radiotherapy plus radiosurgery.

QUESTIONS

What are the effects of interventions for managing brain metastases in adults?. 3

INTERVENTIONS

INTERVENTIONS FOR MANAGING BRAIN METASTASES

Likely to be beneficial

Corticosteroids* New 3

Whole-brain radiotherapy (external beam) (addition of some other interventions to WBRT may be no more effective than WBRT alone; WBRT alone may be effective in selected people) New 8

Unknown effectiveness

Cytotoxic chemotherapy (systemic) New 4

Radiosurgery (stereotactic LINAC radiotherapy or gamma knife) New 12

Surgery New 5

Surgery plus radiosurgery New 8

Surgery plus radiosurgery plus whole-brain radiotherapy (external beam) New 8

Surgery plus whole-brain radiotherapy (external beam) New 6

Whole-brain radiotherapy (external beam) (WBRT) plus radiosurgery (some evidence of improved survival in people with a single unresectable brain metastasis with WBRT plus radiosurgery compared with WBRT alone; no evidence of improved survival in people with multiple brain metastasis) New 11

Unlikely to be beneficial

Radiation sensitisers (no evidence that adding radiation sensitisers to WBRT is more effective than WBRT alone) New 10

Footnote

*Categorisation not based on RCT evidence, RCTs unlikely to be conducted. There is consensus that corticosteroids are effective for symptom relief.

Key points

- Brain (cerebral) metastases may be either solitary or multiple, with or without disseminated disease elsewhere.
- They may present with focal or generalised symptoms, although up to a third of people may be asymptomatic.

  Headache is the most common presenting symptom. Focal weakness, mental change, and seizures are also common.
- The incidence of brain metastases is between 8–11/100,000 people a year.

  The lung is the most common primary site for brain metastases.
- This review only includes adults with brain metastases (cerebral hemispheres and posterior fossa structures) confirmed with a biopsy or by computed tomography or magnetic resonance imaging.
- We found no direct evidence comparing corticosteroids versus no corticosteroids. Such RCTs are unlikely to be undertaken.

  Although we found no direct evidence, there is consensus that corticosteroids are effective for the relief of symptoms.
- Whole brain radiotherapy (external beam) (WBRT) may be effective in some selected people with brain metastases.

  However, there are adverse effects associated with the use of WBRT, which need to be weighed against any potential benefits on an individual basis.

- We don't know whether WBRT plus radiosurgery is more effective than WBRT alone at improving survival in people with between one and four brain metastases.

  However, subgroup analysis in one large RCT found that, in people with a single unresectable brain metastasis, WBRT plus radiosurgery may increase median survival compared with WBRT alone.
- We found insufficient evidence on the effects of systemic cytotoxic chemotherapy, surgery, surgery plus WBRT, and radiosurgery.
- We don't know whether surgery plus radiosurgery or surgery plus radiosurgery plus WBRT are effective as we found no evidence of their effects.
- Current evidence suggests that adding radiation sensitisers to WBRT is unlikely to produce any additional benefit compared with giving WBRT alone.

DEFINITION

Metastases to the central nervous system may occur with tumours of any primary origin. Brain (cerebral) metastases may be either solitary or multiple, with or without disseminated disease elsewhere. Brain metastases may present with focal or generalised symptoms, although up to a third of patients may be asymptomatic. [1] A high index of suspicion is required when managing patients with cancer. Headache is the most common presenting symptom (50% of people). [1] Focal weakness, mental change, and seizures are also common. Although clinical signs can be helpful to localise the lesion(s), the initial diagnostic evaluation is commonly performed with pre- and post-contrast computed tomography (CT) scan. Although CT is commonly done, magnetic resonance imaging (MRI) is considered imaging modality of choice. MRI with gadolinium contrast is performed following the detection of a solitary lesion on CT, or if clinical suspicion remains high. MRI may detect lesions as small as 1.9 mm, and is superior to CT for detection of posterior fossa lesions. [2] More than 10% of solitary lesions will not be metastatic and therefore warrant biopsy. In the case of solitary or multiple metastases in the absence of known malignancy, further investigations should be directed towards the identification of a primary lesion, most commonly from the chest. In this review, we have included only adults with brain metastases (cerebral hemispheres and posterior fossa structures) from any primary source that have been confirmed with biopsy or by CT or MRI, and excluded metastasis to the leptomeninges and peripheral nervous system, where management may be more case specific.

INCIDENCE/ PREVALENCE

The incidence of brain metastasis is 8–11/100,000 people a year. [3] [4] [5] The proportion of people with primary cancers developing brain metastasis varies widely, between 9.6–50.0% depending on the series selected. [3] [5] [6] [7] [8] The lung is the most common primary site, with 9.7–64.0% of people developing brain metastases, while melanoma (6.9–7.4%), renal (6.5–9.8%), breast (5.0–5.1%), and colorectal (1.2–1.9 %) account for most of the remaining cases. [3] [9] Cancer of unknown primary origin represents 15% of cases of brain metastasis. [10]

AETIOLOGY/ RISK FACTORS

Brain metastases are most common in the advanced stages of disseminated disease, [9] but can occur in isolation. Tumour seeding of the brain parenchyma involves a number of steps, including intravasation (reaching the brain vasculature), breaching of the blood–brain barrier, and proliferation and neoangiogenesis (the formation of new blood vessels/vasculature) within the brain. [11] These steps are dependant on the expression of specific regulatory molecules such as matrix metalloproteinases and growth factors.

PROGNOSIS

People with untreated brain metastases have a median survival of about 4 weeks from diagnosis. [12] [13] The addition of corticosteroids may extend this by another 4 weeks. [14] [13] Whole-brain radiotherapy further extends median survival to 3–6 months. [12] [13] The additional benefit of surgery, radiotherapy, chemotherapy, and biological agents alone or in combination depends on tumour type. Prognostic factors predicting a better outcome are solitary lesions, surgical resection, and the use of combined chemotherapy and radiotherapy. [12]

AIMS OF INTERVENTION

To cure, to maintain or improve quality of life and symptoms, to increase overall survival, progression-free survival, with minimal adverse effects of treatment.

OUTCOMES

Overall survival, progression-free survival, pain and other symptoms, neurological function, objective response rates (complete response, partial response), improvement in performance status according to validated scales of daily functioning/activity, quality of life, adverse effects.

METHODS

Clinical Evidence search and appraisal June 2007. The following databases were used to identify studies for this systematic review: Medline and Embase 1986 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health

Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for evaluation in this review were: published systematic reviews and RCTs in any language. RCTs could be open or blinded, and had to contain 20 or more individuals, of whom 80% or more were followed up. There was no minimum length of follow-up required to include studies. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have included only adults with brain metastases that have been confirmed with biopsy or by CT or MRI. We have compared each included intervention versus usual (supportive) care and versus any other included intervention and reported any studies we found. Studies generally included people with one or more brain metastasis and reported results for trial participants as a whole, and we have reported these overall results. However, where studies additionally presented a separate analysis for people with single and multiple brain metastases, we have also reported these results. We have tabulated baseline population data for all RCTs included in this review, including Karnofski score and Recursive partitioning analysis (RPA) status where this has been reported (see table 1, p 16). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as RRs and ORs. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 19).

QUESTION **What are the effects of interventions for managing brain metastases in adults?**

OPTION **CORTICOSTEROIDS** New

Mortality
Compared with corticosteroids plus whole-brain radiotherapy (WBRT) We don't know whether corticosteroids alone are more effective at improving median survival in people with evidence of parenchymal brain metastases (very low-quality evidence).

Treatment success
Compared with corticosteroids plus WBRT We don't know whether corticosteroids alone are more effective at improving remission (defined as an improvement in performance status and neurological deficit) in people with evidence of parenchymal brain metastases (very low-quality evidence).

Note
We found no clinically important results from RCTs comparing corticosteroids versus no corticosteroids in people with brain metastases. Such RCTs are unlikely to be undertaken. There is a consensus that corticosteroids are effective for symptom relief.

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Corticosteroids versus no corticosteroids:
We found one systematic review (search date 2003) [15] examining the use of corticosteroids in people receiving whole-brain irradiation for cerebral metastasis. The review found no RCTs comparing corticosteroids versus no corticosteroids. [15] We found no additional or subsequent RCTs. Such RCTs are unlikely to be performed (see comment below).

Corticosteroids versus corticosteroids plus whole-brain radiotherapy (WBRT):
We found three systematic reviews (search date 2003, [15] search date 2004 [16] [17]) which identified the same RCT (see table 1, p 16). [18] The RCT (48 people with evidence of parenchymal metastasis) compared prednisone alone versus prednisone plus WBRT. [18] Remission was assessed on clinical grounds and defined as an improvement of at least 2 points in "performance status" (scale 0–4, where 0 = normal and 4 = completely bedridden) with a similar improvement in any neurological deficit (0 = no deficit and 4 = complete deficit). The RCT found similar rates of remission between groups (remission: 18/28 [61%] with prednisone plus WBRT *v* 12/19 [63%] with prednisone alone; statistical analysis between groups not reported). [18] In a subgroup analysis by site of primary origin, it found a longer duration of remission with prednisone plus WBRT (median duration of remission; lung [30 people in total]: 13 weeks with prednisolone plus WBRT *v* 5 weeks with prednisone alone; breast [7 people in total]: 15 weeks *v* 8 weeks; other sites [11 people in total]: 8 weeks *v* 0 weeks; absolute numbers in each group not reported, no statistical analysis between groups reported). Statistical differences between subgroups were not tested due to small numbers, which also limits any conclusions that can be drawn. [18] The RCT found a longer median survival with prednisone plus WBRT (14 weeks) compared with prednisone alone (10 weeks) but did not test the significance of differences between groups. People recruited in the RCT were not identified

by computed tomography (CT) or magnetic resonance imaging, as the RCT took place before CT scanning was available (published 1971), and participants were not stratified for known prognostic factors such as age, performance status, or extent of disease. In total, 5/19 (26%) people in the prednisone-only group subsequently received irradiation.

Harms:

Corticosteroids versus no corticosteroids:
We found no RCTs.

Corticosteroids versus corticosteroids plus whole-brain radiotherapy (WBRT):
The RCT reported that 2/48 (4%) people discontinued corticosteroids because of adverse effects (further details not reported), and that all people receiving irradiation had virtually complete alopecia at about 3 weeks. [18]

General harms:
The adverse effects of long-term corticosteroids are well documented. However, it should be noted that the mean survival times for some people may not be long enough for certain long-term complications of corticosteroids to become manifest.

Comment:

Clinical guide:
RCTs comparing corticosteroids versus no corticosteroids, and versus other treatment options, have not been, and are now unlikely to be undertaken. On the basis of observational evidence and experience, most clinicians regard them to be an accepted treatment for the management of brain metastasis. They are considered as a standard supportive care measure for the relief of symptoms associated with cerebral oedema. The minimum dose that provides clinical benefit is recommended.

OPTION CYTOTOXIC CHEMOTHERAPY (SYSTEMIC) New

Mortality
Cytotoxic chemotherapy (systemic) plus whole-brain radiotherapy (WBRT) compared with WBRT alone We don't know whether systemic cytotoxic chemotherapy (with carboplatin or temozolomide) plus WBRT is more effective than WBRT alone at improving median or overall survival in people with one or more brain metastases (very low-quality evidence).

Treatment success
Cytotoxic chemotherapy (systemic) plus WBRT compared with WBRT alone We don't know whether systemic cytotoxic chemotherapy with temozolomide plus WBRT is more effective than WBRT alone at improving radiological response measured by computed tomography or magnetic resonance imaging in people with one or more brain metastases (very low-quality evidence).

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

We found three RCTs of sufficient quality (see comment below; see table 1, p 16). [19] [20] [21]

Systemic cytotoxic chemotherapy alone versus usual care:
We found no RCTs.

Carboplatin plus whole-brain radiotherapy (WBRT) versus WBRT alone:
We found one small RCT (42 people with non-small cell lung cancer, 1 or more brain metastases, inoperable CNS disease or refused surgery, metastasis at sites other than the brain not reported) comparing WBRT plus concomitant carboplatin versus WBRT. [20] Corticosteroids were given to either group as necessary. The RCT found no significant difference between groups in median survival (3.7 months with WBRT plus carboplatin *v* 4.4 months with WBRT; Kaplan–Meier P = 0.64). [20] The RCT also reported on objective response rate assessed by computed tomography (CT) or magnetic resonance imaging (MRI) scan. However, results were based on 27/42 (64%) of those randomised, so we have not reported these data further. The planned accrual of the RCT was 300 people. The RCT was terminated early because of a poor rate of accrual (42 people), and the authors reported that, for this reason, no firm conclusions could be drawn regarding the efficacy of the combined treatment. [20]

Temozolomide plus WBRT versus WBRT alone:
We found two phase II RCTs. [19] [21] People in both RCTs could also receive corticosteroids and anticonvulsants as necessary. The first RCT (82 people with 1 or more brain metastases, not suitable for surgery or radiosurgery, most had previous chemotherapy but not in the 3 weeks prior to trial entry, 56/82 [68%] with extracranial metastasis) reported on radiological response of brain metastases (assessed by CT or MRI — defined as disappearance of any contrast-enhancing lesion or reduction to 50% or less of sum of areas of lesions, all with stable or neurological improvement without need or increased need for dexamethasone) and progression-free survival (appearance

of any new contrast-enhancing lesion or an increase of enhanced area by at least 25%). [21] It found that temozolomide plus WBRT significantly increased the proportion of people with progression-free survival of brain metastasis compared with WBRT alone at 90 days (72% with temozolomide plus WBRT *v* 54% with WBRT; Kaplan–Meier, P = 0.03). Radiological response was assessed in 66/82 (80%) people at 30 days and 35/82 (43%) people at 90 days. However, the RCT performed an intention-to-treat analysis. It found no significant difference between temozolomide plus WBRT and WBRT alone in radiological response at either 30 days or 90 days (reported as not significant, P value not provided). It also found no significant difference between groups in overall survival (results presented graphically, Kaplan–Meier analysis, reported as not significant, P value not reported). [21] The RCT was terminated prematurely because of poor participant accrual. It had initially aimed to recruit 116 people, with possible further expansion after interim evaluations.

The second RCT (52 people; primary site lung, breast, or unknown; 13 people with solitary and 35 people with multiple brain metastases; 12 people with other organ metastases) reported radiological response (assessed by CT or MRI according to WHO criteria) and neurological functional status (assessed on 4-point scale, level I = fully functional to level IV = needs help all the time). [19] Results were based on 45/52 (86%) people randomised. It found that temozolomide plus WBRT significantly increased the proportion of people with response compared with WBRT alone (objective response [complete or partial]: 23/24 [96%] with temozolomide plus WBRT *v* 14/21 [67%] with WBRT alone; P = 0.017). It reported changes in neurological functional status for both groups (changes in the proportion of people with level I–IV function), but did not test the significance of differences between groups, so we have not reported these results further. It found no significant difference between groups in overall survival (median: 8.6 months with temozolomide plus WBRT *v* 7.0 months with WBRT alone; log-rank test, P = 0.447). [19]

Harms:

Systemic cytotoxic chemotherapy alone versus usual care:
We found no RCTs.

Carboplatin plus whole-brain radiotherapy (WBRT) versus WBRT alone:
The RCT reported no significant differences in gastrointestinal or haematological toxicities between groups (no further details reported, absolute numbers and P value not reported). [20]

Temozolomide plus WBRT versus WBRT alone:
The first RCT reported that neutropenia was observed in 15% of people (grade 3 or worse in 12%) and thrombocytopenia in 17% (grade 3 or worse in 10%) with temozolomide plus radiotherapy, and that there were no cases of neutropenia or thrombocytopenia in the radiotherapy-alone arm (absolute numbers and statistical analysis between groups not reported). [21] The second RCT reported that temozolomide plus WBRT significantly increased the proportion of people with nausea (grade 2 or above) and vomiting compared with WBRT alone (nausea: 12/25 [48%] with temozolomide plus WBRT *v* 3/23 [13%] with WBRT alone, P = 0.013; vomiting: 8/25 [32%] *v* 0/23 [0%], P = 0.004). [19] It reported that there were no cases of grade 3 or 4 myelosupression. [19]

Comment:

We found one further RCT comparing WBRT versus WBRT plus chloroethylnitrosureas versus WBRT plus chloroethylnitrosureas plus tegafur in people with brain metastasis due to lung carcinoma. [22] However, some but not all people also had surgery, and results for treatment response were based on 49 of the original 100 people randomised (49%) who had a tumour not suitable for surgery, or in whom surgery had only partially removed the tumour, which is below *Clinical Evidence* inclusion criteria for this review, and so this RCT is not discussed further.

Clinical guide:
The heterogeneity of the identified RCTs and the minimal improvements seen make it difficult to recommend chemotherapy for all people with brain metastasis.

OPTION SURGERY New

Mortality
Compared with surgery plus whole-brain radiotherapy (WBRT) We don't know whether surgery alone is more effective than surgery plus postoperative WBRT at improving overall survival in people with a single brain metastasis treated by complete surgical resection as verified by MRI scan (low-quality evidence).

Treatment success
Compared with surgery plus WBRT Surgery alone may be less effective than surgery plus postoperative WBRT at reducing the recurrence of tumours within the brain in people with a single brain metastasis treated by complete surgical resection as verified by MRI scan, but not in improving how long people remain functionally independent (low-quality evidence).

Note

We found no clinical evidence from RCTs comparing surgery with best supportive care or surgery with radiotherapy.

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Surgery versus usual care:
We found no systematic reviews or RCTs.

Surgery versus radiosurgery:
We found one systematic review (search date 2004) of surgery versus radiosurgery for people with a single brain metastasis from non-small cell lung cancer, which identified no RCTs. [23] We found no subsequent RCTs.

Surgery versus surgery plus WBRT:
See benefits of surgery plus WBRT (external beam), p 6 .

Harms:

Surgery versus usual care:
We found no RCTs.

Surgery versus radiosurgery:
We found no RCTs.

Surgery versus surgery plus WBRT:
See harms of surgery plus WBRT (external beam), p 6 .

Comment:

Surgery versus surgery plus WBRT:
See comment on surgery plus WBRT (external beam), p 6 .

Clinical guide:
In the case of confirmed single brain metastasis, surgery is one option for selected cases to provide local control. There is no role for surgical excision of multiple brain metastases.

OPTION SURGERY PLUS WHOLE-BRAIN RADIOTHERAPY (EXTERNAL BEAM) New

Mortality
Compared with surgery alone We don't know whether surgery plus postoperative whole-brain radiotherapy (WBRT) is more effective at improving overall survival in people with a single brain metastasis treated by complete surgical resection as verified by MRI scan (low-quality evidence).

Compared with WBRT alone We don't know whether surgery plus WBRT is more effective at improving overall mortality at 6 months in people with a single brain metastasis at an operable site (very low-quality evidence).

Treatment success
Compared with surgery alone Surgery plus postoperative WBRT may be more effective than surgery alone at reducing the recurrence of tumours within the brain in people with a single brain metastasis treated by complete surgical resection as verified by MRI scan, but not in improving how long people remain functionally independent (low-quality evidence).

Compared with WBRT alone We don't know whether surgery plus WBRT is more effective at improving the length of functionally independent survival or in improving quality-of-life scores in people with a single brain metastasis at an operable site (very low-quality evidence).

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Surgery plus radiotherapy versus usual care:
We found no systematic review or RCTs.

Surgery plus whole-brain radiotherapy (WBRT) versus surgery alone:
We found one systematic review (search date 2004) [16] which identified one RCT (see table 1, p 16). [24] The RCT (95 people, single brain metastasis, treated with complete surgical resection as verified by MRI scan, 25% had disseminated disease at sites other than brain) compared the addition of postoperative WBRT (50.4 Gy in 28 fractions) versus no subsequent additional WBRT. [24] Recurrence was measured by MRI. Both groups also received corticosteroids. The RCT found that, compared with surgery alone, surgery plus postoperative WBRT significantly decreased the recurrence rate of tumour anywhere in the brain, recurrence rate at the original site of the brain, and recurrence rate at a distant site in the brain other than the original site of the metastasis (recurrence anywhere in brain: 9/49 [18%] with surgery plus WBRT *v* 32/46 [70%] with surgery alone, P less than 0.001; recurrence at site of original metastasis: 5/49 [10%] with surgery plus WBRT *v* 21/46

[46%] with surgery alone, P less than 0.001; recurrence at distant site in brain: 7/49 [14%] with surgery plus WBRT *v* 17/46 [37%] with surgery alone; P less than 0.01). [24] It found that surgery plus postoperative radiotherapy significantly reduced death attributed to neurological causes, but found no significant difference between groups in overall survival (death from neurological causes: 6/43 [14%] with surgery plus WBRT *v* 17/39 [44%] with surgery alone; P = 0.003; overall survival, median length of survival: 48 weeks with surgery plus WBRT *v* 43 weeks with surgery alone, P = 0.39; RR of death 0.91, 95% CI 0.59 to 1.40). [24] It found no significant difference between groups in how long people remained functionally independent (median length of time Karnofsky scores remained 70% or more after treatment: 37 weeks with surgery plus WBRT *v* 35 weeks with surgery alone; P = 0.61; RR 0.84, 95% CI 0.61 to 1.17). [24]

Surgery plus WBRT versus WBRT alone:
We found two systematic reviews (search date 2003; [13] search date 2004 [16]) which identified the same three RCTs, [25] [26] [27] and which pooled results (see table 1, p 16). All three RCTs included highly selected participants with a single brain metastasis in an operable site, and one review noted that this group was not necessarily representative of the majority of people with a single brain metastasis. [13] People in all the RCTs could also receive corticosteroids. Neither systematic review found a significant difference between WBRT plus surgery and WBRT alone in overall mortality at 6 months (3 RCTs: 41/98 [42%] with WBRT plus surgery *v* 53/97 [55%] with WBRT alone; RR = 0.72, 95% CI 0.39 to 1.32; P = 0.28). [16] However, both reviews found significant heterogeneity among RCTs included in the analysis (P = 0.02). [16] One systematic review reported that two included RCTs found that WBRT plus surgery significantly increased overall median survival compared with WBRT alone, while one RCT found no significant difference between groups (first RCT [63 people]: 10 months with WBRT plus surgery *v* 6 months with WBRT alone; P = 0.04; second RCT [48 people]: 9.2 months *v* 3.5 months; P less than 0.01; third RCT [84 people]: 5.6 months *v* 6.3 months, reported as not significant; P value not provided). [16] One systematic review found no significant difference between groups in deaths attributed to neurological causes, although the proportion of deaths was smaller in the combined therapy group (3 RCTs, 21/90 [23%] with WBRT plus surgery *v* 33/95 [35%] with WBRT alone; OR 0.57, 95% CI 0.29 to 1.10; P = 0.09). [13] Two RCTs reported neurological function outcomes. One included RCT found that WBRT plus surgery significantly increased the length of functionally independent survival compared with WBRT alone (48 people; Karnofsky performance score 70% or above: median 38 weeks with WBRT plus surgery *v* 8 weeks with WBRT alone; P less than 0.005). [27] The other included RCT found a longer duration of functionally independent survival (measured by WHO criteria) with WBRT plus surgery compared with WBRT alone, but differences between groups did not reach significance (63 people; results presented graphically, log-rank test P = 0.06). [26] One included RCT (84 people) measured quality of life (based on mean Spitzer quality-of-life scores) and found no significant difference between groups at 1–3 months (P = 0.18) or at 4–6 months (P = 0.79). [25]

Harms:

Surgery plus whole-brain radiotherapy (WBRT) versus usual care:
We found no systematic review or RCTs.

Surgery plus WBRT versus surgery alone:
The RCT did not report harms data. [24] WBRT to a high dose results in permanent total alopecia, somnolence syndrome, and potential long-term neurological sequelae.

Surgery plus WBRT versus WBRT alone:
One systematic review found no significant difference between radiotherapy plus surgery and surgery alone in the occurrence of overall adverse effects (any morbidity, not including mortality: 26/98 [27%] with radiotherapy plus surgery *v* 21/97 [22%] with radiotherapy alone; OR 1.35, 95% CI 0.68 to 2.66; P = 0.39). [13] It found no significant difference between groups in the occurrence of individual adverse effects (including infections, respiratory problems, intracerebral haematoma, or other). However, these individual analyses were based on small numbers of events. [13] The other review reported that surgical mortality at 30 days was between 4–9.8% (first RCT: surgical mortality [30 days from surgery]: 9.8% [4/41] people; second RCT 1-month mortality: 9.4% [3/32] people; third RCT operative mortality [30 days from surgery]: 4.0% [1/25] people), but did not report a statistical analysis between groups for adverse effects. [16]

Comment:

Clinical guide: Surgery plus whole-brain radiotherapy (WBRT) versus surgery alone:
In the RCT comparing surgery plus postoperative radiotherapy versus surgery alone, there was a lack of evidence of any improvement in overall survival. [24] There are also concerns around the potential toxicity of high-dose radiation to the whole brain.

Surgery plus WBRT versus WBRT alone:
One RCT that failed to show a median survival benefit for the addition of surgery had a higher proportion of poor-performance-status patients. Therefore, in selected patients with single metas-

tasis, controlled extracranial disease, and good performance status, surgery may provide additional benefits.

OPTION SURGERY PLUS RADIOSURGERY New

We found no direct information from RCTs about surgery plus radiosurgery in people with brain metastasis.

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits: We found no systematic reviews or RCTs on the effects of surgery plus radiosurgery.

Harms: We found no RCTs.

Comment: None.

OPTION SURGERY PLUS RADIOSURGERY PLUS WHOLE-BRAIN RADIOTHERAPY (EXTERNAL BEAM) New

We found no direct information from RCTs about surgery plus radiosurgery plus whole-brain radiotherapy in people with brain metastasis.

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits: We found no systematic reviews or RCTs on the effects of surgery plus radiosurgery plus whole-brain radiotherapy.

Harms: We found no RCTs.

Comment: None.

OPTION WHOLE-BRAIN RADIOTHERAPY (EXTERNAL BEAM) New

Mortality

Whole-brain radiotherapy (WBRT) plus corticosteroids compared with corticosteroids alone We don't know whether WBRT plus corticosteroids is more effective than corticosteroids alone at improving median survival in people with evidence of parenchymal brain metastases (very low-quality evidence).

Compared with WBRT plus cytotoxic chemotherapy We don't know whether WBRT alone is more effective than systemic cytotoxic chemotherapy (with carboplatin or temozolomide) plus WBRT at improving median or overall survival in people with one or more brain metastases (very low-quality evidence).

Compared with WBRT plus surgery We don't know whether WBRT alone is more effective at improving overall mortality at 6 months in people with a single brain metastasis at an operable site (very low-quality evidence).

Compared with WBRT plus radiation sensitisers WBRT alone seems to be as effective as WBRT plus radiation sensitisers at improving overall survival in people with multiple brain metastases. However, further RCTs are currently being conducted in specific subgroup populations (moderate-quality evidence).

Compared with WBRT plus radiosurgery We don't know whether WBRT alone is more effective at improving overall or mean survival in people with between one and four brain metastases. Subgroup analysis suggests that WBRT alone may be less effective at increasing median survival in people with a single unresectable brain metastasis, but not at increasing survival in people with multiple (2–4) brain metastases at 6 months (very low-quality evidence).

Treatment success

WBRT plus corticosteroids compared with corticosteroids alone We don't know whether WBRT plus corticosteroids is more effective than corticosteroids alone at improving remission (defined as an improvement in performance status and neurological deficit) in people with evidence of parenchymal brain metastases (very low-quality evidence).

Compared with WBRT plus cytotoxic chemotherapy We don't know whether WBRT alone is more effective than systemic cytotoxic chemotherapy with temozolomide plus WBRT at improving radiological response measured by CT or MRI in people with one or more brain metastases (very low-quality evidence).

Compared with WBRT plus surgery We don't know whether WBRT alone is more effective at improving the length of functionally independent survival or in improving quality-of life-scores in people with a single brain metastasis at an operable site (very low-quality evidence).

Compared with WBRT plus radiation sensitisers WBRT alone seems to be as effective as WBRT plus radiation sensitisers at improving local brain tumour response rate or median time to neurological progression in people with multiple brain metastases (moderate-quality evidence).

Compared with WBRT plus radiosurgery WBRT alone may be less effective than WBRT plus radiosurgery at improving local brain tumour control (defined as stable disease or complete or partial response measured by serial MRI scans) at 1 year in people with between one and four brain metastases, but we don't know about performance status or mental status (low-quality evidence).

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Whole-brain radiotherapy (WBRT) plus corticosteroids versus corticosteroids (usual supportive care):
See benefits of corticosteroids, p 3 .

WBRT alone versus WBRT plus surgery:
See benefits of surgery plus WBRT (external beam), p 6 .

WBRT alone versus WBRT plus carboplatin:
See benefits of cytotoxic chemotherapy (systemic), p 4 .

WBRT alone versus WBRT plus temozolomide:
See benefits of cytotoxic chemotherapy (systemic), p 4 .

WBRT alone versus WBRT plus radiation sensitisers:
See benefits of radiation sensitisers plus WBRT (external beam), p 10 .

WBRT alone versus WBRT plus radiosurgery:
See benefits of WBRT (external beam) plus radiosurgery, p 11 .

Harms:

Whole-brain radiotherapy (WBRT) plus corticosteroids versus corticosteroids (usual supportive care):
See harms of corticosteroids, p 3 .

WBRT alone versus WBRT plus surgery:
See harms of surgery plus WBRT (external beam), p 6 .

WBRT alone versus WBRT plus carboplatin:
See harms section of cytotoxic chemotherapy (systemic), p 4 .

WBRT alone versus WBRT plus temozolomide:
See harms section of cytotoxic chemotherapy (systemic), p 4 .

WBRT alone versus WBRT plus radiation sensitisers:
See harms of radiation sensitisers plus WBRT (external beam), p 10 .

WBRT alone versus WBRT plus radiosurgery:
See harms of WBRT (external beam) plus radiosurgery, p 11 .

General harms of WBRT:
We found one systematic review (search date 2004) which included both RCT and observational data (see comment below). [28] Based on included studies, it suggested that, with the exclusion of skin toxicity, up to 40% of people receiving WBRT will have at least one of: fatigue, headache, nausea and vomiting, or otitis media/externa. [28] It also noted that two included papers described complete alopecia in all people who survived long enough for complete alopecia to occur — usually 6–8 weeks. [28]

Comment:

We found one systematic review (search date 2004) examining the effectiveness of WBRT in brain metastases. [28] However, it included both RCT and observational data (8 RCTs, 5 quasi-experimental studies, 12 cohort/prospective studies, 7 observational studies, 7836 people in total). [28] The review did not pool data. Based on included studies, it suggested a possible survival benefit of up to 3 months for “unselected” people who receive WBRT compared with people managed by corticosteroids plus best supportive care. However, included trials showed a marked heterogeneity of participants in terms of pre-treatment variables, interventions used, radiation dose, and outcome measures, and conclusions were based on non-RCT data, so any interpretation should be made with extreme caution.

Clinical guide: multiple metastases:
The modest survival benefits of palliative WBRT should be gauged against patient-performance status and likelihood of significant response, as well as morbidity.

WBRT alone versus WBRT plus surgery:
See comment on surgery plus WBRT (external beam), p 6 .

WBRT alone versus WBRT plus radiosurgery:
See comment on WBRT (external beam) plus radiosurgery, p 11 .

OPTION RADIATION SENSITISERS PLUS WHOLE-BRAIN RADIOTHERAPY (EXTERNAL BEAM) N e w

Mortality
Compared with whole-brain radiotherapy (WBRT) alone Adding radiation sensitisers to WBRT seems to be no more effective than WBRT alone at improving overall survival in people with multiple brain metastases. However, further RCTs are currently being conducted in specific subgroup populations (moderate-quality evidence).

Treatment success
Compared with WBRT alone Adding radiation sensitisers to WBRT seems to be no more effective than WBRT alone at improving local brain tumour response rate or median time to neurological progression in people with multiple brain metastases (moderate-quality evidence).

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Whole-brain radiotherapy (WBRT) plus radiation sensitisers versus usual care:
We found no systematic review or RCTs.

WBRT plus radiation sensitisers versus WBRT alone:
We found two systematic reviews (search date 2004) [16] [17] which identified the same five RCTs in people with multiple brain metastases, and pooled results (see table 1, p 16). One review [17] also included a preliminary report in abstract form of one further RCT that has subsequently been fully published. [29] We have reported this RCT from the full publication. [29] The five RCTs included in both reviews used a variety of radiosensitisers including ionidamide, metronidazole, misonidazole, motexafin gadolinium, and bromodeoxyuridine (BrdU). The reviews pooled data and undertook a similar analysis, and reached similar results. Both reviews found no significant difference in overall survival at 6 months between WBRT plus radiation sensitisers and WBRT alone (4 RCTs; 294/496 [59%] with WBRT plus radiosensitiser *v* 283/511 [55%] with WBRT alone; RR 1.05, 95% CI 0.95 to 1.16; P = 0.3). [17] There was no significant difference between groups in local brain tumour response rate (complete or partial response: 3 RCTs, 41/110 [39%] with WBRT plus radiation sensitiser *v* 40/105 [38%] with WBRT alone; RR 1.00, 95% CI 0.69 to 1.44; P = 1.0). [17] One included RCT (401 people) using gadolinium as a sensitiser found no significant difference between groups in median time to neurological progression (9.5 months with WBRT plus sensitiser *v* 8.3 months with WBRT alone; reported as no significant difference; P value not reported) or in time to progression of the brain-specific quality-of-life assessment (further details not reported). [16] In this RCT, a subgroup analysis of people with lung cancer, recursive partitioning analysis (RPA) class 2 (214 people), found that median time to neurological progression was not reached for the radiosensitiser group, and was 6.3 months for the WBRT alone group (P = 0.013), and that progression-free survival at one year was 18.6% for the radiosensitiser group compared with 10.5% for the WBRT-alone group (absolute numbers and P value not reported). [16] One review reported that, based on the possibility of benefit in this specific subgroup of people with metastasis from lung cancer, a further RCT had been launched. [17]

The subsequently fully published RCT (515 people) examined the use of efaproxiral, an allosteric modifier of haemoglobin. [29] It found no significant difference between WBRT plus efaproxiral plus supplemental oxygen and WBRT plus supplemental oxygen in overall survival (median survival time: 5.4 months with radiotherapy plus oxygen plus efaproxiral *v* 4.4 months with radiotherapy plus oxygen; Kaplan–Meier, HR 0.87, 95% CI not reported; P = 0.16). [29] In an unplanned subgroup analysis by tumour type, it found that the largest treatment effect of efaproxiral was in people with breast cancer, but found no significant difference between groups in people with non-small cell lung cancer, or with other tumour types (breast cancer: 107 people; HR 0.51, 95% CI not reported; P = 0.003; non-small cell lung cancer: 290 people; HR 0.97, 95% CI not reported; P = 0.83; other tumour types: 118 people; HR 1.12, 95% CI not reported; P = 0.58). [29] The RCT found no significant difference between groups in overall response rate (up to 3 lesions assessed by serial scans against baseline, complete plus partial response: 121/265 [46%] with WBRT plus oxygen plus efaproxiral *v* 96/250 [38%] with WBRT plus oxygen; P = 0.1). In a further analysis using a Cox multiple regression analysis adjusting for prognostic factors, the RCT reported a significant benefit

in survival with efaproxiral (HR 0.74, 95% CI 0.64 to 0.90; P = 0.003), and suggested that this benefit may be restricted to that subgroup of people with breast cancer. [29] The RCT reported that a further trial was being undertaken in people with breast cancer brain metastasis. [29]

Harms:

Whole-brain radiotherapy (WBRT) plus radiation sensitisers versus usual care:
We found no systematic review or RCTs.

WBRT plus radiation sensitisers versus WBRT alone:
One systematic review did not report on adverse effects. [16] The other review reported adverse effects of the five included RCTs. [17] It reported that one RCT found the most common side effects of ionidamide and WBRT to be myalgia (68% of people), testicular pain (42%), anorexia (26%), ototoxicity (26%), malaise or fatigue (26%), and nausea and vomiting (19%); one RCT found that 51% of people had nausea and vomiting with metronidazole plus WBRT compared with 3% of people with radiotherapy alone; one RCT found that some people with misonidazole had nausea and vomiting (number not reported); one RCT reported grade 3 and 4 events: hypotension (6%), asthenia (2.6%), hyponatraemia (2.1%), leukopenia (2.1%), hyperglycaemia (1.6%), and vomiting (1.6%), out of 193 people with WBRT plus motexafin gadolinium; and one RCT reported three fatal toxicities in 34 people with WBRT plus bromodeoxyuridine (BrdU) (due to Stevens–Johnson skin reaction in one case and neutropenia and infection in two cases [further detail and statistical comparison between groups for adverse effects not reported]). [17] The subsequent RCT reported that the most common severe adverse effect (grade 3) associated with efaproxiral was hypoxaemia (29/266 [11%] with efaproxiral plus WBRT *v* 3/263 [1%] with WBRT; P value not reported). [29] It reported that all events of hypoxaemia were effectively managed with supplemental oxygen. [29]

Comment:

Clinical guide:
There is insufficient evidence to recommend any radiosensitiser for routine use.

OPTION WHOLE-BRAIN RADIOTHERAPY (EXTERNAL BEAM) PLUS RADIOSURGERY New

Mortality
Compared with whole-brain radiotherapy (WBRT) alone We don't know whether WBRT plus radiosurgery is more effective at improving overall or mean survival in people with between one and four brain metastases. Subgroup analysis suggests that WBRT plus radiosurgery may be more effective at increasing median survival in people with a single unresectable brain metastasis, but not in increasing survival in people with multiple (2–4) brain metastases at 6 months (very low-quality evidence).

Compared with radiosurgery alone Radiosurgery plus WBRT and radiosurgery alone seem equally effective at improving overall survival in people with between one and four brain metastases (moderate-qualtiy evidence).

Treatment success
Compared with WBRT alone WBRT plus radiosurgery may be more effective at improving local brain tumour control (defined as stable disease or complete or partial response measured by serial MRI scans) at 1 year in people with between one and four brain metastases, but we don't know about performance status or mental status (low-quality evidence).

Compared with radiosurgery alone Radiosurgery plus WBRT seems to be more effective than radiosurgery alone at reducing brain tumour recurrence, new brain disease, and the proportion of people requiring salvage therapy in people with between one and four brain metastases, but we don't know about neurological function (moderate-quality evidence).

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Whole-brain radiotherapy (WBRT) plus radiosurgery versus usual care:
We found no systematic reviews or RCTs.

WBRT plus radiosurgery versus WBRT alone:
We found three systematic reviews (search date 2004; [16] [17] search date not reported) [30] which identified the same three RCTs. The three reviews pooled data and performed slightly different analyses. One of these RCTs was published in abstract form only and was not included in the pooled data, so we have not reported it further. The two remaining RCTs (27 people; 331 people) were not blinded and included people with a maximum of four metastatic brain tumours (see table 1, p 16). One included RCT (27 people) had been terminated prematurely at 60% accrual. Tumours had to be less than 4 cm in diameter. The reviews found similar results, and also separately reported data for people with single and multiple brain metastases, and we have reported these data separately below. Overall, in people with single or multiple brain metastases, one review found no significant difference in survival between WBRT plus radiosurgery and WBRT alone (2 RCTs; HR 0.86, 95% CI 0.7 to 1.05; P = 0.54; absolute numbers in analysis not reported). [30] It reported that

one included RCT found no significant difference between groups in the proportion of people whose cause of death was related to uncontrolled metastatic brain disease (neurological death: RR 0.95, 95% CI 0.66 to 1.35; absolute numbers not reported). [30] Another systematic review found that WBRT plus surgery significantly improved local brain tumour control compared with WBRT alone at 1 year (unchanged or improved serial post-treatment MRI scans, judged as either a complete response, partial response, or stable disease; 2 RCTs: 138/177 [78%] with radiotherapy plus radiosurgery *v* 117/181 [65%] with radiotherapy alone; RR 1.20, 95% CI 1.06 to 1.37; P = 0.005). [17] However, the RCTs included in the analysis were heterogeneous (P = 0.04). One included RCT (331 people) reported on performance scores and found that, at 6 months, people with WBRT plus radiosurgery were significantly more likely than those with WBRT alone to have higher Karnofsky Peformance status scores and lower corticosteroid usage, but there was no significant difference between groups in mental-status results. [16] [30] However, the results were based on 154/331 [46%] of those people initially randomised, which is below *Clinical Evidence* inclusion criteria for this review, so we have not reported these data further. **Subgroup analysis in people with a single brain metastasis:** The reviews [16] [17] [30] identified one RCT [31] which presented results separately for people with a single unresectable brain metastasis (see table 1, p 16). In this RCT overall, 104/331 [31%] people had metastasis in the brain alone, while 227/331 [69%] had brain metastasis plus metastasis at one or more extracranial sites. The RCT was adequately powered to investigate a pre-defined hypothesis to detect an improvement in survival time in people with a single brain metastasis alone. [31] Overall (for people with single or multiple metastases), the RCT found no significant difference between WBRT plus radiosurgery and WBRT alone in mean survival (331 people with 1–3 metastasis; 6.5 months with WBRT plus radiosurgery *v* 5.7 months with WBRT alone; P = 0.14). [31] In the planned subgroup analysis restricted to people with a single unresectable brain metastasis, the RCT found that WBRT plus radiosurgery significantly increased median survival compared with WBRT alone (186 people; 6.5 months with radiotherapy plus radiosurgery *v* 4.9 months with radiotherapy alone; P = 0.039). **Subgroup analysis in people with multiple brain metastases:** One review pooled data in people with multiple metastasis only, and found no significant difference in survival between WBRT plus radiosurgery and WBRT alone at 6 months (2 RCTs, people with 2–4 metastasis: 30/77 [39%] with radiotherapy plus radiosurgery *v* 43/81 [53%] with radiotherapy alone; RR 0.72, 95% CI 0.51 to 1.02; P = 0.07). [16]

WBRT plus radiosurgery versus radiosurgery alone:
See benefits of radiosurgery, p 12 .

Harms:

Whole-brain radiotherapy (WBRT) plus radiosurgery versus usual care:
We found no systematic reviews or RCTs.

WBRT plus radiosurgery versus WBRT alone:
The reviews reported that one included RCT (27 people) reported no neurological or systemic morbidity related to stereotactic radiosurgery, while people with WBRT had expectedly developed mild scalp erythema and hair loss. [16] [17] [30] One review reported that the other included RCT (331 people) found that early and late toxicities did not differ greatly between the two treatment arms. [17] However, more people had acute grade 3 and 4 toxicity with WBRT plus radiosurgery (4/160 [3%]) compared with WBRT alone (0/166 [0%]), and more late grade 3 or 4 toxicities in the combined group (6/160 [4%]) compared with the WBRT alone group (3/166 [2%]; further details and statistical analysis between groups not reported). [17] The other review reported no significant difference between groups in acute (within 30 days) or late (within 90 days) toxicities (RR 1.07, 95% CI 0.69 to 1.69; further details and absolute numbers not reported). [30]

WBRT plus radiosurgery versus radiosurgery alone:
See harms of radiosurgery, p 12 .

Comment:

Clinical guide: WBRT plus radiosurgery versus WBRT alone:
Based on evidence from a subgroup analysis of one RCT, there may be benefit for the addition of stereotactic radiosurgery to WBRT for people with a single unresectable brain metastasis. This benefit is more pronounced for those of good performance status. There is insufficient evidence to recommend stereotactic radiosurgery for people with multiple brain metastases.

WBRT plus radiosurgery versus radiosurgery alone:
See comment on radiosurgery, p 12 .

OPTION RADIOSURGERY (STEREOTACTIC LINAC RADIOTHERAPY OR GAMMA KNIFE) New

Mortality

Compared with whole-brain radiotherapy (WBRT) plus radiosurgery Radiosurgery alone and radiosurgery plus WBRT seem equally effective at improving overall survival in people with between one and four brain metastases (moderate-quality evidence).

Treatment success
Compared with WBRT plus radiosurgery Radiosurgery alone seems to be less effective than radiosurgery plus WBRT at reducing brain tumour recurrence rates, new brain disease, and the proportion of people requiring salvage therapy in people with between one and four brain metastases, but we don't know about neurological function (moderate-quality evidence).

Note
We found no clinically important results from RCTs comparing the effects of radiosurgery with usual care.

For GRADE evaluation of interventions for brain metastases, see table, p 19 .

Benefits:

Radiosurgery versus usual care:
We found no systematic review or RCTs.

Radiosurgery alone versus whole-brain radiotherapy (WBRT) plus radiosurgery:
We found one systematic review (search date 2004) [17] which identified one RCT published in abstract form, which has now been subsequently published in full (see table 1, p 16). [32] The RCT (132 people, 1–4 brain metastasis, 64 [48%] with single and 68 [52%] with multiple brain metastases, each less than 3 cm in diameter, extracranial metastasis active in 53 [40%] of people) found no significant difference between WBRT plus radiosurgery and radiosurgery alone in overall survival, or in those deaths attributed to neurological causes (overall survival, mean survival time: 7.5 months with WBRT plus radiosurgery *v* 8 months with radiosurgery alone; log rank, P = 0.42; deaths from neurological causes: 13/65 [23%] with WBRT plus radiosurgery *v* 12/67 [19%] with radiosurgery alone; P = 0.64). [32] It found no significant difference between groups in preservation of neurological function at 1 year (Karnofsky Performance Status score 70 or above: 132 people, 34% with WBRT plus radiosurgery *v* 27% with radiosurgery alone; P = 0.53). [32] It found that WBRT plus radiosurgery significantly reduced brain tumour recurrence compared with radiosurgery alone at 1 year (132 people, 47% with radiotherapy plus radiosurgery *v* 76% with radiosurgery alone; P less than 0.001). It found that WBRT plus radiosurgery significantly reduced new brain disease compared with radiosurgery alone at 1 year, and significantly decreased the proportion of people requiring salvage therapy for progression of brain tumour (new metastasis at distant brain sites: 42% with WBRT plus radiosurgery *v* 64% with radiosurgery alone; log rank, P = 0.003; proportion of people requiring salvage therapy: 10/65 [15%] with WBRT plus radiosurgery *v* 29/67 [43%] with radiosurgery alone; P less than 0.001). [32]

Radiosurgery versus surgery:
See benefits of surgery, p 5 .

Harms:

Radiosurgery versus usual care:
We found no RCTs.

Radiosurgery alone versus whole-brain radiotherapy (WBRT) plus radiosurgery:
The RCT reported that four people had symptomatic acute neurological toxicity with WBRT plus radiosugery compared with eight people with radiosurgery alone (P = 0.36). [32] Seven people had symptomatic late neurological toxicity with WBRT plus radiosurgery compared with three people with radiosurgery alone (P = 0.2). Four people had late toxic effects grade 3 and 4 with WBRT plus radiosurgery (2 radiation necrosis, 2 leukoencephalopathy) compared with two people with radiosurgery only (1 radiation necrosis, 1 seizure). [32]

Radiosurgery versus surgery:
See harms of surgery, p 5 .

Comment:

Clinical guide: Radiosurgery alone versus whole-brain radiotherapy (WBRT) plus radiosurgery:
In people having radiosurgery, the evidence from one RCT suggests that it should be combined with WBRT to decrease intracranial relapse.

GLOSSARY

Karnofsky score Is a measure of performance status based on physical ability (scale 0–100). 100: normal, no complaints or evidence of disease; 90: able to perform normal activity, minor signs and symptoms of disease; 80: able to perform normal activity with effort, some signs and symptoms of disease; 70: cares for self, unable to perform normal activity or to do active work; 60: requires occasional assistance but is able to care for most of own needs; 50: requires considerable assistance and frequent medical care; 40: requires special care and assistance, disabled; 30: hospitalisation indicated, although death not imminent, severely disabled; 20: hospitalisation necessary, active supportive treatment required, very sick; 10: fatal processes progressing rapidly, moribund; 0: death.
Recursive partitioning analysis The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) groups patients with brain metastases into three classes based on clinical criteria with differing outcomes.

Patients with a controlled primary tumour, no other metastatic sites, age under 65 years, and a Karnofsky performance status above 70 (RPA class I) have the best outcomes. RPA class II includes those with KPS at least 70, uncontrolled primary disease, age greater or equal to 65 years, or other metastatic sites than brain. RPA class III represents patients with KPS less than 70 and is associated with the poorest outcomes.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Corticosteroids New option. One systematic review found (search date 2003) which identified no RCTs comparing corticosteroids versus no corticosteroids. [15] Three systematic reviews found (search date 2003, [15] search date 2004) [16] [17] which identified the same small RCT (48 people) [18] comparing corticosteroids versus corticosteroids plus whole-brain radiotherapy. 'Corticosteroids' categorised as Likely to be beneficial (categorisation made by consensus as insufficient RCT evidence found).

Cytotoxic chemotherapy (systemic) New option. Three RCTs identified comparing either carboplatin plus whole-brain radiotherapy (WBRT) versus WBRT alone [20] or temozolomide plus WBRT versus WBRT alone. [19] [21] Two of the RCTs were terminated prematurely because of poor participant accrual. 'Cytotoxic chemotherapy (systemic)' categorised as Unknown effectiveness.

Surgery New option. One systematic review (search date 2004) found [23] which identified no RCTs comparing surgery versus radiosurgery. One systematic review found (search date 2004) [16] which identified one RCT (95 people) [24] comparing surgery versus surgery plus whole-brain radiotherapy. 'Surgery' categorised as Unknown effectiveness.

Surgery plus whole-brain radiotherapy (external beam) New option. One systematic review found (search date 2004) [16] which identified one RCT (95 people) [24] comparing surgery plus whole brain radiotherapy (WBRT) versus surgery alone. Two systematic reviews found (search date 2003; [13] search date 2004) [16] which identified the same three RCTs [25] [26] [27] comparing surgery plus WBRT versus WBRT alone. 'Surgery plus WBRT (external beam)' categorised as Unknown effectiveness.

Surgery plus radiosurgery New option. No RCTs found. 'Surgery plus radiosurgery' categorised as Unknown effectiveness.

Surgery plus radiosurgery plus whole-brain radiotherapy (external beam) New option. No RCTs found. 'Surgery plus radiosurgery plus whole-brain radiotherapy (external beam)' categorised as Unknown effectiveness.

Whole-brain radiotherapy (external beam) New option. Three systematic reviews found (search date 2003, [15] search date 2004) [16] [17] which identified the same small RCT (48 people) [18] comparing corticosteroids plus whole-brain radiotherapy (WBRT) versus corticosteroids. Two systematic reviews found (search date 2003; [13] search date 2004) [16] which identified the same three RCTs [25] [26] [27] comparing WBRT versus WBRT plus surgery. Three RCTs identified comparing either carboplatin plus WBRT versus WBRT alone [20] or temozolomide plus WBRT versus WBRT alone. [19] [21] Two of these RCTs were terminated prematurely because of poor participant accrual. Two systematic reviews (search date 2004) [16] [17] and one subsequently fully published RCT [29] found comparing WBRT plus radiation sensitisers versus WBRT alone. Three systematic reviews (search date 2004; [16] [17] search date not reported) [30] found comparing WBRT versus WBRT plus radiosurgery. One further systematic review (search date 2004) [28] which was a narrative review including both RCT and observational data added to the harms section and comments as background data. 'Whole-brain radiotherapy (external beam) (addition of some other interventions to WBRT may be no more effective than WBRT alone; WBRT alone may be effective in selected people)' categorised as Likely to be beneficial.

Radiation sensitisers plus whole-brain radiotherapy (external beam) New option. Two systematic reviews found (search date 2004) [16] [17] and one subsequently fully published RCT [29] comparing whole-brain radiotherapy (WBRT) plus radiation sensitisers versus WBRT alone. 'Radiation sensitisers (no evidence that adding radiation sensitisers to WBRT is more effective than WBRT alone)' categorised as Unlikely to be beneficial.

Whole-brain radiotherapy (external beam) plus radiosurgery New option. Three systematic reviews found (search date 2004; [16] [17] search date not reported) [30] comparing whole-brain radiotherapy (WBRT) plus radiosurgery versus WBRT alone. One systematic review found (search date 2004) [17] which identified one RCT in abstract form which has subsequently been published in full, [32] comparing WBRT plus radiosurgery versus radiosurgery alone. 'Whole-brain radiotherapy (external beam) (WBRT) plus radiosurgery (some evidence of improved survival in people with a single unresectable brain metastasis with WBRT plus radiosurgery compared with WBRT alone; no evidence of improved survival in people with multiple brain metastasis)' categorised as Unknown effectiveness.

Radiosurgery (stereotactic LINAC radiotherapy or gamma knife) New option. One systematic review found (search date 2004) [17] which identified one RCT in abstract form now subsequently published in full, [32] comparing radiosurgery versus whole-brain radiotherapy plus radiosurgery. One systematic review (search date 2004) found [23] which identified no RCTs comparing radiosurgery versus surgery. 'Radiosurgery (stereotactic LINAC radiotherapy or gamma knife)' categorised as Unknown effectiveness.

REFERENCES

1. Klos KJ, O Neill BP. Brain metastases. *Neurologist* 2004;10:31–46.
2. Schaefer PW, Budzik Jr RF, Gonzalez RG. Imaging of cerebral metastases. *Neurosurg Clin N Am* 1996;7:393–423.
3. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol* 2004;22:2865–2872.

4. Walker AE, Robins M, Weinfeld FD. Epidemiology of brain tumors: the national survey of intracranial neoplasms. *Neurology* 1985;35:219–226.
5. Percy AK, Elveback LR, Okazaki H, et al. Neoplasms of the central nervous system. Epidemiologic considerations. *Neurology* 1972;22:40–48.
6. Johnson JD, Young B. Demographics of brain metastasis. *Neurosurg Clin N Am* 1996;7:337–344.
7. Guomundsson KR. A survey of tumors of the central nervous system in Iceland during the 10-year period 1954-1963. *Acta Neurol Scand* 1970;46:538–552.
8. Fogelholm R, Uutela T, Murros K. Epidemiology of central nervous system neoplasms. A regional survey in Central Finland. *Acta Neurol Scand* 1984;69:129–136.
9. Schouten LJ, Rutten J, Huveneers HA, et al. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002;94:2698–2705.
10. Maesawa S, Kondziolka D, Thompson TP, et al. Brain metastases in patients with no known primary tumor. *Cancer* 2000;89:1095–1101.
11. Tosoni A, Ermani M, Brandes AA. The pathogenesis and treatment of brain metastases: a comprehensive review. *Crit Rev Oncol Hematol* 2004;52:199–215.
12. Lagerwaard FJ, Levendaq PQ, Nowak PJ, et al. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999;43:795–803.
13. Hart MG, Grant R, Walker M, et al. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. Search date 2004. In: The Cochrane Library, Issue 2, 2007. Chichester, UK: John Wiley & Sons, Ltd.
14. Ruderman NB, Hall TC. Use of Glucocorticoids in the Palliative Treatment of Metastatic Brain Tumors. *Cancer* 1965;18:298–306.
15. Millar BM, Bezjak A, Tsao M, et al. Defining the impact and contribution of steroids in patients receiving whole-brain irradiation for cerebral metastases. *Clin Oncol (R Coll Radiol)* 2004;16:339–344.
16. Tsao MN, et al. Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. *Cancer Treat Rev* 2005;31:256–273.
17. Tsao MN, Lloyd N, Wong R,et al. Whole-brain radiotherapy for the treatment of multiple brain metastases. Search date 2004. In: The Cochrane Library, Issue 2, 2007. Chichester, UK: John Wiley & Sons, Ltd.
18. Horton J, Baxter DH, and Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *Am J Roentgenol Radium Ther Nucl Med* 1971;111:334–336.
19. Antonadou D, Paraskevaidis M, Sarris G, et al. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol* 2002;20:3644–3650.
20. Guerrieri M, Wong K, Ryan G, et al. A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. *Lung Cancer* 2004;46:107–111.
21. Verger E, Gil M, Yaya R, et al. Temozolomide and concomitant whole-brain radiotherapy in patients with brain metastases: a phase II randomized trial. *Int J Radiat Oncol Biol Phys* 2005;61:185–191.
22. Ushio Y, Arita N, Hayakawa T, et al. Chemotherapy of brain metastases from lung carcinoma: a controlled randomized study. *Neurosurgery* 1991;28:201–205.
23. Fuentes R, Bonfill X, Exposito J. Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer. Search date 2004. In: The Cochrane Library, Issue 2, 2007. Chichester, UK: John Wiley & Sons, Ltd.
24. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;280:1485–1489.
25. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996;78:1470–1476.
26. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994;29:711–717.
27. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
28. Pease NJ, Edwards A, Moss LJ. Effectiveness of whole-brain radiotherapy in the treatment of brain metastases: a systematic review. *Palliat Med* 2005;19:288–299.
29. Suh JH, Stea B, Nabid A, et al. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *J Clin Oncol* 2006;24:106–114.
30. Stafinski T, Jhangri GS, Yan E, et al. 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 Treat Rev* 2006;32:203–213.
31. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665–1672.
32. Aoyama H, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006;295:2483–2491.

Susan Lalondrelle
Royal Marsden NHS Foundation Trust
London
UK

Vincent Khoo
Royal Marsden NHS Foundation Trust
London
UK

Competing interests: VK and SL declare that they have no competing interests.

Disclaimer

TABLE 1 **Baseline population data for included RCTs.**

Reference number	Participants	Comparison	Single/multiple brain metastases	Other baseline characteristics
[18]	48 people, ages not reported, people with focal signs due to metabolic encephalopathy excluded	Corticosteroids *v* corticosteroids plus WBRT	Not stated (before CT scanning available, published 1971) — people had evidence of parenchymal metastasis (clinical symptoms and signs or abnormal tests such as EEGs, radioisotope brain scans, etc)	Prognostic/severity data not reported. Primary site: lung (30 people); breast (7 people); melanoma (4 people); kidney (3 people); other (4 people)
[20]	42 people, median age 60–63 years, all had non-small cell lung cancer, all people had inoperable CNS disease or had refused surgery	Carboplatin plus WBRT *v* WBRT alone	Single brain metastasis 11/42 (26%) people; multiple brain metastases 31/42 (74%) people	WHO performance status: score 0 = 6 people; score 1 = 21 people; score 2 = 15 people. Neurological function status: score 1 = 21 people; score 2 = 15 people; score 3 = 6 people. Metastasis at sites other than brain not reported
[21]	82 people, mean age 57.8–58.3 years, all people not suitable for surgery or radiosurgery	Temozolomide plus WBRT *v* WBRT alone	Median number of brain metastases: 3 with WBRT *v* 2 with WBRT plus temozolomide	Karnofski performance status (KPS): score 70 or greater = 65/82 (79%) people; score less than 70 = 17/82 (21%) people. Extracranial metastasis: yes = 56/82 (68%) people; no = 26/82 (32%) people. Recursive partitioning analysis (RPA) class: I = 5/82 (6%); II = 60/82 (73%); III = 17/82 (21%). Primary site: lung (42 people); breast (13 people); other (27 people). Previous chemotherapy: yes = 62/82 (76%) people; no = 20/82 (24%) people
[19]	52 people (data only presented for 48 people), median age 61–62 years	Temozolomide plus WBRT *v* WBRT alone	Single brain metastasis 13/48 (27%) people; multiple brain metastases 35/48 (73%) people	Life expectancy of at least 3 months. Eastern Cooperative Oncology Group (ECOG) performance status: 0 = 14/48 (29%) people; 1 = 28/48 (58%) people; 2 = 6/48 (13%) people. Neurological function evaluation: level I = 12 people; level II = 25 people; level III = 11 people. Other organ metastasis = 12/48 (25%) people. Primary site: lung (40 people); breast (5 people); unknown (3 people)
[24]	95 people, median age 58–60 years, people with single metastasis to the brain treated with complete surgical resection (verified by postoperative MRI)	Surgery plus WBRT versus surgery alone	All people had single brain metastasis	Karnofski score: median, 90 (range 70–100) in both groups. Extent of disease other than brain metastasis: none = 34 people; primary tumour only = 37 people; disseminated = 24 people. Primary site: lung (57 people); breast (9 people); other (29 people)
[25]	84 people, mean age 59 years, all people with a single brain metastasis at an operable site	WBRT alone *v* WBRT plus surgery	All people had single brain metastasis	Karnofski performance status: 50% = 6 people; 60% = 12 people; 70% = 15 people; 80% = 15 people; 90% = 26 people; 100% = 6 people. Extent of primary disease: no evidence of primary disease = 18 people; local primary and intracranial metastasis = 28 people; extracranial metastasis = 38 people. Primary site: lung (45 people); breast (10 people); colon or rectum (13 people); skin (4 people); renal (3 people); head and neck (1 person); other (4 people); unknown primary (4 people)
[26]	63 people, mean age 59 years, all with single brain metastasis at an operable site	WBRT alone *v* WBRT plus surgery	All people had single brain metastasis	WHO status: score 0 = 7 people; score 1 = 39 people; score 2 = 17 people. Neurological functional scale: I = 19 people; II = 32 people; III = 12 people. Status of disease: "stable" = 43 people; "progressive" = 20 people. Primary site: lung (33 people); breast (12 people); kidney (4 people); melanoma (6 people); others (8 people)
[27]	48 people, median age 59–60 years, all people with a single brain metastasis at an operable site	WBRT alone *v* WBRT plus surgery	All people had single brain metastasis	Karnofski score for both groups: median, 90% (range 70–100%). Extent of disease other than brain metastasis: none = 10 people; primary tumour only = 20 people; disseminated = 18 people. Primary site: lung (37 people); breast (3 people); gastro-intestinal (3 people); genito-urinary (2 people); melanoma (3 people)

Reference number	Participants	Comparison	Single/multiple brain metastases	Other baseline characteristics
Two systematic reviews [16] [17] included (5 RCTs)	58 people, histologically confirmed cancer and brain metastasis, with no prior WBRT	WBRT plus radiation sensitisers *v* WBRT alone	Multiple brain metastases (further details not reported by reviews)	Further details not reported by reviews
	116 people, adults, neurological symptoms, no prior cranial irradiation or prior treatment with systemic chemotherapy agents that cross the blood–brain barrier	WBRT plus radiation sensitisers *v* WBRT alone	Multiple brain metastases (further details not reported by reviews)	Expected survival more than 4 weeks. Further details not reported by reviews
	859 people, aged 18–75 years	WBRT plus radiation sensitisers *v* WBRT alone	Multiple brain metastases (further details not reported by reviews)	Karnofski performance status of 40 or above; neurological function class (NFC) 1, 2, or 3
	401 people, required WBRT, no prior cranial irradiation, small cell lung cancer and lymphoma and germ-cell tumours excluded, no chemotherapy planned during WBRT	WBRT plus radiation sensitisers *v* WBRT alone	Multiple brain metastases (further details not reported by reviews)	Karnofski performance status of at least 70
	72 people, age above 18 years, no previous brain radiotherapy, no concurrent chemotherapy	WBRT plus radiation sensitisers *v* WBRT alone	Multiple brain metastases (further details not reported by reviews)	Karnofski performance status of at least 70; neurological function class (NFC) 1, or 2.
[29]	515 people, age 18–65 years = 145 people, age 65 years or above = 55 people, no prior treatment for brain metastasis other than resection and with a measurable lesion remaining	WBRT plus radiation sensitisers *v* WBRT alone	Single brain metastasis, 20% in control group and 17% in efaproxiral group; 2–3 brain metastasis, 32% in control group and 30% in efaproxiral group; 3 or more brain metastasis, 47% in control group and 52% in efaproxiral group	Baseline Karnofski performance score: 100 = 16% in control group and 13% in efaproxiral group; 90 = 37% in control group and 46% in efaproxiral group; 80 = 31% in control group and 23% in efaproxiral group; 70 = 16% in control group and 17% in efaproxiral group. Recursive partitioning analysis (RPA): class I = 10% in control group and 11% in efaproxiral group; class II = 90% in control group and 89% in efaproxiral group. Primary cancer: controlled, approximately 25%; uncontrolled, approximately 75%. Primary site: non-small cell lung cancer (55–58% of groups); breast (20–22% of groups); other (22–23% of groups). Extracranial metastasis sites: 0 = 31–36% of groups; 1 to 2 = 4–48% of groups; 3 or above = 18–22% of groups
First RCT reported in three systematic reviews [16] [17] [30]	27 people, lesion 25 mm or less in size	WBRT plus radiosurgery *v* WBRT alone	2–4 metastatic brain tumours (further details not reported by reviews)	Karnofski performance status 70 or above
Second RCT reported in three systematic reviews [16] [17] [31] [30]	331 people, mean age 58.8–59.9 years, with 1–3 newly diagnosed brain metastasis	WBRT plus radiosurgery *v* WBRT alone	Single brain metastasis 186/331 (56%) people; 2 brain metastases 85/331 (26%) people; 3 brain metastases 60/331 (18%) people	Karnofski performance status 90–100 = 198/313 (60%) people; 70–80 = 133/331 (40% people). Recursive partitioning analysis (RPA): class 1 = 91/331 (27%) people; class II = 240/331 (73%) people. Metastasis: brain alone = 31%, brain and one or more extracranial site = 69%. Neurological function: no symptoms = 121 people; minor symptoms = 153 people; moderate symptoms = 55 people; information missing = 2 people. Primary site: lung (211 people); breast (34 people); skin/melanoma (16 people); other (40 people); kidney (4 people); bladder (3 people); colon (6 people); ovarian (3 people); unknown primary (7 people)

Reference number	Participants	Comparison	Single/multiple brain metastases	Other baseline characteristics
[32]	132 people, mean age 62 years, with 1–4 brain metastases, maximum diameter 3 cm by MRI scan	Radiosurgery alone *v* WBRT plus radiosurgery	Single brain metastasis 64/132 (48%) people; 2–4 brain metastases 68/132 (52%) people	Karnofski performance status 90–100 = 78/132 (59%) people; 70–80 = 54/132 (41%) people. Recursive partitioning analysis (RPA): class 1 (aged less than 65 years, no active extracranial disease) = 19/132 (14%) people; class II (aged 65 or over, active extracranial disease) = 113/132 (86%) people. Extracranial metastasis: stable = 79 people; active = 53 people. Primary tumour status: stable = 63 people; active = 69 people. Neurological function: no symptoms, 85 people; minor symptoms, 25 people; moderate symptoms (may or may not require assistance), 22 people; severe symptoms, 0 people. Primary site: lung (88 people); breast (9 people); colorectal (11 people); kidney (10 people); other (14 people)

TABLE **GRADE evaluation of interventions for brain metastases in adults**

Important outcomes	Mortality, treatment success, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions for managing brain metastases in adults?									
1 (48) [18]	Mortality	Corticosteroids *v* corticosteroids plus WBRT	4	–1	0	–2	0	Very low	Quality points deducted for sparse data. Directness points deducted for no statistical comparison between groups and lack of baseline data
1 (48) [18]	Treatment success	Corticosteroids *v* corticosteroids plus WBRT	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for no statistical analysis between groups and lack of baseline data
3 (176) [19] [20] [21]	Mortality	Cytotoxic chemotherapy (with carboplatin or temozolomide) plus WBRT *v* WBRT alone	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for early termination of 2 RCTs
2 (134) [19] [21]	Treatment success	Cytotoxic chemotherapy (with carboplatin or temozolomide) plus WBRT *v* WBRT alone	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Consistency point deducted for conflicting results (inconsistent results for radiological outcomes). Directness point deducted for early termination of 1 RCT
1 (95) [24]	Mortality	Surgery plus WBRT *v* surgery alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty of generalisability of radiotherapy regimen
1 (95) [24]	Treatment success	Surgery plus WBRT *v* surgery alone	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty of generalisability of radiotherapy regimen
3 (195) [13] [16]	Mortality	Surgery plus WBRT *v* WBRT alone	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for heterogeneity among RCTs. Directness point deducted for uncertainty about generalisability of results (highly selected population)
3 (195) [25] [26] [27]	Treatment success	Surgery plus WBRT *v* WBRT alone	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about generalisability of results (highly selected population)
6 (1522) [16] [17] [29]	Mortality	WBRT plus radiation sensitisers *v* WBRT	4	0	0	–1	0	Moderate	Directness point deducted for subgroup analysis
At least 3 (at least 410) [16] [17]	Treatment success	WBRT plus radiation sensitisers *v* WBRT	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (at least 331) [16] [31] [30]	Mortality	WBRT plus radiosurgery *v* WBRT	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for premature termination of 1 RCT and subgroup analysis

Important outcomes	Mortality, treatment success, adverse effects								
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (358) [17]	Treatment success	WBRT plus radiosurgery *v* WBRT	4	0	–1	–1	0	Low	Consistency point deducted for heterogeneity among RCTs. Directness point deducted for high withdrawal rate in performance and mental-status analysis
1 (132) [32]	Mortality	Radiosurgery alone *v* WBRT plus radiosurgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (132) [32]	Treatment success	Radiosurgery alone *v* WBRT plus radiosurgery	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; Consistency: similarity of results across studies; Directness: generaliseability of population or outcomes; Effect size: based on relative risk or odds ratio; WBRT, whole-brain radiotherapy