

# **Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases (Review)**

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## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
BACKGROUND . . . . .	2
OBJECTIVES . . . . .	3
METHODS . . . . .	3
RESULTS . . . . .	9
DISCUSSION . . . . .	11
AUTHORS' CONCLUSIONS . . . . .	12
ACKNOWLEDGEMENTS . . . . .	12
REFERENCES . . . . .	12
CHARACTERISTICS OF STUDIES . . . . .	13
DATA AND ANALYSES . . . . .	18
Analysis 1.1. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 1 Survival. . . . .	18
Analysis 1.2. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 2 Functional Independent Survival. . . . .	19
Analysis 1.3. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 3 Neurological Death. . . . .	19
Analysis 1.4. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 4 Adverse Effects. . . . .	20
WHAT'S NEW . . . . .	21
HISTORY . . . . .	21
CONTRIBUTIONS OF AUTHORS . . . . .	21
DECLARATIONS OF INTEREST . . . . .	21
SOURCES OF SUPPORT . . . . .	22
INDEX TERMS . . . . .	22

[Intervention Review]

# Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

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## ABSTRACT

### Background

The treatment of brain metastasis is generally palliative, with whole brain radiation therapy (WBRT), since most patients have uncontrollable systemic cancer. In certain circumstances, such as single brain metastasis, death may be more likely from brain involvement than systemic disease. In this group surgical resection has been proposed to relieve symptoms and prolong survival.

### Objectives

To assess the clinical effectiveness of surgical resection plus WBRT versus WBRT alone in the treatment of single brain metastasis.

### Search strategy

The following databases were part of a systematic literature search: Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, Cancerlit, Biosis and the Science Citation Index. References of identified studies were hand searched, as was the Journal of Neuro-Oncology over the previous 10 years and Neuro-Oncology over the past two years, including all conference abstracts. Specialists in neuro-oncology were also contacted. The searches were updated in October 2007.

### Selection criteria

Randomised controlled trials (RCTs) comparing surgery and WBRT with WBRT alone, in patients with single brain metastasis.

### Data collection and analysis

Two review authors independently assessed trial quality and extracted data using pre-specified pro-formas.

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## Main results

Three RCTs were identified enrolling 195 patients in total. No significant difference in survival was found (HR 0.72, 95% CI 0.34 to 1.53,  $p = 0.40$ ) although there was heterogeneity between trials ( $I^2 = 82\%$ ). One trial found surgery and WBRT increased the duration of Functionally Independent Survival (FIS) (HR 0.42, 95% CI 0.22 to 0.82,  $p = 0.01$ ). There was some indication that surgery and WBRT might reduce the risk of deaths due to neurological cause: odds ratio (RR = 0.68 95% CI 0.43 to 1.09,  $p = 0.11$ ). The risk of adverse events was similar in both arms.

## Authors' conclusions

Surgery and WBRT may improve FIS but not overall survival. It may also reduce the proportion of deaths due to neurological cause. All these results were in a highly selected group of patients. Patients undergoing surgery did not appear to have any higher risk of adverse events than patients who only had WBRT.

## PLAIN LANGUAGE SUMMARY

**For patients with single brain metastasis there is no good evidence from randomised controlled trials (RCTs) that surgery in addition to whole brain radiation therapy (WBRT) improves overall survival**

Treatment of brain metastasis is usually with WBRT although in selected patients - particularly those with only a single metastasis to the brain - surgical resection may be considered. This review found no evidence that the combination of surgery and WBRT improved overall survival compared with WBRT alone but it may improve the length of time patients remained independent from others for support. The risk of deaths due to neurological cause may also be reduced. Patients undergoing surgery did not appear to have any higher risk of adverse events than patients who only had WBRT. Decisions on the treatment for an individual patient are best made as part of a multidisciplinary team meeting in keeping with NICE guidance.

## BACKGROUND

Brain metastasis are cancers that spread to the brain from a primary site outside of the brain. Metastasis are the most frequent type of brain malignancy, comprising around 50% of all brain tumours, and have an incidence of 14 cases per 100,000 population a year (Counsell 1998). They occur in between 20 to 40% of those with cancer, as determined at autopsy (Posner 1978), with the most common primary sites being lung and breast. Patients usually present with a short history of focal neurological symptoms, symptoms of raised intracranial pressure, or seizures. Symptoms vary depending on the site, size and number of metastasis. Previously around 50% of brain metastases were thought to be single (Delattre 1988), although advances in brain imaging suggest this figure is now closer to 30% (Schaeffer 1996).

Generally, the treatment is palliative, as most patients have uncontrollable cancer outside the brain. Steroids frequently cause a resolution or improvement of symptoms, but side effects can be problematic and without further treatment neurological symp-

oms will recur. Whole brain radiation therapy (WBRT) is the accepted palliative treatment, which may offer relief of symptoms and longer survival (Barker II 2005). It has the benefit that it can be given on an out-patient basis, while side effects are uncommon with modern regimes. Patients who respond to radiation are usually young (less than 60 years), have a good Karnofsky Performance Score (KPS > 70), radiosensitive primary tumours and controlled primary disease with metastatic spread confined to the brain (Diener-West 1989). The optimal dose fractionation schedule for treatment of brain metastases remains uncertain and varies widely (Tsao 2006). Median survival in patients having no treatment after diagnosis of brain metastases is one month, with most patients dying from their neurological disease. For patients taking steroids it is 2 months, and for people taking steroids and undergoing WBRT it is 3 to 6 months (Cairncross 1980).

Surgical resection of single brain metastasis has been proposed to help maintain a patients quality of life (QOL), prevent death directly from the metastasis and prolong survival. In patients with

raised intra to cranial pressure surgery can be life saving and bring immediate relief of symptoms. Surgery also provides the opportunity to assess the histology of the lesion, as some lesions thought to be metastasis may have a more benign origin (e.g. brain abscess), although this may be achieved with biopsy instead. The potential benefits of surgical resection must be balanced against the risks of post to operative morbidity and mortality. Most patients will not be suitable for surgery because of multiple lesions, an inaccessible lesion, active primary disease, or co to morbidity. A surgically accessible lesion can be defined as one that is superficial and can be operated on with minimal resection of surrounding tissue. Following surgery, WBRT is given to prevent local recurrence and target any micro to metastases not detected. One RCT has found those undergoing WBRT after surgery have a reduced local recurrence rate compared with those who have surgery alone (Patchell 1998). Although there are in theory advantages to having a metastasis surgically removed, there are no systematic reviews or meta to analyses in this area, and the choice of treatment is controversial.

## OBJECTIVES

To assess if resection of single brain metastasis followed by WBRT holds any clinical advantage over WBRT alone, and whether such advantages are outweighed by the risks of surgery.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

RCTs.

#### Types of participants

Studies of patients with systemic cancer (primary site confirmed by histology) and a suspected single brain metastasis (on imaging and clinical findings) were included; the brain metastasis did not have to be histologically proven (e.g. by biopsy).

#### Types of interventions

Surgical resection and WBRT versus WBRT alone, defined as:

- Surgical resection: intended complete macroscopic removal of tissue by a neurosurgical technique. Radiosurgery not included.
- WBRT: a technique where the brain is treated with therapeutic doses of radiation therapy aimed at killing the

quickly dividing cells of an existing brain tumour prophylactically to stop the development of tumour cells that are below the resolution of conventional imaging techniques (microscopic metastases). Radiosurgery not included.

### Types of outcome measures

The outcomes of interest were:

- (1) Survival, from the time of randomisation to time of death.
- (2) QOL: using the Linear Analogue Scale, Functional Assessment of Cancer Therapy to Brain, or other equivalent grading. Outcome is time to progression beyond a pre to specified composite score.
- (2) Functionally independent survival (FIS): time to KPS<70 or other grading system from randomisation.
- (3) Neurological death. Whether a person died primarily from their intracerebral metastasis rather than fulminant systemic disease. A neurological death was also one where both systemic and brain metastasis were active at the time of death, as this would be a failure of the brain treatment. Death from neurological cause can involve acute deterioration (from either rapid growth of the metastasis, haemorrhage, invasion of local structure or decompensation of raised intra to cerebral pressure), or more gradual tumour expansion and deterioration of neurologic function.
- (4) Adverse Events; nature (as defined using MedDRA® (Medical Dictionary for Regulatory Authorities) criteria (MedDRA)) and timing of an event following randomisation to a treatment arm

### Search methods for identification of studies

The following databases were part of a systematic literature search: Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, Cancerlit, Biosis and the Science Citation Index. References of identified studies were hand searched, as was the Journal of Neuro to Oncology over the previous 10 years and Neuro to Oncology over the past 2 years, including all conference abstracts. Specialists in neuro to oncology were also contacted. The searches were updated in October 2007.

### Electronic searches

The same principle was used to search each database. Firstly, the terms and phrases identifying all the randomised controlled trials were combined using the Boolean "OR". Secondly, all the terms and phrases describing the disease of interest, namely cerebral metastasis, were combined with "OR". Thirdly, terms describing the intervention of interest i.e. surgical resection or whole brain radiation therapy was also combined with "OR". Items which fulfilled all three criteria were identified by linking the results of these searches with the Boolean 'AND' operator and the results displayed. Wild cards and truncation symbols were used to ensure terms with alternative spelling and/or endings were not missed.

MeSH headings were exploded. The full search strategy is described in [Table 1](#).

**Table 1. Search Strategy**

Database	Search
Central	<ol style="list-style-type: none"> <li>1. central-nervous-system-neoplasms:ME</li> <li>2. brain-neoplasms*1:ME</li> <li>3. metastasis*1:ME</li> <li>4. metastases*1:ME</li> <li>5. secondary*1:ME</li> <li>6. secondaries*1:ME</li> <li>7. OR 1-6</li> <li>8. biopsy:ME</li> <li>9. neurosurgery:ME</li> <li>10. neurosurgical-procedures:ME</li> <li>11. stereotaxic-techniques:ME</li> <li>12. craniotomy:ME</li> <li>13 OR 8-12</li> <li>14. radiation therapy:ME</li> <li>15. radiotherapy:ME</li> <li>16. irradiation:ME</li> <li>17. OR 14-16</li> <li>18. 7 AND 13</li> <li>19. 17 AND 18</li> </ol>
Embase	<ol style="list-style-type: none"> <li>1. clinical trial/</li> <li>2. multicenter study/</li> <li>3. phase 2 clinical trial/</li> <li>4. phase 3 clinical trial</li> <li>5. phase 4 clinical trial</li> <li>6. randomized controlled trial/</li> <li>7. controlled study/</li> <li>8. meta analysis/</li> <li>9. crossover procedure/</li> <li>10. double blind procedure/</li> <li>11. single blind procedure/</li> <li>12. randomization/</li> <li>13. clinical study/</li> <li>14. "0197".tg</li> <li>15. (clin\$ adj25 trial\$).tw.</li> <li>16. ((singl\$ or doubl\$ or triple\$ or treb\$) adj25 (blind\$ or mask\$)).tw.</li> <li>17. random\$.tw</li> <li>18. control\$.tw</li> <li>19. OR/1-17</li> <li>20 limit 19 to human</li> <li>21. brain neoplasm/</li> <li>22 exp central nervous system tumor/</li> <li>23. exp brain cortex/di,su</li> <li>24. brain tumo?r.tw.</li> </ol>

**Table 1. Search Strategy** (Continued)

	<p>25. (metastasis).tw.  26. brain cancer/ or brain stem tumor/ or brain tumor/ or intracranial tumor/ or posterior cranial fossa tumor/  27. OR/21-26  28. brain surgery/ or stereotactic surgery/  29. neurosurgery/  30. "neurosurgical procedures".mp  31. (biops\$ adj25 resect\$).tw.  32. biopsy versus resection.tw.  33. extent of resection.tw  34. multimodality cancer therapy/  35. cytoreductive surgery.tw.  36. OR/28-35  37. radiation therapy/  38. radiotherapy/  39. irradiation/  40. 27 AND 36  41. 20 AND 40</p>
Cancerlit	This database was searched using the same strategy as that used for MEDLINE
Biosis previews	<p>Words or phrases in the Title, Subjects or Abstract were searched.</p> <ol style="list-style-type: none"> <li>1. randomi?ed &amp; control* &amp; trial</li> <li>2. control* &amp; clinical &amp; trial</li> <li>3. random* &amp; allocat*</li> <li>4. double &amp; (blind* , mask*)</li> <li>5. single &amp; (blind* , mask*)</li> <li>6. clinical &amp; trial</li> <li>7. control &amp; group</li> <li>8. control* &amp; trial</li> <li>9. clinical &amp; study</li> <li>10. control* &amp; study</li> <li>11. OR/1-10</li> <li>12. brain &amp; tumo*r</li> <li>13. brain &amp; neoplasm</li> <li>14. brain &amp; cancer</li> <li>15. metastas?s</li> <li>16. secondar*</li> <li>17. tumor [Major Concept]</li> <li>18. OR/12-17</li> <li>19. neurosurg*</li> <li>20. combined &amp; modality &amp; therapy</li> <li>21. stereota* &amp; biopsy</li> <li>22. biopsy &amp; resection</li> <li>23. surg* &amp; treatment</li> <li>24. OR/19-23</li> <li>25. radiation therap</li> <li>26. radiotherapy</li> <li>27. irradiation</li> </ol>

**Table 1. Search Strategy** (Continued)

	<p>28. OR/25-27                  29. 24 AND 28                  30. 18 AND 29                  31. 11 AND 30</p>
Science Citation Index	<p>A similar search strategy to the one for BIOSIS was used. Searches were made in the title, keyword or abstract. Unlike BIOSIS, there was no “major concepts” search facility.                  The differences were as follows:                  (1) “tumo*” was used in place of “tumo?r”                  (2) “central &amp; nervous &amp; system &amp; tumo*” and “central &amp; nervous &amp; neoplasm” were two additional searches                  (3) “extent &amp; resection” was used in place of “extent of resection”</p>
Medline	<p>Terms 1 to 37, used to identify all randomised and clinical controlled trials, were taken from the first two parts of the Highly Sensitive Search Strategy (HSSS) from the Cochrane Handbook appendix 5b.</p> <p>38. exp brain neoplasms/                  39. central nervous system neoplasm/                  40. exp cerebral cortex/ab,pa,an,cy,su                  41. exp Neoplasm Metastasis/                  42. brain metastas\$.tw.                  43. intracranial tum\$.tw.                  44. cerebral metastas\$.tw.                  45. (single adj3 metastas\$).tw.                  46. (solitary adj3 metastas\$).tw.                  47. OR/38-46                  48. limit 32 to human                  49. biopsy.tw.                  50. resection.tw.                  51. exp Brain neoplasms/                  52. brain surgery.tw.                  53. stereotactic surgery.tw.                  54. neurosurgery.tw.                  55. neurosurgical procedures.tw.                  56. cytoreductive surgery.tw.                  57. OR/49-56                  58. limit 57 to human                  59. radiation therapy.tw.                  60. radiotherapy.tw.                  61. irradiation.tw.                  62. exp radiotherapy/                  63. cerebral radiotherapy.tw.                  64. brain radiotherapy.tw.                  65. (brain adj25 radi\$).tw.                  66. (cerebral adj25 radi\$).tw.                  67. (metastas\$ adj25 radi\$). tw.                  68. OR/59-67                  69. limit 68 to human                  70. 58 and 69</p>

**Table 1. Search Strategy** (Continued)

	71. 48 and 70
	72. 37 and 71

**Searching other resources**

**Reference searching**

The references of all identified studies were searched to identify more trials.

**Hand searching**

A hand search of the Journal of Neuro to Oncology for the past 10 years was undertaken in order to identify trials that may not have been picked up by the electronic database searches. This included searching of all conference abstracts published in the journal. Neuro to Oncology was also hand searched

**Personal communication**

Various neuro to oncology specialists were contacted to see if they were aware of any published, unpublished, pending or recently commenced trials. These people included:

- CJ Vecht, Utrecht, Netherlands: Chairman of the EORTC Brain Tumour Group & author of one of the already identified papers.
- M Brada, London, UK: Chairman of National Cancer Research Institute Brain Tumour Section.
- M van den Bent, Chairman of the European Organisation for Research Trials in Cancer (EORTC) Brain Tumour Section, Netherlands

- AH Mintz, Hamilton, Canada: author of one of the already identified papers.
- RA Patchell, Kentucky, USA: author of one of the already identified papers.

**Data collection and analysis**

**Selection of studies**

Identification of studies was made in two stages. Abstracts returned by the original search were examined independently by two review authors and screened to see if they met the inclusion criteria. Next, full texts of the selected references were obtained and likewise examined. At all times any disagreements were resolved through discussion. If sufficient data were not available for assessment of a trial the relevant authors were contacted.

**Data extraction and management**

**Data abstraction**

Two review authors independently abstracted endpoint data and data describing the trial using a pre to specified form designed to complete the information required for Table 2. Differences will be reconciled by discussion or by consultation with a third review author.

**Table 2. Internal Validity**

Characteristic	Patchell 1990	Vecht 1993	Mintz 1996
Power calculation?	Yes (but too optimistic)	No	Yes
Proper randomisation?	Yes	Yes	Yes
Groups similar at baseline?	Yes	Yes	No
Blinding?	No	No	Yes
Eligibility criteria stated?	Yes	Yes	Yes
Objective outcome measures?	Survival: Yes. Others: No	Survival: Yes. Others: No	Survival: Yes. Others: No

**Table 2. Internal Validity** (Continued)

Analysis on an ITT basis?	No	No	Yes
All patients accounted for?	Yes	Yes	Yes
Withdrawals specified?	Yes	Yes	Yes
Withdrawal reasons given?	Yes	Yes	Yes
Conflict of interest?	No	No	No

**Participants**

For each trial, data on the number of patients randomised, analysed and excluded from the investigator's analyses was extracted. The number of patients censored, due to either incomplete follow up, loss to follow up or competing event, were noted. The minimum and maximum follow up length was also noted for use in calculating hazard ratios (HR). The distribution of patients by age, sex, performance status, size of metastasis, time between primary and metastasis, site and activity of primary tumour, as well as other important variables was recorded, where possible.

**Interventions**

Actual numbers of undergoing treatments were assessed, taking into account those with protocol violations, where published. Data on the proportion of patients in the research treatment and control arms who completed radiotherapy as planned, did not start radiotherapy, and who experienced delay were also extracted. Details of total dose and fractionation of WBRT were compared. The number of patients undergoing further therapy and its nature were noted, and any implications discussed. Duration of follow up and ascertainment of morbidity and neurological cause of death were also noted.

**Outcomes**

For time to event data (survival, QOL and FIS) the log hazard ratio and its standard error were abstracted from trial reports. If these were not reported, we digitised electronic versions of the published Kaplan to Meier survival curves using Adobe Photoshop, noted the minimum and maximum follow to up and hence estimated the log (HR) and its standard error using Parmar's methods (Parmar 1998). These calculations were performed independently by two review authors (MGH & HD) using an Excel spreadsheet and a

specially written program in Stata 9.21 (Stata 2005), which were validated using data presented in Table V of Parmar 1998.

For dichotomous outcomes (e.g. neurological death and adverse events) the number of patients in each arm who experienced the event of interest was abstracted in order to calculate a relative risk. For continuous and dichotomous data the number of patients assessed at endpoint was abstracted. Where possible, all data abstracted was that pertaining to an intention to treat analysis. In the case of missing data required for the review outcomes, the study authors were contacted. Data integration into RevMan was performed by the lead author (MGH).

**Statistical methods**

For time to event data hazard ratios were pooled using the generic inverse variance facility of RevMan 4.2. For dichotomous outcomes the relative risk was calculated for each study and statistics from all studies were pooled. For continuous outcomes the mean differences between the treatment arms at the end of follow to up were pooled using the mean difference method otherwise. Random effects models will be used for all meta to analyses (Der Simonian 1986).

If sufficient studies were included, we intended constructing a funnel plot of treatment effect versus precision in order to investigate the likelihood of publication bias. If these plots suggested that treatment effects may not be sampled from a symmetric distribution, as assumed by the random effects model, further meta to analyses will be performed using the fixed effects models. Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).

### Assessment of risk of bias in included studies

Any trial deemed relevant was critically appraised using the following criteria and given a letter code (A, B or C) depending on the findings:

Methods of randomisation was assessed as:

- adequate e.g. a computer to generated random sequence or a table of random numbers (A)
- inadequate e.g. date of birth, clinic ID number or surname (B)
- unclear e.g. not reported (C)

Allocation concealment was assessed as:

- adequate e.g. where allocation concealments could not be foretold (A)
  - inadequate e.g. a computer generated allocation sequence was displayed so treatment providers could see which arm of the trial the next participant was to be assigned to, or kept in a sealed opaque envelope (B)
    - unclear e.g. not reported (C)
    - not used (D)

The blinding of patients, treatment providers and outcome assessors is not possible in a trial of surgery and was not assessed.

Subsequently each trial was allocated to two groups depending on the findings from the critical appraisal:

- Low risk of bias (all answers from the critical appraisal were 'A')
- Moderate/high risk of bias (any answer from the critical appraisal was 'B' or 'C')

Only trials deemed to be of low risk of bias were included.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Out of 860 results from the search strategy a total of three RCTs were identified ([Mintz 1996](#); [Patchell 1990](#); [Vecht 1993](#)). All three studies were deemed to be at low risk of bias and were sufficiently similar in design characteristics to warrant combination of results in meta to analysis. See table of included studies and [Table 3](#) for full details.

**Table 3. External Validity**

Characteristic	Patchell 1990	Vecht 1993	Mintz 1996
Age (mean and range)	Surgery: 59 (44-74), WBRT: 60(49-74)	Surgery: 59 (30-75), WBRT: 60 (32-78)	Surgery 58 (SD 9.9), WBRT 59 (SD 9.0)
Sex (M:F)	Surgery 18:7, WBRT 14:9	Surgery 15:17, WBRT 18:13	Surgery 22:21, WBRT 24:17
KPS (mean and range)	Surgery: 90 (70-100), WBRT: 90 (70-100)	(WHO) Surgery: 0=3, 1=21, 2=8. WBRT 0=4, 1=18, 2=9	Surgery=67%, WBRT=80%
Extra-cranial metastasis	Surgery: 36%, WBRT: 37%	Surgery: 30%, WBRT: 30%	Surgery=49%, WBRT=41%
Extent of surgery	Complete in all cases (CT day 2-5)	Not assessed	95% complete

The first study by was a single institution RCT set in Kentucky, USA ([Patchell 1990](#)). 48 patients were randomised to confirmatory brain tumour biopsy followed by WBRT or surgical resection of metastasis and WBRT. It included mainly young (mean age 60 years) and fit subjects (mean KPS = 90). Randomisation was by computer generated random numbers after stratification for prognostic factors but outcome assessors were not blinded. Outcome measures included survival, functional independence, radiographic changes in tumour size, time to recurrence and cause of death. The log (HRs) for survival and functionally independent

survival and their standard errors, as estimated by Cox regression, reported to us by the trial lead statistician.

The second study was a Dutch multicentre RCT of surgical resection followed by WBRT versus WBRT alone ([Vecht 1993](#)). This randomised 63 mainly young (mean age 60 years) but slightly less fit subjects (WHO score of 2 or less). Randomisation was performed centrally by telephone in blocks after stratification for prognostic factors but outcome assessors were not blinded. The minimum and maximum duration of follow to up were assumed

to be 1 and 70 months respectively. Outcome measures included survival, functionally independent survival and cause of death. The log (HR) and its standard error were estimated from the published survival curves using Parmars methods.

The final study was a multicentre Canadian RCT of surgical resection followed by WBRT versus WBRT alone (Mintz 1996). This randomised 84 young patients (median age 59 years) but entry criteria allowed less fit patients (KPS of 50 or more). Randomisation was by central telephone randomisation after stratification for prognostic factors but outcome assessors were not blinded. Outcome measures were survival, cause of death, functional status (by KPS) and QOL (using Spitzer QOL index), and surgical complications within 30 days. The minimum and maximum duration of follow up were assumed to be 0 and 34 months respectively. The log (HR) and its standard error were estimated from the published survival curves using Parmar's methods.

### Risk of bias in included studies

#### Patient numbers

In all trials the number of patients was very small (84, 48 and 63 in the trials of Mintz 1996; Patchell 1990; Vecht 1993 respectively), due in part to the highly selected nature of cases. In the trial by Patchell, sample size was calculated with a highly optimistic end point in mind, derived from a previous non randomized study (Patchell 1986). In the trial by Vecht, the slow rate of entry of participants meant it took over six years to accrue all their data. This opens up questions as to the standardisation of treatment during this time. The trial by Mintz found 143 capable of being randomized, although only 84 consented to trial randomisation. This demonstrates that it is possible to generate much larger numbers, but only in a large multi to institution study.

#### Selection bias

In the trial by Patchell, selection of cases for randomisation was by a single neurosurgeon, which may have resulted in inclusion of only those most suitable for surgery. However, there was no obvious discrepancy in any prognostic factors between the groups. In the trial by Mintz, it is not clear the reasons why so many people who were suitable for inclusion in the trial refused randomisation when compared with the other trials. There is the possibility then that the group randomised in the Mintz trial is not representative of all those eligible.

#### Performance and attrition bias

As with all trials involving an operation, it would be obvious which patients had surgery. This may bias post to intervention management. Many patients in each group received further therapy, for example surgery or steroids. However, there did not appear to be a clear bias to more intensive follow up therapy in either arm of

any of the trials. There was no obvious bias in the censoring of individuals in any of the trials.

It is not standard practice generally to re to irradiate patients with brain metastases, because usually the brain has received the maximum tolerable dose during initial radiotherapy, and re to irradiation markedly increases the risk of radiation toxicity even if it does extend survival. The high re to treatment rate (25% in the Patchell trial) may reflect the very highly selected nature of patients, with enrolment only of patients who would be suitable for further therapy.

#### Detection bias

In each trial, patients were followed up for monthly intervals up to 6 months, and for longer intervals thereafter (2 to 3 months). It is therefore not known when within this time interval an event occurred, particularly a reduction in FIS. This represents a significant time interval, especially considering the short time to recurrence of these outcomes in the first instance.

As it was not possible to blind clinicians about the treatment allocation after the intervention, there may be bias arising in the determination of neurological death and the diagnosis of adverse effects. Reporting of adverse effects is subjective, and there may be a systematic bias depending on the speciality of the attending clinician. Many criteria are available to improve the objectivity of these diagnoses, but unfortunately none were explicitly noted as being used in the above trials.

#### Effects of interventions

The three RCTs included a total of 195 subjects (Mintz 1996; Patchell 1990; Vecht 1993).

#### Overall survival

The analysis did not demonstrate a statistically significant difference in survival between the two treatments (HR = 0.72, 95% CI 0.34 to 1.53,  $p = 0.40$ ). There was substantial heterogeneity between the trials ( $I^2 = 82%$ ); the trials by Patchell and Vecht both reported better survival in those undergoing surgery and WBRT while that by Mintz reported better survival in patients receiving only WBRT.

#### Functionally independent survival

Only one trial could be included in the analysis (Patchell 1990); the other trials did not include sufficient data in order to calculate the necessary HR and variance. The trial by Vecht did not report FIS for the entire trial population while the trial by Mintz did not present its results graphically. The Patchell trial found that those treated by surgery and WBRT maintained their functional

independence longer than those treated by WBRT alone (HR = 0.42, 95% CI 0.22 to 0.82,  $p = 0.01$ ).

### Neurological death

There was a trend that those treated by surgery were less likely to die from neurological causes (RR = 0.68 95% CI 0.43 to 1.09,  $p = 0.11$ ). No statistical heterogeneity was found between trials ( $I^2 = 0\%$ ).

### Adverse events

The reports of adverse events were difficult to interpret as more than one adverse event is reported for some patients. The statistical analysis did not allow for the clustering of events within patients; correct allowance for this would widen the CIs. Without allowing for this the results do not demonstrate that either treatment was more likely to cause adverse events (RR = 1.27 95% CI = 0.77 to 2.09  $p = 0.35$ ). Mortality at 30 days was also similar in both arms of each of the trials. No statistical heterogeneity between these findings was identified ( $I^2 = 0\%$ ). Individual subcategories did not demonstrate that any one type of complication was significantly more likely in one group than the other.

The Patchell study did not report adverse effects by category. Both of the other studies reported more respiratory infections and more intracerebral haematomas in the WBRT arm. However, they reported contrasting results for infections and other complications: the Vecht study reported three infections in the surgery and WBRT arm, and none in the WBRT alone arm, whereas the Mintz study reported one in the surgery and WBRT arm and three in the WBRT alone arm; Vecht reported nine other complications in the surgery and WBRT arm and none in the other arm whereas Mintz reported one other complication in each arm. The reporting of adverse events was not structured with clear definitions such as the COSTART criteria and may have been biased by informal reporting.

A funnel plot was not constructed as there were only three trials.

## DISCUSSION

Although no statistically significant difference between surgery plus WBRT and WBRT alone was found in the meta analysis, the trials by Patchell and Vecht were in favour of surgery, while that by Mintz was in favour of WBRT alone. The key differences between the trials are the decreased survival of those in WBRT alone in the trial by Patchell, and the decreased survival for those treated by surgery and WBRT in the trial by Mintz. Two possible reasons may account for the findings in the Patchell trial. Firstly, the majority of their patients had non to small cell lung cancer, a highly radio resistant tumour, which would not be expected to respond to WBRT particularly well. Secondly, there may be a

selection bias, as patients were selected for surgery in a specialist unit by a single neuro to surgeon. This may have resulted in randomisation of only patients who were particularly suited for surgery.

In the Mintz trial, the key issue is why patients who underwent surgery had a poorer survival than those who did not. The entry criteria allowed patients with a poorer KPS and a larger percentage had extracranial metastases (Table 2). Patients with a lower KPS and extracranial disease are known to have a poorer survival, hence the potential benefits of surgery may not be applicable in this more ill population. The radiotherapy group had a considerably longer time between primary tumour diagnosis and metastasis than the surgery group, possibly reflecting less aggressive disease, which is known to confer a better survival (Patchell 1990). Furthermore, the entry criteria did not specify a minimum life expectancy of six months, as in the other two trials. The patients examined by Mintz 1996, having in general a lower life expectancy and more active disease, would seem less likely to benefit from surgery. It could be that in this group of patients the surgical approach does not provide any improvement in survival, but in a more selected group (examined in the other two trials) surgery may increase survival.

Although much focus is put on the benefit in survival times, equally important is the benefit to patients' QOL, as few patients were cured overall. No trial directly examined QOL, which is a major shortcoming; functionally independent survival was examined completely in a single trial (Patchell 1990) although KPS is known to correlate poorly with patients' own perception of QOL. The trial did find an improvement in FIS with surgery. In addition, the trial by Vecht found an improvement in FIS in patients treated by surgery who had stable extra to cranial disease, although the trial by Mintz found little difference between arms in the stable extracranial disease subgroup. It has been noted that patients in general maintain their functional independence until a few months before death after both approaches, and that after surgery there is a trend for patients Karnofsky score to improve, although this is mainly in those who have a high score already (Vecht 1993). It would be of benefit for further trials to clarify exactly the nature of this benefit in QOL, especially in regard to a reduction in the dose of long term steroid use (Macdonald 1990).

It is important to note that there are many other important indications for operating on metastases, for example raised intra to cerebral pressure or obstructive hydrocephalus. There may also be other benefits to surgery which were not examined in any of the three RCTs, such as reducing steroid doses, improving control during WBRT and improving some neurological symptoms. In the case of a single brain metastasis without an obvious primary site, the case for resection is well established for histological confirmation. Authors have suggested that for certain radio resistant

tumours, such as non to small cell lung cancer, surgery should always be considered in the management (Patchell 1990).

## AUTHORS' CONCLUSIONS

### Implications for practice

It is difficult to advise either patients or colleagues on the basis of evidence from such small studies. It is important to note that these results were obtained in a highly selected group, with close follow up supervisions and further active interventions in many cases, who are not necessarily representative of the majority of those with single brain metastasis. In this group, the surgical approach may reduce the number of deaths due to neurological cause, while one trial has suggested an increase in the duration of a patients FIS. No improvement in survival was found using either approach while the number of adverse effects was similar in each group. QOL was not directly examined. Those most likely to benefit from surgery are of young age, have good neurological function, and controlled primary disease (Noordijk 1994). Careful attention to prognostic factors will see only those who have the most to gain from surgery being operated on, while those who are less well will avoid unnecessary risks and morbidity. It must not be forgotten that the overall outlook for patients at two years is dismally poor with either intervention, and death is commonly due to systemic disease. Currently, the management for the majority of those with single brain metastasis will be WBRT alone due to active systemic disease and other co to morbidity. Decisions of the most appropriate treatment for an individual patient should be made at an MDT meeting in line with NICE guidance (NICE 2007).

### Implications for research

Further trials in this area would help increase the robustness of the data, both by answering methodological shortcomings and recruiting greater numbers. Follow up should be longer and at shorter intervals. An attempt should be made at reducing follow up bias, perhaps by using clearly set out protocols and criteria for defining adverse effects and neurological causes of death. Statistically, the reporting in trials of HRs and their variance would improve the accuracy in reading data from Kaplan to Meier plots. These results can then be combined in future updates of this review to provide an up to date conclusion on management of single brain metastasis.

Recently, much attention has been given to modern focal radiotherapy techniques, known as Stereotactic Radiosurgery (SRS). A recent RCT of SRS plus WBRT in those with one to four cerebral metastasis found that SRS and WBRT improved survival in those with single brain metastasis compared with WBRT alone (Stafinski 2006). Currently there is no trial that has examined surgery in comparison with SRS although one trial is ongoing (Roos 2008). Management decisions will increasingly be based on using SRS or surgery, rather than conventional surgery and WBRT.

## ACKNOWLEDGEMENTS

Richard Kryscio (lead statistician for the Patchell 1990 trial) for supplying additional data. The lead author (MGH) acknowledges receipt of a Cochrane Gynaecological Cancer Review Group Grant for the update of this review in 2007.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Mintz 1996

Methods	Randomized Controlled Study. Multicentre Central telephone randomization Stratified by: Type (lung:other) Size (<3cm:>=3cm) Extent of primary (no evidence of primary, localised primary disease, localised + extracerebral)	
Participants	Inclusion Criteria: Single intracerebral metastasis Age < 80yrs Histologically verified cancer in last 5 years Karnofsky >= 50. Exclusion Criteria: Brain stem/basal ganglia tumours Underlying medical illness that would preclude adequate follow-up Meningeal metastases Previous cranial RT Immediate resection required Radiosensitive systemic tumours (e.g. SCLC, lymphoma, leukaemia, skin cancer other than melanoma)	
Interventions	surgery plus radiation vs radiation alone WBRT was 3000 cGy therapy over 2 weeks (300cGy x10 fractions). Surgery was aimed at macroscopical excision, with post-operative CT assessment.	
Outcomes	Follow up monthly for first 6 months and every 3 months thereafter; examiner not defined. Follow up consisted of history, physical examination, Karnofsky performance status and Spitzer quality of life index, as well as CT scanning. Outcome measures were; 1. survival, with cause of death (either neurological, systemic or combined) 2. Functional status and quality of life, with functionally independent survival defined as a Karnofsky<70) 3. Treatment complications, for surgery (wound infection, venous thrombosis, pulmonary embolism, myocardial ischaemia and pneumonia)and for radiation (radiation necrosis).	
Notes		
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate

**Patchell 1990**

Methods	Randomized Controlled Study. Single centre “computer generated random numbers” Non-blinded Stratified by: Location (supratentorial:infratentorial) Type (lung: other) Extent of primary (no tumour: stable: progressive)	
Participants	Inclusion Criteria: Single intracerebral metastasis Age >= 18 years Histology of cancer out with the central nervous system Karnofsky >= 70. Exclusion Criteria: Resection not feasible Meningeal Metastases Previous cranial RT Immediate resection required Radiosensitive systemic tumours (e.g SCLC, lymphoma, leukaemia, multiple myeloma, germ cell tumour)	
Interventions	“Resection + cranial radiation” vs “cranial radiation” (but patients with supratentorial tumours randomised to “cranial radiation” were stereotactically biopsied prior to radiation, infratentorial tumours were not biopsied). 56 patients satisfied inclusion and exclusion criteria (Oct 85 - Dec 88) 2 patients declined 54 patients randomised. 6 excluded because histology not metastasis (e.g. 2GBM, 1 LGA, 2 abscesses, 1 inflammatory reaction) 25 randomised to “resection + radiation” vs 23 to “radiation only” Radiation dose 36Gy, 3fractions/day over 12 days	
Outcomes	Follow-up every 3 months by neurological exam and imaging(CT/MRI). Outcome measures: Death (30 days from surgery; neurological death; non-neurological death) Length of survival Time to recurrence (by imaging) Clinical improvement (change in Karnofsky) Morbidity (Karnofsky 30 days post-treatment < pre-treatment) “Quality of Life” (length of time Karnofsky >=70)	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate

**Vecht 1993**

Methods	Randomized Controlled Study. Multicentre Central telephone randomization Non-blinded Stratified by: Centre (block sizes of 4) Type (lung: other) Extent of primary (no tumour/stable: progressive)	
Participants	Inclusion criteria: age $\geq 18$ years, histologically verified extracranial malignancy, apparent presence of single brain metastasis as documented on CT, Karnofsky $\leq 70$ or WHO scale $< 2$ with neurological function $\leq$ , life expectancy $< 6$ months, fit for treatment and informed consent. Exclusion criteria were small cell lung cancer, malignant lymphoma, and documented or suspected meningeal disease or intracranial tumour deposits other than thn a single parenchymal brain metastasis.	
Interventions	“neurosurgical excision plus radiotherapy” vs “radiotherapy alone”. Surgery was by macroscopical excision. Radiotherapy wa a total of 40Gy in 2 weeks, 2 fractions per day. 66 patients were randomised between January 1st 1985 and January 1st 1991. 2 were excluded due to challenge of their diagnosis, while 1 was excluded due to delay in treatment initiation. Of the remaining 63, 32 were randomised to the surgical arm and 31 to the radiotherapy alone arm.	
Outcomes	Patients were seen once a month during the first 6 months, then every 2 months thereafter. Data recorded were WHO status, neurological functional scale, neurological examination, and patients residence.	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Yes	A - Adequate

GBM: glioblastoma multiforme  
LGA: low grade astrocytoma  
RT: radiotherapy  
SCLC: small cell lung cancer  
WBRT: whole brain radiation therapy  
WHO: World Health Organisation

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

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Noordijk 1994	This is the same study as reported by Vecht et al. The paper more specifically looks at the possible effects of age and extracranial tumour activity on magnitude of difference between the randomized groups.
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## DATA AND ANALYSES

### Comparison 1. Surgery + Radiotherapy vs Radiotherapy

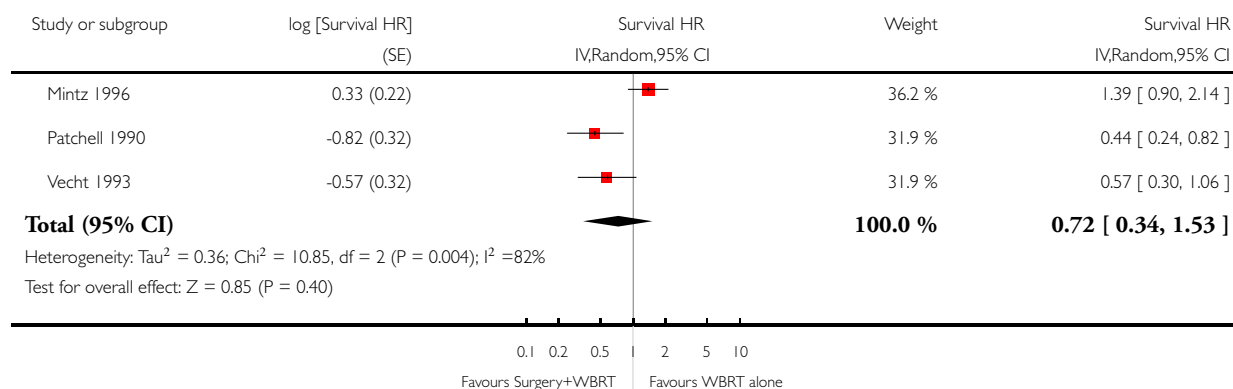
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	3		Survival HR (Random, 95% CI)	0.72 [0.34, 1.53]
2 Functional Independent Survival	1		HR (Random, 95% CI)	0.42 [0.22, 0.82]
3 Neurological Death	3	185	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.43, 1.09]
4 Adverse Effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Any Morbidity	3	195	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.77, 2.09]
4.2 Infections	2	147	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.07, 24.66]
4.3 Respiratory Problems	2	147	Risk Ratio (M-H, Random, 95% CI)	2.28 [0.54, 9.63]
4.4 Intracerebral Haematoma	2	147	Risk Ratio (M-H, Random, 95% CI)	4.78 [0.56, 41.09]
4.5 Other	2	147	Risk Ratio (M-H, Random, 95% CI)	4.33 [0.22, 84.71]

#### Analysis 1.1. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 1 Survival.

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 1 Survival

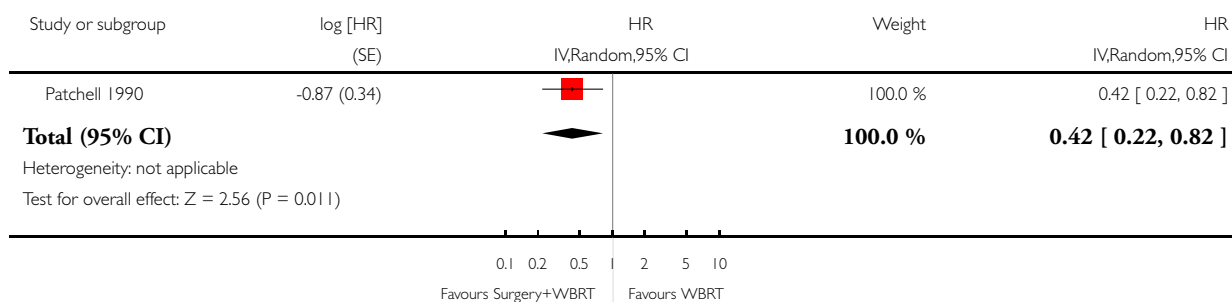


### Analysis 1.2. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 2 Functional Independent Survival.

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 2 Functional Independent Survival

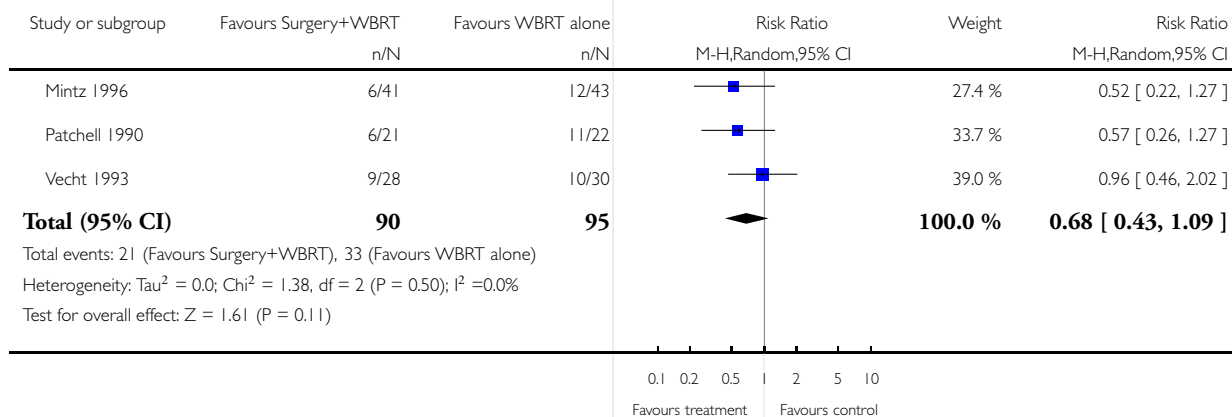


### Analysis 1.3. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 3 Neurological Death.

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 3 Neurological Death

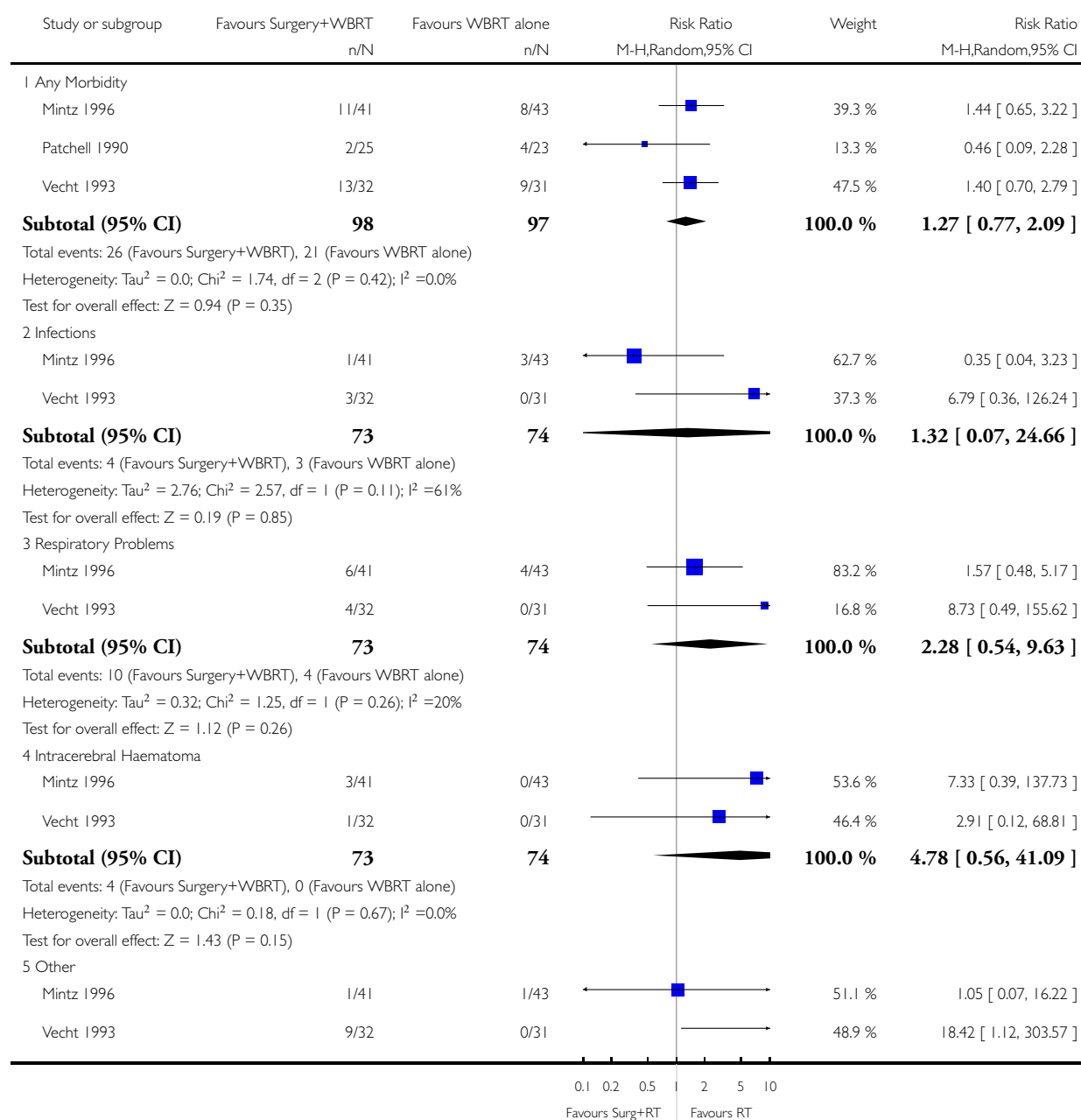


### Analysis 1.4. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 4 Adverse Effects.

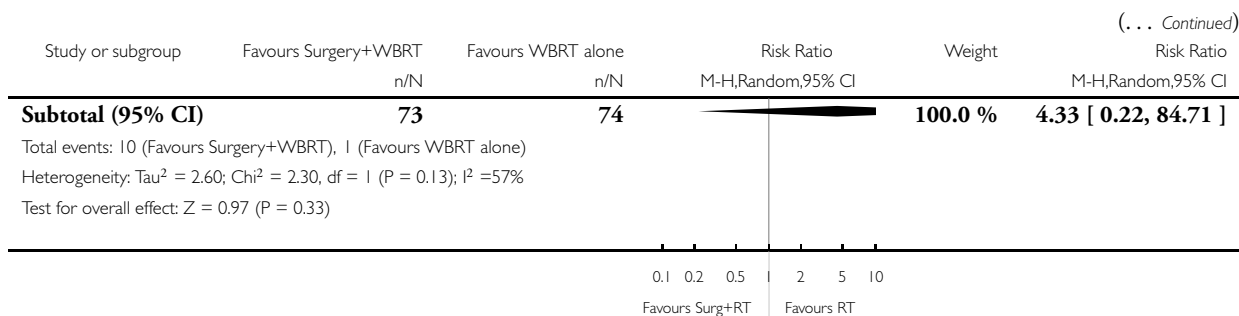
Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 4 Adverse Effects



(Continued ...)



## WHAT'S NEW

Last assessed as up-to-date: 8 October 2007.

29 April 2008	New search has been performed	Converted to new review format.
9 October 2007	New search has been performed	Searches were re-run on 10 October 2007. No additional trials were identified.

## HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2004

11 July 2004	New citation required and conclusions have changed	Substantive amendment
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## CONTRIBUTIONS OF AUTHORS

Dr Hart performed the statistical analysis, helped in the text of the review and was involved in the editing process. Dr Grant performed the literature search, analysis, helped write the text of the review, and oversaw the final draft. Dr Walker assisted in the literature search strategy was involved in discussions about the analysis and helped in the text of the review. Dr Dickinson supervised the statistical analysis, and was involved in the editing of the final draft.

## **DECLARATIONS OF INTEREST**

None known.

## **SOURCES OF SUPPORT**

### **Internal sources**

- Dr Hart was the recipient of a Cochrane Gynaecological Cancer Review Group Grant, UK.

### **External sources**

- No sources of support supplied

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Brain Neoplasms [\*radiotherapy; secondary; \*surgery]; Combined Modality Therapy; Cranial Irradiation [\*methods]; Randomized Controlled Trials as Topic

### **MeSH check words**

Humans