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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

[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 since most patients have uncontrollable systemic cancer. Historically, whole brain radiation therapy (WBRT) has been the treatment of choice, although more recently focused radiation therapy e.g. stereotactic radiosurgery (SRS) has developed a role in selected patients. 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 patients with single brain metastasis.

Search methods

The following databases were part of a systematic literature search: Cochrane Central Register of Controlled Trials (CENTRAL Issue 2, 2010), MEDLINE, EMBASE, CancerLit, Biosis and the Science Citation Index. References of identified studies were hand searched, as were the Journal of Neuro-Oncology and Neuro-Oncology, including all conference abstracts. Specialists in neuro-oncology were contacted for further information. The searches for MEDLINE and EMBASE were updated in October 2007 and December 2010.

Selection criteria

Randomised controlled trials (RCTs) comparing surgery and WBRT with WBRT alone in patients of all ages with proven or suspected single brain metastasis.

Data collection and analysis

Two review authors independently assessed the search results for relevance, undertook critical appraisal according to known guidelines and extracted data using a pre-specified pro-forma.

Main results

Three RCTs were identified enrolling 195 patients in total. No significant difference in survival was found (hazard ratio (HR) 0.72, 95% CI 0.34 to 1.55, P = 0.40) although there was heterogeneity between trials (I^2 = 83%). 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 (relative risk (RR) 0.68, 95% CI 0.43 to 1.09, P = 0.11). The risk of adverse events was not statistically proven to be different between arms although actual event numbers were higher in the surgery arm.

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 were not reported to have any higher risk of adverse events than patients who only had WBRT.

PLAIN LANGUAGE SUMMARY

Surgery and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

For patients with single brain metastasis there is good evidence from randomised controlled trials (RCTs) that surgery in addition to whole brain radiation therapy (WBRT) does not improve overall survival.Treatment of brain metastasis is usually palliative although in selected patients - particularly those with only a single metastasis to the brain - surgery could be considered. This review analysed the evidence from three RCTs, enrolling a select group of patients, and found that the combination of surgery and WBRT did not improve overall survival compared with WBRT alone. The addition of surgery may improve the length of time patients remained independent from others for support and there is a suggestion it may also reduce the risk of death due to neurological causes. Patients undergoing surgery were not reported have a 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.

BACKGROUND

Description of the condition

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 symptoms will recur (Kaal 2004). 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 two months, and for people taking steroids and undergoing WBRT it is three to six months (Cairncross 1980).

Description of the intervention

Whole brain radiation therapy (WBRT) has historically been the accepted palliative treatment of choice with potential benefits including relief of symptoms and longer survival (Barker II 2005). Patients who respond to radiation are usually less than 60 years old, have a good Karnofsky Performance Score (KPS) (greater than 70), have 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 2009).

Focal radiotherapy techniques, such as stereotactic radiosurgery (SRS), have been developed that focus higher radiotherapy doses on the metastasis but with less damage to surrounding brain than WBRT (Patil 2010). This has been proposed to provide increased local control and potentially fewer long-term cognitive side-effects (Andrews 2004).

Surgical resection involves a craniotomy and surgical excision of the lesion. It is commonly performed under general anaesthesia although can be performed 'awake' when cortical stimulation is justified to identify eloquent tissue. The lesion is removed using microsurgical techniques or macroscopically. Post-operatively the patient will recover in more intensively monitored environments initially prior to discharge. Most patients will not be suitable for surgery because of multiple lesions, a surgically inaccessible lesion location, active primary disease, or co-morbidity.

Following surgery or SRS, WBRT is usually recommended to prevent local recurrence and target any micro-metastases not detected on initial imaging; this management is based on the findings of a single RCT that found those undergoing WBRT after surgery have a reduced local recurrence rate compared with those who had surgery alone (Patchell 1998). Previosuly, symptomatic radiation induced dementia was previously believed to be rare with modern dosing schedules, with one chart-review study revealing a frequency of less than 5% (DeAngelis 1989). Recent studies have increasingly recognised the cognitive effects of WBRT, particularly with an increase in survival times, and questioned the routine use of WBRT after surgery or SRS (Aoyama 2006; Chang 2009; Roos 2006; Soffieti 2010).

How the intervention might work

Surgical resection provides its main benefits through direct removal of the targeted mass lesion. It 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 intracranial 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 an alternative origin requiring different treatment (e.g. brain abscess). The potential benefits of surgical resection must be balanced against the risks of post-operative morbidity and mortality.

Whole brain radiation therapy (WBRT) is designed to treat identified metastasis as well as prophylaxis against any 'micro-metastasis' not detected on pre-intervention imaging. Radiation therapy in general is aimed at inducing terminal damage to the DNA of neoplastic cells. It is administered on an out-patient basis for five days a week over two weeks.

Why it is important to do this review

Although there are in theory advantages to having a metastasis surgically removed there is also a definite risk involved with undergoing surgery. There are no systematic reviews or meta-analyses in this area and the choice of treatment is controversial. In order to improve patient outcomes maximise the use of resources it is necessary to have a clear description of the potential risks and benefits of surgery in treating patients with single brain metastasis.

OBJECTIVES

To assess if surgical resection followed by WBRT holds any clinical advantage over WBRT alone in the treatment of single brain metastasis.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs meeting the selection criteria (Criteria for considering studies for this review). External signs of each surgery are usually clinically obvious meaning blinding is difficult and was not an inclusion criteria. Foreign language journals were eligible for inclusion.

Types of participants

Patients with proven systemic cancer (i.e. primary site confirmed by histology) and a suspected single brain metastasis (on imaging and clinical findings) were included. Imaging had to include at least CT although ideally contrast enhanced MRI to optimise sensitivity for detecting multiple metastasis. Additional imaging modalities (e.g. positron emission tomography or magnetic resonance spectroscopy) were not mandatory. The brain metastasis did not have to be histologically proven pre-hoc (e.g. by biopsy). Patients

should have been stratified by age, performance status, primary tumour and extent of systemic disease as these are the strongest prognostic factors (Noordijk 1994). Performance status could be recorded using the KPS (Karnofsky 1948) or the World Health Organisation Score (WHO/ECOG) (WHO 1982).

Types of interventions

Surgical resection and WBRT versus WBRT alone, defined as:

- Surgical resection: all procedures where the pre-operative aim was to remove more tissue than is necessary for diagnosis. The technique normally involved general anaesthesia, craniotomy and attempted total macroscopic microsurgical resection of the lesion. All aids to achieving surgical resection - including neuro-navigation, 5-ALA/Gliloan guided resection, awake craniotomy, Sonowand and intra-operative MRI - were eligible for inclusion. Extent of resection was often graded as either total macroscopic, partial or de-bulking; all of which were eligible for inclusion. Assessment of complete resection could have been made by the surgeons operating opinion but ideally by early post-operative imaging (Hensen 2008).
- WBRT: conventional whole brain radiotherapy fractionation schedules were 3000 cGy in 10 fractions or 2000 cGy in 5 fractions. There is currently no evidence that alternative schedules or administration of radiosensitising agents improves patient outcomes (Tsao 2009).
- Stereotactic Radiosurgery (SRS): techniques such as LINAC, Gamma Knife, Cyberknife or proton beam were not eligible for inclusion in either arm of this review.
- Post-operative care: was decided by the individual attending physician on an individual patient basis in light of the absence of specific evidence based therapies at this stage.

Types of outcome measures

Primary outcomes

- Survival: was the length of time (in days, weeks or months) from randomisation to death.

Secondary outcomes

- Time to progression (TTP)/progression free survival (PFS): open and thorough criteria were used to define recurrence according to clinical symptoms, imaging or increasing steroid therapy (Wen 2010).
- Quality of Life (QoL): measured using a reliable and objective grading measure, for example the EORTC QLQC30/BN-20 and FACT-BrS (Mauer 2008).
- Functionally independent survival (FIS): time to KPS less than 70 or other grading system from randomisation.
- 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 also involved acute deterioration (from either rapid growth of the metastasis, haemorrhage, invasion of local structure or decompensation of raised intra-cerebral pressure) or more gradual tumour expansion and deterioration of neurologic function. Care was taken to try and distinguish any contribution that treatment related morbidity may have contributed.
- Symptom control: improvement of symptoms, or a prolonged maintenance of symptoms without deterioration.
- Adverse Events (AE): nature, as defined using MedDRA (Medical Dictionary for Regulatory Authorities) criteria, and timing (MedDRA 2008). Examples included: haematoma, wound complications, infection (and site), CSF leak, oedema, seizures and general medical complications. Further procedures required for complications should have been noted. Both the total number of complications and complications per patient should have been stated.
- Mortality: cause specific immediately following procedure and at 30 days

Search methods for identification of studies

The following databases were part of a systematic literature search: Cochrane Central Register of Controlled Trials (CENTRAL Issue 4, 2010), 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 for MEDLINE and EMBASE were updated in October 2007 and December 2010.

Electronic searches

The same principle was used to search each database. Firstly, the terms and phrases identifying all the randomised controlled trials (RCTs) 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 strategies are described in the Appendices.

Searching other resources

Reference searching

The references of all identified studies were searched for additional trials.

Hand searching

A hand search of the Journal of Neuro-Oncology and Neuro-oncology were 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 journals.

Personal communication

Neuro-oncology experts were contacted to see if they were aware of any published, unpublished, pending or recently commenced trials. These people included:

- Michael Brada, London, UK: Chairman of National Cancer Research Institute Brain Tumour Section.
- Martin J van den Bent, Chairman of the European Organisation for Research Trials in Cancer (EORTC) Brain Tumour Section, Netherlands

The following RCT primary authors were also contacted:

- Charles J Vecht (Utrecht, Netherlands: Chairman of the EORTC Brain Tumour Group and author of one of the already identified papers).
- Arlan H Mintz (Hamilton, Canada: author of one of the identified papers)
- Roy A Patchell (Kentucky, USA: author of one of the identified papers)

In addition for the 2010 update the following experts were contacted:

- Michael Weller (University Hospital Zurich, Switzerland),
- Wolfgang Wick (Heidelberg, Germany)
- Susan Short (University College Hospital, London)
- Roger Stupp (University of Lausanne, Switzerland).

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 (MGH & RG) 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 trial authors were contacted.

Data extraction and management

For included studies, two review authors (MGH & RG) independently abstracted data on characteristics of patients, interventions, study quality, endpoints and deviations from protocol using a pre-specified form designed to complete the information required for the table of characteristics of included studies (Table 1; Table 2). Differences were reconciled by discussion or by consultation with a third review author.

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 (HRs).

Interventions

Actual numbers of participants 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 the type were noted, and any implications discussed. Duration of follow up, and ascertainment of morbidity and neurological cause of death were also noted.

Assessment of risk of bias in included studies

Trials deemed relevant were critically appraised according to a checklist (Fowkes 1991) and the criteria reported in the NHS Centre for Reviews and Dissemination report (CRD 2009). Tables were constructed to summarise internal and external validity (Juni 2001). Trials were allocated according to risk of bias as described in the Cochrane Handbook (Higgins 2009). Critical appraisal was performed by two independent review authors (MGH & RG). Any disputes were resolved through discussion.

Measures of treatment effect

- Time to event data (survival, TTP/PFS, FIS): the log hazard ratio (logHR)and its standard error were abstracted from trial reports. If these were not reported, we digitised electronic versions of the published Kaplan-Meier survival curves using Adobe Photoshop, noted the minimum and maximum follow to up and hence estimated the logHR 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 921 (Stata 2005), which were validated using data presented in Table V of Parmar 1998.
- Continuous outcomes (QoL and symptoms): the final value and standard deviation of the outcome of interest in each treatment arm at the end of the follow-up was abstracted.
- Dichotomous outcomes (neurological death, adverse events and mortality): the number of patients in each treatment arm who experienced the outcome of interest was abstracted in order to estimate a relative risk (RR).
- For continuous and dichotomous data we abstracted the number of patients assessed at endpoint was abstracted.
- Where possible all data abstracted was that pertaining to an intention to treat (ITT) analysis.

Unit of analysis issues

If the HR and its variance were not presented we attempted to abstract the data required to estimate them (Parmar 1998).

Dealing with missing data

In the case of missing data required for the review outcomes the study authors were contacted.

Assessment of heterogeneity

Heterogeneity between studies was assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which could not be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001).

Assessment of reporting biases

We intended to construct 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 would be performed using the fixed effects models.

Data synthesis

Integration of data into RevMan 5.0.25 was performed by a single author (MGH).

- Time to event data: HRs and variance were pooled using the generic inverse variance function of RevMan 5.0.25
- Continuous outcomes: we pooled the weighted mean differences between the treatment arms at the end of the follow-up using the mean difference method if all trials have measured the outcome on the same scale or used the standardised mean difference method.
- Dichotomous outcomes: the RR for each study was calculated and then all studies were pooled

Random effects models were used for all meta-analyses (Der Simonian 1986).

Subgroup analysis and investigation of heterogeneity

- In light of the known benefits of chemotherapy in primary disease we planned to assign trials including chemotherapy to a separate subgroup analysis.
- A funnel plot of treatment effect versus prevision with the data from all studies included was proposed if sufficient studies were identified in order to investigate the likelihood of publication bias

Sensitivity analysis

Studies that included objective blinded early post-operative MRI in their assessment of extent of resection were subjected to a subsequent sensitivity analysis.

RESULTS

Description of studies

Results of the search

The original search strategy revealed 860 results out of which three RCTs were identified as meeting the inclusion criteria (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-analysis. See table of included studies and Table 2 for full details of each study.

The update on 21st December 2010 identified 176 references in MEDLINE, 376 references in EMBASE and 27 references in CENTRAL. No new studies were identified for inclusion.

Included studies

The first study by was a single institution RCT set in Kentucky, USA (Patchell 1990). It randomised 48 patients to confirmatory brain tumour biopsy followed by WBRT or surgical resection of metastasis and WBRT. Randomisation was by computer generated random numbers after stratification for prognostic factors but outcome assessors were not blinded. It included mainly young (mean age 60 years) and fit subjects (mean KPS = 90). All participants underwent pre-operative MRI whilst those in the radiotherapy arm also underwent biopsy. Outcome measures included survival, functional independence, radiographic changes in tumour size, time to recurrence and cause of death. The logHRs for survival and FIS and their standard errors, as estimated by Cox regression, were reported to us by the trial's lead statistician.

The second study was multi-centre RCT set in the Netherlands. It randomised 63 patients to surgical resection followed by WBRT versus WBRT alone (Vecht 1993). Randomisation was performed centrally by telephone in blocks after stratification for prognostic factors but outcome assessors were not blinded. The participants were mainly young (mean age 60 years) but slightly less fit (WHO score of 2 or less) than in the previous study. Only CT imaging had to be performed and biopsy was not mandatory in the radiotherapy only group. 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 (Parmar 1998).

The final study was a multi-centre RCT set in Canada. It randomised 84 patients to surgical resection followed by WBRT versus WBRT alone (Mintz 1996). Randomisation was by central telephone randomisation after stratification for prognostic factors but outcome assessors were not blinded. This patients were mainly young (median age 59 years) but entry criteria allowed less fit patients (KPS of 50 or more) than in the previous two studies. Only CT imaging was required and biopsy was only undertaken when the diagnosis was in doubt. 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 to up were assumed to be 0 and 34 months respectively. The logHR and its standard error were estimated from the published survival curves (Parmar 1998).

Excluded studies

A single RCT was identified for possible inclusion (Noordijk 1994) but on retrieval of the full article it was noted that it was a review of prognostic factors in a previously reported RCT (Vecht 1993) rather than unique data in its own right.

Risk of bias in included studies

Allocation

All studies included adequate methods of randomising patients. In the trial by Patchell (Patchell 1990), 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 (Mintz 1996), 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.

Blinding

No studies were blinded. This is likely due to the obvious clinical signs of those who underwent craniotomy which would make blinding difficult and probably unreliable. For these reasons blinding was not a strict pre-requisite for inclusion into this review but nevertheless it is a source of potential bias for all secondary outcomes but not for the primary outcome of survival.

Incomplete outcome data

Only the Mintz study provided an ITT analysis (Mintz 1996). In all studies, however, withdrawals and reasons were given for all participants.

Selective reporting

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.

Other potential sources of bias

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.

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.

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 1.55, P = 0.40). There was substantial heterogeneity between the trials (I^2 = 83%); 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%).

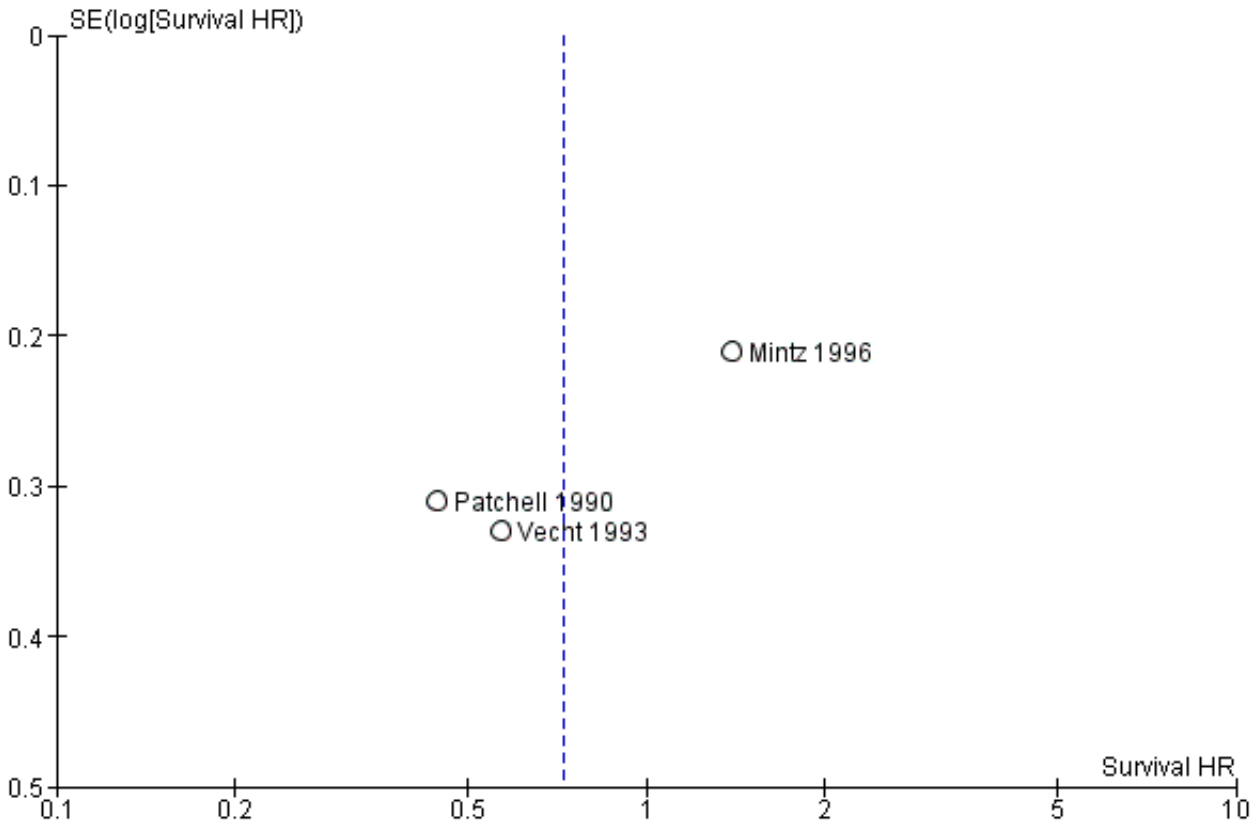
Adverse events

The reports of adverse events were difficult to interpret as more than one adverse event was reported for some patients and this was not clearly described in the included RCTs. 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. The Vecht study reported complications in the surgical arm as: respiratory problems (4), intracerebral haematoma (1), infectious disease (3) and other complications (9). These were in 13 patients and serious in 4. The Mintz study reported: infections (surgery 1 versus WBRT 1); haematoma (surgery 3 versus WBRT 0); other (surgery 7 versus WBRT 7). The reporting of adverse events was not structured with clear definitions and may have been biased by informal reporting.

A funnel plot on included studies was constructed (Figure 1).

Figure 1. Funnel plot survival



DISCUSSION

Summary of main results

Although no statistically significant difference between surgery plus WBRT and WBRT alone was found in the meta to analysis, the trials by Patchell and Vecht were in favour of surgery (Patchell 1990; Vecht 1993), while that by Mintz was in favour of WBRT alone (Mintz 1996). 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-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 neurosurgeon. This may have resulted in randomisation of only patients who were particularly suited to 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 1). 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, having in general a lower life expectancy and more active disease, would seem less likely to benefit from surgery (Mintz 1996). 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.

Overall completeness and applicability of evidence

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; FIS was examined in only one trial although KPS is known to correlate poorly with patients' own perception of QoL. The one trial did find an improvement in FIS with surgery (Patchell 1990). In addition the trial by Vecht found an improvement in FIS in patients treated by surgery who had stable extra-cranial disease (Vecht 1993), although the trial by Mintz found little difference between arms in the stable extra-cranial disease subgroup (Mintz 1996). 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 the patients' KPS 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 steroids (Macdonald 1990).

Quality of the evidence

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-randomised 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 (Vecht 1993). This opens up questions as to the standardisation of treatment during this time. The trial by Mintz found 143 capable of being randomised, although only 84 consented to trial randomisation (Mintz 1996). This demonstrates that it is possible to generate much larger numbers, but only in a large multi to institution study.

Potential biases in the review process

This review only included the results of highly selected series of patients and the findings are not necessarily applicable to a larger cohort of those with brain metastasis. It is important to note that there are many other important indications for operating on metastases, for example raised intra-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-small cell lung cancer, surgery should always be considered in the management (Patchell 1990).

Agreements and disagreements with other studies or reviews

Another systematic review and meta-analysis has been published (Mintz 2007). This review heavily cites this Cochrane review and the conclusions are appropriately concordant. Another systematic review and evidence based practice guideline has been published (Gaspar 2010). This review stated that surgical resection plus WBRT for single brain metastasis is an effective treatment based on the findings of the three known RCTs also included in this Cochrane review. Only a descriptive analysis of the RCTs was performed and the omission of a meta-analysis is a disappointing shortcoming of their review. We have shown that the correct interpretation of the three RCTs is critically dependent on the meta-analysis, which reveals that surgery does not lead to a longer survival time compared to WBRT alone, necessitating that our conclusions surpass the findings in their review. Other non-systematic review articles in the field have broadly recommended surgery for single brain metastasis based on the findings of the two selected RCTs that are in favour of surgery (Ewend 2005). This Cochrane review offers a higher level of evidence due to it's meta-analysis, thorough discussion of individual RCTs, and transparent methodology aimed at producing un-biased conclusions.

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 of patients - under close follow-up and receiving further active therapy in many cases - who are not necessarily representative of the majority of those with single brain metastasis. In this group, the surgical approach did not improve OS. Surgery may reduce the number of deaths due to neurological cause, while one trial has suggested an increase in the duration of a patients FIS. Adverse events were similar in each group whilst 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, 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-morbidity. Decisions of the most appropriate treatment for an individual patient should be made at an MDT meeting in line with NICE guidance (NICE 2006).

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 patients examined at closer intervals. Statistically, the reporting in trials of HRs and their variance would improve the accuracy in reading data from Kaplan-Meier plots. These results could 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 focal radiotherapy techniques, known as Stereotactic Radiosurgery (SRS). A meta-analysis (Stafinski 2006) and a Cochrane review (Patil 2010) of three RCTS (Andrews 2004; Chougle 2000; Kondziolka 1999) comparing SRS and WBRT versus WBRT alone both found that combination therapy improved survival in only those with single but not multiple brain metastasis. A single RCT has examined surgery and WBRT in comparison with SRS and found, after terminating prematurely, that survival and local control is comparable but distant recurrences more common with SRS alone (Muacevic 2008); another similar RCT is on-going (Roos 2008). In the future the management of single brain metastasis is likely to focus on surgery versus SRS and the role of WBRT (Aoyama 2006; Chang 2009; Roos 2006; Soffieti 2010).

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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 x 10 fractions). Surgery was aimed at macro-scopical 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).

Mintz 1996 *(Continued)*

	3. Treatment complications, for surgery (wound infection, venous thrombosis, pulmonary embolism, myocardial ischaemia and pneumonia) and for radiation (radiation necrosis).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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

Patchell 1990 *(Continued)*

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	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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 >= 18 years, histologically verified extracranial malignancy, apparent presence of single brain metastasis as documented on CT, Karnofsky <= 70 or WHO scale < 2 with neurological function <=, 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 a single parenchymal brain metastasis.
Interventions	"neurosurgical excision plus radiotherapy" vs "radiotherapy alone". Surgery was by macro-scopical excision. Radiotherapy was 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.

Vecht 1993 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	

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]*

Study	Reason for exclusion
Noordijk 1994	This is a subsequent report on the same trial as reported by Vecht 1993. The paper more specifically looks at the possible effects of age and extracranial tumour activity on magnitude of difference between the randomised groups.

DATA AND ANALYSES

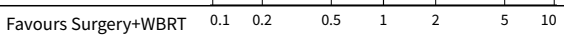
Comparison 1. Surgery + Radiotherapy vs Radiotherapy

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, 1.55]
2 Functional Independent Surival	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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
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]

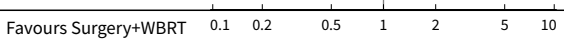
Analysis 1.1. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 1 Survival.

Study or subgroup	Surgery and WBRT N	WBRT alone N	log[Survival HR] (SE)	Survival HR IV, Random, 95% CI	Weight	Survival HR IV, Random, 95% CI
Patchell 1990	1	1	-0.8 (0.31)		32.28%	0.44[0.24,0.81]
Vecht 1993	1	1	-0.6 (0.33)		31.42%	0.57[0.3,1.08]
Mintz 1996	1	1	0.3 (0.21)		36.3%	1.39[0.92,2.1]
Total (95% CI)					**100%**	**0.72[0.34,1.55]**
Heterogeneity: Tau²=0.37; Chi²=11.52, df=2(P=0); I²=82.63%						
Test for overall effect: Z=0.83(P=0.4)						



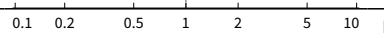
Analysis 1.2. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 2 Functional Independent Surival.

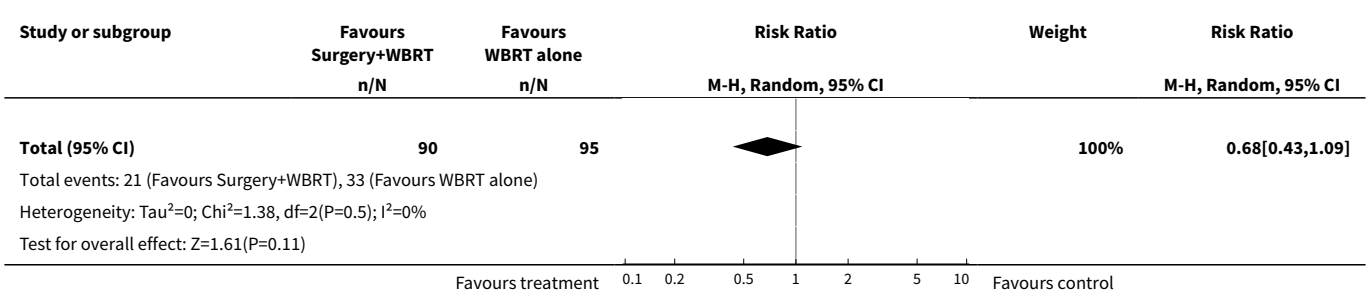
Study or subgroup	Surgery and WBRT N	WBRT alone N	log[HR] (SE)	HR IV, Random, 95% CI	Weight	HR IV, Random, 95% CI
Patchell 1990	1	1	-0.9 (0.34)		100%	0.42[0.22,0.82]
Total (95% CI)					**100%**	**0.42[0.22,0.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.56(P=0.01)						



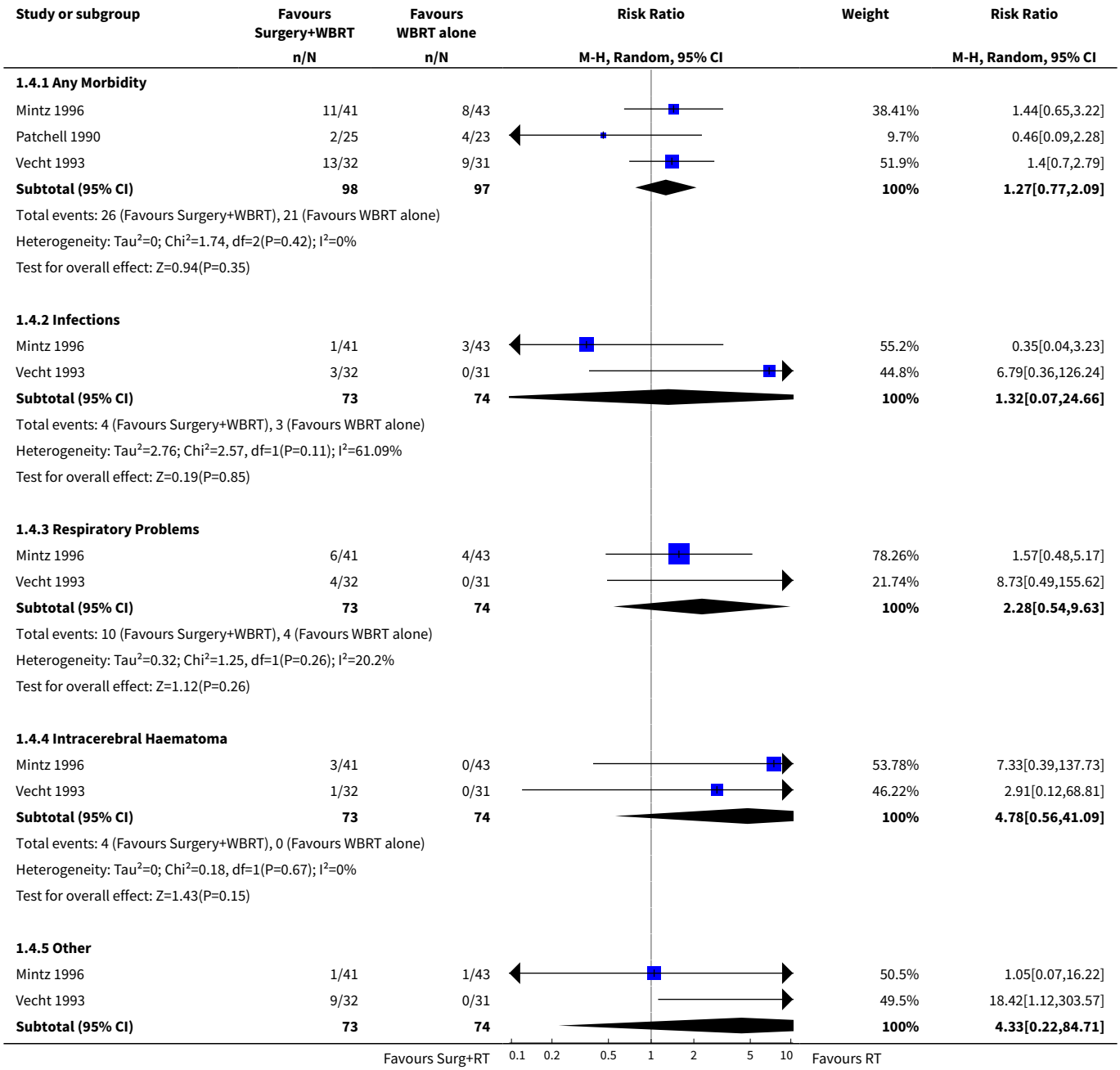
Analysis 1.3. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 3 Neurological Death.

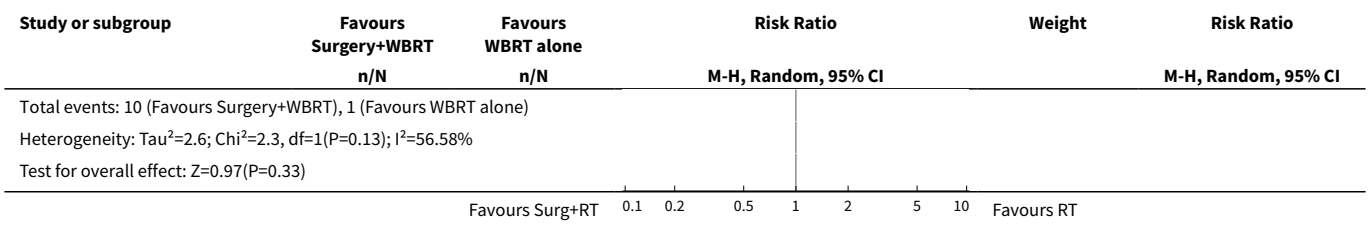
Study or subgroup	Favours Surgery+WBRT n/N	Favours WBRT alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mintz 1996	6/41	12/43		27.36%	0.52[0.22,1.27]
Patchell 1990	6/21	11/22		33.66%	0.57[0.26,1.27]
Vecht 1993	9/28	10/30		38.98%	0.96[0.46,2.02]





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





ADDITIONAL TABLES

Table 1. 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	No
Eligibility criteria stated?	Yes	Yes	Yes
Objective outcome measures?	Survival: Yes. Others: No	Survival: Yes. Others: No	Survival: Yes. Others: No
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

Table 2. External Validity

Characteristic	Patchell 1990	Vecht 1993	Mintz 1996
Age (mean and range)	Surgery: 59 (44 to 74), WBRT: 60 (49 to 74)	Surgery: 59 (30 to 75), WBRT: 60 (32 to 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 to 100), WBRT: 90 (70 to 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%

Table 2. External Validity *(Continued)*

Extent of surgery	Complete in all cases (CT day 2 to 5)	Not assessed	95% complete

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Brain Neoplasms explode all trees
#2 (brain or cerebral or intracranial or intracerebral) near/5 (metasta* or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)
#3 (#1 OR #2)
#4 MeSH descriptor Radiotherapy explode all trees
#5 Any MeSH descriptor with qualifier: RT
#6 radiotherap*
#7 radiation
#8 irradiation
#9 WBRT
#10 (#4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 MeSH descriptor Neurosurgical Procedures explode all trees
#12 Any MeSH descriptor with qualifier: SU
#13 neurosurg*
#14 surg*
#15 (#11 OR #12 OR #13 OR #14)
#16 (#3 AND #10 AND #15)
#17 (#16), from 2007 to 2010

Appendix 2. MEDLINE search strategy

1 exp Brain Neoplasms/
2 ((brain or cerebral or intracranial or intracerebral) adj5 (metasta* or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*))
3 1 or 2
4 exp Radiotherapy/
5 radiotherapy.fs.
6 radiotherap*.mp.
7 radiation.mp.
8 irradiation.mp.
9 WBRT.mp.
10 4 or 5 or 6 or 7 or 8 or 9
11 exp Neurosurgical Procedures/
12 surgery.fs.
13 neurosurg*.mp.
14 surg*.mp.
15 11 or 12 or 13 or 14
16 3 and 10 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 randomized.ab.
20 placebo.ab.
21 clinical trials as topic.sh.
22 randomly.ab.
23 trial.ti.
24 17 or 18 or 19 or 20 or 21 or 22 or 23
25 16 and 24
26 limit 25 to yr="2007 - 2010"

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

Appendix 3. EMBASE search strategy

1 exp brain tumor/
2 ((brain or cerebral or intracranial or intracerebral) adj5 (metasta* or cancer* or tumor* or tumour* or neoplas* or carcinoma* or malignan*)).mp.
3 1 or 2
4 exp radiotherapy/
5 cancer radiotherapy/
6 rt.fs.
7 radiotherap*.mp.
8 radiation.mp.
9 irradiation.mp.
10 WBRT.mp.
11 4 or 5 or 6 or 7 or 8 or 9 or 10
12 exp neurosurgery/
13 su.fs.
14 neurosurg*.mp.
15 surg*.mp.
16 12 or 13 or 14 or 15
17 3 and 11 and 16
18 crossover procedure/
19 double blind procedure/
20 randomized controlled trial/
21 single blind procedure/
22 random*.mp.
23 factorial*.mp.
24 crossover*.mp.
25 cross over*.mp.
26 cross-over*.mp.
27 placebo*.mp.
28 (doubl* adj blind*).mp.
29 (singl* adj blind*).mp.
30 assign*.mp.
31 allocat*.mp.
32 volunteer*.mp.
33 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34 17 and 33
35 limit 34 to yr="2007 - 2010"

key
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, fs=floating subheading

Appendix 4. Biosis previews search strategy

Words or phrases in the Title, Subjects or Abstract were searched.
1. randomi?ed & control* & trial
2. control* & clinical & trial
3. random* & allocat*
4. double & (blind* , mask*)
5. single & (blind* , mask*)
6. clinical & trial
7. control & group
8. control* & trial
9. clinical & study
10. control* & study
11. OR/1-10
12. brain & tumo*r
13. brain & neoplasm
14. brain & cancer
15. metastas?s
16. secondar*
17. tumor [Major Concept]

18. OR/12-17
19. neurosurg*
20. combined & modality & therapy
21. stereota* & biopsy
22. biopsy & resection
23. surg* & treatment
24. OR/19-23
25. radiation therap
26. radiotherapy
27. irradiation
28. OR/25-27
29. 24 AND 28
30. 18 AND 29
31. 11 AND 30

Appendix 5. Science Citation Index search strategy

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 & nervous & system & tumo*" and "central & nervous & neoplasm" were two additional searches
(3) "extent & resection" was used in place of "extent of resection"

WHAT'S NEW

Date	Event	Description
17 July 2018	Amended	Next stage expected date amended.
24 May 2018	Review declared as stable	This review is currently not a priority topic area.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 4, 2004

Date	Event	Description
29 December 2010	New search has been performed	Search strategies amended and updated. Text reviewed but conclusions unchanged. No new RCTs included.
9 October 2007	New search has been performed	Searches were re-run on 10 October 2007. No additional trials were identified.
11 July 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- MGH performed the statistical analysis, helped in the text of the review and was involved in the editing process.
- RG 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.
- HD supervised the statistical analysis, and was involved in the editing of the final draft.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

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

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Nil.

NOTES

Nil.

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