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External beam radiation dose escalation for high grade glioma (Review)

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[Intervention Review]

External beam radiation dose escalation for high grade glioma

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ABSTRACT

Background

This is an updated version of the original Cochrane Review published in Issue 8, 2016.

High grade glioma (HGG) is a rapidly growing brain tumour in the supporting cells of the nervous system, with several subtypes such as glioblastoma (grade IV astrocytoma), anaplastic (grade III) astrocytoma and anaplastic (grade III) oligodendroglioma. Studies have investigated the best strategy to give radiation to people with HGG. Conventional fractionated radiotherapy involves giving a daily radiation dose (called a fraction) of 180 cGy to 200 cGy. Hypofractionated radiotherapy uses higher daily doses, which reduces the overall number of fractions and treatment time. Hyperfractionated radiotherapy which uses a lower daily dose with a greater number of fractions and multiple fractions per day to deliver a total dose at least equivalent to external beam daily conventionally fractionated radiotherapy in the same time frame. The aim is to reduce the potential for late toxicity. Accelerated radiotherapy (dose escalation) refers to the delivery of multiple fractions per day using daily doses of radiation consistent with external beam daily conventionally fractionated radiotherapy doses. The aim is to reduce the overall treatment time; typically, two or three fractions per day may be delivered with a six to eight hour gap between fractions.

Objectives

To assess the effects of postoperative external beam radiation dose escalation in adults with HGG.

Search methods

We searched CENTRAL, MEDLINE Ovid and Embase Ovid to August 2019 for relevant randomised phase III trials.

Selection criteria

We included adults with a pathological diagnosis of HGG randomised to the following external beam radiation regimens: daily conventionally fractionated radiotherapy versus no radiotherapy; hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy; hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy or accelerated radiotherapy versus daily conventionally fractionated radiotherapy.

Data collection and analysis

The primary outcomes were overall survival and adverse effects. The secondary outcomes were progression free survival and quality of life. We used the standard methodological procedures expected by Cochrane. We assessed the certainty of the evidence using the GRADE approach.

Main results

Since the last version of this review, we identified no new relevant trials for inclusion. We included 11 randomised controlled trials (RCTs) with 2062 participants and 1537 in the relevant arms for this review. There was an overall survival benefit for people with HGG receiving postoperative radiotherapy compared to the participants receiving postoperative supportive care. For the four pooled RCTs (397 participants), the overall hazard ratio (HR) for survival was 2.01 favouring postoperative radiotherapy (95% confidence interval (CI) 1.58 to 2.55; P < 0.00001; moderate-certainty evidence). Although these trials may not have completely reported adverse effects, they did not note any significant toxicity attributable to radiation. Progression free survival and quality of life could not be pooled due to lack of data.

Overall survival was similar between hypofractionated and conventional radiotherapy in five trials (943 participants), where the HR was 0.95 (95% CI 0.78 to 1.17; P = 0.63; very low-certainty evidence. The trials reported that hypofractionated and conventional radiotherapy were well tolerated with mild acute adverse effects. These trials only reported one participant in the hypofractionated arm developing symptomatic radiation necrosis that required surgery. Progression free survival and quality of life could not be pooled due to the lack of data.

Overall survival was similar between hypofractionated and conventional radiotherapy in the subset of two trials (293 participants) which included participants aged 60 years and older with glioblastoma. For this category, the HR was 1.16 (95% CI 0.92 to 1.46; P = 0.21; high-certainty evidence).

There were two trials which compared hyperfractionated radiotherapy versus conventional radiation and one trial which compared accelerated radiotherapy versus conventional radiation. However, the results could not be pooled.

The conventionally fractionated radiotherapy regimens were 4500 cGy to 6000 cGy given in 180 cGy to 200 cGy daily fractions, over five to six weeks.

All trials generally included participants with World Health Organization (WHO) performance status from 0 to 2 and Karnofsky performance status of 50 and higher.

The risk of selection bias was generally low among these RCTs. The number of participants lost to follow-up for the outcome of overall survival was low. Attrition, performance, detection and reporting bias for the outcome of overall survival was low. There was unclear attrition, performance, detection and reporting bias relating to the outcomes of adverse effects, progression free survival and quality of life.

Authors' conclusions

Postoperative conventional daily radiotherapy probably improves survival for adults with good performance status and HGG compared to no postoperative radiotherapy.

Hypofractionated radiotherapy has similar efficacy for survival compared to conventional radiotherapy, particularly for individuals aged 60 years and older with glioblastoma.

There are insufficient data regarding hyperfractionation versus conventionally fractionated radiation (without chemotherapy) and for accelerated radiation versus conventionally fractionated radiation (without chemotherapy).

There are HGG subsets who have poor prognosis even with treatment (e.g. glioblastoma histology, older age and poor performance status). These HGG individuals with poor prognosis have generally been excluded from randomised trials based on poor performance status. No randomised trial has compared comfort measures or best supportive care with an active intervention using radiotherapy or chemotherapy in these people with poor prognosis.

Since the last version of this review, we found no new relevant studies. The search identified three new trials, but all were excluded as none had a conventionally fractionated radiotherapy arm.

PLAIN LANGUAGE SUMMARY

Radiation dose escalation for malignant glioma

Background

This is an updated version of the original Cochrane Review published in Issue 8, 2016. High grade glioma (HGG) is a rapidly growing brain tumour (cancer) in the supporting cells of the nervous system, with several subtypes such as glioblastoma (grade IV astrocytoma), anaplastic (grade III) astrocytoma and anaplastic (grade III) oligodendroglioma. It affects about 5 in 100,000 people per year in Europe and North America. A number of studies have investigated the best strategy to give radiation to people with HGG, this review looks at these studies to see what they found. Due to toxicity, radiation is not given all in one day. In order to balance toxicity and tumour control, smaller doses of radiation are given over several days.

Conventional radiotherapy involves giving daily radiation dose (called a fraction) of 180 cGy to 200 cGy per day. Hypofractionated radiotherapy refers to the use of a higher daily dose of radiation (greater than 200 cGy per day) which typically reduces the overall number of fractions and the overall treatment time.

Hyperfractionated radiotherapy refers to the use of a lower daily dose of radiation (less than 180 cGy per day), a greater number of fractions and multiple fractions delivered per day to deliver a total dose at least equivalent to external beam daily conventionally fractionated radiotherapy (beam of radiation directed from outside the body), in the same time frame. The aim with this approach is to reduce the potential for late toxicity, which is a side affect occurring more than 3 month after treatment is completed.

Accelerated radiotherapy (dose escalation) refers to the delivery of multiple fractions per day using daily doses of radiation consistent with external beam daily conventionally fractionated radiotherapy doses. The aim is to reduce the overall treatment time; typically, two or three fractions per day may be delivered with a six to eight hour gap between fractions.

The aim of the review
To examine the effectiveness and safety of external beam radiation dose escalation (higher radiation doses) in people newly diagnosed with HGG.

What are the main findings?
We found 11 trials (1537 participants in the relevant treatment groups for this review). People with a poor prognosis (likelihood of recovery) generally were not eligible for entry into the clinical trials based on their poor level of health. There was an overall survival benefit for people with HGG receiving postoperative (after surgery to remove some or all of the tumour) conventional radiotherapy compared to the participants receiving supportive care after surgery. Hypofractionated radiotherapy has similar effectiveness for survival as compared to conventional radiotherapy, particularly for people aged 60 years and older with glioblastoma. There were no clear differences in side effects between these different treatment groups. There was insufficient data regarding other outcomes, namely progression free survival (survival without the cancer getting worse) and quality of life between these different treatment groups.

There are insufficient data regarding the outcomes of survival, side effects, progression free survival and quality of life for hyperfractionation versus conventionally fractionated radiation and for accelerated radiation versus conventionally fractionated radiation.

Certainty**of the evidence**
The certainty of the evidence ranged from very low to high. Some of the trials were at a higher risk of bias due to missing details regarding how they divided participants into treatment groups, how many patients were lost to follow-up (after care) and possible selective reporting of outcomes such as side effects.

Only five of the 11 included trials were published after the year 2000. Most trials included in the analysis were published before 2000 and are now considered out of date. These older trials did not distinguish between the various subtypes of HGG, and they used outdated radiotherapy techniques such as whole brain radiotherapy rather than local radiotherapy (targeted only to the tumour and not the whole brain).

What are the conclusions?
Postoperative conventional daily radiotherapy improves survival for adults with good functional well-being and HGG compared to no postoperative radiotherapy. Hypofractionated radiotherapy has similar efficacy for survival compared to conventional radiotherapy, particularly for people aged 60 years and older with glioblastoma. Since the last version of this review in 2016, we found no new relevant studies for inclusion.

Summary of findings 1. Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone) for high grade glioma

Daily conventionally fractionated radiotherapy vs no radiotherapy (supportive care alone) for high grade glioma

Patient or population: people with high grade glioma
Settings: postoperative setting
Intervention: radiation vs no radiation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No radiation	Radiation				
Overall survival	**Study population**		**HR 2.01** (1.58 to 2.55)	397 (4 studies)	⊕⊕⊕⊖ **Moderate** [a,b,c]	—
	1000 per 1000	**1000 per 1000** (1000 to 1000)				
	High risk population					
	1000 per 1000	**1000 per 1000** (1000 to 1000)				
Adverse effects	—	—	Not estimable	289 (3 studies)	—	Could not be pooled
Progression free survival	—	—	Not estimable	81 (1 study)	—	—
Quality of life	—	—	Not estimable	81 (1 study)	—	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-certainty: we are very uncertain about the estimate.

[a]The Andersen 1978 trial did not truly conceal the randomisation process as allocation was based on dates of birth. Attrition was not completely described in all the trials. Downgraded one level based on risk of bias.
[b]The trials used outdated radiotherapy techniques such as whole brain radiotherapy and did not use magnetic resonance imaging to define the intracranial tumour extent. Downgraded one level based on indirectness.
[c]All trials showed a benefit with the use of postoperative radiation as compared to no radiation. The effect size was large with an HR 2.0 (95% CI 1.58 to 2.55) and a significant P value (P < 0.00001). Upgraded one level.

Summary of findings 2. Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy for high grade glioma

Hypofractionated radiotherapy vs daily conventionally fractionated radiotherapy for high grade glioma

Patient or population: people with high grade glioma
Settings:
Intervention: hypofractionated radiation vs conventional radiation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional radiation	Hypofractionated radiation				
Overall survival	**Study population**		**HR 0.95** (0.78 to 1.17)	943 (5 studies)	⊕⊝⊝⊝ **Very low** [a,b]	—
	1000 per 1000	**1000 per 1000** (1000 to 1000)				
	High risk population					
	1000 per 1000	**1000 per 1000** (1000 to 1000)				
Adverse effects	Could not be pooled	Could not be pooled	Not estimable	848 (4 studies)	—	—
Progression free survival	Not reported	Not reported	Not estimable	0 (0)	—	—
Quality of life	Could not be pooled	Could not be pooled	Not estimable	361 (3 studies)	—	—

Overall survival for subgroup aged ≥ 60 years glioblastoma	**Study population**		**HR 1.16** (0.92 to 1.46)	293 (2 studies)	⊕⊕⊕⊕ **High**	—
	1000 per 1000	**1000 per 1000** (1000 to 1000)				
	High risk population					
	1000 per 1000	**1000 per 1000** (1000 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High-certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty**:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: we are very uncertain about the estimate.

[a]Attrition was incompletely described in all the trials except for Roa 2004 and Malmstrom 2012. Phillips 2003 had high risk of bias as the study was closed early due to poor accrual. The publication only included 68 participants. The authors did not comment on the planned sample size. Downgraded two levels for very serious risk of bias.
[b]Only two trials examined people with glioblastoma aged ≥ 60 years (Malmstrom 2012; Roa 2004). The other older trials did not separate the results for grades 3 and 4 glioma neither was molecular subtype analysis available for the older outdated trials. Downgraded one level (serious) for indirectness.

BACKGROUND

This is an updated version of the original Cochrane Review published in Issue 8, 2016. Based on histopathological features, in 2007 World Health Organization (WHO) categorised gliomas from grade I (lowest grade) to grade IV (highest grade). High grade glioma (HGG) is defined as WHO grades III and IV. The incidence of HGG is approximately 5 per 100,000 person-years in Europe and North America (Narayanan 2014). Gliomas account for almost 80% of primary brain tumours (Schwartzbaum 2006), and WHO grade IV glioblastoma is the most common type. Other types of malignant glioma are anaplastic astrocytoma, anaplastic oligodendroglioma and mixed anaplastic oligoastrocytoma (all WHO grade III).

The median overall survival for glioblastoma is just over one year (DeAngelis 2001; Stupp 2005). Numerous randomised studies have shown an overall survival benefit, favouring postoperative radiation compared to supportive care or single agent chemotherapy (Andersen 1978; Kristiansen 1981; Sandberg-Wollheim 1991). A Medical Research Council (MRC) study comparing radiation doses of 6000 centiGray (cGy) in 30 daily fractions to 4500 cGy in 20 daily fractions showed a small benefit favouring the higher dose (Bleehen 1991).

For most adults with HGG, specifically WHO grade IV, standard treatment involves maximal safe resection followed by radiation and chemotherapy (Stupp 2005). Although research has shown overall survival improving with temozolomide chemotherapy administered concurrently with radiation and postradiation for six months, the pattern of recurrence did not change (Oh 2011). The majority of recurrent HGG grows within 2 cm of the initially treated tumour target. With prolonged overall survival, there has been renewed interest in dose escalation as a way to improve local control, with the intent to further improve overall survival. However, radiation dose escalation is limited by radiation toxicity (Reddy 2013; Sminia 2012). The use of radiation to the brain has acute adverse effects such as fatigue, hair loss, increased intracranial pressure and possible late toxicity such as permanent radiation damage causing neurological symptoms, known as radiation brain necrosis.

The optimal postoperative radiation dose and fractionation regimen has been the subject of research for decades, with several randomised controlled trials (RCTs) focusing on radiotherapy practice. With modernisation of radiotherapy delivery, there have been studies on hypofractionated (Bauman 1994), hyperfractionated (Shin 1983), and accelerated radiation regimens (Brada 1999; see Description of the intervention).

The aim of hypofractionated radiation is to shorten overall treatment time, reducing the number of radiation treatment visits and hence radiation machine time and patient inconvenience. The aim of hyperfractionation is to potentially reduce late radiation toxicity by reducing the dose per fraction while still maintaining the intended tumour treatment dose. The aim of accelerated radiation is to reduce the overall treatment time by administering multiple radiation treatments per day. This regimen impedes the repopulation of rapidly growing tumour cells and theoretically improves tumour control. The focus of this Cochrane systematic review is to examine the benefits and harms of external beam radiation dose escalation for HGG.

We have excluded the topic of concurrent chemotherapy plus standard or dose escalated radiation versus radiation alone for HGG, as another Cochrane Review has examined this topic (Stewart 2002). We have also excluded radiosurgery and brachytherapy boost trials, as the focus of this review was exclusively external beam radiotherapy.

Description of the condition

The 2007 WHO grading system has four categories (Louis 2007).

- Grade I: slow growing, non-malignant tumours associated with long term overall survival.
- Grade II: relatively slow growing tumours that sometimes recur as higher grade tumours.
- Grade III: malignant tumours that often recur as higher grade tumours.
- Grade IV: rapidly growing, very aggressive malignant tumours.

This Cochrane Review studied participants with WHO grade III and IV gliomas. Specific histologies for grade III glioma are: anaplastic astrocytoma, anaplastic oligodendroglioma and mixed anaplastic oligoastrocytoma. Grade IV gliomas are glioblastoma.

Description of the intervention

Initial treatment for adults with malignant glioma is surgical with the intent to perform a maximal safe resection. This allows pathological confirmation of the radiographic diagnosis, improving local control and overall survival (Carapella 2011). In situations where resection is not safe, biopsy alone is considered to obtain pathology.

Following surgery, radiation and usually chemotherapy are standard treatments. For most people with glioblastoma, the approach is to treat with 6000 cGy of external beam radiation delivered in 200 cGy fractions per day (Monday to Friday excluding weekends) over six weeks with concurrent and adjuvant chemotherapy using temozolomide (Stupp 2005). However, for people with very poor prognosis HGG (e.g. older people with poor performance status and a diagnosis of glioblastoma), comfort measures without active intervention may be considered. People over the age of 65 years with glioblastoma may also be treated with chemotherapy alone or radiation using a shorter course (Arvold 2014; Malmstrom 2012; Roa 2004; Wick 2012).

Definitions of external beam radiation treatment regimens

Daily conventionally fractionated radiotherapy refers to the delivery of 180 cGy to 200 cGy per day.

Hypofractionated radiotherapy refers to the use of a higher daily dose of radiation (greater than 200 cGy per day) which typically reduces the overall number of fractions and therefore the overall treatment time.

Hyperfractionated radiotherapy refers to the use of a lower daily dose of radiation (less than 180 cGy per day), a greater number of fractions and multiple fractions delivered per day in order to deliver a total dose at least equivalent to external beam daily conventionally fractionated radiotherapy in the same time frame. The aim with this approach is to reduce the potential for late toxicity.

Accelerated radiotherapy refers to the delivery of multiple fractions per day using daily doses of radiation consistent with external beam daily conventionally fractionated radiotherapy doses. The aim is to reduce the overall treatment time; typically, two or three fractions per day may be delivered with a six to eight hour gap between fractions.

This systematic review focuses on external beam radiation dose escalation trials in people with HGG, and we have considered the following comparisons.

- Daily conventionally fractionated radiotherapy versus no radiotherapy.
- Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy.
- Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy.
- Accelerated radiotherapy versus daily conventionally fractionated radiotherapy.

How the intervention might work

The aim of postoperative radiation is to treat residual tumour cells within the surgical bed and those known to infiltrate beyond the surgical site, which typically lie 1.5 cm beyond the tumour bed/residual disease. The therapeutic intent is to improve local control and overall survival.

Why it is important to do this review

There has been no published Cochrane Review on this clinical question and no consensus as to optimal external beam radiation dose prescription. Furthermore, there are questions as to the appropriate radiation scheme specific to age, with some studies indicating an overall survival detriment with higher doses (Malmstrom 2012). There continues to be variability in practice (Ghose 2010), thus necessitating a high quality systematic review to guide practice.

The last two meta-analyses published did not appear in the Cochrane Library (Fine 1993; Laperriere 2002), and are now considered out of date. Therefore, a meta-analysis focused on radiation dose and delivery could provide evidence to support current practice and potentially guide future trials in the era of concurrent chemoradiotherapy.

OBJECTIVES

To assess the effects of postoperative external beam radiation dose escalation in adults with HGG.

METHODS

Criteria for considering studies for this review

Types of studies

Phase III randomised controlled trials (RCTs). Blinding was not possible due to the nature of radiation delivery and thus was not a criterion for eligibility.

Types of participants

- Adults (18 years of age and older).
- Pathological diagnosis of HGG (glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma).

Types of interventions

All external beam radiotherapy regimens.

- Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone).
- Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy.
- Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy.
- Accelerated radiotherapy versus daily conventionally fractionated radiotherapy.

Types of outcome measures

Primary outcomes

- Overall survival (survival time in months from randomisation to death from any cause).
- Adverse effects (a qualitative description of adverse effects was provided when adverse effects could not be pooled quantitatively).

Secondary outcomes

- Progression free survival in months from randomisation to disease progression or death.
- Quality of life using validated quality of life measurements (a qualitative description of quality of life was provided when quality of life could not be pooled quantitatively).

Search methods for identification of studies

Electronic searches

For the original review in 2015, we searched the following electronic databases for studies.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9) in the Cochrane Library (Appendix 1);
- MEDLINE (1977 to October 2015) (Appendix 2);
- Embase (1980 to October 2015) (Appendix 3).

For the update, we searched:

- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 8) in the Cochrane Library (Appendix 1);
- MEDLINE via Ovid (October 2015 to August week 3 2019) (Appendix 2);
- Embase via Ovid (October 2015 to 2019 week 34) (Appendix 3).

We identified all relevant articles on PubMed and used the 'related articles' feature to perform further searches for newly published articles.

Searching other resources

Unpublished and grey literature

We searched the following databases for ongoing trials.

- MetaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/rct).
- National Cancer Institute Physicians Data Query (PDQ) (www.cancer.gov/cancertopics/pdq).
- National Cancer Institute database (www.cancer.gov/clinicaltrials).

Handsearching

We handsearched the citation lists of included studies, key textbooks and previous systematic reviews. We handsearched the reports of conferences in the following sources.

- American Society for Therapeutic Radiation Oncology.
- Canadian Association of Radiation Oncology.
- European Society for Radiotherapy and Oncology.
- Society of Neuro-Oncology.
- European Association of Neuro-Oncology (EANO).
- British Neuro-Oncology Society (BNOS).

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching into EndNote (endnote.com/), and removed duplicates. Two review authors (LK, MT) independently examined the remaining references. We excluded studies that clearly did not meet the inclusion criteria, and we obtained copies of the full text of potentially relevant references. Two review authors (LK, MT) independently assessed the eligibility of retrieved studies. We resolved any disagreement by discussion between the two review authors, involving a third review author (AS) if necessary. We documented the reasons for exclusion.

Data extraction and management

For included studies, we extracted the following data.

- Author, year of publication and journal citation.
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design (RCTs).
- Study population:
  - total number enrolled;
  - participant characteristics;
  - age (median and mean);
  - comorbidities;
  - baseline performance status;
  - tumour grade;
  - surgical extent.
- Intervention/comparator:
  - daily conventionally fractionated radiotherapy versus no radiotherapy;
  - hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy;
  - hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy;
  - accelerated radiotherapy versus daily conventionally fractionated radiotherapy.
- Risk of bias in study (Assessment of risk of bias in included studies).
- Duration of follow-up.
- Outcomes (for each outcome, we extracted the outcome definition and unit of measurement).
- Results (we extracted the number of participants allocated to each intervention group, the total number analysed for each outcome and the missing participants).

We extracted results as follows.

- For time-to-event data (survival), we extracted the log of the hazard ratio (log(HR)) and its standard error from trial reports. If studies did not report these, we attempted to estimate the log(HR) and its standard error using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events or deaths), if it was not possible to use HRs we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- If reported, we extracted both unadjusted and adjusted statistics.
- Where possible, we extracted all data relevant to an intention to treat analysis, analysing participants in the groups to which they were assigned.
- We noted the time points at which trials collected and reported outcomes.

Two review authors (LK, MT) independently performed data extraction using a data abstraction form specially designed for the review. We resolved differences between authors by discussion, involving a third review author (AS) if necessary.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies using the Cochrane tool for assessing risk of bias (Higgins 2011). Specifically, we evaluated the following domains (Appendix 4).

- Selection bias: random sequence generation and allocation concealment.
- Performance bias: blinding of participants and personnel was not possible due to the nature of radiation delivery.
- Detection bias: blinding of outcome assessment was not possible as the outcome assessors were not blinded to the intervention that the participant received.
- Attrition bias: incomplete outcome data.
- Reporting bias: selective reporting of outcomes.
- Other possible sources of bias.

Two review authors (LK, MT) independently applied the 'Risk of bias' tool, resolving differences by discussion or by appeal to a third review author (AS). We summarised results in both a 'Risk of bias' graph (Figure 1) and a 'Risk of bias' summary (Figure 2) (Higgins 2011). We interpreted results of our meta-analyses in light of the findings with respect to risk of bias.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

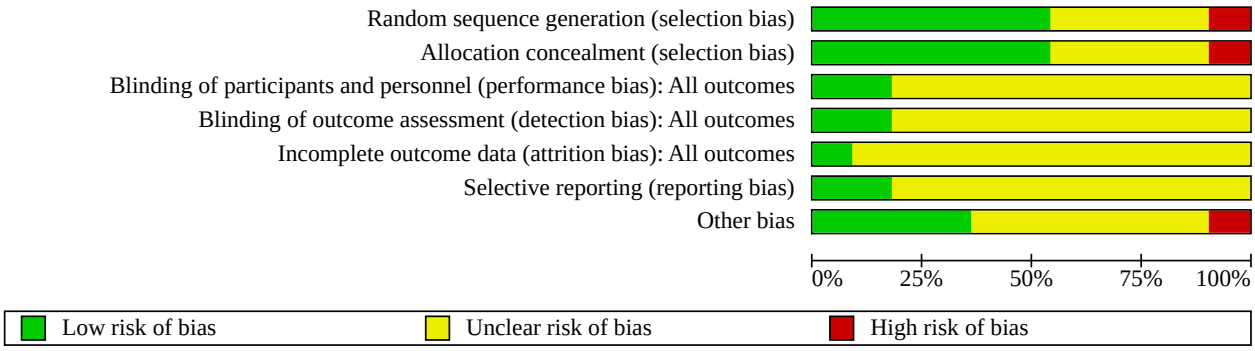
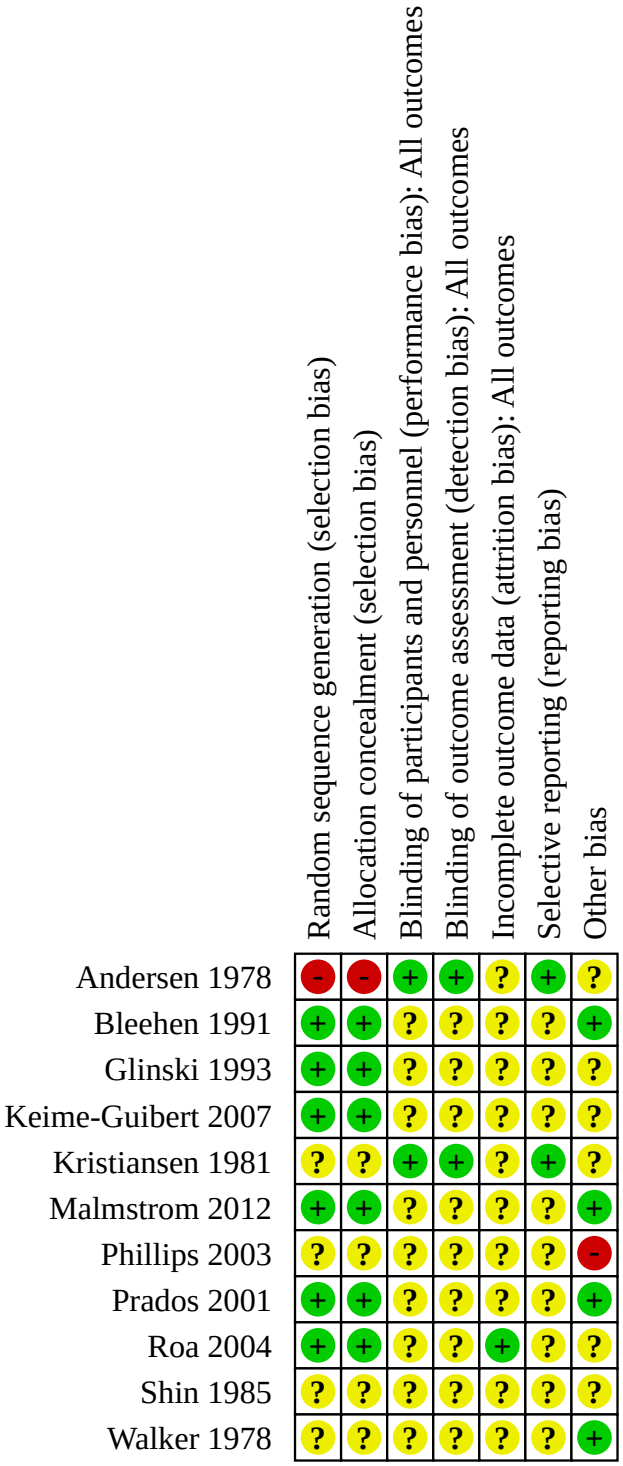


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We used the following measures of treatment effect.

- For time-to-event data, we used HR and 95% confidence intervals (CI).
- For dichotomous outcomes, we used RR and 95% CIs.
- For continuous outcomes, we used mean difference (MD) where studies used the same scale or standardised mean difference (SMD) where studies used different scales, both with 95% CIs.

Unit of analysis issues

We did not include cluster-randomised trials or trials in which participants received more than one intervention. Furthermore, we did not consider multiple observations for the same outcome to be applicable.

Dealing with missing data

We did not impute missing outcome data for the primary outcomes. If data were missing or if only imputed data were reported, we contacted trial authors to request data on the outcomes only in participants who were assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots and by estimating the percentage of heterogeneity between trials that could not be ascribed to sampling variation, using a formal statistical test of the significance of the heterogeneity (Deeks 2001; Higgins 2003). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Assessment of reporting biases

We examined funnel plots corresponding to meta-analysis to assess the potential for small study effects such as publication bias, if we identified a sufficient number of studies (i.e. more than 10).

Data synthesis

For clinically similar studies, we pooled results in meta-analyses using the Cochrane statistical software, Review Manager 5 (Review Manager 2014). We used the random-effects model for analyses.

For time-to-event data, we pooled HRs using the generic inverse variance method in Review Manager 5 (Review Manager 2014).

Certainty of evidence

We presented the overall certainty of the evidence for each outcome according to the GRADE approach, which takes into account issues not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Langendam 2013). We created 'Summary of findings' tables based on the methods described the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the GRADE checklist and GRADE Working Group quality of evidence definitions (Meader 2014).

- **High-certainty:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate-certainty:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low-certainty:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low-certainty:** we are very uncertain about the estimate.

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis of results, where possible for people with HGG aged 60 years and older, 65 years of age and older, and 70 years of age and older.

Sensitivity analysis

We performed sensitivity analyses by excluding studies at high risk of bias.

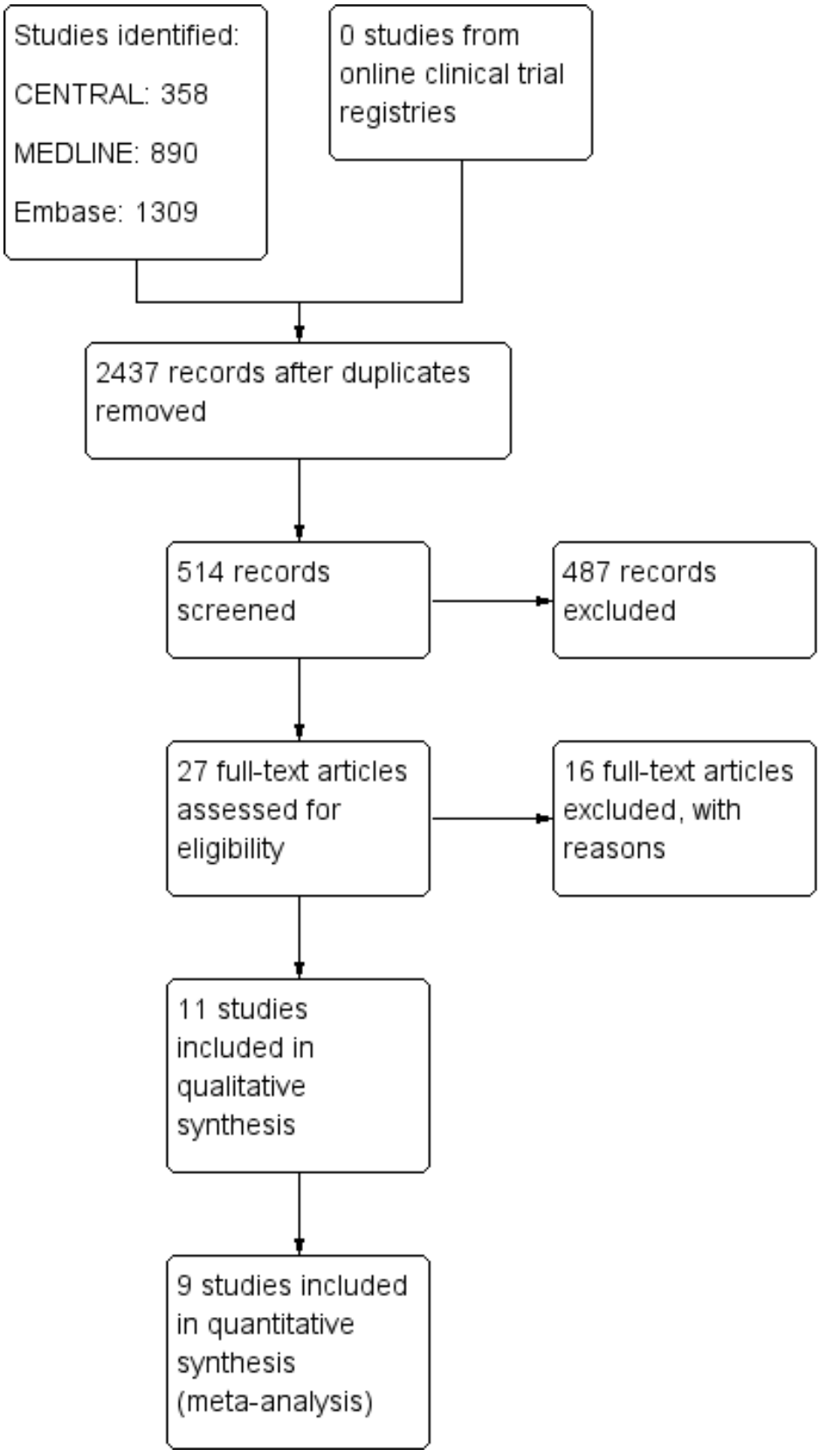
RESULTS

Description of studies

Results of the search

Our searches from 2016 and 2019 yielded 358 records from CENTRAL, 890 records from MEDLINE and 1309 records from Embase. After deduplication and abstract screening, we retained 27 studies for full text screening and possible inclusion. We excluded studies that were not randomised trials and studies that did not involve the interventions of interest, which left 11 trials. Searches of online clinical trial registries identified no additional trials. Figure 3 shows the PRISMA flow diagram of study selection.

Figure 3. Study flow diagram.



Included studies

We identified 11 studies for inclusion from full text screening (see Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification tables).

- Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone): four trials (397 participants in the meta-analysis).
- Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy: five trials (944 participants in the meta-analysis).
- Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy: one trial (81 participants).
- Accelerated radiotherapy versus daily conventionally fractionated radiotherapy: one trial (115 participants).

Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone)

Four RCTs assessed postoperative external beam radiotherapy versus no postoperative external beam radiotherapy (Andersen 1978; Kristiansen 1981; Walker 1978; Keime-Guibert 2007).

- Andersen 1978 included 108 adults with glioblastoma. Participants born on even dates did not receive postoperative radiotherapy, and those born on odd dates received postoperative radiotherapy. The postoperative radiation dose was 4500 cGy to whole brain, given over 4.5 to 5.0 weeks. Fifty-one participants were treated with radiation alone and 57 participants had no radiation and no chemotherapy.
- Keime-Guibert 2007 randomised 81 participants aged 70 years and over with newly diagnosed anaplastic astrocytoma or glioblastoma to:
  * arm 1: supportive care alone (42 participants);
  * arm 2: radiotherapy alone consisting of 5000 cGy given in daily fractions of 180 cGy (39 participants).
- Kristiansen 1981 was a prospective RCT that randomised 118 participants with grade III or IV astrocytoma to one of three arms:
  * arm 1: 4500 cGy postoperative radiotherapy given daily in 180 cGy daily fractions to whole brain and bleomycin (excluded from the meta-analysis).
  * arm 2: 4500 cGy postoperative radiotherapy given daily in 180 cGy daily fractions to whole brain and placebo (35 participants).
  * arm 3: no postoperative radiation or chemotherapy (38 participants).
- Walker 1978 accrued 303 participants with grade III or IV astrocytoma from 1 September 1969 to 1 October 1972. The radiotherapy dose was 5000 cGy to 6000 cGy given daily over six to seven weeks to the whole brain. The trial had the following four arms:
  * arm 1: supportive care alone (42 participants);
  * arm 2: carmustine chemotherapy alone (excluded from the meta-analysis);
  * arm 3: radiotherapy alone (93 participants);
  * arm 4: carmustine and radiotherapy (excluded from the meta-analysis).

Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy

Five included trials randomised participants to hypofractionated radiotherapy or conventionally fractionated radiotherapy (Bleehen 1991; Glinski 1993; Malmstrom 2012; Phillips 2003; Roa 2004).

- Bleehen 1991 randomised 474 participants with malignant grade III or IV astrocytoma to 4500 cGy in 20 daily fractions (hypofractionated regimen) versus 6000 cGy in 30 daily fractions (conventional fractionation). The hypofractionated arm was given to a volume that encompassed all known and potential tumour. The conventional radiotherapy arm was given such that the initial 4000 cGy was given to a volume similar to the hypofractionated arm. Then a dose of 2000 cGy in 10 daily fractions was given to a reduced volume encompassing the visible tumour volume with a 1 cm margin. Most participants (68%) were aged between 18 and 59 years. Only 21% of participants were age 60 to 73 years.
- Glinski 1993 was a prospective RCT consisting of 44 participants with glioblastoma and 64 participants with anaplastic astrocytoma. The hypofractionated arm consisted of 2000 cGy in five daily fractions to the whole brain. After a four-week break, another 2000 cGy in five daily fractions was given to the whole brain followed by another four-week break and a final 1000 cGy boost in five daily fractions to the gross visible tumour plus a 3 cm margin. The conventional fractionation arm was 5000 cGy in 25 daily fractions to the whole brain plus a 1000 cGy in five daily fraction boost to the gross tumour plus a 3 cm margin. The median age of participants was 43 years in the conventional arm and 46 years in the hypofractionated arm.
- Malmstrom 2012 included 291 adults with glioblastoma over the age of 60 years, who were randomised to one of three arms. The trial used local radiotherapy (gross tumour volume plus a margin for suspected microscopic disease and day to day variation).
  * Arm 1: temozolomide chemotherapy alone (arm not included in the meta-analysis).
  * Arm 2: hypofractionated radiotherapy (3400 cGy in 10 daily fractions, 98 participants).
  * Arm 3: conventional fractionation (6000 cGy in 30 daily fractions, 100 patients).
- Phillips 2003 randomised 68 participants diagnosed with either anaplastic astrocytoma (in adults older than 45 years) or glioblastoma (adults, any age). These participants were randomised to hypofractionation (3500 cGy in 10 daily fractions) or conventional fractionation (6000 cGy in 30 daily fractions). The treatment volume was the visible tumour and oedema with a 3 cm margin to the field edge. The median age in the conventional arm was 59 years and in the hypofractionated arm was 58 years.
- Roa 2004 included people aged 60 years or older with glioblastoma. One hundred participants were recruited to the study and 95 were randomised to either hypofractionated radiotherapy (4000 cGy in 15 daily fractions) versus conventional radiotherapy (6000 cGy in 30 daily fractions). For participants randomised to the conventional radiotherapy arm, 4600 cGy in 23 daily fractions was prescribed to the planning target volume, defined as the preoperative enhancing tumour plus oedema with a 2.0 or 2.5 cm margin. Then 1400 cGy in seven

daily fractions was given to the preoperative enhancing tumour (without oedema) plus a 2.5 cm margin.

Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy

One trial randomised participants to hyperfractionated radiotherapy (with or without chemotherapy) or conventional radiotherapy (without chemotherapy).

- Shin 1985 randomised people to one of three arms. They randomised 38 participants to conventional fractionation (5800 cGy in 30 daily fractions), 43 participants to hyperfractionation (6141 cGy in 89 cGy fractions given three times a day every two to four hours for 4.5 weeks) and 43 patients to the same hyperfractionation plus misonidazole.

Accelerated radiotherapy versus daily conventionally fractionated radiotherapy

One trial included an accelerated radiotherapy arm and a daily conventionally fractionated radiotherapy arm, without chemotherapy.

- Prados 2001 randomised 231 adults with glioblastoma to one of four arms. The radiation volume where the dose was prescribed was defined as the contrast enhancing mass plus 3 cm.
  * Arm 1: accelerated fractionation, 7040 cGy in 44 fractions given twice a day (57 participants).
  * Arm 2: accelerated fractionation as arm 1 plus difluoromethylornithine (DFMO).
  * Arm 3: daily conventional fractionated radiotherapy, 5940 cGy in 180 cGy daily fractions (58 participants).
  * Arm 4: daily conventional fractionated radiotherapy plus DFMO.

As there were no other trials of accelerated radiotherapy versus daily conventional fractionated radiotherapy without chemotherapy, a meta-analysis was not possible.

Excluded studies

Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone)

We excluded the following studies.

- Sandberg-Wollheim 1991 randomised participants who were all treated with procarbazine, lomustine (CCNU) and vincristine (PCV) chemotherapy. Half the participants received postoperative radiotherapy and the other half did not receive postoperative radiotherapy. Because there was no arm with supportive care alone, this trial was excluded.
- Shapiro 1976 randomised participants who were all treated with chemotherapy (carmustine (BCNU) and vincristine). Half the participants received postoperative radiotherapy and the other half did not receive postoperative radiotherapy. Because there was no arm with supportive care alone, this trial was excluded.
- Walker 1980 randomised 467 participants to one of four groups: arm 1 received semustine (MeCCNU) chemotherapy; arm 2 received radiotherapy, arm 3 received carmustine plus radiotherapy and arm 4 received semustine plus radiotherapy. Because there was no arm with supportive care alone, this trial was excluded.
- Wick 2012 randomised participants aged 65 years and older to temozolomide chemotherapy alone versus radiotherapy alone. Because there was no arm with supportive care alone, this trial was excluded.

Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy

We excluded the following studies.

- Guedes de Castro 2017 reported a subset analysis of the Roa 2015 trial. As such this publication was excluded.
- Hatlevoll 1985 randomised 280 participants to hypofractionated radiation alone versus conventional radiation alone or combined with lomustine, misonidazole or both chemotherapy agents (eight arms in total). The results of the radiation alone arms were not described.
- Roa 2015 randomised 98 participants to 40 Gy in 15 daily fractions versus 25 Gy in five daily fractions. Both arms were hypofractionated radiation regimens. As there was no daily conventionally fractionated radiation arm, this trial was excluded.

Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy

We excluded the following studies.

- Ali 2018 randomised 712 participants to hyperfractionated radiation 72 Gy in 60 fractions given twice daily with carmustine versus 60 Gy in 30 daily fractions given with carmustine. Since all arms had chemotherapy and not radiation alone, this trial was excluded.
- Deutsch 1989 randomised participants to one of four arms. As all arms had chemotherapy and not radiation alone, this trial was excluded.
  * Arm 1: conventional radiotherapy (6000 cGy in 30 to 35 daily fractions) plus carmustine.
  * Arm 2: conventional radiotherapy plus streptozotocin.
  * Arm 3: hyperfractionated radiotherapy (6600 cGy in 60 fractions given twice daily) plus carmustine.
  * Arm 4: conventional radiotherapy with metronidazole followed by carmustine.
- Fulton 1984 did not randomise all participants: 9/42 participants were sequentially treated with hyperfractionation after the conventional radiotherapy arm was closed.
- Ludgate 1988 randomised participants to hyperfractionated radiation or conventional radiation. However, survival results could not be pooled as the authors showed survival curves for three different age groups rather than the total included participants in each arm of the trial.
- Payne 1982 randomised 157 adults with grade III or IV astrocytoma to 5000 cGy in 25 daily fractions (conventional radiotherapy) versus 3600 cGy to 4000 cGy in 36 to 40 fractions of 100 cGy fractions given every three hours. All participants received oral lomustine. Because there was no radiation alone arm, this trial was excluded.
- Shin 1983 reported an RCT in 35 adults with grade III or IV astrocytoma treated with hyperfractionation or conventional radiation. Since both arms received chemotherapy (lomustine), this trial was excluded.

Accelerated radiotherapy versus daily conventionally fractionated radiotherapy

We excluded the following studies.

- Buckner 2006 examined conventional and accelerated radiotherapy with carmustine or with carmustine and cisplatin. As there were no radiotherapy alone arms, this trial was excluded.
- Marshall 2006 randomised participants to standard or accelerated radiotherapy. However, all the arms had chemotherapy. There was no radiation alone arm. As such, this trial was excluded. In addition, the authors did not report overall survival or progression free survival.
- Simpson 1976 had no conventionally fractionated radiotherapy standard arm.

Risk of bias in included studies

We assessed the risk of bias in included studies using the Cochrane tool for assessing risk of bias, evaluating the following domains (Appendix 4; Characteristics of included studies table; Figure 1; Figure 2) (Higgins 2011).

Allocation

We assessed the method used to generate the allocation sequence as conferring a low risk of bias when investigators used any truly random process and when treatment allocation was protected before and until assignment. Andersen 1978 used a quasi-random process (odd or even date of birth to assign treatment arm), so we classified this study at high risk of bias for this category. Four trials did not describe the randomisation process in sufficient detail and thus we classified their risk of selection bias as unclear (Kristiansen 1981; Phillips 2003; Shin 1985; Walker 1978). The rest of the trials had a low risk of selection bias.

Blinding

Blinding of participants and personnel is not possible due to the nature of radiation delivery. None of the trials performed blinding of outcome assessment.

Blinding would not affect the outcome of overall survival and as such for this outcome, blinding was associated with low risk. However, lack of blinding may be associated with bias for the outcomes of adverse effects, progression free survival and quality of life. The extent to which lack of blinding may have biased the outcomes of adverse effects, progression free survival and quality of life was deemed to be unclear.

Incomplete outcome data

We defined low risk as less than 10% of participants not completing the outcome assessment. Not all of the studies described the percentage of missing data with sufficient detail to make a judgment (classified as unclear risk).

Selective reporting

All studies provided data for overall survival. Overall survival was deemed not to be subject to reporting bias. Other outcomes reported in the included trials such as progression free survival, quality of life and adverse effects may have been subject to possible selective outcomes reporting bias.

We examined funnel plots for the outcomes of overall survival (Figure 4; Figure 5). However, we did not run any tests for funnel plot asymemetry, as there were fewer than 10 studies in the meta-analyses. The test power was too low to distinguish chance from real asymmetry.

Figure 4. Funnel plot of comparison: 1 Radiation versus no radiation, outcome: 1.1 Overall survival.

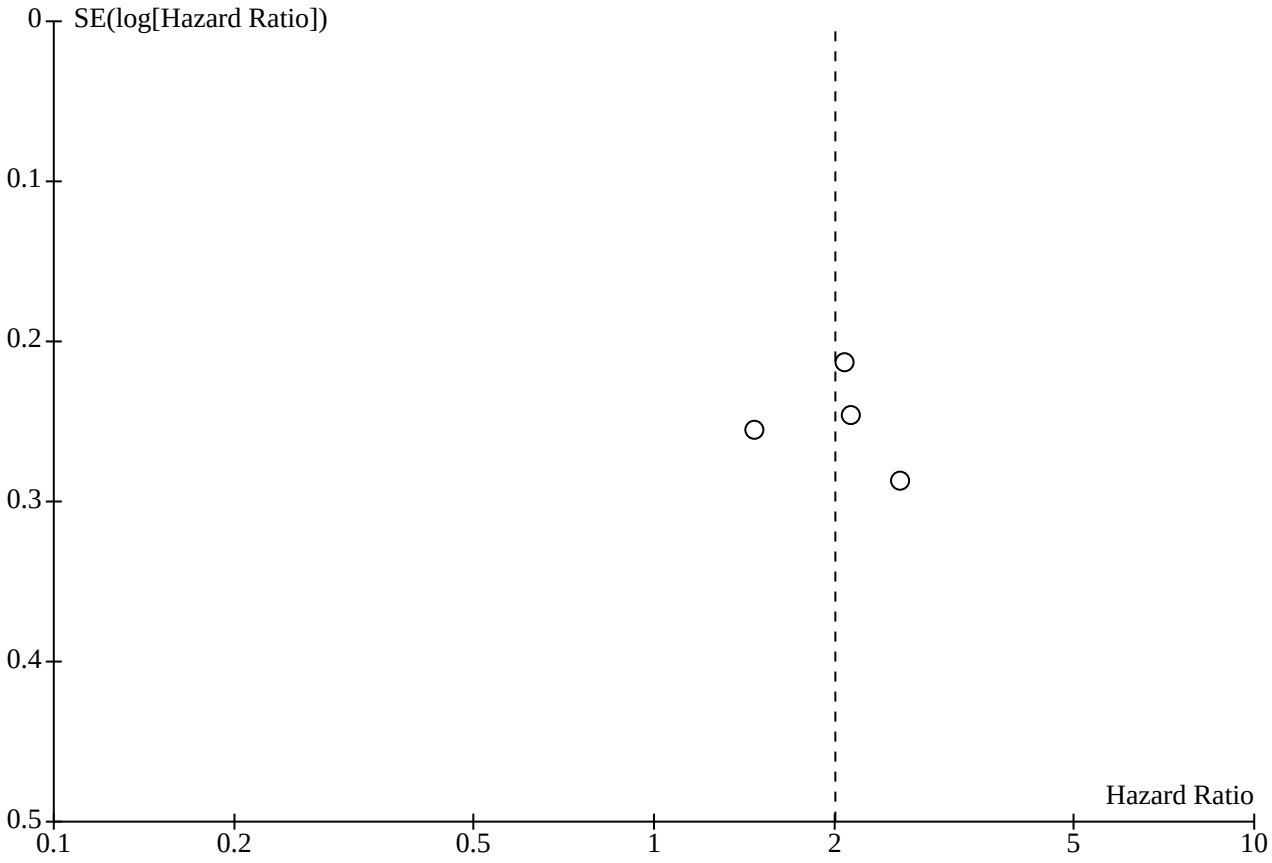
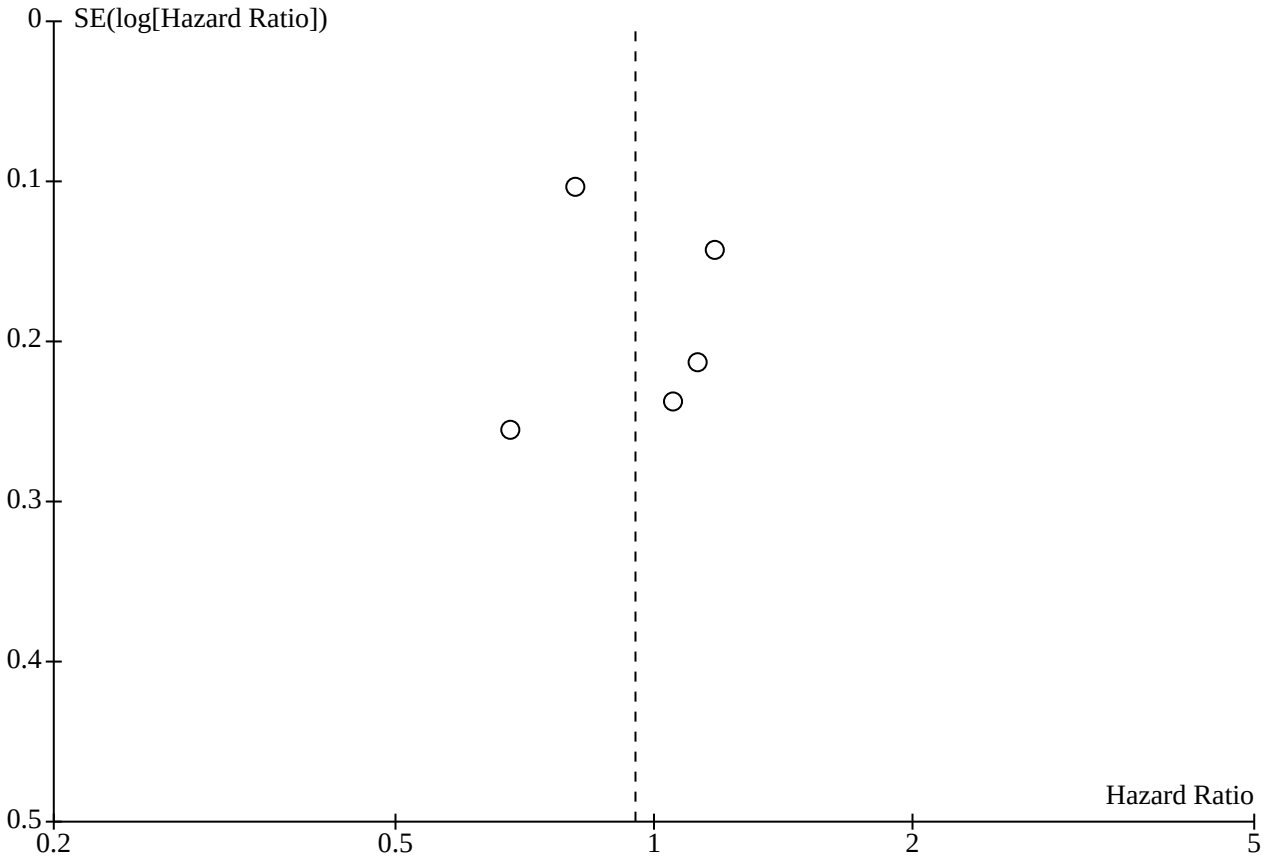


Figure 5. Funnel plot of comparison: 2 Hypofractionated radiation versus conventional radiation, outcome: 2.1 Overall survival.



Other potential sources of bias

We included size of study as another possible source of bias. The definition of risk was defined as follows: low risk (200 or more participants in total), unclear risk (50 to 199 participants in total), high risk (fewer than 50 participants in total).

Effects of interventions

See: **Summary of findings 1** Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone) for high grade glioma; **Summary of findings 2** Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy for high grade glioma

Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone)

The meta-analysis for this comparison included four RCTs in adults with HGG comparing conventional postoperative radiotherapy versus no postoperative radiation (Andersen 1978; Keime-Guibert 2007; Kristiansen 1981; Walker 1978).

Overall survival

Overall, there was benefit for postoperative radiotherapy compared to no radiotherapy (HR 2.01, 95% confidence interval (CI) 1.58 to 2.55; P < 0.00001; Analysis 1.1). The included trials were assessed as of moderate-certainty based on GRADE methodology (Summary of findings 1; Appendix 5).

The analysis for heterogeneity for the trials examining overall survival between postoperative radiotherapy and no radiotherapy revealed the following characteristics: I^2 = 0%, P = 0.51. This suggests that heterogeneity may not be important.

For the sensitivity analysis, we rated Andersen 1978 at high risk of bias and excluded it from the analysis (Analysis 1.2). This resulted in continued benefit for postoperative radiotherapy compared to no radiotherapy (HR 2.20, 95% CI 1.67 to 2.90; P < 0.00001).

The subgroup analysis (based on age 60 years and over, 65 years and over and 70 years and over) was not possible.

Adverse effects

Andersen 1978 did not describe adverse events.

Keime-Guibert 2007 reported that all participants in the radiotherapy group tolerated the treatment. One participant had transient somnolence shortly after the completion of radiation.

Kristiansen 1981 reported no serious complications during the trial. Irradiation and bleomycin were well tolerated.

Walker 1978 described haematological toxicity with carmustine. In general, the authors reported that therapy was well tolerated; they did not encounter any serious complications secondary to haematological changes, and they did not note any significant toxicity attributable to radiation.

Progression free survival

One trial reported progression free survival. Keime-Guibert 2007 reported that the median progression free survival was 14.9 weeks with radiotherapy versus 5.4 weeks with supportive care alone (P < 0.001).

Quality of life

One trial reported quality of life. Keime-Guibert 2007 reported that global assessments in health-related quality of life did not differ significantly between groups.

Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy

Five trials randomised adults with HGG to hypofractionated radiation or conventional radiation (Bleehen 1991; Glinski 1993; Malmstrom 2012; Phillips 2003; Roa 2004).

Overall survival

The HR for overall survival between hypofractionated radiation versus conventional radiation was 0.95 (95% CI 0.78 to 1.17; P = 0.63; Analysis 2.1). The included trials were very low-certainty based on GRADE assessment (Summary of findings 2; Appendix 6).

The analysis for heterogeneity for the trials examining overall survival for postoperative hypofractionated radiotherapy versus conventional radiotherapy revealed the following characteristics: I^2 = 43%, P = 0.13. This suggests that there may be moderate heterogeneity.

For the subgroup analysis based on age, people with glioblastoma over the age of 60 years were pooled (Malmstrom 2012; Roa 2004), the HR for overall survival was 1.16 (95% CI 0.92 to 1.46; P = 0.21). The included trials were high-certainty based on GRADE assessment (Summary of findings 2; Appendix 7). The analysis for heterogeneity for the trials examining overall survival for postoperative hypofractionated radiotherapy versus conventional radiotherapy (for the subgroup of glioblastoma participants aged 60 year and older) revealed the following characteristics: I^2 = 0%, P = 0.86. This suggests that heterogeneity may not be important.

No other subgroup analysis based on age (aged 65 years and over, aged 70 years and over) could be pooled.

Adverse effects

Bleehen 1991 reported that 83% of participants treated to 4500 cGy compared to 81% treated to 6000 cGy reported no adverse events from the radiotherapy. There were no major differences in acute adverse effects between the two radiotherapy arms.

Glinski 1993 reported that radiotherapy was well tolerated in the hypofractionated and conventionally fractionated groups. All participants had total alopecia and mild erythema of the scalp. Investigators reported skin reactions in the hypofractionated group to be no more severe than those in the conventionally fractionated group. One participant in the hypofractionated group developed symptomatic radiation necrosis requiring surgery.

Malmstrom 2012 reported that the most common grade 3 to 4 adverse events in the temozolomide alone group were neutropenia (12/119 participants) and thrombocytopenia (18/119 participants). Two participants had fatal infections (1/119 participants in the temozolomide group and 1/100 in the conventional radiotherapy group). Another participant in the temozolomide group had grade 2 thrombocytopenia and died after complications from surgery for gastrointestinal bleeding.

Phillips 2003 reported acute toxicity as mild and equally distributed between the two arms. Investigators did not report late toxicity.

Roa 2004 did not describe adverse effects.

Progression free survival

None of the trials reported on progression free survival.

Quality of life

Because of the low number of participants who completed the European Organisation for Research and Treatment of Cancer quality of life questionnaires (EORTC QLQ-30), Malmstrom 2012 suggested caution in the interpretation of this outcome. Nevertheless, participants in the temozolomide chemotherapy alone group reported better quality of life compared to participants in the radiotherapy groups.

Phillips 2003 also reported that the number of completed quality of life questionnaires was too low for any formal comparisons.

Roa 2004 used the Functional Assessment of Cancer Therapy – Brain (FACT-Br) quality of life questionnaire. However, number of completed quality of life questionnaires was too low to make meaningful comparisons between conventional and hypofractionated radiotherapy.

No other included hypofractionated trials reported on quality of life outcomes.

Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy

One trial compared hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy (Shin 1985).

Overall survival

Shin 1985 reported that the one year actuarial survival was 20% for conventional fractionation versus 41% for hyperfractionation (P = 0.007). This trial did not provide subgroup analyses by age.

Adverse effects

Shin 1985 described more skin reactions (erythema, dry and moist desquamation) in the hyperfractionated group compared to the conventionally fractionated group.

Progression free survival

Shin 1985 did not report progression free survival.

Quality of life

Shin 1985 did not report quality of life.

Accelerated radiotherapy versus daily conventionally fractionated radiotherapy

One trial included an accelerated radiotherapy arm and a daily conventionally fractionated radiotherapy arm, without chemotherapy (Prados 2001).

Overall survival

Prados 2001 reported a median overall survival of 40 weeks for the accelerated arm and 37 weeks for the conventionally fractionated radiotherapy (P = 0.48).

Subgroup analysis by age was not reported (Prados 2001).

Adverse effects

Prados 2001 reported that the treatment arms containing DFMO resulted in more toxicity (i.e. myelosuppression) than those receiving radiotherapy alone. Based on the National Cancer Institute (NCI) Common Toxicity Criteria, grade 3 or 4 myelosuppression occurred in 2/57 participants treated with accelerated radiation plus DFMO, 1/59 participants treated with conventional radiation plus DFMO and 1/57 participants treated with accelerated radiation alone. None of the 58 participants treated with conventional radiotherapy developed grade 3 or 4 myelosuppression. Grades 3 and 4 gastrointestinal toxicity was also more common in the DFMO arms (one participant in the accelerated radiotherapy plus DFMO arm and three in the conventional radiotherapy plus DFMO arm), versus the arms without DFMO (no participants). Skin reactions during radiation were mild and were equally balanced among all four arms. There was grade 3 ototoxicity (three participants) only in the DFMO arms. Authors reported no cases of cerebral necrosis from radiation.

Progression free survival

Prados 2001 reported 19 weeks of progression free survival for the accelerated arm versus 16 weeks for the conventionally fractionated radiotherapy arm (P = 0.32).

Quality of life

Prados 2001 did not report quality of life.

DISCUSSION

Summary of main results

Since the last version of this review, there were no new relevant studies.

Postoperative conventional daily radiotherapy improves survival for adults with good functional well-being and HGG compared to no postoperative radiotherapy (supportive care alone).

Hypofractionated radiotherapy has similar efficacy for survival compared to conventional radiotherapy, particularly for people aged 60 years and older with glioblastoma.

There is insufficient data regarding hyperfractionation versus conventionally fractionated radiation (without chemotherapy) and insufficient data regarding accelerated radiation versus conventionally fractionated radiation (without chemotherapy).

There are HGG subsets who have poor prognosis even with treatment (e.g. glioblastoma histology, older age and poor performance status). These people with poor prognosis for HGG have generally been excluded from randomised trials based on poor performance status. No randomised trial has compared comfort measures or best supportive care with an active intervention using radiotherapy or chemotherapy in these people with poor prognosis.

Overall completeness and applicability of evidence

Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone)

Overall, there was a survival benefit for postoperative conventionally fractionated radiotherapy compared to no radiotherapy (HR 2.01, 95% CI 1.58 to 2.55; P < 0.00001; Analysis 1.1; moderate-certainty evidence; Summary of findings 1).

The trials generally included only incomplete descriptions of radiation toxicity. Some of the trials reported no significant toxicity attributable to radiation (Keime-Guibert 2007; Kristiansen 1981; Walker 1978).

It is important to note that all the included trials (except for Keime-Guibert 2007) ranging from 1978 to 1981. Since then, there have been many advances.

- Improved pathological diagnosis (histological and molecular), to distinguish between glioblastoma and high grade oligodendroglioma.
- Improved clinical (e.g. age, performance status) and pathological prognostic factor determination (e.g. MGMT (O[6]-methylguanine-DNA methyltransferase) methylation, 1p, 19 q LOH, and mutated isocitrate dehydrogenase also known as mIDH1 status).
- Use of imaging for radiation planning (transition from planning based on computed tomography to magnetic resonance imaging (MRI)).
- Advances in radiation planning techniques (progression from two dimensional radiation planning to three dimensional radiation planning, transition from whole brain radiotherapy to local radiotherapy).

Most postradiotherapy recurrence (more than 90% of cases) occurs at the original site (Hochberg 1980; Wallner 1989). Based on the recurrence pattern and better tumour localisation using MRI, local radiotherapy targeted to the visible tumour plus a margin in the order of 2 cm is currently used rather than whole brain radiotherapy. The use of whole brain radiotherapy in people with HGG unnecessarily exposes normal brain tissue to radiation toxicity without improving tumour control or overall survival.

In addition, these older trials included adults with grade III and grade IV glioma, whereas there is now a consensus that trials should no longer group these HGG grades together, as the clinical behaviour and prognosis of grade III and IV glioma are very different. Specialists can now perform molecular diagnoses for subtypes of glioma, such as 1p, 19q LOH for oligodendroglioma, which are helpful for differentiating grade III oligodendroglioma from high grade astrocytoma. The median survival for treated grade III anaplastic oligodendroglioma with 1p, 19q LOH is about 15 years (Cairncross 2013; Van den Bent 2013). Adults with glioblastoma, however, have much shorter overall survival. A modern population-based study in adults diagnosed with primary malignant brain

tumours in Europe from 2000 to 2007 reported that five year overall survival for glioblastoma was only 6% (Visser 2015). Even within glioblastoma, MGMT methylation and mIDH1 status further refine prognosis and is predictive of treatment outcomes (Macaulay 2015).

Applicability of the evidence

It is also important to note that while postoperative conventionally fractionated radiotherapy for malignant glioma is generally associated with improved overall survival compared to no postoperative radiotherapy, the included trials could not provide information as to whether certain subsets of people (e.g. poor performance status, multiple lobe involvement, older age) have a significant overall survival advantage with the use of postoperative radiotherapy. In this group, comfort measures or supportive care alone may be the best option.

Wick 2012 included participants with anaplastic astrocytoma or glioblastoma aged 65 years and over. In this trial, temozolomide alone was no different from radiotherapy alone in terms of overall survival. Median event free survival was longer in those with MGMT promoter methylation who received temozolomide versus radiotherapy (8.4 months, 95% CI 5.5 to 11.7 with temozolomide alone versus 4.6 months, 95% CI 4.2 to 5.0 with radiotherapy alone; P < 0.0001).

Wick 2012 indicated that in people aged 65 years and over with anaplastic astrocytoma or glioblastoma, the option of postoperative temozolomide chemotherapy is not inferior to postoperative radiotherapy. In this group, people with methylated MGMT have longer event free survival when treated with temozolomide chemotherapy compared to radiotherapy alone.

Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy

Overall, hypofractionated radiotherapy has similar efficacy for survival compared to conventional radiotherapy. The HR for overall survival between hypofractionated radiation and conventional radiation was 0.95 (95% CI 0.78 to 1.17; P = 0.63; Analysis 2.1; very low-certainty evidence; Summary of findings 2).

Radiation toxicities in Bleehen 1991 and Glinski 1993 were similar between hypofractionated and conventional radiotherapy.

Subgroup analysis for people with glioblastoma aged 60 years and older

The benefit of hypofractionated radiotherapy is reduced overall treatment time, which is less burdensome, particularly in older frail people, compared to a protracted radiotherapy course. In the subgroup analysis for the two trials that included participants with glioblastoma, all aged 60 years and over, survival was similar with hypofractionated radiation compared to conventionally fractionated radiation (HR 1.16, 95% CI 0.92 to 1.46; P = 0.21; Analysis 2.2; high-certainty evidence; Summary of findings 2).

In Malmstrom 2012, all participants had glioblastoma and were aged 60 years or older. Median overall survival was longer with temozolomide compared to conventional radiotherapy (8.3 months, 95% CI 7.1 to 9.5 with temozolomide versus 6.0 months, 95% CI 5.1 to 6.8 with conventional radiotherapy; HR 0.70, 95% CI 0.52 to 0.93; P = 0.01), but not compared to hypofractionated radiotherapy (7.5 months, 95% CI 6.5 to 8.6; HR 0.85, 95% CI 0.64 to 1.12; P = 0.24).

In particular for the subset of people with glioblastoma (aged 70 years and over), Malmstrom 2012 reported that overall survival was worse for conventional radiotherapy (6000 cGy in 30 daily fractions) than either hypofractionated radiotherapy (3400 cGy in 10 daily fractions) or temozolomide chemotherapy. The HR for temozolomide versus conventional radiotherapy was 0.35 favouring temozolomide (95% CI 0.21 to 0.56; P < 0.0001). The HR for hypofractionated radiotherapy versus conventional radiotherapy was 0.59 favouring hypofractionated radiotherapy (95% CI 0.37 to 0.93; P = 0.02).

In terms of overall adverse events in Malmstrom 2012, there were more infections/fever in the conventional radiotherapy arm (14%) than in the hypofractionated arm (7%). In addition, there were more intracranial haemorrhages in the conventional arm (3%) versus the hypofractionated arm (0%). Seizures occurred in 13% of participants in the conventional arm versus 7% in the hypofractionated arm. Haematological adverse effects were more common in participants treated with temozolomide (grades 2 to 4 neutropenia, pancytopenia, thrombocytopenia ranged from 2% to 21%) compared to none of the participants treated with radiotherapy. Nausea and vomiting were also more common in participants treated with temozolomide (incidence of grades 2 and 3 nausea and vomiting ranged from 3% to 7%) than in participants treated with radiotherapy (1% to 5%).

Roa 2004 reported no difference in overall survival for people aged 60 years and older with glioblastoma treated with hypofractionated radiotherapy (4000 cGy in 15 daily fractions) compared to conventional radiotherapy (6000 cGy in 30 daily fractions). Overall survival was 5.6 months for hypofractionated radiotherapy compared to 5.1 months for conventional radiotherapy (P = 0.57).

Applicability of the evidence

The included trials in this meta-analysis do not provide sufficient data to determine the optimal dose fractionation schemes for anaplastic glioma (astrocytoma, oligodendroglioma) as the included trials have combined results for anaplastic glioma and glioblastoma. However, there are trials which have focused solely on glioblastoma management.

Glioblastoma in people up to the age of 70 years

We found one trial with five year follow-up data that defined the standard of care for adults with glioblastoma up to age 70 years with WHO performance status 0 to 2, who have no contraindication to radiotherapy or temozolomide chemotherapy (Stupp 2005; Stupp 2009). Adults treated with postoperative conventionally fractionated radiotherapy (6000 cGy in 30 daily fractions) had better overall survival with the addition of concurrent and adjuvant temozolomide chemotherapy versus the same postoperative radiotherapy alone. At two years, overall survival was 27.2% (95% CI 22.2 to 32.5) with radiotherapy versus 10.9% (95% CI 7.6 to 14.8) with radiotherapy plus temozolomide (P < 0.0001). Whether similar outcomes could be achieved with hypofractionated radiotherapy and temozolomide chemotherapy is not known in this group of people.

Conventionally fractionated radiotherapy (6000 cGy in 30 daily fractions) with concurrent and adjuvant temozolomide

chemotherapy is the standard of care for adults with glioblastoma eligible for treatment.

Glioblastoma in people aged 60 years and older

For the pooled subgroup analysis of people aged 60 years and older with glioblastoma in the Malmstrom 2012 and Roa 2004 trials, hypofractionated radiotherapy is associated with similar survival as compared to conventionally fractionated radiation.

We found one study that reported on a phase III randomised trial of hypofractionated radiotherapy (4000 cGy in 15 daily fractions) alone versus the same radiotherapy and temozolomide chemotherapy in glioblastoma people aged 65 years and older (Perry 2017). The addition of temozolomide chemotherapy to hypofractionated radiation was associated with improved survival compared to hypofractionated radiation alone (HR 0.67, 95% CI 0.56 to 0.80; P <0.001) and improved progression free survival (HR 0.50, 95% CI 0.41 to 0.60; P < 0.001).

Glioblastoma in people aged 70 years and older

For people aged 70 years and over with glioblastoma and methylated MGMT, temozolomide alone (without postoperative radiotherapy) is an option.

Hyperfractionated radiotherapy versus daily conventionally fractionated radiotherapy

There are insufficient data regarding hyperfractionation versus conventionally fractionated radiation (without chemotherapy).

The use of hyperfractionated radiotherapy is inconvenient, requires significant radiation machine time and is associated with more severe acute skin reactions compared to conventional radiation (Shin 1985).

Accelerated radiotherapy versus daily conventionally fractionated radiotherapy

There is insufficient data regarding accelerated radiation versus conventionally fractionated radiation (without chemotherapy).

The use of accelerated radiotherapy is inconvenient and requires significant radiation machine time. Toxicity attributable to radiation was similar between the accelerated and conventional radiation arms in the Prados 2001 trial.

Prados 2001 defined progression as an increase in the size of the contrast enhancing tumour based on MRI of at least 25% using the product of the two longest perpendicular diameters or the development of new lesions.

Current practice favours MRI for assessment of progression rather than CT due to greater sensitivity to small lesions and better visualisation of the posterior fossa compared to CT. However, there has been increasing recognition that enlargement of contrast enhancement after treatment for HGG may be the result of treatment effect rather than true tumour growth (Huang 2015). Within three months from the end of radiation treatment, 20% to 30% of adults show increased contrast enhancing tumour size that settled with time without changes in treatment, known as pseudoprogression. Failure to recognise pseudoprogression is prone to artificially shorten the progression free survival interval.

To address this issue and others, in 2010 the Response Assessment in Neuro-Oncology (RANO) Working Group proposed updated response criteria for HGG (Wen 2010). The revised criteria include radiographic findings and incorporates steroid use and clinical status. Furthermore, the 2010 RANO criteria excludes adults with enlarging contrast enhancement during the first 12 weeks after radiation from entry into new clinical trials unless the progression is largely outside the radiation field.

The Prados 2001 trial predates the 2010 RANO criteria. As such, progression free survival data from Prados 2001 may not be an accurate reflection of true tumour progression.

Quality of the evidence

Based on the GRADE criteria (Appendix 5; Appendix 6; Appendix 7), the certainty of the evidence ranged from very low to high-certainty (Summary of findings 1; Summary of findings 2). We classified some trials at a higher risk of bias when they did not clearly describe the method of randomisation or details relating to attrition. Only 5/11 trials were published after the year 2000; most are, therefore, out of date. These older trials did not distinguish the various subtypes of HGG such as glioblastoma and anaplastic oligodendroglioma and used outdated radiotherapy techniques such as whole brain radiotherapy rather than localised radiotherapy.

Potential biases in the review process

This meta-analysis is biased towards older outdated trials. The older trials are severely flawed because, at the time of investigation, the importance of pathologically separating glioblastoma from anaplastic astrocytoma or anaplastic oligodendroglioma was still unknown. Radiation planning techniques in the older trials were also outdated (lack of MRI based planning and lack of local radiotherapy volumes). Furthermore, outcomes stratified by known prognostic factors, both clinical and molecular are missing from many of the older trials.

Agreements and disagreements with other studies or reviews

This meta-analysis agrees with the older meta-analyses (Fine 1993; Laperriere 2002). However, this present meta-analysis differs from the older meta-analyses as radiotherapy arms without chemotherapy were considered. Furthermore, the present meta-analysis includes more recent trials and it includes further information regarding the use of hypofractionation in people with glioblastoma aged over 60 years.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review, we found no new relevant trials.

There is moderate-certainty evidence that postoperative conventional daily radiotherapy probably improves survival for adults with good performance status and high grade glioma (HGG) compared to no postoperative radiotherapy (supportive care alone). Our certainty in the effect is at risk of bias due to the lack of applicability from the age of the studies and heterogeneous participants recruited.

There is very low-certainty evidence that hypofractionated radiotherapy has similar efficacy for survival as compared to

conventional radiotherapy, also due to the risk of bias and lack of applicability arising from the age of the studies and heterogeneous participants recruited. However, there is high-certainty evidence that hypofractionated radiotherapy has similar efficacy for survival, particularly for the subgroup of people aged 60 years and older with glioblastoma.

There are HGG subsets who have poor prognosis even with treatment (e.g. older people with glioblastoma with poor performance status). Randomised trials have generally excluded people with poor prognosis from randomised trials on this basis.

There is insufficient evidence regarding the benefits (overall survival, progression free survival, quality of life) and risks associated with hyperfractionated radiation or accelerated radiation as compared to conventional radiation (without chemotherapy).

Implications for research

Classification of gliomas based on molecular characteristics will help identify more homogeneous groups of people for trial entry. Further research is necessary to explore the use of novel chemotherapy or molecular targeted agents with various radiation regimens. Not only are the outcomes of overall survival and complete reporting of toxicity important, but future trials should also report on validated quality of life outcomes.

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CHARACTERISTICS OF STUDIES

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

Andersen 1978

Study characteristics	
Methods	Randomised, phase III trial Treatment period: 1963–1967 Follow-up: 3 years
Participants	108 adults with glioblastoma (grade IV astrocytoma) from 4 US medical centres; 73% aged 50–70 years; baseline performance status not described; 64% men and 36% women
Interventions	Arm 1: postoperative radiotherapy: 4500 cGy in daily fractionation over 4.5–5.0 weeks Arm 2: no postoperative radiotherapy
Outcomes	Crude survival presented as survival curves up to 20 months
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants born on odd dates received postoperative radiotherapy whereas those born on even dates did not.
Allocation concealment (selection bias)	High risk	Randomisation was based on odd or even dates of birth. The protection of treatment allocation before and until assignment was deemed to be at high risk of bias.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel was not possible due to the nature of radiation delivery. However, blinding would not have biased the outcome of survival.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although there was no blinding of the outcome (survival), blinding would not have biased the assessment of this outcome.

Andersen 1978 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described.
Selective reporting (reporting bias)	Low risk	The study's prespecified outcome (survival) that was of interest in this review was reported in the prespecified way.
Other bias	Unclear risk	Size of study bias: 108 participants.

Bleehen 1991

Study characteristics	
Methods	Randomised, phase III trial Trial period: April 1983 to September 1988 Minimum follow-up: 14 months
Participants	474 participants from 15 centres in the UK and 1 centre from South America randomised (33% grade III, 6% grade III/IV, 61% grade IV glioma); 15% aged 18–39 years, 20% aged 40–49 years, 33% aged 50–59 years, 32% aged 60–73 years; baseline WHO performance status 13% 0, 40% 1, 27% 2, 18% 3, 2% 4; percentage women and men not described
Interventions	Arm 1: hypofractionated: 4500 cGy in 20 daily fractions Arm 2: conventional: 6000 cGy in 30 daily fractions
Outcomes	Survival (Kaplan-Meier survival curves presented to 36 months) Neurological status (Medical Research Council scale) measured during radiotherapy, immediately after radiotherapy WHO performance status measured at each visit and during the follow-up period (time point for assessment and attrition not fully described) Adverse events (time point for assessment not described)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation at the Medical Research Council Trials office.
Allocation concealment (selection bias)	Low risk	Protection of treatment allocation before and until assignment was deemed low risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel was not possible due to the nature of radiation delivery and would not have impacted the assessment of survival. However, lack of blinding may have biased the other outcomes of interest for this review (i.e. adverse effects).

Bleehen 1991 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was no blinding of outcome assessments. However, lack of blinding is associated with low risk for the outcome of survival and unclear risk for the outcomes of interest for this review (i.e. adverse effects).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition for the outcomes of survival, neurological status, performance status and adverse effects not reported.
Selective reporting (reporting bias)	Unclear risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review were reported in the prespecified way. For the outcomes of interest for this review, adverse effects may have been prone to reporting bias. The extent to which adverse effects may have be subject to selective reporting is unknown.
Other bias	Low risk	Size of study bias: 474 participants.

Glinski 1993

Study characteristics	
Methods	Randomised, phase III trial Trial period: enrolled April 1984 to December 1989 Follow-up: not described
Participants	108 randomised, 104 evaluable (59% grade III and 41% grade IV astrocytoma) from Krakow, Poland; median age 45 years; baseline Karnofsky performance status 59% 60 or more and 41% less than 60; 45% men and 55% women
Interventions	Arm 1: conventional: 5000 cGy in 25 daily fractions with 1000 cGy boost in 5 daily fractions to the gross tumour with 3cm margin Arm 2: hypofractionated: 3 courses separated by 1 month intervals, 2000 cGy in 5 daily fractions, 2000 cGy in 5 daily fractions, 1000 cGy in 5 daily fractions
Outcomes	Survival (Kaplan-Meier curves presented up to 2 years) Adverse events (time point for assessment not described)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers.
Allocation concealment (selection bias)	Low risk	Protection of treatment allocation before and until assignment was deemed to be low risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel was not possible due to the nature of radiation delivery. Lack of blinding was associated with low bias for the outcome of survival. The degree in which lack of blinding may have biased the assessment of adverse effects was unknown.

Glinski 1993 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessments would not have biased survival and was associated with unclear bias for the outcome of adverse effects.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described.
Selective reporting (reporting bias)	Unclear risk	All of the study's prespecified (survival and adverse effects) outcomes that are of interest in the review were reported in the prespecified way. Adverse events may be prone to selective reporting. The extent to which selective reporting occurred for adverse events is unknown.
Other bias	Unclear risk	Size of study bias: 108 randomised.

Keime-Guibert 2007

Study characteristics	
Methods	Randomised, phase III trial Treatment period: February 2001 to January 2005; analysis reported in January 2005 Median follow-up: 21 weeks (90% of participants died)
Participants	81 participants with glioblastoma (grade IV astrocytoma) from 10 centres in France; median age 74 years; baseline Karnofsky performance status score 53% 70, 36% 80, 9% 90, 2% 100; 63% men and 37% women
Interventions	Arm 1: supportive care alone Arm 2: radiotherapy alone: 5000 cGy given in daily fractions of 180 cGy
Outcomes	Overall survival (Kaplan-Meier curves presented up to 90 weeks) Progression free survival (Kaplan-Meier curves presented up to 55 weeks) Karnofsky performance status (time point for assessment not described) Quality of life (baseline, day 30, day 60, day 90, day 135 with compliance of 93% and 90% at baseline to 60% and 67% at day 135) Mini-Mental Status Examination (time point for assessment not described) Mattis Dementia Rating Scale (baseline, day 60 and day 135 with compliance of 74% and 79% at baseline to 47% and 46% at day 135) Neuropsychiatric Inventory (baseline, day 60 and day 135 with compliance of 79% and 95% at baseline to 47% and 44% at day 135)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centrally randomised (10 institutions participated).

Keime-Guibert 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	Protection of treatment allocation before and until assignment was deemed low risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding of participants and personnel was not possible due to the nature of radiation delivery. Lack of blinding was associated with low risk of bias for the outcome of overall survival and unclear risk of bias for the outcomes of interest in this review (i.e. progression free survival and quality of life).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Low risk of bias was associated with the lack of outcome assessment blinding for overall survival. The risk of bias was unclear with the lack of outcome assessment blinding for progression free survival and quality of life.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described.
Selective reporting (reporting bias)	Unclear risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review were reported in the prespecified way. For the outcomes of interest relevant for this review, quality of life may be prone to selective reporting.
Other bias	Unclear risk	Size of study bias: 85 participants.

Kristiansen 1981

Study characteristics	
Methods	Randomised, phase III trial Treatment period: 1974–1978 Follow-up: not described
Participants	118 participants randomised from Scandinavian countries (Denmark, Finland, Norway and Sweden); grade III and IV astrocytomas included but percentage of each histology not described; mean age 55 years; mean baseline performance status described as unable to work but able to take care of him/herself; 60% men and 40% women
Interventions	Arm 1: 4500 cGy postoperative radiotherapy given daily in 180 cGy daily fractions to whole brain + bleomycin Arm 2: 4500 cGy postoperative radiotherapy given daily in 180 cGy daily fractions to whole brain + placebo Arm 3: no postoperative radiation or chemotherapy
Outcomes	Survival (Kaplan-Meier curve presented up to 33 months) Performance status (curves presented up to 12 months)
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Kristiansen 1981 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Unclear risk	Protection of treatment allocation before and until assignment was unclear as the method of randomisation was not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel was not possible due to the nature of radiation delivery and was associated with low risk of bias for the outcome of interest in this review (i.e. survival).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Lack of outcome assessment blinding was associated with low risk of bias for the outcome of survival.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described.
Selective reporting (reporting bias)	Low risk	Study protocol available and the study's prespecified survival outcome was of interest for this review.
Other bias	Unclear risk	Size of study bias: 118 randomised.

Malmstrom 2012

Study characteristics	
Methods	Randomised, phase III trial Trial period: accrued 2 February 2000 to 18 June 2009; at the time of data analysis (1 January 2011) only 4 participants remained alive and a further 3 were lost to follow-up
Participants	342 enrolled, 291 randomised (all aged 60 years or older with glioblastoma) from 28 centres in Austria, Denmark, France, Norway, Sweden, Switzerland and Turkey; median age 70 years (range 60–88 years); baseline WHO performance score 78% for 0–1 and 22% for 2–3; 59% men and 41% women
Interventions	Arm 1: temozolomide chemotherapy alone (arm not included in the meta-analysis) Arm 2: hypofractionated radiotherapy: 3400 cGy in 10 daily fractions Arm 3: conventional fractionation: 6000 cGy in 30 daily fractions. Local radiotherapy (gross tumour volume + a margin for suspected microscopic disease and day to day variation) used
Outcomes	Survival (Kaplan-Meier curves presented up to 36 months) Quality of life (baseline, 6 weeks and 3 months) Adverse events (time point for assessment not described)
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Malmstrom 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated randomisation centrally.
Allocation concealment (selection bias)	Low risk	Protection of treatment allocation before and until assignment was low risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding of participants and personnel was associated with low risk of bias for the outcome of survival and unclear risk of bias for the outcomes of quality of life and adverse events.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessments was associated with low risk of bias for survival and unclear risk of bias for quality of life and adverse events.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was described and < 10% of participants were lost to follow-up for the primary outcome of survival and adverse events. Quality of life outcomes were available in 83% of participants at baseline, 59% at 6 weeks and 44% at 3 months. As such, there may have been bias in quality of life outcomes due to attrition.
Selective reporting (reporting bias)	Unclear risk	Study protocol available and all of the study's prespecified (primary and secondary) outcomes that were of interest in this review were reported in the prespecified way. Quality of life and adverse effects may have been prone to selective reporting. The degree in which selective reporting occurred for quality of life and adverse is unknown.
Other bias	Low risk	Size of study bias: 291 randomised.

Phillips 2003

Study characteristics	
Methods	Randomised, phase III trial Trial period: accrued from 14 February 1990 to 22 February 1996; all participants died by the analysis date (14 January 2002)
Participants	69 enrolled, 68 randomised (10% grade III and 90% grade IV astrocytoma) from Australia; 16% aged ≤ 45 years and 84% aged > 45 years; baseline ECOG performance status 34% 0, 53% 1, 9% 2 and 4% 3; 72% men and 28% women
Interventions	Arm 1: conventional: 6000 cGy in 30 daily fractions Arm 2: hypofractionated: 3500 cGy in 10 daily fractions
Outcomes	Survival (Kaplan-Meier curves presented up to 60 months) Adverse events (time point for assessment not described)
Notes	Study closed early due to poor accrual; results published based on incomplete accrual (68 participants analysed). The authors did not comment on the planned sample size.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Phillips 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Protection of treatment allocation before and until assignment was deemed unclear as the method of randomisation was not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding of participants and personnel was associated with low risk of bias for the outcome of survival and unclear risk of bias for adverse events.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessments was associated with low risk of bias for survival and unclear risk of bias for adverse events.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was not described.
Selective reporting (reporting bias)	Unclear risk	Study protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way. Adverse effects may have been subjected to selective reporting. The degree in which selective reporting occurred for adverse effects was unknown.
Other bias	High risk	Study was closed early due to poor accrual. The publication only included 68 participants. The authors did not comment on the planned sample size.

Prados 2001

Study characteristics	
Methods	Randomised, phase III trial Treatment period: accrual and time period not described
Participants	231 people with glioblastoma (grade IV astrocytoma) randomised from a single centre in the US; median age 57 years, median baseline Karnofsky performance status 90; 59% men and 41% women
Interventions	Arm 1: accelerated fractionation: 7040 cGy in 44 fractions given twice a day Arm 2: accelerated fractionation as arm 1 + DFMO Arm 3: daily conventional fractionated radiotherapy: 5940 cGy in 180 cGy daily fractions Arm 4: daily conventional fractionated radiotherapy as arm 3 + DFMO
Outcomes	Survival (Kaplan-Meier curve presented up to 400 weeks) Progression free survival (Kaplan-Meier curve presented up to 250 weeks) Adverse events (time point for assessment was not described)
Notes	
Risk of bias	

Prados 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The allocation to treatment group was done by adaptive randomisation, balancing the groups by stratifying for known prognostic variables.
Allocation concealment (selection bias)	Low risk	Protection of treatment allocation before and until assignment was at low risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding of participants and personnel was associated with low risk of bias for the outcome of survival and unclear risk of bias for progression free survival and adverse events.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessment was associated with low risk of bias for survival and unclear risk of bias for progression free survival and adverse events.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was not described.
Selective reporting (reporting bias)	Unclear risk	Study protocol available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way. Adverse effects may have been prone to selective reporting. The degree in which selective reporting occurred for adverse effects was unknown.
Other bias	Low risk	Size of study bias: 231 randomised.

Roa 2004

Study characteristics	
Methods	Randomised, phase III trial Treatment period: accrued 1996 to 2001; trial closed in October 2001; at the time of the final analysis, all participants died.
Participants	100 participants with glioblastoma (grade IV astrocytoma) randomised (all aged 60 years and over) from 4 Canadian centres; mean age 72 years; median baseline Karnofsky performance status 70; 58% men and 42% women but 2 participants withdrew after randomization, 1 went to alternative therapy and another 2 others died before starting radiotherapy.
Interventions	Arm 1: hypofractionated: 4000 cGy in 15 daily fractions Arm 2: conventional: 6000 cGy in 30 daily fractions; participants randomised to the conventional radiotherapy arm, 4600 cGy in 23 daily fractions was prescribed to the planning target volume (PTV), defined as the preoperative enhancing tumour plus oedema with a 2.0 or 2.5 cm margin. Then 1400 cGy in seven daily fractions was given to the preoperative enhancing tumour (without oedema) plus a 2.5 cm margin.
Outcomes	Survival (Kaplan-Meier curve presented up to 24 months) Quality of life (baseline, 3 weeks, 6 weeks, 3 months, 6 months) Performance status (baseline, 3 weeks, 6 weeks, 3 months, 6 months) Steroid requirements (time point for assessment not described)

Roa 2004 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	Protection of treatment allocation before and until assignment was deemed to be low risk.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding of participants and personnel was associated with low risk of bias for the outcome of survival and unclear risk of bias for quality of life.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessments was associated with low risk of bias for survival and unclear risk of bias for quality of life.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was described with all participants accounted for in terms of survival. The completion rates for quality of life scores was 45% out of all requested quality of life questionnaires given to participants at baseline, 3 weeks, 6 weeks, 3 months and 6 months of follow-up. The quality of life completion rate was deemed too low to make meaningful comparisons and as such, the authors did not comment on quality of life outcomes.
Selective reporting (reporting bias)	Unclear risk	Study protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest in this review were reported in a prespecified way. Quality of life may be prone to selective reporting. The extent to which selective reporting occurred for quality of life was unknown.
Other bias	Unclear risk	Size of study bias: 100 participants randomised.

Shin 1985

Study characteristics

Methods	Randomised, phase III trial Treatment period: accrued January 1981 to March 1984; analysis July 1984 Median follow-up: not described
Participants	124 randomised (71% grade III and 29% IV astrocytoma) from 2 Canadian centres; 62% aged ≥ 60 years and 38% < 60 years; 65% with Karnofsky performance status ≥ 70 and 35% with Karnofsky performance status < 70; percentage men and women not provided
Interventions	Arm 1: hyperfractionation: 6141 cGy in 69 fractions given as 89 cGy per fraction 3 times a day Arm 2: hyperfractionation as arm 1 + misonidazole Arm 3: conventional fractionation: 5800 cGy in 30 daily fractions
Outcomes	Survival (Kaplan-Meier curve presented up to 600 days)

Shin 1985 *(Continued)*

	Progression free survival (median time to progression)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described.
Allocation concealment (selection bias)	Unclear risk	Protection of treatment allocation before and until assignment was unclear as the method of randomisation was not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding of participants and personnel associated with low risk of bias for the outcome of survival and unclear risk of bias for progression free survival.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessments associated with low risk of bias for survival and unclear risk of bias for progression free survival.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was not described.
Selective reporting (reporting bias)	Unclear risk	Publication did not describe the protocol for follow-up assessment. The degree in which there may have been selective reporting for progression free survival was unknown.
Other bias	Unclear risk	Size of study bias: 124 randomised.

Walker 1978

Study characteristics

Methods	Randomised, phase III trial Treatment period: accrued 1 September 1969 to 1 October 1972 Median follow-up: not provided
Participants	303 randomised (10% grade III and 90% IV astrocytoma) from 10 centres in the US; median age 57 years; baseline performance status not described; 64% men and 36% women
Interventions	Arm 1: supportive care alone Arm 2: carmustine alone Arm 3: radiotherapy alone: 5000–6000 cGy given daily over 6–7 weeks to the whole brain Arm 4: carmustine + radiotherapy as arm 3
Outcomes	Survival (survival curves presented up to 24 months) Adverse events (time of assessment not provided)

Walker 1978 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation described as based on a telephone call to the study central office. No other details were included in the publication.
Allocation concealment (selection bias)	Unclear risk	Protection of treatment allocation before and until assignment was unclear as the method of randomisation was incompletely described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding of participants and personnel associated with low risk of bias for the outcome of survival and unclear risk for adverse events.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Lack of blinding for outcome assessment associated with low risk of bias for survival and unclear risk of bias for adverse events.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition not described.
Selective reporting (reporting bias)	Unclear risk	Study protocol was available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way. Adverse events may have been prone to selective reporting. The extent to which selective reporting occurred for adverse events is unknown.
Other bias	Low risk	Size of study bias: 303 randomised.

DFMO: difluoromethylornithine; ECOG: European Co-operative Oncology Group; WHO: World Health Organization.

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

Study	Reason for exclusion
Ali 2018	Randomised 712 participants to hyperfractionated radiation 72 Gy in 60 fractions given twice daily with carmustine vs 60 Gy in 30 daily fractions given with carmustine. Since all arms had chemotherapy and not radiation alone, this trial was excluded.
Buckner 2006	Trial examined conventional and accelerated radiotherapy with carmustine or with carmustine + cisplatin. As there was no radiotherapy alone arm, this trial was excluded.
Deutsch 1989	Trial randomised participants to 1 of 4 groups Arm 1: conventional radiotherapy: 6000 cGy in 30 to 35 daily fractions + carmustine. Arm 2: conventional radiotherapy + streptozotocin. Arm 3: hyperfractionated radiotherapy: 6600 cGy in 60 fractions given twice daily + carmustine. Arm 4: conventional radiotherapy with metronidazole followed by carmustine. As all arms received chemotherapy and not radiation alone, this trial was excluded.

Study	Reason for exclusion
Fulton 1984	Not all the participants were randomised; 9/42 participants were sequentially treated with hyperfractionation after the conventional radiotherapy arm was closed.
Guedes de Castro 2017	Reported a subset analysis of the Roa 2015 trial. As such this publication was also excluded.
Hatlevoll 1985	Randomised 280 participants to hypofractionated radiation alone vs conventional radiation alone or combined with lomustine, misonidazole or both chemotherapy agents (8 arms in total). The results of the radiation alone arms were not described.
Ludgate 1988	Randomised participants to hyperfractionated radiation vs conventional radiation. However, survival results could not be pooled as the authors showed survival curves for 3 different age groups rather than the total included participants in each arm of the trial.
Marshall 2006	Randomised participants to standard vs accelerated radiotherapy. However, all the arms had chemotherapy and there was no radiation alone arm. As such, this trial was excluded. The authors did not report overall survival or progression free survival outcomes.
Payne 1982	Randomised 157 adults with grade III or IV astrocytoma to 5000 cGy in 25 daily fractions (conventional radiotherapy) vs 3600–4000 cGy in 36–40 fractions of 100 cGy fractions given every 3 hours. All participants received oral lomustine. Because there was no radiation alone arm, this trial was excluded.
Roa 2015	Randomised 98 participants to 40 Gy in 15 daily fractions vs 25 Gy in 5 daily fractions. Both arms were hypofractionated radiation regimens. As there was no daily conventionally fractionated radiation arm, this trial was excluded.
Sandberg-Wollheim 1991	Randomised participants who were all treated with procarbazine, lomustine and vincristine chemotherapy. Half the participants received postoperative radiotherapy and the other half did not receive postoperative radiotherapy. Because there was no arm with supportive care alone or radiation alone, this trial was excluded.
Shapiro 1976	Randomised participants who were all treated with chemotherapy (carmustine and vincristine). Half the participants received postoperative radiotherapy and the other half did not receive postoperative radiotherapy. Because there was no arm with supportive care alone, this trial was excluded.
Shin 1983	Randomised controlled trial in 35 adults with grade III or IV astrocytoma treated with hyperfractionation or conventional radiation. Since both arms received chemotherapy (lomustine), this trial was excluded.
Simpson 1976	No conventionally fractionated radiotherapy standard arm in this trial.
Walker 1980	Randomised 467 participants to 1 of 4 groups Arm 1: semustine chemotherapy Arm 2: radiotherapy Arm 3: carmustine + radiotherapy Arm 4: semustine + radiotherapy Because there was no arm with supportive care alone, this trial was excluded.
Wick 2012	Randomised participants aged ≥ 65 years to temozolomide chemotherapy alone vs radiotherapy alone. Because there was no arm with supportive care alone, this trial was excluded.

DATA AND ANALYSES

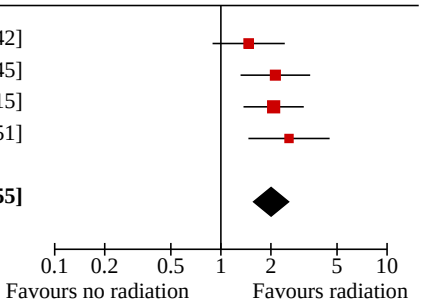
Comparison 1. Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	4		Hazard Ratio (IV, Random, 95% CI)	2.01 [1.58, 2.55]
1.2 Overall survival (sensitivity analysis)	3		Hazard Ratio (IV, Random, 95% CI)	2.20 [1.67, 2.90]

Analysis 1.1. Comparison 1: Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Andersen 1978	0.385	0.2552	23.2%	1.47 [0.89 , 2.42]
Keime-Guibert 2007	0.755	0.246	25.0%	2.13 [1.31 , 3.45]
Kristiansen 1981	0.731	0.213	33.4%	2.08 [1.37 , 3.15]
Walker 1978	0.944	0.287	18.4%	2.57 [1.46 , 4.51]
Total (95% CI)			**100.0%**	**2.01 [1.58 , 2.55]**

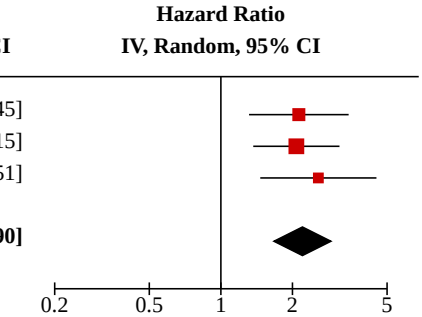
Heterogeneity: Tau² = 0.00; Chi² = 2.32, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 5.65 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone), Outcome 2: Overall survival (sensitivity analysis)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Keime-Guibert 2007	0.755	0.246	32.6%	2.13 [1.31 , 3.45]
Kristiansen 1981	0.731	0.213	43.5%	2.08 [1.37 , 3.15]
Walker 1978	0.944	0.287	23.9%	2.57 [1.46 , 4.51]
Total (95% CI)			**100.0%**	**2.20 [1.67 , 2.90]**

Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 2 (P = 0.82); I² = 0%
Test for overall effect: Z = 5.62 (P < 0.00001)
Test for subgroup differences: Not applicable



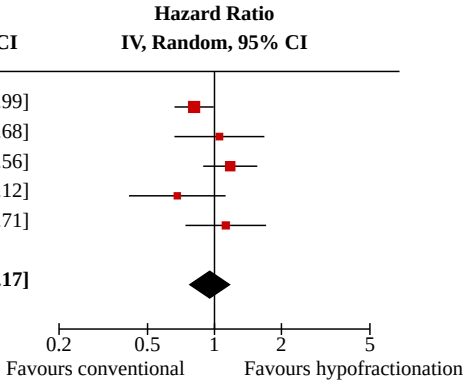
Comparison 2. Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall survival	5		Hazard Ratio (IV, Random, 95% CI)	0.95 [0.78, 1.17]
2.2 Overall survival (aged 60 years and older glioblastoma)	2		Hazard Ratio (IV, Random, 95% CI)	1.16 [0.92, 1.46]

Analysis 2.1. Comparison 2: Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy, Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Bleehen 1991	-0.211	0.1034	32.6%	0.81 [0.66 , 0.99]
Glinski 1993	0.051	0.2375	13.8%	1.05 [0.66 , 1.68]
Malmstrom 2012	0.163	0.1428	25.3%	1.18 [0.89 , 1.56]
Phillips 2003	-0.3853	0.2552	12.4%	0.68 [0.41 , 1.12]
Roa 2004	0.117	0.213	16.0%	1.12 [0.74 , 1.71]
Total (95% CI)			**100.0%**	**0.95 [0.78 , 1.17]**

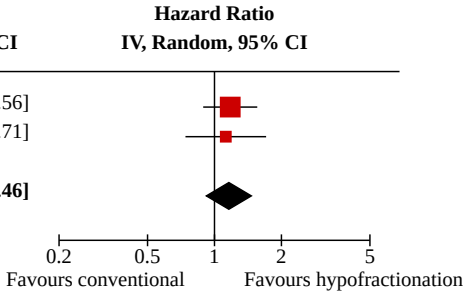
Heterogeneity: Tau² = 0.02; Chi² = 7.08, df = 4 (P = 0.13); I² = 43%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy, Outcome 2: Overall survival (aged 60 years and older glioblastoma)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Malmstrom 2012	0.163	0.1428	69.0%	1.18 [0.89 , 1.56]
Roa 2004	0.117	0.213	31.0%	1.12 [0.74 , 1.71]
Total (95% CI)			**100.0%**	**1.16 [0.92 , 1.46]**

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glioma] explode all trees
#2 (glioma* or glioblastoma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma*)
#3 #1 or #2
#4 MeSH descriptor: [Radiotherapy] explode all trees
#5 Any MeSH descriptor with qualifier(s): [Radiotherapy - RT]
#6 (radiotherap* or radiation or irradiation)
#7 #4 or #5 or #6

#8 (fraction* or hyperfractionat* or hypofractionat* or accelerat* or dose or dosage)
#9 MeSH descriptor: [Dose Fractionation] this term only
#10 #8 or #9
#11 #7 and #10
#12 MeSH descriptor: [Brachytherapy] explode all trees
#13 MeSH descriptor: [Radiosurgery] explode all trees
#14 brachytherapy or radiosurgery
#15 #11 or #12 or #13 or #14
#16 #3 and #15

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Glioma/
2 (glioma* or glioblastoma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma*).mp.
3 1 or 2
4 exp Radiotherapy/
5 radiotherapy.fs.
6 (radiotherap* or radiation or irradiation).mp.
7 4 or 5 or 6
8 (fraction* or hyperfractionat* or hypofractionat* or accelerat* or dose or dosage).mp.
9 dose fractionation/
10 8 or 9
11 7 and 10
12 brachytherapy.mp. or Brachytherapy/
13 radiosurgery.mp. or Radiosurgery/
14 11 or 12 or 13
15 3 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.
20 clinical trials as topic.sh.
21 randomly.ab.
22 trial.ti.
23 16 or 17 or 18 or 19 or 20 or 21 or 22
24 15 and 23

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

Appendix 3. Embase (Ovid) search strategy

1 exp glioma/
2 (glioma* or glioblastoma* or astrocytoma* or oligodendroglioma* or oligoastrocytoma*).mp.
3 1 or 2
4 exp radiotherapy/
5 rt.fs.
6 (radiotherap* or radiation or irradiation).mp.
7 4 or 5 or 6
8 (fraction* or hyperfractionat* or hypofractionat* or accelerat* or dose or dosage).mp.
9 radiation dose fractionation/
10 8 or 9
11 7 and 10
12 bracytherapy.mp. or exp brachytherapy/
13 radiosurgery.mp. or exp radiosurgery/
14 11 or 12 or 13
15 3 and 14
16 crossover procedure/
17 double-blind procedure/
18 randomized controlled trial/
19 single-blind procedure/

20 random*.mp.
21 factorial*.mp.
22 (crossover* or cross over* or cross-over*).mp.
23 placebo*.mp.
24 (double* adj blind*).mp.
25 (singl* adj blind*).mp.
26 assign*.mp.
27 allocat*.mp.
28 volunteer*.mp.
29 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 15 and 29

key:
[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 4. Assessment of risk of bias

Random sequence generation

- Low risk of bias, e.g. participants assigned to treatments on basis of a computer-generated random sequence or a table of random numbers.
- High risk of bias, e.g. participants assigned to treatments on basis of date of birth, clinic identification number or surname, or no attempt to randomise participants.
- Unclear risk of bias, e.g. not reported, information not available.

Allocation concealment

- Low risk of bias, e.g. where the allocation sequence could not be foretold.
- High risk of bias, e.g. allocation sequence could be foretold by participants, investigators or treatment providers.
- Unclear risk of bias, e.g. not reported.

Attrition

We recorded the proportion of participants whose outcomes were not reported at the end of the study. We coded a satisfactory level of loss to follow-up for each outcome as:

- low risk of bias, if less than 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
- high risk of bias, if more than 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms;
- unclear risk of bias if loss to follow-up was not reported.

Selection reporting of outcomes

- Low risk of bias, e.g. review reported all outcomes specified in the protocol.
- High risk of bias, e.g. it was suspected that outcomes were selectively reported.
- Unclear risk of bias, e.g. it was unclear whether outcomes had been selectively reported.

Appendix 5. GRADE checklist (daily conventionally fractionated radiotherapy versus no radiotherapy (supportive care alone): four trials)

Risk of bias

1. *Was random sequence generation used (i.e. no potential for selection bias)?* Andersen 1978 had a high risk of bias as randomisation was dependent on even or odd dates of birth.
2. *Was allocation concealment used (i.e. no potential for selection bias)?* Not applicable.
3. *Was there blinding of participants and personnel (i.e. no potential for performance bias)?* Not applicable.
4. *Was there blinding of outcome assessment (i.e. no potential for detection bias)?* Not applicable.
5. *Was an objective outcome used?* Yes, overall survival is objective and is the primary outcome. Adverse effects, progression free survival and quality of life are subject to reporting bias.
6. *Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential attrition bias)?* Attrition was not completely described in all the trials.
7. *No other biases reported (no potential of other bias*)? No

8. *Did the trials end as scheduled (i.e. not stopped early)?* Yes.

Overall risk of bias was downgraded as serious (–1).

Inconsistency

1. *Point estimates did not vary widely (i.e. no clinical meaningful inconsistency)?* The point estimates for survival did not vary widely.
2. *To what extent do confidence intervals overlap?* The confidence intervals with the point estimates are similar across the studies.
3. *Was the direction of effect consistent?* Yes.
4. *What was the magnitude of statistical heterogeneity (as measured by the I^2 statistic)?* 0%
5. *Was the test for heterogeneity statistically significant ($P < 0.1$)?* The test for heterogeneity was P = 0.51

Overall risk of inconsistency was not downgraded.

Indirectness

1. *Were the populations in included studies applicable to the target population?* Only Malmstrom 2012 and Roa 2004 focused on people with glioblastoma aged 60 years and older. Andersen 1978 only included people with glioblastoma. The other included trials included a heterogeneous group of grades III and IV glioma and did not separate the results for grades III or IV glioma.
2. *Were the interventions in included studies applicable to target intervention?* The older trials (other than Malmstrom 2012; Roa 2004) included outdated radiotherapy techniques (whole brain radiotherapy and 2 dimensional radiation planning techniques).
3. *Was the included outcome not a surrogate outcome?* The intended outcomes of overall survival, adverse events, progression free survival and quality of life are not surrogate outcomes.
4. *Was the outcome timeframe sufficient?* Yes.
5. *Were the conclusions based on direct comparisons?* Yes.

Overall risk of indirectness was downgraded as serious (–1).

Imprecision

1. *Was the confidence interval for the pooled estimate not consistent with benefit and harm?* The pooled estimate was consistent with benefit.
2. *What was the magnitude of the median sample size?* Sample size ranged from 73 to 135 participants.
3. *What was the magnitude of the number of included studies?* Four trials included.
4. *Was the outcome a common event (e.g. occurs more than 1/100)?* Yes, the outcome of survival (death) was a common event.
5. *Was there no evidence of serious harm associated with treatment?* There was no evidence of serious harm associated with radiotherapy as compared to no radiotherapy.

Overall risk of imprecision was not downgraded.

Publication bias

1. *Did the authors conduct a comprehensive search?* Yes.
2. *Did the authors search for grey literature?* Yes.
3. *Authors did not apply restrictions to study selection on the basis of language?* Yes, restricted to English.
4. *There was no industry influence on studies included in the review?* No industry influence.
5. *There was no evidence of funnel plot asymmetry?* Too few number of trials to assess for funnel plot asymmetry.
6. *There was no discrepancy in findings between published and unpublished trials?* No unpublished trials retrieved.

Overall risk of publication bias was undetected.

Appendix 6. GRADE checklist (hypofractionated radiotherapy daily conventionally fractionated radiotherapy: five trials)

Risk of bias

1. *Was random sequence generation used (i.e. no potential for selection bias)?* All the trials except Phillips 2003 described the method of randomisation and used methods for randomisation with no potential for selection bias.
2. *Was allocation concealment used (i.e. no potential for selection bias)?* Not applicable.
3. *Was there blinding of participants and personnel (i.e. no potential for performance bias)?* Not applicable.
4. *Was there blinding of outcome assessment (i.e. no potential for detection bias)?* Not applicable.

5. *Was an objective outcome used?* Overall survival was objective. Adverse events, progression free survival and quality of life are subject to reporting bias.
6. *Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential attrition bias)?* Attrition was well described in Malmstrom 2012 and Roa 2004 but not well described in the other trials.
7. *No other biases reported (no potential of other bias)?* Phillips 2003 had a high risk of bias as the study was closed early due to poor accrual. The publication only included 68 participants.
8. *Did the trials end as scheduled (i.e. not stopped early)?* Yes.

Overall risk of bias was downgraded as very serious (–2).

Inconsistency

1. *Point estimates did not vary widely (i.e. no clinical meaningful inconsistency)?* The point estimates did not vary widely.
2. *To what extent do confidence intervals overlap?* The confidence intervals overlap.
3. *Was the direction of effect consistent?* The direction of no effect was consistent.
4. *What was the magnitude of statistical heterogeneity (as measured by the I^2 statistic)?* 43%.
5. *Was the test for heterogeneity statistically significant ($P < 0.1$)?* P = 0.13.

Overall risk of inconsistency was not downgraded.

Indirectness

1. *Were the populations in included studies applicable to the target population?* Only Malmstrom 2012 and Roa 2004 included glioblastoma participants age 60 years and older. The other trials did not report results on glioblastoma or anaplastic astrocytoma separately.
2. *Were the interventions in included studies applicable to target intervention?* All the trials except for Malmstrom 2012 and Roa 2004 used outdated radiotherapy techniques.
3. *Was the included outcome not a surrogate outcome?* Overall survival, adverse effects, progression free survival and quality of life were not surrogate outcomes.
4. *Was the outcome timeframe sufficient?* Yes.
5. *Were the conclusions based on direct comparisons?* Yes.

Overall risk of indirectness downgraded as serious (–1).

Imprecision

1. *Was the confidence interval for the pooled estimate not consistent with benefit and harm?* Confidence interval for the pooled effect consistent with no benefit and no harm.
2. *What was the magnitude of the median sample size?* Sample size varied from 68 to 474 participants per trial.
3. *What was the magnitude of the number of included studies?* 5 included trials.
4. *Was the outcome a common event (e.g. occurs more than 1/100)?* Yes, survival (death) was a common event.
5. *Was there no evidence of serious harm associated with treatment?* No evidence of serious harm.

Overall risk of imprecision was not downgraded.

Publication bias

1. *Did the authors conduct a comprehensive search?* Yes.
2. *Did the authors search for grey literature?* Yes.
3. *Authors did not apply restrictions to study selection on the basis of language?* Studies restricted to English.
4. *There was no industry influence on studies included in the review?* No industry influence.
5. *There was no evidence of funnel plot asymmetry?* Too few number of trials to assess for funnel plot asymmetry.
6. *There was no discrepancy in findings between published and unpublished trials?* No discrepancy.

Overall risk of publication bias was undetected.

Appendix 7. GRADE checklist (hypofractionated radiotherapy versus daily conventionally fractionated radiotherapy for subgroup aged 60 years and older glioblastoma: two trials)

Risk of bias

1. *Was random sequence generation used (i.e. no potential for selection bias)? Yes.*
2. *Was allocation concealment used (i.e. no potential for selection bias)?* Not applicable.

3. *Was there blinding of participants and personnel (i.e. no potential for performance bias)?* Not applicable.
4. *Was there blinding of outcome assessment (i.e. no potential for detection bias)?* Not applicable.
5. *Was an objective outcome used?* The outcome of survival is objective. Adverse events, progression free survival and quality of life are subject to reporting bias.
6. *Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential attrition bias)? Yes.*
7. *No other biases reported (no potential of other bias)?* No.
8. *Did the trials end as scheduled (i.e. not stopped early)?* Yes.

Overall risk of bias was not downgraded.

Inconsistency

1. *Point estimates did not vary widely (i.e. no clinical meaningful inconsistency)?* Point estimates did not vary widely.
2. *To what extent do confidence intervals overlap?* Confidence intervals overlap.
3. *Was the direction of effect consistent?* Consistent no effect.
4. *What was the magnitude of statistical heterogeneity (as measured by the I^2 statistic)?* 0%.
5. *Was the test for heterogeneity statistically significant ($P < 0.1$)?* P = 0.86.

Overall risk of inconsistency was not downgraded.

Indirectness

1. *Were the populations in included studies applicable to the target population?* Yes, all people with glioblastoma aged 60 years and older.
2. *Were the interventions in included studies applicable to target intervention?* All the trials used contemporary radiation planning techniques.
3. *Was the included outcome not a surrogate outcome?* Overall survival, adverse events, progression free survival and quality of life were not surrogate outcomes.
4. *Was the outcome timeframe sufficient?* Yes.
5. *Were the conclusions based on direct comparisons?* Yes.

Overall risk of indirectness was not downgraded.

Imprecision

1. *Was the confidence interval for the pooled estimate not consistent with benefit and harm?* Yes, consistent with no effect.
2. *What was the magnitude of the median sample size?* The sample size ranged from 95 to 198 participants.
3. *What was the magnitude of the number of included studies? 2* trials included.
4. *Was the outcome a common event (e.g. occurs more than 1/100)?* Yes.
5. *Was there no evidence of serious harm associated with treatment?* No evidence of serious harm.

Overall risk of imprecision was not downgraded.

Publication bias

1. *Did the authors conduct a comprehensive search?* Yes.
2. *Did the authors search for grey literature?* Yes.
3. *Authors did not apply restrictions to study selection on the basis of language?* Studies restricted to English.
4. *There was no industry influence on studies included in the review?* No industry influence.
5. *There was no evidence of funnel plot asymmetry?* Too few number of trials to assess for funnel plot asymmetry.
6. *There was no discrepancy in findings between published and unpublished trials?* No.

Publication bias was undetected.

WHAT'S NEW

Date	Event	Description
5 August 2020	Amended	Republished to correct review format error.

HISTORY

Protocol first published: Issue 1, 2015
Review first published: Issue 8, 2016

Date	Event	Description
11 May 2020	New citation required but conclusions have not changed	No new studies identified for inclusion. Conclusions remain unchanged.
11 May 2020	New search has been performed	New search August 2019.
27 January 2015	Amended	Text amendment

CONTRIBUTIONS OF AUTHORS

All review authors participated in the design and execution of the protocol. All review authors participated in the preparation of the full review.

DECLARATIONS OF INTEREST

Luluel Khan: has received a grant from Society of Neuro Oncology to attend Cochrane training workshop.
Hany Soliman: none known.
Arjun Sahgal: is an advisor/consultant with Abbvie, Merck, Roche, Varian (Medical Advisory Group), Elekta (Gamma Knife Icon), BrainLAB, and VieCure (Medical Advisory Board); is a board member for International Stereotactic Radiosurgery Society (ISRS); has received past educational seminars with Elekta AB, Accuray Inc., Varian (CNS Teaching Faculty), BrainLAB, Medtronic Kyphon; has received travel accommodations/expenses by Elekta, Varian, BrainLAB; and also belongs to the Elekta MR Linac Research Consortium, Elekta Spine, Oligometastases and Linac Based SRS Consortia. None of the above are related to the current work.
James Perry: has received compensation for an advisory role with Jay Pharma unrelated to this review.
Wei Xu: none known.
May N Tsao: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Society of Neuro-Oncology, USA

  Cochrane Fellowship Grant (for Dr Luluel Khan)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have added the GRADE approach to classify the certainty of the evidence as high, moderate, low or very low. We added adverse effects as another primary outcome and progression free survival and quality of life as secondary outcomes. As contemporary radiation management for HGG is highly dependent on age (a strong prognostic factor), we added the following subgroup analyses, where possible: aged 60 years and over, aged 65 years and over, and aged 70 years and over.

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Brain Neoplasms [mortality] [pathology] [*radiotherapy]; Cranial Irradiation [*methods] [mortality]; Disease-Free Survival; *Dose Fractionation, Radiation; Glioma [mortality] [pathology] [*radiotherapy]; Quality of Life; Randomized Controlled Trials as Topic; Survival Analysis

MeSH check words

Adult; Aged; Humans; Middle Aged