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[Intervention Review]

Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas

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ABSTRACT

Background

This is an update of the review originally published in 2011 and first updated in 2015.

In most people with low-grade gliomas (LGG), the primary treatment regimen remains a combination of surgery followed by postoperative radiotherapy. However, the optimal timing of radiotherapy is controversial. It is unclear whether to use radiotherapy in the early postoperative period, or whether radiotherapy should be delayed until tumour progression occurs.

Objectives

To assess the effects of early postoperative radiotherapy versus radiotherapy delayed until tumour progression for low-grade intracranial gliomas in people who had initial biopsy or surgical resection.

Search methods

Original searches were run up to September 2014. An updated literature search from September 2014 through November 2019 was performed on the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 11), MEDLINE via Ovid (September 2014 to November week 2 2019), and Embase via Ovid (September 2014 to 2019 week 46) to identify trials for inclusion in this Cochrane review update.

Selection criteria

We included randomised controlled trials (RCTs) that compared early versus delayed radiotherapy following biopsy or surgical resection for the treatment of people with newly diagnosed intracranial LGG (astrocytoma, oligodendroglioma, mixed oligoastrocytoma, astroblastoma, xanthoastrocytoma, or ganglioglioma). Radiotherapy may include conformal external beam radiotherapy (EBRT) with linear accelerator or cobalt-60 sources, intensity-modulated radiotherapy (IMRT), or stereotactic radiosurgery (SRS).

Data collection and analysis

Three review authors independently assessed the trials for inclusion and risk of bias, and extracted study data. We resolved any differences between review authors by discussion. Adverse effects were also extracted from the study report. We performed meta-analyses using a random-effects model with inverse variance weighting.

Main results

We included one large, multi-institutional, prospective RCT, involving 311 participants; the risk of bias in this study was unclear. This study found that early postoperative radiotherapy was associated with an increase in time to progression compared to observation (and delayed radiotherapy upon disease progression) for people with LGG but did not significantly improve overall survival (OS). The median progression-free survival (PFS) was 5.3 years in the early radiotherapy group and 3.4 years in the delayed radiotherapy group (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.45 to 0.77; $P < 0.0001$; 311 participants; 1 trial; low-quality evidence). The median OS in the early radiotherapy group was 7.4 years, while the delayed radiotherapy group experienced a median overall survival of 7.2 years (HR 0.97, 95% CI 0.71 to 1.33; $P = 0.872$; 311 participants; 1 trial; low-quality evidence). The total dose of radiotherapy given was 54 Gy; five fractions of 1.8 Gy per week were given for six weeks. Adverse effects following radiotherapy consisted of skin reactions, otitis media, mild headache, nausea, and vomiting. Rescue therapy was provided to 65% of the participants randomised to delayed radiotherapy. People in both cohorts who were free from tumour progression showed no differences in cognitive deficit, focal deficit, performance status, and headache after one year. However, participants randomised to the early radiotherapy group experienced significantly fewer seizures than participants in the delayed postoperative radiotherapy group at one year (25% versus 41%, $P = 0.0329$, respectively).

Authors' conclusions

Given the high risk of bias in the included study, the results of this analysis must be interpreted with caution. Early radiation therapy was associated with the following adverse effects: skin reactions, otitis media, mild headache, nausea, and vomiting. People with LGG who underwent early radiotherapy showed an increase in time to progression compared with people who were observed and had radiotherapy at the time of progression. There was no significant difference in overall survival between people who had early versus delayed radiotherapy; however, this finding may be due to the effectiveness of rescue therapy with radiation in the control arm. People who underwent early radiation had better seizure control at one year than people who underwent delayed radiation. There were no cases of radiation-induced malignant transformation of LGG. However, it remained unclear whether there were differences in memory, executive function, cognitive function, or quality of life between the two groups since these measures were not evaluated.

PLAIN LANGUAGE SUMMARY

Are there any differences in survival between people with low-grade glioma having early compared with delayed radiotherapy at the time of progression?

The issue

Low-grade gliomas (LGG) are brain tumours that predominantly affect young adults. They grow at slower rates and are typically associated with a favourable prognosis compared with high-grade gliomas. One of the most common presenting symptoms of people with LGG are seizures. Although, there are no definitive guidelines on the management of LGGs, most people with LGGs are treated with a combination of surgery followed by radiotherapy. However, it is unclear whether to use radiotherapy in the early postoperative period, or to delay until the disease progresses.

Aim of the review:

We aimed to compare the timing of radiotherapy from early (the postoperative period) or whether it should be delayed until the disease (tumour) re-occurs.

What are the main findings?

From the literature search in September 2014, we included one randomised controlled trial, involving 311 participants, that looked at early or delayed radiotherapy given at the time of disease progression in people with LGG. This study was well-designed and reported useful data on survival, but did not include other clinically important information, such as functional independent survival (functional, or neurological impairment, or both) and quality of life. Therefore, we felt that the trial was of unclear quality. People who received early (soon after surgery) radiotherapy had a longer time until their disease progressed than people who only had radiotherapy once the disease had progressed. However, the people that were initially observed had similar survival to the people who had early radiotherapy. Quality of life measures such as memory, executive function, and cognitive deterioration differences were not evaluated in either group. The findings did not suggest that people who received early radiotherapy lived longer than those had delayed radiotherapy. However, people who had early radiotherapy had better control over their seizures than those who had delayed radiotherapy. The toxic effects of radiotherapy were rated as minimal in both groups using a grading system which measured severity and included skin reactions, ear inflammation, mild headache, nausea, and vomiting.

Update searches in November 2019 found no new articles which met the inclusion criteria. No articles were considered eligible for inclusion in this review update.

What are the conclusions?

Based on the current evidence, the results should be interpreted with caution. It is unclear whether or not early radiotherapy is better than delayed radiotherapy because survival was the same in both groups. People who had early radiotherapy experienced longer periods of tumour remission compared with patients who had delayed radiotherapy. However, it is unclear if these people suffered increased rates of cognitive impairment, neuroendocrine dysfunction, or radiation necrosis compared with people who had delayed radiotherapy. Toxic effects of radiation were minimal in both groups and there were no cases of second malignancies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table 1

Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas

Patient or population: People with supratentorial and histologically proven low-grade astrocytoma (including incompletely resected grade I pilocytic astrocytomas); WHO performance status 0 to 2 or Karnofski performance of 60 or more; age between 16 and 65 years; no other significant systemic diseases or malignancies interfering with follow-up; not pregnant. Note: People with completely resected small grade I tumours (pilocytic astrocytoma), optic nerve glioma, brainstem glioma, and third ventricular gliomas were ineligible.

Settings: Between March 1986 and September 1997, eligible participants from the inpatient or outpatient settings from 24 institutions across Europe randomly allocated to intervention or control group

Intervention: Early radiotherapy

Comparison: Delayed radiotherapy at the time of recurrence

Outcomes	Illustrative comparative risks		Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Overall survival Median 7.8 years follow-up	See comment	See comment	HR 0.97 (0.71 to 1.33)	311 (1 trial)	⊕⊕ ¹ Low	Due to the way HRs are calculated, the assumed and corresponding risks were not estimated.
Progression-free survival Median 7.8 years follow-up	See comment	See comment	HR 0.59 (0.45 to 0.77)	311 (1 trial)	⊕⊕ ¹ Low	Due to the way HRs are calculated, the assumed and corresponding risks were not estimated.

CI: confidence interval; HR: hazard ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

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

Low quality: 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 quality: We are very uncertain about the estimate.

¹We downgraded the quality of evidence to low from moderate (from the initial draft) after more careful assessment of the risk of bias in Karim 2002; Van den Bent 2005. Specifically, we felt that the lack of allocation concealment, blinding of participants and blinding of outcome assessment introduced sufficient bias to skew the true effects of early versus

delayed postoperative radiation therapy on survival and progression-free survival. These biases raise concerns about the precision and accuracy of the point estimates and associated CIs used to report the primary outcomes.

BACKGROUND

Description of the condition

This is an update of the review originally published in 2011 ([Venteicher 2011](#)), and updated in 2015 ([Venteicher 2011](#)).

Low-grade gliomas (LGG) comprise a group of uncommon, progressive, and slow-growing central nervous system (CNS) tumours that affect approximately 3000 and 9000 people per year in the USA and Europe, respectively, and account for 20% of all gliomas ([Ostrom 2014](#); [RARECARE 2011](#)). The incidence of LGG peaks in adulthood, with increased prevalence among whites and men ([Ostrom 2014](#)). Compared to the quick pace of tumour progression in people with high-grade glioma, those with LGG typically live with the disease for between five to 20 years. Mean overall survival (OS) ranges from three to six years, four to seven years, and nine to 12 years for three common types of LGG (astrocytoma, mixed oligoastrocytoma, and oligodendroglioma, respectively) ([Jaeckle 2011](#); [Ohgaki 2005](#); [Shaw 1997](#)). Median progression-free survival (PFS) for people with LGG who were treated in the post-temozolomide era was 22 months ([Quinn 2003](#)). In 45% to 74% of cases, LGG subsequently transforms into higher grade glioma ([Jaeckle 2011](#)). Determining the optimal management of people with LGG, given their relatively long survival, has been a carefully studied topic that as yet remains controversial.

Most people with LGG (approximately 80%) present with seizures ([Chang 2008a](#)). Other presentations include personality changes, headache, nausea, and lethargy ([DeAngelis 2001](#)). Neurological symptoms largely reflect the location and size of the tumour. LGG commonly occupies frontal or temporal lobes, particularly the supplemental motor area and insula ([Duffau 2004](#)). Gliomas have a predilection for growing along white matter tracts into adjacent territories and the contralateral hemisphere. Diagnosis suggested by computerised tomography (CT) or magnetic resonance imaging (MRI), typically as a non-enhancing lesion with little mass effect or vasogenic edema, is confirmed by microscopic analysis of a surgical tissue sample. Pathology establishes two key characteristics: the grade and subtype. LGG include grade 1 and 2 gliomas as defined by the World Health Organization (WHO) classification scheme ([Louis 2007](#)). WHO grade 1 tumours, such as pilocytic astrocytomas, are amenable to surgical cure by gross total resection (GTR). In unfortunate cases, involvement of eloquent cortex or key vascular structures may limit the ability to obtain a GTR. WHO grade 2 tumours are not readily cured surgically; these include diffuse astrocytoma, oligodendroglioma, mixed oligoastrocytoma, xanthoastrocytoma, astroblastoma, and ganglioglioma. WHO grade 2 and incompletely resected WHO grade 1 tumours are often grouped together in clinical trials, as clinical course is protracted and multi-modality therapies are usually required.

Initial management is based on symptomatology. Since most present with seizures, anti-epileptic drugs (AEDs) are often employed for early seizure control ([Soffietti 2010](#)), but about half of these people are refractory to AEDs ([Chang 2008a](#)). For tumours displaying vasogenic edema (increased fluid in the extracellular space of the brain) on MRI, steroids are often given. In rarer cases, the tumour may cause obstructive hydrocephalus (abnormal increase in the intracranial volume of cerebrospinal fluid resulting from obstruction of cerebrospinal fluid pathways in the ventricular

system or subarachnoid space) or increased intracranial pressure necessitating decompressive or drainage manoeuvres. Once these initial measures are taken, the patient is then considered for further management based on prognostic factors such as the patient's age, symptoms, mental and performance status, location and size of tumour, involvement of eloquent cortex, contrast enhancement on MRI, and histologic/genetic aberrations of the tumour ([Chang 2008b](#); [Daniels 2011](#); [Lote 1997](#); [Pignatti 2002](#); [Scerrati 1996](#); [Schiff 2007](#); [Yeh 2005](#)).

Further management involves surgery, radiotherapy, chemotherapy, or a combination of these modalities. Surgery is first-line therapy whose chief role is to provide tissue to confirm the diagnosis. In addition, a goal of achieving more extensive resection (over biopsy alone) is often favoured because, in retrospective analyses, it is associated with prolonged survival ([Claus 2005](#); [Keles 2001](#); [McGirt 2008](#); [Sanai 2008](#); [Schomas 2009](#); [Smith 2008](#); [Van Veelen 1998](#)), greater seizure control ([Chang 2008a](#)), and reduced risk of transformation to a higher grade ([Chaichana 2010](#); [Smith 2008](#)).

The next most common step in management is radiotherapy: either early radiotherapy (within a few weeks of surgery) or delayed radiotherapy (at time of clinical or imaging progression). Controversy exists on its optimal timing ([Chan 2010](#)). Radiation induces apoptosis of mitotically active tumour cells (programmed cell death of actively dividing cancer cells), but also damages normal surrounding brain tissue. Radiation causes oedema from breakdown of the blood-brain barrier, reactive gliosis (a non-specific change of glial cells in response to damage to the CNS), and a general pro-inflammatory state ([Kim 2008](#)). Early adverse effects of radiation include headache, dizziness, ear inflammation, nausea, vomiting, seizure, altered level of consciousness, alopecia, dermatitis, urinary incontinence, and personality change ([CTCAE 2009](#)). Late clinical consequences of brain irradiation include leukoencephalopathy, neurocognitive decline, reduced quality of life (QoL), and tissue necrosis that may mimic tumour progression ([Douw 2009](#); [Surma-aho 2001](#)). The toxic effects of radiotherapy must be carefully weighed against the benefits for tumour control, including an improvement of seizures ([Rudà 2013](#)).

Promising alternative therapeutic modalities include stereotactic radiosurgery (SRS) and chemotherapy. SRS can produce long-term control with an acceptable toxicity profile ([Combs 2005](#); [Heppner 2005](#); [Plathow 2003](#); [Wang 2006](#)), and is generally reserved for inoperable tumours in close proximity to critical structures. Similarly, chemotherapy has potential either as a concurrent treatment or substitute for radiotherapy and can also improve seizure control ([Rudà 2012](#)). Studies have focused primarily on a three-drug regimen of procarbazine, lomustine, and vincristine (PCV) or single agent temozolomide. Ongoing randomised controlled trials (RCTs) are evaluating whether temozolomide can substitute for radiotherapy ([EORTC-22033-26033-ROG-BTG](#)), or whether concurrent temozolomide and radiotherapy is superior to radiotherapy alone for postoperative tumour control ([NCT00978458](#); [NCT00114140](#)). While standard use of these alternative modalities await trial completion, the current primary effective treatment regimen remains a combination of surgery followed by radiotherapy.

Description of the intervention

The most common approach to people with LGG includes surgery (biopsy or resection) followed by either early (within a few weeks) or delayed (at the time of clinical progression) radiotherapy. Options for radiotherapeutic delivery exist, which include conformal EBRT, IMRT, and SRS. Each uses dedicated CT or MRI to guide dosimetry and planning, but vary in the technique used to specifically irradiate the tumour while minimising exposure of normal brain tissue. Sources for high-energy photons include cobalt-60 or a linear accelerator, with typical dosage in the 45 to 60 Gy range, delivered in 1.8 to 2.0 Gy fractions over a four- to eight-week period. Standard radiation treatment fields target the tumour bed with a small (usually 2 cm) margin. Radiation produces double-stranded DNA breaks and reactive oxygen species in the target tissue, resulting in damage to cycling cells of the tumour but also to normal brain tissue caught in the irradiated field.

How the intervention might work

The diffusely infiltrative nature of LGG makes even GTRs unlikely to be curative. Early radiotherapy is employed to arrest or kill any residual tumour cells, which may prolong time to tumour recurrence and increase survival. However, early radiotherapy will lead to earlier onset of late adverse effects of radiation, including neurocognitive decline and reduced QoL. In contrast, a strategy of delayed radiotherapy administered at time of tumour recurrence delays radiation exposure and its late adverse effects, but may allow tumour recurrence to occur more quickly.

Why it is important to do this review

A fundamental question in the management in LGG has been whether to use radiotherapy in the early postoperative period, or whether radiotherapy should be delayed until tumour progression occurs. Reasons why LGG has been difficult to study in large clinical trials include: (1) the diagnosis is uncommon requiring multi-institution participation and longer enrolment times; and (2) people with LGG have long survival times requiring extensive follow-up. Therefore, consolidating data from available trials through systematic review may provide sufficient power to generate new insights into this uncommon and controversial disease. In addition, in light of new treatment modalities becoming available on an ongoing basis, summarising the currently available literature will be important in the design of future clinical trials for people with LGG.

OBJECTIVES

To assess the effects of early postoperative radiotherapy versus radiotherapy delayed until tumour progression for low-grade intracranial gliomas in people who had initial biopsy or surgical resection.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs.

Types of participants

We included people who met the following criteria:

- Any age.
- Intracranial LGG.
- Histological types: astrocytoma, oligodendroglioma, mixed oligoastrocytoma, astroblastoma, xanthoastrocytoma, or ganglioglioma. This must be determined based on pathology review.
- Grade: WHO grade 2 or incompletely resected WHO grade 1. This must be determined based on pathology review.
- People will have undergone surgery, including: biopsy, partial resection (PR; less than 50%), subtotal resection (STR; 50 to 89%) or GTR (greater than 90%). This will be determined by either intra-operative judgement or by radiologic evaluation by the patient's primary neurosurgical team.

We excluded people documented as meeting any of the following criteria at time of trial entry:

- People who received previous cranial radiation.
- People who underwent craniotomy other than for biopsy or resection for the LGG.
- People who received previous chemotherapy.

Types of interventions

We limited interventions to the comparison of early postoperative radiotherapy versus radiotherapy delayed until tumour progression following biopsy or surgical resection in LGG management. Radiotherapy may include conformal EBRT with linear accelerator or cobalt-60 sources, IMRT, or SRS. In cases where glioma progression occurs following postoperative early or delayed radiotherapy, rescue therapy may involve a combination of repeat surgery, repeat radiotherapy, or chemotherapy and these cases were recorded.

Types of outcome measures

Primary outcomes

1. OS, defined as survival until death from all causes from time of randomisation.
2. PFS, defined as survival until evidence of tumour recurrence is documented by CT or MRI scan.

We defined recurrence according to [Revised Assessment in Neuro-Oncology](#) (RANO) criteria if data were available (see 'Local tumour control' in [Secondary outcomes](#) and [Appendix 1](#)).

Secondary outcomes

1. Survival after progression (SAP), defined as survival after patient shows radiological evidence of tumour progression until death from all causes. Please refer to [Differences between protocol and review](#).
2. Functionally independent survival (FIS), defined as: (1) a Karnofsky Performance Scale (KPS) score of $\geq 70\%$ ([Karnofsky 1949](#); [Karnofsky 1951](#)); (2) Medical Research Council neurologic functional status (MRC-NFS) score of one to two ([MRC 1983](#)); or (3) WHO Performance Scale (WHO-PS) score of zero to two ([Zubrod 1960](#)). These scales classify people according to functional, or neurological impairment, or both (see [Appendix 2](#)).
3. Disease-specific survival (DSS), defined by survival until death due to neurological cause from time of randomisation.

4. Steroid requirement, rated as worsened, unchanged, or improved.
5. Seizure frequency, rated as increased, unchanged, or decreased.
6. Local tumour control, rated by CT or MRI compared with baseline scan; based on RANO response criteria for LGG (Van den Bent 2011) (see Appendix 1).
7. Cause of death.
8. QoL, as measured using a scale validated through reporting of norms in a peer-reviewed publication such as the European Organisation for Research and Treatment of Cancer (EORTC) Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) (Aronson 1993), EORTC brain tumour module (QLQ-BN20) (Taphoorn 2010), Functional Assessment of Cancer Therapy: General (FACT-G) or FACT- brain (FACT-Br) (Weitzner 1995), or the MD Anderson Symptom Inventory for brain tumour MDASI-BT (Armstrong 2006).
9. Adverse events caused by radiotherapy, which cannot be attributed to the tumour, as graded per the Common Terminology Criteria for Adverse Events (CTCAE 2009). Adverse events are graded on up to a five-point scale outlined below. See CTCAE 2009 for specific grading of each adverse event:
 - Adverse events included the following: headache (graded one to three), dizziness (graded one to three), otitis/ear inflammation (graded one to five), nausea (graded one to three), depressed level of consciousness (graded one to five), seizure (graded one to five), personality change (graded one to five), CNS necrosis (graded one to five), CNS symptoms not otherwise specified (graded one to five), alopecia (graded one to two), dermatitis (graded one to five), and urinary incontinence (graded one to three).
 - * Grade 1: 'mild' defined as asymptomatic or mild symptoms with no intervention necessary.
 - * Grade 2: 'moderate' defined as requiring only minimal, local, or non-invasive intervention.
 - * Grade 3: 'severe' defined as disabling but not immediately life-threatening requiring hospitalisation.
 - * Grade 4: 'life-threatening' and requiring urgent intervention.
 - * Grade 5: 'death' related to adverse event(s).

Search methods for identification of studies

Electronic searches

We searched, up to September 2014, the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2014, Issue 8) (Appendix 3), MEDLINE (1948 to Aug week 3, 2014) (Appendix 4), and Embase (1980 to Aug week 3, 2014) (Appendix 5). All relevant articles were identified on PubMed and we carried out a further search for newly published articles using the 'related articles' feature.

Update searches were run in November 2019 on the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 11), MEDLINE via Ovid (September 2014 to November week 2, 2019), and Embase via Ovid (September 2014 to 2019 week 46).

Searching other resources

Unpublished and grey literature

We searched the [MetaRegister of Controlled Trials](#) (MRCT), Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, and www.cancer.gov/clinicaltrials for ongoing trials. We agreed a priori that if ongoing trials which had not been published were identified through these searches, we would contact the principal investigators to request any relevant data. We approached the major co-operative trial groups active in this area in a similar manner.

Conference proceedings and abstracts were searched through ZETOC (<http://zetoc.mimas.ac.uk>).

We searched for theses and dissertations through WorldCat (<http://firstsearch.oclc.org>).

Handsearching

We checked the reference lists of included studies, key textbooks, and previous systematic reviews by handsearching. Journal and conference materials over the past year were handsearched in the following sources:

- British Journal of Cancer.
- Neurosurgery.
- Annual Meeting of the American Society for Radiation Oncology (ASTRO).
- Annual Meeting of the American Association for Neurological Surgeons (AANS).
- Annual Meeting of European Society of Medical Oncology (ESMO).
- Annual Meeting of the American Society of Clinical Oncology (ASCO).

Correspondence

We contacted the authors of relevant trials and experts at major hospitals performing clinical trials to identify further data which may or may not have been published.

Language

We sought papers in all languages and performed translations, if necessary.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to the reference management database Endnote (ENDNOTE 2014). We removed duplicates and three review authors (AV, JMS, CP) independently examined the remaining references. The review authors were not blinded to the author(s) or affiliations of the studies. We excluded studies which clearly did not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Three review authors (AV, JMS, CP) independently assessed the eligibility of retrieved papers. We resolved disagreements by discussion between all review authors, and documented the reasons for exclusion of studies.

Data extraction and management

For included studies, we extracted data as recommended in Chapter 7 (Higgins 2011b) of Higgins 2011a. This included data on the following:

- Author, year of publication and journal citation (including language).
- Country.
- Setting.
- Inclusion and exclusion criteria.
- Study design, methodology.
- Study population
 - * total number enrolled
 - * patient characteristics
 - * age
 - * sex
 - * comorbidities
 - * previous treatment
 - * neurological performance.
- Tumour details at diagnosis
 - * tumour size
 - * tumour location
 - * tumour histology.
- Intervention details
 - * details of surgery
 - ☐ extent of biopsy/resection.
 - * details of radiotherapy
 - ☐ type
 - ☐ dose
 - ☐ fractions
 - ☐ time from surgery until radiotherapy
 - ☐ tumour progression at the time of radiotherapy
 - ☐ duration.
 - * details of rescue therapy
 - ☐ surgery, chemotherapy and/or additional radiotherapy at the time of relapse.
- Risk of bias in study (Assessment of risk of bias in included studies).
- Duration of follow-up.
- Outcomes, which included OS, PFS, SAP, FIS, local tumour control, cause of death, steroid requirement, seizure frequency, DSS, adverse events, and QoL (Types of outcome measures).

We extracted data on outcomes as follows:

- For time-to-event data (e.g. OS, PFS, SAP, DSS and local tumour control rates), we extracted the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998. If these variables could not be estimated, we reported available proportions with corresponding P values.
- For dichotomous outcomes (e.g. adverse events or deaths if it was not possible to use a HR), 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 these were not

reported, we attempted to estimate them from other reported statistics. If these variables could not be estimated, we reported available proportions with corresponding P values.

- For continuous outcomes (e.g. QoL measures), we extracted the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) (if trials measured outcomes on the same scale) or standardised MDs (if trials measured outcomes on different scales) between treatment arms and its standard error.

Where possible, all data extracted were those relevant to an intention-to-treat (ITT) analysis, in which participants are analysed in groups to which they are assigned.

We noted the time points at which outcomes were collected and reported.

Three review authors (AV, JMS, CP) extracted data independently onto a data extraction form specially designed for this Cochrane review. We resolved any differences between review authors by discussion.

Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using the following questions and criteria (see Chapter 8 (Higgins 2011c) of Higgins 2011a):

Sequence generation

Was the allocation sequence adequately generated?

- Low, e.g. a computer-generated random sequence or a table of random numbers.
- High, e.g. date of birth, clinic ID-number or surname.
- Unclear, e.g. not reported.

Allocation concealment

Was allocation adequately concealed?

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

Blinding

We restricted the assessment of blinding to blinding of outcome assessors, since it was not possible to blind participants and treatment providers to the different interventions.

Was knowledge of the allocated interventions adequately prevented during the trial?

- Low.
- High.
- Unclear.

Performance bias

Was similar care provided to participants in treatment and control groups other than the intervention of interest?

- Low, e.g. the investigators followed both groups on similar schedules of neurologic exam and brain imaging.
- High, e.g. the investigators followed each group according to different schedules.
- Unclear, e.g. not reported.

Incomplete reporting of outcome data

We recorded the proportion of participants whose outcomes were not reported at the end of the trial.

Were incomplete outcome data adequately addressed?

- Low, if < 20% of participants were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms.
- High, if > 20% of participants were lost to follow-up or reasons for loss to follow-up differed between treatment arms.
- Unclear, if loss to follow-up was not reported.

Selective reporting of outcomes

Were reports of the study free of suggestion of selective outcome reporting?

- Low, e.g. if review reported all outcomes specified in the protocol ([Venteicher 2011](#)).
- High, otherwise.
- Unclear, if insufficient information available.

Other potential threats to validity

Was the study apparently free of other problems that could put it at a high risk of bias?

- Low.
- High.
- Unclear.

Three review authors (AV, JMS, CP) independently applied the 'Risk of bias' tool and we resolved differences by discussion. We presented results in both a 'Risk of bias' graph and a 'Risk of bias' summary. We interpreted results of meta-analyses in light of the findings with respect to risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- For time-to-event data, we used the HR, where possible.
- For dichotomous outcomes, we used the RR.
- For continuous outcomes, we used the MD between treatment arms or the standardised MD where outcomes were not measured on the same scale.

Unit of analysis issues

Three review authors (AV, JMS, CP) reviewed unit of analysis issues according to [Higgins 2011a](#) and we resolved differences by discussion. These included reports where:

- Groups of individuals were randomised together to the same intervention (i.e. cluster-RCTs);
- Individuals underwent more than one intervention (e.g. in a cross-over trial, or simultaneous treatment of multiple sites on each individual); or

- There were multiple observations for the same outcome (e.g. repeated measurements, recurring events, measurements on different body parts).

Dealing with missing data

We did not impute missing outcome data.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between studies which could not be ascribed to sampling variation ([Higgins 2003](#)), and by a formal statistical test of the significance of the heterogeneity ([Deeks 2001](#)). We investigated and reported possible reasons for heterogeneity. In studies demonstrating evidence of substantial heterogeneity, Heterogeneity (I^2) was defined according to the study by Higgins et al ([Higgins 2003](#)) where I^2 values of 25%, 50% and 75% are categorised as low, moderate and high, respectively.

Assessment of reporting biases

Three review authors (AV, JMS, CP) reviewed and recorded reporting biases.

Data synthesis

If sufficient, clinically-similar studies were available, we pooled the results in meta-analyses.

- For time-to-event data, we pooled HRs using the generic inverse variance facility of [Review Manager \(RevMan\)](#).
- For dichotomous outcomes, we calculated the RR for each study and then pooled the estimates.
- For continuous outcomes, we pooled the MDs between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale, otherwise we pooled standardised mean differences (SMDs).

We used fixed-effect models with inverse variance weighting for all meta-analyses ([DerSimonian 1986](#)). A random-effects model was originally stated in the protocol; however, given that our meta-analysis only included one study, we opted to use a fixed-effect computational model to report a more descriptive analysis of the included study ([Borenstein 2009](#)).

Subgroup analysis and investigation of heterogeneity

We analysed outcome measures including OS, PFS, SAP, FIS, steroid requirement, seizure frequency, QoL, and adverse effects of radiotherapy after stratifying by the following clinical characteristics (if data were available): age, histologic subtype, tumour size and location, extent of resection, performance score, approach of radiotherapy used (conformal EBRT, IMRT, SRS), types of rescue therapy (repeat resection, repeat radiotherapy, chemotherapy), genetic aberrations (p53 status, 1p/19q status), and date of trial.

We considered the following clinical factors during interpretation of any heterogeneity: age, tumour size, histologic subtype, definition used for 'tumour recurrence' and PFS, and length of follow-up.

Sensitivity analysis

Two review authors (AV, CP) determined the requirement for sensitivity analysis and we resolved differences through discussion, according to [Higgins 2011a](#). Sensitivity analysis for trial eligibility and analysis would be required if the search produced multiple trials with high risk of bias. This would indicate whether or not conclusions would have differed if eligibility was restricted to trials without high risk of bias for the outcome concerned.

RESULTS

Description of studies

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

Results of the search

In the initial literature search in September 2014, We identified 1281 references in MEDLINE including Cancer-Lit, 1683 in Embase and 539 in CENTRAL, giving a total of 3503 references. We did not find any additional studies from unpublished and grey

literature, reference lists, or correspondence. There were 2333 unique references after we removed duplicates. Of these, we excluded 2323 after screening by title/abstract. We retrieved 10 full-text articles, eight of which were excluded as they did not meet the intervention criteria. From the full-text screening of the remaining two, it was noted that the reference by Karim in 2002 was the antecedent of the latest prospective RCT trial by [Van den Bent 2005](#). Since [Van den Bent 2005](#) refers to the long-term efficacy of the primary trial by Karim 2002, it will henceforth be referred to as Karim 2002: [Van den Bent 2005](#). We analysed the data from Karim 2002: [Van den Bent 2005](#), as this trial met our inclusion criteria and provided the most salient results to address our original question. We described Karim 2002: [Van den Bent 2005](#) in the [Characteristics of included studies](#) section. The original trial by Karim 2002 is the earlier European Organisation for Research and Treatment of Cancer (EORTC) study of the [Van den Bent 2005](#) cohort that provided an interim analysis comparing early radiotherapy with delayed radiotherapy. The interim analysis provided minimal clinical significance compared with the long-term results generated by [Van den Bent 2005](#). Please see [Figure 1](#) for the PRISMA study flow diagram.

Figure 1. PRISMA study flow diagram 2015.

An updated literature search for the period from September 2014 through to November 2019 was performed on 18 November 2019. We identified 964 new records and 11 additional articles were identified by searching through the references in the identified records. After exclusion of duplicate articles, 959 articles were

screened by title/abstract. Twenty-four articles were selected for full-text review. Figure 2 shows the study flow diagram for the review update. No new article met the inclusion criteria to be considered eligible for inclusion in this review update.

Figure 2. PRISMA study flow diagram for 2020 update.

Included studies

One RCT met our inclusion criteria. Karim 2002: [Van den Bent 2005](#) was a prospective, multi-centre RCT that presented the long-term results of a 1986 EORTC trial (Karim 2002) that compared early radiotherapy with delayed radiotherapy for people with LGGs. Participants from 24 participating institutions across Europe were randomly assigned to either early postoperative radiotherapy of 54 Gy in fractions of 1.8 Gy per week for six weeks or deferred radiotherapy until the time of progression (control group). Eligible participants had to have a histologically-confirmed

diagnosis of low-grade astrocytoma, oligodendroglioma, mixed oligoastrocytoma, or incompletely resected pilocytic astrocytoma, with a WHO performance status of zero to two, or KPS of at least 60. In this trial, 154 people were assigned early radiotherapy and 157 people served as controls. There were 63 (41%) females in the early radiotherapy group and 52 (33%) in the control group. The median age of people who had early radiotherapy was 36.5 years, while those who had delayed radiotherapy had a median age of 41 years. The early radiotherapy group (5.3 years) had a statistically significantly higher median PFS compared with the control group (3.4 years) ($P < 0.0001$), and there was a 20% improvement in five-

year PFS due to early radiotherapy (35% versus 55%). However, OS was similar between the two groups; the median survival in the early radiotherapy group was 7.4 years compared with 7.2 years in the control group ($P = 0.872$). The early radiotherapy group experienced slightly better performance status, as seizures were better controlled in this group. The trial authors did not assess participant's QoL or long-term physical or cognitive changes. The median follow-up time for all participants was 93 months. At the time of relapse, no further treatment at progression was given or documented for 13 (11.5%) participants in the control group and 32 (34%) participants in the early radiotherapy group. Salvage radiotherapy was given to 73 (65%) of participants in the control group and four (4%) of participants in the irradiated group. At the time of recurrence, chemotherapy was given to 18 (16%) participants in the control group and 35 (37%) participants who had early radiotherapy.

Excluded studies

Of the 2333 unique references identified, we excluded 2323 as they did not meet the prespecified participant and outcome criteria. Eight studies were excluded as they did not meet the intervention criteria. For the review update, of the 959 unique references identified, we excluded 935 as they did not meet the prespecified participant and outcome criteria. Twenty four full-text articles were excluded, please see the [Characteristics of excluded studies](#) section for the reasons for exclusion of these studies.

Risk of bias in included studies

The sole trial we evaluated, Karim 2002: [Van den Bent 2005](#), had an overall high risk of bias. We classified three out of seven criteria used to assess risk of bias as having unclear risk of bias, while the other four criteria had low risk of bias. Please see [Figure 3](#) for the 'Risk of bias' graph and [Figure 4](#) for the 'Risk of bias' summary.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 4. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Karim 2002: Van den Bent 2005 successfully randomised by stratification as various participant traits were distributed equally among both groups of participants, and "at baseline the treatment and control groups were not different with regard to sex, age, WHO performance status, MRC neurological function status, extent of surgery, histology, maximum diameter of the tumour, or whether the tumour crossed the midline". However, there was no statement of effort to conceal allocation. Since this was an unblinded trial,

it is conceivable that post-intervention management could affect survival and PFS.

Blinding

Participants in the early radiotherapy and delayed radiotherapy groups could not be blinded to the results of the random allocation due to the study design. The study indicated that the 'corresponding author had full access to all the data' suggesting lack of concealment of the assigned treatment to the patient groups from the study authors. However, as far as the outcome

assessment is concerned, it is not clear whether the treatment assignment was concealed from the investigators responsible for data interpretation.

Incomplete outcome data

Of the 311 participants randomised to either early or delayed radiotherapy in Karim 2002: [Van den Bent 2005](#), eight (2.6%) were ineligible for analysis due to incomplete data before entry to the trial, performance status greater than two or older than 65 years of age, and missing follow-up data. Most participant characteristic variables (sex, age in years, WHO performance status, MRC-NFS, extent of resection, histology, diameter, and tumour crossing the midline) had missing information, but these proportions were balanced across both groups. Despite random assignment to the control group, three participants received early radiotherapy (total dose of 50 to 54 Gy). These missing data are unlikely to influence the true effect of radiotherapy timing on outcomes for people with LGGs.

Selective reporting

We reported all of Karim 2002: [Van den Bent 2005](#)'s prespecified (primary) outcomes that were of interest in this Cochrane review in the prespecified way. This included OS and PFS, as well as the neurological signs and symptoms at one year in participants who were progression-free at two years.

Other potential sources of bias

Random sequence generation and missing data (selection bias)

Karim 2002: [Van den Bent 2005](#) randomised participants to treatments at the EORTC Data Center or the MRC Cancer Trials Office by use of a minimisation technique and stratification according to treatment institute, histology (astrocytoma versus oligodendroglioma or oligoastrocytoma), and extent of resection

(biopsy versus partial, subtotal, or total). Karim 2002: [Van den Bent 2005](#) had missing baseline characteristics in both groups of participants, which may potentially predispose the trial to selection bias. However, there was a balance in the distribution of missing baseline characteristics between both groups, minimising the likelihood that selection bias would affect one group over the other.

Intervention/exposure bias

This trial also has the potential for intervention, or exposure, bias since the trial authors evaluated performance status based only upon tumour progression. The study authors conceded that "because the patients in the control group (those who received delayed radiotherapy) progressed earlier, there might be a bias in favour of the control group". However, they limited this possibility by performing a post hoc analysis on participants' neurological signs and symptoms at one year only in participants who were progression-free at two years. This prevented any participant with an undetected progression at the one-year mark from biasing the analysis.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings table 1](#)

All outcomes reported in this section are based on results from the multi-institutional, prospective RCT by Karim 2002: [Van den Bent 2005](#).

Overall survival

The difference in median OS between the group who received early radiotherapy and the group who received delayed radiotherapy was not statistically significant (7.2 versus 7.4 years, respectively, log-rank $P = 0.873$; HR 0.97, 95% CI 0.71 to 1.33; [Figure 5](#)).

Figure 5. Forest plot of comparison: 1 Early versus delayed radiotherapy, outcome: 1.1 Overall survival.

Progression-free survival

People who were randomised to early radiotherapy demonstrated statistically significantly longer PFS than people randomised to

delayed radiotherapy (5.3 versus 3.4 years, respectively, long-rank $P < 0.0001$; HR 0.59, 95% CI 0.45 to 0.77; [Figure 6](#)).

Figure 6. Forest plot of comparison: 1 Early versus delayed radiotherapy, outcome: 1.2 Progression-free survival.

Survival after progression

SAP was 3.4 years for the delayed radiotherapy group versus 1.0 years for the early radiotherapy group (log-rank $P < 0.0001$).

Functionally independent survival

One of the inclusion criteria of this trial required participants to have a WHO performance status of zero to two, or KPS

of ≥ 60 , and the trial authors documented WHO performance status and MRC-NFS baseline characteristics in most participants at the time of randomisation. However, Karim 2002: [Van den Bent 2005](#) did not report FIS outcomes in the form of WHO performance status, KPS, or MRC-NFS. Instead, they investigated whether participants free from tumour progression had any neurological signs and symptoms by performing a post hoc analysis of participants' clinical examination at one year. They found "no differences between the two groups for cognitive deficit, focal deficit, performance status, and headache (data not shown)".

Disease-specific survival

Karim 2002: [Van den Bent 2005](#) did not calculate DSS.

Steroid requirement

Karim 2002: [Van den Bent 2005](#) did not assess steroid requirements.

Seizure frequency

At baseline, there were no differences between early and delayed radiotherapy groups in seizure control ($P = 0.8701$). However, at one year follow-up, 26 of 102 (25%) participants who were irradiated had seizures compared with 29 of 71 (41%) participants who had not been irradiated ($P = 0.0329$).

Local tumour control

Karim 2002: [Van den Bent 2005](#) evaluated tumour progression by comparing follow-up CT scans with the baseline scan; however, the investigators did not utilise the RANO response criteria for LGG. Among the 311 participants, 217 (70%) had progressed and 156 (50%) had died after follow-up or a median time of 7.8 years.

Cause of death

Among the 156 participants that died, 142 participants (91%) died from a progressive brain tumour, 12 participants (8%) died from unrelated causes, and no information on the cause of death was available for two participants (1%).

Quality-of-life

Karim 2002: [Van den Bent 2005](#) did not assess QoL.

Adverse events

Adverse events were not classified according to [CTCAE 2009](#). The trial authors indicated that "toxic effects were modest in general, and mainly consisted of skin reactions, otitis, mild headache, nausea, and vomiting. Irradiation was interrupted in six participants because of acute reactions". The trial did not report rates of cognitive impairment or rates of possible radiotherapy-induced leucoencephalopathy. Their findings do not support the speculation that early radiotherapy might induce malignant transformation of LGG, as there was no difference in progression to a high-grade tumour upon disease recurrence between both groups (statistical data not provided).

DISCUSSION

Summary of main results

The large, multi-institutional, prospective RCT of Karim 2002: [Van den Bent 2005](#) demonstrated that early postoperative radiotherapy is associated with an increase in time to progression compared to

observation (and delayed radiotherapy upon disease progression) for people with LGG but does not improve OS. The median PFS was 5.3 years in the early radiotherapy group and 3.4 years in the delayed radiotherapy group (HR 0.59, 95% confidence interval (CI) 0.45 to 0.77; $P < 0.0001$). However, the median OS did not show a statistically significant difference between the groups. The median OS in the early radiotherapy group was 7.4 years, while the delayed radiotherapy group experienced a median OS of 7.2 years (HR 0.97, 95% CI 0.71 to 1.33; $P = 0.872$).

The trial authors used stratified randomisation to equally distribute clinical prognostic factors, such as age, tumour size, functional status, and extent of resection, among both treatment groups. After a median follow-up time of 7.8 years (93 months), approximately 70% of participants had progressed and 50% had died. Adverse effects were minimal; they mainly consisted of skin reactions, otitis media, mild headache, nausea, and vomiting. Participants in both cohorts who were free from tumour progression showed no differences in cognitive deficit, focal deficit, performance status, and headache. However, participants randomised to the early radiotherapy group experienced significantly fewer seizures than participants in the delayed radiotherapy group at one year follow-up (25% versus 41%, $P = 0.0329$, respectively).

Using an ITT analysis, 55% of participants irradiated early did not show any evidence of tumour progression at five years, compared with 35% of participants who had delayed radiotherapy. Also at five years, 68% of participants in the early radiotherapy group were alive compared with 66% of participants in the delayed radiotherapy group. They provided rescue therapy to 65% of the participants randomised to delayed radiotherapy and 4% of the participants randomised to early radiotherapy. This led to a median SAP of 3.4 years for participants with delayed radiotherapy and one year for the participants with early radiotherapy. The results from Karim 2002: [Van den Bent 2005](#) indicate that the timing of radiotherapy is less important for prolonging survival provided it is given at some point during the treatment course and optimal rescue therapy can be readily provided for participants who undergo delayed radiotherapy. Notably, Karim 2002: [Van den Bent 2005](#) did not investigate what type of long term QoL their participants experienced. Therefore, it is not known whether improved time to progression is associated with long-term cognitive or neurological deterioration in participants with LGGs.

Overall completeness and applicability of evidence

The optimal treatment of LGG remains controversial, and current guidelines on the management of people with an alleged LGG are not based on established clinical evidence. We aimed to evaluate the fundamental question of whether to use radiotherapy in the early postoperative period, or whether radiotherapy should be delayed until tumour progression occurs. Our search yielded one large, multi-institutional trial by Karim 2002: [Van den Bent 2005](#) that sought to elucidate the optimal timing of radiotherapy in people with LGG who have good pre-treatment functional status. This trial showed that early radiotherapy significantly improves PFS compared with observation and delayed radiotherapy until disease progression. However, there was no difference in OS between these two groups, mainly because most people who received delayed radiotherapy were also given some form of rescue therapy. The trial also analysed symptom burden in people who had no evidence of progression and showed that early radiotherapy improves seizure control better than delayed radiotherapy. However, the

trial authors assessed tumour control using CT scan instead of MRI, and imaging methods were not guided by specific imaging parameters and endpoints. Furthermore, the trial authors did not adequately report adverse effects of radiotherapy and they did not evaluate people's postoperative functional status. The greatest limitation of this trial, however, is the lack of data on participant's QoL and cognitive function. Cognitive deterioration may eventually occur from deleterious effects of early radiotherapy or disease progression in people who opt for delayed radiotherapy. This trial affirms the efficacy of radiotherapy in the treatment of LGG, but the optimal time to give radiation therapy still remains unclear because the effect of early versus delayed radiotherapy on neurocognitive deterioration is not known.

Quality of the evidence

One large multi-institutional RCT, Karim 2002: [Van den Bent 2005](#), forms the basis of our systematic review and its conclusions. Overall, we determined that this trial had a high risk of bias after careful evaluation of the criteria we used to assess risk of bias. Given this risk of bias, the results and conclusions of this Cochrane review must be interpreted in the context of this uncertainty. See [Figure 3](#) for the 'Risk of bias' graph and [Figure 4](#) for the 'Risk of bias' summary. The lack of allocation concealment, blinding of participants and blinding of outcome assessment introduces various types of biases that may conceivably skew the true effects of early versus delayed postoperative radiation therapy on survival and PFS. For these reasons, we attributed a low GRADE quality of evidence for the OS and PFS outcome parameters reported in Karim 2002: [Van den Bent 2005](#).

This large trial showed an increase in PFS after early radiotherapy versus delayed radiotherapy. Since most patients randomised to delayed radiotherapy received some form of rescue therapy at the time of disease progression, there was no significant difference in median OS between the two cohorts. The primary endpoints of this trial were PFS and OS, but the trial authors also assessed SAP, neurological symptoms at one year in people who had not shown evidence of disease progression, seizure frequency, and cause of death. Local tumour control was also included but was not assessed using the RANO response criteria for LGG. Adverse effects were briefly mentioned but they were not quantified or classified according to [CTCAE 2009](#) standards. Other clinically important outcomes such as FIS, DSS, steroid requirement, and QoL were not evaluated. Hence, our systematic review's internal validity is limited since all of the results and conclusions are based on this single large RCT (Karim 2002: [Van den Bent 2005](#)).

Potential biases in the review process

We performed a comprehensive search, including a thorough search of the grey literature. We screened all identified studies and three review authors independently extracted data. We restricted the included studies to RCTs as these provide the strongest level of evidence available. Hence, we have attempted to reduce bias in the review process. However, the greatest threat to the validity of the review is likely to be the possibility of publication bias, i.e. studies that did not find the treatment to have been effective may not have been published.

Agreements and disagreements with other studies or reviews

EORTC 22845 by Karim 2002: [Van den Bent 2005](#) is the only trial that investigated the role of radiation timing on survival for people with LGG.

There are two randomised trials that investigated different radiation doses in the management of LGGs: [Karim 1996](#) (EORTC 22844) and [Shaw 2002](#) (NCCTG). These trials provided class I evidence showing no advantage for higher versus lower radiation doses.

Radiation therapy has been shown to improve seizure control in people with LGG. A retrospective study by [Warnke 1997](#) reported a seizure control rate of 79% using stereotactic interstitial radiosurgery at six months for people with LGG with medically refractory seizures. Conventional radiation can also reduce seizure frequency in people with LGG and medically refractory seizures ([Rogers 1993](#)).

One of the strongest arguments for delaying or withholding radiotherapy in people with LGG is the risk of radiotherapy-induced leucoencephalopathy, which can result in cognitive dysfunction. [Douw 2009](#) evaluated the cognitive status of 65 people with LGG who had neuropsychological follow-up at a mean of 12 years and were free of tumour progression. People who received radiation therapy performed worse in measures of executive functioning, attentional functioning, and information processing speed compared with people who did not receive radiation therapy. However, it is uncertain whether early radiotherapy can postpone neurological deterioration.

AUTHORS' CONCLUSIONS

Implications for practice

Given the high risk of bias in the included trial, the results of this analysis must be interpreted with caution. Early radiation therapy was associated with the following adverse effects: skin reactions, otitis media, mild headache, nausea, and vomiting. People with LGG who underwent early radiotherapy showed an increase in time to progression compared with people who were observed and had radiotherapy at the time of progression. There was no significant difference in OS between people who had early versus delayed radiotherapy; however, this finding may be due to the effectiveness of rescue therapy with radiation in the control arm. People who underwent early radiation had better seizure control at one year than people who underwent delayed radiation. There were no cases of radiation-induced malignant transformation of LGG. However, it remains unclear whether there were differences in memory, executive function, or cognitive function between the two groups since QoL measures were not evaluated.

Implications for research

Future trials need to include a rigorous comparison of the QoL, cognitive performance, and functional status of people undergoing early versus delayed radiotherapy for LGG. These trials ideally would have long-term follow-up data to effectively monitor for significant neurocognitive side effects of intracranial radiotherapy in people with LGG.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Van den Bent 2005

Methods

Multi-centre RCT. Participants were actively recruited between March 1986 and September 1997.

Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas (Review)

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Van den Bent 2005 (Continued)

This was the largest included multi-centre RCT with 311 total participants randomised to early radiotherapy or deferred radiotherapy until the time of progression.

An ITT analysis included 154 participants randomised to early radiotherapy; of these participants, 1 was ineligible for the study and 7 had no data on radiotherapy. This analysis also randomised 157 participants to the delayed radiotherapy group. Of the participants, 7 were ineligible and 3 received early radiotherapy.

A sensitivity analysis included 124 participants in the delayed radiotherapy arm (control arm) and 119 participants in the radiotherapy arm. In this analysis, participants with pilocytic astrocytomas, ineligible participants, and participants who were diagnosed with an anaplastic tumour at histology review were excluded.

The histological diagnosis of the review pathologist was used; if not available, then the diagnosis of the local pathologist was used.

Extent of resection was classified by the neurosurgeon at the time of surgery as follows: aspiration or biopsy, resection with less than 50% tumour removal, 50 to 89% tumour removal, or 90 to 100% tumour removal.

300 participants gave a power of 0.8; this allowed the detection of an increase in OS from 60% to 75% ($\alpha = 0.05$, 2-sided test) for participants in the early radiotherapy and delayed radiotherapy groups.

Participants	<p>Eligible male and female participants from 24 institutions across Europe were randomly allocated to either early radiotherapy or delayed radiotherapy at the time of recurrence (control group).</p> <p>Inclusion criteria: participants between 16 and 65 years of age with supratentorial and histologically proven low-grade astrocytoma (including incompletely resected grade I pilocytic astrocytomas), low-grade oligoastrocytoma, or low-grade oligodendroglioma according to the 1979 WHO Classification for Central Nervous System Tumors. Participants also had to have a WHO performance status 0 to 2 of Karnofski performance score of 60 or more and they could not have any other significant systemic diseases or malignancies that may interfere with follow-up.</p> <p>Exclusion criteria: participants with completely resected small grade I tumours (pilocytic astrocytoma), optic nerve glioma, brainstem glioma, third ventricular glioma, and mostly infratentorial glioma; and participants that were pregnant</p> <p>Participants in both groups had similar baseline characteristics at the time of randomisation.</p>
Interventions	<p>All participants received 54 Gy in five fractions of 1.8 Gy per week for 6 weeks of radiotherapy with megavolt photons (4 to 10 MV) and Cobalt-60 sources. The tumour shown on the preoperative CT scan was irradiated with a margin of 2 cm, and the target volume was reduced to a margin of 1 cm around the tumour after 45 Gy. A maximum of 8 weeks between operation and the start of radiotherapy was allowed.</p> <p>Early radiotherapy: 154 assessed for primary endpoint; 8 participants were ineligible or had no data on radiotherapy</p> <p>Delayed radiotherapy: 157 assessed for primary endpoint; 10 participants were ineligible or received early radiotherapy</p>
Outcomes	<p>The primary endpoints were PFS and OS. These endpoints were calculated from the day of randomisation to the date of the first event. The trial authors defined the date of progression as the date of the CT scan that showed or confirmed tumour progression.</p> <p>Neurologic signs and symptoms at 1 year were analysed in participants who were still progression-free at 2 years in both cohorts.</p> <p>Clinical and radiological follow-up was done at the same intervals for both treatment groups. In the first 2 years after randomisation, clinical follow-up and contrast-enhanced CT scans were done every 4 months, and thereafter once a year until tumour progression. After tumour progression, participants were followed up for survival only.</p>

Van den Bent 2005 (Continued)

The median follow-up time for these participants was 93 months.

Notes	<p>This publication is the follow-up trial to Karim 2002.</p> <p>Tumour size, crossing of the tumour over the midline, and radiological follow-up for determination of tumour progression were performed by CT scan, not MRI.</p> <p>The operating surgeon estimated extent of resection and postoperative CT scanning was not required. However, both treatment groups were balanced according to the type of surgery.</p> <p>The trial authors modified the histological diagnosis for a substantial number of participants after central pathology review, but these factors were balanced for the two treatment groups.</p> <p>Post hoc analysis found no differences between the two groups for cognitive deficit, focal deficit, performance status, and headache (data not shown in trial). At 1 year, participants in the early radiotherapy group had better seizure control than participants in the delayed radiotherapy group ($P = 0.03$).</p> <p>Data on participants' QoL or long-term physical and cognitive changes was not collected.</p> <p>Ethics committees of the local hospitals participating in the trial approved the study design.</p> <p>Funding sources had no role in the data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication.</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random allocation of patients to treatments was done at the EORTC Data Center or the MRC Cancer Trials Office by use of a minimisation technique and stratification according to treatment institute, histology (astrocytoma vs oligodendroglioma or oligoastrocytoma), and extent of resection (biopsy vs partial, subtotal, or total)".
Allocation concealment (selection bias)	High risk	There was no mention of allocation concealment in the manuscript.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants was impossible due to the design of the trial. Though the trial mentioned that the "corresponding author had full access to all the data", it remained unclear if the personnel were blinded to participant treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessment was likely not blinded because the trial mentioned that the "corresponding author had full access to all the data".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of the 311 participants randomised to either early or delayed radiotherapy, fewer than 8 (2.6%) had missing follow-up data. These missing data were unlikely to influence the true effect of radiotherapy timing on outcomes for participants with LGGs.
Selective reporting (reporting bias)	Low risk	All of the trial's prespecified (primary and secondary) outcomes that are of interest in this Cochrane review were reported in the prespecified manner. However, QoL was expected for the review but not reported in the study.
Other bias	Unclear risk	There were missing baseline characteristics in both groups of participants, which may potentially predispose the trial to selection bias. However, both groups showed a balanced distribution of missing baseline characteristics, minimising the likelihood that selection bias would affect one group over the other.

Van den Bent 2005 (Continued)

The trial authors evaluated performance status in this trial upon tumour progression: "Because the patients in the control group (those who received delayed radiotherapy) progressed earlier, there might be a bias in favour of the control group. We have circumvented this possibility by studying the signs and symptoms including performance status at 1 year in the subgroup that was free from progression at 2 years. This approach ensures that participants with undetected progression do not bias the analysis".

CT: computed tomography

EORTC: European Organisation for Research and Treatment of Cancer

Gy: Gray

ITT: intention to treat

LGG: low grade glioma

MRI: magnetic resonance imaging

MV: megavolt

OS: overall survival

PFS: progression free survival

RCT: randomised controlled trial

vs: versus

WHO: World Health Organisation

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Barbiero 2017	Wrong intervention. Radiotherapy plus chemotherapy
Barsoum 2014	Systematic review. Not Grade I or II low-grade gliomas
Baumert 2016	Wrong comparator. Chemotherapy compared with radiotherapy
Brown 2015	Wrong Indicator - no radiotherapy
Daniels 2011	Delayed RT was not a variable considered in this analysis.
Dirven 2019	Wrong comparator, not related to timing of radiotherapy
Hachem 2017	Not focused on low-grade glioma
Hottinger 2016	Wrong intervention. Radiotherapy and chemotherapy
Jaekle 2014	Book chapter. Not related to timing of radiotherapy in oligodendrogliomas
Jiang 2017	Not related to timing of radiotherapy
Kiebert 1998	Did not include data on participants who received RT at tumour progression
Laack 2015	Review article. Not related to timing of radiotherapy
Le Rhun 2016	Review article. Not related to timing of radiotherapy
Lukas 2014	Meeting updates, no mention of timing of radiotherapy
Mandonnet 2018	Review article. Discussed different therapeutic modalities for low-grade gliomas. No additional data on timing of radiotherapy

Study	Reason for exclusion
Morrall 2019	Wrong intervention. Radiotherapy plus chemotherapy
Mushtaq 2016	Wrong comparator, not related to timing of radiotherapy
Nageshwara Rao 2014	Review article. Not related to timing of radiotherapy
Prabhu 2014	Participants underwent adjuvant RT and not delayed RT
Sahgal 2013	Retrospective population-based study design; RT details and protocol were not reported.
Schiff 2017	Review article with chemotherapy
Shaw 2002	Participants who had adjuvant RT and salvage RT at progression were not directly compared.
Shaw 2012	Participants underwent adjuvant RT and not delayed RT.
SNO 2017	Wrong comparator. Not related to timing of radiotherapy
Starke 2016	No discussion about timing of radiotherapy
Taphoorn 1994	Not a RCT; did not include patients with tumour recurrence or progression
Van Den Bent 2014	Focussed on chemotherapy for low-grade gliomas
Van Den Bent 2016	Not focused on grade I or II oligodendrogliomas
Vigliani 1996	Not a RCT; did not include patients with delayed RT or data about OS or PFS
Wang 2019	No discussion about timing of radiotherapy
Youland 2017	Chemotherapy added to therapy

OS: overall survival

PFS: progression free survival

RCT: randomised controlled trial

RT: radiotherapy

DATA AND ANALYSES

Comparison 1. Early versus delayed radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	1	311	Hazard Ratio (Fixed, 95% CI)	0.97 [0.71, 1.33]
2 Progression-free survival	1	311	Hazard Ratio (Fixed, 95% CI)	0.59 [0.45, 0.77]

Analysis 1.1. Comparison 1 Early versus delayed radiotherapy, Outcome 1 Overall survival.

Analysis 1.2. Comparison 1 Early versus delayed radiotherapy, Outcome 2 Progression-free survival.

APPENDICES

Appendix 1. Local tumour control

The RANO criteria ([Wen 2010](#)):

- Complete response, satisfying all of the following criteria:
 - a. Complete disappearance of the lesion on T2 or FLAIR (or CT) abnormality (if enhancement had been present, it must have resolved completely).
 - b. No new lesions, no new T2 or FLAIR (or CT) abnormalities apart from those consistent with radiation effects, and no new or increased enhancement.
 - c. Patients must be off corticosteroids or only on physiological replacement doses.
 - d. Patients should be stable or improved clinically.
- Partial response, satisfying all of the following criteria:
 - a. ≥ 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR (or CT) sustained for at least four weeks.
 - b. No new lesions, no new T2 or FLAIR (or CT) abnormalities apart from those consistent with radiation effects, and no new or increased enhancement.
 - c. Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan.
 - d. Patients should be stable or improved clinically.
- Minor response, satisfying all of the following criteria:
 - a. Decrease of the area of non-enhancing lesion on T2 or FLAIR (or CT) between 25% and 50%.
 - b. No new lesions, no new T2 or FLAIR (or CT) abnormalities apart from those consistent with radiation effects, and no new or increased enhancement.
 - c. Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan.
 - d. Patients should be stable or improved clinically.
- Stable, defined as not qualifying as complete response, partial response, minor response, or recurrence; as well as satisfying all of the following criteria:

- a. Stable area of non-enhancing abnormalities on T2 or FLAIR (or CT).
- b. No new lesions, no new T2 or FLAIR (or CT) abnormalities apart from those consistent with radiation effects, and no new or increased enhancement.
- c. Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan.
- d. Patients should be stable or improved clinically.
- Recurrence, defined by any of the following:
 - a. Development of new lesions or increase of enhancement (radiological evidence of malignant transformation).
 - b. A 25% increase of the T2 or FLAIR (or CT) non-enhancing lesion, while on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events.
 - c. Definite clinical deterioration not attributable to other causes apart from the tumour, or decrease in corticosteroid dose.
 - d. Failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders.

Note that T2 and FLAIR refer to sequences obtained with standard MRI scans.

Appendix 2. Functionally independent survival scales

Karnofsky Performance Scale

The KPS score runs from 100% to 0%, where 100% is perfect health and 0% is death ([Karnofsky 1949](#), [Karnofsky 1951](#)):

- 100% - normal, no complaints, no signs of disease.
- 90% - capable of normal activity, few symptoms or signs of disease.
- 80% - normal activity with some difficulty, some symptoms or signs.
- 70% - caring for self, not capable of normal activity or work.
- 60% - requiring some help, can take care of most personal requirements.
- 50% - requires help often, requires frequent medical care.
- 40% - disabled, requires special care and help.
- 30% - severely disabled, hospital admission indicated but no risk of death.
- 20% - very ill, urgently requiring admission, requires supportive measures or treatment.
- 10% - moribund, rapidly progressive fatal disease processes.
- 0% - death.

Medical Research Council Neurological Functional Status (MRC-NFS)

The MRC-NFS is scored from one to five ([MRC 1983](#)):

1. No neurological deficit.
2. Some neurological deficit but function adequate for useful work.
3. Neurological deficit causing moderate functional impairment, e.g. able to move limb(s) only with difficulty, moderate dysphasia, moderate paresis, some visual disturbance (e.g. field defect).
4. Neurological deficit causing major functional impairment, e.g. inability to use limb(s), gross speech or visual disturbances.
5. No useful function, inability to make conscious responses.

WHO Performance Scale (WHO-PS)

The WHO-PS is scored from 0 to four ([Zubrod 1960](#)):

0. Normal activity.
1. Symptoms, but nearly fully ambulatory.
2. Some bed time, but needs to be in bed < 50% of normal daytime. Capable of self-care but no work.
3. Needs to be in bed > 50% of normal daytime. Capable of limited self-care.
4. Unable to get out of bed.

Appendix 3. CENTRAL search strategy

#1 MeSH descriptor Glioma explode all trees

#2 glioma*

#3 astrocytoma*

#4 oligodendroglioma*

#5 ganglioglioma*

#6 oligoastrocytoma*

#7 xanthoastrocytoma*
#8 astroblastoma*
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Radiotherapy explode all trees
#11 radiotherap* or radiosurg*
#12 radiation
#13 irradiation
#14 Any MeSH descriptor with qualifier: RT
#15 (#10 OR #11 OR #12 OR #13 OR #14)
#16 (#9 AND #15)

Appendix 4. MEDLINE search strategy

MEDLINE Ovid

1 exp Glioma/
2 glioma*.mp.
3 astrocytoma*.mp.
4 oligodendroglioma*.mp.
5 ganglioglioma*.mp.
6 oligoastrocytoma*.mp.
7 xanthoastrocytoma*.mp.
8 astroblastoma*.mp.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp Radiotherapy/
11 (radiotherap* or radiosurg*).mp.
12 radiation.mp.
13 irradiation.mp.
14 radiotherapy.fs.
15 10 or 11 or 12 or 13 or 14
16 9 and 15
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 randomized.ab.
20 placebo.ab.
21 clinical trials as topic.sh.
22 randomly.ab.
23 trial.ti.
24 17 or 18 or 19 or 20 or 21 or 22 or 23
25 16 and 24

Key:

mp = title, original title, abstract, name of substance word, subject heading word, unique identifier

fs = floating subheading

ab = abstract

sh = subject heading

ti = title

Appendix 5. EMBASE search strategy

EMBASE Ovid

1 exp glioma/
2 glioma*.mp.
3 astrocytoma*.mp.
4 oligodendroglioma*.mp.
5 ganglioglioma*.mp.
6 oligoastrocytoma*.mp.
7 xanthoastrocytoma*.mp.
8 astroblastoma*.mp.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 exp radiotherapy/
11 stereotactic radiosurgery/

12 (radiotherap* or radiosurg*).mp.
13 radiation.mp.
14 irradiation.mp.
15 rt.fs.
16 10 or 11 or 12 or 13 or 14 or 15
17 9 and 16
18 crossover procedure/
19 randomized controlled trial/
20 single blind procedure/
21 random*.mp.
22 factorial*.mp.
23 (crossover* or cross over* or cross-over).mp.
24 placebo*.mp.
25 (doubl* adj blind*).mp.
26 (singl* adj blind*).mp.
27 assign*.mp.
28 allocat*.mp.
29 volunteer*.mp.
30 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31 17 and 30

WHAT'S NEW

Date	Event	Description
15 January 2020	New citation required but conclusions have not changed	The conclusions of this Cochrane review are still considered up to date.
15 January 2020	New search has been performed	Full update searches run 18 November 2019. No potentially relevant new studies identified.

CONTRIBUTIONS OF AUTHORS

CP had the original idea for the protocol ([Venteicher 2011](#)) and helped review initial protocol drafts. AV wrote the protocol and search strategy. JMS reviewed the updated search, performed data extraction, and wrote the [Results](#) and [Discussion](#) sections.

DECLARATIONS OF INTEREST

Sanjay Dhawan - none known.
Chirag G Patil - none known.
Clark Chen - none known.
Andrew S Venteicher - none known.

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- None, Other.

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Research support to ASV

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. SAP was an outcome that was not in the original published protocol, but we later included it because it was felt to be a meaningful outcome variable reported in Karim 2002: [Van den Bent 2005](#).
2. We did not contact trial authors to request information from participants excluded from analysis. Participants were appropriately excluded from Karim 2002: [Van den Bent 2005](#) if they had "incomplete data before entry to the study, performance status greater than 2 or older than 65 years of age, and missing follow-up data".
3. We originally stated in the protocol that we would use a random-effects model; however, given that our meta-analysis only included one trial, we opted to use a fixed-effect computational model to report a more descriptive analysis of the included trial ([Borenstein 2009](#)).
4. We removed the 'Characteristics of excluded studies' paragraph from the [Results](#) section and we completed a '[Characteristics of excluded studies](#)' table detailing reasons for exclusion of pertinent studies.
5. Decisions relating to the [Assessment of heterogeneity](#) were added to that section.

INDEX TERMS

Medical Subject Headings (MeSH)

Brain Neoplasms [mortality] [*radiotherapy] [surgery]; Disease-Free Survival; Glioma [*radiotherapy] [surgery]; Postoperative Care; Progression-Free Survival; Radiosurgery; Radiotherapy [methods]; Randomized Controlled Trials as Topic; Time Factors; Watchful Waiting

MeSH check words

Humans