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[Intervention Review]

External beam radiation dose escalation for high grade glioma

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ABSTRACT

Background

The incidence of high grade glioma (HGG) is approximately 5 per 100,000 person-years in Europe and North America.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 9), MEDLINE (1977 to October 2015) and Embase (1980 to end October 2015) 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.

1. Daily conventionally fractionated radiation therapy versus no radiation therapy.
2. Hypofractionated radiation therapy versus daily conventionally fractionated radiation therapy.
3. Hyperfractionated radiation therapy versus daily conventionally fractionated radiation therapy.
4. Accelerated radiation therapy versus daily conventionally fractionated radiation therapy.

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 used the GRADE approach, as outlined by Cochrane, to interpret the overall quality of the evidence from included studies.

Main results

We included 11 randomised controlled trials (RCTs) with a total of 2062 participants and 1537 in the relevant arms for this review. There was an overall survival benefit for HGG participants 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 (95% confidence interval (CI) 1.58 to 2.55, $P < 0.00001$), moderate GRADE quality evidence favouring postoperative radiotherapy. 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 versus 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 GRADE quality evidence. The trials reported that hypofractionated and conventional radiotherapy were well tolerated with mild acute adverse effects. These trials only reported one patient 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 also similar between hypofractionated versus conventional radiotherapy in the subset of two trials (293 participants) which included 60 years and older participants with glioblastoma. For this category, the HR was 1.16 (95% CI 0.92 to 1.46, P = 0.21), high GRADE quality evidence.

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

The conventionally fractionated radiation therapy regimens were 4500 to 6000 cGy given in 180 to 200 cGy daily fractions, over 5 to 6 weeks.

All these 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 randomized trials. 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 improves survival for adults with good performance status and HGG as compared to no postoperative radiotherapy.

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

There is 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 poor prognosis HGG individuals have generally been excluded from the 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 poor prognosis patients.

PLAIN LANGUAGE SUMMARY

Radiation dose escalation for malignant glioma

Background:
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. 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 for people with HGG, so there is a need to look at these studies closely to see what they say. 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 radiation therapy involves giving daily radiation of 180 to 200 cGy per day. Hypofractionated radiation therapy refers to the use of a higher daily dose of radiation (> 200 cGy per day) which typically reduces the overall number of fractions and therefore the overall treatment time.

Hyperfractionated radiation therapy refers to the use of a lower daily dose of radiation (< 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 radiation therapy in the same time frame. The aim with this approach is to reduce the potential for late toxicity.

Accelerated radiation therapy refers to the delivery of multiple fractions per day using daily doses of radiation consistent with external beam daily conventionally fractionated radiation therapy 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 in newly diagnosed people with HGG.

What are the main findings?

We found 11 trials (1537 participants in the relevant arms for this review) that met the criteria for our review. People with a poor prognosis generally were not eligible for entry into the randomised trials based on their poor level of health. There was an overall survival benefit for HGG participants receiving postoperative conventional radiotherapy compared to the participants receiving supportive care after surgery. Hypofractionated radiation therapy has similar efficacy for survival as compared to conventional radiotherapy, particularly for individuals aged 60 and older with glioblastoma. There were no clear differences in side effects (adverse effects) between these different treatment groups. There was insufficient data regarding other outcomes, namely progression-free survival and quality of life between these different treatment groups.

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

Quality of the Evidence:

The quality 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 and possible selective reporting of outcomes such as adverse effects.

Only 5 out of the 11 included trials were published after the year 2000. The majority of the trials included in the meta-analysis were published before 2000 and are now 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 radiation therapy has similar efficacy for survival as compared to conventional radiotherapy, particularly for individuals aged 60 and older with glioblastoma.