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Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD009229.
DOI: 10.1002/14651858.CD009229.pub2.

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[Intervention Review]

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

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Editorial group: Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group.
Publication status and date: New, published in Issue 6, 2015.

Citation: Sarmiento JM, Venteicher AS, Patil CG. Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD009229. DOI: 10.1002/14651858.CD009229.pub2.

ABSTRACT

Background

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

We searched up to September 2014 the following electronic databases: the Cochrane Register of Controlled Trials (CENTRAL, Issue 8, 2014), MEDLINE (1948 to Aug week 3, 2014), and EMBASE (1980 to Aug week 3, 2014) to identify trials for inclusion in this Cochrane review.

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 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 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 value < 0.0001; 311 participants; 1 trail; 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 value = 0.872; 311 participants; 1 trail; 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 value = 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 undergo 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 remains unclear whether there are 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 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 searches 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.

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.