

When should radiotherapy for low-grade glioma be given—immediately after surgery or at the time of progression?

GLOSSARY

WHO PERFORMANCE STATUS

A scale designed by the World Health Organisation and used by doctors to describe the physical health of patients, ranging from 0 (most active) to 4 (least active)

KARNOFSKY PERFORMANCE STATUS (KPS)

A 0% (dead) to 100% (fully active) scoring system to assess the well being of cancer patients and their ability to perform ordinary tasks

KAPLAN-MEIER ANALYSIS

A conditional probability strategy used for estimation of survival in clinical trials with censored observations

TEMOZOLOMIDE

Oral agent that alkylates DNA at the O6 and N7 positions of guanine

Original article van den Bent MJ *et al.* (2005) Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* **366**: 985–990

SYNOPSIS

KEYWORDS astrocytoma, efficacy, oligodendroglioma, radiotherapy, survival

BACKGROUND

There are no evidence-based guidelines to direct the treatment of patients with low-grade glioma, and it remains unclear whether early treatment has an impact on outcome.

OBJECTIVE

To compare the long-term efficacy of early, postoperative radiotherapy for low-grade glioma with that of delayed treatment, including radiotherapy, when tumor progression occurs.

DESIGN AND INTERVENTION

Patients aged 16–65 years were included if they had supratentorial and histologically proven low-grade astrocytoma, or low-grade oligoastrocytoma or oligodendroglioma, WHO PERFORMANCE STATUS of 0–2 or KARNOFSKY PERFORMANCE STATUS (KPS) ≥ 60 , and no other systemic diseases or malignancies. Participants were randomized to receive early radiotherapy (within 8 weeks of resective surgery), or treatment, including radiotherapy, when tumor progression occurred (control). Clinical and CT examination were carried out at baseline, every 4 months for 2 years, and then every year until tumor recurrence. The total radiotherapy dose was 54 Gy (in 5 fractions of 1.8 Gy/week for 6 weeks). Data were analyzed by intention to treat. Event-free rates were assessed using KAPLAN-MEIER ANALYSIS. The two study groups were compared using the log-rank test.

OUTCOME MEASURES

The primary outcomes were the durations of progression-free survival and overall survival

times, both calculated from the date of randomization to the date of progression.

RESULTS

Among the 311 patients randomized, after a median of 7.8 years of follow-up, tumor progression had occurred in 217 patients (70%), and 156 patients (50%) had died. Known causes of death were progressive brain tumor ($n=142$, 91%) and unrelated causes ($n=12$, 8%). Low-grade gliomas were identified pathologically in 186/253 patients (74%), and anaplastic tumors (including astrocytomas, oligoastrocytomas and oligodendrogliomas) were found in 48/253 patients (19%). The median overall survival was 7.4 years (95% CI 6.1–8.9 years) in the control group and 7.2 years (95% CI 6.4–8.6 years) in the treatment group (hazard ratio 0.97, 95% CI 0.71–1.34), with no significant difference between groups (log-rank $P=0.873$). Median progression-free survival was 3.4 years (95% CI 2.9–4.4 years) among control patients, and 5.3 years (95% CI 4.6–6.3 years) in the early radiotherapy group (hazard ratio 0.59, 95% CI 0.45–0.77), with significantly longer progression-free survival in those receiving early radiotherapy (log-rank $P<0.0001$). After progression, survival times were 3.4 years in the control group and 1.0 year in the radiotherapy group (overall log-rank $P<0.0001$). Seizure control was similar in the two groups at baseline, but 1 year after surgery the number of progression-free patients with seizures was 26/102 (25%) in the radiotherapy group, and 29/71 (41%) in the control group ($P=0.0329$). Radiotherapy was interrupted owing to acute reactions in six patients; other toxic effects were moderate, including skin reactions, otitis and mild headache.

CONCLUSION

Compared with treatment at the time of tumor progression, immediate postoperative radiotherapy lengthens progression-free survival by 2 years, but overall survival is unchanged.

COMMENTARY

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The European Organisation for Research and Treatment of Cancer (EORTC) study 22845 is an important trial in a series of dose-response studies for low-grade gliomas. Previous Radiation Therapy Oncology Group (RTOG) and EORTC studies failed to show an improvement in local control or survival with high doses of radiation.^{1,2} The current study addressed a very important, but unanswered question: can radiation be delayed for low-grade gliomas?

While the study showed no improvement in overall survival, the 5-year progression-free survival in the upfront radiation arm was 55%, compared with 35% in the control arm (log-rank $P < 0.0001$). As speculated by the authors, the lack of an overall survival benefit could be due to the effectiveness of salvage radiation. The acute toxicity of the radiation was modest, with only six patients having treatment interruptions. Radiation did not cause malignant transformation of low-grade gliomas in this study, and other studies that used careful neuropsychological assessments failed to show cognitive deficits from radiation.^{3,4} The argument that radiation might cause malignant transformation of low-grade gliomas or neurotoxicity is not sufficiently compelling to omit upfront therapy in low-grade gliomas.

Since no difference in survival was noted in this study, an important question to address is quality of life. Unfortunately, since this component of the study was optional and few participated, this issue could not be addressed. Progression of disease can lead to worsening neurological impairment. As demonstrated in this study, seizures were better controlled in the upfront radiation arm. Some patients might worry about the lack of active treatment and higher rate of progression without upfront treatment. A key question that needs to be answered is what impact delaying radiation therapy has on quality of life.

Are there subsets of patients in whom upfront radiation might not provide any advantage? Based on the data from the RTOG 9110 trial, patients who are younger than 40 years old, have tumors less than 5 cm, and have a gross total resection, have a better overall survival.² To test the hypothesis that radiation can be delayed in these patients, the phase II arm

of RTOG 9802 observed patients who were younger than 40 years old and underwent gross total resections. RTOG 9802 also assessed the role of adjuvant PCV (procarbazine, lomustine and vincristine) chemotherapy in a phase III setting for older patients and those with less than a gross total resection. RTOG 9802 has completed enrollment and we await the results. Given the efficacy of TEMOZOLOMIDE in brain tumors, particularly glioblastoma multiforme,⁵ RTOG 0424 is assessing the role of concurrent and adjuvant temozolomide with radiation for high-risk, low-grade gliomas.

Another question to be answered is whether upfront chemotherapy can replace radiation as the initial therapy for low-grade gliomas. The EORTC is conducting a study comparing temozolomide alone to radiation alone. In addition to studying progression-free survival, quality of life will be assessed.

The EORTC 22845 study addressed a key question and showed a benefit for upfront radiation. Yet, there are many questions to be answered regarding the optimal treatment of low-grade gliomas, many of which will be addressed by the above-mentioned studies. Further understanding of the biology of low-grade gliomas and identification of molecular markers is needed to develop individualized treatment strategies.

References

- 1 Karim AB *et al.* (1996) A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) Study 22844. *Int J Radiat Oncol Biol Phys* **36**: 549–556
- 2 Shaw E *et al.* (2002) Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. *J Clin Oncol* **20**: 2267–2276
- 3 Klein M *et al.* (2002) Effect of radiotherapy and other treatment-related factors on mid-term to long-term cognitive sequelae in low-grade gliomas: a comparative study. *Lancet* **360**: 1361–1368
- 4 Brown PD *et al.* (2003) Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the Folstein Mini-Mental State Examination. *J Clin Oncol* **21**: 2519–2524
- 5 Stupp R *et al.* (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* **352**: 987–996

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Competing interests

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PRACTICE POINT

Upfront radiation improves progression-free survival and should be offered as an option to patients presenting with low-grade gliomas