When should radiotherapy for low-grade glioma be given: straight after surgery or at progression?

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

The European Organisation for Research and Treatment of Cancer (EORTC) study 22845 (see opposite) 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 five-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 tumours 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 enrolment and we await the results. Given the efficacy of temozolomide (an oral agent that alkylates DNA at the O6 and N7 positions of guanine) in brain tumours, particularly glioblastoma multiforme,[5] RTOG 0424 is assessing the role of concurrent and

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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 individualised treatment strategies.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

MJ van den Bent, D Afra, O de Witte, 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*

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 tumour 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 randomised to receive early radiotherapy (within 8 weeks of resective surgery), or treatment, including radiotherapy, when tumour progression occurred (control). Clinical and CT examination were carried out at baseline, every 4 months for 2 years, and then every year until tumour recurrence. The total radiotherapy dose was 54 Gy (in 5 fractions of 1.8 Gy/week for 6 weeks). Data were analysed by intention to treat. Event-free rates were assessed using Kaplan-Meier analysis, a conditional probability strategy used for estimation of survival in clinical trials with censored observations. 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 randomisation to the date of progression.

Results. Among the 311 patients randomised, after a median of 7.8 years of follow-up, tumour progression had occurred in 217 patients (70%), and 156 patients (50%) had died. Known causes of death were progressive brain tumour (n = 142, 91%) and unrelated causes (n = 12, 8%). Low-grade gliomas were identified pathologically in 186/253 patients (74%), and anaplastic tumours (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.

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

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

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