# Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial

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## Summary

**Background** Postoperative policies of "wait-and-see" and radiotherapy for low-grade glioma are poorly defined. A trial in the mid 1980s established the radiation dose. In 1986 the EORTC Radiotherapy and Brain Tumor Groups initiated a prospective trial to compare early radiotherapy with delayed radiotherapy. An interim analysis has been reported. We now present the long-term results.

**Methods** After surgery, patients from 24 centres across Europe were randomly assigned to either early radiotherapy of 54 Gy in fractions of 1·8 Gy or deferred radiotherapy until the time of progression (control group). Patients with low-grade astrocytoma, oligodendroglioma, mixed oligoastrocytoma, and incompletely resected pilocytic astrocytoma, with a WHO performance status 0–2 were eligible. Analysis was by intention to treat, and primary endpoints were overall and progression-free survival.

**Findings** 157 patients were assigned early radiotherapy, and 157 control. Median progression-free survival was 5·3 years in the early radiotherapy group and 3·4 years in the control group (hazard ratio 0·59, 95% CI 0·45–0·77; p<0·0001). However, overall survival was similar between groups: median survival in the radiotherapy group was 7·4 years compared with 7·2 years in the control group (hazard ratio 0·97, 95% CI 0·71–1·34; p=0·872). In the control group, 65% of patients received radiotherapy at progression. At 1 year, seizures were better controlled in the early radiotherapy group.

**Interpretation** Early radiotherapy after surgery lengthens the period without progression but does not affect overall survival. Because quality of life was not studied, it is not known whether time to progression reflects clinical deterioration. Radiotherapy could be deferred for patients with low-grade glioma who are in a good condition, provided they are carefully monitored.

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## Introduction

Many aspects of treatment for low-grade glioma are controversial. No evidence-based guidelines exist for the "wait and see" policy in young patients with low-grade glioma who present with seizures only; the effectiveness of extensive resection compared with more limited surgical procedures and the use of chemotherapy is unknown. The effectiveness of radiotherapy is also unclear.

In the mid 1980s, European investigators explored the role of radiotherapy in two randomised studies. The first study (EORTC 22844)[1] investigated the presence of a dose–response relation for patients with low-grade glioma who were treated with radiotherapy. Together with a similar American study,[2] this study made clear that within a range of 45 to 65 Gy given in fractions of 1·8 Gy, the progression-free survival and overall survival in patients with low-grade glioma is independent of the radiation dose given. Now a radiation dose of 50–54 Gy in fractions of 1·8 Gy is the accepted treatment for low-grade glioma.

The second EORTC trial (EORTC 22845) addressed a more fundamental question. This study, activated in 1986, is the only randomised study in low-grade glioma to compare an active treatment with a conservative approach (the "wait-and-see" policy). The study assessed the efficacy of early radiotherapy versus deferred treatment (including radiotherapy) at the time of progression. An interim analysis of this study was done in 1998, which found no overall survival benefit of early radiotherapy, although it did show a small increase in progression-free survival.[3] At the interim analysis which was done after a minimum follow-up duration of 14 months (median 60 months), only 30% of patients had died and 49% had progressed. We now present the long-term results of the study with a median follow-up of 93 months.

## Methods

### Patients

Before entry to the study (and during follow-up) physical and neurological assessments were done, including the WHO performance status and the Medical Research Council neurological function scale (panel). Eligibility criteria were: a) 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 Tumours;[4] b) WHO performance status 0–2 or Karnofski

**Panel: Medical Research Council neurological function scale**

1 No neurological deficit
2 Some deficit but adequate function for useful work
3 Deficits causing moderate functional impairment—eg, moderate dysphasia, moderate paresis, or visual disturbances such as field defect
4 Deficit causing major functional impairment—eg, inability to use limb, gross speech impairment, or visual disturbances
5 Inability to make conscious responses

performance of 60 or more; c) age between 16 and 65 years; d) no other significant systemic diseases or malignancies interfering with follow-up; e) not being pregnant. Patients with completely resected small grade I tumours (pilocytic astrocytoma), optic nerve glioma, brainstem glioma, third ventricular glioma, and mostly infratentorial glioma were not eligible. We used the histological diagnosis of the review pathologist; if it was not available, we used the diagnosis of the local pathologist. The neurosurgeon classified the extent of resection at the time of surgery as: aspiration or biopsy, resection with less than 50% tumour removal, 50–89% tumour removal, or 90–100% tumour removal. A CT scan immediately after the operation was not required.

## Procedures

Between March, 1986, and September, 1997, eligible patients from 24 institutions across Europe were randomly allocated to either early radiotherapy or further treatment (including radiotherapy) at the time of recurrence (control group). 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[5] and stratification according to treatment institute, histology (astrocytoma *vs* oligodendroglioma or oligoastrocytoma), and extent of resection (biopsy *vs* partial, subtotal, or total). Data were collated and analysed at the EORTC Data Center.

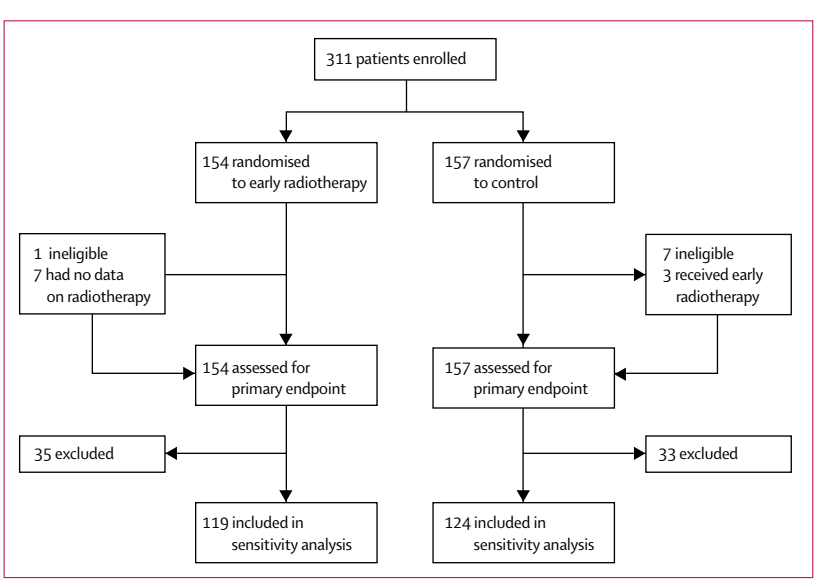


*Figure 1:* Trial profile

At baseline, the size of the tumour and crossing of the tumour over the midline were assessed on CT scan by the local investigator. Whether the tumour showed enhancement on the CT scan was not registered centrally. 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, patients were followed up for survival only.

The total dose of radiotherapy given was 54 Gy; five fractions of 1·8 Gy per week were given for 6 weeks. All fields were treated on each treatment day. 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. Both megavolt photons (4–10 MV) and Cobalt-60 sources were allowed. The dose was specified according to the International Commission on Radiological Units Report 29.[6] Radiotherapy planning included the use of dedicated CT, treatment-planning computers, and standard simulators. Depending on the tumour location and size, patients were treated with different techniques, such as two parallel-opposed fields, two angled fields with wedge filters, or multiple convergent fields. A maximum of 8 weeks between operation and the start of radiotherapy was allowed.

## Statistical analysis

The primary endpoints of the study were progression-free survival and overall survival, which were calculated from the day of randomisation to the date of the first event. The date of progression was defined as the date of the CT scan that showed or confirmed progression. Patients without event were regarded as censored observation at the last follow-up visit.

The study sample size was calculated from an expected median survival of 2·15 years without radiotherapy. To detect an increase from 20% to 40% in 5-year survival after radiotherapy, randomisation of 200 patients was needed to guarantee 40 events in the best treatment group 3·8 years after the start of the study. However, patients' survival was noted to be better than expected during the study, and the number of patients needed for sufficient power was recalculated. 300 patients gave power of 0·80, allowing the detection of an increase in overall survival from 60% to 75% ($\alpha$=0·05, two-sided test).

Analysis was by intention to treat. A separate analysis was done that excluded the non-eligible patients, patients with pilocytic astrocytomas, and patients with anaplastic tumours at central pathology review.

The Kaplan-Meier analysis was used to estimate event-free rates. The log-rank test (at a two-sided 5% significance) was used to compare the two study groups. A hazard ratio, with 95% CIs from a Cox model, summarises the effect; a non-parametric CI is given for the median.[7] The Greenwood formula was used to calculate CIs around event rates. Distribution of categorical variables was compared by the $\chi^2$ test.[8] Ethics committees of the local hospitals participating in the trial approved the study design. Patients gave written or oral informed consent before they were randomly allocated to a treatment group.

### Role of the funding source

The funding sources had no role in the data collection, data analysis, data interpretation, writing of the report, or in the decision to submit it for publication. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

## Results

311 patients were randomised, of whom 303 (97%) were eligible; reasons for non-eligibility were incomplete data before entry to the study, performance status greater than 2 or older than 65 years of age, and missing follow-up data (figure 1). After follow-up for a median of 7·8 years (March 2004), 217 (70%) patients had progressed and 156 patients had died (50%). 142 (91%) patients died from a progressive brain tumour, 12 (8%) patients died from unrelated causes, and no information on the cause of death was available for 2 (1%) patients.

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 (table 1). Pathological review was possible for 253 (81%) patients and confirmed the presence of a low-grade glioma in 186 (74%) patients. Anaplastic tumours, including astrocytomas, oligoastrocytomas, and oligodendrogliomas, were found in 48 (19%) patients. Other high-grade tumours (including glioblastoma multiforme [GBM]) were present in 9 (4%) patients.

The median radiation dose given was 54 Gy (range 45·0–64·8 Gy) and the median number of fractions was 30 (range 24–33). Despite random assignment to the control group, three patients received early radiotherapy (to a total dose of 50–54 Gy). Of the patients randomised to the radiotherapy group, 49 were treated with Cobalt-60 sources and 98 with megavoltage equipment; no data were available for the other seven patients.

Toxic effects were modest in general, and mainly consisted of skin reactions, otitis, mild headache, and some nausea or vomiting. Irradiation was interrupted in six patients because of acute reactions.

| | No early radiotherapy n=157 | Early radiotherapy n=154 |
|---|---|---|
| **Sex** | | |
| Male | 100 (64%) | 91 (59%) |
| Female | 52 (33%) | 63 (41%) |
| Missing | 5 (3%) | 0 |
| **Age in years** | | |
| Median (range) | 41·0 (17·0–68·0) | 36·5 (15·0–69·0) |
| Number <30 years | 27 (17%) | 31 (20%) |
| Number >50 years | 33 (21%) | 29 (19%) |
| **WHO performance status** | | |
| 0 | 63 (40%) | 67 (44%) |
| 1 | 68 (43%) | 68 (44%) |
| 2 | 18 (12%) | 16 (10%) |
| Other, including missing | 8 (5%) | 3 (2%) |
| **Medical Research Council neurological function scale** | | |
| 1 | 89 (57%) | 98 (64%) |
| 2 | 48 (31%) | 41 (27%) |
| 3 | 11 (7·0%) | 12 (8%) |
| 4 | 4 (3%) | 3 (2%) |
| Missing | 5 (3%) | 0 (0%) |
| **Extent of resection** | | |
| Biopsy or <50% | 56 (36%) | 52 (34%) |
| 50–89% resection | 27 (17%) | 33 (21%) |
| Gross total (>90%) | 66 (42%) | 66 (43%) |
| Missing | 8 (5%) | 3 (2%) |
| **Histology*** | | |
| Astrocytoma | 78 (50%) | 80 (52%) |
| Oligodendroglioma | 19 (12%) | 23 (15%) |
| Mixed oligoastrocytoma | 25 (16%) | 15 (10%) |
| Pilocytic astrocytoma | 2 (1%) | 2 (1%) |
| Anaplastic tumours | 20 (13%) | 28 (18%) |
| Other (including grade IV and missing) | 13 (8%) | 6 (4%) |
| **Diameter** | | |
| <5 cm | 84 (54%) | 90 (58%) |
| >5 cm | 49 (31%) | 42 (27%) |
| Missing | 24 (15%) | 22 (14%) |
| **Tumour crossing the midline** | | |
| No | 115 (73%) | 126 (82%) |
| Yes | 22 (14%) | 15 (10%) |
| Missing | 20 (13%) | 13 (9%) |

*From review except if not available, in which case local was used.

*Table 1:* **Patient characteristics at the time of randomisation**

On intention-to-treat analysis, the difference in overall survival between the group who received radiotherapy and the control group was not significant (figure 2, table 2; log-rank p=0·873). However, patients randomised to radiotherapy had a longer period of progression-free survival than the controls (figure 3, table 2; log-rank p<0·0001). At 5 years, 55% (95% CI 46·7–63·3) of the irradiated patients were still free from progression compared with 35% (26·7–42·5) of the control group. Median progression-free survival was 5·3 years (4·6–6·3) compared with 3·4 years (4·6–6·3) in the control group.

At the time of relapse, most patients were treated with various combinations of surgery, chemotherapy, and radiotherapy. No further treatment at progression was given or documented for 13 (11·5%) of the patients in the control group and 32 (34%) of the irradiated patients. Salvage radiotherapy was given to 73 (65%) of the patients in the control group and 4 (4%) of the patients in the irradiated group. Chemotherapy was given to 18 (16%) of

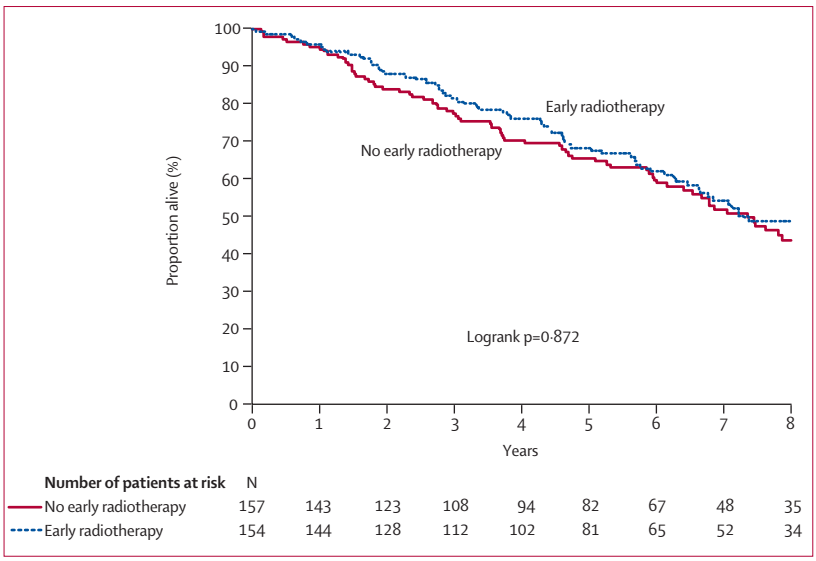


*Figure 2:* **Overall survival by intention-to-treat analysis**
Number of events: O=80 for control group; O=76 for early radiotherapy group.

the control group and 35 (37%) of the irradiated group at the time of recurrence, and there was no difference in reoperation rate. Survival after progression was 3·4 years for the control group versus 1·0 years for the irradiated group (overall log-rank p<0·0001).

Sensitivity analyses included 124 patients in the control arm and 119 patients in the radiotherapy arm; patients with pilocytic astrocytomas, ineligible patients, and patients who were diagnosed with an anaplastic tumour at histology review were excluded. Median survival was 7·9 years (95% CI 6·8–10·6) in the control group versus 7·1 years (6·1–8·8) in the radiotherapy group. Again, progression-free survival was superior in the radiotherapy group. 96 patients in the control group progressed versus 73 patients in the irradiated group (hazard ratio 0·63, 0·47–0·86). The median progression-free survival was 3·7 years (3·2–4·8) in the control group and 5·4 years (4·7–6·4) in the radiotherapy arm (log-rank p=0·003). At 5 years, 37·5% (28·6–46·3) in the control group were alive and progression-free versus 54·8% (45·3–64·3) in the radiotherapy group (hazard ratio 0·63; 0·47–0·86).

Of the 94 patients in the irradiated group who had a recurrence, local assessment of the site of the recurrence identified that four were outside the irradiation field and five were in a borderline area of the irradiated field. In 44 patients in the control group and 36 patients in the radiotherapy group, histology confirmed the recurrence (these samples have not been reviewed). This showed high-grade tumours in 29 (66%) patients in the control group and in 26 (72%) patients in the irradiated group. In the others a low-grade tumour was found.

To investigate whether patients free from tumour progression had any neurological signs and symptoms, the neurological signs and symptoms at 1 year were analysed in patients who were still progression-free at 2 years. The use of this subset ensures that the acute effects of treatment have subsided, and that patients who are already progressing at 1 year but have not yet been diagnosed with progression are excluded from the analysis. Post-hoc analysis found no differences between the two groups for cognitive deficit, focal deficit, performance status, and headache (data not shown). Although at baseline there were no differences between the two groups in seizure control (p=0·8701), at 1 year 26 of 102 (25%) patients who were irradiated had seizures by contrast with 29 of 71 (41%) patients who had not been irradiated (p=0·0329). Similar analyses at other time points have not been done.

| | No early radiotherapy (n=157) | Early radiotherapy (n=154) | Hazard ratio (95% CI) |
|---|---|---|---|
| **Overall survival** | | | |
| Median years (95% CI) | 7·4 (6·1–8·9) | 7·2 (6·4–8·6) | 0·97 (0·71–1·34) |
| Proportion alive at 5 years | 65·7% (57·8–73·5) | 68·4% (60·7–76·2) | |
| **Progression-free survival** | | | |
| Median years (95% CI) | 3·4 (2·9–4·4) | 5·3 (4·6–6·3) | 0·59 (0·45–0·77) |
| Proportion free from progression at 5 years | 34·6% (26·7–42·5) | 55·0% (46·7–63·3) | |

*Table 2:* **Survival and progression-free survival**

## Discussion

This study shows that immediate post-operative irradiation in patients with low-grade glioma increases the median progression-free survival by 2 years, without affecting overall survival. The interim analysis presented some differences in progression-free survival, but these were of little clinical significance.[3] In that analysis, early radiotherapy increased 5-year progression-free survival by only 7% (from 37% to 44%). In the present analysis, the improvement in 5-year progression-free survival due to early irradiation was 20% (35% *vs* 55%). The absence of a survival benefit for early radiotherapy is probably due to the effectiveness of salvage radiotherapy in the control group at recurrence. Most patients in the control group received irradiation at the time of recurrence, and survival after progression was significantly longer in the control group than in the early radiotherapy group. Therefore radiotherapy might be effective at the time of recurrence as well as immediately after surgery.

This study was initiated in the mid 1980s. Since then, several clinical advances have been made that would have affected the conduct of the trial if it were to start now. First, with widespread use of MRI, the tumour can be more accurately delineated and treatment planning improved. It is unlikely that use of this technique would have affected the outcome of the trial, because most tumour recurrences occurred within the radiation portals. However, the tumour diameter might have been found to be larger, which is of prognostic importance,[2,9] if it had been assessed from MRI scans rather than CT scans. Future studies should study the effect of the size of the

tumour on the prognosis, as measured by T2-weighted MRI or FLAIR MRI.

Second, in this study the surgeon estimated the extent of resection during surgery and post-operative CT scanning was not required. However, this estimate is no longer appropriate because studies published after this research began have shown that the surgeon's estimate of the extent of resection is unreliable.[10] The surgeons in this study probably overestimated the extent of resection—more than 40% of patients were reported to have had a more than 90% resection—but we do not think that this overestimate will affect the study outcome because even if the type of surgery is classified as either "biopsy" or "more extensive resection", both treatment groups were balanced according to the type of surgery.

Third, histological diagnosis was modified for a substantial number of patients after central pathology review. 26% of patients for whom pathology review was available were diagnosed with a high-grade tumour. High interobserver variation is common in neuro-oncological studies and reflects the absence of objective criteria for the diagnosis and grading of various gliomas.[11,12] Most of the discordant cases were diagnosed at review as having either an anaplastic astrocytoma, an oligoastrocytoma, or an anaplastic oligodendroglioma. In patients who have a biopsy, a sample error might also contribute to a misclassification, both for tumour grade and tumour lineage. Again, these factors were balanced for the two treatment groups. The subgroup analysis, which excluded patients with high-grade tumour, confirmed the finding of the intention-to-treat analysis. Moreover, the intention-to-treat analysis reflects everyday clinical practice, where decisions about post-surgical treatment are made from the local pathology, and not from the central pathology-review diagnosis. The observed variability is inherent to the absence of objective criteria to distinguish low-grade tumours from high-grade tumours.

Perhaps the most noteworthy shortcoming of the research is the absence of a quality-of-life study. Participation in the quality-of-life study was optional, and the few centres that participated in this part of the study prevent any meaningful analysis of these data. Therefore, whether the difference in time to progression is a reflection of time to clinical deterioration is unknown. In view of the absence of a difference in overall survival, this might be the most relevant question: is early radiotherapy able to postpone neurological deterioration? Some studies have shown that patients with tumour control have a better quality of life and cognition than patients with tumour progression.[13] Data on performance status were obtained in this study, but only until progression. Because the patients in the control group 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 patients with undetected progression do not bias the analysis. No major differences were seen between the two groups, except for better seizure control in the irradiated groups. In particular, the performance status was equally distributed between the two groups.

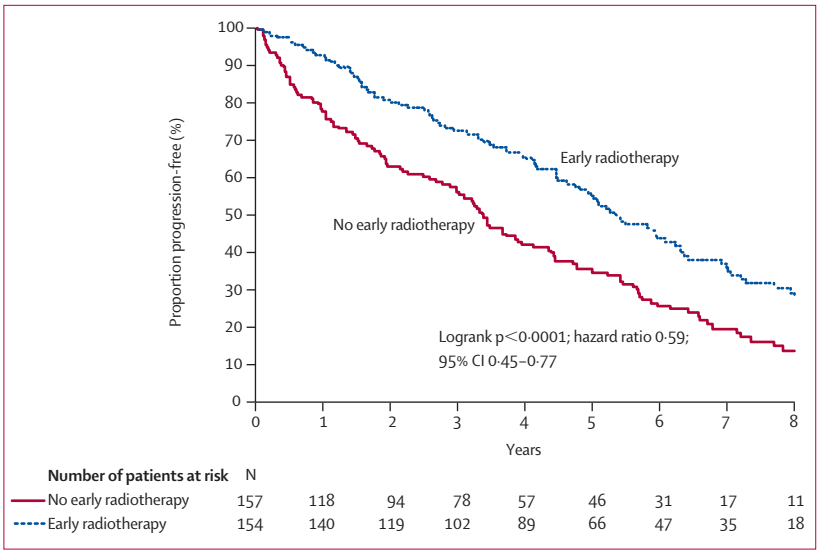


*Figure 3:* **Progression-free survival by intention-to-treat analysis**
Number of events: O=121 for control group; O=96 for early radiotherapy group.

Even if the timing of radiotherapy does not affect the survival of patients, it could still affect the quality of life. At the time of recurrence many patients develop new focal deficits or cognitive impairments, suggesting that the time to neurological deterioration might be a more appropriate endpoint than survival in future studies.

There is a widely held view that radiotherapy might contribute to cognitive dysfunction in patients with low-grade glioma, which has been used as an argument to withhold radiotherapy in these patients as long as possible.[14,15] This question is especially relevant in patients with a good prognosis, who are at risk of delayed side-effects of brain irradiation such as radiotherapy-induced leucoencephalopathy.[16] However, this view has been challenged by a case-control study with a detailed neuro-psychological assessment that failed to provide evidence for the harmful effects of irradiation on cognitive function, provided fractions of 2 Gy or less were used.[17] The study showed that the most important factors related to cognitive dysfunction were having a low-grade glioma and taking anti-epileptic drugs. No prospective study has addressed this issue. A study by the North Central Cancer Treatment Group in which patients with low-grade glioma were screened for radiotherapy-induced cognitive deterioration with the mini mental state examination did not support subsequent cognitive effects.[18] Additionally, formal neuropsychological testing of a small subset of 20 patients confirmed there was no evidence of cognitive deterioration.[19]

Past speculation that early radiotherapy might induce malignant transformation of low-grade glioma was not supported by our findings. Data obtained at second surgery at the time of recurrence showed that 65–72% of patients relapsed with a high-grade tumour, without a difference between the two treatment groups.

How should patients with a low-grade glioma be treated? Because the time to clinical or radiological progression is typically long, a "wait and see" policy can be defended for younger patients presenting with seizures only. In these patients, treatment can be withheld until the time of radiological or clinical progression. In patients with focal deficits, signs of high intracranial pressure, or cognitive deficits, treatment should be initiated without delay. Treatment should consist of a resection as extensive as possible. If the site and extent of the tumour prevents meaningful resection, a biopsy is needed to obtain histological proof of malignancy. Irradiation can then be recommended for most patients. There is no evidence that irradiation given with modern techniques to involved fields might worsen the condition of the patient, and irradiation prolongs progression-free survival. Two randomised trials have shown that giving a dose of 45–54 Gy to the tumour area with a margin of 1–2 cm is sufficient.[1,2] In young patients with seizures only who have had a substantial resection, radiotherapy can be withheld until further progression. Whether there is a role for chemotherapy in newly diagnosed low-grade glioma is unclear. Small phase II trials show the efficacy of chemotherapy in both low-grade oligodendroglioma and low-grade astrocytoma.[20–22] RTOG and EORTC studies are studying the role of chemotherapy in low-grade glioma.

**Contributors.**

A B M F Karim, D Afra, O de Witte, M Ben Hassel, S Schraub, K Hoang Xuan, R Mirimanoff, and P-O Malmström were responsible for the protocol design and conduct of the study; A B M F Karim coordinated the study; M Piérart obtained the data; L Collette and M J van den Bent analysed the data; M J van den Bent wrote the report with contributions from all authors.

**Conflict of interest statement**

We declare that we have no conflict of interest.

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