Survival, Prognostic Factors, and Therapeutic Efficacy in Low-Grade Glioma: A Retrospective Study in 379 Patients

By Knut Lote, Thore Egeland, Bjarne Hager, Beth Stenwig, Kari Skallerud, Jon Berg-Johnsen, Ingebjørg Storm-Mathisen, and Henry Hirschberg

Purpose: We report survival, prognostic factors, and treatment efficacy in low-grade glioma.

Patients and Methods: A total of 379 patients with histologic intracranial low-grade glioma received postoperative radiotherapy (n = 361) and intraarterial carmustine (BCNU) chemotherapy (n = 153). Overall survival and prognostic factors were evaluated with the SPSS statistical program (SPSS Inc, Chicago, IL).

Results: Median survival (all patients) was 100 months (95% confidence interval [CI], 87 to 113); in age group 0 to 19 years (n = 41), 226 months; in age group 20 to 49 years (n = 263), 106 months; in age group 50 to 59 years (n = 49), 76 months; and for older patients (n = 26), 39 months. Projected survival at 10 and 15 years was 42% and 29%, respectively. Patient age, World Health Organization (WHO) performance status, tumor computed tomography (CT) contrast enhancement, mental changes, or initial corticosteroid dependency were significant independent prognostic factors (P < .05), while histologic subgroup, focal deficits, presence of seizures, prediagnostic symptom duration, tumor category, and tumor stage were not. Patients aged 20 to 49 years with no independent negative prognostic factors (n = 132) had a median survival time of 139 months versus 41 months in patients with two or more factors (n = 33). Patients who presented with symptoms of expansion (n = 97) survived longer when resected (P < .03); otherwise no survival benefit was associated with initial tumor resection compared with biopsy. Intraarterial chemotherapy and radiation doses more than 55 Gy were not associated with prolonged survival. Among 66 reoperated patients, 45% progressed to high-grade histology within 25 months.

Conclusion: Prognosis in low-grade glioma following postoperative radiotherapy seems largely determined by the inherent biology of the glioma and patient age at diagnosis.


The natural course of a low-grade glioma is that of an indolent or slowly growing CNS tumor that in some patients, may persist for decades, while other patients with similar histology for largely unknown reasons may die within a few years.1,6 Age is a salient prognostic factor. Pilocytic and cerebellar astrocytomas of childhood,1,3,6 as well as hemispheric low-grade gliomas in children and teenagers,1,3,7 have an excellent prognosis. Adult low-grade gliomas are usually more aggressive, with median reported survival times that range from 3 to 5 years1,2,6,9 to 7 to 9 years in a recent series of reports.10-14 Reported negative prognostic factors in low-grade glioma include reduced performance9,11 mental changes,3,9,12 and focal neurologic deficits.1,11 Histologic grade2,6,10 or contrast enhancement on computed tomography (CT)2,13 are of prognostic value in some,2,6,12,13 but not all1,10 studies. Seizures are a common presenting symptom of reported positive prognostic significance.1,5,12,13

Controversy exists with regard to optimal management of adult low-grade gliomas. Macroscopic complete surgical resection may improve survival compared with partial resection. The infiltrative nature of these tumors, where tumor cells have been demonstrated beyond the area of radiologic abnormalities,18,20 may exclude surgical cure.

Radiotherapy may be of benefit in low-grade glioma.1,4,11 although conclusive data for such benefit are still incomplete.2,5,10,12 Serious late radiation effects may occur after radiation doses of 45 to 60 Gy to the brain,21,22 especially in small children.16,24 Chemotherapy has not been shown to prolong survival in low-grade gliomas, although tumor regression may be induced.6,25

We report age distribution, prognostic factors, efficacy of treatment, and survival in 379 patients with low-grade glioma seen at a single institution during the CT era.

Patients and Methods

The records of all patients with primary CNS tumors seen at the Norwegian Radium Hospital during the years 1980 to 1995 were retrospectively registered in a database. The hospital is a regional cancer center that serves a population of 1.6 million living in Eastern and Southern Norway outside the town of Oslo. During the years 1980 to 1987, the hospital also served as a radiotherapy center for Norwegian Radium Hospital; Department of Neurosurgery, Oslo City Hospital; and Departments of Statistics, Pathology, Pediatrics, and Neurosurgery, National Hospital, Oslo, Norway.

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Radiotherapy. Adult patients with performance status worse than the population in the two northern regions of Norway. All regional glioma patients had to register at the hospital if they were to receive radiotherapy. Adult patients with performance status worse than the population in the two northern regions of Norway. All regional glioma patients had to register at the hospital if they were to receive radiotherapy. Megavoltage equipment was used in all patients who received radiotherapy.

Variables registered included month and year of first symptom, type of symptoms experienced before admittance, date of radiologic diagnosis, CT and magnetic resonance image (MRI) findings, histologic diagnosis according to the WHO classification system, WHO functional status at first stay in the hospital, as well as data with regard to tumor localization, tumor category and stage, treatment, and survival. Patients usually underwent surgery at either of the two Neurosurgical Departments in our catchment area before admission to the Norwegian Radium Hospital. Histologic diagnosis was obtained in 90.6% of all registry patients. All consecutive 379 patients with primary intracranial histological low-grade gliomas (astrocytoma, oligodendroglioma, or mixed glioma) are included in this report.

The prediagnostic period was defined as months that elapsed from the first tumor-related symptom to radiologic tumor diagnosis. Survival was calculated from the date of radiologic diagnosis to death or to date of last observation. All patients were monitored until death or to December 31, 1995. Date of death for deceased patients were obtained either from case records or from the Census Bureau.

Statistics

The SPSS statistical package was used for data evaluation and presentation. Tables were tested for statistical significance by chi-square tests. Two-sided P values are reported throughout. Differences between means were tested using the two-sample t test. Survival curves were produced according to the Kaplan-Meier method and differences in survival tested for statistical significance by the log-rank test. For the purpose of multivariate Cox regression, patients diagnosed before 1980 (n = 18) were excluded from the analysis. Separation analysis with these patients included did not materially alter hazards ratios, 95% confidence intervals (CIs), or P values.

With regard to the multivariate model, there are several algorithms and principles to follow searching for optimal prognostic factors. We used the manual procedure described in Collett. First, a number of Cox regressions, each with one covariate, were performed. Prognostic variables with P values less than .10 were considered as candidates for the multivariate model. In the final model, only covariates with P values less than .05 were accepted. The P values were calculated in the usual way, being based on likelihood ratio tests. We mainly used plots to check the adequacy of the model. No strong claims are made in cases in which we fail to reject a hypothesis. Therefore, power calculations are omitted.

RESULTS

A total of 379 patients (231 males and 148 females) with histologic low-grade gliomas were seen at the Norwegian Radium Hospital during the years 1980 to 1995. Sex did not significantly influence survival (P > .09, Kaplan-Meier log-rank test). Mean and median ages were 37 and 38 years, respectively (range, 3 to 72 years). Age distribution in 10-year age groups is shown in Fig 1.

Only patients with a definite histologic diagnosis of low-grade glioma are included in the present report. Astrocytoma was by far the largest histologic subgroup (n = 268), followed by oligodendroglioma (n = 69) and mixed glioma (n = 42).

Radiologic diagnosis was based on CT with or without MRI in 369 patients (97.4%), on MRI alone in five patients (1.3%) and on other methods, usually angiography, in five patients (1.3%).

All patients had a surgical procedure to obtain tissue for histologic diagnosis. Operations were registered as biopsy procedures or resections according to the surgical report. Retrospective evaluation of the degree of surgical resection in resected patients was not attempted.

Radiotherapy was usually given within 1 to 2 months following surgery in patients who did not receive intraarterial chemotherapy. A total of 369 patients received external fractionated radiotherapy. Patients were irradiated to local fields (n = 320), or to whole brain fields (n = 47). Field specifications were lacking for two patients. Ten patients were not irradiated and a further eight patients received total doses less than 45 Gy. Fraction dose was 1.8 Gy, and only eight irradiated patients received less than 25 fractions. A total of 361 patients received fractionated external radiotherapy to accumulated doses in the 45- to 70.4-Gy range. The standard fractionation regimen was 1.8 Gy five times a week to a total dose of 54 Gy, and 250 patients were so treated. As a matter of policy, no patients in WHO performance group 4 and few patients in group three received radiotherapy.

A total of 179 patients received chemotherapy during their illness, usually in the first 2 to 4 months following surgery, or at clinical relapse. Chemotherapy consisted of intraarterial carmustine (BCNU) in 153 patients, lomustine, procarbazine, and vincristine (PCV) in 22 patients, and other regimens in four patients. Patients selected for intraarterial BCNU had to be younger than 55 years, with WHO functional status 2 or better, and with tumor location in brain areas that receive blood supply from the internal carotid artery. These selection criteria alone probably ensured that patients who received intraarterial chemotherapy had a better than average prognosis.

Survival by Pretreatment Prognostic Factors

Age. Forty-one patients were younger than 20 years. Tumor localization in these young patients was cerebellum (n = 10), n. opticus (n = 1), hemispheres (n = 23), and other intracranial loci in seven patients. Histology was astrocytoma (n = 28), oligodendroglioma (n = 7), and mixed glioma (n = 6). Within the astrocytoma subgroup, histology was juvenile astrocytoma (n = 9), pilo-
cyclic astrocytoma \((n = 1)\), and astrocytoma in the remaining 18 patients.

Patient age was a prominent prognostic factor as shown in Table 1 and Fig 2. Children and teenagers had a 10-year survival rate of 80%. Separate analysis showed that survival in age groups 20 to 29 years, 30 to 39 years, and 40 to 49 years was not substantially different, while patients in age groups 50 to 59 and those older than 60 years had successively worse prognoses. Accordingly, the Kaplan-Meier plot shows survival in age groups 0 to 19 years, 20 to 49 years, 50 to 59 years, and older than 60 years. The differences in survival are highly significant \((P < .001, \text{log-rank; Fig 2})\). The overall median survival duration in all patients \((n = 379)\) was 100 months \((95\% \text{ CI, 87 to 113})\). The projected overall survival rate \((\text{all patients})\) was 42\% at 10 years and 29\% at 15 years.

**Histologic diagnosis.** No difference in survival between patients with astrocytoma \((n = 268)\), oligodendroglioma \((n = 69)\), or mixed glioma \((n = 42)\) was discernible \((\text{Kaplan-Meier log-rank test})\). Our data indicate that there are no significant differences in prognoses among the three major histologic subgroups of low-grade glioma. Admittedly, the oligodendroglioma and mixed glioma groups are small. However, when survival in astrocytoma patients \((\text{median, 105 months; 95\% CI, 92 to 118})\) was compared with survival in the combined group \((n = 111)\) of oligodendroglioma and mixed glioma patients \((\text{median, 86 months; 95\% CI, 69 to 103})\), there was no significant difference in survival by log-rank test.

**WHO performance groups.** WHO performance status was registered after surgery at admission to the Norwegian Radium Hospital. There was no significant difference in survival between patients with performance scale 0 compared with patients with scale 1 \((\text{log-rank, } P = .1)\). However, when the patients were separated in group 1, WHO 0 to 1 \((n = 344)\), versus group 2, WHO 2 to 3 \((n = 35)\), patient performance status was a powerful predictor of survival \((P < .001, \text{log-rank; Fig 3})\). Patients with minimal or no functional deficits had the best prognosis.

**Focal neurologic deficits.** Patients with affected visual fields \((n = 51)\), cranial nerve palsies, or paralytic deficits of any degree \((n = 78)\) had impaired survival compared with

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**Table 1. Median Survival With 95\% Confidence Intervals by Age Group**

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>No of Patients</th>
<th>Median Survival (months)</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>0-19</td>
<td>41</td>
<td>226</td>
<td>67-385</td>
</tr>
<tr>
<td>20-49</td>
<td>263</td>
<td>106</td>
<td>93-119</td>
</tr>
<tr>
<td>50-59</td>
<td>49</td>
<td>76</td>
<td>40-112</td>
</tr>
<tr>
<td>60+</td>
<td>26</td>
<td>39</td>
<td>28-50</td>
</tr>
</tbody>
</table>
patients without these symptoms and signs ($P < .0415$ and $P < .0015$, respectively, Kaplan-Meier log-rank test). There was no sex difference with regard to cranial nerve palsies or pareses. However, males were at greater risk for visual deficits as a symptom of their glioma ($P < .0055$, $\chi^2$ test).

**Nausea and emesis.** Nausea or emesis at admission was seen in 58 patients and was not significantly associated with shortened survival ($P = .19$, Kaplan-Meier log-rank test) compared with patients without these symptoms ($n = 321$).

**Mental Changes.** Patients with any degree of tumor-related cognitive or emotional mental changes registered by themselves, their relatives, or doctor at admission ($n = 106$) had a significantly worse prognosis ($P < .0001$, Kaplan-Meier log-rank test; Fig 4) compared with patients without mental changes at admission ($n = 273$).

**Presence of seizures.** A total of 85% of all patients with histologic low-grade intracranial glioma developed seizures during their illness. Most patients (78%) had their first seizure before radiologic tumor diagnosis, and 7% afterwards. There was no sex difference in seizure prevalence. Patients with seizures ($n = 322$) had a nonsignificant trend toward longer mean duration of the prediagnostic period compared with patients with no seizures (10 months vs 6 months, $P = .3$, two-sample t test), but the presence of seizures was not associated with prolonged survival ($P = .5$, Kaplan-Meier log-rank test). However, the high prevalence of seizures may tend to diminish the weight of seizures as a prognostic factor within the low-grade group.
Tumor category and stage. It was possible to assign 364 patients to their respective tumor category. Reliable initial CT descriptions or images were missing in 15 patients. There was no significant survival difference between T1 and T2 patients. When survival in patients with T1 and T2 tumors (n = 128) was compared with survival in the group of patients with T3 and T4 tumors (n = 236), the difference was statistically significant (P = .014, Kaplan-Meier log-rank test; Fig 5). Although there was a trend towards longer survival in stages I and II, the difference was not statistically significant (P = .2). We conclude that the tumor-node-metastasis (TNM) staging system in its present form is of marginal value as a prognostic factor in low-grade gliomas.

Tumor CT contrast enhancement. In 353 patients, it was possible to assess tumor contrast enhancement on the initial diagnostic CT scan. Reliable data were missing in 26 cases. The presence of tumor contrast enhancement (n = 84) was a prominent negative prognostic factor (P = .0001, Kaplan-Meier log-rank test; Fig 6) compared with patients (n = 269) with a hypodense, nonenhancing tumor, which was the typical finding in most patients. No significant difference was seen between patients younger than 20 years or those older with regard to the frequency of contrast enhancement. Most of the few patients younger than 20 years of age with juvenile astrocytoma (n = 9) had tumor contrast enhancement, and they still had an excellent prognosis. Contrast enhancement in children or teenagers with low-grade glioma does not necessarily indicate an adverse prognosis. Tumor calcifications were seen in 70 patients, 50 of whom had oligodendroglioma or mixed glioma, which were more likely to show tumor calcifications than astrocytoma (P < .001, χ² test). The presence of detectable calcifications on CT was of
diagnostic value, but had no discernible prognostic impact on patient survival.

Length of prediagnostic period. The median duration of symptoms before radiologic tumor diagnosis in patients with low-grade gliomas was 6 months (range, 0 to 300). Forty-two patients had a prediagnostic period greater than 5 years, and the duration of the prediagnostic period was greater than 10 years for 14 patients. One might expect patients who harbor such indolent tumors to have better prospects for long-term survival following tumor diagnosis. However, patients with a prediagnostic period greater than 12 months did not survive significantly longer from the time of radiologic diagnosis than patients with shorter prediagnostic periods (Kaplan-Meier log-rank test).

Synopsis of prognostic factors. Table 2 presents an overview of prognostic factors tested in univariate analysis and not found significant in multivariate analysis. Table 3 lists the five prognostic factors found to be significant in multivariate analysis.

Treatment-Related Prognostic Factors

Corticosteroid dependency. Patients who needed corticosteroids in any dose for palliation of symptoms at admission (n = 50) had significantly reduced survival compared with other patients (P < .001, Kaplan-Meier log-rank test; Fig 7). However, the median survival time in corticosteroid-dependent patients was 43 months (95% CI, 20 to 66 months). Thus, corticosteroid dependency during the initial postoperative clinical course of a low-grade glioma does not necessarily indicate immediate demise.

Survival according to type of initial surgery. All patients had a surgical procedure to obtain tissue for histologic diagnosis. Whenever possible, the neurosurgeon performed a macroscopically radical resection. A total of 272 patients were resected with partial or total macroscopic tumor volume reduction. Retrospective assessment of the degree of resection was not attempted. A biopsy procedure, usually stereotactic, was performed in 103 patients. In four patients, the surgical procedure could not retrospectively be classified with certainty. By univariate analysis, there was no difference in survival between patients who initially underwent tumor resection with tumor volume reduction compared with patients who initially only had a biopsy procedure (P = .7, Kaplan-Meier log-rank test; Fig 8). In the subset of patients (n = 97) who presented with nausea and/or emesis or corticosteroid dependency (eg, serious symptoms of an expansive lesion), resected patients (n = 77) survived significantly longer (median, 64 months; 95% CI, 10 to 118) than patients (n = 20) who only had a biopsy procedure (median, 23
Table 3. Prognostic Factors Found Significant in Multivariate Cox's Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazards Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO performance 2-3 v 0-1</td>
<td>2.258</td>
<td>1.422-3.586</td>
<td>.0006</td>
</tr>
<tr>
<td>Any mental changes present</td>
<td>2.067</td>
<td>1.510-2.830</td>
<td>.0001</td>
</tr>
<tr>
<td>Contrast enhancement present</td>
<td>1.918</td>
<td>1.354-2.718</td>
<td>.0002</td>
</tr>
<tr>
<td>Corticosteroid dependency initially present</td>
<td>1.570</td>
<td>1.028-2.397</td>
<td>.0370</td>
</tr>
<tr>
<td>Age +1 year v age</td>
<td>1.029</td>
<td>1.017-1.041</td>
<td>.0001</td>
</tr>
</tbody>
</table>

NOTE. Patients diagnosed before 1980 (n = 18) were excluded from the analysis. Hazards ratios for mortality for the 5 statistically significant independent negative prognostic variables are listed with their respective 95% CIs and P values.

months; 95% CI, 10 to 36; P < .0287, Kaplan-Meier log-rank test; Fig 9). However, even within this subgroup, the type of initial surgical treatment did not qualify as a significant independent prognostic factor for survival in multivariate analysis.

Fourteen patients who initially underwent biopsy and 50 patients initially resected were reoperated with tumor resection at relapse. Thus, few patients with initial biopsy were resected at relapse. In two additional patients who did not initially have surgery, the histologic diagnosis was obtained at relapse. Thirty-six patients relapsed with low-grade histology, 16 progressed to anaplastic gliomas, and 14 progressed to glioblastomas. Overall, 30 of 66 patients (45%) with an initial low-grade glioma showed histologic progression to high-grade gliomas at relapse. The median time to clinical relapse that necessitated reoperation was 25 months. The median survival duration calculated from the date of reoperation was 19.5 months (range, 0.6 to 136).

Survival according to radiotherapy. Since 361 of 379 patients received conventionally fractionated postoperative radiation to doses of at least 45 Gy, we could not assess the effect, if any, of radiotherapy in treated compared with untreated low-grade glioma patients. Most patients received 54 Gy in 30 fractions over 6 weeks, although total dose varied somewhat during the years 1980 to 1995. Thus, it was possible to define three dose ranges: total dose 45 to 50 Gy (n = 45), total dose 51 to 55 Gy (n = 277), and total dose ≥ 56 Gy (n = 39). Patients who for various reasons received doses less than 45 Gy (n = 8) or no radiotherapy at all (n = 10) were excluded from the analysis. Survival was not statistically different for the three dose levels (P = .2, Kaplan-Meier log-rank test). Thus, we could not observe any dose-response with regard to survival in the dose range 45 to 70.4 Gy. Nor was there any difference in survival between patients who received radiation to local fields (n = 320) compared with patients who received whole-brain irradiation (n = 47).

Survival according to chemotherapy. PCV chemotherapy,22 as well as intraarterial chemotherapy with BCNU in selected low-grade glioma patients, was used during the years 1983 to 1995.25,31 Patients selected for chemotherapy usually received four courses during 4 months before radiotherapy. Two hundred patients had no chemotherapy, four received different regimens, 22 received PCV chemotherapy, and 153 received four courses of intraarterial BCNU, intravenous vincristine, and oral procarbazine.31 PCV chemotherapy did not seem
to influence survival in the few patients treated. Intraarterial BCNU chemotherapy was of no statistically significant benefit for survival compared with the group that received no chemotherapy (P = .35, Kaplan-Meier log-rank test; Fig 10). It is noteworthy that patients selected for intraarterial BCNU were younger, had a better performance status, less often had contrast enhancement on CT, and less often had mental changes. Although marginally so, they were in a prognostically advantageous group. Chemotherapy did induce tumor regression in some patients, but these responses did not statistically prolong survival in treated compared with untreated low-grade glioma patients.

Multivariate Analysis of Prognostic Factors

Prognostic factors in the multivariate Cox model were selected from candidate factors with P values less than .10 as described earlier. Only the five factors presented in Table 3 were significant independent prognostic factors at P levels less than .05. Hazards ratios computed relative to the reference case are given with 95% CIs and their respective P values. Statistically significant independent risk factors for mortality in our low-grade glioma patients were age, WHO performance status 2 to 3, presence of any mental or cognitive changes, corticosteroid dependency, and tumor contrast enhancement on the initial CT scan (Table 3). Whether the 18 patients diagnosed before 1980 were included or excluded from the multivariate analysis did not materially affect the computed hazards ratios, 95% CIs, or P values. The median survival time and the proportion who survived 10 years among 132 patients aged 20 to 49 years without any of the previous independent risk factors were 139 months (95% CI, 101 to 177) and 60%, respectively; the median survival time
and 10-year survival rate in 33 patients with two or more risk factors were 41 months (95% CI, 22 to 60) and 16%.

**DISCUSSION**

Age at diagnosis in adult patients with low-grade gliomas shows an incidence maximum in the fourth decade of life in a population-based report from Norway and in larger series from single institutions. The observed age distribution in our low-grade glioma patient population recruited from a defined geographic region indicates that the patients are representative for the disease. A notable exception is that few children and young patients and few children with juvenile or pilocytic astrocytomas are included. Our treatment policy usually did not include radiotherapy in children operated for low-grade gliomas, who generally have an excellent prognosis after surgical treatment. A few adult patients in WHO performance groups 3 to 4 may not have been referred for radiotherapy. All other low-grade patients in our region received radiotherapy at the hospital, so selection of patients by the referral pattern was minimal.

We further confirm the good prognosis for patients younger than 20 years of age found in other investigators, as well as the successively worse prognosis that can be expected in older age groups. The profound effect of age on prognosis renders any median survival calculated for low-grade glioma patients meaningless if their age at diagnosis is not clearly stated. The median survival time for our patients in age group 20 to 49 years was 9 years, which is comparable to other recent reports.

We did not observe any plateau in survival during the first 15 years following diagnosis. This finding contrasts to previous reports on patient materials that included a larger proportion of children, which tends to show a plateau in survival curves after 3 to 5 years of observation, probably largely due to the excellent prognosis of the many included children. Survival curves in studies that report adult patients show no plateau phase, although the median survival time was considerably shorter than in our report. Although prognosis may appear favorable compared with high-grade brain tumors, most patients will ultimately die of their low-grade glioma.

The present histologic subdivision of low-grade gliomas into astrocytoma, oligodendroglioma, and mixed glioma has been generally accepted. Our retrospective study indicates that if tumor morphology fits the histologic criteria of a low-grade glioma, further subdivision may not much increase the prognostic value of the histologic diagnosis.

Performance status, focal neurologic deficits, mental changes, seizures, symptoms of expansion, and contrast enhancement on CT have all been reported as possible prognostic factors in gliomas. Most investigators agree that age, performance status, mental changes, and seizures are of prognostic value, while the implications of TNM category, contrast enhancement, macroscopic radical surgery, and radiotherapy, as well as radiotherapy dose, are still debated.

Performance status remained an important prognostic factor in our study, although the difference between the prognostic impact of WHO performance grade 0 compared with grade 1 was marginal. However, a highly significant difference in survival and hazards ratio for mortality was observed between performance scales 0 to 1 compared with scales 2 to 3.
Focal neurologic deficits may affect performance and did have a significant univariate negative impact on survival in affected patients. For unknown reasons, males seemed to be at an increased risk for affection of vision.

Headache, nausea, and emesis are symptoms usually associated with large expansive intracranial lesions, and therefore these symptoms are readily understandable as a negative prognostic factor in low-grade gliomas. In our study, initial symptoms of expansion did not qualify as a statistically significant negative prognostic factor in affected patients. However, in patients who needed initial corticosteroid treatment to alleviate these symptoms, such corticosteroid dependency was a significant negative prognostic factor in univariate and multivariate analysis. Considering the large number of hypotheses statistically tested, we admit that the associated multivariate P value of .037 is by no means as convincing as the remaining P values of Table 3, all less than .001. The latter small P values would remain clearly significant following, eg, Bonferroni corrections that account for multiple tests.

Like other investigators, we found that the presence of mental changes in low-grade glioma patients was a strong independent negative prognostic factor for survival, with a hazards ratio of approximately 2.

In some contrast to the results reported by Karim et al in their large prospective study, tumor category according to the Internation Union Against Cancer (UICC) TNM classification was, in our experience, a prognostic factor limited to univariate significance only. Karim et al discerned between T1a (tumor diameter < 3 cm) and T1b (diameter 3 to 5 cm), and prognosis in the two T1 subgroups differed considerably. We adhered to the original T1 definition (tumor diameter < 5 cm). A prospective investigation, even a large multicenter study of 6 years accrual duration, may allow for more precise collection of radiologic data, possibly making tumor category assessment in the study by Karim et al more exact than our own retrospective tumor category classification. On the other hand, the median survival time in their heavily selected patients was only 6 years, compared with more than 8 years in our largely unselected regional patients; so, subtle differences in our respective patient populations may have differently influenced tumor category assessments and the relative weight of tumor subtype as a prognostic factor in the two studies.

Tumor contrast enhancement on initial CT was a significant univariate, as well as multivariate, negative prognostic factor for survival, with approximately a doubled hazards ratio in affected patients. A report from 1981 based on few patients concluded that tumor contrast enhancement was of no prognostic value in low-grade glioma, while two later reports based on much larger series found enhancement to be of negative prognostic impact. A recent large study again found tumor enhancement of no significant prognostic value. In the present study, initial pretreatment tumor contrast enhancement on CT definitely was a strong negative prognostic factor in low-grade glioma patients.

Our data confirm the textbook adage that calcification in a brain tumor is a radiologic marker that favors a diagnosis of oligodendroglioma. Calcification was also seen in a third of patients with mixed low-grade gliomas, but was otherwise of no prognostic significance.

The presence of seizures has long been recognized as a possible positive prognostic factor in brain tumors. Eighty-five percent of our low-grade glioma patients experienced seizures. A glance at the Kaplan-Meier survival graph might suggest that the death rate of unaffected patients was slightly increased during the first 2 to 3 years following diagnosis, although the difference did not reach univariate statistical significance. Thus, we could not confirm that the presence of seizures is a positive prognostic factor in low-grade gliomas diagnosed and treated in the CT era.

The well-recognized inherent tendency of low-grade gliomas to develop gradually anaplasia and increasingly aggressive biology was confirmed by our finding that 45% of reoperated patients had progressed from an initial low-grade glioma to a high-grade glioma at a median time of 25 months after the first operation. Since only selected patients were reoperated, the true extent of transformation in the total patient population may have been considerably higher.

The median duration of the symptomatic period prior to radiologic diagnosis was 6 months in our patients. The duration of this prediagnostic period varied considerably, but its length did not significantly influence survival from diagnosis. Possibly, low-grade gliomas at the time of diagnosis have reached a potential for growth and anaplastic dedifferentiation that renders median duration of the symptomatic period before diagnosis immaterial to further prognosis. Also, the present sensitive neuroradiologic methods may tend to considerably shorten the length of the prediagnostic period compared with patient materials accrued before the CT era.

The efficacy and indications for various treatment modalities in patients with low-grade glioma are debated. A number of reports indicate that complete surgical resection is curative in juvenile or pilocytic astrocytomas in children, and may also render adult patients with low-grade gliomas tumor-free, or at least secure longer survival than for nonresectable patients.
In our patients, a macroscopically complete resection was performed whenever possible. However, compared with biopsy followed by radiotherapy, tumor volume reduction by resection followed by radiotherapy was not associated with increased duration of survival in our low-grade glioma patients, except in the subgroup of patients who presented with symptoms of increased intracranial pressure. Debunking surgery was associated with prolonged survival in this subset of patients. Few patients who underwent initially biopsy were resected at relapse, so our data indicate that initial tumor resection does not prolong survival in low-grade glioma patients who do not show clear symptoms of expansion, provided the patients have received postoperative radiotherapy. A possible explanation is that the effect of radiotherapy was so great that any effect of tumor resection was overshadowed. However, a distinct plateau phase following radiotherapy might then be expected to appear on survival curves, and that was not the case. An equally plausible interpretation is that either treatment modality may be of marginal survival benefit for most patients with adult low-grade gliomas. Believers and nonbelievers in the efficacy of radiotherapy in patients with low-grade gliomas are awaiting the results of ongoing prospective randomized trials. Serious late effects of radiotherapy may include endocrine dysfunction, intellectual impairment, radionecrosis, or second tumors. Late sequelae in children are especially troubling. Retrospective nonrandomized reports indicate a survival benefit from higher radiation doses, but no dose-response effect of radiotherapy on survival has been found in a recent large prospective randomized study. Nor could we demonstrate a dose-response effect of radiotherapy on survival in our retrospective study, although any effect must have been large to be detectable.

The risk of second tumors following radiation to the brain probably is approximately 1% to 2% after 10 to 20 years. Concerns that malignant anaplastic changes may be induced by radiation in low-grade gliomas are not corroborated in the present report, in which 45% of operated patients had progressed to high-grade gliomas at a median interval of 25 months after radiotherapy, a short induction period for a putative radiation-induced cancer. Nor did we observe any increased death rate after 10 to 15 years of observation, which might conceivably arise if a substantial number of patients developed more aggressive tumors as a late effect of radiotherapy.

Chemo therapy may induce tumor responses in patients with low-grade gliomas, although no clear survival benefits from chemotherapy have been demonstrated. The PCV regimen did not have any discernible impact on survival in our adult low-grade glioma patients after correction for selection criteria.

We conclude that in low-grade glioma patients who have received postoperative radiotherapy, prognosis seems largely predetermined by the inherent tumor biology and age at diagnosis. Age, tumor contrast enhancement, mental changes, reduced performance status, and initial corticosteroid dependency are important independent negative prognostic factors in these patients.

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