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Low-grade gliomas of the cerebral hemispheres in children: an analysis of 71 cases

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Low-grade gliomas constitute the largest group of cerebral hemispheric tumors in the pediatric population. Although complete tumor resection is generally the goal in the management of these lesions, this can prove difficult to achieve because tumor margins may blend into the surrounding brain. This raises several important questions on the long-term behavior of the residual tumor and the role of adjuvant therapy in the management of these lesions.

To examine these issues, the authors reviewed their experience in 71 children with low-grade cerebral hemispheric gliomas who were treated at their institution between 1956 and 1991 and assessed the relationship between clinical, radiographic, pathological, and treatment-related factors and outcome. Only seven patients in the series died, one from perioperative complications, five from progressive disease, and one (a child with neurofibromatosis) from a second neoplasm. For the 70 patients who survived the perioperative period, overall actuarial survivals at 5, 10, and 20 years were 95%, 93%, and 85%, respectively; progression-free status was maintained in 88%, 79%, and 76%, respectively. On univariate analysis, the factor that was most strongly associated with both overall and progression-free survival was the extent of tumor resection ($p = 0.013$ and $p = 0.015$, respectively). A relationship between extent of resection and progression-free survival was present both in patients with pilocytic astrocytomas ($p = 0.041$) and those with nonpilocytic tumors ($p = 0.037$). Histopathological diagnosis was also associated with overall survival on univariate analysis; poorer results were seen in the patients with nonpilocytic astrocytoma compared to those with other low-grade gliomas, such as pilocytic astrocytoma, mixed glioma, and oligodendroglioma ($p = 0.021$). The use of radiotherapy was not associated with a significant improvement in overall survival ($p = 0.6$). All three patients who ultimately developed histologically confirmed anaplastic changes in the vicinity of the original tumor had received prior radiotherapy, 20, 46, and 137 months, respectively, before the detection of malignant progression. In addition, children who received radiotherapy had a significantly higher incidence of late cognitive and endocrine dysfunction than the nonirradiated patients ($p < 0.01$ and 0.05, respectively).

The authors conclude that children with low-grade gliomas of the cerebral hemispheres have an excellent overall prognosis. Complete tumor resection provides the best opportunity for long-term progression-free survival. However, even with incomplete tumor excision, long-term progression-free survival is common. The findings in this study do not support the routine use of postoperative radiotherapy after an initial incomplete tumor resection: although irradiation appears to increase the likelihood of long-term progression-free survival, overall survival is not improved significantly, and long-term morbidity may be increased.

KEY WORDS • astrocytoma • cerebral hemispheres • glioma • radiation therapy • surgical approach • children

LOW-GRADE gliomas constitute the largest group of cerebral hemispheric tumors in the pediatric population.[5,18,51,63] The vast majority of these neoplasms can be classified into one of four histological subgroups: 1) pilocytic astrocytomas; 2) nonpilocytic ("diffuse") fibrillary and protoplasmic astrocytomas; 3) low-grade oligoastrocytomas; and 4) oligodendrogliomas. Although it is generally agreed that, when feasible, complete tumor resection is the optimum treatment for these lesions, this goal often proves difficult to achieve. In many cases, the tumor blends imperceptibly into the surrounding brain, making it impossible to conclusively delineate tumor boundaries. Accordingly, in tumors involving functionally significant cortex, the surgeon may perform an incomplete tumor resection to minimize the risk of producing serious neurological injury. Even in cases in which a radiographically confirmed complete resection has been performed, it is not uncommon on microscopic examination to find neoplastic cells infiltrating to the resection margin. This phenomenon raises important questions on the long-term behavior of the residual gross or microscopic tumor and the role of adjuvant therapy in its management. Although a number of studies involving adults with low-grade gliomas of the cerebral hemispheres have attempted to resolve these issues,[6,15,19,22,25,28,32,33,38,39,41,43,44,50,52,54,56–59,61,62,64,66] the findings in such studies may not be

directly applicable to the pediatric population because of potential age-related differences in the biology of these tumors[32,39,54] and the vulnerability of the pediatric nervous system to treatment-induced sequelae.

First, it remains uncertain whether the risk of disease progression in children with low-grade hemispheric gliomas is influenced by the extent of tumor resection[32,33,39,43,56,61] and whether, as in adults with low-grade gliomas,[19,32,39,43,44,56,61] there is a significant incidence of late tumor recurrence even in those patients who undergo a presumed gross total tumor resection. Second, studies involving adults with low-grade hemispheric astrocytomas have generated conflicting results regarding the efficacy of radiotherapy in controlling residual disease.[6,19,22,25,32,33,39,41,43,44,50,52,54,56–59,61,64,66] In those studies in which a benefit has been found,[6,19,22,32,33,43,56,57,59,64] it has often been limited to individuals in poor prognostic groups, such as older patients or those with subtotal tumor removal. The benefit of this modality for pediatric hemispheric low-grade glioma is even less clear.[3,12,24,26,34,36,37,41,53,54] In view of the well-known risks of radiation therapy to the developing nervous system,[9,13,14,16,29,60] it is essential to be certain that this treatment, when employed, is effective in improving outcome. Although attempts have been made to examine this issue in a prospective, randomized multiinstitutional study format, such investigations have been severely hampered by difficulties in the accrual of patients who are randomly assigned to radiotherapy versus no radiotherapy treatment arms. Third, the contribution of histological subtype, for example, pilocytic versus nonpilocytic astrocytoma, to long-term outcome in pediatric supratentorial low-grade gliomas remains undefined. Although there is a suggestion that adults with hemispheric pilocytic astrocytomas fare better than those with nonpilocytic astrocytomas[7,21,22,41,56] and that children with pilocytic cerebellar astrocytomas have a better prognosis than those with diffuse, nonpilocytic cerebellar astrocytomas,[23,67] comparable studies involving pediatric hemispheric gliomas have been lacking in the literature. Finally, the long-term incidence of malignant progression in low-grade hemispheric gliomas of childhood remains uncertain. Although 13.3% to 32% of adult low-grade astrocytomas will manifest malignant histological features within 5 to 10 years of diagnosis, and as many as 79% of progressive tumors will become malignant histologically,[32,38,43,44,49,61,62] anaplastic progression of pediatric low-grade gliomas appears to be comparatively uncommon.[10,26,37,41,65]

To study these issues, we reviewed overall survival, progression-free survival, and functional outcome in 71 children with low-grade hemispheric astrocytomas, oligoastrocytomas, and oligodendroglioma managed at the Children's Hospital of Pittsburgh between 1956 and 1991. Other common supratentorial glial neoplasms such as gangliogliomas and gliomas of the thalamus and optic pathways were excluded from this study because they are likely to constitute prognostically distinct groups.

Clinical Material and Methods

Patient Population

The patient population in this study was obtained from a detailed review of the Tumor Registry Data Bank, Neurooncology Clinic records, and pathology reports of children with biopsy-proven brain tumors who were treated between 1956 and 1991 at the Children's Hospital of Pittsburgh. Seventy-three cases of reported nonmalignant astrocytic, oligodendroglial, or mixed astrocytic/oligodendroglial tumors involving the cerebral hemispheres (excluding optic pathway gliomas) were selected for review; three patients with cerebral hemispheric gliomas that also involved the basal ganglia were included in the series. These lesions accounted for 8.5% of 859 biopsy-proven brain tumors that were treated at our institution during the above interval. In comparison, 160 cerebellar low-grade gliomas and 46 cerebral malignant gliomas were treated during the same period.

An independent microscopic examination of the tissue sections from these cases was performed by a neuropathologist (D.C.) who did not have direct involvement in making the original histopathological diagnosis or knowledge of the patient's outcome after treatment. In cases of discrepancy between the original histopathological diagnosis and the "current" diagnosis, an additional reviewer was enlisted to classify the tumor in the most appropriate histopathological subgroup. Because one of the goals of this study was to relate the contribution of tumor histology to outcome in children with low-grade hemispheric gliomas, lesions containing a mixture of astrocytic and oligodendroglial elements and those with a predominant oligodendroglial component were included along with predominantly astrocytic tumors in the study cohort. Seventy-one cases fulfilled established criteria[31] for pilocytic or nonpilocytic low-grade astrocytoma, low-grade oligoastrocytoma, or benign oligodendroglioma and formed the basis for the present study. Two lesions that were originally classified as "astrocytoma" were found on repeat review to be "anaplastic astrocytoma" and were excluded from the study group.

Hospital and clinic records, operative notes, and results of preoperative and follow-up examinations and imaging studies were obtained through a detailed review of medical records and neurooncology clinic charts. Long-term outcome data in patients who had reached adulthood, and were no longer followed at Children's Hospital, were obtained through the results of yearly outcome assessments performed by the Tumor Registry Data Bank on the basis of information provided by the patient, the patient's family, or the physician. Recent information was obtained in all but five of these patients; four of the five had been without disease progression for at least 10 years before being lost to follow up.

Overall Management Philosophy

Although a number of surgeons were involved in the operative and postoperative treatment of these patients, the overall philosophy of management for children with low-grade cerebral hemispheric gliomas has been remarkably consistent at our institution during the past four decades. In each case, every effort was made to obtain a complete tumor resection when feasible. Before 1976, the determination of the extent of resection was based solely on the surgeon's evaluation. Since that time, radiographic confirmation by computerized tomography (CT), or, more

recently, magnetic resonance (MR) imaging has routinely been obtained. Electrocorticography was not used in the tumor resection of patients with preoperative seizures during the time period encompassed by this study.

In general, patients undergoing complete resection did not receive postoperative radiation therapy. In those cases in which less than a complete resection was performed, the decision on whether to proceed with adjuvant radiotherapy was at the discretion of the neurosurgeon and neurooncology team. Although techniques of radiotherapy have evolved during the course of this study, dosing parameters have been relatively consistent since the 1960s. In general, patients were treated with limited-field radiotherapy administered to the tumor volume and a margin of surrounding brain. Only two of 35 patients undergoing radiotherapy received a dose to the tumor bed of less than 5000 cGy. In addition, all but two patients received megavoltage radiation. An acknowledged limitation of this study is that the decision on whether to administer postoperative radiotherapy was often made somewhat arbitrarily on a case-by-case basis.

Examination of Treatment Parameters

For each patient included in the study, a series of clinical, diagnostic, and treatment parameters were recorded. These included 1) tumor location as defined by preoperative imaging studies and intraoperative examination (including all sites of involvement when multiple areas were involved); 2) side (left or right); 3) presence of a variety of preoperative symptoms and signs; 4) overall duration of symptoms before diagnosis; 5) severity of preoperative neurological impairment, that is, none, mild (subtle hemiparesis or word-finding difficulties), or severe (dense hemiparesis or obtundation); 6) patient age at operation; 7) year of operation; 8) presence of a tumor cyst with a mural nodule; 9) extent of tumor resection (total, near total ($>$ 90% tumor removal), subtotal) as assessed by the operating surgeon and, when available, postoperative imaging; 10) histopathological diagnosis of the tumor (pilocytic astrocytoma, astrocytoma, mixed oligoastrocytoma, oligodendroglioma); 11) operative complications; 12) use of postoperative radiation therapy; and 13) long-term outcome (duration of overall survival and survival without disease progression, functional and neurological status, seizure control, and late cognitive and endocrine sequelae). In patients with tumor progression, information was collected on the histopathology of the progressive tumor (when available), the treatment employed, and the postprogression outcome.

General Features of the Study Group

The study group consisted of 35 girls and 36 boys; the tumor involved the left hemisphere in 42 children and the right in 29. Twenty-three children were younger than 5 years of age at the time of diagnosis, 18 were between 5 and 10 years of age, and 30 were between 10 and 18 years of age. The most common presenting symptoms were seizures in 41 patients, headache in 29, vomiting in 22, and hemiparesis in 16. Less common symptoms included visual loss in 11 children, lethargy in 10, personality changes in eight, aphasia in six, and hemisensory complaints in four. Papilledema, the most common finding on examination, was detected in 19 children. Various focal findings were detected in 32 children: in 26, these neurological deficits were mild; and six had severe neurological deficits.

Twenty-four children were diagnosed and underwent operative intervention before 1976; in these patients, assessments of tumor size, location, the presence or absence of a cyst, and extent of resection were based on the surgeon's impression. The remaining patients underwent preoperative CT and, more recently, MR imaging examinations, which in the majority of cases were supplemented by postoperative studies to assess extent of resection. The tumor involved the parietal lobe in 27 children, the frontal lobe in 25, the temporal lobe in 21, and the occipital lobe in 12; in 14 children, more than one lobe was involved. Twenty-three children had lesions with a large cystic component; in 12 cases, a well-defined mural nodule was present.

Twenty-one children underwent resections judged to be complete based on the surgeon's evaluation and/or radiological criteria; 12 underwent near total resections ($>$ 90% tumor removal); 38 underwent subtotal resections of which 26 involved 50% to 90% tumor removal and 12 consisted of more limited resections ($<$ 50% tumor removal). When original imaging studies were available for review, the assessment of resection extent was based on comparison of measurements of the cross-sectional area of the tumor between postoperative and preoperative axial images. In cases in which the original studies were not available, determination of extent of resection was based on the neuroradiology report, which typically described the maximum diameter of the residual versus the original tumor. For patients treated before the availability of CT, extent of resection was based solely on the surgeon's impression. Complete or nearly complete resections were obtained in 13 of 24 patients (54%) treated before 1976 and 20 of 47 (43%) treated more recently. Histopathological examination disclosed pilocytic astrocytoma in 22 patients, nonpilocytic low-grade astrocytoma in 20, mixed oligoastrocytoma in 21, and oligodendroglioma in eight.

Radiotherapy was administered to only two patients who underwent complete tumor resection. In contrast, 33 patients undergoing less than complete resection received adjuvant radiotherapy after the initial operation.

Statistical Analysis

Survival curves were generated using the Kaplan–Meier[30] method with tumor progression and death as the two endpoints. Patients lost to follow-up study were censored at the time of last examination or correspondence. One child, who underwent subtotal excision of a low-grade oligoastrocytoma, died during the perioperative period and was excluded from outcome analyses.

The effect of the aforementioned parameters on survival and progression-free survival in the 70 patients surviving the perioperative period was examined in a series of univariate analyses using the Mantel–Cox[35] log-rank test to assess the strength of association of individual parameters with outcome. Cox[8] multivariate analysis was then used with those variables shown to be significant on univariate analysis to identify the parameters that were

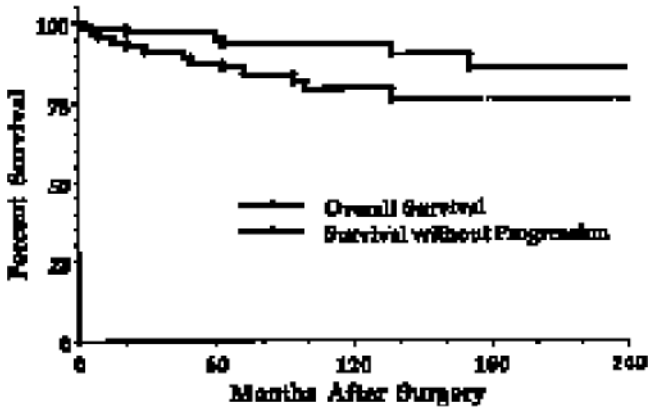

FIG. 1. Graph depicting overall survival *(solid line)* and progression-free survival *(dashed line)* in 70 children with low-grade hemispheric gliomas who survived the perioperative period.

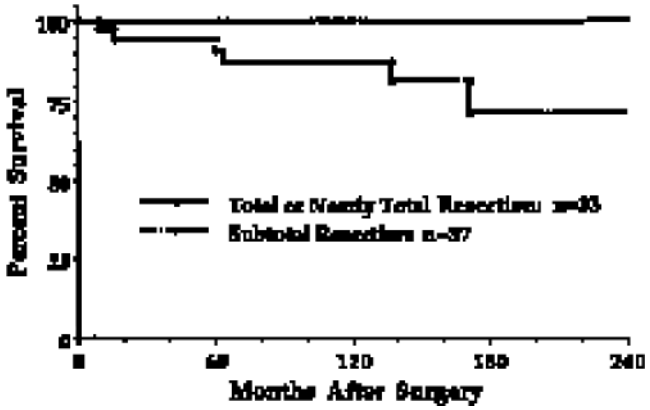

FIG. 2. Graph illustrating overall survival for the 33 patients who underwent total or nearly total (> 90%) tumor resection *(solid line)* and for the 37 who underwent less aggressive tumor resection *(dashed line)*. The difference between the respective curves is significant at p = 0.013.

independently predictive of outcome after adjusting for the other covariates.

Since previous studies have suggested that pilocytic astrocytomas constitute a group that is distinct prognostically from other low-grade gliomas,[7,21,22,41,56] separate analyses of the relationship between the aforementioned parameters and both survival and progression-free survival were performed for children with pilocytic and nonpilocytic tumors. In addition, because the use of radiotherapy in this series was generally restricted to patients with subtotal tumor resection, we were concerned that the potentially poorer long-term results in such patients might obscure any beneficial effect of radiotherapy in analyses using the whole study cohort. Accordingly, a separate analysis of the effect of radiotherapy on outcome was performed for patients undergoing incomplete tumor resection.

Other issues examined separately were the relationship between the extent of tumor resection and postoperative seizure control and the relationship between the use of postoperative radiotherapy and the presence of overt cognitive and endocrine dysfunction on long-term follow up. The strength of association of these parameters and outcomes was assessed using chi-square analysis.

Results

Factors Affecting Postoperative Survival

With a median follow-up time of 99 months (range 1 to 420 months), only seven patients in the study cohort have died: one from perioperative complications, five from progressive disease, and one from dissemination of a glioblastoma of the conus medullaris 171 months after resection of the intracranial tumor. The latter patient had type I neurofibromatosis and no evidence of disease progression from the supratentorial tumor. Actuarial survival rates 5, 10, and 20 years after surgery were 94%, 92%, and 84%, respectively. In the 70 children who survived the perioperative period, actuarial survival rates were 95%, 93%, and 85%, respectively (Fig. 1).

Thirteen individuals in the series have had documented disease progression during the period of the study. The patient who died of a second neoplasm was not included among the group with disease progression and, for the purposes of progression-free outcome analysis, was censored at the time of death. Progression-free survival rates 5, 10, and 20 years after surgery in the 70 patients surviving the perioperative period were 88%, 79%, and 76%, respectively (Fig. 1).

Table 1 presents the results of univariate analyses of the relationship between potential prognostic factors and both progression-free and overall survival for the 70 children surviving the perioperative period. Numbers of patients within each of the subgroups as well as the values associated with the univariate comparisons of outcome between the respective subgroups are indicated. Two variables were found to have a significant effect on progression-free survival: 1) extent of resection; and 2) the presence of headache as a presenting symptom. However, on multivariate analysis, only extent of resection was shown to be associated independently with a significant effect on progression-free survival ($p < 0.05$).

Two variables were found to be significantly related to overall survival: 1) extent of resection; and 2) histopathological diagnosis (nonpilocytic astrocytoma vs. other low-grade gliomas). Because of the small number of deaths in this series, a multivariate analysis using these two covariates was not feasible.

The relationship between extent of resection and both overall and progression-free survival is indicated in Figs. 2 and 3, respectively. None of the 33 patients undergoing complete or nearly complete tumor resection has died, in comparison to six of 37 (16.2%) who underwent less complete tumor removal (p = 0.013). Only two of the 33 children (6.1%) undergoing complete or nearly complete resections have had disease progression, compared with 11 of 37 (29.7%) who underwent less complete resections (p = 0.015). Moreover, none of the 21 patients who underwent complete tumor resection has either died (p = 0.051) or experienced disease progression (p = 0.007) during the follow-up period of the study.

In comparison to the effect of extent of resection on outcome, the histopathological diagnosis had a less signifi-

TABLE 1

Univariate analyses of the relationship between various prognostic parameters and survival and progression-free status in 70 children with low-grade hemispheric astrocytomas who survived the perioperative period

Prognostic Parameter	No. of Cases	Overall Survival at 10 yrs (%)	p Value	Progression-Free Survival at 10 yrs (%)	p Value
tumor location*					
parietal	27	92	0.80	77	0.86
frontal	25				
temporal	21	94		81	
occipital	12				
hemisphere involved					
lt	42	94	0.60	80	0.73
rt	28	92		79	
headache					
yes	28	96	0.21	96	0.011
no	42	92		69	
vomiting					
yes	21	90	0.49	90	0.16
no	49	95		74	
preoperative seizure					
yes	40	91	0.14	73	0.09
no	30	96		87	
lethargy					
yes	10	100	0.29	79	0.95
no	60	92		79	
personality change					
yes	8	100	0.35	73	0.64
no	62	92		79	
aphasia					
yes	6	100	0.61	67	0.36
no	64	93		81	
visual loss					
yes	10	90	0.40	77	0.33
no	60	94		90	
paresis					
yes	16	87	0.13	78	0.82
no	54	96		80	
sensory loss					
yes	4	75	0.20	38	0.18
no	66	95		82	
papilledema					
yes	19	90	0.70	90	0.10
no	51	95		72	
duration of preoperative symptoms					
<6 mos	32	96	0.15	82	0.49
≥6 mos	38	91		77	
<12 mos	42	95	0.26	83	0.36
≥12 mos	28	92		74	
severity of preop neuro impairment					
none	39	97	0.60	82	0.53
mild-moderate	26	88		72	
severe	5	100	0.48	75	0.96
age at operation					
<5 yrs	23	95	0.72	69	0.65
≥5 yrs	47	93		85	
<10 yrs	41	87	0.37	74	0.55
≥10 yrs	29	89		85	
yr of operation					
before 1975	23	82	0.27	82	0.49
1975 and after	47	100		75	
cyst with a mural nodule					
yes	12	100	0.13	75	0.98
no	58	91		81	
extent of tumor resection†					
total	21	100	0.051	100	0.007
nearly total (>95%)	12	100	0.013	81	0.015
subtotal	37	87		67	
tumor histology‡					
nonpilocytic astrocytoma	20	82	0.021	76	0.71
pilocytic astrocytoma	22	95	0.70	86	0.55
mixed oligoastrocytoma	20	100	0.185	83	0.98
oligodendroglioma	8	100	0.40	67	0.73
postoperative radiotherapy					
yes	35	90	0.12	83	0.59
no	35	97		75	
postoperative radiotherapy after subtotal tumor resection					
yes	33	89	0.60	82	0.014
no	16	94		40	

* Comparisons between tumors in the parietal lobe and other locations are shown; comparisons between other combinations of locations also fail to demonstrate a significant association with either survival or progression-free survival; † p values reflect the significance of differences in outcome between patients undergoing total tumor resection and incomplete tumor removal (top entry), and between patients undergoing total or nearly total resection and those undergoing less extensive resections (bottom entry); ‡ p values reflect the significance of differences in outcome between tumors in each histological group and all others.

cant impact on either overall or progression-free survival. Whereas four of 20 patients with nonpilocytic astrocytoma died during the follow-up period, only two of 50 children with either juvenile pilocytic astrocytoma, oligoastrocytoma, or oligodendroglioma died ($p = 0.021$). Differences in outcome between individual histological subgroups, such as pilocytic versus nonpilocytic astrocytoma, did not reach statistical significance. As a group, the patients with nonpilocytic astrocytoma were less likely to have had aggressive tumor resection: only seven of 20 patients (35%) with nonpilocytic astrocytoma had a complete or nearly complete resection versus 26 of 50 children (52%) with other low-grade gliomas. No significant effect of the histological appearance on progression-free survival was detected.

As noted previously, special attention was directed toward analyzing prognostic factors separately in patients with pilocytic astrocytomas and nonpilocytic tumors. Extent of resection was the only factor that was significantly associated with progression-free survival in both groups (Figs. 4 and 5). In the pilocytic group, none of the nine patients who underwent complete resection has had progressive disease, compared to four of 13 who underwent incomplete resections ($p = 0.041$). In the nonpilocytic group, none of 12 patients who underwent complete resections and only one of 21 who underwent greater than 90% resection have had disease progression compared to eight of 27 who had less extensive resections ($p = 0.06$ and 0.037, respectively). Because of the small number of deaths in the pilocytic and nonpilocytic groups (two of 22

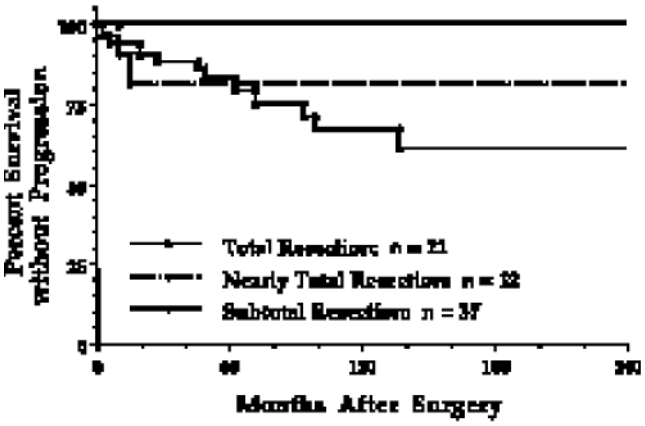

FIG. 3. Progression-free survival distribution is shown for the 21 patients who underwent total resection *(solid line)*, the 12 who underwent nearly total tumor resection *(dashed line)*, and the 37 who underwent less aggressive tumor resection *(dotted line)*. The differences between the progression-free survival of patients undergoing total resection versus incomplete resection, and of children undergoing either total or nearly total resection versus less extensive resection are significant at p = 0.007 and p = 0.013, respectively.

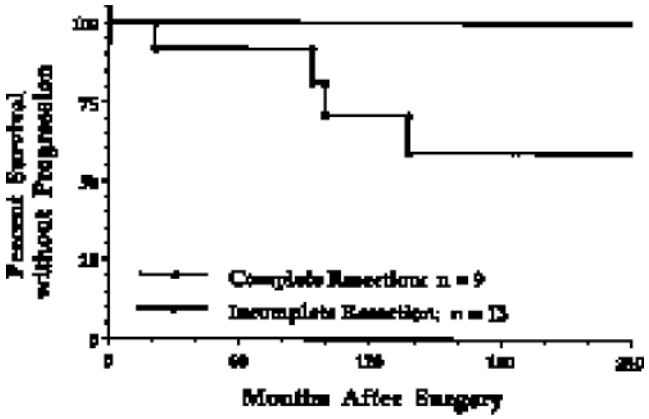

FIG. 4. Graph showing progression-free survival for the nine patients with pilocytic astrocytomas who underwent complete resection *(solid line)* and the 13 who underwent incomplete resection *(dashed line)*. The difference between the survival curves is significant at p = 0.041.

and four of 48 patients, respectively), no significant association between clinical or treatment factors and overall survival could be detected. However, the relationship between extent of resection and overall survival approached significance in both groups (p = 0.1 and 0.08, respectively). For all other parameters examined, probability exceeded 0.1.

Attention was also directed to examining the efficacy of radiotherapy in preventing disease progression in children undergoing incomplete tumor excision. Figure 6 illustrates the effect of radiotherapy on progression-free survival in the subgroup of 49 patients undergoing incomplete tumor removal: only six of 33 patients receiving radiotherapy had disease progression compared to seven of 16 not receiving radiotherapy (p = 0.014). However, as shown in Fig. 7, the use of this modality after an initial incomplete tumor removal had no significant effect on overall survival (p = 0.6).

Complications and Treatment-Related Sequelae

Only one patient died as a result of tumor resection; death was caused by a hematoma within the resection cavity. Six children had other operative complications consisting of permanent focal neurological deficits such as hemiparesis, which were either caused by or significantly exacerbated by their tumor resection. One other child had an incisional cerebrospinal fluid leak. Not unexpectedly, many children with preoperative deficits from the tumor had persistent deficits postoperatively.

Late sequelae presumably related to treatment included obvious cognitive difficulties in 15 children that necessitated removal from regular classes and/or placement in a special education program and, ultimately, led to an inability to work outside a sheltered environment. In addition, seven patients had endocrine dysfunction that in five affected all of the anterior pituitary hormonal axes and in two was limited to growth hormone insufficiency; two of these seven patients had precocious puberty. Since this series did not systematically measure cognitive and endocrine function in the remaining patients who had no overt signs of late intellectual or endocrinological dysfunction, it is likely that the above figures underestimate the true incidence of late morbidity. All but three of the children with cognitive deficits and one of the patients with endocrine dysfunction had received radiotherapy for their tumors. Thus, the incidence of cognitive and endocrine dysfunction was 34% and 17%, respectively, among the children receiving radiotherapy versus 8.6% and 2.9% in the group not receiving radiotherapy, an association that was significant at the $p < 0.01$ and $p < 0.05$ levels, respectively.

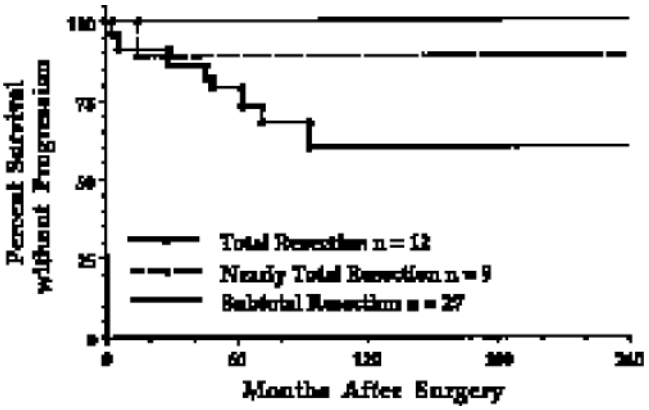

FIG. 5. Progression-free survival distribution is shown for the 12 patients with nonpilocytic low-grade gliomas who underwent total resection *(solid line)*, the nine who underwent nearly total resection *(dashed line)*, and the 27 who underwent subtotal resection *(dotted line)*. Differences in progression-free survival between the groups undergoing total resection versus incomplete resection, and those undergoing total or nearly total resection vs. subtotal resection have p values of 0.06 and 0.037, respectively.

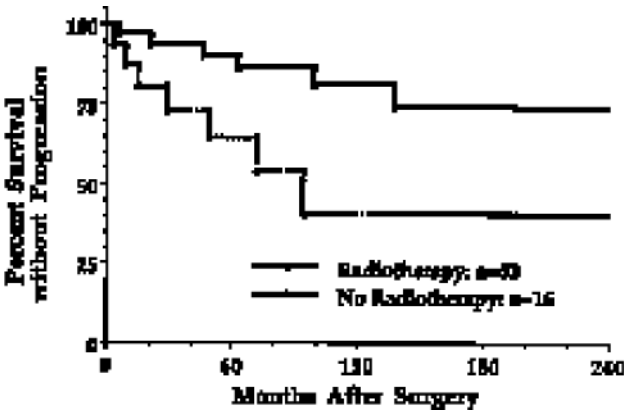

FIG. 6. Graph showing progression-free survival distribution in 33 children who underwent incomplete tumor removal and received postoperative radiotherapy *(solid line)* compared with progression-free survival of 16 patients who underwent incomplete tumor removal but did not receive postoperative radiotherapy *(dashed line)*. The difference between the survival curves is significant ($p = 0.014$).

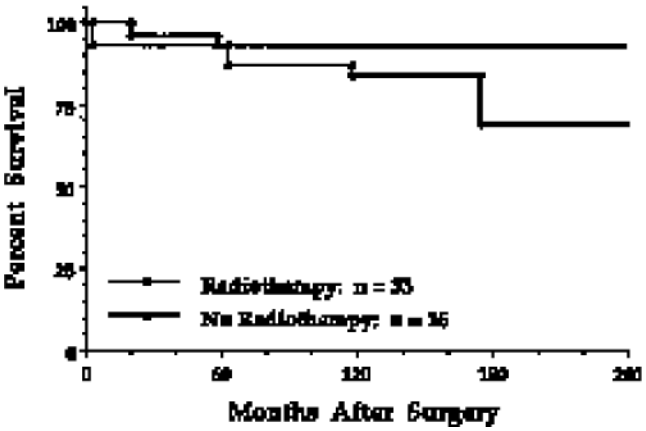

FIG. 7. Overall survival distribution in the 33 patients who underwent incomplete tumor removal and received postoperative radiotherapy *(solid line)* is less favorable than in the 16 with incomplete resections who did not receive radiotherapy *(dashed line)*. This difference between the survival curves does not reach statistical significance.

Ten patients were troubled by intermittent seizures during the follow-up period despite administration of regular anticonvulsant medications; seizures were among the presenting symptoms in seven of these patients. Thirty-three of the 40 patients (82.5%) who presented with seizures have been seizure-free or had fewer than one per year postoperatively; however, in the subgroup of 17 children who had seizures for more than 12 months preoperatively, this level of seizure control was achieved in only 11 (64.7%). No correlation was noted between extent of tumor resection and postoperative seizure control ($p = 0.56$, chi-square test). However, this analysis is complicated by the fact that a significant percentage of the patients with good seizure control remain on long-term anticonvulsant medication.

Outcome After Tumor Recurrence

Eleven of the 13 patients with documented tumor progression received additional therapeutic intervention. Four children underwent a complete or nearly complete tumor resection at a second operation; two of these patients received radiotherapy after the second resection. All four children are progression-free with follow-up intervals of 6 to 93 months after the second operation. Four patients underwent repeat subtotal tumor excision, supplemented in two cases with adjuvant radiotherapy and in three cases with chemotherapy. Two of these children died within 1 year of progression, but two are alive with stable disease 12 and 180 months postoperatively. One boy was treated with local radiotherapy for progressive tumor growth 1 year after a nearly complete initial resection. Although the lesion regressed completely, he later developed a second lesion at the margin of the radiotherapy field. A biopsy was taken, and it was found to be an anaplastic astrocytoma, which was treated with stereotactic radiosurgery; the tumor regressed completely and the child remains free of further progression 48 months after radiosurgery. One other child received stereotactic irradiation as the initial treatment at the time of recurrence and has stable disease at 13 months follow up. One child underwent aspiration of a large cystic tumor recurrence without further tumor resection or adjunctive therapy and died 4 months later. The two children who did not undergo additional treatment died within several months of disease progression.

The histopathological features of the tumor at progression could be ascertained in eight of the 13 patients with progressive disease. In five, the tumor was similar in appearance to the initial resection specimen. Three patients (4.3% of those surviving the perioperative period) had malignant progression of their lesions: 1) a pilocytic astrocytoma to anaplastic mixed glioma 137 months postoperatively; 2) a nonpilocytic astrocytoma to anaplastic astrocytoma 46 months postoperatively; and 3) a mixed glioma to anaplastic astrocytoma 32 months postoperatively. The first two patients had received radiotherapy after the initial operation and the third patient was the child previously referred to who had received radiotherapy 1 year postoperatively when tumor progression was detected at the primary site. In the latter patient, the anaplastic lesion, which was detected 20 months after irradiation, was not directly contiguous with the original tumor, but was in the margin of the radiation treatment field. The first two patients ultimately died of progressive tumor growth. The third child had a focal area of progression 36 months after receiving stereotactic radiosurgery to the second lesion; this regressed after repeat radiosurgery.

Because postmortem examinations were not permitted by the families of the three patients who died of tumor progression without undergoing a second resection and histopathological information was not available in two of the survivors, the overall incidence of malignant transformation among the tumors in this series remains uncertain. Assuming malignant progression in these five cases in addition to the three documented cases, the incidence of this event would be only 11.4% for overall series.

Discussion

Overall Outcome

The results from the present study highlight the generally excellent long-term prognosis of children with low-grade hemispheric gliomas. In comparison to the results of previous studies that have dealt with adult patients, in which median survivals typically ranged from 4 to 8.5 years and long-term survivals from 20% to 50%,[6,17,19,22,25,32,33,39,41,43,44,50,52,54,56–59,61,62,64,66] the children in this series manifested a strikingly lower incidence of both death and disease progression. The differences were particularly notable for patients undergoing an aggressive tumor resection: whereas 10% to 50% of adults will die of tumor progression within 5 to 10 years of a presumed complete or nearly complete resection,[19,32,39,43,44,56,61] none of the patients in this series had disease progression after a complete resection and only two children had progression after a nearly complete resection; both are alive and well. In addition, the majority of patients in this series who underwent less aggressive resections had no evidence of further tumor growth. Moreover, only 4.3% of patients had histologically proven malignant progression of tumor, an incidence that is well below the levels reported in adult patients with low-grade gliomas, which range from 13.3% to 32%.[32,38,43,44,49,61,62] Even if the patients in this series in whom the histological diagnosis at progression was uncertain are assumed to have developed malignant lesions, the incidence of anaplastic progression would still be below the range reported in adults.

The above observations are not altogether unexpected, because it has long been recognized that age at the time of diagnosis is one of the most powerful predictors of long-term outcome in patients with low-grade gliomas.[32,39,54] Laws and colleagues[32] noted that patients younger than 19 years of age at diagnosis had a five-year survival rate of 83%, compared to 35% in patients between 20 and 49 years of age and 12% in those 50 or older. In addition, the excellent survivals achieved in this series are in keeping with the results of several smaller series of pediatric patients with hemispheric low-grade gliomas, where long-term survival has typically exceeded 60% to 70%.[3,11,24,26,37,41] In agreement with our findings, the incidence of malignant progression in these studies[26,37,41] as well as in reports of pediatric low-grade gliomas in other locations[10,23,55,65] has been extremely low, particularly in patients who have not received radiotherapy. It is likely that the generally favorable results among children with these tumors reflects certain age-related features of the biology of their tumors and/or of host–tumor interactions that account for the surprisingly low incidence of postoperative tumor progression, even among children who have undergone subtotal resections.

Extent of Resection as a Predictor of Outcome

Our analysis of the factors that correlated with survival and progression-free survival indicated that extent of resection was the factor most strongly associated with outcome in the study group. This parameter has also been associated with increased survival time in a number of series involving adults with low-grade hemispheric gliomas.[32,33,43,61] None of the 21 patients who underwent a complete tumor resection had disease progression, compared to two of 12 (17%) undergoing nearly complete resections and 11 of 37 (30%) undergoing subtotal resections. A significant association between extent of resection and progression-free survival was found for patients with both pilocytic and nonpilocytic tumors. A greater extent of resection was also associated with a significantly longer overall survival in the full study group; this distinction was most clearly illustrated in comparisons between patients undergoing complete or nearly complete resections and those undergoing less extensive resections. An acknowledged limitation of the study is that definition of the extent of resection was based on the surgeon's judgment, rather than imaging criteria in cases treated before 1976; however, with the routine use of postoperative CT or MR studies in recent years, we have had only one case in which there was a categorical discrepancy between the surgeon's impression (a presumed near total resection) and the postoperative imaging (subtotal resection). Although formal volumetric analysis of resection extent would have been preferable as a means of assessing extent of resection, the absence of preoperative imaging studies in many patients in this series made such an analysis impossible. Finally it is important to emphasize that the association between extent of resection and survival does not prove that a more extensive resection produced a better outcome. Tumors that were resected aggressively may have differed biologically from those that were not.

Relationship Between Histopathological Features and Outcome

A number of previous studies involving adults or both adults and children with hemispheric low-grade gliomas have indicated that the histopathological appearance of the tumor may be a strong determinant of long-term outcome.[21,22,41,56] In particular, tumors with pilocytic features seem to have a more favorable outcome than nonpilocytic low-grade astrocytomas.[7,21,22,41,56] For example, Shaw, *et al.*,[56] reported 5- and 10-year survival rates of 85% and 79% in patients with pilocytic astrocytomas compared to 51% and 23% in patients with ordinary astrocytomas or oligoastrocytomas. Histological features have also been reported to be an important determinant of outcome in children with cerebellar astrocytomas. Gjerris and Klinken[23] have reported that patients with pilocytic astrocytomas have a dramatically better outcome than those with "diffuse" astrocytomas that lacked these pilocytic features. Winston and Gilles[67] also noted that histological pattern was an important predictor of outcome in children with cerebellar astrocytomas.

A similar trend toward poorer overall survival among patients with nonpilocytic astrocytomas as compared to those with pilocytic astrocytomas, oligoastrocytomas, and oligodendrogliomas was found in the present series on univariate analysis, although no definite effect of histological appearance on progression-free survival was detected. The outcome in patients with pilocytic tumors was not significantly different from that obtained in the overall group of nonpilocytic tumors or from the subgroup with nonpilocytic astrocytomas, although such a relationship may have been more apparent with a larger sample size. Because the number of patients who died or experi-

enced disease progression was small, it was also not possible to perform a meaningful assessment of the effect on outcome of the histological appearance independent of the effect of resection extent; a multiinstitutional study with a substantially larger sample size will probably be required to evaluate this issue conclusively. Based on the results of the present series, it is conceivable that the generally less favorable outcome in the nonpilocytic group may simply reflect the fact that these lesions were radically resected less often.

As a group, nonpilocytic astrocytomas are typically not well circumscribed, blending imperceptibly into the surrounding brain without a clear margin.[51] The poorly marginated nature of these lesions is exemplified by their appearance on MR imaging. Whereas pilocytic astrocytomas typically show crisply defined areas of low signal intensity on T_1-weighted images, high signal on T_2-weighted images, and dense enhancement that may be diffuse or in the form of a mural nodule, the nonpilocytic tumors generally appear as poorly marginated areas of hypointensity on T_1-weighted images, hyperintensity on T_2-weighted images, with little if any enhancement, and ill-defined tumor boundaries. Although a complete or nearly complete resection can be achieved with nonpilocytic tumors that arise in noneloquent areas of the brain, their radical resection from eloquent cortex is often not feasible because of the unacceptable risks of permanent neurological morbidity from removal of tumor-infiltrated but nonetheless functional brain at the periphery of the lesion. Following complete or nearly complete resection, patients with nonpilocytic hemispheric gliomas had an excellent long-term prognosis that in this series was comparable to that of patients with pilocytic tumors. In this regard, extent of resection was significantly associated with progression-free survival in both patient groups. A trend toward improved overall survival for patients in both groups who underwent more extensive resections was also noted.

In addition to histological appearance, it has become increasingly apparent in recent years that a number of other characteristics of neoplastic glial cells may play important roles in predicting outcome. For example, proliferative potential as assessed by bromodeoxyuridine labeling index has been reported to be a strong predictor of outcome in children and adults with low-grade astrocytomas[48] and may indicate those patients with otherwise benign-appearing lesions who may be at increased risk for disease progression. Moreover, Piepmeier, *et al.*,[45] recently reported that low-grade astrocytomas with comparatively few cells showing staining with antiglial fibrillary acidic protein and A2B5 antibodies exhibited an apparently slower growth rate than tumors with more extensive immunoreactivity, implying not only that these two groups of tumors may arise from different astrocyte lineages, but also that they may manifest different growth properties. In the future, it is likely that further refinements in the assessment of proliferative potential and elucidation of molecular markers indicative of a tumor's biological behavior may enhance the ability to predict the growth properties of a given neoplasm and the likelihood of recurrence following treatment.

Role of Radiotherapy

The efficacy of radiotherapy for children[3,12,24,34,36,37,53] and adults[6,19,22,25,32,33,39,41,43,44,50,52,54,56–59,61,64,66] with low-grade hemispheric gliomas has long been uncertain, particularly in patients undergoing subtotal tumor resection. Although a benefit of radiotherapy on survival has been detected in selected subgroups of adult patients with subtotally resected low-grade astrocytomas, oligodendrogliomas, and oligoastrocytomas,[6,19,22,32,33,43,56,57,59,64] a survival advantage with radiotherapy is less certain for adults undergoing total resection and for children undergoing either total or subtotal resection. Because of difficulties in accruing suitable numbers of patients for a prospective, randomized study of the efficacy of postoperative radiotherapy compared to no radiotherapy, even with multiinstitutional study groups, and the extended follow-up periods that would be required for such an endeavor, it is unlikely that a large-scale prospective, randomized study will effectively answer this question in the near future. In the absence of such data, particular attention was directed in the present investigation to examining the potential role of radiotherapy in the treatment of low-grade hemispheric gliomas, and recognition was given to the limitations inherent in a retrospective, nonrandomized approach to the problem.

It is apparent from this study that radiotherapy has no role in the initial management of totally resected hemispheric low-grade gliomas in children; none of the patients who underwent complete tumor resection without postoperative radiotherapy had subsequent disease progression. For patients undergoing subtotal resection, the benefit of radiotherapy is also debatable. Although we found a significant increase in progression-free survival as well as an associated decrease in the incidence of tumor progression in patients receiving radiotherapy, overall survival was unaffected. This reflected the fact that in those patients undergoing incomplete resection without radiotherapy who ultimately manifested disease progression, the residual tumor had remained well localized to the initial site of involvement and rarely displayed increased invasiveness. This localization made the lesion amenable to repeat resection that was often more extensive than the first, followed by adjuvant therapy if indicated. Only one of seven such patients has subsequently died of disease progression compared to four of six patients who developed disease progression despite receiving postoperative radiotherapy. In addition, the only patients in the series who had evidence of malignant transformation of the tumor had received prior radiotherapy. These observations are consistent with those of Dirks and colleagues,[10] which indicated that all patients with low-grade cerebellar and chiasmal gliomas that had undergone anaplastic changes in the vicinity of the original tumor had also received radiotherapy.

The utility of routinely providing radiotherapy after an incomplete resection is also challenged by our observation that nine of 16 (56%) patients who underwent incomplete excisions without adjunctive radiotherapy have had no progression of disease with a median follow up of 68 months. These results agree with recent observations on the behavior of low-grade gliomas in other locations, such as the chiasmatic/hypothalamic region, cerebellum, and

brainstem.[1,27,46,55] After an aggressive, but nonetheless subtotal, resection of such lesions to decrease the local mass effect produced by the tumor, the residual neoplasm often will either enlarge slowly or remain quiescent, even in the absence of further treatment. These findings suggest that a subgroup of low-grade juvenile glial tumors may actually manifest decelerating growth kinetics over time, particularly after a radical resection, and thus may be best managed with aggressive surgery and close follow up, with reservation of adjuvant therapy for those lesions that do manifest recurrent growth and require a second resection.

Complications and Treatment-Related Sequelae

Operative mortality in the present series was 1.4% and operative morbidity was generally limited to exacerbation of preoperative deficits in 8.5% of patients. Late sequelae included clear cut cognitive impairment in 21% of children and endocrinopathy in 10% of patients, almost all of whom had received postoperative radiotherapy. Because a detailed assessment of cognitive and endocrine function was not systematically performed, the above figures likely underestimate the true incidence of cognitive and endocrine sequelae. Although the absence of serial preoperative and postoperative cognitive and endocrine testing in irradiated and nonirradiated patients in this series makes it impossible to conclusively link the aforementioned sequelae to the use of postoperative radiotherapy, our observation of a significant association between irradiation and both cognitive and endocrine dysfunction is in keeping with the well-known risks of radiation therapy to the developing nervous system.[9,13,14,16,29,39,60]

Long-term seizure control was achieved in 82.5% of patients with preoperative seizures, despite the fact that tumor resections were all performed without electrocorticography. However, these results should not be taken to endorse a uniform policy of "lesionectomy" in patients with medically intractable epilepsy secondary to cerebral hemispheric low-grade gliomas. First, few of our patients had intractable seizures preoperatively. In many, the tumor was resected within several months of an initial seizure. The outcome with respect to postoperative seizure control in such patients cannot be equated with the results that would be achieved in a population of patients with medically intractable epilepsy secondary to their tumors. In the 17 patients in our series experiencing seizures for more than 12 months preoperatively, postoperative seizure control was achieved in only 64.7%. Second, even among the patients who did enjoy good seizure control postoperatively, the vast majority had been maintained chronically on anticonvulsant medications. Accordingly, during the last several years at our institution, electrocorticography has been employed in selected patients who have a long-standing seizure disorder in association with a low-grade glioma, to identify and facilitate resection of epileptogenic foci in the vicinity of the primary lesion and to possibly increase the number of patients who can be rendered seizure-free without anticonvulsant medications.[2]

Conclusion

Low-grade gliomas of the cerebral hemispheres in children generally carry an excellent long-term prognosis. Extent of resection is the factor associated most strongly with outcome: complete resection provides the best opportunity for long-term progression-free survival. However, even with incomplete tumor removal, long-term progression-free survival is commonly achieved. Anaplastic progression of the residual tumor appears to be infrequent, particularly in patients who have not received radiotherapy. In view of the risks of irradiation to the developing nervous system noted in the present study and in previous reports, and the uncertain benefits of this modality for children with low-grade gliomas, we now favor deferring radiotherapy in children with hemispheric low-grade gliomas after an initial aggressive resection, regardless of whether small amounts of residual tumor are present postoperatively. For the occasional patient younger than 6 years of age who undergoes an extensive tumor resection and experiences tumor progression, we now often administer chemotherapy in an attempt to defer radiotherapy; this approach has shown some efficacy in controlling the growth of low-grade gliomas.[4,20,40,42,47] Patients older than 6 years of age in the above instances are gen-erally treated with focal conventional radiotherapy. In selected cases, residual or progressive lesions may be amenable to a second attempt at radical tumor debulking. In addition, foci of residual or progressive tumor may also be amenable to treatment with stereotactic radiosurgical techniques.

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References

1. Alvord EC Jr, Lofton S: Gliomas of the optic nerve or chiasm. Outcome by patients' age, tumor site, and treatment. **J Neurosurg 68:**85–98, 1988
2. Berger MS, Ghatan S, Haglund MM, et al: Low-grade gliomas associated with intractable epilepsy: seizure outcome utilizing electrocorticography during tumor resection. **J Neurosurg 79:** 62–69, 1993
3. Bloom HJG, Glees J, Bell J: The treatment and long-term prognosis of children with intracranial tumors: a study of 610 cases, 1950–1981. **Int J Radiat Oncol Biol Phys 18:**723–745, 1990
4. Brown MT, Friedman HS, Oakes WJ, et al: Chemotherapy for pilocytic astrocytomas. **Cancer 71:**3165–3172, 1993
5. Bruce DA, Schut L, Sutton LN: Supratentorial brain tumors in children, in Youmans JR (ed): **Neurological Surgery, ed 3.** Philadelphia: WB Saunders, 1990, pp 3001–3016
6. Chin HW, Hazel JJ, Kim TH, et al: Oligodendrogliomas. I. A clinical study of cerebral oligodendrogliomas. **Cancer 45:** 1458–1466, 1980
7. Clark GB, Henry JM, McKeever PE: Cerebral pilocytic astrocytoma. **Cancer 56:**1128–1133, 1985
8. Cox DR: Regression models and life tables. **J R Stat Soc (B) 2:**187–220, 1972
9. Danoff BF, Cowchock FS, Marquette C, et al: Assessment of the long-term effects of primary radiation therapy for brain tumors in children. **Cancer 49:**1580–1586, 1982
10. Dirks PB, Jay V, Becker LE, et al: Development of anaplastic changes in low-grade astrocytomas of childhood. **Neurosurgery 34:**68–78, 1994
11. Dohrmann GJ, Farwell JR, Flannery JT: Astrocytomas in chil-

dren: a population-based study. **Surg Neurol 23:**64–68, 1985
12. Dohrmann GJ, Farwell JR, Flannery JT: Oligodendrogliomas in children. **Surg Neurol 10:**21–25, 1976
13. Donahue B: Short- and long-term complications of radiation therapy for pediatric brain tumors. **Pediatr Neurosurg 18:** 207–217, 1992
14. Duffner PK, Cohen ME, Thomas PRM, et al: The long-term effects of cranial irradiation on the central nervous system. **Cancer 56:**1841–1846, 1985
15. Earnest F III, Kernohan JW, Craig WM: Oligodendrogliomas. A review of two hundred cases. **Arch Neurol Psychiatry 63:** 964–976, 1950
16. Ellenberg L, McComb JG, Siegel SE, et al: Factors affecting intellectual outcome in pediatric brain tumor patients. **Neurosurgery 21:**638–644, 1987
17. Eyre JH, Crowley JJ, Townsend JJ, et al: A randomized trial of radiotherapy versus radiotherapy plus CCNU for incompletely resected low-grade gliomas: a Southwest Oncology Group study. **J Neurosurg 78:**909–914, 1993
18. Farwell JR, Dohrmann GJ, Flannery JT: Central nervous system tumors in children. **Cancer 40:**3123–3132, 1977
19. Fazekas JT: Treatment of grade I and II brain astrocytomas. The role of radiotherapy. **Int J Radiat Oncol Biol Phys 2:**661–666, 1977
20. Gajjar A, Heideman RL, Kovnar EH, et al: Response of pediatric low grade gliomas to chemotherapy. **Pediatr Neurosurg 19:**113–120, 1993
21. Garcia DM, Fulling KH: Juvenile pilocytic astrocytoma of the cerebrum in adults. A distinctive neoplasm with favorable prognosis. **J Neurosurg 63:**382–386, 1985
22. Garcia DM, Fulling KH, Marks JE: The value of radiation therapy in addition to surgery for astrocytomas in the adult cerebrum. **Cancer 55:**919–927, 1985
23. Gjerris F, Klinken L: Long-term prognosis in children with benign cerebellar astrocytoma. **J Neurosurg 49:**179–184, 1978
24. Gol A: Cerebral astrocytomas in childhood. A clinical study. **J Neurosurg 19:**577–582, 1962
25. Gol A: The relatively benign astrocytomas of the cerebrum. A clinical study of 194 cases. **J Neurosurg 8:**501–506, 1961
26. Hirsch JF, Rose CS, Pierre-Kahn A, et al: Benign astrocytic and oligodendroglial tumors of the cerebral hemispheres in children. **J Neurosurg 70:**568–572, 1989
27. Hoffman HJ, Humphreys RP, Drake JM, et al: Optic pathway/hypothalamic gliomas: a dilemma in management. **Pediatr Neurosurg 19:**186–195, 1993
28. Horrax G, Wu WQ: Postoperative survival of patients with intracranial oligodendroglioma with special reference to radical tumor removal. A study of 26 patients. **J Neurosurg 8:** 473–479, 1951
29. Kanev PM, Lefebvre JF, Mauseth RS, et al: Growth hormone deficiency following radiation therapy of primary brain tumors in children. **J Neurosurg 74:**743–748, 1991
30. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. **J Am Stat Assoc 53:**457–481, 1958
31. Kleihues P, Burger PC, Scheithauer BW, et al: **Histological Typing of Tumours of the Central Nervous System, ed 2.** Berlin: Springer-Verlag, 1993
32. Laws ER Jr, Taylor WF, Clifton MB, et al: Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. **J Neurosurg 61:**665–673, 1984
33. Leibel SA, Sheline GE, Wara WM, et al: The role of radiation therapy in the treatment of astrocytomas. **Cancer 35:** 1151–1157, 1975
34. Mandigers CMPW, Lippens RJJ, Hoogenhout J, et al: Astrocytoma in childhood: survival and performance. **Pediatr Hematol Oncol 7:**121–128, 1990
35. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. **Cancer Chemother Rep 50:**163–170, 1966
36. Marsa GW, Probert JC, Rubinstein LJ, et al: Radiation therapy in the treatment of childhood astrocytic gliomas. **Cancer 32:** 646–655, 1973
37. Mercuri S, Russo A, Palma L: Hemispheric supratentorial astrocytomas in children. Long-term results in 29 cases. **J Neurosurg 55:**170–173, 1981
38. Müller W, Afra D, Schröder R: Supratentorial recurrences of gliomas. Morphological studies in relation to time intervals with astrocytomas. **Acta Neurochir 37:**75–91, 1977
39. North CA, North RB, Epstein JA, et al: Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy. **Cancer 66:**6–14, 1990
40. Packer RJ, Lange B, Ater J, et al: Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. **J Clin Oncol 11:**850–856, 1993
41. Palma L, Guidetti B: Cystic pilocytic astrocytomas of the cerebral hemispheres. Surgical experience with 51 cases and long-term results. **J Neurosurg 62:**811–815, 1985
42. Petronio J, Edwards MSB, Prados M, et al: Management of chiasmal and hypothalamic gliomas of infancy and childhood with chemotherapy. **J Neurosurg 74:**701–708, 1991
43. Philippon JH, Clemenceau SH, Fauchon FH, et al: Supratentorial low-grade astrocytomas in adults. **Neurosurgery 32:** 554–559, 1993
44. Piepmeier JM: Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. **J Neurosurg 67:**177–181, 1987
45. Piepmeier JM, Fried I, Makuch R: Low-grade astrocytomas may arise from different astrocyte lineages. **Neurosurgery 33:**627–632, 1993
46. Pollack IF, Hoffman HJ, Humphreys RP, et al: The long-term outcome after surgical treatment of dorsally exophytic brainstem gliomas. **J Neurosurg 78:**859–863, 1993
47. Pons MA, Finlay JL, Walker RW, et al: Chemotherapy with vincristine (VCR) and etoposide (VP-16) in children with low-grade astrocytoma. **J Neurooncol 14:**151–158, 1992
48. Prados MD, Krouwer HGJ, Edwards MSB, et al: Proliferative potential and outcome in pediatric astrocytic tumors. **J Neurooncol 13:**277–282, 1992
49. Recht LD, Lew R, Smith TW: Suspected low-grade glioma: is deferring treatment safe? **Ann Neurol 31:**431–436, 1992
50. Reedy DP, Bay JW, Hahn JR: Role of radiation therapy in the treatment of cerebral oligodendroglioma: an analysis of 57 cases and a literature review. **Neurosurgery 13:**499–503, 1983
51. Rekate HJ, Rakfal SM: Low-grade astrocytomas of childhood. **Neurol Clin 9:**423–440, 1991
52. Roberts M, German WJ: A long term study of patients with oligodendrogliomas. Follow-up of 50 cases, including Dr. Harvey Cushing's series. **J Neurosurg 24:**697–700, 1966
53. Sanford RA, Kun LE, Langston JW, et al: Pitfalls in the management of low grade gliomas, in Marlin AE (ed): **Concepts in Pediatric Neurosurgery.** Basel: Karger, 1991, Vol 11, pp 133–149
54. Scanlon PW, Taylor WF: Radiotherapy of intracranial astrocytomas: analysis of 417 cases treated from 1960 through 1969. **Neurosurgery 5:**301–308, 1979
55. Schneider JH Jr, Raffel C, McComb JG: Benign cerebellar astrocytomas of childhood. **Neurosurgery 30:**58–63, 1992
56. Shaw EG, Daumas-Duport C, Scheithauer BW, et al: Radiation therapy in the management of low-grade supratentorial astrocytomas. **J Neurosurg 70:**853–861, 1989
57. Sheline GE, Boldrey E, Karlsberg P, et al: Therapeutic considerations in tumors affecting the central nervous system: oligodendrogliomas. **Radiology 82:**84–89, 1964
58. Shenkin HA: The effect of roentgen-ray therapy on oligodendrogliomas of the brain. **J Neurosurg 22:**57–59, 1965
59. Shimizu KT, Tran LM, Mark RJ, et al: Management of oligodendrogliomas. **Radiology 186:**569–572, 1993
60. Silber JH, Radcliffe J, Peckham V, et al: Whole-brain irradia-

tion and decline in intelligence: the influence of dose and age on IQ score. **J Clin Oncol 10:**1390–1396, 1992

61. Soffietti R, Chiò A, Giordana MT, et al: Prognostic factors in well-differentiated cerebral astrocytomas in the adult. **Neurosurgery 24:**686–692, 1989
62. Vertosick FT Jr, Selker RG, Arena VC: Survival of patients with well-differentiated astrocytomas diagnosed in the era of computed tomography. **Neurosurgery 28:**496–501, 1991
63. Walker ML, Fried A, Pattisapu J: Tumors of the cerebral hemispheres in children, in McLaurin RL, Schut L, Venes JL, et al (eds): **Pediatric Neurosurgery. Surgery of the Developing Nervous System, ed 2.** Philadelphia: WB Saunders, 1989, pp 373–382
64. Wallner KE, Gonzales M, Sheline GE: Treatment of oligodendrogliomas with or without postoperative irradiation. **J Neurosurg 68:**684–688, 1988
65. Wallner KE, Gonzales MF, Edwards MSB, et al: Treatment results of juvenile pilocytic astrocytoma. **J Neurosurg 69:** 171–176, 1988
66. Weir B, Elvidge AR: Oligodendrogliomas. An analysis of 63 cases. **J Neurosurg 29:**500–505, 1968
67. Winston K, Gilles FH, Leviton A, et al: Cerebellar gliomas in children. **J Natl Cancer Inst 58:**833–838, 1977

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