Survival and functional outcome of childhood spinal cord low-grade gliomas

Clinical article

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Object. Intramedullary spinal cord low-grade gliomas (LGGs) are rare CNS neoplasms in pediatric patients, and there is little information on therapy for and outcome of these tumors in this population. Furthermore, most patient series combine adult and pediatric patients or high- and low-grade tumors, resulting in controversial data regarding optimal treatment of these children. To clarify these issues, the authors performed a regional population-based study of spinal cord LGGs in pediatric patients.

Methods. All pediatric patients with LGGs treated during the MR imaging era (1985–2007) were identified in the comprehensive database of the Hospital for Sick Children in Toronto. Data on demographics, pathology, treatment details, and outcomes were collected.

Results. Spinal cord LGGs in pediatric patients constituted 29 (4.6%) of 635 LGGs. Epidemiological and clinical data in this cohort were different than in patients with other spinal tumors and strikingly similar to data from pediatric patients with intracranial LGGs. The authors observed an age peak at 2 years and a male predominance in patients with these tumors. Histological testing revealed a Grade I astrocytoma in 86% of tumors. Although 5-year progression-free survival was 88% for patients undergoing GTR and 5-year overall survival was 92%, all patients were alive at a median follow-up of 8.2 years. Five-year progression-free survival was 88 ± 13% for patients undergoing GTR and 34 ± 11% for those undergoing all other therapies, respectively (p = 0.02). Chemotherapy and radiation therapy showed similar efficacy, achieving sustained tumor control in most patients. However, this excellent survival rate was associated with an 83% rate of significant neurological and orthopedic sequelae.

Conclusions. This study provides basic data on the incidence, clinical course, and outcome of spinal cord LGGs in pediatric patients. The similarities between spinal and intracranial LGGs in pediatric patients showing excellent survival but high morbidity suggest that a less aggressive approach may be the preferable treatment option for these patients. (DOI: 10.3171/2009.4.PEDS08411)

Key Words • spinal cord • low-grade glioma • chemotherapy • radiation therapy • astrocytoma

Low-grade gliomas in pediatric patients are a heterogeneous group of tumors that together are the most common CNS neoplasm in this population. Astrocytomas are the predominant pathological subtype, followed by mixed gliomas, gangliogliomas, oligodendrogliomas, and other rare low-grade glial tumors. Most subtypes of LGGs in pediatric patients are treated by resection, which, when feasible, can offer long-term tumor control. However, for LGGs in pediatric patients, which are not amenable to GTR, radiation therapy has been traditionally used as an adjuvant therapy. In the last 15 years, chemotherapy has progressively replaced radiation as first-line therapy, especially for young children with intracranial LGGs. Most of our knowledge relates to supratentorial LGGs in children. Our knowledge concerning spinal cord LGGs in pediatric patients is still lagging behind with respect to treatment strategies and management. This lag is mainly due to the rarity of the disease and the lack of comprehensive data regarding the incidence, risk factors, optimal treatment, and long-term sequelae for spinal cord LGGs in childhood.

Most published retrospective series discuss spinal cord LGGs in pediatric patients in the context of all spinal
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cord tumors, combining children and adults\textsuperscript{6,33} or high- and low-grade tumors.\textsuperscript{4,25,38} This methodology results in a wide range of survival estimates, from 45 to 75\% in different patient series. Furthermore, large reference centers introduce potential bias with respect to incidences of specific pathological subtypes\textsuperscript{24} and may overemphasize the role of cancer predisposition in the pathogenesis of spinal cord LGGs in children.\textsuperscript{29} To address the true incidence, pathological subtypes, distribution, and outcome of spinal cord LGGs in pediatric patients, we used the unique status of the Hospital for Sick Children in Toronto—which is the only neurosurgical and neurooncology center in southern Ontario, Canada—to perform a regional population-based study in the era of evolving management of pediatric spinal cord LGGs.

**Methods**

We performed a retrospective regional center–based study of pediatric patients with spinal cord LGGs during the MR imaging era (1985–2007). Canada has a government-funded, regionalized health care system, especially for specialized services.\textsuperscript{19} Children with brain tumors are, therefore, treated at university-affiliated teaching hospitals of their region and there are no national or international referrals. There are 5 centers in Ontario, and each center has a specific pattern of referral. The Hospital for Sick Children in Toronto serves a catchment area of 5 million people and therefore can be considered for a population-based study. Databases from the Division of Pathology, the Division of Pediatric Oncology, the Pediatric Brain Tumor Program, and the NF clinic were used to identify the patients. Data on demographics, presenting symptoms, surgical interventions, chemotherapy, and radiation treatment, as well as outcome and long-term sequelae, were collected for each patient.

Patient inclusion criteria were age at diagnosis < 18 years, intramedullary tumor, and nonependymal Grade I or II glial tumor as per WHO criteria.\textsuperscript{24} Excluded were patients referred from other centers, patients with disseminated disease to the brain and spine, or extramedullary tumor location.

Surgical intervention was defined as follows: 1) GTR = clean surgical field under the microscope at the end of the procedure, accompanied by no evidence of residual disease on postoperative MR imaging; 2) STR = resection of > 50\% of the tumor bulk; 3) PR = resection < 50\%; and 4) biopsy = surgery to obtain a tissue sample for pathological examination.

Disease progression was defined as new or worsening clinical symptoms and/or tumor growth on 2 consecutive imaging studies. For survival analysis, in the determination of PFS, events were classified as relapse or death from any cause and PFS was established from the date of diagnosis to the date of the event. Patients not experiencing an event at the time of analysis were censored at the time of last contact. The Kaplan-Meier method was used to estimate probabilities of PFS and overall survival using standard errors calculated according to the Greenwood formula. Groups were compared using the log-rank test. A probability value < 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS statistical program (SPSS, Inc.).

We recorded all neurological and orthopedic signs and symptoms at presentation and at last follow-up. Surgical interventions for spinal complications were recorded as well. For an objective functional outcome measure, we used the McCormick scale previously reported for use with spinal tumors\textsuperscript{8,24} (Table 1).

**Results**

Between the years 1985 and 2007, 635 children with LGGs were treated at the Hospital for Sick Children in Toronto. Twenty-nine (4.6\%) had intramedullary spinal cord LGGs and comprised the study group. Median age at diagnosis was 5.8 years (range 1.39–14.62 years) and the median follow-up was 8.2 years (range 0.02–15.47 years). There was an age peak of the disease in patients between 1 and 2 years of age. The disease was diagnosed in 8 patients between 1 and 2 years of age, and 12 (41\%) of all pediatric patients with spinal cord LGGs were diagnosed before the age of 4 years, followed by a low incidence rate beyond this age (Fig. 1). There was a male predominance (72\%) in the study population, with no correlation between age and sex. Two patients (6.9\%) had an underlying diagnosis of NF: 1 with NF1 and 1 with NF Type 2. These patients accounted for only 0.15\% of our registered clinic patients with NF1. For comparison, the percentage of patients with NF1 with optic pathway glioma was 15\% (95 of 633) at our institution.

The predominant tumor location was cervical (45\%)

<table>
<thead>
<tr>
<th>TABLE 1: McCormick Functional Scale*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
</tbody>
</table>

* From McCormick et al., 1990.
followed by thoracic (28%) and thoracolumbar (10%; Table 2; Fig. 2). No primary lumbar (conus only) pediatric spinal cord LGG was observed.

Histological testing revealed a Grade I astrocytoma in 86% of all patients. Only 1 patient (3%) had a ganglioglioma (Table 2). At recurrence, 3 of 16 biopsied tumors had a different pathological diagnosis: 2 previously Grade I astrocytomas were diagnosed as gangliogliomas, and 1 diagnosis was changed to a glioneuronal tumor. Interestingly, 1 of these gangliogliomas was diagnosed as an astrocytoma at further recurrence.

**Clinical Presentation**

Most patients presented with a very long history of progressive symptoms. Median time from initial symptom to diagnosis was 10 months (range 1–84 months). No patient was diagnosed before 1 year of life although most infants in this series had prolonged nonspecific complaints and delayed or regressive developmental milestones. Young patients presented with nonspecific crying episodes followed by motor weakness and torticollis. Older patients presented with back pain, progressive kyphoscoliosis, and motor dysfunction. Patients with subacute presentation (time to diagnosis of < 3 months) demonstrated either severe irritability, necessitating further examination in the hospital, or acute painful torticollis. One patient presented with acute paraplegia due to intratumoral bleed. Patients with progressive scoliosis experienced a very long time until diagnosis (mean duration 26 months). Of 8 patients with progressive scoliosis, only 1 received the diagnosis because of isolated spinal deformity, whereas 7 developed motor dysfunction that led to the appropriate examination. There was no association between age, tumor location, and time to diagnosis. Overall, pain and limb weakness were the most common symptoms leading to diagnosis (Table 2).

**Initial Disease Management**

All patients underwent surgery as primary intervention and all but 1 patient had undergone an attempted resection. Gross-total resection was achieved in 9 patients (31%), of whom only 1 subsequently experienced tumor recurrence and underwent GTR again. Subtotal resection was performed in 16 patients (55%) and PR in 3 (10.5%). After surgery, the majority of patients (83%) underwent observation and were treated at the time of further progression. Medical therapy was administered only for patients with significant tumor burden after attempted incomplete resection. Initial adjuvant therapy at diagnosis included chemotherapy in 4 patients and radiation treatment in 1 patient.

**Management and Survival Outcomes**

All patients were alive at a median follow-up of 8.5 years (range 2.7–14.6 years). Fourteen patients experienced tumor progression at a median of 2.3 years (range 0.4–5.1 years; Table 3). Only 1 patient (7%) experienced tumor dissemination at a third recurrence, 6 years after the initial presentation of a mixed glioma. Five-year PFS for the entire group of patients was 48% (95% CI 35–67) (Fig. 3A). The extent of resection was the most significant determinant of outcome. Five-year PFS for pediatric patients with spinal cord LGGs who underwent GTR versus all
procedures other than GTR was 88 ± 13% and 34 ± 11%, respectively (p = 0.02; Fig. 3B). Details of further treatment in progressive pediatric spinal cord LGG are shown in Table 3. Nine of 13 patients aged < 5 years at diagnosis had further progression whereas only 5 of 16 older patients experienced tumor progression (p = 0.05), suggesting different tumor biology.

Four patients were treated with chemotherapy at initial presentation and 5 additional patients were treated with chemotherapy at recurrence. Three patients received a second course of chemotherapy at further progression. Initial chemotherapy consisted of a combination of vincristine and carboplatin (in 7 patients), the TPCV (thioguanine, procarbazine, lomustine, and vincristine) regimen in 1 patient, and single-agent carboplatin in 1 patient. At further progression, second-line chemotherapy included TPCV in 1 patient, vinblastine monotherapy in 1 patient, and a combination of vinblastine and carboplatin in 1 patient. In total of 12 chemotherapy regimens administered, tumors showed a stable disease response in 9 patients and a minor response in 2 patients after chemotherapy. One tumor progressed and was treated with radiation therapy.

Of the 9 patients who were treated with chemotherapy, 5 experienced progression at a median time of 2.1 years (range 0.4–3.8 years), requiring additional surgery in 1 patient, additional chemotherapy in 3 patients, and radiation therapy in 2 patients. After the second course of chemotherapy, only 1 patient experienced further tumor progression and underwent repeat resection followed by radiation therapy. Overall, after a mean time from last progression of 4.2 years, only 2 (18%) of 11 patients who were treated using either repeated surgeries or a combined resection/chemotherapy approach required radiation therapy.

Radiation therapy was delivered to 5 patients: 1 as a part of his initial treatment and 4 at recurrence. Two patients had recurrent disease after radiation, which was treated with additional resection and chemotherapy, with no further recurrence. The 2 patients who were treated with radiation therapy after chemotherapy failure were progression-free for 2.4 and 6.0 years after therapy (Table 3).

Long-Term Sequelae

Eighty-three percent of patients experienced considerable morbidity affecting daily life (Table 4). Major orthopedic interventions were required in 35% of children, mainly for severe kyphoscoliosis. Significant neurological sequelae such as hemiparesis, paraparesis, and neurogenic bladder requiring intermittent catheterization were observed in 52% of patients. In contrast, most patients were functionally independent. A McCormick scale score of I–II was observed in 79% of children. Furthermore, most patients improved neurologically and functionally when comparing their condition at presentation to that at last follow-up. However, 74% of the children who were found to have significant kyphoscoliosis did not have spinal deformity at presentation. The extent of surgery, radiation therapy, and/or chemotherapy did not affect functional outcome. Patient age and time until diagnosis did not affect presenting or long-term neurological and/or orthopedic complications. Patients with a thoracic tumor location showed significantly more major orthopedic sequelae than patients with tumors located in the cervical spine (p = 0.003).

Discussion

This unique regional population–based study provides
some new insights into certain epidemiological, clinical, and outcome parameters that have significant importance for the treatment of these patients. There are no clear epidemiological data for pediatric patients with spinal cord LGGs. Previous epidemiological studies included either all spinal cord tumors or different grades such as high-grade astrocytomas. The 5% incidence rate of all LGGs in pediatric patients and 1.8% rate of all brain tumors in pediatric patients in our database is lower than previously described. This low incidence rate may explain the small patient series obtained even in national studies and implies that future prospective trials may warrant a different approach, such as an international registry.

Previous reports suggested that patients with NF have a higher incidence of pediatric spinal cord LGG; as many as 5% of patients with NF1 were reported to develop such tumors. The data retrieved from our institutional comprehensive databases of NF1 and pediatric LGG do not support these findings. This discrepancy may be explained by referral bias of such patients to specialized centers. Patients with NF1 tend to have extramedullary and extraspinalplexiform neurofibromas manifesting with similar symptoms to those caused by LGGs. Patients with NF2 typically present with different spinal tumors such as ependymomas. Due to this difference in the underlying spinal disease and to the inherent specifics of NF1 and NF2 noted above, these patients need to be treated in a very different manner than patients with pediatric spinal cord LGG.

We found similarities between pediatric spinal cord LGGs and pediatric intracranial LGGs arising in the midline and the optic pathways. The distribution of the pathological subtypes in pediatric spinal cord LGGs was very similar to that of pediatric intracranial LGGs, revealing a predominance of Grade I/juvenile pilocytic astrocytomas (Table 2). These data are in contrast to other mixed patient series, which reported a high frequency of rare tumors such as gangliogliomas and a predominance of adult-type Grade II tumors. These data also highlight the known practice variation among pathologists and the urgent need for objective biological markers to distinguish between pathological subtypes.

The ages of the pediatric patients with spinal cord LGG were strikingly similar to those of pediatric patients with intracranial LGG. More than one-third of the patients in this study received a diagnosis before the age of 4 years. This characteristic is in contrast to spinal ependymomas, which present later in life and have a different spinal location (p = 0.03). Figure 2 illustrates this discrepancy and compares our series of patients with spinal cord LGGs to other spinal gliomas previously investigated by our group.

Clinical behavior of the disease in this study was also very similar to that in pediatric patients with intracranial LGG. Younger patients showed a higher rate of recurrence, in accordance with recent results from the COG9952 protocol, which demonstrated higher progression rates for younger pediatric patients with LGG and optic pathway tumors, with excellent overall survival. Constantini et al. reported a very high success rate in a group of patients < 3 years old with a mixed group of spinal cord tumors. However, this study also revealed a trend toward reduced expected survival for these patients after a prolonged follow-up.

Although Sharma and colleagues reported distinct genetic signatures between juvenile pilocytic astrocytomas originating from different locations in the CNS, the clinical course and outcome of pediatric spinal cord LGG in our patient series suggest a common biological background. Furthermore, we recently reported telomere length as a possible biological explanation for the tenden-
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TABLE 3: Clinical course of progressive tumors*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age at Dx (yrs)</th>
<th>Time to 1st Progression (yrs)</th>
<th>Time to 2nd Progression (yrs)</th>
<th>Time to 3rd Progression (yrs)</th>
<th>Time From Last Progression (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>1.4</td>
<td>STR, chemo 3.89</td>
<td>GTR</td>
<td></td>
<td>10.72</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1.5</td>
<td>PR 5.00</td>
<td>chemo</td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1.5</td>
<td>PR, chemo 2.10</td>
<td>chemo</td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>1.6</td>
<td>STR, chemo 2.22</td>
<td>chemo</td>
<td></td>
<td>3.7</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>1.8</td>
<td>PR, RT 5.12</td>
<td>STR 1.17</td>
<td>STR, chemo 0.75</td>
<td>GTR, chemo 7.5</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>1.9</td>
<td>STR 2.55</td>
<td>STR 6.38</td>
<td>chemo</td>
<td>GTR</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>2.2</td>
<td>STR 3.22</td>
<td>GTR</td>
<td></td>
<td>7.7</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>3.8</td>
<td>GTR 1.29</td>
<td>GTR</td>
<td></td>
<td>3.9</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>4.2</td>
<td>STR 1.20</td>
<td>chemo 2.27</td>
<td>chemo</td>
<td>STR, RT 2.4</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>7.2</td>
<td>STR 2.25</td>
<td>STR 4.88</td>
<td>biopsy, RT</td>
<td>1.2</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>7.8</td>
<td>STR 2.20</td>
<td>GTR</td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>10.17</td>
<td>STR 3.34</td>
<td>STR 1.09</td>
<td>GTR</td>
<td>2.0</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>11.23</td>
<td>biopsy, chemo 0.40</td>
<td>RT</td>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>13.26</td>
<td>STR 1.30</td>
<td>STR, RT 1.9</td>
<td>GTR</td>
<td></td>
</tr>
</tbody>
</table>

* chemo = chemotherapy; RT = radiation treatment.

cy of pediatric LGG at a young age to progress for a longer period of time. Figure 3C reveals similar initial progression rates but lack of late recurrences in older patients with pediatric spinal cord LGG, which is compatible with our hypothesis. We are currently examining these clinical and biological issues in pediatric spinal cord LGG.

This study reemphasizes the role of resection in pediatric patients with spinal cord LGGs. The rate of GTR was lower in our study than in other patient series. Constantini and associates reported a 76% rate of GTR in a large series of patients with intramedullary spinal cord tumors. This group, however, included other tumors such as ependymomas and gangliogliomas, which may be more amenable to complete surgical removal. Spinal cord LGGs in pediatric patients are usually more heterogeneous tumors with large cysts, both within the tumor and at the superior and inferior margins. Infiltration and

different margins with normal tissues often make complete resection difficult. Gross-total resection does not appear to improve PFS in other mixed patient series, but does appear to be the most important factor for PFS in spinal cord LGGs in pediatric patients.

Unfortunately, this study, in agreement with others, confirms the associated long-term morbidity of this disease. Newer techniques allowed more aggressive surgeries and successful resections but failed to prevent significant long-term morbidity, as previously reported in pediatric spinal cord LGG. We quantified the additional morbidity associated with pediatric spinal cord LGG and found that more than a third of patients will require additional orthopedic surgeries for kyphoscoliosis, and more than half will have significant motor dysfunction. Although difficult to quantify, most patients reported pain associated with their status, which can have a significant effect on a patient’s daily life. The contrast between these data and the acceptable functional outcome quantified using the McCormick scale is intriguing. However, this contrast may relate to failure of that scale to capture the daily difficulties of these patients. The low mortality but high morbidity rates of pediatric spinal cord LGG highlights the need to focus on functional outcome rather than survival.

Chemotherapy may contribute to reducing morbidity, particularly for incompletely resected tumors. However, despite strong evidence that chemotherapy has a role in the management of unresectable LGG in pediatric patients, reports of the use of chemotherapy in pediatric spinal cord LGG are scarce. Historically, chemotherapy was introduced to delay radiation treatment in young children with LGG. However, today many of these patients are treated using a combination of repeated chemotherapy courses and surgical interventions, and avoid radiotherapy. Several small case series reported efficacy

TABLE 4: Long-term sequelae in 29 pediatric patients with spinal cord LGGs

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Presentation</th>
<th>Last FU</th>
<th>Improved</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>motor dysfunction</td>
<td>20 (69%)</td>
<td>15 (52%)</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>kyphoscoliosis</td>
<td>8 (28%)</td>
<td>19 (66%)</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>orthopedic intervention</td>
<td>0</td>
<td>10 (35%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>McCormick scale score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>17</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>13</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>overall dysfunction</td>
<td>22 (76%)</td>
<td>24 (83%)</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

* FU = follow-up; NA = not applicable.
for chemotherapy in pediatric spinal cord LGG.\textsuperscript{8,16,22} The sample sizes in these studies were very small (2, 3, and 8 patients) and therefore the ability to form conclusions is limited. Prolonged follow-up of the French study on 8 patients revealed very good PFS and improved functional outcome.\textsuperscript{14} Therefore, our report of 9 patients treated with chemotherapy, 3 of them with repeated courses, adds significant insight into this controversial issue. We found no difference in tumor control between chemotherapy and radiotherapy treatments in pediatric patients with spinal cord LGG. Furthermore, repeated courses of chemotherapy were safe and offered long-term control in some patients. Radiotherapy treatments in pediatric patients with spinal cord gliomas were safe and offered long-term control in some patients. This finding is similar to findings in pediatric LGG from other origins within the CNS. Moreover, similar to previous reports\textsuperscript{9} repeated surgery is feasible and safe for pediatric patients with spinal cord LGG and may offer long-term tumor control.

Conclusions

This regional population–based study found a resemblance in the pathological and clinical course of pediatric intracranial LGGs and pediatric spinal cord LGGs. This disease has a low mortality rate but causes significant long-term morbidity, especially for younger patients. Combining pediatric spinal cord LGGs with other spinal cord intramedullary tumors may be inappropriate for clinical and therapeutic purposes. We suggest that the approach currently used for pediatric intracranial LGGs should be used for pediatric spinal cord LGGs. That is, because it is a chronic disease, aggressive therapies should be reserved for specific cases only. Due to the rarity of pediatric spinal cord LGG, international registries may be necessary to truly address these issues in the future.

Disclosure

This work was supported by a grant from the Brain Tumor Society. Katrin Scheinemann, M.D., is funded by a grant from the “Gala for Hope.”

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Childhood spinal cord low-grade glioma

Portions of this work were presented in abstract/poster form in May 2008 at the Department of Pediatrics Research Day, The Hospital for Sick Children, Toronto, Canada, and in July 2008 at the International Symposium of Pediatric Neurooncology, Chicago, Illinois.
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