

## Cerebellar astrocytomas in children

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### Abstract

Cerebellar astrocytomas, as a group, carry a more favorable prognosis than most other brain tumors, because these neoplasms generally are histologically benign and amenable to extensive resection. However, it is clear that a number of factors have an impact on prognosis. In particular, resection extent has been strongly associated with progression-free survival: patients undergoing gross total resection appear to have a substantially better prognosis than those undergoing incomplete resection. Brainstem invasion, which is the factor that most often precludes a complete resection, has also been associated with a less favorable prognosis. In addition, histological features indicative of malignancy are clearly associated with a poor outcome.

In contrast to the above observations, which have been established convincingly in the literature, a number of issues regarding cerebellar astrocytomas remain unresolved. First, the correlation between histology and prognosis among patients with low-grade cerebellar astrocytomas is uncertain: in some series, pilocytic astrocytomas have been associated with a better prognosis than non-pilocytic tumors, but in other studies, no such relationship has been observed. Second, the role of radiotherapy after incomplete resection of a low-grade cerebellar astrocytoma remains problematic. In view of the lack of convincing data in this regard, many groups, including our own, defer radiotherapy until there is evidence of progressive disease that is surgically unresectable. Finally, the frequency of follow-up in patients with cerebellar astrocytomas remains largely empirical. Although most recurrences are detected within a few years after initial surgery, late recurrences are well known, which raises the question of when and if such patients should be regarded as 'cured' of their disease. Long-term multi-institutional natural history studies are in progress to address the above issues.

### Introduction

Cerebellar astrocytomas comprise roughly 10 to 20% of intracranial tumors in children [23] and are notable for their generally favorable long-term prognosis [11, 12–15, 17]. Since Cushing first reported on his experience with these tumors in 1931 [9], a full body of literature has emerged, consisting primarily of retrospective reviews from single institutions. In four articles from 1986 and 1987, Ilgren and Stiller [17–20] summarized the results of forty major series published between 1926 and 1984 encompass-

ing 2916 cases. Since that time, at least 16 major series have been published [1, 2, 5, 8, 10, 12, 13, 15, 16, 21, 25, 28, 31, 38–40]. Despite the large number of cases that have been reported, many issues concerning these tumors remain unresolved. The purpose of the present article is to update what is known about cerebellar astrocytomas with regard to preoperative characteristics, histology, treatment, and prognosis based on the recent literature and a review of our own experience (Table 1), and to identify areas of controversy.

Table 1. Outcome in 83 patients with cerebellar astrocytomas treated between 1975 and 1993

	No progression	Progression	Median time to progression	Death
Low-grade astrocytomas (n = 72)				
Total resection (n = 57)	51	6	23 mo	0
Subtotal resection (n = 15)	8	7 <sup>1</sup>	15 mo	1
With radiation (n = 10)	8	2		
Without radiation (n = 5)	0	5 <sup>2</sup>		
High-grade astrocytomas (n = 11)	0	11	9 mo	10

<sup>1</sup> The difference between the frequency of disease progression in the total resection and subtotal resection groups was statistically significant at the  $p < 0.01$  level (Chi square with Yates' correction).

<sup>2</sup> The difference between the frequency of disease progression in the subtotal resection group among patients treated with or without radiotherapy was statistically significant at the  $p < 0.01$  level (Fisher's exact test).

## Pre-operative characteristics

### Patient age

Cerebellar astrocytomas are diagnosed most frequently in patients between 1 and 40 years of age with 70% occurring in childhood [20]. The mean age at presentation in all patients including adults is 14.5 years [2, 15, 20] and in the pediatric population alone is 6.5 years [1, 2, 8, 12, 20, 38]. Younger age has been associated with a more favorable prognosis [2, 12, 15, 20, 25], although this may reflect age-related differences in tumor biology [15]. For example, pilocytic astrocytomas are encountered more commonly in children than adults, whereas high-grade cerebellar astrocytomas occur more frequently in adults than children [19].

### Sex

Cerebellar astrocytomas are found in equal numbers within the sexes [2, 8, 12, 20, 40]. A decline in tumor incidence for females around the time of puberty has been noted by some authors [20], but not confirmed by most reports. Likewise, there is no significant difference in prognosis between the sexes.

### Mode of presentation

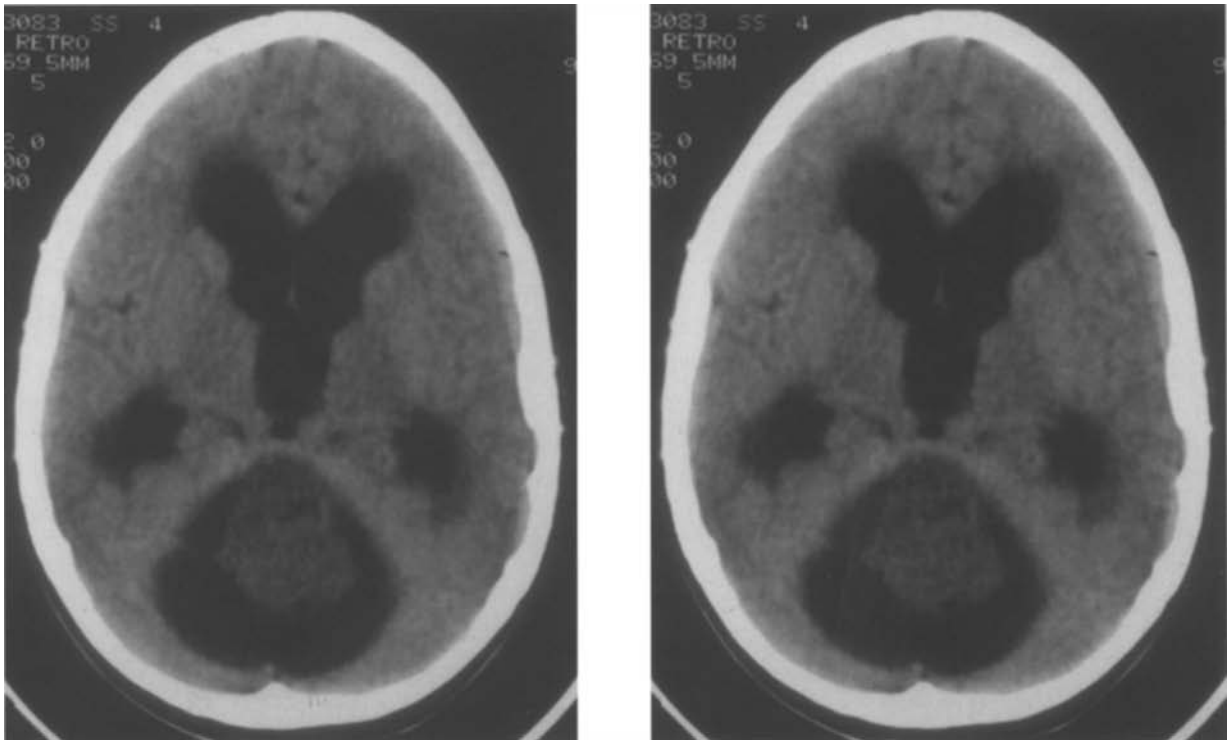
Since cerebellar astrocytomas generally are slow-

growing tumors, symptoms often progress insidiously during a period of months or, in some cases, years before diagnosis. The median duration of symptoms before diagnosis in our series and in most other recent studies is approximately 3 months. This protracted course contrasts with the more rapid symptom progression characteristic of medulloblastoma, ependymoma, and brainstem glioma.

Presenting symptoms and signs from cerebellar astrocytoma are usually a reflection of increased intracranial pressure and include headache, vomiting, and papilledema. Cerebellar dysfunction, such as ataxia and dysmetria, and brainstem impairment are also seen in a percentage of patients. The prognosis is not significantly affected by the duration or nature of the presenting symptoms except in patients with evidence of brainstem dysfunction who appear to have a less favorable outcome [10, 20, 31, 39]. The latter observation may reflect the fact that such patients are more likely to have tumor that invades the brainstem, which may itself constitute an adverse prognostic factor.

### Imaging

Computed tomography (CT) typically reveals a tumor that is hypodense or isodense to the surrounding brain on unenhanced images. After administration of intravenous contrast, the vast majority of tumors exhibit enhancement, which may be uniform, ring-like, or in the form of a mural nodule [7, 27] (Fig. 1). Foci of calcification are seen in 10–20% of



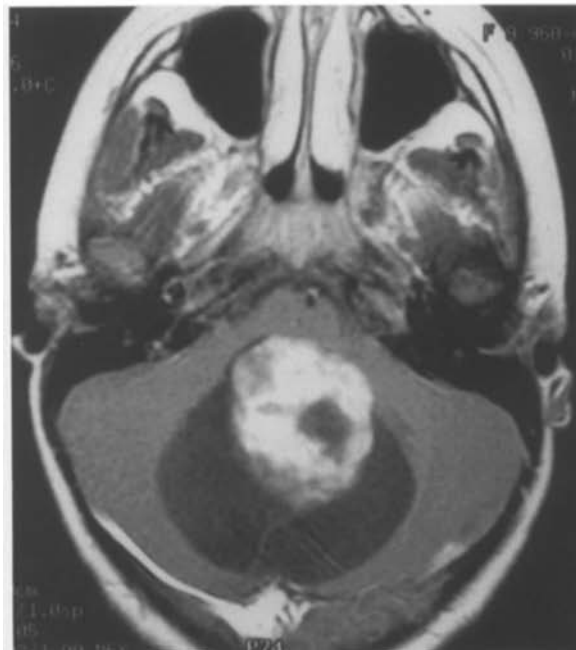
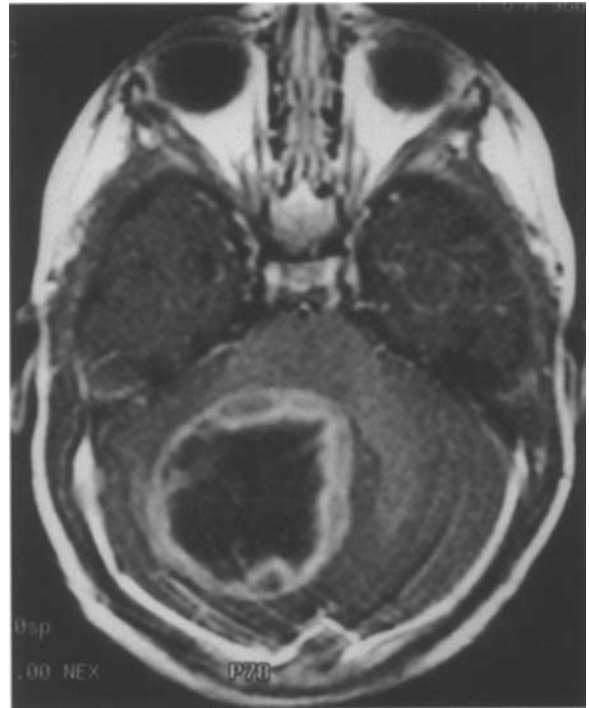
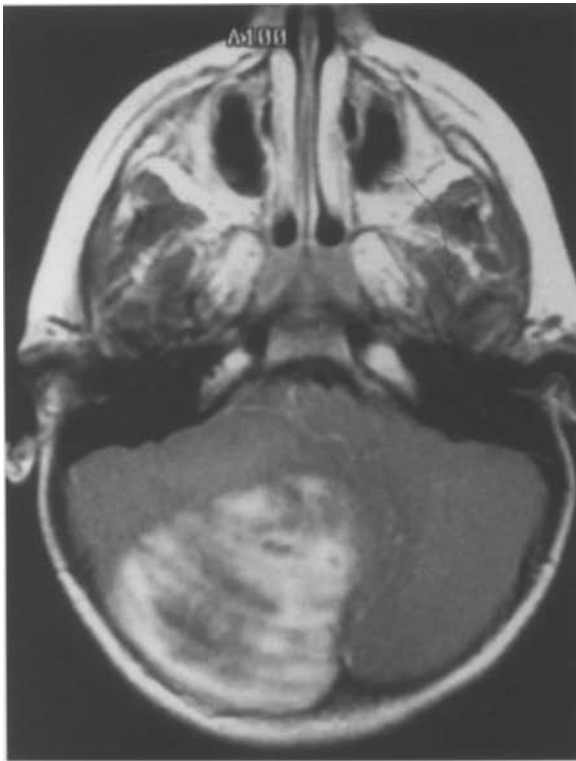
*Fig. 1. A:* This axial CT image shows a hypodense vermian astrocytoma, which is characterized by a large mural nodule in association with a huge surrounding cyst. *B:* After administration of intravenous contrast, the lesion shows fairly uniform enhancement. Ventrally, a plane is apparent between the tumor nodule and the surrounding brain tissue.

cases and cysts are seen in approximately 70% of tumors [7, 27]. Magnetic resonance imaging (MRI) typically reveals a tumor that is hypointense or isointense to the surrounding brain on T1-weighted images and hyperintense to brain on T2-weighted images which enhancement that may be uniform (Fig. 2A), nodular (Fig. 2B), or ring-like (Fig. 2C).

Cerebellar astrocytomas involve the vermis and cerebellar hemispheres with approximately equal frequency [20]. Hydrocephalus is apparent with most vermian astrocytomas and with a significant percentage of hemispheric lesions. In addition, significant compression or actual invasion of the cerebellar peduncles or brainstem is seen most commonly with vermian tumors; it is sometimes difficult to distinguish between these two patterns of growth preoperatively.

## Histology

Several authors have compared specific components of histology to patient prognosis with some contradictory results. Although it is generally agreed that lesions with histological features of malignancy, such as frequent mitotic figures, hypercellularity, necrosis, and nuclear pleomorphism, carry a worse prognosis than low-grade lesions [19, 34, 41], it remains uncertain whether the large group of low-grade tumors can be further divided based on histology into prognostically meaningful subgroups. Several classification systems for cerebellar astrocytomas have been proposed that have attempted to address this issue. The two most widely recognized systems are discussed below.



*Fig. 2.* Axial T1-weighted MR images, enhanced by administration of intravenous gadolinium, which show different appearances of cerebellar astrocytomas. A: A solid cerebellar hemispheric tumor. B: A cystic vermian tumor with a large mural nodule. The non-enhancing cyst wall was free of tumor. C: A cystic vermian tumor with a thick enhancing cyst wall. In this case, the wall was comprised of tumor.

#### *Winston-Gilles classification*

While evaluating cerebellar astrocytomas for specific histological components associated with prognosis, Winston *et al.* [41] found clusters of features that correlated with survival. Glioma A tumors displayed microcysts, leptomeningeal deposits, Rosenthal fibers, or foci of oligodendroglia. Glioma B tumors displayed a combination of perivascular pseudorosettes, hypercellularity, mitosis, necrosis, and/or calcification in the absence of any glioma A feature. Glioma C tumors consisted of the remaining neoplasms that did not fit into these categories. Ten-year survivals in patients treated since 1948 with glioma A, B, and C tumors were 94%, 29%, and 69%, respectively [41]. These authors also noted an increased frequency of glioma A tumors during the previous 40 years [11]. A more recent series confirmed these observations with 100% versus

41% 5-year survival for patients with glioma A versus those with glioma B [8].

Although this classification system appears to provide a significant correlation between histology and prognosis among cerebellar gliomas, this schema does not directly address the issue of whether prognostically useful subgroups of low-grade gliomas, which are encompassed by the glioma A group, can be identified. In addition, the glioma B classification represents a heterogeneous group of tumors that includes high-grade astrocytomas and ependymomas, which themselves would be subdivided in most classification schemes [18, 41]. Finally, the literature is divided as to the prognostic significance of several of the characteristic histological features used in this classification system, including calcification, Rosenthal fibers, foci of oligodendroglia, leptomeningeal deposits, perivascular pseudorosettes, and hypercellularity [4, 5, 18, 19].

#### *Juvenile pilocytic astrocytoma versus diffuse (non-pilocytic) astrocytoma*

An alternative classification scheme that was popularized by Russell and Rubinstein [34] and largely adopted by the World Health Organization [22], subdivides cerebellar astrocytomas into pilocytic and non-pilocytic groups. Pilocytic tumors exhibit a biphasic appearance with compact areas of bipolar cells associated with Rosenthal fibers interposed with areas of loosely aggregated astrocytes associated with granular bodies and microcysts; these lesions correspond to World Health Organization grade I tumors. These neoplasms comprise roughly 80% of cerebellar astrocytomas of childhood [14, 15, 23, 34] and generally are well circumscribed. However, as many as 20% exhibit invasion into surrounding structures, such as the brainstem [15]. So-called 'diffuse' or non-pilocytic astrocytomas are essentially identical in appearance to low grade astrocytomas found within the central nervous system in adults and correspond to World Health Organization grade II tumors. These lesions typically display a monotonous proliferation of fibrillary or protoplasmic astrocytes with or without microcysts and characteristically exhibit poorly circumscribed bor-

ders with invasion of neoplastic cells into the surrounding parenchyma [14, 15, 34].

Although it is assumed that the distinction between these two groups of astrocytomas is of prognostic value, this has yet to be proven conclusively. In support of this distinction, Gjerris and Klinken [14] noted a 25-year survival rate of 94% in 31 children with 'juvenile' (pilocytic) cerebellar astrocytomas vs. only 38% in 13 children with 'diffuse' (non-pilocytic) tumors. Similarly, Hayostek *et al.* [15] found a substantial difference in survival between these variants. However, in both studies, other differences between the pilocytic and non-pilocytic groups may have also contributed to the disparities that were noted in their prognoses. For example, in the study of Hayostek *et al.*, the median age of patients with pilocytic versus diffuse tumors was 12 years versus 52 years, respectively. In addition, gross total resection was achieved in 53% of the pilocytic tumors as compared to only 19% of the non-pilocytic tumors. Both age and extent of resection are known to have strong correlations with survival.

In contrast to the above results, several recent studies have suggested that pilocytic and non-pilocytic astrocytomas have similar prognoses [4, 18, 31, 35] and that the major predictor of outcome is not the histological appearance of the tumor, but whether or not a complete resection is obtained. Adding to the controversy is the fact that many tumors display characteristics of both variants, leading to difficulty in classification [18, 34]. Moreover, in many series, such as our own, the percentage of patients that exhibit disease progression is too low to allow a meaningful assessment of the contribution of histology to outcome, independent of the effect of resection extent. In an attempt to thoroughly address the issue of whether or not histology is associated with outcome, an ongoing multi-institutional study of the Children's Cancer Group and the Pediatric Oncology Group is following the natural history of both completely and incompletely resected low-grade gliomas, using consistent histological criteria to separate pilocytic and non-pilocytic tumors, in the hope of identifying distinctions in the long-term progression-free survival of these two groups.

## Treatment

### *Gross Total Resection (GTR)*

The primary treatment of cerebellar astrocytomas is surgical excision. In reports prior to 1985, ten-year survival for patients with GTR of tumor has ranged from 52% to 100% [17]. More recent studies report survivals of greater than 90% at 10 years after GTR [2, 13, 16, 21, 25, 40, 41] and several series in the microsurgical era note 100% survival with up to twenty years of follow-up [1, 16, 40]. In our own series, only 6 of 57 patients with low-grade astrocytomas in whom a gross total resection was achieved have had tumor progression with a median follow-up of 11 years. All of these patients are currently alive and disease-free after a second presumed complete resection.

Given the above results, radiation therapy and chemotherapy are not indicated after GTR of benign cerebellar astrocytomas [1, 5]. Although a small percentage of patients do exhibit disease progression after an apparently complete resection, most such cases are amenable to repeat resection. If a radiographically complete resection can again be achieved, adjuvant therapy may not be required. Since these tumors generally grow slowly, recurrences may occur many years after the original operation [5, 30]. Unlike primitive tumors, such as medulloblastoma and neuroblastoma, cerebellar astrocytoma does not follow Collin's Law, which states that a neoplasm should recur within a follow-up period equal to the patient's age at diagnosis plus nine months [5]. Therefore, patients need long-term follow-up and cannot be regarded as 'cured' at a standard interval after resection.

In view of the generally favorable results after a complete resection of these tumors, we view this as the surgical goal in most patients. A caveat in the removal of these tumors is that for lesions that exhibit a mural nodule with a non-enhancing cyst wall (e.g., Fig. 2B), removal of the nodule is generally sufficient to prevent tumor recurrence. Histopathological examination of focal biopsies of the cyst wall in such cases demonstrates gliosis without actual tumor infiltration. In contrast, for lesions that exhibit a thick cyst wall (e.g., Fig. 2C), complete re-

section of the cyst lining is required in order to minimize the chances for subsequent disease progression. In such cases, histopathological examination of the cyst wall invariably shows tumor involvement.

Using modern surgical techniques, a gross total excision can typically be achieved with minimal morbidity other than possible exacerbation of ataxia and dysmetria. However, a percentage of patients do exhibit more serious impairments of motor, cognitive, and speech function [26, 28, 33]. These deficits are generally transient, but in some cases the patient may exhibit persistent impairments. In our experience, such deficits are generally seen after excision of large vermian tumors that involve the cerebellar peduncles bilaterally [33]. Although we do not believe that involvement of the cerebellar peduncles by tumor is a contraindication to attempting a complete resection, such cases clearly require meticulous microsurgical technique to minimize injury to the cerebellar peduncles and to avoid trauma to the adjacent brainstem. In contrast, frank infiltration of the brainstem by tumor, which is seen in approximately 10% of cerebellar astrocytomas, does constitute a practical limit to complete resection in certain cases. Accordingly, in some series, such tumors have constituted a less favorable prognostic group [10, 19].

### *Subtotal Resection (STR)*

When a gross total resection would result in unacceptable morbidity, an aggressive subtotal resection is recommended. This approach is indicated when there is extensive infiltration of the brainstem or in rare instances of leptomeningeal spread [3, 32, 37]. STR results in significantly decreased progression-free survival (PFS) as compared to GTR (Table 1). In prior studies, five- and ten-year PFS after STR has ranged from 29% to 80% and 0 to 79%, respectively [1, 2, 8, 13, 16, 17, 40]. Since most recurrences are amenable to re-exploration and resection, overall survival has been as high as 86% at ten years in these reports. In agreement with the above studies, our experience indicates a high frequency of progression (7 of 15 patients) for tumors that are resect-

ed subtotally; however, these results also indicate that the progressive disease can almost always be controlled with a combination of reexploration and, if indicated, adjuvant radiotherapy. Only one of our patients with progressive disease after an initial subtotal resection has died; the remainder are currently alive and free of further progression with a median follow-up of four years from initial progression.

Thus, although gross total resection is certainly the goal in the management of these tumors, it is clear that if this is not feasible, long-term survival is still possible despite the presence of obvious residual tumor [4, 5, 35]. Schneider *et al.* [35], noted that only 4 of 12 patients with radiographically apparent residual tumor had disease progression with a mean follow-up of 4.9 years. It is presently unknown why certain tumors remain quiescent for extended periods of time after a subtotal resection. This may reflect alterations in blood supply resulting from the resection [17] or decelerating growth kinetics within the tumor over time. However, it is clear that incompletely resected tumors may recur many years after an initial operation. In the UCSF experience [40], PFS was 74% at 10 years, but only 41% at 20 years, which calls attention to the importance of maintaining close long-term follow-up in patients with apparent residual disease.

The efficacy of postoperative radiotherapy after STR is unclear from the literature. Most reported studies have consisted of patients who were treated in a consistent fashion (e.g., either with or without radiotherapy), making it impossible to determine the effect of this modality on survival. Several series that have included some patients treated with postoperative irradiation and others without did not demonstrate an improvement in overall survival [12, 13, 17, 21, 25, 39, 41]; however, one report suggested a slight improvement in PFS [13]. In our own experience, radiation did produce a significant decrease in the frequency of disease progression (Table 1), but had no impact on overall survival. Moreover, radiation carries long-term risks of functional impairment for the immature nervous system and may predispose to the development of malignant degeneration within the residual tumor [6, 36]. Thus, although a substantial percentage of incom-

pletely resected lesions may ultimately require radiotherapy, the chance to avoid the use of this modality in some children and to delay its use for several years in others may constitute a significant benefit in terms of improving overall functional outcome.

The uncertain risks and benefits of radiation for these tumors have complicated attempts to define the indications for the use of this modality after an initial subtotal resection. In view of this uncertainty, one goal of the original Children's Cancer Group and Pediatric Oncology Group low-grade glioma study was to address the role of radiotherapy in the management of these patients using a prospective, randomized format. Unfortunately, difficulties in entering prospectively randomized patients have precluded completion of this phase of the study.

In the absence of convincing evidence favoring the routine use of radiotherapy, we currently advocate irradiation only for tumors that have progressed after two presumed total excisions or for those that exhibit progressive growth after an initial operation and cannot be completely resected. Early experience at our institution and elsewhere with stereotactic radiosurgery and stereotactic radiotherapy for the treatment of focal areas of tumor recurrence suggests that this modality may prove useful in managing small areas of unresectable disease in critical locations, such as the brainstem. However, as with all treatments for an inherently benign process, many years of follow-up will be required to fully assess the efficacy of this modality for these lesions.

#### *Special considerations in the management of cerebellar high-grade gliomas*

A small number of cerebellar astrocytomas closely resemble high-grade gliomas (anaplastic astrocytoma or glioblastoma multiforme) seen supratentorially. In most reports, these lesions comprise less than 5% of all cerebellar astrocytomas; conversely, only 5% of all high-grade astrocytomas are found in the cerebellum [9, 19, 34]. However, in our series, these lesions accounted for 13% of cerebellar astrocytomas. The biological behavior of cerebellar malignant gliomas is similar to that of high-grade astro-

cytomas found elsewhere with a very poor prognosis for long-term survival. Such lesions are invasive, biologically aggressive, and poorly controlled even after apparently complete excision. Despite the use of postoperative radiotherapy and, in many cases, chemotherapy, median survival among our patients was only 9 months. Two patients had leptomeningeal dissemination of their disease at presentation and two others showed evidence of dissemination shortly after diagnosis; one of these patients also had evidence of systemic metastases. Only one of our 11 patients is a long-time survivor; after a single episode of disease progression at 46 months postoperatively, which was treated with aggressive resection and a second course of adjuvant radiotherapy, this child is currently disease-free 92 months after diagnosis. In view of the generally poor results in these patients, novel approaches to adjuvant therapy are clearly needed.

## Conclusion

Low-grade cerebellar astrocytomas are associated with a substantially better prognosis than most other central nervous system tumors. Gross total resection of the lesion provides the greatest likelihood of long-term PFS. When this is not possible, subtotal resection may allow an extended period of disease control; however, a significant percentage of lesions ultimately progress and require additional therapy. At present, the role of radiation therapy after an incomplete resection remains uncertain. We currently reserve this modality for patients with unresectable residual disease after a single episode of disease progression and for those who have progressive disease after a second apparent complete resection. In view of the generally indolent growth of these lesions, long-term follow-up is needed because disease progression may occur many years after an initial operation. In contrast to the favorable results achieved with low-grade cerebellar astrocytomas, the prognosis for patients with high-grade lesions remains poor after conventional surgery, radiotherapy and chemotherapy.

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