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Predicting disease progression in childhood cerebellar astrocytoma

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Abstract Pediatric cerebellar astrocytomas are frequently curable by complete surgical resection. However, even incompletely resected tumors may lie dormant indefinitely or spontaneously involute, and tumors thought to be completely excised have reappeared in the same location several years later. Because of the unpredictable nature of some cerebellar astrocytomas, this study was designed to analyze several variables for their potential value in predicting disease progression. The charts of 78 children treated at a children's hospital between 1966 and 1993 were reviewed; 62 tumors were pilocytic, 13 were fibrillary, and 3 were mixed oligoastrocytomas. Four children had the additional diagnosis of neurofibromatosis type 1, and those children were considered separately. Of the remaining 74 children, 48 underwent postoperative contrast-enhanced computerized tomography or magnetic resonance imaging. Of those 48 children, 17 had residual disease, and in 15 cases the tumor volume could be measured. Frequently the surgeon's report conflicted with the postoperative scan regarding the presence of residual disease. However, the surgeon's report of brainstem infiltration correlated highly with residual disease on postoperative imaging. On univariate Cox analysis, sex, age, tumor location, and tumor morphology did not show prognostic significance. In spite of their differences, the surgeon's report of residual tumor and the presence of residual disease on postoperative imaging were similar in their correlation with disease progression. However, on multivariate analysis, the volume of residual tumor was most closely linked with disease progression. Only the presence of fibrillary histology significantly complemented the volume of residual tumor as a negative prognostic indicator.

Key words Cerebellar astrocytoma · Extent of tumor resection · Pediatric brain tumor · Volumetric analysis

Introduction

Central nervous system neoplasms are second only to leukemia as the most common type of cancer affecting children. Of these tumors, 45%–60% are located infratentorially, and astrocytomas rank second only to medulloblastomas in frequency in that location [46]. Thus, low-grade cerebellar astrocytomas constitute 12%–18% of all pediatric brain tumors [15, 49, 62]. Fortunately, cerebellar astrocytomas are associated with lengthy periods of survival following complete or even partial surgical resection [1–3, 6, 12–14, 19–21, 24, 28, 48, 51, 56, 58, 59]. However, some of these tumors recur years after an apparently complete resection [3, 5, 14, 24, 28, 37, 44, 48, 55], and some incompletely resected tumors remain static [3, 6, l2–14, 20, 2l, 48, 5l, 58] or even regress [14, 51]. The purpose of this retrospective study was to analyze several prognostic variables influencing outcome. In particular, the volume of residual disease, as documented on postoperative imaging

studies, was evaluated for its role in influencing disease progression.

Clinical material and methods

Selection of patients

The tumor registry at Children's Hospital and Medical Center, Seattle, Washington, was reviewed to identify patients with the histopathological diagnosis of low-grade cerebellar astrocytoma who were treated between October 1966 and June 1993. Patients whose tumors arose primarily in the brainstem were excluded.

Histopathological criteria

For the identified patients, all available pathology reports were reviewed. Cases of anaplastic astrocytoma and glioblastoma multiforme were excluded. In cases of low-grade astrocytoma where the pathology reports did not clearly specify a pilocytic or fibrillary histology, the original slides were reviewed by one pathologist. Tumors were classified as pilocytic, fibrillary, or mixed oligoastrocytoma. As initially described by Russell and Rubinstein [50], classic pilocytic or "juvenile" astrocytomas contain abundant Rosenthal fibers and microcysts within a mixed spongy and compact glial background. Fibrillary or "diffuse" tumors consist of a monotonous and tightly compacted array of cells with mild to moderate degrees of nuclear hyperchromatism and atypia. The presence of small foci of oligodendroglial differentiation within the astrocytoma is not uncommon [14, 29, 50, 61]. In rare cases where foci of oligodendroglia are strikingly differentiated or constitute a very large fraction of the tumor, classification as a mixed oligoastrocytoma is warranted [50].

Clinical review

The patients' charts were reviewed to determine their sex, age at diagnosis, and type and duration of presenting signs and symptoms. The coexisting diagnosis of neurofibromatosis was noted.

Diagnostic imaging review

The available diagnostic imaging studies were reviewed. Before 1978, patients were evaluated using a variety of imaging modalities including arteriography, pneumoencephalography, radionuclide brain scan, and electroencephalography. After April 1978, computerized tomography (CT) was used. After November 1984, patients were evaluated with a combination of CT and magnetic resonance (MR) imaging. Preoperative intravenous contrast-enhanced CT or MR images were obtained for 55 children, and those films were reviewed. The presence of hydrocephalus on the films was noted. The location of the tumor, i.e., whether midline in the vermis or lateral in the cerebellar hemisphere, was also assessed. The tumors were also categorized into groups based on their morphologic appearance.

Treatment review

The treatment of hydrocephalus was noted from the chart. Operative reports were reviewed to determine the surgeon's appraisal of brainstem infiltration by the tumor and the extent of tumor resection. Imaging studies performed within 1 month of surgery were also reviewed to assess the extent of resection. A complete resection was equivalent to absence of evidence of residual bulky contrast-enhancing tumor on initial postoperative CT or MR imaging. Linear enhancement at the resection margins secondary to perioperative inflammation and neovascularization may develop 3–5 days after surgery [8]. Such linear enhancement was not considered to represent residual tumor. For patients with residual disease on postoperative films that had centimeter reference scales present, the volume of residual disease was calculated based on the technique of quantitative volumetric analysis [16]. Briefly, a video-camera image of each CT or MR axial slice was digitally captured using RasterOps MediaGrabber (Santa Clara, Calif.). By using NIH Image 1.51 public domain software, the reference scale on each video image was measured, and the program was calibrated. The circumference of the contrast-enhancing mass was traced and its area calculated. The volume of the entire lesion was determined by multiplying the area of each slice by the slice thickness and adding all the slices together. In patients with incomplete resections and reference scales on both the preoperative and postoperative scans, the percentage of resection was also calculated. Patients with the coexistent diagnosis of neurofibromatosis were excluded from this volumetric analysis because of the difficulty in assessing the extent of their astrocytic tumors, which were largely non-contrast-enhancing.

Follow-up review

From 1986 on, follow-up imaging studies were performed every 3–6 months for the first few years after surgery, followed by yearly scans thereafter. Before 1986, imaging studies were obtained on a variable timetable. Stable disease was defined as no significant change in tumor size on follow-up imaging studies, provided that the patient was neurologically stable at the time of the most recent clinic appointment or the most recent correspondence with the patient's primary physician. The complete disappearance of bulky contrast-enhancing tumor that was present on the immediate postoperative scan was considered to represent tumor involution. Tumor progression was defined as any tumor enlargement on follow-up imaging studies, regardless of the patient's condition. The time from the first operation to tumor involution, tumor progression, or last follow-up evaluation was noted. In cases of disease progression, the treatment modalities used, the success of those treatments, and the histopathology of any surgical specimens were reviewed.

Statistical analysis

Potential prognostic factors were evaluated by univariate and multivariate Cox proportional hazards models [11] by using EGRET 1.02.01 (Statistics and Epidemiology Research Corporation, Seattle, Wash.). For each model, each variable was assigned a regression coefficient, b, and a hazard ratio, e^b, which approximates the relative risk (RR). Tests for significance were based on the Wald statistic [60].

Results

Clinical characteristics

Entry criteria were met by 78 children (39 male, 39 female). Ages at the time of diagnosis ranged between 6 months and 17 years (mean age, 7.1 years). The most common symptom at the initial time of presentation was headache (83%) (Table 1). Other typical symptoms included nausea and vomiting (78%), gait disorder (56%), and behavioral changes (32%). The mean duration of symptoms in the entire patient population was 5.1 months

Table 1 Symptoms and signs in 78 patients with benign pediatric cerebellar astrocytomas

Clinical presentation	No. of patients	Percentage of patients
Symptoms		
Headache	65	83
Nausea and vomiting	61	78
Balance or gait difficulty	44	56
Behavioral change	25	32
Incoordination	21	27
Weight loss or poor gain	16	20
Appetite loss	13	17
Somatic pain	12	15
Blurred vision	11	14
Diplopia	10	13
Dizziness	10	13
Limb disuse or weakness	7	8
Strabismus	4	5
Fever	4	5
Tremor	4	5
Dysarthria	2	3
Seizure	2	3
Signs		
Ataxia	69	88
Appendicular dysmetria	46	58
Papilledema	43	55
Wide-based gait	21	27
Positive Babinski sign	17	22
Positive Romberg sign	16	20
Nystagmus	16	20
Dysdiadochokinesia	15	19
Hyperreflexia	13	16
Strabismus	12	15
Head tilt	10	13
Intention tremor	9	11
Suture separation	7	9
Anisocoria	6	8
Diminished gag reflex	3	4
Hyporeflexia	2	3
Visual deficit	2	3

(range, 5 days to 3 years). Ataxia was the most common sign (88%) at the time of the initial neurological examination. Additional findings included appendicular dysmetria (59%), papilledema (55%), and wide-based gait (27%). Four patients, all male, had the diagnosis of neurofibromatosis type-1.

Histopathological findings

Of 78 tumors, 62 were classified as pilocytic astrocytoma, 13 as fibrillary astrocytoma, and three as mixed oligoastrocytoma. Small foci of oligodendroglial differentiation were found in nine of the astrocytomas. Of the four patients with neurofibromatosis, two had tumors that were pilocytic and two had fibrillary tumors. Eleven children underwent reoperation for disease progression, and none of their tumors showed evidence of malignant transformation.

Diagnostic imaging characteristics

In the four patients with the diagnosis of neurofibromatosis, one astrocytic tumor was found in the midline, two were located laterally, and one occupied both the midline and one cerebellar hemisphere. Three tumors were solid and almost entirely non-contrast-enhancing. The fourth tumor was cystic with an enhancing mural nodule. Two of these patients were documented to have multicentric intracranial lesions consistent with glial tumors. One child had hypothalamic and optic chiasm pilocytic astrocytomas, while another patient had a right temporal pleomorphic xanthoastrocytoma. A third child had extension of cerebellar tumor into the brainstem in addition to cervical neurofibromas and basal ganglia signal abnormalities most likely representing hamartomas.

Of the 74 patients without neurofibromatosis, 51 had preoperative CT or MR studies. The most common appearance, found in 19 patients (37%), was that of a solid contrast-enhancing mass with small intratumoral cysts. Twelve (24%) of the patients had tumors with solid elements with small intratumoral cysts mixed with non-contrast-enhancing cystic parts. Another 12 children (24%) had cystic tumors in which the entire cyst wall enhanced after intravenous administration of contrast agent. The pathognomonic finding of a cystic lesion with an enhancing mural nodule was seen in only eight (16%) of the patients. Figure 1 shows representative photographs of the four distinct morphologies. In cystic and mixed solid and cystic tumors, the enhancing cyst wall has been documented to represent tumor [9, 37, 63] and was resected when possible. Fifty-three percent of tumors were located in the vermis, 36% were found in one cerebellar hemisphere, and 11% involved both the vermis and one hemisphere. No significant correlation was found between the presence or absence of midline involvement and any of the tumor morphologies. The vast majority (92%) of patients had some degree of hydrocephalus, as demonstrated on the reviewed imaging studies.

Treatment of hydrocephalus

All patients were placed on a regimen of dexamethasone (2–4 mg every 8 h) before surgery. Lethargy due to obstructive hydrocephalus required placement of a ventriculoperitoneal shunt in ten patients or a ventriculostomy in 6 patients before tumor resection. At the time of tumor resection, a ventriculoperitoneal shunt was placed in 4 patients, whereas in 48 patients an external ventriculostomy was inserted. Postoperatively, hydrocephalus continued to cause symptoms referable to increased intracranial pressure sufficient to warrant placement of a ventriculoperitoneal shunt in 19 patients. A subgaleal pseudomeningocele developed over the operative site in 18 patients, requiring aspiration in 3 children or a cystoperitoneal shunt in 5 patients.

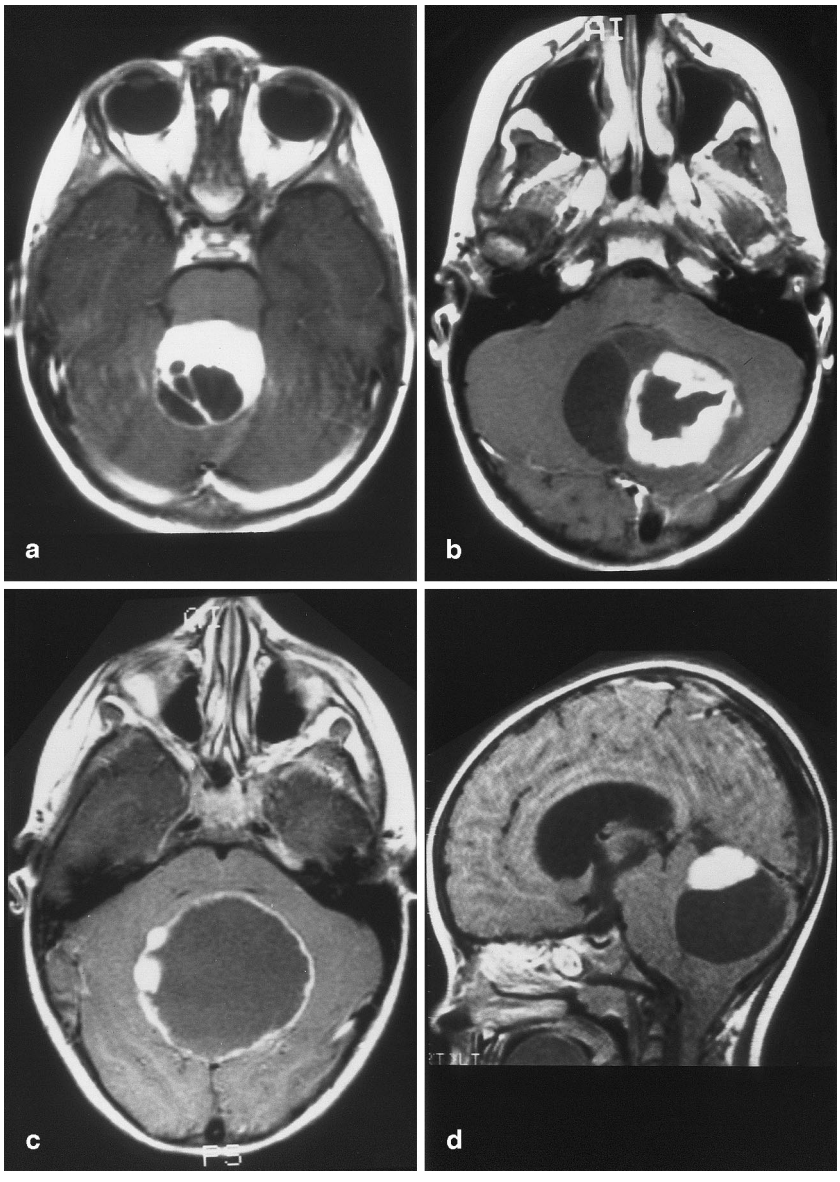


Fig. 1a–d Contrast-enhanced T1-weighted images of four children with cerebellar astrocytomas without neurofibromatosis. **a** Solid vermian tumor with small intratumoral cysts. **b** Tumor which is half solid with intratumoral cyst, half cystic with non-contrast-enhancing cyst wall. **c** Cystic vermian contrast-enhancing tumor. **d** Cyst with a contrast-enhancing mural nodule

Tumor resection

Of the four children with neurofibromatosis, three had cerebellar astrocytomas resected. Two of the resections were complete according to the surgeon's report and postoperative imaging. The third patient, with a solid tumor occupying the entire left hemisphere as well as the vermis, had debulking of approximately 60%. In the fourth patient, only a biopsy was performed because of extensive brainstem invasion by the solid tumor.

One patient with neurofibromatosis and a completely excised solid cerebellar astrocytoma also had multiple debulkings of a progressive hypothalamic astrocytoma. The patient with the incomplete resection of the cerebellar astrocytoma also had total resection of a temporal pleomorphic xanthoastrocytoma. The patient with a cerebellar biopsy subsequently had multiple debulkings of cervical neurofibromas.

For all 74 patients with cerebellar astrocytoma but without neurofibromatosis, the surgeon's operative report was reviewed. Brainstem infiltration was reported in 18 patients (24%), and 25 patients (34%) were thought to have incomplete resections. In 48 of these 74 patients, CT scans made with contrast agent (46 patients) or MR images (2 patients) were obtained during the immediate postoperative period at a mean of 4.7 days (range, 1–34 days) after surgery. Upon review of these scans, 17 (35%) of patients showed evidence of residual disease. When the operative report of these 48 patients was compared to the postoperative imaging studies, the surgeon's report

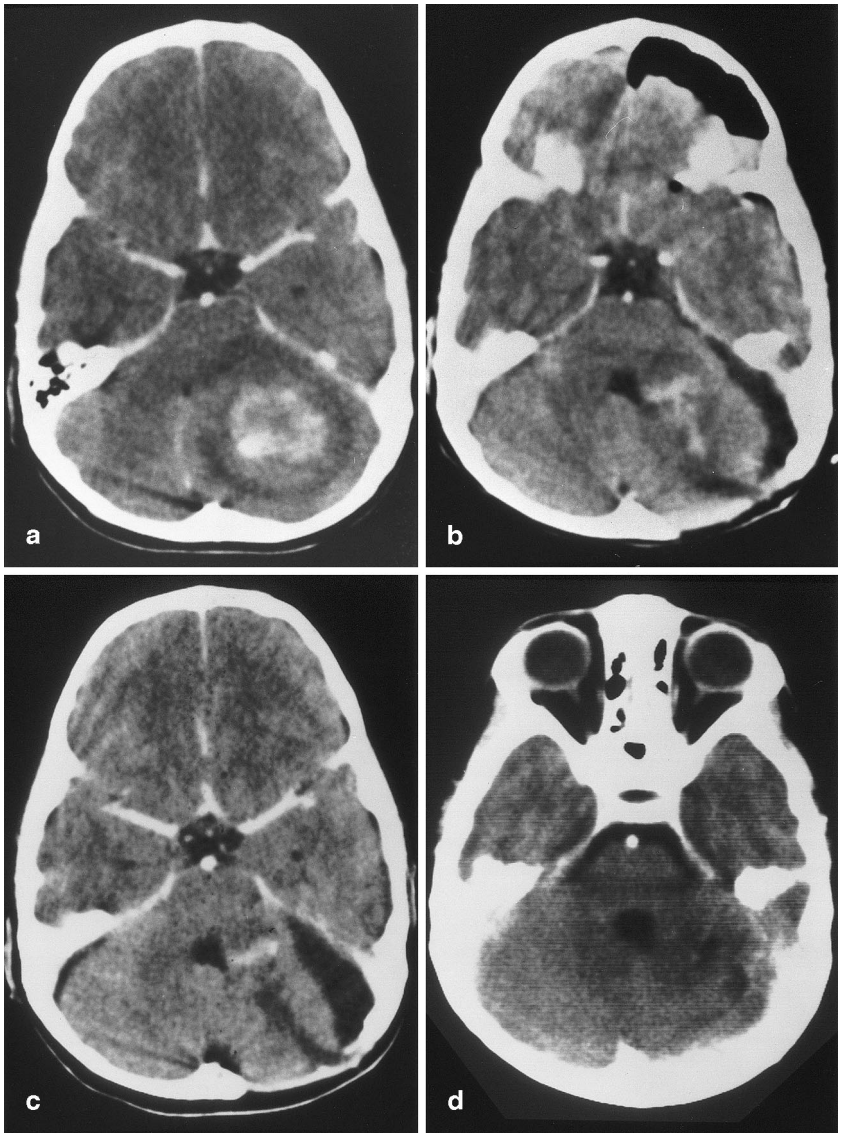


Fig. 2a–d Serial contrast-enhanced axial CT images of a mostly solid left-hemispheric involuting cerebellar astrocytoma. **a** Preoperative scan. **b** Residual tumor 4 days postoperatively. **c** One month postoperatively. **d** No evidence of tumor 3 months postoperatively

of brainstem infiltration correlated highly (χ^2=8.5, P=0.004) with postoperative residual tumor documented on imaging studies. In seven of nine patients reported by the surgeon to have brainstem infiltration, postoperative imaging demonstrated residual disease. In contrast, only 10 of 39 cases with no reported brainstem involvement had residual tumor on postoperative scans. However, in 7 of 35 cases (20%), when the surgeon reported a gross total resection, postoperative imaging showed residual tumor. In 3 of 12 cases (25%), the surgeon reported residual disease that was not confirmed on postoperative imaging studies.

In 15 of 17 patients with residual disease on postoperative scans, reference scales were present and tumor volumes were calculated. Postoperative tumor volumes for all 46 patients who could be evaluated for this variable ranged from 0.0 to 13.6 cm^3, with a mean of 1.1 cm^3. In 12 of 17 patients who showed postoperative disease on imaging studies, both preoperative and postoperative films had reference scales, and the percent of resection was calculated. Considering all 43 children evaluated for this variable, the extent of resection ranged from 46% to 100% (mean 95%).

Radiation therapy

In one patient with neurofibromatosis, tumor resection was not attempted because of extensive brainstem infiltration, and radiation therapy was the primary treatment. In another patient, recurrent hypothalamic tumor was treated with radiation therapy. Of 74 patients without neurofibromatosis, 14 also received postoperative radiation

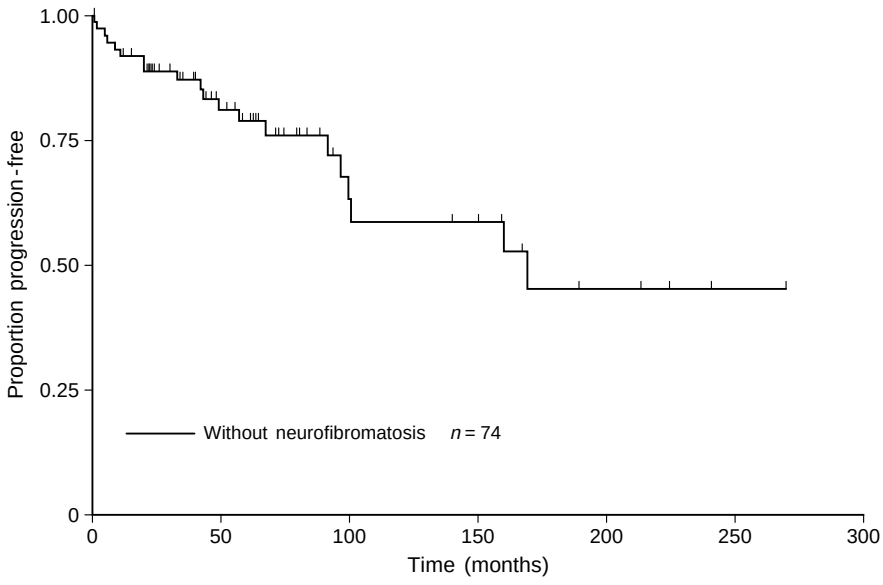


Fig. 3 Kaplan-Meier curve showing time to tumor progression in 74 patients without neurofibromatosis

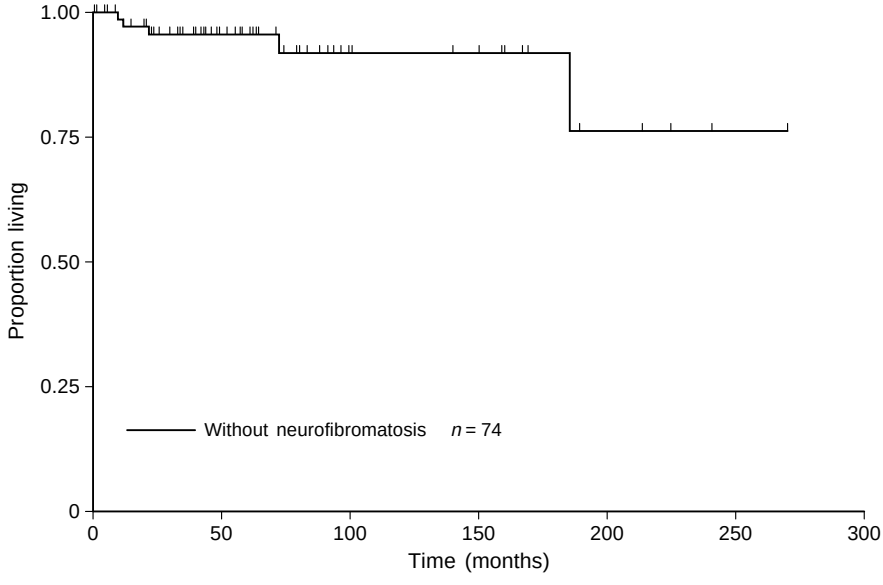


Fig. 4 Kaplan-Meier curve showing time of survival in 74 patients without neurofibromatosis

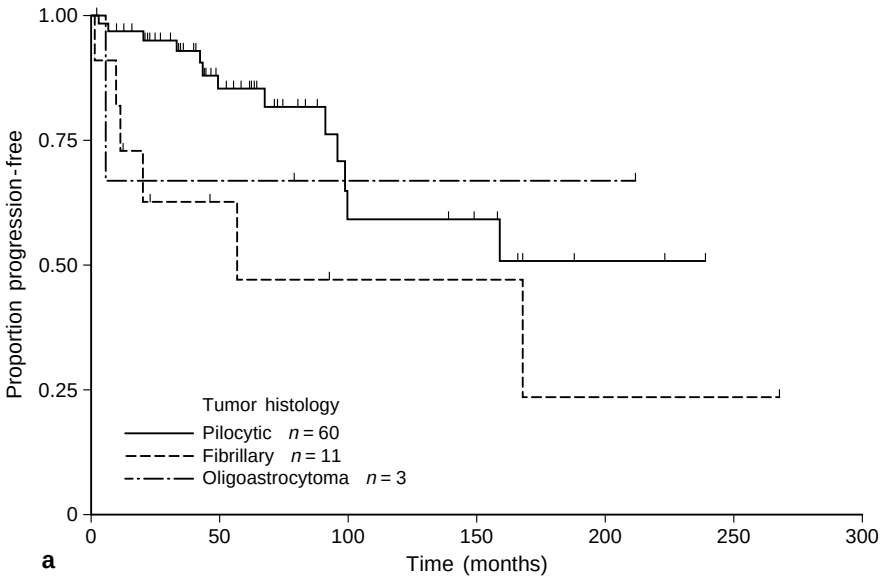
therapy consisting of 4075–5400 cGy to the posterior fossa. In two of those patients, radiation therapy was based on the surgeon's report of residual tumor without confirmatory postoperative imaging. For one patient, neither the surgeon's report nor the postoperative imaging indicated the presence of residual disease, yet the patient received radiation therapy.

Recurrence patterns

In the children with neurofibromatosis, all of the cerebellar tumors remained static after surgery (three patients) or radiation therapy (one patient). One child died of a progressive hypothalamic tumor.

Tumor involution

Among the 74 patients without neurofibromatosis, results were more varied. Of the 17 patients with residual disease demonstrated on postoperative imaging, four (24%) had complete spontaneous disappearance of residual tumor of 0.1 cm^3 to 2.5 cm^3 (mean, 1.2 cm^3) on follow-up scans over a 3- to 49-month period (mean, 21 months) (Fig. 2). The immediate postoperative images for three of these pa-



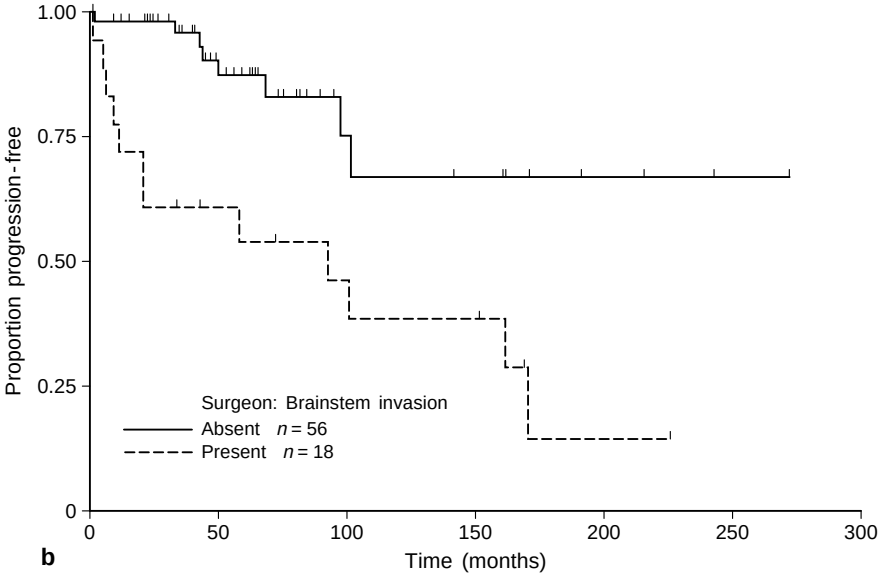


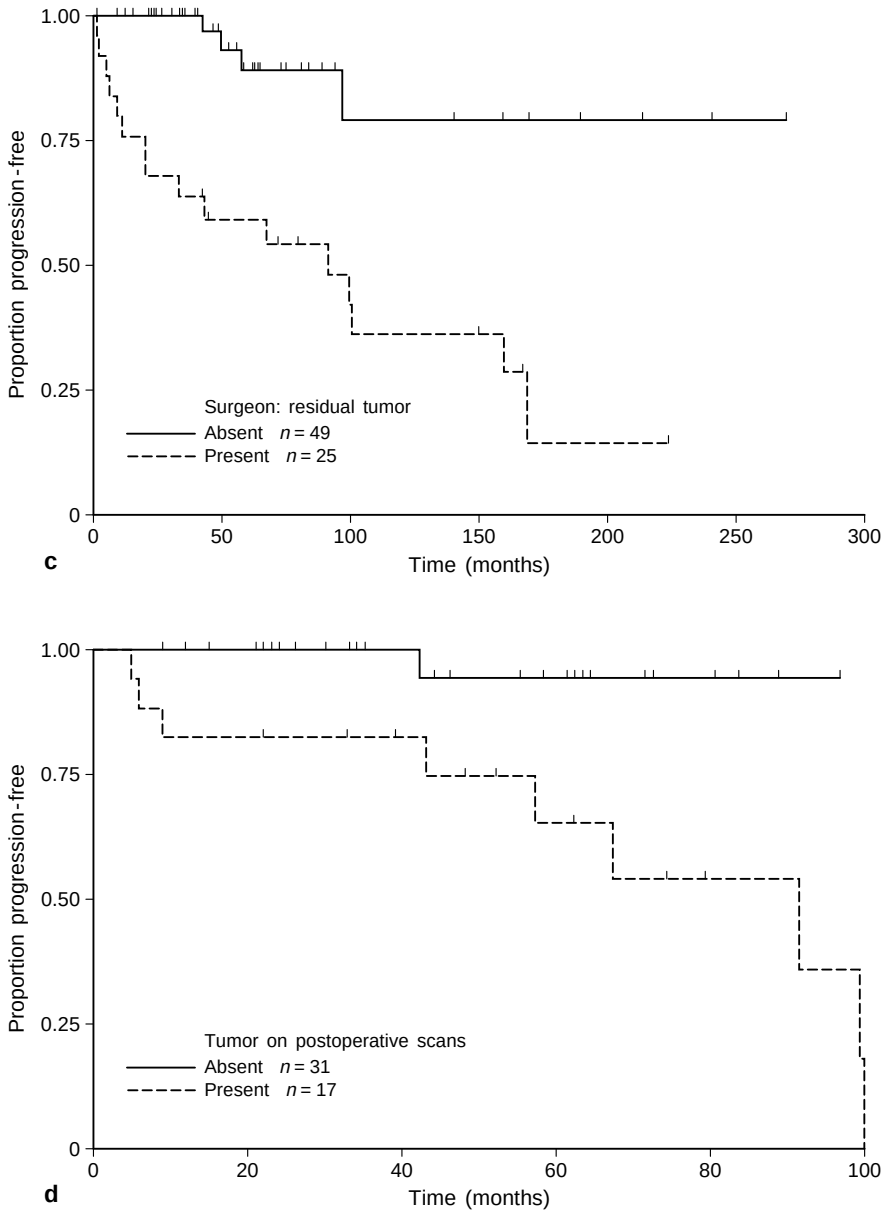
Fig. 5a–d Kaplan-Meier curves showing time to tumor progression in patients without neurofibromatosis, stratified by categorical variables found to be significant on univariate Cox regression analysis. Radiation therapy is not included as a variable. **a** Tumor histopathology. **b** Brainstem infiltration reported by surgeon. **c** Surgeon's report of residual tumor. **d** Residual tumor on postoperative imaging

tients were CT scans done respectively at 2, 3, and 4 days postoperatively. For the fourth patient, the first postoperative scan was an MR image obtained at 26 days. In three of the four cases, the surgeon had estimated a gross total resection. None of these children received radiation therapy postoperatively.

Tumor progression

Of 74 patients without neurofibromatosis, 20 (27%) had disease progression demonstrated on follow-up imaging from 1 month to 168 months (mean, 54 months) following the original diagnosis (Fig. 3). Of the 48 children who had immediate postoperative imaging studies, one of 31 patients who had showed no residual tumor had recurrence of an apparently completely resected tumor at 42 months. Nine of 17 patients who showed residual disease on postoperative imaging had disease progression from 5 months to 100 months (mean, 53 months) following their diagnosis. For 26 children, no postoperative imaging was performed. In 2 of 14 patients, the surgeon reported gross total resection but follow-up imaging showed the tumors recurred 49 and 96 months later respectively. In 8 of 12 patients, when intraoperative residual tumor was evident, disease progression occurred from 1 month to 168 months (mean, 52 months) after diagnosis. Five of the total of 20 recurrences were documented to occur beyond the time period defined by Collins' law, i.e., an interval greater than the patient's age at diagnosis plus 9 months [3, 10].

Fig. 5 (Continued)



Treatment of tumor progression

At the time of recurrence of the cerebellar astrocytoma, 11 children underwent another tumor resection which was subtotal on postoperative scans in 8 cases. Four children, one of whom originally received postoperative radiation therapy, received radiation therapy at the time of recurrence. Five of the 11 patients, one of whom received radiation therapy at the time of recurrence, died of disease progression at a mean of 60 months (range, 10–184 months) following the initial diagnosis (Fig. 4).

Follow-up

The 69 patients who are currently alive have been followed for a mean of 76 months (range, 3–268 months) from the time of their original diagnosis.

Progression-free survival analysis

Because of the differences in tumor appearance on imaging studies (three patients), the multicentric nature of their

Table 2 Univariate Cox analysis of disease progression in patients with benign pediatric cerebellar astrocytoma and no neurofibromatosis

	No. of patients analyzed	RR[a]	95% confidence interval	*P* value
Age (years)	74	1.0	(0.9, 1.1)	0.487
Sex				
Female	39	–[b]	–	–
Male	35	1.2	(0.5, 2.8)	0.742
Tumor location on imaging studies				
Exclusively lateral	18	–[b]	–	—
Midline involvement	33	0.9	(0.2, 3.1)	0.825
Tumor morphology on imaging studies				
Solid with small cysts	19	–[b]	–	–
Half solid, half cystic	12	23.4	(0.6, 18.5)	0.164
Cystic	12	1.0	(0.3, 12.0)	0.980
Cyst with mural nodule	8	2.1	(0.3, 16.1)	0.465
Tumor histopathology				
Pilocytic	60	–[b]	–	–
Fibrillary	11	2.7	(1.0, 7.4)	0.041
Oligoastrocytoma	3	1.2	(0.2, 9.2)	0.867
Surgeon's assessment of brainstem infiltration				
Absent	56	–[b]	–	–
Present	18	4.3	(1.7, 10.6)	0.002
Surgeon's report of residual tumor				
Absent	49	–[b]	–	–
Present	25	7.3	(2.4, 22.0)	<0.001
Residual tumor on postoperative imaging				
Absent	31	–[b]	–	–
Present	17	10.1	(1.2, 83.6)	0.032
Volume of tumor left (cm^3)	46	1.5	(1.2, 1.8)	<0.001
Percentage of tumor resected	43	0.9	(0.9, 1.0)	0.002
Postoperative radiation therapy				
Not used	60	–[b]	–	–
Used	14	3.3	(1.4, 8.1)	0.008

[a] Relative risk based on hazard ratio
[b] Reference category

disease (two patients), and the altered treatment approach (one patient), all four patients with neurofibromatosis were segregated for the purpose of survival analysis.

Univariate analysis

By univariate Cox analysis, fibrillary histology (RR=2.7, *P*=0.041), intraoperative evidence of brainstem involvement (RR=4.3, *P*=0.002), surgeon's report of residual tumor (RR=7.3, *P*<0.001), residual tumor on postoperative imaging (RR=10.1, *P*=0.032), volume in cubic centimeters of residual tumor (RR=1.5, *P*<0.001), percentage of tumor resected (RR=0.9, *P*=0.002), and radiation therapy (RR=3.3, *P*=0.008) were significant prognostic factors influencing tumor recurrence (Table 2). The influence of each significant categorical variable, except radiation therapy, is shown with Kaplan-Meier curves [33] (Fig. 5).

Among 15 patients with residual tumor on postoperative scans, the time to complete disease involution was also considered by using the Cox model. Tumors of larger residual volume demonstrated a smaller probability of involuting, although this trend was not statistically significant (RR=0.7, *P*=0.407).

Multivariate analysis

Using multivariate Cox analysis, a manual stepwise regression analysis of the statistically significant variables was undertaken. For each pair of variables analyzed, patients with missing values were excluded. First, the four measures of the extent of surgical resection were considered. Visualization of any residual tumor on postoperative imaging (RR=6.1, *P*=0.128) was not significantly better than the surgeon's report of residual tumor (RR=2.6, *P*=0.314) at predicting the hazard of disease progression. However, the volume of residual tumor proved to be the best predictor of the hazard of disease progression. When compared in turn to the surgeon's report of residual tumor (RR= 1.4, *P*=0.782) or residual tumor on postoperative imaging (RR=3.3, *P*=0.345), only the volume of residual tumor retained statistical significance (RR=1.4, *P*=0.015 and RR=1.4, *P*=0.012, respectively). The volume of residual tumor was nearly statistically significant (RR=1.7, *P*=0.059) even when compared to the percent of tumor resected, which added no predictive information (RR=1.0, *P*=0.681).

The volume of residual tumor was then analyzed simultaneously with each remaining variable to identify other predictors of disease progression. Volume retained statistical significance in all cases. Brainstem involvement had a nonsignificant endangering effect (RR=3.0, *P*=0.295). Postoperative radiation therapy had a nonsignificant protective effect (RR=0.6, *P*=0.647), indicating that the increased risk of recurrence associated with postoperative radiation therapy is a spurious effect of the predominant use of radiation therapy in patients with incompletely resected tumor who are at a higher risk of recurrence. The presence of fibrillary histology was the only variable found to contribute significantly toward disease progression (RR=18.0, *P*=0.011). Neither brainstem infiltration nor postoperative radiation therapy achieved statistical significance when analyzed together with both the volume of residual tumor and fibrillary histology.

Thus, only the presence of fibrillary histology contributes significantly to the volume of residual tumor in explaining the hazard of disease progression. Pilocytic tumors of small postoperative volume have the best prognosis. The increasing risk of disease progression with larger volumes of residual tumor is illustrated in Fig. 6.

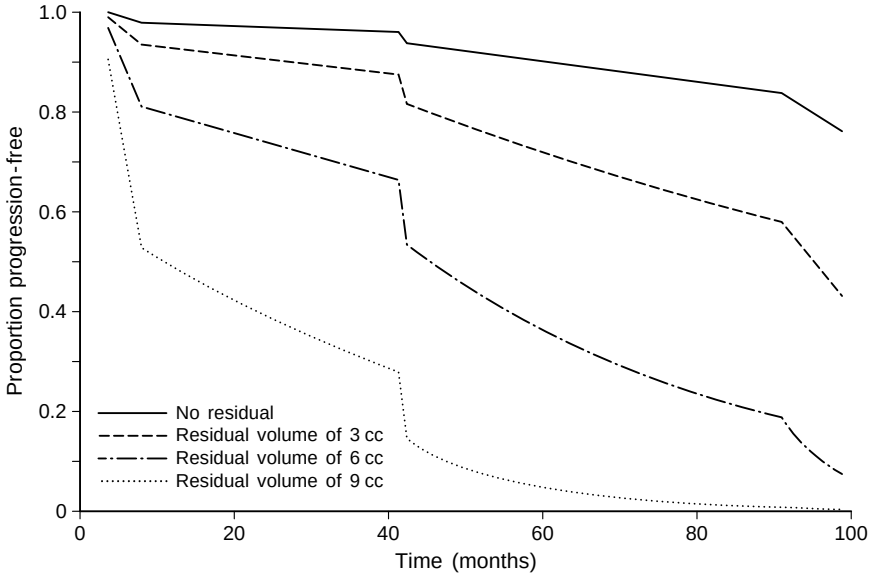


Fig. 6 Graph showing the theoretical progression-free survival probability in patients without neurofibromatosis and with residual tumor of various volumes based on univariate Cox regression analysis of 48 children with cerebellar astrocytomas

Discussion

Since Cushing's original report describing pediatric cerebellar astrocytomas in 1931 [13], the benefits of complete resection have repeatedly been emphasized [1, 2, 6, 14, 19, 24, 28, 51, 54, 56, 59]. However, these tumors may behave in an unpredictable fashion. Cerebellar astrocytomas may recur following complete surgical excision [3, 5, 14, 24, 28, 37, 44, 48, 55]. Some of these cases reported in the earlier literature may have been incomplete resections that were misinterpreted as complete by the surgeon [51]. The poor agreement between the surgeon's operative estimate of residual disease and the presence or absence of residual disease on postoperative imaging has been documented previously [51] and is substantiated by this study. Furthermore, these tumors may not follow simple exponential growth patterns after surgery, often recurring beyond the time period predicted by Collins' law [3, 10]. In the present series, 25% of recurrences indeed violated Collins' law, a figure compatible with percentages in other series [3]. Nonetheless, most recurrences occurred within 54 months in this study and similarly short periods in the literature [28]. On occasion, cerebellar astrocytomas that are incompletely resected remain dormant indefinitely. Long periods of progression-free survival in the presence of static residual tumor have been documented elsewhere [3, 6, 12–14, 20, 21, 48, 51, 58] in addition to the present study. Moreover, cases of apparent complete spontaneous involution of documented residual tumor have also been reported in the literature [14, 51] and in the present study.

Extent of resection

Some of the unpredictability, at least in the behavior of incompletely resected tumors, may be linked to the volume of residual tumor. Tumors with a smaller postoperative volume had a significantly reduced risk of progression. There was also a trend for these smaller residual lesions to regress completely, although this was not statistically significant. These findings may be related to the relative rates of cell loss and cell division, perhaps reflecting a change in the ability of the tumor to maintain an adequate level of autocrine growth factors [25, 51]. Thus, maximizing the extent of resection, even if a complete tumor resection is not possible, is of critical importance in optimizing the patient's chance for a prolonged progression-free survival.

Brainstem involvement

The most common reason for an incomplete resection in this study, as in others [51, 59], was brainstem involvement. Many studies have documented the adverse prognostic effect of brainstem invasion [3, 22, 31, 45, 51, 54, 58, 59]. However, as suggested by Schneider et al. [51] and the present study, there may be no significant adverse risk with tumors that infiltrate the brainstem aside from that explained by the volume of residual tumor.

Tumor location and morphology

Although some authors have found a poorer prognosis for patients with midline tumors, beyond that explained by brainstem involvement [31, 59], this study and others [6, l4, l7] have found no such correlation. Similarly, this study does not verify an affinity of predominantly cystic tumors for the hemispheres, as opposed to solid tumors in the midline, as described by some authors [1, 34, 36]. This study also was unable to verify the conclusion of some investigators that patients with cystic tumors have a better prognosis than those with predominantly solid lesions [23, 29, 38, 42, 54]. None of the radiographic morphologies identified in the present series showed significant power in explaining the risk of disease progression. Others also have failed to find prognostic value between solid and cystic tumors [3, 14, 41].

Patient age and sex

Sex is generally regarded as a prognostically insignificant factor [14, 27, 31], as it was in the present study. The influence of age, however, is more controversial. Some series report earlier recurrences in children of younger age groups, i.e., younger than 5 years old [14, 31], but no difference in overall survival [2, 14]. In the present series, there was no effect of increasing age on the risk of disease progression.

Neurofibromatosis

Although cerebellar astrocytomas associated with neurofibromatosis have occasionally been associated with a malignant phenotype [32], none of the four patients in this study demonstrated malignant features and none showed disease progression. Moreover, benign brainstem gliomas found in patients who have neurofibromatosis may have an unusually favorable prognosis [43].

Histology

The influence of tumor histology in determining outcome also has been debated. Some studies have reported a protective effect associated with the presence of oligodendroglial foci [40, 61], whereas others have not verified this finding [29]. In this study, the diagnosis of mixed oligoastrocytoma had no prognostic significance. Fibrillary histology has been associated with a poorer prognosis in most series [12, 14, 22, 26, 40, 41, 54], although some researchers have been unable to confirm this finding [2, 37, 45, 51, 58]. The present study shows that fibrillary tumors have a significantly increased risk of progression that complements the predictive power of the volume of residual tumor. In this series of patients, recurrent tumors that underwent repeat resection all had a histology that was unchanged from the original diagnosis, a finding mirrored in many studies [2, 3, 14, 51]. Cases of malignant transformation reported in the literature are extremely rare [5, 7, 35, 48, 53, 57]. In nearly every reported case of malignant transformation, the original tumor was treated with radiation therapy [3, 18, 30, 44, 52, 59].

Radiation therapy

The role of adjuvant radiation therapy is still unclear as it is documented in the literature. Certainly, most authors agree that radiation therapy is not indicated in cases of documented total resection [1, 2, 14, 26, 59]. Some authors report that radiation therapy is beneficial in the presence of residual disease [2, 24, 39]. However, other authors have been unable to document a protective effect of radiation therapy [3, l8, 20, 28, 54]. This study also showed that radiation therapy did not significantly influence progression-free survival when controlling for the volume of residual tumor and the presence of fibrillary histology. Thus, there currently is no role for postoperative radiation therapy in the treatment of a benign cerebellar astrocytoma.

Treatment of recurrences

Recurrences, as in the primary tumor setting, are best treated surgically. A complete tumor resection is sometimes possible [2, 37, 51, 55], as it was in 3 of 11 reoperations in the present series. Routine surveillance scans with contrast enhancement should be performed every 4 months for the first 2–3 years, every 6 months for the next 2 years, and then yearly until a period of 8–10 years after the initial diagnosis is reached [4].

Conclusions

For benign pediatric cerebellar astrocytomas, the risk of postoperative disease progression increases significantly in the presence of larger postoperative tumor volumes and fibrillary histology. Aggressive surgical resection, by minimizing the volume of postoperative disease, can maximize the long-term survival of children with these benign yet sometimes unpredictable tumors.

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