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Spinal cord astrocytomas: long-term results comparing treatments in children

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Abstract Technology enabling radical resection has expanded treatment options for children with spinal cord astrocytomas. Comparison of long-term survival and neurological function after complete tumor removal with more conservative treatment may determine whether radical surgery can improve outcome in well-differentiated and anaplastic spinal cord astrocytomas. In all, 18 children with spinal cord astrocytomas were initially treated between 1976 and 1992 with biopsy in 6, subtotal removal in 7, and complete resection in 5. Seven had anaplastic tumors. Nine children treated before 1988 received radiotherapy. Survival after a median follow-up of 11 years was 82% (9/11). Five patients with anaplastic tumors are alive between 12 and 18 years after treatment. No patient relapsed after total resection, whereas more than two-thirds treated with other than complete resection relapsed within 3 years (P=0.029). All but 1 patient with symptomatic relapse received radiotherapy (P=0.059). Magnetic resonance imaging more than 3 years postoperatively showed no recurrences in 13 of the 15 survivors and asymptomatic progression in the other 2. Although excellent long-term survival was seen, frequent relapse was associated with either incomplete resection or radiotherapy. Prolonged relapse-free survival was observed in all patients treated with complete resection, including 3 with anaplastic tumors.

Key words Astrocytoma · Glioblastoma · Spinal cord tumor · Treatment

Introduction

The options available for managing intramedullary spinal cord astrocytomas have expanded dramatically over the last 2 decades. The operating microscope [18], ultrasonic aspirator [8], plated bayonet [13], laser [22] and equipment for intraoperative ultrasonography [14, 32] have made extensive tumor removal possible. Magnetic resonance imaging (MRI) has improved preoperative evaluation, determination of resection extent, and diagnosis of asymptomatic disease progression [19]. Complete surgical resection has been recommended as the best treatment based on the excellent short-term results achieved by some workers [2, 6, 9–12, 15, 16, 21]. However, others have suggested that radiotherapy offers similar results without the risk of neurological worsening that may occur after complete resection [24–26, 28, 30, 34].

Excellent long-term survival in children with well-differentiated tumors precludes analysis of outcome in studies with short follow-up, whereas rapid disease progression in children with anaplastic tumors suggests inadequacy of available treatments. Moreover, postoperative neuro-imaging is essential to detect asymptomatic disease progression, when relapse can occur after a long interval. Finally, the rarity of these tumors necessitates collection

of smaller series to demonstrate treatment advantages. Therefore, we report the long-term treatment and postoperative neuro-imaging results in a consecutive series of children with a median follow-up of 11 years in the context of related literature to determine the efficacy of complete resection and radiotherapy in the management of children with well-differentiated and anaplastic spinal cord astrocytomas.

Patients and methods

Patients

Eighteen children with spinal cord astrocytomas were diagnosed and treated at Children's Hospital of Pittsburgh between 1976 and 1992, representing 86% (18/21) of all intramedullary spinal cord tumors evaluated; 5 children treated since 1992 were not included in this series because of short follow-up. The hospital and office records of the patients were reviewed. All patients or parents were interviewed by telephone to determine the current clinical status. Functional condition was graded by the classification proposed by McCormick et al. [28] (Table 1). Original histopathology and most recent postoperative MRI studies were examined in a blinded fashion.

There were 11 boys and 7 girls, whose ages ranged from 0.6 years to 17.9 years. The mean age at presentation was 9.2 years with a median age of 8.6 years. Three patients died 3 months, 6 months, and 15 years after diagnosis. Follow-up for the remaining 15 patients ranged from 3 to 18 years, with a mean and median follow-up of 11 years.

Clinical presentation

The duration of signs and symptoms ranged from 1 week to 6 years, with a mean of 50 weeks and median of 10.5 weeks. There were 9 children with grade I and 7 with grade II functional status. Initial symptoms included weakness in 15 cases, pain in 13 and scoliosis in 6; 1 patient presented with paraplegia, 3 with quadriparesis, 3 with hemiparesis, 3 with paraparesis, and 5 with monoparesis. Sensory examination was abnormal in 6, with only 1 child having a distinct sensory level. Sphincteric disturbance was only seen in 4.

Imaging studies

Although originally evaluated with myelography and subsequently with postmyelographic computed tomography (CT), patients have been evaluated with MRI since 1986. Sagittal and axial images are performed and followed by enhanced studies with gadolinium. Multiple echo sequences are used to differentiate cystic and solid components. In 12 cases the tumors were located in the cervicothoracic region. Lower thoracic or conus tumors were found in 5 children, and 1 had a holocord astrocytoma.

Table 1 Functional grading scale (proposed in [28])

Grade	Selected functional status
I	Normal or focal deficit/normal gait
II	Mild deficit/impaired independent gait
III	Moderate deficit/assisted gait
IV	Severe deficit/nonambulatory

Surgical treatment

Initial surgery included biopsy in 6, subtotal resection in 7, and total resection in 5. Concurrent procedures with biopsy included drainage of tumor cysts in 4 and fusion for scoliosis in 1. No patient underwent a biopsy alone after 1986. Eight procedures in 4 patients were subsequently performed for recurrent neurological symptoms related to tumor relapse, including placement of a cystoperitoneal shunt 2 years after biopsy, re-exploration with subtotal resection 4 months after and cystoperitoneal shunting with revision 2 and 3 years after biopsy, ventriculoperitoneal shunting 5 days and re-exploration with subtotal resection 9 days after subtotal removal, and re-exploration with subtotal removal 3 years after and total resection with fusion for progressive scoliosis 6 years after initial subtotal removal. Total resection was confirmed by MRI in 5 of 6 patients eventually undergoing total removal; the 6th patient has not had a postoperative MRI.

Intraoperative somatosensory evoked potential monitoring was routinely used. In the last 7 years, an osteoplastic laminotomy has been performed to help prevent postoperative kyphoscoliosis [1, 33]. Intraoperative ultrasound was utilized only occasionally. The intraoperative microscope was used for tumor removal, and the ultrasonic aspirator was used in 9 of 10 cases operated upon after 1983.

Six surgical complications were operatively treated in 4 patients, including pseudomeningocele repair 2 years after and fusion for progressive kyphosis 4 years after biopsy, pseudomeningocele repair 2 months after and tether release 15 years after subtotal removal, perioperative repair of a cerebrospinal fluid leak after a second subtotal resection, and perioperative re-exploration for deterioration secondary to gelfoam swelling after subtotal removal.

Adjuvant therapy

Prior to 1988 9 children received radiation therapy with total doses ranging from 31 to 50 Gy. Irradiation was given to 3 patients in each group undergoing either total removal, subtotal removal or biopsy. Of 7 children with malignant tumors, 5 received radiotherapy. No patients received chemotherapy.

Statistical analysis

Survival and relapse-free intervals were analyzed using the product-limit estimate of the survivorship function as described by Kaplan-Meier. Differences between curves were examined with the Wald Chi-square and likelihood ratio tests using the LIFETEST procedure (SAS Institute, Cary, N. C.). The Fischer exact test was used to compare the occurrence of death, relapse, operative complication and neurological worsening among various factors, including age at diagnosis in the 1st or 2nd decade, diagnosis before or after 1983 (availability of the ultrasonic aspirator), preoperative neurological condition, extent of resection, use of radiotherapy, or degree of anaplasia. An α=0.05 level of significance was used.

Results

Histopathological evaluation revealed well-differentiated astrocytomas in 11, anaplastic astrocytomas in 5, and glioblastoma multiforme in 2 children (Figs. 1, 2). Astrocytic neoplasms were graded on the three-tiered system employed by the World Health Organization [23], which is similar to the classification scheme of Ringertz [35]. The survival distribution for all children is summarized in Fig. 3. The 5-year survival was 88% (14/16), 10-year sur-

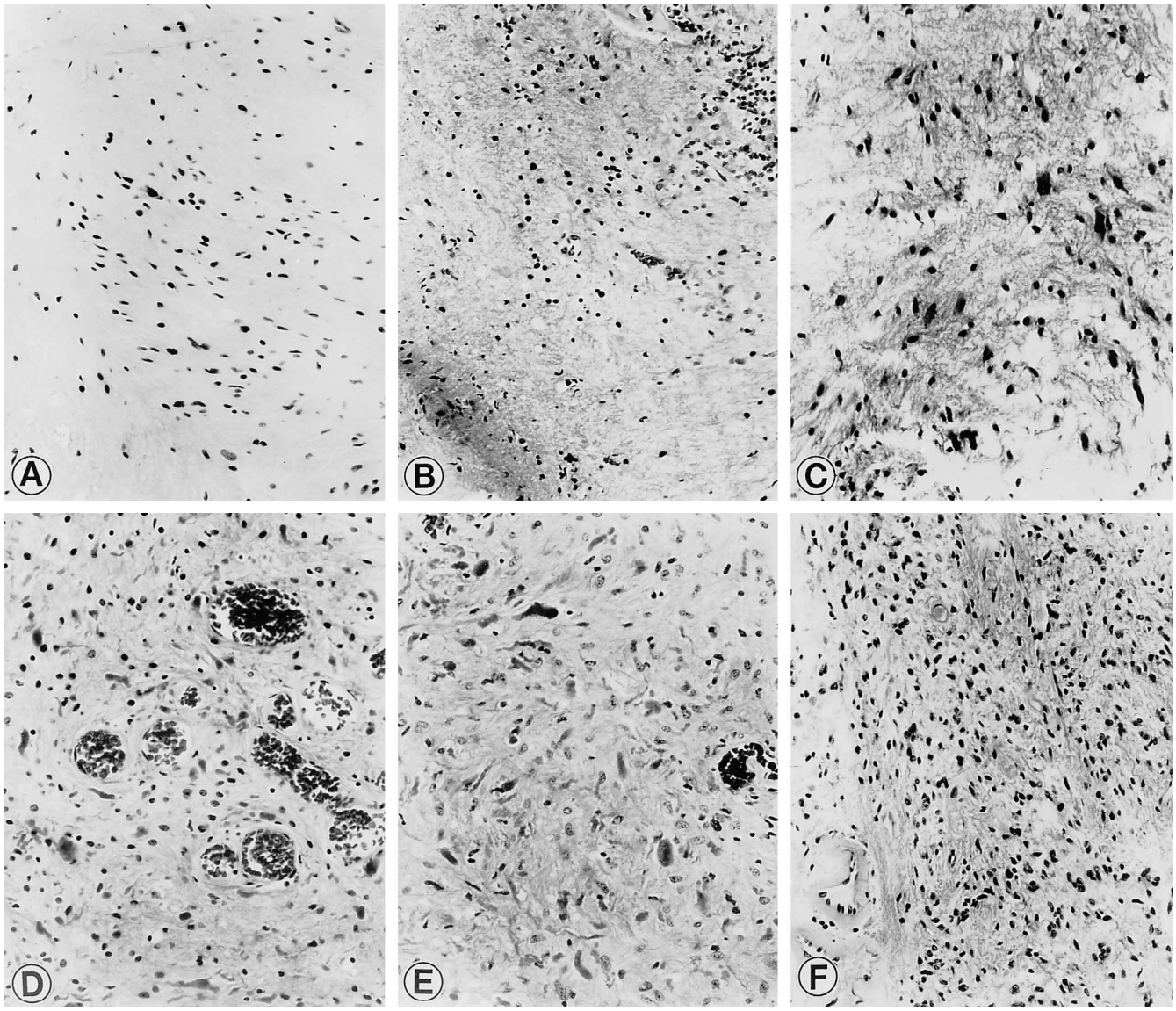

Fig. 1 **A** Case 5: well-differentiated astrocytoma, composed of dispersed and haphazardly arranged hyperchromatic and pleomorphic astrocytes. (H&E, ×200). **B** Case 3: astrocytoma, characterized by scattered clusters of atypical astrocytes within a dense fibrillary background of glial processes. (H&E, ×200). **C** Case 2: astrocytoma, containing occasional pleomorphic cells in a loose fibrillary intercellular matrix. (H&E, ×200). **D** Case 4: astrocytoma, composed of moderate cellularity with numerous dilated vascular channels with inconspicuous endothelial cells. (H&E, ×200). **E** Case 7: astrocytoma, containing excessive number of Rosenthal fibers within a dense astrocytic background. (H&E, ×200). **F** Case 13: anaplastic astrocytoma, characterized by hypercellularity and occasional blood vessels with thick, hyaline walls. (H&E, ×200)

vival, 83% (10/12), and 15-year survival, 63% (5/8). The clinical presentation and outcome are summarized in Table 2.

There were 9 children who improved and 7 who were unchanged immediately after their operations. Both patients who worsened had total tumor removal; 1 was paraplegic and the other, paraparetic. There was a trend toward neurological deterioration after complete resection (P=0.069). Other operative complications occurred in 4 children: 3 patients who had received postoperative radiotherapy required reoperation for repair of pseudomeningoceles or a cerebrospinal fistula, and each of these additionally required fusion for progressive kyphoscoliosis; 1 patient with subtotal resection developed delayed paraparesis secondary to gelfoam swelling beneath the osteoplastic laminotomy, but the weakness resolved after re-exploration and gelfoam removal. No differences in the occurrence of operative complications were detected in comparisons of age, year of diagnosis, preoperative neurological condition, extent of resection, or degree of anaplasia.

The relapse-free interval was defined as the time between initial treatment and either clinical progression, ra-

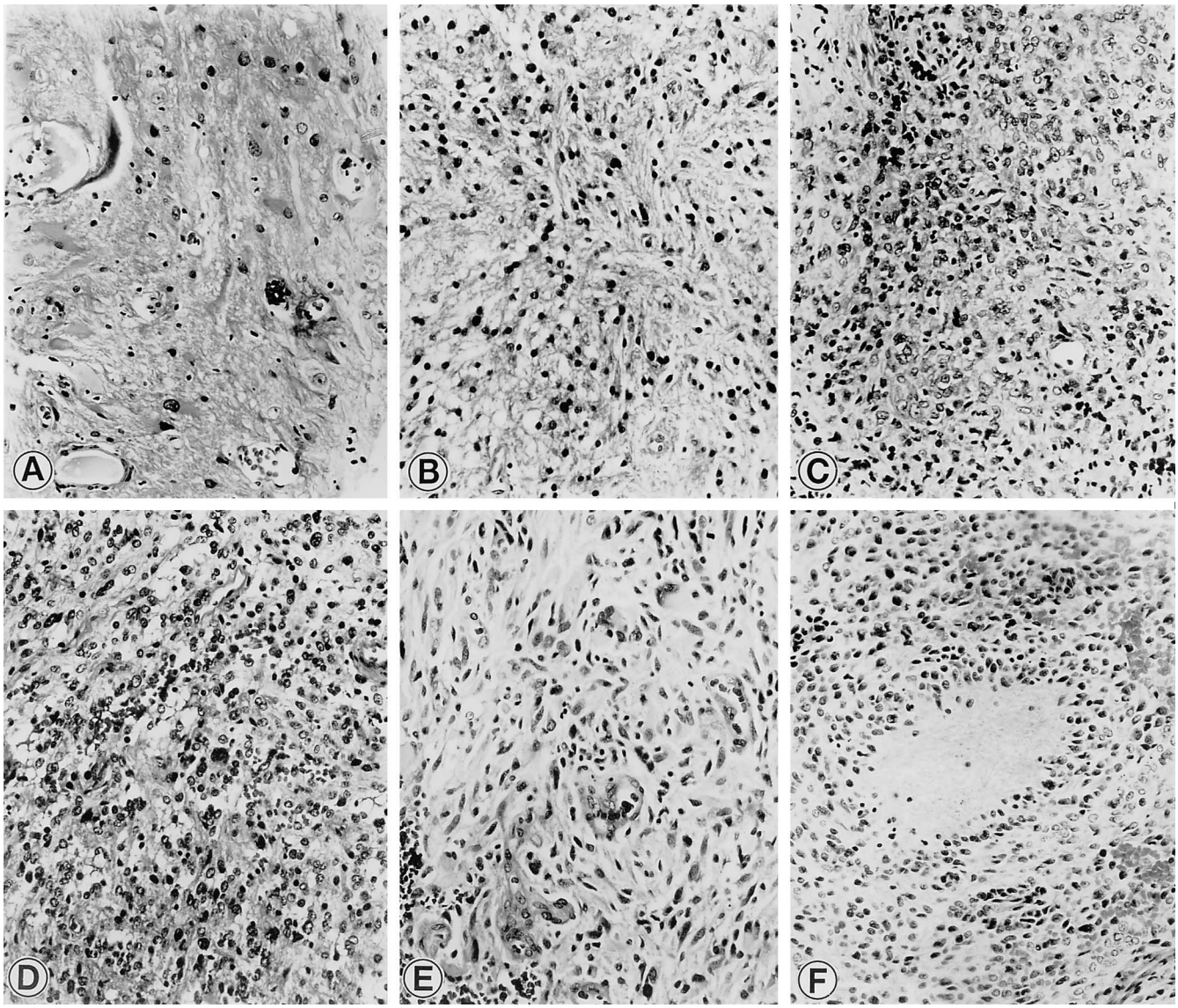

Fig. 2 **A** Case 14: anaplastic astrocytoma composed of bizarre astrocytes, some with abundant glassy cytoplasm and modest vascularity. (H&E, ×200). **B** Case 6: astrocytoma showing streaming of elongated hyperchromatic astrocytes and inconspicuous endothelial hyperplasia. (H&E, ×200). **C** Case 16: anaplastic astrocytoma, composed of closely packed atypical astrocytes with dense chromatin, few prominent nucleoli and scant cytoplasm. (H&E, ×200). **D** Case 15: anaplastic astrocytoma, formed of bizarre hyperchromatic and pleomorphic cells in a compact arrangement with dispersed microcavitation. (H&E, ×200). **E** Case 18: glioblastoma multiforme, exhibiting prominent cellular atypism with some astrocytes showing multiplicity of nuclei and prominent vascular-endothelial hyperplasia. (H&E, ×200). **F** Case 17: glioblastoma multiforme, characterized by high cell density, foci of necrosis and brisk nuclear atypism. (H&E, ×200)

diographic progression or death. No patient treated with complete resection had a relapse during follow-up ranging from 5 to 14 years (P=0.029), whereas 9 of 13 treated with less than total removal had a relapse (Fig. 4). Recurrent symptoms were treated with re-exploration. Eight of nine relapses occurred within 3 years of the initial treatment. All children with symptomatic relapses had received radiotherapy (P=0.059), except for 1 who died 3 months after subtotal removal of a glioblastoma (Fig. 5). Death from disease progression with subarachnoid metastases also occurred 6 months after subtotal resection with radiotherapy of an anaplastic tumor in another. A third patient with a single relapse after 2 years died of a methicillin-resistant *Staphylococcal* empyema 15 years after initial biopsy with radiotherapy for a well-differentiated tumor; the autopsy did not include spinal cord examination. One patient with two episodes of relapse after subtotal resection with radio-

Table 2 Summary of children with spinal cord astrocytomas treated at Children's Hospital of Pittsburgh between 1976 and 1992 (*XRT* radiotherapy, *F/U* time since diagnosis, *A* astrocytoma, *ANA* anaplastic astrocytoma, *GBM* glioblastoma multiforme)

Case	Age[a]	Sex	Topography	Type[b]	Preoperative grade[c]	Surgery	Postoperative change	XRT	Postoperative MRI	Current	F/U
1	8.3	M	T5-T7	A	II	Biopsy[d]	Improved	45 Gy	None	I	18 years
2	1.8	F	C1-T2	A	I	Biopsy[d]	Improved	43 Gy	No enhancement	I	17 years
3	14.9	M	T6-T12	A	I	Biopsy[d]	Unchanged	50 Gy	None	Death	15 years
4	11.1	F	Holocord	A	I	Total	Worse	None	No enhancement	III	12 years
5	15.3	M	C4-T4	A	II	Biopsy[d]	Improved	None	Unenhanced cyst	I	10 years
6	17.5	F	T2-T4	A	I	Biopsy[e]	Unchanged	50 Gy	Stable nodule	IV	9 years
7	13.4	M	T6-Conus	A	II	Total	Unchanged	None	No enhancement	I	8 years
8	7.5	M	C5-T3	A	II	Total	Worse	None	No enhancement	IV	5 years
9	1.6	M	T2-T10	A	I	Subtotal	Improved	None	Stable nodule	I	5 years
10	8.8	M	C4-C7	A	II	Subtotal	Improved	None	Enlarging nodule	I	4 years
11	8.5	M	T10-T11	A	I	Subtotal	Unchanged	None	Enlarging nodule	I	3 years
12	11.4	F	T11-L2	ANA	II	Subtotal	Improved	50Gy	No enhancement	I	18 years
13	5.3	M	C3-T1	ANA	I	Subtotal[f]	Improved	50 Gy	No enhancement	I	17 years
14	14.2	F	Conus	ANA	I	Biopsy[d]	Improved	None	Unenhanced cyst	I	17 years
15	7.3	F	C1-C4	ANA	I	Total	Unchanged	45 Gy	No enhancement	I	14 years
16	0.6	F	C2-C6	ANA	II	Subtotal	Unchanged	31 Gy	None	Death	6 months
17	0.7	M	C5-L1	GBM	III	Total	Improved	40 Gy	None	III	12 years
18	17.9	M	T9-L1	GBM	IV	Subtotal	Unchanged	None	None	Death	3 months

[a] Years (at diagnosis)
[b] Histopathological grade
[c] Functional grade of McCormick et al. [28]
[d] Underwent cyst drainage with biopsy
[e] Underwent subtotal removal 4 months later
[f] Underwent subtotal removal 3 years later, then total removal after 3 more years

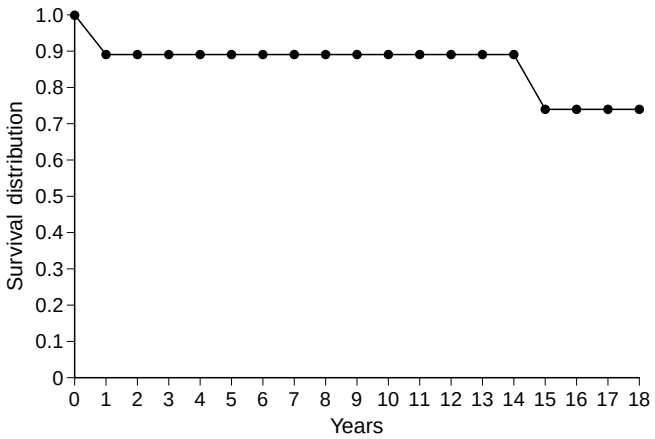

Fig. 3 Product-limit estimate of survival in our 18 patients

therapy has been relapse-free for 11 years after total removal was achieved at the third re-exploration. No differences in occurrence of relapse were detected in comparisons of age, year of diagnosis, preoperative neurological condition, or degree of anaplasia.

Of the 15 survivors, 11 ambulate independently (grade I). Two patients treated with total removal of extensive tumors ambulate with severe limitations (grade III). Two patients are paraplegic after total removal of a cervicothoracic astrocytoma and an intraspinal neurofibroma, respectively (grade IV). Only 1 patient developed new postoperative scoliosis. Although there was a trend toward better neurological outcome among children diagnosed in their first decade (P=0.12), no differences were detected among the various factors examined.

Postoperative MRI was performed in 13 of the 15 survivors; all studies reviewed were obtained at least 3 years postoperatively. Five of six patients with total tumor removal (one initially had subtotal removal) had postopera-

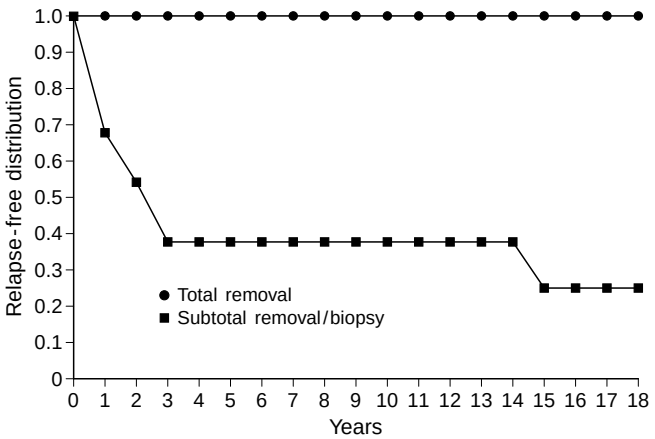

Fig. 4 Comparison of product-limit estimate of relapse-free interval between total and less than total removal

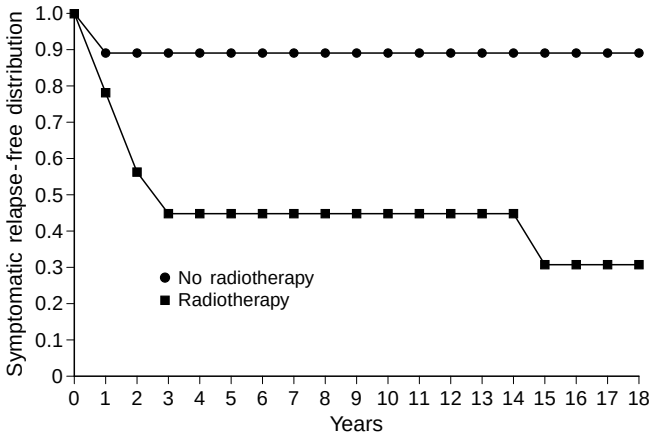

Fig. 5 Comparison of product-limit estimate of relapse-free interval between radiotherapy (*XRT*) and no radiotherapy

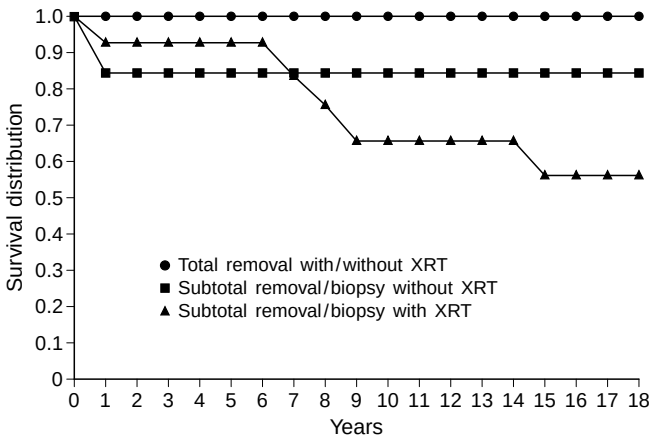

Fig. 6 Comparison of product-limit estimates of survival in 37 patients (from [6], [36], and this series) treated with total removal or less than total removal, with or without radiotherapy

tive MRI; none showed evidence of recurrent tumor between 4 and 10 years postoperatively. The other has a stable paraparesis 12 years after resection with radiotherapy of a glioblastoma multiforme. Of 9 patients treated with less than complete removal, 6 showed no progression of disease on postoperative MRI obtained 4–16 years postoperatively; 3 had received radiotherapy. Of the remaining 3 children, 2 have slight enlargement of residual tumor without neurological symptoms, whereas 1 without an MRI has a stable monoparesis 18 years after biopsy and radiotherapy of a well-differentiated tumor.

Five children with anaplastic tumors are alive. All but one have minimal neurological signs; the other ambulates with severe limitations. Three were treated with complete tumor removal and radiotherapy; one of these had relapsed twice after subtotal resection with radiotherapy before having a total resection. One of two with incomplete tumor removal received radiotherapy. The other has been relapse-free with a nonenhancing cyst on postoperative MRI. This group was too small to determine the efficacy of adjuvant radiotherapy.

Discussion

Intramedullary spinal cord astrocytomas are uncommon childhood tumors. Most of the 5–10% of pediatric central nervous system tumors occurring in the spinal cord are low-grade astrocytomas [7, 9, 31]. The rarity of this disease with frequent long-term survival creates difficulty in analyzing various treatment methods. Comparison of this report with previous studies of well-differentiated and anaplastic spinal cord astrocytomas will justify the conclusions regarding the treatment of this disease.

We observed excellent long-term survival and confirmed tumor control by MRI in children managed with surgery and/or radiotherapy. Although radical resection was associated with some neurological worsening, relapse was common after incomplete resection and radiotherapy. Moreover, all wound complications occurred in patients receiving radiotherapy. Five patients with anaplastic tumors are alive more than 12 years after initial treatment. Three were relapse-free after complete removal with radiotherapy, 1 after incomplete removal without radiotherapy, and 1 with radiotherapy. Despite the trend toward better neurological outcome with younger age, differences related to age, year of treatment, preoperative neurological condition, or degree of anaplasia were not observed. Although conclusions are limited by the small number of patients treated and the retrospective review of management, we achieved long-term follow-up with postoperative MRI, comparisons among treatments, and independent verification of histopathology.

Several surgeons recommend complete resection, reserving radiotherapy for children with progressive disease in whom complete resection cannot be safely achieved [6, 9–12, 16, 27]. Epstein's group [10–12, 16] have demonstrated that radical resection of tumors could be achieved without neurological deterioration in most patients. A 90% survival at 5 years was observed, with a mean follow-up of less than 7 years after complete tumor removal. Since most had failed less aggressive treatment elsewhere, complete resection was advocated. Although this comparatively favorable outcome does not account for those patients without relapse after incomplete resection that would not be referred, others have observed frequent relapse within the first 2 years in children treated with incomplete resection [21, 27]. Despite advocating surgical removal, DeSousa et al. [6] reported that five of seven children survived 6–30 years after biopsy. None of these studies included postoperative MRI results.

Other investigators have recognized a long postoperative course despite persistent disease and caution against advocating radical resection in all cases [28, 36, 38]. Woo et al. [38] reported 62% survival with residual disease at 10 years in children with central nervous system astrocytomas, but did not detail the histopathology or treatment given for spinal tumors. Similarly, Rossitch et al. [36] reported symptom-free survival in two thirds despite incomplete resection after a mean nine year follow-up. Since relapse occurred in 1 patient 35 years after "gross total resection," the extent of asymptomatic progression cannot be determined without postoperative neuro-imaging.

Radiotherapy has been recommended both as a supplement to radical removal [34] and as a primary treatment [28, 30, 37]. Reimer and Onofrio [34] reported 100% 8-year survival with subtotal resection, compared with 43% 8-year survival with biopsy. Although the addition of radiation was recommended, only 1 patient did not receive radiotherapy, precluding comparison among treatments. In another study, Schwade et al. [37] had two of four children die 2 and 11 years after incomplete removal or biopsy despite radiotherapy. Recently, O'Sullivan et al. [30] concluded that radiation without resection is effective and can achieve long-term control. Although reported 10-year survival and relapse-free survival were 83% and 71% respectively, no comparison was made with survival in patients who underwent resection alone. Moreover, 4 of the 31 patients developed a secondary malignancy, and 2 others with well-differentiated tumors relapsed at 6 and 14 years with anaplastic astrocytomas within the irradiated volume. Similarly, Minehan et al. [29] concluded that survival was longest among patients with nonpilocytic tumors treated with biopsy and radiotherapy, whereas survival was poorer among patients with pilocytic tumors treated with more aggressive tumor removal.

Individual survival periods were reported in 19 patients in two series [6, 36]. These were combined with our survival observations in 18 patients to improve the power of detecting significant differences among treatments (Fig. 6). Although the LIFETEST procedure did not demonstrate a difference between extent of resection or use of radiotherapy, because of the large number of survivors in each group, 100% survival was only seen in patients treated with complete removal. Moreover, the risk of death in those treated with radiotherapy was 1.5 times that in those only treated surgically.

Since long-term survival in patients with anaplastic spinal cord astrocytomas is unusual, most published results combine outcome in children and adults. Six-month survival was only 50% in two studies [2, 12]; none of these patients survived beyond 2 years [4, 5, 12, 15, 16, 26, 34]. Among 19 patients with poorly-differentiated astrocytomas reported by Cohen et al. [2], the longest survival was 28 months, with 2 alive 17 months after treatment. However, in two studies reported survival for up to 3 years was observed after treatment for spinal cord glioblastoma multiforme [20, 24]. Moreover, O'Sullivan et al. [30] had 2 children alive 10 and 16 years after diagnosis; the extent of resection was not specified although both received radiotherapy. Leptomeningeal dissemination was frequently seen [3, 4, 17, 21].

Current studies are limited by combining patients having tumors with biologically different behavior based on patient age or tumor type, follow-up of less than a decade, lack of comparisons among treatment groups, inclusion of patients treated elsewhere with other regimens, lack of histopathological verification, and lack of postoperative MRI follow-up. Although radical resection was occasionally complicated by neurologic sequelae, 100% survival free of relapse was only achieved with complete tumor removal. Radiotherapy was associated with frequent relapse and wound complications within 3 years. In this series, we also demonstrated long-term relapse-free survival in children with anaplastic spinal cord astrocytomas, most of whom underwent complete resection with radiotherapy. We recommend removal of as much tumor as is safely feasible. Radiotherapy with incomplete resection for well-differentiated tumors achieves long-term survival at the expense of frequent relapse, wound complications, malignant transformation and secondary malignancy. Complete removal of anaplastic tumors can result in relapse-free survival similar to that of patients treated with well-differentiated tumors; the additional benefit of radiotherapy is unknown.

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