Long-term disease and neurological outcomes in patients with pediatric intramedullary spinal cord tumors

Clinical article

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Object. Radical resection is recommended as the first-line treatment for pediatric intramedullary spinal cord tumors (IMSCTs), but it is associated with morbidity, including risk of neurological decline and development of postoperative spinal deformity. The authors report long-term data on clinical and treatment determinants affecting disease survival and neurological outcomes.

Methods. Case records for pediatric patients (< 21 years of age at presentation) who underwent surgery for IMSCTs at the authors' institution between January 1975 and January 2010 were analyzed. The patients' demographic and clinical characteristics (including baseline neurological condition), the treatment they received, and their disease course were reviewed. Long-term disease survival and functional outcome measures were analyzed.

Results. A total of 55 patients (30 male and 25 female) were identified. The mean duration of follow-up ($\pm$ SEM) was 11.4 ± 1.3 years (median 9.3 years, range 0.2–37.2 years). Astrocytomas were the most common tumor subtype (29 tumors [53%]). Gross-total resection (GTR) was achieved in 21 (38%) of the 55 patients. At the most recent follow-up, 30 patients (55%) showed neurological improvement, 17 (31%) showed neurological decline, and 8 (15%) remained neurologically stable. Patients presenting with McCormick Grade I were more likely to show functional improvement by final follow-up ($p = 0.01$) than patients who presented with Grades II–V. Kaplan-Meier actuarial tumor progression-free survival rates at 5, 10, and 20 years were 61%, 54%, and 44%, respectively; the overall survival rates were 85% at 5 years, 74% at 10 years, and 64% at 20 years. On multivariate analysis, GTR ($p = 0.04$) and tumor histological grade ($p = 0.02$) were predictive of long-term survival; GTR was also associated with improved 5-year progression-free survival ($p = 0.01$).

Conclusions. The prognosis for pediatric IMSCTs is favorable with sustained functional improvement expected in a significant proportion of patients on long-term follow-up. Long-term survival at 10 years (75%) and 20 years (64%) is associated with aggressive resection. Gross-total resection was also associated with improved 5-year progression-free survival (86%). Hence, the treatment benefits of GTR are sustained on extended follow-up. (<http://thejns.org/doi/abs/10.3171/2014.1.PEDS13316>)

KEY WORDS • intramedullary tumors • disease-free survival • spine • gross-total resection • functional improvement • oncology • spinal cord

THE primary treatment goal for pediatric intramedullary spinal cord tumors (IMSCTs) is to optimize tumor control through gross-total resection (GTR) when feasible, often with adjunct chemotherapy and radiation therapy. Advancements in surgical techniques and intraoperative neurological monitoring methods have enabled improvements in resection, neurological outcomes, and overall disease survival (OS).^{4,11,14,22,24,30,31,35,40,52} However, resection is associated with risks of neurological decline and development of secondary skeletal deformity.^{4,5,21,42} Additionally, within the pediatric popu-

lation, chemotherapy and radiation therapy may produce long-term adverse effects given the growth potential of the developing nervous system.^{27,36} Long-term disease outcomes are further influenced by factors such as tumor grade, tumor histology, and neurological disability at presentation.^{5,7,14,15,19,21,38,42,50} Hence, establishing the long-term natural history of primary disease and prognosis of clinical treatments is critical for guiding management choices and for determining whether treatment benefits are sustained in the long run.

In this article, the first of a 2-part series, we aim to identify clinical and treatment factors that assist in prediction of long-term disease and neurological outcomes. In contrast to previous reports, extended longitudinal follow-up of our study population enabled us to assess long-term disease outcomes beyond the 1st decade.^{4,18,23,30,31,38,51}

Abbreviations used in this paper: GTR = gross-total resection; HR = hazard ratio; IMSCt = intramedullary spinal cord tumor; OS = overall (disease) survival; PFS = progression-free survival; STR = subtotal resection.

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The second article of the series addresses the long-term incidence and risk factors for development of spinal deformity in the same patient population.¹

Methods

Patients with a histopathological diagnosis of intramedullary tumor in the pediatric age group (< 21 years at presentation) were identified through a retrospective search of the neurosurgery inpatient database at the University of Iowa Hospitals and Clinics for the time period from January 1975 to January 2010. Patient records were reviewed for: 1) patient demographic characteristics, 2) clinical presentation, 3) surgical treatment, 4) chemotherapy and/or radiation therapy received, and 5) final clinical outcomes (based on clinical and radiographic evaluation by the Neurosurgery, Pediatric Oncology, and Pediatric Orthopedic Services). The senior author (A.H.M.) was the primary surgeon for most of the patients.

Preoperative and postoperative functional assessment was performed using the modified McCormick functional scale,^{29,31} with grades defined as follows: Grade I, neurologically intact with normal gait with or without mild focal deficit; Grade II, independent ambulation and functioning in presence of sensorimotor deficit with mild to moderate gait difficulty; Grade III, independent with external aid with moderate neurological deficit; Grade IV, functional dependence with severe moderate to severe deficits; and Grade V, paraplegic or quadriplegic requiring wheelchair with upper-extremity impairment. Imaging characteristics of the tumor were determined through preoperative CT myelography (when applicable) and MRI. Baseline and follow-up radiographic assessment of skeletal deformity was undertaken in consultation with the Pediatric Orthopedic Service.

Operative Technique

An osteoplastic laminoplasty was planned in all children unless preoperative imaging studies indicated significant mass effect that necessitated extensive decompression, often with the aid of a fascial graft, or in instances when preoperative imaging studies indicated a high probability of incomplete resection given a lack of clearly defined tumor margins. Neurophysiological monitoring with somatosensory evoked potentials was used in the last 3 decades; motor evoked potentials were adjuncts used in the last decade.

Intraoperative ultrasonography was used to identify the tumor and any accompanying syrinx cavities. A midline myelotomy was performed, spanning the levels involved by tumor. Initial biopsies were obtained from the areas that showed the most enhancement on preoperative MR imaging. Tumor debulking was initiated at the caudal end of the tumor, usually within the syrinx cavity. This was aided by high-powered microscopy and microsurgical technique with suction, ultrasonic aspiration, and cottonoid patty wisps soaked with thrombin. Bipolar cautery was infrequently needed. Circumferential dissection was extended in all planes where a distinct tumor–spinal cord interface could be identified. The mean arterial pressure was monitored carefully and maintained above 70 mm

Hg (this is critical), with vasopressor support as needed. In our opinion, laminoplasty is advantageous in aiding future instrumentation if needed, improving wound healing, and preventing CSF leaks.

Surgical records were reviewed to determine surgical approach, degree of resection, and additional intraoperative surgical findings. Degree of resection was determined through intraoperative assessment of tumor removal and verified by means of MR images obtained 1–3 days after surgery. Tumor resection was classified as GTR if the surgeon's and radiographic assessment were in agreement. In all other cases, subtotal resection (STR) was determined to have occurred. If laminectomy was performed at C-7 or T-1, the cervicothoracic junction was considered to be involved. If it was performed at T-12 or L-1, the thoracolumbar junction was considered to be involved. The score for deficit on presentation was calculated based on the presence or absence of motor, sensory, bladder, or bowel deficits, with the presence of each deficit counting for 1 point, such that the scores could range from 0 (no deficits) to 4 (deficits in each category).

Patients were also followed up in consultation with the Pediatric Oncology and Radiation Oncology Services to determine whether adjunctive therapy should be administered. The University of Iowa Human Subjects Office Institutional Review Board approved this retrospective study.

Statistical Analysis

Descriptive data were presented as proportions and means with standard error of means (mean $\pm$ SEM). Univariate analysis for all outcomes analysis was performed using the Pearson chi-square test and logistic regression. Statistical significance for both uni- and multivariate analyses was set at $p < 0.05$. Progression-free survival (PFS) and OS (defined as disease survival) rates were estimated by Kaplan-Meier survival estimates and 95% confidence intervals. Multivariate analysis of survival was done by means of survival regression using the underlying Weibull distribution. Goodness of fit was assessed by means of survival graphs, log-survival plots, and Schoenfeld residual plots to assess proportionality. Variables with univariate p values < 0.1 were then entered into a survival regression model for multivariate analysis. The survival assumption was verified. Input variables that had p values < 0.05 after this analysis were reported as being statistically significant on multivariate analysis. All statistical analysis was performed using SAS software version 9.3.

Results

Clinical Demographics

A total of 55 patients (30 male and 25 female) were identified who were treated during the study period (January 1975 to January 2010) (Table 1). Forty-seven patients (85%) presented to our service for primary treatment, and 8 patients (15%) had a history of prior surgical treatment. Magnetic resonance imaging was available for imaging on initial presentation for 44 patients (80%); CT myelog-

TABLE 1: Clinical and demographic characteristics of the study population*

Characteristic	Value
age in yrs	
mean $\pm$ SEM	10 $\pm$ 1
range	0.5–21
sex	
male	30 (55)
female	25 (45)
clinical presentation	
time from symptom onset in mos	
mean $\pm$ SEM	7.4 $\pm$ 1.5
range	0.1–60
pain	29 (52)
motor deficit	33 (60)
sensory deficit	42 (76)
bladder deficit	21 (38)
bowel deficit	10 (18)
imaging findings†	
syrinx	16 (36)
contrast enhancement	40 (91)
margins	
diffuse	29 (66)
circumscribed	15 (34)
no. of vertebral levels involved	
mean $\pm$ SEM	4 $\pm$ 1
range	1–11
spinal level	
cervicomedullary	20 (36)
cervicothoracic‡	7 (13)
thoracic	15 (27)
thoracolumbar§	8 (15)
lumbar	5 (9)
histological diagnosis	
astrocytoma	29 (53)
Grade II	22 (40)
Grade III	6 (11)
Grade IV	1 (2)
ependymoma	12 (22)
Grade II	8 (15)
Grade III	4 (7)
ganglioglioma	7 (13)
hemangioblastoma	3 (5)
others (PNET)	4 (7)
histological grade	
low	43 (78)
high (III–IV)	12 (22)

(continued)

TABLE 1: Clinical and demographic characteristics of the study population* (continued)

Characteristic	Value
duration of FU in yrs	
mean $\pm$ SEM	11.4 $\pm$ 1.3
range	0.2–37.2

* Values represent numbers of cases (%) unless otherwise indicated. FU = follow-up; PNET = primitive neuroectodermal tumor.

† MRI studies were unavailable in 11 patients. Thus, the percentage values for this category were calculated using a denominator of 44.

‡ Cervicothoracic: if tumor located within the cervical or thoracic region extended to or involved the C7–T1 levels.

§ Thoracolumbar: if tumor located within the thoracic or lumbar region extended to or involved the T11–L1 levels.

raphy was used for diagnostic imaging in the remaining 11 patients (20%).

Sensory deficits were the most common presenting symptom (present in 42 cases [76%]). The cervicomedullary junction was the most common tumor site (being the site in 20 cases [36%]). Astrocytomas comprised the most common tumor histological subtype (29 tumors [53%]), followed by ependymomas (12 tumors [22%]). Overall, low-grade tumors predominated (43 tumors [78%]) within the study population. In 40 (91%) of the 44 cases in which MRI was used for initial imaging, the tumors showed contrast enhancement. The tumor margins were well defined radiologically in 15 (34%) of these cases; in the remaining 29 cases (66%), the tumors had diffuse, ill-defined borders on preoperative imaging.

Surgical Treatment

Surgery resulted in GTR in 21 patients (38%) and STR in the remaining 34 patients (62%) (Table 2). The overall incidence of surgical complications was 5% (3 cases: wound infection in 2 cases and delayed wound healing in 1 case). There were no intra- or postoperative deaths related to surgical intervention. In all, 12 patients (22%) developed hydrocephalus requiring ventriculoperitoneal shunt placement (in 9 cases) or significant syringomyelia that necessitated syrinx-subarachnoid shunt insertion (in 3).

Postoperative Neurological Status

Within the immediate postoperative period, the overall incidence of new-onset neurological deficit or progression of preexisting neurological deficit was 27% (15 cases) (Table 2). Progression of underlying motor deficit or development of new-onset motor symptoms occurred in 11 patients (20%). Of these 11 patients, 7 (63%) demonstrated neurological improvement during the follow-up period (median time from surgery to neurological improvement: 3 months). Underlying disease progression led to continued motor decline in 3 (27%) of these patients. Similarly, new-onset or progressive sensory deficits were encountered in 8 patients (14.5%) within the postoperative period. Neurological recovery was noted in 4 (50%) of these

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TABLE 2: Clinical treatment and outcomes on long-term follow-up*

Variable	Value
surgery	
no. of tumor surgeries	
1	39 (71)
2	11 (20)
3–4	5 (9)
laminectomy	41 (75)
mean no. of levels	5
range of no. of levels	1–11
laminoplasty	14 (25)
mean no. of levels	5
range of no. of levels	3–6
extent of resection	
GTR	21 (38)
STR	34 (62)
complications	3 (5)
shunt placement	12 (22)
recurrence or progression	26 (47)
time to recurrence or progression in yrs	
mean $\pm$ SEM	3.3 $\pm$ 1
range	0.1–20
treatment of recurrence	
surgery	9 (16)
chemo	16 (29)
RT	28 (51)
observation	10 (18)
PFS†	
5 yrs	61
10 yrs	54
20 yrs	44
OS†	
5 yrs	85
10 yrs	74
20 yrs	64

* Values represent numbers of cases (%) unless otherwise indicated. chemo = chemotherapy; RT = radiotherapy.

† The values shown are means of Kaplan-Meier product limit estimates. See text for confidence intervals.

8 (median 7 months postoperatively). The remaining patients showed disease progression with continued decline in overall neurological function. The incidence of new-onset bowel or bladder dysfunction was 1.8% (1 case) and the incidence of progression in preexisting bowel or bladder deficit was 5.5% (3 cases), respectively.

Long-Term Neurological Outcomes

The mean time to neurological improvement ($\pm$ SEM) was 4.4 $\pm$ 0.8 months (median 2.5 months, range 1.0–24 months). Postoperative neurological improvement was noted in 23 (70%) of the 33 patients with initial motor

deficits, 27 (64%) of the 42 with sensory deficits, 4 (19%) of the 21 with bladder deficits, and 4 (40%) of the 10 with bowel deficits on presentation.

The mean duration of follow-up ($\pm$ SEM) was 11.4 $\pm$ 1.3 years (median 9.3 years, range 0.2–37.2 years). By final follow-up, 30 patients (55%) showed neurological improvement and 17 (31%) showed neurological decline, while 8 (15%) remained neurologically stable (Table 3). Of patients who showed postoperative neurological improvement, the median duration of time from surgery until symptom improvement was 4 $\pm$ 1 months (range 0–24 months). Patients who presented with McCormick Grade I were more likely to show functional improvement by final follow-up (p = 0.01, Fisher's test), as compared with patients who presented with Grades II–V. Conversely, patients who presented with McCormick Grades I and II were more likely to show functional improvement or remain stable by final follow-up (p = 0.04, Fisher exact test) than patients who presented with Grades III–V. Motor deficits were most likely to show improvement on long-term follow-up (with improvement seen in 23 [70%] of 33 cases), followed by sensory deficits (with improvement seen in 27 [64%] of 42 cases) (Table 4).

Adjunct Therapy

Chemotherapy was used in 16 patients (29%). It was used as adjuvant therapy in 11 patients (20%) and for treatment of tumor recurrence or progression in 5 (9%). Radiotherapy was used in 28 patients (51%)—as adjuvant therapy in 23 patients (42%) and for treatment of tumor recurrence or progression in 5 patients (9%).

Survival and PFS Outcomes

Disease recurrence/progression was noted in 26 patients (47%). The mean time from the primary surgical procedure to the onset of recurrence or progression was 3 months. The Kaplan-Meier actuarial tumor PFS rates at 5, 10, and 20 years were 61% (95% CI 46%–72%), 54% (95% CI 39%–66%), and 44% (95% CI 27%–60%), respectively; OS rates were 85% (95% CI 75%–95%) at 5 years, 74% (95% CI 61%–87%) at 10 years, and 64% (95% CI 46%–82%) at 20 years (Table 2 and Fig. 1).

On analyzing predictors for OS, the following variables were found to be significant on univariate analysis: tumor grade, functional grade on presentation and initial discharge, resection, shunt placement, use of chemo- and/or radiotherapy, and number of tumor surgeries. On multivariate analysis, GTR (hazard ratio [HR] 8.83, p < 0.04), tumor grade (HR 0.24, p = 0.02), and number of tumor resections (HR 0.26, p = 0.03) were found to be predictive of long-term survival (Table 5 and Fig. 2). The 10-year OS rate was 61% (95% CI 42%–80%) in patients who underwent STR as compared with 94% (95% CI 84%–100%) in patients who underwent GTR. Similarly, the 10-year OS was 82.3% (95% CI 67%–93%) in patients with low-grade tumors in comparison with 51% (95% CI 18%–77%) in patients with high-grade tumors. For the patients who underwent only 1 tumor resection procedure, the 10-year OS was 87% (95% CI 72%–95%) as compared with patients who underwent more than 1 resection procedure, for whom the OS was 48% (95% CI 25%–75%).

TABLE 3: Summary of functional and neurological outcomes stratified by functional grade at initial presentation*

Grade at Presentation	No. of Pts (%)	Funct'l Grade at Last FU					Neurol Cond at Last FU (no. of pts. [%])		
		I	II	III	IV	V	Improved	Stable	Worse
I	19 (34)	17	1		1		12 (63)	6 (32)	1 (5)
II	18 (32)	9	2	3		4	10 (55)	1 (6)	7 (39)
III	6 (11)		3			3	2 (34)	—	4 (66)
IV	6 (11)	1	2		1	2	3 (50)	—	3 (50)
V	6 (11)		2		1	3	3 (50)	1 (17)	2 (33)

* Funct'l = functional; Neurol Cond = neurological condition; Pts = patients.

Functional grade on presentation, resection, shunt placement, use of chemo- and/or radiotherapy, and number of tumor surgeries were found to be predictive of long-term PFS on univariate analysis. Only number of tumor resections > 1 (HR 8.7, $p = 0.01$) significantly correlated with PFS on multivariate analysis (Table 6).

We also analyzed determinants of short-term (5-year) PFS. On multivariate analysis, GTR (HR 4.59, $p = 0.01$), use of radiation therapy (HR 0.33, $p = 0.04$), and preoperative functional Grades III and IV (HR 8.37, $p < 0.01$) were significantly correlated with 5-year PFS. Of these 3 factors, only GTR led to improved 5-year PFS (86% 5-year PFS in patients who had GTR as compared with 47% 5-year PFS in patients who had STR; multivariate $p = 0.04$; Kaplan-Meier analysis). Inclusion of radiation therapy was associated with lower 5-year PFS (57% in patients who received radiation therapy as compared with 19% those who did not receive any adjuvant or delayed radiation therapy) and represents an inherent selection bias.

We found no correlation between any of the clinical or treatment factors and functional improvement by the last follow-up.

Discussion

Optimal management of pediatric IMSTs entails careful consideration of management options, given the lifetime morbidity of neurological disease in pediatric patients. Considerations include the natural history of primary disease following resection, iatrogenic risk of neurological progression following surgery, developmental and biomechanical immaturity of the pediatric spine, and susceptibility of the developing nervous system to adjunct chemo-radiotherapy treatments. Our results provide an over-

TABLE 4: Summary of neurological deficits at initial presentation and improvement at last follow-up

Deficit	No. of Pts w/ Deficit	No. of Pts (%) w/ Improvement at Last FU
motor	33	23 (70)
sensory	42	27 (64)
bladder	21	4 (19)
bowel	10	4 (40)

view of the long disease course and outcomes in pediatric patients with intramedullary tumors following treatment through direct follow-up extending beyond the 1st decade after treatment for the first time. We have further identified demographic, clinical, and treatment factors that predict neurological improvement and disease outcomes on long-term follow-up. Our results indicate that favorable (74% at 10 years and 63% at 20 years) long-term OS rates may be observed in the pediatric population with intramedullary tumors. On multivariate analysis, extent of resection is the most significant predictor of extended long-term survival and 5-year PFS. Functional improvement was observed in approximately 50% of all patients by last follow-up and was even seen in patients initially presenting with the worst functional status (Grades IV–V).

FIG. 1. Upper: Overall disease survival in study group as determined with the Kaplan-Meier method. **Lower:** Overall PFS in study group determined similarly. Vertical hatches indicate censored events.

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TABLE 5: Factors associated with overall disease survival

Factor	Alive (%)	Dead (%)	Univariate Analysis p Value	Multivariate Analysis	
				HR	p Value
age					
<5 (n = 20)	15 (75)	5 (25)	0.0912		
6–13 (n = 18)	10 (56)	8 (44)			
14–21 (n = 17)	15 (88)	2 (12)			
sex					
male (n = 30)	22 (73)	8 (27)	0.912		
female (n = 25)	18 (72)	7 (28)			
pathology					
tumor histology					
astrocytoma (n = 31)	20 (65)	11 (35)	0.4733		
ependymoma (n = 10)	8 (80)	2 (20)			
ganglioglioma (n = 7)	6 (86)	1 (14)			
other (n = 7)	6 (86)	1 (14)			
grade					
high grade (n = 43)	6 (50)	6 (50)	0.0456*	0.24	0.02
low grade (n = 12)	34 (79)	9 (21)			
clinical presentation					
deficit score					
≤2 (n = 39)	30 (77)	9 (23)	0.2753		
>2 (n = 16)	10 (63)	6 (38)			
funct'l grade on presentation					
I–II (n = 37)	31 (84)	6 (16)	0.0163*		
III (n = 6)	2 (33)	4 (67)			
IV–V (n = 12)	7 (58)	5 (42)			
tumor location†					
cervical (n = 27)	20 (74)	7 (26)	0.8720		
thoracic (n = 23)	16 (70)	7 (30)			
lumbar (n = 5)	4 (80)	1 (20)			
myelotomy levels					
cervical (n = 24)	17 (71)	7 (29)	0.9615		
thoracic (n = 27)	20 (74)	7 (26)			
lumbar (n = 4)	3 (75)	1 (25)			
syrinx					
yes (n = 16)	14 (88)	2 (12)	0.4601		
no (n = 28)	22 (79)	6 (21)			
margins					
circumscribed (n = 15)	13 (87)	2 (13)	0.5487		
diffuse (n = 29)	23 (79)	6 (21)			
enhancement					
yes (n = 40)	32 (80)	8 (20)	0.3227		
no (n = 4)	4 (100)	0 (0)			
no. of vertebral levels involved					
1–2 (n = 13)	10 (77)	3 (23)	0.0739		
3–4 (n = 18)	14 (78)	4 (22)			
5–6 (n = 14)	12 (86)	2 (14)			
>7 (n = 10)	4 (40)	6 (60)			

(continued)

TABLE 5: Factors associated with overall disease survival (*continued*)

Factor	Alive (%)	Dead (%)	Univariate Analysis p Value	Multivariate Analysis	
				HR	p Value
surgical treatment					
resection					
GTR (n = 21)	20 (95)	1 (5)	0.0032*	8.83	0.04
STR (n = 34)	20 (59)	14 (41)			
shunt placement					
yes (n = 12)	4 (33)	36 (84)	0.0005*		
no (n = 43)	8 (67)	7 (16)			
no. of tumor surgeries					
1 (n = 39)	32 (82)	7 (18)	0.0153*	0.26	0.03
>1 (n = 16)	8 (50)	8 (50)			
functional status on discharge					
I–II (n = 38)	31 (82)	7 (18)	0.0654*		
III (n = 5)	2 (40)	3 (60)			
IV–V (n = 12)	7 (58)	5 (42)			
adjuvant therapy					
chemo/RT used					
chemo & RT (n = 10)	4 (40)	6 (60)	0.0005*		
RT (n = 16)	8 (50)	8 (50)			
chemo (n = 6)	6 (100)	0 (0)			
none (n = 23)	22 (96)	1 (4)			
indication for chemo					
not used (n = 39)	30 (77)	9 (23)	0.4411		
adjuvant or recurrence (n = 15)	10 (67)	5 (33)			
indication for RT					
not used (n = 27)	26 (96)	1 (4)	0.0002*		
adjuvant or recurrence (n = 25)	13 (52)	12 (48)			

* Factors included in multivariate analysis. The following factors were used in the multivariate model based on survival regression using an underlying Weibull distribution: tumor grade, functional grade on presentation, tumor span, resection, shunt placement, functional status on discharge, use of chemotherapy and/or radiotherapy, indication for radiotherapy, and number of tumor surgeries.

† Tumor localization and span were categorized as cervical (including cervicomedullary, cervical, and cervicothoracic segments [C7–T1]), thoracic (thoracic and thoracolumbar segments [T11–L1]), and lumbar (lumbar/conus).

Although the fact that this study is a single-institution case series might be seen as a limitation, it minimizes bias due to patient selection and treatment. In contrast to previous studies,^{4,8,23,30,51} this study reports on disease outcomes over an extended follow-up beyond the 1st decade after surgery and thereby serves to better define the disease course and treatment outcomes for pediatric IMSCTs.

Rates of Long-Term Disease Survival

In our series, the 10-year survival rate (74%) is consistent with that reported by Constantini et al. and also falls within the range of previous additional studies.^{4,38,48} With a mean follow-up of approximately 11.5 years, we determined the 20-year disease survival rate to be 64%. Our extended follow-up enabled us to determine that up to 44% of patients were free of progression 20 years posttreatment. This indicates relatively favorable disease

outcomes for a potentially debilitating disease affecting children and adolescents. These long-term follow-up results therefore provide the first report of disease survival estimates beyond 1 decade posttreatment.

Determinants of Long-Term Survival

On univariate analysis, factors that significantly correlated with OS were functional status on presentation, histological grade, extent of resection, and CSF shunt placement. These factors have been observed to be predictive of OS in previous studies. Additional factors significant on univariate analysis included number of tumor surgeries and need for adjuvant therapy, which are surrogate markers for disease progression. On multivariate analysis, extent of resection, tumor histology grade, and number of tumor resection procedures were significantly predictive of long-term disease survival.

Fig. 2. Upper: Comparison of disease survival between patients who underwent GTR (dashed line) and STR (solid line). Lower: Comparison of disease survival between patients with low (LG, dashed line) and high (HG, solid line) tumor histological grades. Vertical hatches indicate censored events.

Extent of Resection. Since initially advocated, GTR remains the definitive surgical goal in the treatment of IMSTs.^{6,11,14} Results from previous studies have been ambiguous on the survival predictive value of resection, with some studies indicating improved long-term survival and neurological outcomes,^{6,13} while others support the role for limited resections followed by adjuvant therapies.^{33,36,48} This discrepancy is in part attributed to the heterogeneity in surgical versus radiographic assessment of tumor resection and variability in defined surgical margins that often limits resection.^{19,25} The extent of tumor resection and benefits of GTR correlate with tumor histology.^{16,20,23,45} Low-grade pilocytic astrocytoma subtypes are much more likely to be associated with defined tumor margins than are higher-grade astrocytomas. This may also account for variability in reported rates of GTR for astrocytomas and hence confounds the predictive association between extent of resection and disease outcomes.^{41–43}

The overall GTR rate in our series (38%) was lower than that previously reported by some authors⁴ but in line with the rate reported by others.⁴⁴ In contrast to earlier studies,^{2,33} our results support the beneficial role for GTR, where feasible, in long-term disease survival and prevention of disease progression over extended follow-up.³⁰

The predictive value of extent of resection was maintained across our cumulative case series. This finding is significant, since astrocytomas were the most prevalent histological subtype in our series and are frequently associated with indistinct tumor margins. Our results therefore emphasize the importance of resection in predicting long-term disease and neurological outcomes within the pediatric age group.¹¹

In addition, extent of resection was also significantly associated with improved PFS in this study, in contrast to an earlier study that did not find an association between GTR and PFS in astrocytomas.¹⁶ Of particular note, the survival advantage of GTR was maintained at the 5-year time point in contrast to an earlier report that indicated similar results for GTR and STR in terms of PFS beyond 3 years of follow-up.⁴

Tumor Histology and Grade. Tumor grade was also significantly associated with disease survival outcome on multivariate analysis, in line with findings of earlier studies that describe the prognostic value of tumor grade.^{17,33} In contrast to earlier studies, however, we did not find any statistically significant association with histological subtype.^{4,23,33} Tumor margins and hence extent of resection are directly related to tumor grade and histological subtype. Hence, our finding of the prognostic value of resection extent is an indirect reflection of this underlying association. This is supported by the observation that the major tumor histological subtype/grade were low-grade astrocytomas, ependymomas, and gangliogliomas, which are typically slow-growing and indolent tumors.²

Hydrocephalus and Syringomyelia

Development of symptomatic hydrocephalus and/or syringomyelia necessitating shunt placement was a significant factor in our group on univariate analysis. The association between hydrocephalus and intramedullary tumors has been well described, both as a presenting symptom and as a manifestation of disease progression.^{37,49} Obstruction of CSF occurs through leptomeningeal disease in patients with high-grade tumors and secondary to altered CSF viscosity and tumor hemorrhage.^{34,39} Rostral extension of syringomyelia to the cervicomedullary junction can also cause hydrocephalus by mechanical obstruction of CSF outlet pathways in low-grade intramedullary tumors. The presence of syringomyelia in patients with low-grade tumors such as ependymomas and hemangioblastomas was not found to be associated with long-term disease outcomes.⁴¹ Similarly, shunt placement was indirectly found to be negatively correlated with survival due to an association with high-grade lesions.⁴

Importantly, hydrocephalus may precede or accompany development of neurological symptoms secondary to the underlying tumor and may also develop postoperatively. It often occurs with delayed onset, thereby mandating long-term radiological follow-up.³⁴ In our series, there was no significant association between tumor grade and incidence of secondary hydrocephalus and/or syringomyelia. We chose to categorize patients with secondary hydrocephalus and syringomyelia together for outcome analysis, since in our experience these conditions had a

TABLE 6: Factors associated with disease progression

Characteristic	No Progression (%)	Progression (%)	Univariate Analysis p Value	Multivariate Analysis	
				HR	p Value
age in yrs					
<5 (n = 20)	11 (55)	9 (45)	0.3007		
6–13 (n = 18)	7 (39)	11 (61)			
14–21 (n = 17)	11 (65)	6 (35)			
sex					
male (n = 30)	16 (53)	14 (47)	0.9214		
female (n = 25)	13 (52)	12 (48)			
pathology					
tumor histology					
astrocytoma (n = 31)	13 (42)	18 (58)	0.2979		
ependymoma (n = 10)	7 (70)	3 (30)			
ganglioglioma (n = 7)	4 (57)	3 (43)			
other (n = 7)	5 (71)	2 (29)			
grade					
high (n = 43)	5 (42)	7 (58)	0.3854		
low (n = 12)	24 (56)	19 (44)			
clinical presentation					
deficit score					
<2 (n = 39)	23 (59)	16 (41)	0.1474		
>2 (n = 16)	6 (38)	10 (63)			
functional grade on presentation					
I–II (n = 37)	23 (62)	14 (38)	0.0804*		
III (n = 6)	1 (17)	5 (83)			
IV–V (n = 12)	5 (42)	7 (58)			
tumor location					
cervical (n = 27)	14 (52)	13 (48)	0.4227		
thoracic (n = 23)	11 (48)	12 (52)			
lumbar (n = 5)	4 (80)	1 (20)			
myelotomy levels					
cervical (n = 24)	12 (50)	12 (50)	0.6453		
thoracic (n = 27)	14 (52)	13 (48)			
lumbar (n = 4)	3 (75)	1 (25)			
syrinx					
yes (n = 16)	8 (50)	8 (50)	0.6471		
no (n = 28)	16 (57)	12 (43)			
margins					
circumscribed (n = 15)	6 (50)	6 (50)	0.7625		
diffuse (n = 29)	16 (55)	13 (45)			
enhancement					
yes (n = 40)	20 (50)	20 (50)	0.0555*		
no (n = 4)	4 (100)	0 (0)			
tumor span					
1–2 vertebral levels (n = 13)	8 (61)	5 (38)	0.4497		
3–4 vertebral levels (n = 18)	10 (56)	8 (44)			
5–6 vertebral levels (n = 14)	8 (57)	6 (43)			
>7 vertebral levels (n = 10)	3 (30)	7 (70)			

(continued)

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TABLE 6: Factors associated with disease progression (continued)

Characteristic	No Progression (%)	Progression (%)	Univariate Analysis p Value	Multivariate Analysis	
				HR	p Value
surgical treatment					
extent of resection					
GTR (n = 21)	16 (76)	5 (24)	0.0062*	0.06	
STR (n = 34)	13 (38)	21 (62)			
shunt placement					
yes (n = 12)	3 (25)	9 (75)	0.0296*		
no (n = 43)	26 (60)	17 (40)			
functional status on discharge					
I–II (n = 38)	24 (63)	14 (37)	0.0603		
III (n = 5)	1 (20)	4 (80)			
IV–V (n = 12)	4 (33)	8 (67)			
adjuvant treatment					
chemo/RT used					
chemo & RT (n = 10)	2 (20)	8 (80)	0.0033*		
RT (n = 16)	2 (31)	11 (69)			
chemo (n = 6)	4 (67)	2 (33)			
none (n = 23)	18 (78)	5 (22)			
indication for chemo					
not used (n = 39)	23 (59)	16 (41)	0.2104		
adjuvant or recurrence (n = 15)	6 (40)	9 (60)			
indication for RT					
not used (n = 27)	20 (74)	7 (26)	0.0057*	0.22	
adjuvant or recurrence (n = 25)	9 (36)	16 (64)			
no. of tumor surgeries					
1 (n = 39)	26 (67)	13 (33)	0.0012*	8.7	0.01
>1 (n = 16)	3 (19)	13 (81)			
functional status on final follow-up					
I–II (n = 48)	27 (56)	21 (44)	0.3819		
III (n = 4)	1 (25)	3 (75)			
IV–V (n = 3)	1 (33)	2 (67)			

* Factors included in multivariate analysis.

similar presentation, both required CSF diversion, and were both associated with a significant effect on long-term disease survival. In our opinion, the pathogenesis of secondary syringomyelia is a manifestation of obstruction of subarachnoid CSF drainage pathways within the spine—either due to local disease progression or as a consequence of tissue reparative mechanisms and scarring. This is supported by our clinical observations of neurological improvement following placement of syrinx-subarachnoid shunts.

Additional Factors Associated With OS and PFS

Age as Null Predictor. In our experience, age does not affect OS, disease progression, or the rate of functional improvement. This indicates that despite the potential morbidity associated with resection, surgery is well tolerated, and GTR, when safely feasible, should be the primary treatment goal. Hence, this mandates prompt tumor

resection even in infants presenting with severe deficits. This is consistent with earlier studies.^{4,17,46}

Number of Tumor Resections. Overall survival was significantly lower in patients who underwent more than 1 tumor resection procedure as compared with patients who had 1 resection only (50% vs 82%, respectively). This reflects the greater rate of disease progression in the former group (81%) as compared with that of patients who had 1 resection (22%; Table 6).

Tumor Characteristics. We did not find any prognostic significance for additional tumor characteristics, such as preoperative syrinx, tumor margins, contrast enhancement, or spinal level. Significantly, longitudinal tumor span was not associated with adverse survival outcomes, indicating that even extensive multisegment intramedullary tumors can be resected with minimal adverse impact on disease survival, consistent with earlier reports.^{10,12,47}

Natural History and Long-Term Neurological Outcomes Following Surgery

Clinical Presentation. In our pediatric series, the most common location for tumor presentation was the cervicomedullary junction (36%), followed by the thoracic spine (27%). Astrocytomas (53%) were the most prevalent histological subtype, consistent with earlier studies.^{3,4} Despite the pattern of contrast enhancement on MRI (91%), most of these tumors were low grade (78%).⁸ Although the average time interval from symptom development to clinical presentation was 7 months, most patients (67%) presented with McCormick Grade I–II functional status. This underscores previous observations that, unlike their intracranial counterparts, intramedullary low-grade gliomas should be primarily managed surgically on discovery to avoid any further neurological deterioration.

Rate of Improvement. Sensory deficits (76%) were the most prevalent type of neurological deficit on initial presentation, with motor symptoms (60%) next in prevalence. Most patients experienced improvement in their preoperative neurological deficit following resection. The prevalence of postoperative improvements was 70% and 64% for initial motor and sensory deficits, respectively. Improvement in preoperative bowel (40%) and bladder (9%) deficits were much less consistent. Overall, 55% of the study group experienced neurological improvement by the last clinical follow-up visit. This is within the range of previously reported rates of neurological improvement.^{16,51} Importantly, our extended follow-up enables us to conclude that our reported rates of neurological improvement are well maintained beyond the 1st decade postoperatively. Stratification by functional grade on presentation indicated that the rate of neurological improvement was in the range of 55%–63% for patients presenting with Grades I–II functional status and 50% for patients presenting with more severe grades, IV–V. Preoperative functional status was the only significant predictor of postoperative neurological improvement in our series, consistent with earlier studies.^{23,42,50} Hence, we concur with Garcés-Ambrossi et al.¹⁶ that neurological restoration rather than preservation⁴⁵ should be the treatment goal, especially in the pediatric age group.

Postoperative Neurological Decline. Despite widespread use of intraoperative neurophysiological monitoring, immediate postoperative neurological decline has been widely reported.^{7,28,29} This has been attributed to operative manipulation of the dorsal columns during the surgical myelotomy and reactive tissue edema with temporary neuronal injury and may correlate with poorer preoperative neurological status.^{14,20} The incidence of new-onset neurological deficits and/or progression of preexisting deficits in the immediate postoperative period in our series was 27% (occurring in 15 of 55 cases). The majority of motor-related symptoms (63%) were transient (median time to resolution 3 months). Sensory deficits resolved postoperatively in 50% of cases (median time to resolution 7 months). This is consistent with previous reports.¹⁹

Role of Adjunct Therapy

The role of both chemo- and radiotherapy is ambig-

uous in the literature, with reports of indeterminate, improved, and no survival advantages conferred by these adjuncts.^{2,9,22,26,32,33,36,44,46} The overall rate of tumor progression in our series was 47%, with a mean onset of 3 years postoperatively (mean [$\pm$ SEM] 3.3 ± 1 years, range 0.1–20 years). Radiotherapy was used following disease progression or recurrence in 51% of the 55 patients, while chemotherapy was used in 29% of the patients. The independent survival and/or treatment benefit of these adjunct therapies could not be determined for lack of randomization of treatment modalities inherent to retrospective reviews. In our study group, inclusion of adjuvant therapies did not significantly improve OS. Inclusion of radiotherapy was statistically associated with 5-year PFS and represents an intrinsic selection bias because patients receiving radiotherapy are at high risk of disease progression.

Conclusions

Assessments of long-term OS and disease progression in children with intramedullary tumors show that GTR and tumor grade are the most significant factors in survival. Moreover, the survival advantages conferred by GTR appear to sustain beyond the 1st decade after treatment. Gross-total resection was associated with improved PFS at 5 years. Kaplan-Meier analysis showed the rate of PFS to be 44% for as long as 2 decades postoperatively. Long-term follow-up also demonstrated prolonged OS, especially in patients in whom there was no sign of disease progression. Neurological improvement occurred in 55% of patients postoperatively and was sustained by surviving patients over long-term follow-up.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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