Role of resection and adjuvant therapy in long-term disease outcomes for low-grade pediatric intramedullary spinal cord tumors

Raheel Ahmed, MD, PhD,¹ Arnold H. Menezes, MD,² and James C. Torner, PhD³

¹Division of Neurosurgery, The Hospital for Sick Children, Toronto, Canada; and Departments of ²Neurosurgery and

³Epidemiology, University of Iowa Hospitals and Clinics, Iowa City, Iowa

OBJECTIVE Surgical excision is the mainstay treatment for resectable low-grade intramedullary spinal cord tumors (IMSCTs) in the pediatric age group. Chemotherapy and radiation treatments are generally reserved for progressive or recurrent disease. Given the indolent nature of low-grade tumors and the potential side effects of these approaches, their long-term treatment benefits are unclear. The aim of the study was to determine long-term disease outcomes and the therapeutic roles of surgery and adjuvant therapies in pediatric patients with low-grade IMSCTs over an extended follow-up period.

METHODS Case records for all pediatric patients (< 21 years of age) with a histopathological diagnosis of low-grade IMSCT were selected over a period from January 1975 to January 2010. Outcome variables including McCormick functional grade, overall survival (OS), and progression-free survival (PFS) were analyzed with respect to demographic and treatment variables.

RESULTS Case records of 37 patients with low-grade IMSCTs were identified, with a mean follow-up duration of 12.3 ± 1.4 years (range 0.5–37.2 years). Low-grade astrocytomas were the most prevalent histological subtype ($n = 22$, 59%). Gross-total resection (GTR) was achieved in 38% of patients ($n = 14$). Fusion surgery was required in 62% of patients with pre- or postoperative deformity (10 of 16). On presentation, functional improvement was observed in 87% and 46% of patients in McCormick Grades I and II, respectively, and in 100%, 100%, and 75% in Grades III, IV, and V, respectively. Kaplan-Meier PFS rates were 63% at 5 years, 57% at 10 years, and 44% at 20 years. OS rates were 92% at 5 years, 80% at 10 years, and 65% at 20 years. On multivariate analysis, shunt placement (hazard ratio [HR] 0.33, $p = 0.01$) correlated with disease progression. There was a trend toward improved 5-year PFS in patients who received adjuvant chemotherapy and radiation therapy (RT; 55%) compared with those who did not (36%). Patients who underwent subtotal resection (STR) were most likely to undergo adjuvant therapy (HR 7.86, $p = 0.02$).

CONCLUSIONS This extended follow-up duration in patients with low-grade IMSCTs beyond the first decade indicates favorable long-term OS up to 65% at 20 years. GTR improved PFS and was well tolerated with sustained functional improvement in the majority of patients. Adjuvant chemotherapy and RT improved PFS in patients who underwent STR. These results emphasize the role of resection as the primary treatment approach, with adjuvant therapy reserved for patients at risk for disease progression and those with residual tumor burden.

<http://thejns.org/doi/abs/10.3171/2016.5.PEDS15356>

KEY WORDS intramedullary spinal cord tumor; gross-total resection; low-grade tumor; disease-free survival; spine; oncology

THE majority of intramedullary spinal cord tumors (IMSCTs) in the pediatric age group are low-grade gliomas, comprising low-grade astrocytomas and ependymomas.^{14,36} The mainstay treatment consists of resection, with extent of resection shown to be directly correlated with disease outcomes.^{12,13,23} Gross-total resection

(GTR), although feasible with the advent of neurophysiological monitoring and microsurgical techniques, is associated with a risk of neurological decline.^{25,26} Disease outcomes in pediatric patients, therefore, need to be assessed over a long-term follow-up period, in light of the neurological disability, risk for secondary spinal deform-

ABBREVIATIONS GTR = gross-total resection; IMSCT = intramedullary spinal cord tumor; OS = overall survival; PFS = progression-free survival; RT = radiation therapy; STR = subtotal resection.

SUBMITTED June 13, 2015. **ACCEPTED** May 16, 2016.

INCLUDE WHEN CITING Published online July 15, 2016; DOI: 10.3171/2016.5.PEDS15356.

mity, and natural history of slow-growing low-grade tumors.^{8,15,44,54,55} Hence, it is important to weigh the surgical benefits of GTR for disease control relative to quality of life and functional outcome measures over long-term follow-up.

Chemotherapy and radiation therapy (RT) are often used for the management of both high- and low-grade tumors with progressive disease.^{7,10,11,19,20} In contrast, the treatment indications of adjuvant chemotherapy and RT are less clear for low-grade gliomas following subtotal resection (STR), given the inherent benign natural history of the tumor.

We undertook a retrospective analysis of clinical outcomes in pediatric patients with low-grade IMSCTs, focusing on clinical factors that correlate with disease outcomes. In contrast to earlier studies,^{16,32,35,45,52,53} our extended clinical follow-up beyond the first decade allows long-term assessment of disease outcomes. We also determined clinical factors that aid in decision-making for adjuvant chemotherapy and RT.

Methods

Pediatric patients (< 21 years of age) with a histopathological diagnosis of low-grade (Grade I or II) IMSCT were identified from the neurosurgery database at the University of Iowa Hospitals and Clinics, over a study period extending from January 1975 to January 2010. Patient records were systematically reviewed for: 1) demographics, 2) clinical presentation, 3) surgical treatment, 4) chemotherapy and/or RT received, and 5) final clinical outcomes. Pre- and postoperative clinical and radiographic evaluation were undertaken in a multidisciplinary manner by Pediatric Neurosurgery, Orthopedics, Medical Oncology, and Radiation Oncology services. Baseline and follow-up clinical and radiographic assessment of skeletal deformity, and determination and timing of skeletal fusion when needed, was undertaken in consultation with the Pediatric Orthopedics service. The senior author (A.H.M.) was the primary surgeon for the majority of patients. Computed tomography myelograms were used for radiographic diagnosis for the earlier part of the study until the time that MRI was routinely used. Pre- and postoperative functional assessment was undertaken through the modified McCormick functional scale, as previously described.^{2,30,31} The deficit score on presentation was calculated through the presence (score = 1) or absence (score = 0) of motor, sensory, bladder, or bowel deficits. The University of Iowa Human Subjects Office Institutional Review Board approved this retrospective study.

Operative Technique

Operative techniques for pediatric IMSCTs at our institution have been described in detail previously.² Briefly, an osteoplastic laminoplasty was planned in all children unless preoperative imaging studies indicated significant mass effect that necessitated extensive decompression. A laminectomy was performed with the aid of a fascial graft in instances when preoperative imaging studies indicated a high probability of incomplete resection, given a lack of clearly defined tumor margins. Neurophysiological moni-

toring with somatosensory evoked potentials was used in the last 3 decades; motor-evoked potentials were adjuncts used in the last decade. A midline myelotomy spanned tumor segments. The initial biopsies were obtained from the most enhancing areas on preoperative MRI. Tumor dissection was aided by high-powered microscopy and a microsurgical technique with suction, ultrasonic aspiration, and cottonoid patty wisps soaked with thrombin. Bipolar cautery was infrequently needed. Circumferential dissection was then extended in all planes where a distinct tumor–spinal cord interface could be identified. Careful monitoring of the mean arterial pressure is critical (above 70 mm Hg), with vasopressor support as needed. Infiltrative tumors underwent significant debulking of the grossly enhancing areas, and in these situations a duraplasty was performed. In all other cases, a primary dural closure was accomplished and laminae/spinous processes were replaced. In our opinion, a laminoplasty is advantageous in aiding future instrumentation if needed, improving wound healing, and preventing CSF leak.

The degree of resection was determined through intraoperative assessment of tumor removal, additionally verified through immediate (1–3 day) postoperative MRI. Tumor resection was classified as GTR if the surgeon's and radiologist's assessments were in agreement. In all other cases, an STR was determined to have occurred.

Statistical Analysis

Univariate analysis for all outcomes analysis was performed using the Pearson chi-square test and logistic regression. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier analysis. Multivariate analysis of survival was performed using logistic regression for dichotomous end points and survival regression using the underlying Weibull distribution for time to event analysis. Goodness of fit was assessed by survival graphs, log-survival plots, and Schoenfeld residual plots to assess proportionality. Univariate statistical associations were first calculated, and variables with *p* values < 0.1 were then entered into a survival regression model for multivariate analysis. The proportional hazards assumption was verified. Input variables that had *p* values < 0.05 after this analysis were reported as statistically significant on multivariate analysis. All statistical analysis was performed using SAS software (version 9.3, SAS Inc.). Statistical significance for both univariate and multivariate analysis was set at *p* < 0.05.

Results

A total of 37 patients were identified with low-grade IMSCTs who received their primary or secondary treatment at the University of Iowa during the study period. Baseline demographics are summarized in Table 1. The average interval from symptom development to clinical presentation was 8.1 months (range 0.1–60 months). Sensory neurological deficits were most common (*n* = 29, 78%) on presentation, followed by motor deficits (*n* = 20, 54%). The cervicomedullary region was most commonly involved (*n* = 13, 35%). Low-grade astrocytomas were the most prevalent histological subtype (*n* = 22, 59%).

TABLE 1. Clinical and demographic characteristics of the study population

Characteristic	Value (%)
Age (yrs)	
Mean $\pm$ SEM	10.4 $\pm$ 1.1
Range	0.5–21
Sex	
Male	17 (46)
Female	20 (54)
Time from symptom onset (mos)	
Mean $\pm$ SEM	8.1 $\pm$ 1.8
Range	0.1–60
Pain	20 (54)
Motor deficits	20 (54)
Sensory deficits	29 (78)
Bladder deficits	12 (32)
Bowel deficit	6 (16)
Imaging findings*	
Syrinx	12 (40)
Contrast enhancement	29 (97)
Margins	
Diffuse	21 (70)
Circumscribed	9 (30)
No. of vertebral levels involved†	
Mean $\pm$ SEM	5 $\pm$ 1
Range	1–11
Spinal level	
Cervicomedullary	13 (35)
Cervicothoracic‡	5 (14)
Thoracic	10 (27)
Thoracolumbar§	4 (11)
Lumbar	5 (14)
Histological diagnosis	
Astrocytoma	22 (59)
Ependymoma	8 (22)
Ganglioglioma	7 (19)
Duration of follow-up (yrs)	
Mean $\pm$ SEM	12.3 $\pm$ 1.4
Range	0.5–37.2

* MRI studies were available for 30 patients.

† Levels encompassing tumor and syrinx segments.

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

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

Surgical Treatment and Outcomes

The majority of patients underwent a single resection procedure during the study period ($n = 25$, 68%; Table 2). A spinal laminectomy was undertaken in 73% of patients ($n = 27$). GTR was achieved in 38% of the patients ($n = 14$). GTR rates were 18.2% for astrocytomas, 87.5% for ependymomas, and 42.9% for gangliogliomas. To determine

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

Variable	Value (%)
No. of tumor surgeries	
1	25 (68)
2	8 (22)
3–4	4 (11)
Laminectomy	27 (73)
Mean no. of levels	5
Range of no. of levels	1–11
Laminoplasty	10 (27)
Mean no. of levels	4
Range of no. of levels	3–6
Extent of resection	
GTR	14 (38)
STR	23 (62)
Complications*	2 (5)
Shunt placement†	8 (22)
Recurrence or progression	16 (43)
Time to recurrence or progression (yrs)	
Mean $\pm$ SEM	4.3 $\pm$ 1.4
Range	0.1–20
Treatment of recurrence ($n = 16$)‡	
Surgery	8 (50)
Chemotherapy	3 (19)
RT	4 (25)
Observation	6 (38)
PFS (yrs)§	
5	63%
10	57%
20	44%
OS (yrs)§	
5	92%
10	80%
20	65%

* Operative complications: wound dehiscence ($n = 1$), meningitis ($n = 1$).

† Shunt: ventriculoperitoneal shunt ($n = 5$), syrinx-subarachnoid shunt ($n = 3$).

‡ Treatment approaches are not mutually exclusive.

§ The values shown are means of Kaplan-Meier product-limit estimates (see text for 95% CIs).

predictors for the extent of resection, various clinical factors at presentation were evaluated. On univariate analysis, age at presentation (< 6 years, 6–16 years, > 14 years; $p = 0.02$) and tumor subtype ($p = 0.002$) were found to be significantly associated with the extent of resection on univariate analysis. These variables were not significant on multivariate analysis.

Neurological Outcomes

The mean follow-up duration was 12.3 ± 1.4 years (range 0.5–37.2 years). Comparison of functional status between initial presentation and last clinical follow-up evaluation using McCormick functional grades indicated that 87% of patients (13/15) who presented with Grade I

status experienced neurological improvement. Of patients who presented with Grade II status ($n = 13$), 46% (6/13) experienced improvement in their functional state. The rates of functional improvement were 100% (3/3) for Grade III, 100% (2/2) for Grade IV, and 75% (3/4) for Grade V patients.

In all, 15 (75%) of the 20 patients who presented with motor deficits experienced neurological improvement by the last follow-up evaluation. Similarly, 72% of patients (21/29) with sensory deficits on presentation showed neurological improvement. The rates for improvement in bladder and bowel deficits were 17% (2/12) and 50% (3/6), respectively.

The incidence of spinal deformity on presentation was 11% ($n = 4$). Postoperative deformity was present in 32% ($n = 12$) of patients at a mean interval of 1.1 ± 0.6 years. Fusion surgery was required in 62% of patients with deformity (10/16). The mean interval until fusion surgery was 4.3 ± 0.9 years (range 0.7–10 years). More than 1 fusion procedure was required in 30% of patients (3/10) while the remainder of the patients underwent a single fusion procedure.

Long-Term Disease Outcomes

In all, 43% ($n = 16$) of patients experienced disease recurrence or progression at a mean interval of 4.3 ± 1.4 years from their initial treatment. PFS was determined to be 63% (95% CI 45%–77%) at 5 years, 57% (95% CI 38%–71%) at 10 years, and 44% (95% CI 24%–63%) at 20 years (Table 2, Fig. 1). OS was 92% (95% CI 77%–97%) at 5 years, 80% (95% CI 59%–91%) at 10 years, and 65% (95% CI 37%–82%) at 20 years (Table 2, Fig. 1).

Disease outcomes were also stratified by extent of resection. For patients with GTR ($n = 14$, 38%), PFS was 92% (95% CI 54%–99%) at 5 years and 10 years, and 68% (95% CI 16%–92%) at 20 years. OS was 100% (95% CI 0) at 5 years, 10 years, and 20 years (Fig. 2). For the remainder of patients who underwent STR ($n = 23$, 62%) PFS was 45% (95% CI 24%–64%) at 5 years, 34% (95% CI 15%–55%) at 10 years, and 27% (95% CI 10%–48%) at 20 years. OS was 87% (95% CI 64%–95%) at 5 years, 66% (95% CI 37%–83%) at 10 years, and 38% (95% CI 27%–78%) at 20 years (Fig. 2).

To determine predictors for OS, clinical and treatment factors were correlated with survival status (alive vs deceased). On univariate analysis, functional status on presentation, extent of resection, shunt placement, use of adjuvant therapy, indication for RT, mode of disease progression management, and number of tumor surgeries were found to correlate significantly with survival status. Shunt placement was the most significant factor on univariate analysis (HR = 0.331, $p = 0.0128$). On multivariate analysis, none of these variables were independently associated with OS.

Using the same input variables, predictors for disease progression were similarly determined. Resection, shunt placement, use of adjuvant therapy, indication for RT, mode of disease progression management, and number of tumor surgeries correlated with disease progression on univariate analysis. On multivariate analysis, shunt placement (HR 0.33, $p = 0.01$) correlated with disease progression.

FIG. 1. Kaplan-Meier estimate of OS and PFS for all patients over the course of the study.

The impact of adjuvant therapy on disease outcomes was also assessed within the subset of patients who underwent STR. Of the 7 patients treated with chemotherapy, 3 patients underwent adjuvant therapy while 4 patients received chemotherapy for treatment of disease recurrence. Of the 15 patients who were treated with RT, 12 patients underwent adjuvant therapy while 3 patients received RT for disease recurrence. For patients who underwent STR, the inclusion of chemotherapy and RT was not significantly associated with OS. Five-year PFS showed an improved trend in patients who received adjuvant therapy following STR (55%) as compared with patients who did not receive adjuvant therapy (36%). However, this difference was not statistically significant (p value nonsignificant).

We therefore attempted to define the treatment indications for chemotherapy and RT. Clinical and treatment factors were correlated with the use of chemotherapy and RT, retrospectively. On univariate analysis, functional grade on presentation, shunt placement, extent of resection, tumor span, and number of tumor resection surgeries were found to be significant. These factors were included in a multivariate model that showed that extent of resection was significantly associated with use of adjuvant therapy (HR 7.86, $p = 0.02$, 95% CI 1.3–47.03).

Discussion

The indolent nature of low-grade pediatric IMSTs necessitates that assessment of treatment outcomes must take into account the need for extended clinical follow-up. Our long-term follow-up duration, extending beyond the first decade, indicates favorable outcomes with OS up to 80% and PFS up to 57% at 10 years in pediatric patients with low-grade IMSTs. Resection was well tolerated with sustained functional improvement observed in the majority of patients. The inclusion of adjuvant chemotherapy and RT for patients following an STR was associated with a trend in PFS. In addition, the extent of resection was identified retrospectively as a significant treatment criterion for adjuvant therapy. Previous reports have either pooled all histological subtypes³⁷ or both adult and pediatric patients together.^{19,28} Our report focuses on long-term outcomes in

low-grade IMSCTs and retrospectively analyzes clinical factors that aid in decision-making in the use of adjuvant chemotherapy and RT.

Role of Resection

The most common subtypes of low-grade gliomas in the pediatric age group are Grades I and II astrocytomas and low-grade ependymomas.^{27,45} GTR rates of up to 75% have been reported for IMSCTs in pediatric patients.⁷ Lower rates of GTR have been reported in series with a higher proportion of astrocytomas that are typically associated with infiltrative borders.⁴⁵ Our results indicate that tumor subtype is strongly associated with extent of resection, with higher rates of GTR in ependymomas (87.5%) as compared with astrocytomas (18.2%), consistent with findings from earlier reports.^{21,24}

GTR is recognized as the primary treatment of choice for these tumors.^{12,13,42} In pediatric patients with low-grade gliomas, GTR is associated with significantly prolonged PFS^{43,45,51} and OS.³⁸ Yet, additional studies have reported limited benefits of GTR. The extent of resection was not found to correlate with OS within a multicenter consortium of French hospitals, with survival rates of 66% at 5 years and 60% at 10 years within this group.⁴ Despite varying results reported on the role of surgery, consensus evidence suggests a beneficial role of GTR in spinal low-grade gliomas in pediatric patients.¹⁷

The ideal treatment goal of radical tumor resection must also be balanced by the potential for long-term neurological morbidity in pediatric patients. Tumor location, preoperative neurological status, and the presence of spinal deformity can further impact long-term functional and neurological outcomes following GTR of IMSCTs.^{16,44} Similar considerations for the morbidity of GTR in intracranial gliomas have been highlighted by reports of permanent neurological deficits in as many as 18% of pediatric patients following GTR of low-grade cerebellar astrocytomas.⁶

In our study group, the overall rate of GTR was 38%. This rate is consistent with the preponderance of astrocytomas (59%) in our group, that typically present with diffuse borders (70%) and hence indistinct surgical planes of resection. Given the indolent nature of low-grade IMSCTs, our results focused on assessment of long-term disease outcomes. On extended clinical follow-up, GTR was significantly associated with improved PFS and OS. There is a clear discordance in OS and PFS rates between patients who undergo GTR and STR, respectively (Fig. 2). PFS was approximately 34% at 10 years in patients who underwent STR as compared with approximately 92% at 10 years in those who underwent GTR. OS was associated with GTR on univariate analysis ($p = 0.01$) but did not reach statistical significance on multivariate analysis, probably due to sample size limitation. Hence, our results emphasize the important role of GTR in improving long-term disease outcomes. This is concordant with clinical data on intracranial low-grade gliomas in the pediatric age group that indicate that disease outcome measures are most significantly affected by the extent of resection.⁴⁷ This finding also highlights a key difference in the natural history of intramedullary low-grade gliomas in contrast to the intracranial low-grade

FIG. 2. Kaplan-Meier estimate of patient OS (upper) and PFS (lower) stratified by extent of resection.

gliomas that are associated with relatively better/prolonged PFS rates of 45%–56% following STR at 8 years.⁵³

Our results indicate that surgery is well tolerated in the pediatric age group, and up to approximately 75% of patients experienced significant improvement in their preoperative motor and sensory deficits. The majority of patients (87%) who presented in McCormick Grade I showed functional improvement, with up to 75%–100% of patients in Grades IV and V also experiencing functional improvement by at least 1 functional grade. In all, 27% (10/37) of patients required a fusion surgery for associated spinal deformity that was within the reported range of secondary deformity in IMSCTs.^{8,48,55,56} Hence, our long-term (more than 1 decade) assessment of disease outcomes indicates significantly improved OS and PFS following GTR as compared with STR. Concurrent assessment of McCormick functional grades indicates that GTR was well tolerated with improvement and/or preservation of baseline functional status over an extended follow-up period.

Role of Adjuvant Chemotherapy

Consensus guidelines on the postoperative management use of adjuvant treatments including RT and chemotherapy are lacking, given the relatively rare incidence of these tumors and the heterogeneity within patients with

respect to age, histology, grade, degree of resection, and tumor location. Chemotherapy treatment regimens have been proposed with the therapeutic rationale of improving disease outcomes following partial resection or disease progression, to avert long-term disease progression and delay the use of RT in newly diagnosed gliomas.¹⁰ Polychemotherapy enabled an OS rate of 87.5% over a median follow up of 4.8 years, with 4 patients (50%) in continuous remission without the use of any RT (study group, n = 8). Chemotherapy has also been effective in enabling partial response or stable disease in patients with leptomeningeal disease at onset, a subset that is typically associated with poor outcomes.⁵ Hence, the inclusion of chemotherapy after incomplete resection may delay or avoid the use of RT.

Chemotherapy is generally well tolerated in the majority of patients, with minimal toxicity.^{40,41} Hence, a conservative resection combined with adjuvant therapy has also been recommended for intramedullary low-grade astrocytomas.⁵² In addition, the therapeutic efficacy of chemotherapy has been reported to be comparable to radiotherapy regimens.⁴⁵

Role of Adjuvant RT

Adjuvant therapy is associated with improved survival following STR for IMSCtS.^{22,38} Adjuvant radiotherapy following resection significantly improved PFS in a pooled sample population of patients with ependymoma.²⁷ PFS was significantly improved in patients who underwent STR followed by adjuvant RT as compared with those who underwent GTR only.^{20,27} Disease survival up to 59% at 5 years and 43%–52% at 10 years has been reported for patients with astrocytomas treated with adjuvant radiotherapy (median dose 50 Gy) following biopsy or STR.^{9,20,28,34} In-field failure with local tumor recurrence is the most common form of disease recurrence in patients who received postoperative RT.^{1,28,33,49} Local failure rates for ependymomas following postoperative adjuvant RT range from 0% to 11%.^{22,27} Similarly, for low-grade astrocytomas, local failure rates range from 22% to 56%.²²

Other studies have reported conflicting treatment experiences with adjuvant RT. Within a multicenter patient cohort, the inclusion of RT was not found to benefit OS for patients who underwent GTR or STR.⁴ The inclusion of postoperative RT was not associated with disease progression, nor with OS in patients with astrocytomas or ependymomas.¹

RT in pediatric patients with IMSCtS is complicated by both the toxicity and long-term sequelae induced by radiation. These sequelae include development of secondary malignancy,³⁷ secondary anaplastic changes,⁹ increased risk of secondary spinal deformity,³⁹ and radiation-induced myelitis.²⁹ Myelotoxicity of RT is related to the dose per daily fraction, and the location and length of cord segment that is irradiated.²² High-dose RT up to 50 Gy over large treatment fields can be associated with risks of radiation-induced deficits, including spastic quadriplegia.⁵² Radiation doses in the 5500–6000-cGy range are associated with a 6% risk of radiation myelitis.²⁹ Pediatric patients are more susceptible and radiation-induced myelopathy is often observed at lower doses. The neurocognitive effects of radiation and secondary myelopathy are apparent in children at lower doses than in adults.^{46,50}

Treatment Indications of Chemotherapy and RT

The treatment rationales for chemotherapy and RT are more clearly defined for high-grade IMSCtS and for patients with low-grade tumors with typically diffuse and surgically unresectable tumors that show disease progression.^{3,10,18} In contrast, the treatment indications for chemotherapy and RT are less well defined for patients with low-grade tumors following an STR, when expectant management by clinical observation must be weighed against the treatment option of chemotherapy and RT for adjuvant indications or for treatment of disease recurrence at a later time point.

Given PFS rates following STR of 45% and 34% at 5 years and 10 years, respectively, it is important to identify clinical parameters that can predict at-risk subgroups that would benefit from adjuvant therapies. In our study, we therefore focused on identifying clinical factors that aid in decision-making for inclusion of chemotherapy and RT following an STR. Our results indicate that the inclusion of adjuvant chemotherapy and RT was more likely in patients with residual tumor burden following STR. Thus, patients with extensive IMSCtS that were partially resected were more likely to receive chemotherapy or RT. This clinical factor will aid in treatment decisions for adjuvant therapy following STR. The mean interval until disease progression was more than 4 years in our series, underscoring the need for long-term follow-up and surveillance imaging in postoperative management of pediatric patients with low-grade IMSCtS.

Conclusions

Our results indicate that on extended long-term follow-up, surgical management of low-grade pediatric IMSCtS is associated with favorable neurological and disease outcome measures. GTR enables improvement in OS and PFS. The addition of adjuvant chemotherapy and RT following STR is associated with an improved trend in PFS. Residual tumor disease following STR is most significantly associated with use of adjuvant chemotherapy and RT.

References

1. Abdel-Wahab M, Etuk B, Palermo J, Shirato H, Kresl J, Yapi-cier O, et al: Spinal cord gliomas: A multi-institutional retrospective analysis. *Int J Radiat Oncol Biol Phys* **64**:1060–1071, 2006
2. Ahmed R, Menezes AH, Awe OO, Torner JC: Long-term disease and neurological outcomes in patients with pediatric intramedullary spinal cord tumors. *J Neurosurg Pediatr* **13**:600–612, 2014
3. Balmaceda C: Chemotherapy for intramedullary spinal cord tumors. *J Neurooncol* **47**:293–307, 2000
4. Bouffet E, Pierre-Kahn A, Marchal JC, Jouvet A, Kalifa C, Choux M, et al: Prognostic factors in pediatric spinal cord astrocytoma. *Cancer* **83**:2391–2399, 1998
5. Chamberlain MC: Leptomeningeal metastasis. *Curr Opin Oncol* **22**:627–635, 2010
6. Cochrane DD, Gustavsson B, Poskitt KP, Steinbok P, Kestle JR: The surgical and natural morbidity of aggressive resection for posterior fossa tumors in childhood. *Pediatr Neurosurg* **20**:19–29, 1994
7. Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ: Radical excision of intramedullary spinal cord

- tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. **J Neurosurg** **93** (2 Suppl):183–193, 2000
8. de Jonge T, Sluiter H, Dubouset J, Miladi L, Wicart P, Illés T: Late-onset spinal deformities in children treated by laminectomy and radiation therapy for malignant tumours. **Eur Spine J** **14**:765–771, 2005
9. Dirks PB, Jay V, Becker LE, Drake JM, Humphreys RP, Hoffman HJ, et al: Development of anaplastic changes in low-grade astrocytomas of childhood. **Neurosurgery** **34**:68–78, 1994
10. Doireau V, Grill J, Zerah M, Lellouch-Tubiana A, Couanet D, Chastagner P, et al: Chemotherapy for unresectable and recurrent intramedullary glial tumours in children. **Br J Cancer** **81**:835–840, 1999
11. Duffner PK, Krischer JP, Burger PC, Cohen ME, Backstrom JW, Horowitz ME, et al: Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. **J Neurooncol** **28**:245–256, 1996
12. Epstein F: Spinal cord astrocytomas of childhood. **Adv Tech Stand Neurosurg** **13**:135–169, 1986
13. Epstein F, Epstein N: Surgical treatment of spinal cord astrocytomas of childhood. A series of 19 patients. **J Neurosurg** **57**:685–689, 1982
14. Epstein FJ, Farmer JP: Pediatric spinal cord tumor surgery. **Neurosurg Clin N Am** **1**:569–590, 1990
15. Fassett DR, Clark R, Brockmeyer DL, Schmidt MH: Cervical spine deformity associated with resection of spinal cord tumors. **Neurosurg Focus** **20**(2):E2, 2006
16. Garcés-Ambrossi GL, McGirt MJ, Mehta VA, Sciubba DM, Witham TF, Bydon A, et al: Factors associated with progression-free survival and long-term neurological outcome after resection of intramedullary spinal cord tumors: analysis of 101 consecutive cases. **J Neurosurg Spine** **11**:591–599, 2009
17. Goh KY, Velasquez L, Epstein FJ: Pediatric intramedullary spinal cord tumors: is surgery alone enough? **Pediatr Neurosurg** **27**:34–39, 1997
18. Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, et al: Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. **J Clin Oncol** **19**:1288–1296, 2001
19. Huddart R, Traish D, Ashley S, Moore A, Brada M: Management of spinal astrocytoma with conservative surgery and radiotherapy. **Br J Neurosurg** **7**:473–481, 1993
20. Hulshof MC, Menten J, Dito JJ, Dreissen JJ, van den Bergh R, González González D: Treatment results in primary intraspinal gliomas. **Radiother Oncol** **29**:294–300, 1993
21. Innocenzi G, Raco A, Cantore G, Raimondi AJ: Intramedullary astrocytomas and ependymomas in the pediatric age group: a retrospective study. **Childs Nerv Syst** **12**:776–780, 1996
22. Isaacson SR: Radiation therapy and the management of intramedullary spinal cord tumors. **J Neurooncol** **47**:231–238, 2000
23. Jallo GI, Danish S, Velasquez L, Epstein F: Intramedullary low-grade astrocytomas: long-term outcome following radical surgery. **J Neurooncol** **53**:61–66, 2001
24. Karikari IO, Nimjee SM, Hodges TR, Cutrell E, Hughes BD, Powers CJ, et al: Impact of tumor histology on resectability and neurological outcome in primary intramedullary spinal cord tumors: a single-center experience with 102 patients. **Neurosurgery** **68**:188–197, 2011
25. Klekamp J: Treatment of intramedullary tumors: analysis of surgical morbidity and long-term results. **J Neurosurg Spine** **19**:12–26, 2013
26. Kothbauer K, Deletis V, Epstein FJ: Intraoperative spinal cord monitoring for intramedullary surgery: an essential adjunct. **Pediatr Neurosurg** **26**:247–254, 1997
27. Kukreja S, Ambekar S, Sin AH, Nanda A: Cumulative survival analysis of patients with spinal myxopapillary ependymomas in the first 2 decades of life. **J Neurosurg Pediatr** **13**:400–407, 2014
28. Linstadt DE, Wara WM, Leibel SA, Gutin PH, Wilson CB, Sheline GE: Postoperative radiotherapy of primary spinal cord tumors. **Int J Radiat Oncol Biol Phys** **16**:1397–1403, 1989
29. Marcus RB Jr, Million RR: The incidence of myelitis after irradiation of the cervical spinal cord. **Int J Radiat Oncol Biol Phys** **19**:3–8, 1990
30. McCormick PC, Stein BM: Intramedullary tumors in adults. **Neurosurg Clin N Am** **1**:609–630, 1990
31. McGirt MJ, Chaichana KL, Atiba A, Attenello F, Woodworth GF, Jallo GI: Neurological outcome after resection of intramedullary spinal cord tumors in children. **Childs Nerv Syst** **24**:93–97, 2008
32. McGirt MJ, Chaichana KL, Atiba A, Attenello F, Yao KC, Jallo GI: Resection of intramedullary spinal cord tumors in children: assessment of long-term motor and sensory deficits. **J Neurosurg Pediatr** **1**:63–67, 2008
33. McLaughlin MP, Buatti JM, Marcus RB Jr, Maria BL, Mickel PJ, Kedar A: Outcome after radiotherapy of primary spinal cord glial tumors. **Radiat Oncol Investig** **6**:276–280, 1998
34. McLaughlin MP, Marcus RB Jr, Buatti JM, McCollough WM, Mickel JP, Kedar A, et al: Ependymoma: results, prognostic factors and treatment recommendations. **Int J Radiat Oncol Biol Phys** **40**:845–850, 1998
35. Merchant TE, Kiehna EN, Thompson SJ, Heideman R, Sanford RA, Kun LE: Pediatric low-grade and ependymal spinal cord tumors. **Pediatr Neurosurg** **32**:30–36, 2000
36. Miller DC: Surgical pathology of intramedullary spinal cord neoplasms. **J Neurooncol** **47**:189–194, 2000
37. O'Sullivan C, Jenkin RD, Doherty MA, Hoffman HJ, Greenberg ML: Spinal cord tumors in children: long-term results of combined surgical and radiation treatment. **J Neurosurg** **81**:507–512, 1994
38. Oh MC, Ivan ME, Sun MZ, Kaur G, Safaei M, Kim JM, et al: Adjuvant radiotherapy delays recurrence following subtotal resection of spinal cord ependymomas. **Neuro Oncol** **15**:208–215, 2013
39. Otsuka NY, Hey L, Hall JE: Postlaminectomy and postirradiation kyphosis in children and adolescents. **Clin Orthop Relat Res** (354):189–194, 1998
40. Packer RJ, Lange B, Ater J, Nicholson HS, Allen J, Walker R, et al: Carboplatin and vincristine for recurrent and newly diagnosed low-grade gliomas of childhood. **J Clin Oncol** **11**:850–856, 1993
41. Pons MA, Finlay JL, Walker RW, Puccetti D, Packer RJ, McElwain M: Chemotherapy with vincristine (VCR) and etoposide (VP-16) in children with low-grade astrocytoma. **J Neurooncol** **14**:151–158, 1992
42. Rossitch E Jr, Zeidman SM, Burger PC, Curnes JT, Harsh C, Anscher M, et al: Clinical and pathological analysis of spinal cord astrocytomas in children. **Neurosurgery** **27**:193–196, 1990
43. Safaei M, Oh MC, Kim JM, Aranda D, Tarapore PE, Cage TA, et al: Histologic grade and extent of resection are associated with survival in pediatric spinal cord ependymomas. **Childs Nerv Syst** **29**:2057–2064, 2013
44. Sandalcioğlu IE, Gasser T, Asgari S, Lazorisak A, Engelhorn T, Egelhof T, et al: Functional outcome after surgical treatment of intramedullary spinal cord tumors: experience with 78 patients. **Spinal Cord** **43**:34–41, 2005
45. Scheinemann K, Bartels U, Huang A, Hawkins C, Kulkarni AV, Bouffet E, et al: Survival and functional outcome of childhood spinal cord low-grade gliomas. Clinical article. **J Neurosurg Pediatr** **4**:254–261, 2009
46. Schultheiss TE, Kun LE, Ang KK, Stephens LC: Radiation

- response of the central nervous system. **Int J Radiat Oncol Biol Phys** 31:1093–1112, 1995
47. Shaw EG, Wisoff JH: Prospective clinical trials of intracranial low-grade glioma in adults and children. **Neuro Oncol** 5:153–160, 2003
 48. Shikata J, Yamamuro T, Shimizu K, Saito T: Combined laminoplasty and posterolateral fusion for spinal canal surgery in children and adolescents. **Clin Orthop Relat Res** (259):92–99, 1990
 49. Shirato H, Kamada T, Hida K, Koyanagi I, Iwasaki Y, Miyasaka K, et al: The role of radiotherapy in the management of spinal cord glioma. **Int J Radiat Oncol Biol Phys** 33:323–328, 1995
 50. Sundaresan N, Gutierrez FA, Larsen MB: Radiation myelopathy in children. **Ann Neurol** 4:47–50, 1978
 51. Timmermann B, Kortmann RD, Kühl J, Meisner C, Slavc I, Pietsch T, et al: Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. **Int J Radiat Oncol Biol Phys** 46:287–295, 2000
 52. Townsend N, Handler M, Fleitz J, Foreman N: Intramedullary spinal cord astrocytomas in children. **Pediatr Blood Cancer** 43:629–632, 2004
 53. Wisoff JH, Sanford RA, Heier LA, Sposto R, Burger PC, Yates AJ, et al: Primary neurosurgery for pediatric low-grade gliomas: a prospective multi-institutional study from the Children's Oncology Group. **Neurosurgery** 68:1548–1555, 2011
 54. Woodworth GF, Chaichana KL, McGirt MJ, Sciubba DM, Jallo GI, Gokaslan Z, et al: Predictors of ambulatory function after surgical resection of intramedullary spinal cord tumors. **Neurosurgery** 61:99–106, 2007
 55. Yao KC, McGirt MJ, Chaichana KL, Constantini S, Jallo GI: Risk factors for progressive spinal deformity following resection of intramedullary spinal cord tumors in children: an analysis of 161 consecutive cases. **J Neurosurg** 107 (6 Suppl):463–468, 2007
 56. Yasuoka S, Peterson HA, MacCarty CS: Incidence of spinal column deformity after multilevel laminectomy in children and adults. **J Neurosurg** 57:441–445, 1982

Disclosures

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

Author Contributions

Conception and design: Menezes, Ahmed. Acquisition of data: Ahmed. Analysis and interpretation of data: all authors. Drafting the article: Menezes, Ahmed. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Menezes. Statistical analysis: Ahmed, Torner. Study supervision: Menezes.

Supplemental Information

Previous Presentations

Portions of this work were presented as a poster at the AANS Annual Meeting in 2013.

Correspondence

Arnold H. Menezes, Department of Neurosurgery, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., 1824 JPP, Iowa City, IA 52242. email: arnold-menezes@uiowa.edu.