Cervicomedullary tumors in children

Joseph H. McAbee, BS,¹ Joseph Modica, BS,² Clinton J. Thompson, PhD,³
Alberto Broniscer, MD,^{4,5} Brent Orr, MD, PhD,⁶ Asim F. Choudhri, MD,^{7–9} Frederick A. Boop, MD,^{7,9–11}
and Paul Klimo Jr., MD, MPH^{7,9–11}

¹School of Medicine, Wake Forest University, Winston-Salem, North Carolina; ²University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, New York; ³George Washington University Milken Institute School of Public Health, Washington, DC; and ⁴Department of Oncology, St. Jude Children's Research Hospital; ⁵Department of Pediatrics, University of Tennessee Health Science Center; ⁶Department of Pathology, St. Jude Children's Research Hospital; ⁷Department of Neurosurgery, University of Tennessee Health Science Center; ⁸Department of Radiology, University of Tennessee Health Science Center; ⁹Le Bonheur Neuroscience Institute, Le Bonheur Children's Hospital; ¹⁰Department of Surgery, St. Jude Children's Research Hospital; and ¹¹Semmes-Murphey Neurologic & Spine Institute, Memphis, Tennessee

OBJECT Cervicomedullary tumors (CMTs) represent a heterogeneous group of intrinsic neoplasms that are typically low grade and generally carry a good prognosis. This single-institution study was undertaken to document the outcomes and current treatment philosophy for these challenging neoplasms.

METHODS The charts of all pediatric patients with CMTs who received treatment at St. Jude Children's Research Hospital between January 1988 and May 2013 were retrospectively reviewed. Demographic, surgical, clinical, radiological, pathological, and survival data were collected. Treatment-free survival and overall survival were estimated, and predictors of recurrence were analyzed.

RESULTS Thirty-one children (16 boys, 15 girls) with at least 12 months of follow-up data were identified. The median age at diagnosis was 6 years (range 7 months–17 years) and the median follow-up was 4.3 years. Low-grade tumors (Grade I or II) were present in 26 (84%) patients. Thirty patients underwent either a biopsy alone or resection, with the majority of patients undergoing biopsy only (n = 12, 39%) or subtotal resection (n = 14, 45%). Only 4 patients were treated solely with resection; 21 patients received radiotherapy alone or in combination with other treatments. Recurrent tumor developed in 14 children (45%) and 4 died as a result of their malignancy. A high-grade pathological type was the only independent variable that predicted recurrence. The 5- and 10-year treatment-free survival estimates are 64.7% and 45.3%, respectively. The 5- and 10-year overall survival estimate is 86.7%.

CONCLUSIONS Children with CMTs typically have low-grade neoplasms and consequently long-term survival, but high risk of recurrence. Therapy should be directed at achieving local tumor control while preserving and even restoring neurological function.

<http://thejns.org/doi/abs/10.3171/2015.5.PEDS14638>

KEY WORDS cervicomedullary tumor; low-grade neoplasm; radiation; chemotherapy; outcomes; resection; oncology

CERVICOMEDULLARY tumors (CMTs) are rare intramedullary neoplasms centered at the junction of the cervical spine and brainstem. The majority of these tumors are histologically benign, slow-growing gliomas that typically present with a long duration of symptoms.⁴² These symptoms fall into two categories: lower brainstem dysfunction, and myelopathy.^{16,36} Patients whose tumor

focus is within the medulla first develop nausea and vomiting, obstructive hydrocephalus, failure to thrive, lower cranial nerve dysfunction, chronic aspiration, sleep apnea, and head tilt. When the tumor focus is in the upper cervical spine, characteristic features are neck pain; progressive weakness with changes in gait, hand preference, and motor regression in younger patients; hyper- or hyporeflexia;

ABBREVIATIONS CMT = cervicomedullary tumor; GBM = glioblastoma multiforme; GTR = gross-total resection; HGG NOS = high-grade glioma, not otherwise specified; NTR = near-total resection; OS = overall survival; PD = progressive disease; RT = radiotherapy; SD = stable disease; STR = subtotal resection; TFS = treatment-free survival.

SUBMITTED November 14, 2014. **ACCEPTED** May 27, 2015.

INCLUDE WHEN CITING Published online June 26, 2015; DOI: 10.3171/2015.5.PEDS14638.

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

pathologic reflexes; and sensory symptoms.^{28,33} Facial pain is also a common presenting symptom.¹⁸ Given these lesions' radiographic, pathological, and clinical similarities, some researchers have postulated that CMTs are mainly tumors of the cervical spine with rostral extension into the medulla.³⁷ Regardless of its anatomical origin, as the tumor expands, patients will often develop a mixture of signs and symptoms.

For many years, brainstem gliomas and CMTs were generally thought to be inoperable due to their location and their perceived high risk of neurological morbidity. The advent of MRI in the 1980s brought about recognition that brainstem tumors are a heterogeneous collection of tumor types with major differences in presentation and survival, resulting in various classification systems.^{9,23,32} The classification system by Choux et al. proposes 4 distinct types of brainstem tumors, with Type IV being cervicomedullary.¹³ With regard to potential surgical treatment, some argue that there are two groups: diffuse pontine gliomas and all other gliomas.²⁷

With advancements in neuroimaging (e.g., tractography), and intraoperative technology (e.g., ultrasound, neurophysiological monitoring, and MRI), resection of CMTs is feasible in many cases.^{10–12,23,35,39} Because most CMTs are low grade, they tend to grow circumferentially around pial structures and are redirected at interfaces with white matter tracts. Thus, the medial lemniscus and pyramidal decussating fibers halt their spread into the pontomedullary junction and direct their growth toward the fourth ventricle.^{17,36} This growth restriction can sometimes result in a well-defined tumor plane, making resection easier for the surgeon.²⁰

Some believe that resection should be the treatment of choice for CMTs.^{4,16,24,38,40} Patients with longer prodrome and less severe neurological deficits prior to resection typically have the lowest risk of sustaining a significant neurological deficit after surgery, and in general have a favorable overall survival prognosis.^{1,14,33,38} However, depending on the tumor pathological and radiographic characteristics, radiotherapy (RT) and/or chemotherapy may supplement or be considered a better primary treatment than surgery.² Surgery, in such cases, would be reserved for tissue diagnosis only. We present our series of pediatric CMTs and propose a treatment algorithm for de novo tumors based on our experience.

Methods

Study Population

The study was approved by the institutional review boards of St. Jude Children's Research Hospital and Le Bonheur Children's Hospital. We conducted a retrospective review to identify children with an intramedullary CMT diagnosed between January 1988 and May 2013. Patients were enrolled in the study if they had pathological confirmation of their tumor type by biopsy or resection at Le Bonheur Children's Hospital or at an outside institution with at least 12 months of follow-up. In 1 patient the tumor was diagnosed postmortem (see details below). Patients who died within the 1st year as a result of tumor progression were also included. Each patient's initial and all

follow-up imaging and pathology reports were reviewed and treatment options deliberated during a weekly multidisciplinary pediatric neurooncology conference. In cases where the initial surgery or biopsy was performed at another facility, the pathological diagnosis was independently verified by a board-certified neuropathologist (B.O.).

Definitions

A cervicomedullary neoplasm was defined as an intramedullary tumor that spans the cervicomedullary junction. All tumors were therefore intrinsic, but may have had an exophytic portion, which was defined as a breach through the pial boundary of the upper spinal cord or lower brainstem. Extramedullary primary or metastatic tumors located at the cervicomedullary junction were excluded.

Extent of resection was based on postoperative MRI findings, with gross-total resection (GTR), near-total resection (NTR), and subtotal resection (STR) being defined as no evidence of residual tumor, $\geq 90\%$ excision, and $< 90\%$ excision, respectively. Recurrence was defined as tumor regrowth after prior imaging showed no evidence of residual tumor; progression was defined as growth of tumor that was present on prior imaging. Time to first recurrence or progression was defined as the number of days from start of first-line definitive therapy (i.e., surgery, chemotherapy, or RT) to the date on which second-line therapy was initiated. This time interval was designated "treatment-free survival" (TFS). Time to subsequent recurrence(s) was the number of days between treatments. Total follow-up was the number of days from date of diagnosis to last clinic follow-up or death. At last follow-up, we classified patients as either having stable disease (SD) or progressive disease (PD) based on their most recent MRI findings. Patients who had a GTR with no evidence of regrowth at last follow-up were still labeled as having SD rather than being disease free.

Data Collection and Outcomes

Demographic, surgical, clinical, radiological, pathological, and survival data were collected. The TFS and overall survival (OS) were calculated. The following variables were evaluated as possible predictors of recurrence using Cox proportional hazards regression analysis (Stata/SE v13.1, StataCorp): patient age at diagnosis, sex, race, tumor pathology (low grade vs high grade), and whether RT was part of the initial treatment.

Results

Presentation and Pathological Findings

We identified 31 children with CMTs; the characteristics of this population are shown in Table 1. The median age at diagnosis was 6 years (range 7 months–17 years) and 16 (52%) were male. The median follow-up was 4.3 years (range 0.3–26.4 years), and there were 4 deaths.

Sixteen patients presented with hemiparesis (52%), 14 with cranial neuropathies (45%), 11 with pain and/or sensory changes (35%), and 15 with ataxia (48%). One patient was found to have an associated genetic disorder (neurofibromatosis Type 2). The median duration of preoperative symptoms was 60 days (range 3–1460), with 2 tumors

TABLE 1. Characteristics in 31 patients with CMTs

Variable	Value*
Age at Dx (yrs)	
Median	6
Mean	7.0
Range	7 mos–17 yrs
Sex	
Male	16 (52)
Female	15 (48)
Race	
White	22 (71)
Black	8 (26)
Other	1 (3)
FU in yrs	
Median	4.3
No. w/ <5	18
No. w/ 5–9	6
No. w/ 10–15	1
No. w/ >15	6
Presentation	
Hydrocephalus	8 (26)
Nausea/vomiting	5 (16)
Headache	5 (16)
Ataxia	15 (48)
Altered gait	6 (19)
Impaired balance	5 (16)
Hemiparesis (unilat or bilat)	16 (52)
Cranial neuropathy (unilat or bilat)	14 (45)
Pain & numbness	11 (35)
Duration of preop symptoms (days)	
Median	60
Mean	257
Range	3–1460
Tumor appearance	
Intrinsic	31 (100)
Exophytic component	6 (19)
Syrinx present	8 (26)
WHO grade	
I	21 (68)
II	5 (16)
III	2 (6)
IV	3 (10)

Dx = diagnosis; FU = follow-up.

* Unless otherwise indicated, values are the number of patients (%).

found incidentally. Patients with low-grade tumors had a longer median duration of preoperative symptomatology (180 days) than patients with high-grade tumors (30 days). On initial imaging, 6 patients (19%) had exophytic tumor components, 8 (26%) had a syrinx, and 8 (26%) had hydrocephalus.

Twenty-one patients had WHO Grade I tumors (68%), 5 had Grade II tumors (16%), 2 had Grade III (6%), and 3

had Grade IV (10%). Grade I tumors were pilocytic astrocytomas (n = 12), gangliogliomas (8), and an angiocentric glioma (1). Grade II tumors were diffuse astrocytomas (4) and an ependymoma (1). There were 5 patients with malignant neoplasms. One patient had a Grade III tumor (anaplastic ependymoma) and 3 had Grade IV (glioblastoma multiforme [GBM]). The other Grade III tumor was designated high-grade glioma, not otherwise specified (HGG NOS) and had no slides available for review.

Treatments

Table 2 contains the first-line treatment, extent of definitive surgery, and overall treatment combinations for our patients. First-line treatment was highly variable. Thirty of 31 patients had some form of surgical intervention (either biopsy or resection). One patient from the late 1980s was treated with RT and her high-grade tumor was diagnosed postmortem. Surgery was the sole treatment in 4 patients (13%). Two patients with gangliogliomas presented with mild symptoms, underwent open biopsies, and are being followed with serial imaging that has—to date—demonstrated stable disease. Of all the patients who were treated with resection, 6 (19%) had undergone a previous biopsy or STR prior to their definitive resection. Overall, 21 patients underwent 1 surgery, 7 have undergone 2

TABLE 2. Summary of treatments rendered in 31 patients with CMTs

Variable	No. (%)
1st line of Tx	
RT only	1 (3)
Bx only	2 (6)
Bx + more extensive op	1 (3)
Bx + chemo	2 (6)
Bx + RT	6 (19)
Bx + more extensive op + chemo	1 (3)
Bx + chemo + RT	2 (6)
Bx + more extensive op + chemo + RT	1 (3)
Resection only	6 (19)
Resection + chemo	4 (13)
Resection + RT	4 (13)
Resection + chemo + RT	1 (3)
Extent of most definitive op	
Bx	12 (39)
GTR	3 (10)
NTR	1 (3)
STR	14 (45)
Had previous op before most definitive op	6 (19)
Mode of Tx	
Bx only	2 (6)
Op only	4 (13)
RT only	1 (3)
Op + RT	10 (32)
Op + chemo	4 (13)
Op + RT + chemo	10 (32)

Bx = biopsy; chemo = chemotherapy; Tx = treatment.

surgeries, and 2 patients had 3 surgeries. The most common mode of treatment throughout each patient's overall treatment history was surgery with subsequent focal RT (n = 10, 32%), followed by surgery with subsequent RT and chemotherapy (n = 10, 32%). Five patients developed kyphosis or instability following treatment for their CMT, 4 of whom required an occipitocervical fusion.

Recurrence, TFS, and OS

Table 3 shows clinical differences and differences in tumor pathological type between the 14 (45%) patients who experienced tumor progression requiring treatment and the 17 (55%) who did not. All 5 patients with high-grade tumors experienced recurrence, whereas only 9 (35%) of the 26 patients with low-grade tumors did. Ten patients (59%) without recurrent disease received RT as part of their initial treatment, whereas 6 patients (43%) with recurrent disease did. Of these 6 patients, 4 had high-grade neoplasms. When analyzing only patients with low-grade neoplasms and removing the 2 patients who have not received any treatment thus far (n = 24 patients), 10/15 (67%) patients without recurrent disease had RT as part of their initial treatment, whereas only 1/9 (11%) with recurrent disease had RT. A high-grade pathological type was the sole predictor of recurrence (HR 29.29, 95% CI 4.0–222.8, $p < 0.001$). At final follow-up, all patients without recurrent disease are alive with SD. Of those who did have recurrence, 4 died due to disease progression, 2 have PD, and 8 have SD (2 of whom are currently receiving chemotherapy).

Table 4 provides further details on the 14 patients who developed recurrent disease. The median time to treatment for tumor progression was 423 days (range 88–5654 days). In 7 patients, tumor progression requiring treatment occurred within 1 year of their initial treatment. The 5- and 10-year TFS rates are 64.7% (95% CI 44.2%–79.2%) and 45.3% (95% CI 23%–65.2%), respectively. Six of the 9 patients who did not receive RT initially received radiation as salvage therapy after tumor progression; all of them currently have SD. The disease status of the 3 remaining radiation-naïve patients includes 1 patient with SD who is receiving chemotherapy, 1 patient with SD after a second GTR, and 1 patient with PD after multiple recurrences. Three children have developed a second recurrence at a median time of 108 days (range 70–2613 days).

A total of 4 patients have died. All 4 died due to disease progression from high-grade tumors (3 GBMs and 1 HGG NOS) within 1 year of diagnosis (median 228 days). Thus,

the 5- and 10-year OS rates are the same at 86.7% (95% CI 68.4%–94.8%). Figure 1 shows the TFS and OS curves.

Discussion

This study represents one of the largest series of children with CMTs.^{4,16,33,38,42} Cervicomedullary tumors are a rare group of diverse tumors. The majority of patients have low-grade tumors with long duration of preoperative symptoms. The variable pathological findings in our series were similar to those in other studies.^{33,38} As with any entity in which a low-grade pathological type is predominant, overall survival is high, but so is the risk of recurrence requiring further treatment.^{15,42} Fourteen (45%) of our children developed a recurrence at a median and mean time of 354 and 1193 days, respectively. Four patients died, all with high-grade tumor pathological types and all within 1 year of diagnosis. With a median follow-up of 4.3 years, our 5- and 10-year OS estimate was 86.7%, whereas our 5- and 10-year TFS estimates were 64.7% and 45.3%, respectively.

These estimates are similar to those in the study by Weiner et al., which reported a 5-year progression-free and total survival of 60% and 89%, respectively.³⁸ Their study found that patients with longer preoperative duration of symptoms (i.e., > 15 weeks) had a longer progression-free survival. Similarly, Robertson et al. reported that patients with CMT who have a protracted duration of symptoms prior to diagnosis typically have a more indolent, low-grade neoplasm with high likelihood of long overall survival.³³ Indeed, our patients with low-grade tumors had a significantly longer median duration of preoperative symptoms (25.7 weeks) compared with the ones with high-grade lesions (4.3 weeks). All of our patients with high-grade tumors experienced a recurrence or progression after first-line therapy, compared with only 35% of patients with low-grade tumors, again similar to the study of Weiner et al., in which their patients with high-grade tumors experienced a higher proportion of tumor progression compared with those who had low-grade tumors (75% vs 30%). A high-grade pathological type was the only statistically independent predictor of recurrence in our series. In some of our patients the tumors recurred as late as 8–15 years after the initiation of their primary treatment; therefore, long-term follow-up (minimum of 10 years) is essential to neurologic preservation and overall survival.

The variety of initial treatments is due to a number of factors, the most important being age at diagnosis, tumor pathological type, and extent of resection. In addition, available treatments, opinions, and knowledge regarding these treatments emerge and change with time, which is a significant factor for our population that includes patients whose treatment dates back to the late 1980s. Surgery has and will continue to play a major role in these tumors, but few will be effectively managed by surgery alone. In our series, only 4 children have been treated with resection only. Whereas some studies have argued for radical excisions alone,^{4,16,29} we believe that effective treatment for CMTs is often multimodal, typically starting with resection. Surgery allows one to make a diagnosis, decompress the brainstem and cervical spinal cord, and treat an as-

TABLE 3. Characteristics of 31 patients with and without recurrent disease

Variable	No Recurrence (n = 17)	Recurrence (n = 14)
Median age at Dx (yrs)	7	5
Sex (M/F)	9/8	7/7
Race (white/black/other)	11/5/1	11/3/0
Pathological type	All low grade	5 high grade; 9 low grade
RT as part of initial Tx	10 (59%)	6 (43%)
Status at last FU	All SD	4 died, 2 PD, 8 SD

TABLE 4. Characteristics of the 14 patients who experienced tumor recurrence or progression

Case No.	Age (yrs) at Dx, Sex	Pathological Type	Initial Tx	Time to 1st Recurrence (days)	Second-Line Tx	Subsequent Recurrences (days), Tx	Status at Last FU
1	14, F	HGG NOS	Bx + chemo + RT	193	None	None	Dead
2	8, F	GBM	RT	263	None	None	Dead
3	2, M	JPA	Bx + chemo	189	STR	108, RT	SD
4	6, F	JPA	STR + RT	2723	Bx + chemo	None	PD
5	2, M	JPA	STR	261	Chemo	None	SD
6	4, M	GG	STR + chemo	453	RT	None	SD
7	12, M	DA	NTR	438	RT	None	SD
8	17, M	GBM	STR + RT + chemo	284	None	None	Dead
9	13, F	GBM	Bx + RT + chemo	109	None	None	Dead
10	1, F	JPA	STR + chemo	2734	Chemo	70, Chemo	PD
11	0.8, F	DA	STR + chemo	88	RT	None	SD
12	16, M	AE	STR + chemo	423	STR + GTR + RT	None	SD
13	4, F	JPA	STR	2891	STR + RT	2613, Bx + chemo	SD
14	1, M	JPA	GTR	5654	GTR	None	SD

AE = anaplastic ependymoma; DA = diffuse astrocytoma; GG = ganglioglioma; JPA = juvenile pilocytic astrocytoma.

sociated syrinx or obstructive hydrocephalus. Complete resection is often not possible because of poorly demarcated tumor borders or an unacceptably high risk of neurological deficit. More importantly, complete resection of selected histopathological tumor types, such as pilocytic astrocytomas, may not be necessary because small foci of residual tumor may remain quiescent for some time.⁷ Thus, surgery will not be curative in many instances in low-grade tumors and never with high-grade lesions. Intraoperative MRI, ultrasound, neurophysiological monitoring, and stereotaxy are valuable tools for the surgeon trying to achieve a maximal safe resection. Postoperative sagittal deformity is a well-described risk factor for children who undergo surgery for an intramedullary spinal cord tumor; other risk factors include the presence of a syrinx, multilevel surgery, young age, and preoperative deformity.^{3,41} Five of our patients developed a significant postoperative kyphosis, with 4 of them eventually requiring spinal stabilization and fusion.

FIG. 1. The OS and TFS curves for the 31 children in our study.

Similar to our experience with focal brainstem tumors, RT is an excellent treatment option for CMTs.²⁶ It can be the primary or salvage treatment for low-grade tumors or it can be used in conjunction with chemotherapy for the primary treatment of malignant tumors. Among our patients with low-grade tumors who received RT ($n = 16$), there were only 2 failures. Di Maio et al. reported that a less aggressive initial surgical approach may be indicated for CMTs that demonstrate enhancing tumor interposed with nonenhancing tissue that is continuous with normal cervical spinal cord and/or medulla, and/or a poorly defined tumor/brainstem interface with abnormal low T1 signal extending beyond the obvious tumor into the brainstem on MRI. They argue that when these MRI characteristics are present, chemotherapy and/or RT may be better treatment options and provide local control, survival, and neurological outcome advantages.¹⁴ Although RT was not found to be statistically protective against tumor recurrence among all patients or those with low-grade tumors only, this is probably a result of the low number of patients rather than a true lack of association.

Chemotherapy is generally not considered the sole treatment but more as adjuvant therapy in conjunction with surgery, or salvage treatment for recurrent or progressive disease. In young children, chemotherapy is often selected to allow as much physical and neurocognitive growth and development as possible before committing them to RT. Although chemotherapy may yield disease stabilization or objective responses in a large percentage of patients, these results are not long lasting, with the 5-year progression-free survival in the 30%–40% range.³¹ However, much research is currently devoted to developing targeted therapy based on the tumor's disrupted molecular fingerprint.^{4,16,22,34} For example, in a study of 32 posterior fossa pilocytic astrocytomas, it was found that 100% of the tumors studied harbored genetic aberrations leading to the activation of the ERK/MAPK pathway. In addition,

the *KIAA1549-BRAF* gene fusions were identified with high frequency.¹⁹ Other studies have shown that loss of the *NF1* gene allows hyperactivation of the oncogene *KRAS*,³⁴ and a microtubule-binding drug, EM011, can decrease the expression of cancer progression genes like *EGFR*, *mTORC1*, and multiple matrix metalloproteinases.⁵ The ERK/MAPK pathway represents an intriguing route of targeted therapy with drugs, such as MEK inhibitors, for patients in whom an aggressive resection is not possible or not desired. Subsets of infratentorial gangliogliomas were also found to contain either *BRAF* V600E mutations or *KIAA1549-BRAF* fusions,^{6,21} suggesting a potential for targeted therapies in the future for the majority of CMTs (pilocytic astrocytomas and gangliogliomas).

Treatment Recommendations

We have created a decision-making pathway tree for treating children with a newly diagnosed tumor (Fig. 2). It is based on our experience and current knowledge of CMTs and may serve as a guide, with the understanding that treatment should always be individualized and modified as new research emerges. High-quality preoperative imaging is critical. If the borders of the neoplasm are clearly defined

and tractography shows the ascending/descending tracts to be displaced by the tumor, then maximal safe resection should be carried out (Fig. 3). This is particularly necessary when there is significant mass effect on the spinal cord or brainstem or when there is impending obstructive hydrocephalus. Children will typically develop a glial cyst at the most rostral border of the tumor with the pons, and a syrinx at the inferior border of the tumor. Once a syrinx develops, it has been our observation that it will progress until the tumor is surgically addressed. Furthermore, performing the myelotomy at the junction of the syrinx and tumor helps the surgeon distinguish tumor from normal tissue. The rostral glial cyst can also help define a superior margin unless the cyst wall enhances, in which case it is lined with neoplastic cells. Resection should be done with caution in areas of the tumor in which the surgeon is not confident where the interface between tumor and normal neural tissue exists, as well as in areas in which the neural tissue has been markedly thinned by the tumor. In these circumstances, it may be prudent to be less aggressive so as to prevent irreversible neurological damage. Endoscopic third ventriculostomy is an excellent option for the treatment of obstructive hydrocephalus that cannot be remedied with tumor resection.²⁵

FIG. 2. Treatment algorithm for children with newly diagnosed CMT. For patients who fall on the right-hand side of the flow diagram, "Treat" denotes nonsurgical modalities (radiation and/or chemotherapy).

FIG. 3. Case 1. This 2-year-old boy presented with a 2-month history of left hemiparesis. On preoperative MRI he was found to have a large expansile mass (pilocytic astrocytoma) at the cervicomedullary junction resulting in uplifting of the inferior portion of the floor of the fourth ventricle without direct extension above the obex, and a smooth thin circumferential rim of relatively uninvolved parenchyma (**A and B**). Frontal projection diffusion tensor fiber tracking (**C**) showing intact fiber tracts draped around the anterior aspect of the lesion. Intraoperative and 6-week postoperative MRI (**D and E**) demonstrating small enhancing residual lesion along the superior margin of the resection cavity. Asymptomatic progression was found on 6-month imaging, so the patient was started on chemotherapy and has been progression free as of 1 year later. Figure is available in color online only.

If the preoperative imaging suggests a tumor that is infiltrative, that does not have a distinct margin, or that has grown into adjacent structures such as the pons and cerebellar peduncles, then we believe the only surgical procedure that is indicated is an open biopsy (Fig. 4). Tumors that infiltrate white matter tracts cannot be aggressively debulked without risk of significant neurological morbidity. This is true of both high-grade and low-grade infiltrative tumors, and accordingly diffusion tensor imaging can help in surgical planning for these lesions.^{12,29,30} When performing an open biopsy, the target site should be one that has the greatest chance of making a diagnosis with an adequate tissue specimen, such as an area that is brightly enhancing, active on MR perfusion, or an easily accessible exophytic portion of the tumor. Subtotal resection provides no oncological benefit; it is of importance if the patient has other issues, such as an effaced cervicomedullary junction, syrinx, or obstructive hydrocephalus. Therefore, we believe that after biopsy, postsurgical RT and/or chemotherapy may represent an effective alternative to overly aggressive resection in patients with infiltrative or inoperable CMTs (Fig. 5). If the biopsy confirms a low-grade neoplasm, then the current severity and history of the patient's symptoms are important determinants of the decision-making process. If the child is minimally affected or nonsymptomatic, then a follow-up plan of serial clinic visits with imaging is reasonable. Otherwise, radiation or chemotherapy should be initiated. An exception to this philosophy would be in children with infiltrative diffuse astrocytomas. These patients will probably require

further treatment, given the risk of malignant degeneration over the course of the child's life.⁸ If the biopsy reveals a malignancy, then the child will automatically require further treatment.

Strengths and Limitations

Although our study details the experience of a single institution with a relatively large number of pediatric patients with CMTs, it is subject to the limitations of all retrospective reviews. At the time of data collection, the median follow-up time was 4.3 years, which is short when dealing with a disease in which a low-grade pathological type is predominant. Eighteen patients had less than 5 years of follow-up, which limits conclusions based on TFS and OS. Because the pathological findings, combination of treatments, and time course of treatment administration were quite variable, the critical examination and recommendation of optimal treatment modalities, new chemotherapy drug efficacy, and adequate resection is limited in its strength.

Conclusions

Cervicomedullary tumors are rare, typically low-grade, focal tumors that can present with a long duration of symptoms due to compression of medullary and cervical spinal structures. Resection has traditionally been the treatment of choice for CMTs and still plays a significant role. New radiographic and surgical techniques, particularly intraoperative MRI and diffusion tensor imaging, can help ensure

FIG. 4. Case 2. This 12-year-old boy presented with left perioral numbness and discomfort. Admission MRI depicted a patchy enhancing intramedullary mass in the left dorsolateral aspect of the cervicomedullary junction with T2 prolongation extending beyond the margins of the enhancement (**A–C**). Axial T1-weighted postgadolinium image (**D**) obtained at the same level with directionally encoded fractional anisotropy overlay shows diminished fractional anisotropy in the left dorsolateral aspect of the spinal cord, corresponding to the expected location of the spinal trigeminal tract and causing the ipsilateral jaw pain. Coronal (**E**) and sagittal (**F**) T1-weighted postcontrast images with diffusion tensor fiber tracking overlay show disruption of fibers by the mass. An open biopsy provided the diagnosis of ganglioglioma. Because of his continued facial symptoms, the patient was treated with focal radiotherapy and his discomfort gradually resolved. Images reprinted from Choudhri AF, Whitehead MT, Klimo P Jr, Montgomery BK, Boop FA: Diffusion tensor imaging to guide surgical planning in intramedullary spinal cord tumors in children. *Neuroradiology* 56:169–174, 2014. With kind permission from Springer Science and Business Media. Figure is available in color online only.

FIG. 5. Case 3. This 19-year-old woman originally underwent an STR of her pilocytic astrocytoma when she was 4 years old. Eight years later, her tumor progressed, and she underwent another STR followed by proton beam therapy. Seven years later, she developed a second recurrence (solid and cystic) that caused obstructive hydrocephalus (**A–C**). An endoscopic third ventriculostomy was performed, followed by an open biopsy to confirm the original pathological findings. She was started on a new, molecular-targeted chemotherapy (MEK inhibitor), with shrinkage of both the enhancing solid and dorsally exophytic cystic components (**D and E**).

that the maximum amount of tumor is resected while simultaneously providing the minimum amount of associated morbidity. Radiation therapy, and possibly new, targeted chemotherapy drugs, can be effective at maintaining local control of tumor progression while also providing further relief of symptoms. Therefore, adjuvant therapies represent a possible alternative to overly aggressive resection. Patients with CMTs typically enjoy long-term survival. Despite this, late recurrences can occur, which highlights the necessity of long-term (i.e., 10 years or more) clinical and radiographic follow-up.

Acknowledgment

We thank Andrew J. Gienapp (Department of Medical Education, Methodist University Hospital, Memphis, and Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN) for technical and copy editing, preparation of the manuscript and figures for publishing, and publication assistance with this manuscript.

References

- Abbott R, Shiminski-Maher T, Epstein FJ: Intrinsic tumors of the medulla: predicting outcome after surgery. **Pediatr Neurosurg** 25:41–44, 1996
- Abbott R, Shiminski-Maher T, Wisoff JH, Epstein FJ: Intrinsic tumors of the medulla: surgical complications. **Pediatr Neurosurg** 17:239–244, 1991–1992
- Ahmed R, Menezes AH, Awe OO, Mahaney KB, Torner JC, Weinstein SL: Long-term incidence and risk factors for development of spinal deformity following resection of pediatric intramedullary spinal cord tumors. **J Neurosurg Pediatr** 13:613–621, 2014
- 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
- Ajeawung NF, Joshi HC, Kamnasaran D: The microtubule binding drug EM011 inhibits the growth of paediatric low grade gliomas. **Cancer Lett** 335:109–118, 2013
- Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, et al: Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. **Pediatr Blood Cancer** 61:1101–1103, 2014
- Benesch M, Eder HG, Sovinz P, Raith J, Lackner H, Moser A, et al: Residual or recurrent cerebellar low-grade glioma in children after tumor resection: is re-treatment needed? A single center experience from 1983 to 2003. **Pediatr Neurosurg** 42:159–164, 2006
- Broniscer A, Baker SJ, West AN, Fraser MM, Proko E, Kocak M, et al: Clinical and molecular characteristics of malignant transformation of low-grade glioma in children. **J Clin Oncol** 25:682–689, 2007
- Brotchi J, Dewitte O, Levivier M, Balériaux D, Vandesteene A, Raftopoulos C, et al: A survey of 65 tumors within the spinal cord: surgical results and the importance of preoperative magnetic resonance imaging. **Neurosurgery** 29:651–657, 1991
- Cheng JS, Ivan ME, Stapleton CJ, Quinones-Hinojosa A, Gupta N, Auguste KI: Intraoperative changes in transcranial motor evoked potentials and somatosensory evoked potentials predicting outcome in children with intramedullary spinal cord tumors. **J Neurosurg Pediatr** 13:591–599, 2014
- Choudhri AF, Klimo P Jr, Auschwitz TS, Whitehead MT, Boop FA: 3T intraoperative MRI for management of pediatric CNS neoplasms. **AJNR Am J Neuroradiol** 35:2382–2387, 2014
- Choudhri AF, Whitehead MT, Klimo P Jr, Montgomery BK, Boop FA: Diffusion tensor imaging to guide surgical planning in intramedullary spinal cord tumors in children. **Neuroradiology** 56:169–174, 2014
- Choux M, Lena G, Do L: Brainstem tumors, in Choux M, Di Rocco C, Hockley A, et al (eds): **Pediatric Neurosurgery**. New York: Churchill Livingstone, 2000, pp 471–491
- Di Maio S, Gul SM, Cochrane DD, Henderson G, Sargent MA, Steinbok P: Clinical, radiologic and pathologic features and outcome following surgery for cervicomedullary gliomas in children. **Childs Nerv Syst** 25:1401–1410, 2009
- Donaldson SS, Laningham F, Fisher PG: Advances toward an understanding of brainstem gliomas. **J Clin Oncol** 24:1266–1272, 2006
- Epstein F, Wisoff J: Intra-axial tumors of the cervicomedullary junction. **J Neurosurg** 67:483–487, 1987
- Epstein FJ, Farmer JP: Brain-stem glioma growth patterns. **J Neurosurg** 78:408–412, 1993
- Epstein N, Epstein F, Allen JC, Aleksic S: Intractable facial pain associated with a ganglioglioma of the cervicomedullary junction: report of a case. **Neurosurgery** 10:612–616, 1982
- Forshe T, Tatevossian RG, Lawson AR, Ma J, Neale G, Ogunkolade BW, et al: Activation of the ERK/MAPK pathway: a signature genetic defect in posterior fossa pilocytic astrocytomas. **J Pathol** 218:172–181, 2009
- 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
- Gupta K, Orisme W, Harreld JH, Qaddoumi I, Dalton JD, Punchihewa C, et al: Posterior fossa and spinal gangliogliomas form two distinct clinicopathologic and molecular subgroups. **Acta Neuropathol Commun** 2:18, 2014
- Hargrave D: Paediatric high and low grade glioma: the impact of tumour biology on current and future therapy. **Br J Neurosurg** 23:351–363, 2009
- Jallo GI, Biser-Rohrbaugh A, Freed D: Brainstem gliomas. **Childs Nerv Syst** 20:143–153, 2004
- Jallo GI, Danish S, Velasquez L, Epstein F: Intramedullary low-grade astrocytomas: long-term outcome following radical surgery. **J Neurooncol** 53:61–66, 2001
- Klimo P Jr, Goumnerova LC: Endoscopic third ventriculocisternostomy for brainstem tumors. **J Neurosurg** 105 (4 Suppl):271–274, 2006
- Klimo P Jr, Pai Panandiker AS, Thompson CJ, Boop FA, Qaddoumi I, Gajjar A, et al: Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience. **J Neurosurg Pediatr** 11:274–281, 2013
- Mauffrey C: Paediatric brainstem gliomas: prognostic factors and management. **J Clin Neurosci** 13:431–437, 2006
- Morota N, Deletis V, Lee M, Epstein FJ: Functional anatomic relationship between brain-stem tumors and cranial motor nuclei. **Neurosurgery** 39:787–794, 1996
- Nair AP, Mehrotra A, Das KK, Srivastava AK, Sahu RN, Kumar R: Clinico-radiological profile and nuances in the management of cervicomedullary junction intramedullary tumors. **Asian J Neurosurg** 9:21–28, 2014
- Phillips NS, Sanford RA, Helton KJ, Boop FA, Zou P, Tekautz T, et al: Diffusion tensor imaging of intraaxial tumors at the cervicomedullary and pontomedullary junctions. Report of two cases. **J Neurosurg** 103 (6 Suppl):557–562, 2005
- Raabe E, Kieran MW, Cohen KJ: New strategies in pediatric gliomas: molecular advances in pediatric low-grade gliomas as a model. **Clin Cancer Res** 19:4553–4558, 2013
- Recinos PF, Sciubba DM, Jallo GI: Brainstem tumors: where are we today? **Pediatr Neurosurg** 43:192–201, 2007
- Robertson PL, Allen JC, Abbott IR, Miller DC, Fidel J,

- Epstein FJ: Cervicomedullary tumors in children: a distinct subset of brainstem gliomas. **Neurology** **44**:1798–1803, 1994
34. Sadighi Z, Slopis J: Pilocytic astrocytoma: a disease with evolving molecular heterogeneity. **J Child Neurol** **28**:625–632, 2013
35. Sala F, Krzan MJ, Deletis V: Intraoperative neurophysiological monitoring in pediatric neurosurgery: why, when, how? **Childs Nerv Syst** **18**:264–287, 2002
36. Squires LA, Constantini S, Miller DC, Epstein F: Diffuse infiltrating astrocytoma of the cervicomedullary region: clinicopathologic entity. **Pediatr Neurosurg** **27**:153–159, 1997
37. Sridhar K, Sridhar R, Venkatprasanna G: Management of posterior fossa gliomas in children. **J Pediatr Neurosci** **6** (Suppl 1):S72–S77, 2011
38. Weiner HL, Freed D, Woo HH, Rezai AR, Kim R, Epstein FJ: Intra-axial tumors of the cervicomedullary junction: surgical results and long-term outcome. **Pediatr Neurosurg** **27**:12–18, 1997
39. Winestone JS, Lin J, Sanford RA, Boop FA: Subependymal hemangioblastomas of the cervicomedullary junction: lessons learned in the management of two cases. **Childs Nerv Syst** **23**:761–764, 2007
40. Xu QW, Bao WM, Mao RL, Yang GY: Aggressive surgery for intramedullary tumor of cervical spinal cord. **Surg Neurol** **46**:322–328, 1996
41. 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
42. Young Poussaint T, Yousuf N, Barnes PD, Anthony DC, Zurakowski D, Scott RM, et al: Cervicomedullary astrocytomas of childhood: clinical and imaging follow-up. **Pediatr Radiol** **29**:662–668, 1999

Author Contributions

Conception and design: Klimo. Acquisition of data: Klimo, McAbee, Modica, Orr, Choudhri. Analysis and interpretation of data: Klimo, McAbee, Modica, Boop. Drafting the article: Klimo, McAbee, Modica, Choudhri. Critically revising the article: all authors. Reviewed submitted version of manuscript: Klimo. Approved the final version of the manuscript on behalf of all authors: Klimo. Statistical analysis: Thompson. Study supervision: Klimo.

Correspondence

Paul Klimo Jr., Semmes-Murphey Neurologic & Spine Clinic, 6325 Humphreys Blvd., Memphis, TN 38120. email: pklimo@semmes-murphey.com.