



Primary Spinal Cord Astrocytomas: Two-Center Clinical Experience of Low- and High-Grade Lesions

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■ **OBJECTIVE:** Primary spinal cord astrocytomas are rare, fatal, and poorly studied.

■ **METHODS:** This study included a 2-center, retrospective analysis of primary spinal cord astrocytoma patients from 1997 to 2020. Patients with drop metastases or without at least one follow-up were excluded.

■ **RESULTS:** Seven World Health Organization grade I, 6 grade II, 7 grade III, and 4 grade IV astrocytoma patients were included. Older patients had higher grades (median 20 years in grade I vs. 36.5 in grade IV). The median follow-up was 15 months. Thirteen patients were discharged to rehabilitation. Eight patients demonstrated radiographic progression. Adjuvant therapy was utilized more in higher grades (5 of 13 grades III vs. all 11 grades IIIIV). Six patients died (1 death in grades III vs. 5 in grades IIIIV). Ten patients had worsened symptoms at the last follow-up. The median progression-free survival in grade I, II, III, and IV tumors was 116, 36, 8, and 8.5 months, respectively. The median overall survival in grade I, II, III, and IV tumors was 142, 69, 19, and 12 months, respectively. Thrombotic complications occurred in 2 patients, one with isocitrate dehydrogenase wild type glioblastoma.

■ **CONCLUSIONS:** Outcomes worsen with higher grades and lead to difficult postoperative periods. Clinicians should be vigilant for thromboembolic complications. Further research is needed to understand these rare tumors.

INTRODUCTION

Primary spinal cord astrocytomas represent a rare pathological process with limited (OS) and progression-free survival (PFS) data. Previous studies estimate that only 4%–8% of all spinal tumors are primarily formed in the spinal cord, with ependymomas more frequent in the adult population and astrocytomas more common in pediatric patients.^{1–6} Gliomas tend to represent a particularly rare subset.^{2,7,8} They use the same histopathological and molecular classification schemes as their intracranial counterparts, although anatomic location modulates treatment strategies and prognosis.^{6,7,9} Previous studies have noted poor outcomes for high-grade spinal cord gliomas. Although lower-grade tumors have a better prognosis, they can be associated with significant morbidity due to the density of fiber tracts in the spinal cord.^{2,5,10–12} The primary treatment modality

Key words

- Central nervous system neoplasms
- Glioma
- Postoperative complications
- Spinal cord neoplasms
- Temozolomide

Abbreviations and Acronyms

- DLGT:** Diffuse leptomeningeal glioneuronal tumor
DVT: Deep venous thrombosis
GTR: Gross total resection
IDH: Isocitrate dehydrogenase
KPS: Karnofsky Performance Scale
NF1: Neurofibromatosis type I
OS: Overall survival
PE: Pulmonary embolism
PFS: Progress-Free survival
RT: Radiation therapy
STR: Subtotal resection

UTI: Urinary tract infection

WHO: World Health Organization

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for high-grade spinal gliomas is similar to intracranial glioblastoma, including surgery (maximizing the extent of resection when safely possible), radiation therapy (RT), and chemotherapy depending on the grade and extent of resection.^{4,5,11,13,14}

Because of the general rarity of these tumors, most studies are limited to case reports and small case series. The objective of this study is to report treatment methods and outcomes for patients specifically with primary spinal cord astrocytomas treated at the University of Virginia and Tufts Medical Center while also highlighting presenting symptoms and associated comorbid conditions in this rare patient cohort.

MATERIALS AND METHODS

This is a retrospective analysis approved by the Institutional Review Boards at University of Virginia and Tufts Medical Center. Records were screened for all patients undergoing surgery for spinal cord tumors with pathologically confirmed diagnosis of glioma between 1997 and 2020. Cases were excluded if they had no follow-up encounter after the date of last discharge, if the tumors were related to drop metastasis from a primary intracranial lesion, or if the pathology diagnosed nonglial tumors or ependymomas. Baseline patient characteristics, treatment data, and outcomes were collected for each patient. In particular, we recorded

preoperative and postoperative Karnofsky Performance Scale (KPS) scores, presenting symptoms, type of surgery and number of spinal levels affected, World Health Organization (WHO) grade, postoperative complications (including thromboembolic events, new neurologic deficits in hospital, fluid leaks, bacteremia/sepsis, severe pain), length of hospital stay, disposition (home vs. rehabilitation facility), adjuvant therapies, final status of signs and symptoms (symptoms worsened/improved/stable at the last follow-up relative to presenting symptoms), need for spinal instrumentation, recurrences, and mortality. Figures were generated in GraphPad Prism (GraphPad Software, San Diego, USA).

RESULTS

Twenty-four patients met inclusion criteria in the study. Baseline characteristics can be found in **Table 1**. There were 7 patients in WHO grade I, 6 in grade II, 7 in grade III, and 4 in grade IV. Overall, the patients ranged in age from 3 to 80 years, and 13 (54.2%) were male. A notable past medical history for all patients included scoliosis in 5 (20.8%) and neurofibromatosis type I (NF1) in 2 (8%). In both NF1 patients, the tumor presented symptomatically and was not discovered incidentally or with screening. Two patients were otherwise without exam deficits at the time of surgery, both lesions having been

Table 1. Baseline Characteristics

| Characteristic | Overall (n = 24) | WHO Grade I (n = 7) | WHO Grade II (n = 6) | WHO Grade III (n = 7) | WHO Grade IV (n = 4) |
|------------------------------------------|----------------------|------------------------|-------------------------|--------------------------|-------------------------|
| Age | 33.9 ± 25.7 (3–80) | 24.7 ± 20 (4–61) | 38.2 ± 37.1 (3–80) | 36.3 ± 23.9 (9–70) | 39.5 ± 23.2 (19–66) |
| Number of Males, (%) | 13/24 (54.2) | 5/7 (71.4) | 4/6 (66.7) | 3/7 (42.9) | 1/4 (25) |
| Past medical history, number (%) | | | | | |
| Scoliosis | 5/24 (20.8) | 1/7 (14.3) | 3/6 (50) | 0 | 1/4 (25) |
| Neurofibromatosis type I | 2/24 (0.08) | 0 | 0 | 1/7 (14.3) | 1/4 (25) |
| Preoperative KPS | 72.9 ± 21.6 (30–100) | 67.1 ± 22.9 (30–90) | 90 ± 8.9 (80–100) | 68.6 ± 21.2 (30–90) | 65 ± 26.5 (30–90) |
| Number of presenting symptoms (%) | | | | | |
| Motor deficits | 17/24 (70.8) | 6/7 (85.7) | 3/6 (50) | 5/7 (71.4) | 3/4 (75) |
| Sensory symptoms | 12/24 (50) | 3/7 (42.9) | 3/6 (50) | 4/7 (57.1) | 2/4 (50) |
| Back pain | 7/24 (29.2) | 1/7 (14.3) | 2/6 (33.3) | 2/7 (28.6) | 2/4 (50) |
| Bowel/bladder dysfunction | 6/24 (25) | 2/7 (28.6) | 0 | 2/7 (28.6) | 2/4 (50) |
| No symptoms | 2/24 (8.3) | 0 | 2/6 (33.3) | 0 | 0 |
| Number of tumor locations (%) | | | | | |
| Cervicomedullary | 2/24 (8.3) | 1/7 (14.3) | 0 | 1/7 (14.3) | 0 |
| Cervical | 6/24 (25) | 2/7 (28.6) | 1/6 (16.7) | 1/7 (14.3) | 2/4 (50) |
| Thoracic | 12/24 (50) | 4/7 (57.1) | 3/6 (50) | 4/7 (57.1) | 1/4 (25) |
| Thoracolumbar | 4/24 (16.7) | 0 | 2/6 (33.3) | 1/7 (14.3) | 1/4 (25) |
| Total follow-up, median (range) (months) | 15 (0–214) | 142 (1–204) | 67.5 (1–147) | 19 (1–214) | 11 (0–17) |

All presented as "mean ± standard deviation (range)" unless otherwise specified.
KPS, Karnofsky Performance Scale; WHO, World Health Organization.

Table 2. Surgical Courses

| | Overall (n = 24) | WHO Grade I (n = 7) | WHO Grade II (n = 6) | WHO Grade III (n = 7) | WHO Grade IV (n = 4) |
|--------------------------------------------------|---------------------|------------------------|-------------------------|--------------------------|-------------------------|
| Extent of resection, number (%) | | | | | |
| STR | 21/24 (87.5) | 5/7 (71.4) | 6/6 (100) | 6/7 (85.7) | 4/4 (100) |
| GTR | 3/24 (12.5) | 2/7 (28.6) | 0 | 1/7 (14.3) | 0 |
| IDH mutation status, number (%) | | | | | |
| Not tested | 17/24 (70.8) | 6/7 (85.7) | 4/6 (66.7) | 5/7 (71.4) | 2/4 (50) |
| Wild type | 7/24 (29.2) | 1/7 (14.3) | 2/6 (33.3) | 2/7 (28.6) | 2/4 (50) |
| Postoperative/hospital complications, number (%) | | | | | |
| DVT | 2/24 (8.3) | 1/7 (14.3) | 1/6 (16.7) | 0 | 0 |
| PE | 1/24 (4.2) | 0 | 0 | 0 | 1/4 (25) |
| Any other complication | 5/24 (20.8) | 3/7 (42.9) | 0 | 1/7 (14.3) | 1/4 (25) |
| New neurologic deficit, number (%) | 6/24 (25) | 1/7 (14.3) | 2/6 (33.3) | 2/7 (28.6) | 1/4 (25) |
| Length of stay (days), median (range) | 6 (2–68) | 7 (4–68) | 4.5 (2–6) | 6 (3–8) | 11.5 (7–53) |
| Disposition, number (%) | | | | | |
| Home | 11/24 (45.8) | 3/7 (42.9) | 5/6 (83.3) | 2/7 (28.6) | 1/4 (25) |
| Rehabilitation facility | 13/24 (54.2) | 4/7 (57.1) | 1/6 (16.7) | 5/7 (71.4) | 3/4 (75) |
| Adjuvant therapy | | | | | |
| RT | 4/24 (16.7) | 0 | 2/6 (33.3) | 2/7 (28.6) | 0 |
| Chemotherapy | 5/24 (20.8) | 2/7 (28.6) | 1/6 (16.7) | 1/7 (14.3) | 1/4 (25) |
| RT + chemotherapy | 6/24 (25) | 0 | 0 | 4/7 (57.1) | 3/4 (75) |
| None | 9/24 (37.5) | 5/7 (71.4) | 3/6 (50) | 1/7 (14.3) | 0 |

All presented as "mean ± standard deviation (range)" unless otherwise specified.
DVT, deep venous thrombosis; GTR, gross total resection; IDH, isocitrate dehydrogenase; PE, pulmonary embolism; RT, radiotherapy; STR, subtotal resection; WHO, World Health Organization.

discovered during magnetic resonance imaging for scoliosis workup. The other patients presented with motor symptoms (70.8%), sensory symptoms (50%), back pain (29.2%), and bowel and/or bladder dysfunction (25%). The majority of tumors were located in the thoracic spine and thoracolumbar junction (16, 66.7%). Patients were followed for a median of 15 months (range, 0–214). The tumors showed a proclivity for the thoracic spine except in the WHO grade IV subgroup, in which 2 of 4 tumors occurred in the cervical spine.

Operative and hospital courses are detailed in **Table 2**. Gross total resection (GTR) was determined intraoperatively and confirmed by lack of residual lesion radiographically during the postoperative period in 3 patients. Twenty-one remaining patients (87.5%) had subtotal resection (STR). Thirteen (54.2%) tumors were low-grade gliomas (WHO grade III), while 11 (45.8%) were high-grade gliomas (WHO grade III/IV). Most of the cases (17, 70.8%) were operated before isocitrate dehydrogenase (IDH) testing became routine; the 7 (29.2%) who were tested were IDH wild type (1 grade I, 2 grade II, 2 grade III, and 2 grade IV). Eleven patients (45.8%) in total had complications, with 3 of those including deep venous thrombosis (DVT) or pulmonary

embolism (PE). One PE occurred in a patient with wild-type glioblastoma; one DVT occurred in a patient with worsened postoperative weakness, as well as subdural fluid collections managed conservatively with improvement, and another occurred in a case with recurrence as diffuse leptomeningeal glioneuronal tumor (DLGT; discussed later). Six (25%) developed new postoperative neurologic deficits. One patient had a small fluid leak repaired with sutures, one developed pneumonia, one had pneumothorax, and one had cerebrospinal fluid leak and urinary tract infection (UTI). There were no significant differences between preoperative and postoperative KPS scores when looking within each WHO group. The median hospital stay was 6 days. A majority of patients (13, 54.2%) were discharged to rehabilitation facilities. Eleven patients (45.8%) received postoperative radiotherapy (2 grade II, 6 grade III, and 3 grade IV tumors); 10 of these patients also received chemotherapy (1 grade II, 5 grade III, and 4 grade IV tumors). As expected, adjuvant therapy was utilized in more high-grade lesions than in low-grade lesions (2 of 7 grade I lesions and 3 of 6 grade II lesions received any adjuvant therapy, while all grade III and IV tumors received adjuvant treatment).

Table 3. Outcomes

| | Overall (n = 24) | WHO Grade I (n = 7) | WHO Grade II (n = 6) | WHO Grade III (n = 7) | WHO Grade IV (n = 4) |
|------------------------------------------------------|----------------------|---------------------|----------------------|-----------------------|----------------------|
| Status of symptoms at the last follow-up, number (%) | | | | | |
| Improved KPS | 10/24 (41.7) | 5/7 (71.4) | 3/6 (50) | 2/7 (28.6) | 0 |
| Stable KPS | 4/24 (16.7%) | 1/7 (14.3) | 1/6 (16.7) | 1/7 (14.3) | 1/4 (25) |
| Worsened KPS | 10/24 (41.7) | 1/7 (14.3) | 2/6 (33.3) | 4/7 (57.1) | 3/4 (75) |
| KPS at the last follow-up | 71.3 ± 18.7 (30–100) | 80 ± 12.9 (60–100) | 83.3 ± 18.6 (50–100) | 62.9 ± 11.1 (50–80) | 52.5 ± 20.6 (30–70) |
| Recurrence or progression, number (%) | 8/24 (33.3) | 1/7 (14.3) | 3/6 (50) | 3/7 (42.9) | 2/4 (50) |
| Time to recurrence (months), median (range) | 12 (1–125) | 116 | 36 (6–125) | 8 (1–12) | 8.5 (3–14) |
| Additional treatments for recurrence, number (%) | | | | | |
| RT + chemotherapy + surgery | 1/24 (4.2) | 0 | 1/6 (16.7) | 0 | 0 |
| Chemotherapy + surgery | 1/24 (4.2) | | 1/6 (16.7) | 0 | 0 |
| RT + chemotherapy | 1/24 (4.2) | 0 | 0 | 1/7 (14.3) | 0 |
| Chemotherapy | 3/24 (12.5) | 0 | 1/6 (16.7) | 1/7 (14.3) | 1/4 (25) |
| Surgery | 2/24 (8.3) | 1/7 (14.3) | 0 | 1/7 (14.3) | 0 |
| Required spinal fusion, number (%) | 2/24 (8.3) | 0 | 1/6 (16.7) | 1/7 (14.3) | 0 |
| Death during follow-up, number (%) | 6/24 (25) | 0 | 1/6 (16.7) | 2/7 (28.6) | 3/4 (75) |
| Overall survival (months), median (range) | 16.5 (0–214) | 142 (1–204) | 69 (2–147) | 19 (1–214) | 12 (0–17) |
| Age at death | 57.8 ± 20.2 (21–79) | - | 79 | 70 | 46.7 ± 23.2 (21–66) |

All presented as "mean ± standard deviation (range)" unless otherwise specified.
KPS, Karnofsky Performance Scale; RT, radiotherapy; WHO, World Health Organization.

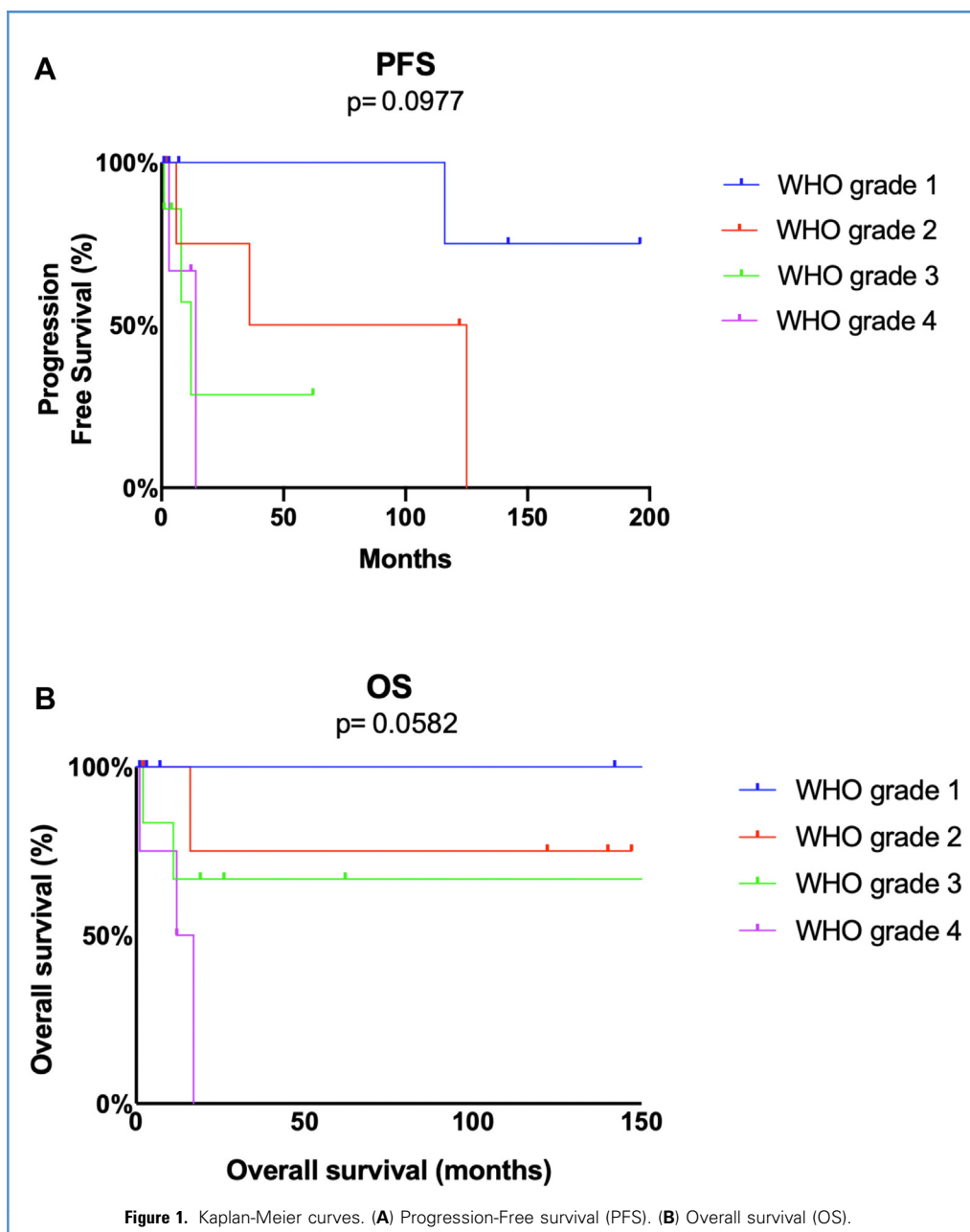
Outcomes are listed in **Table 3**. Preoperative and postoperative KPS scores within each WHO grade did not appear markedly different. Tumors recurred in 8 (33.3%) patients, and 6 patients (25%) died; these patients were not always the same patients with recurrent disease. There was 1 recurrence in WHO grade I (116 months), 3 in grade II (median 36 months postoperatively), 3 in WHO grade III (median 8 months), and 2 recurrences in WHO grade IV (median 8.5 months) (**Figure 1A**). There were no deaths encountered in WHO grade I lesions, 1 in WHO grade II (16.7 months), 2 in WHO grade III (median 6.5 months), and 3 in WHO grade IV (median 12 months) (**Figure 1B**). Some of the deaths occurred due to poor overall functional status and comorbid disease in the absence of radiographic progression. The mean age of death in WHO grade IV tumors was 46.7 years, while 1 patient with grade II and 1 with grade III died at ages 79 and 70, respectively. The OS in grade I, II, III, and IV tumors was 142, 69, 19, and 12 months, respectively. All recurrences occurred in subtotaly resected tumors.

Perioperative characteristics of each individual patient are shown in **Table 4**. After recurrence, combinations of repeat

surgery, RT, and chemotherapy were used. In one patient, a grade II astrocytoma recurred 125 months after original surgery as a DLGT. Another patient had recurrence of a grade III anaplastic astrocytoma 8 months after surgery; because the patient was fully paraplegic after recurrence, spinal cord transection and subsequent GTR of the tumor were utilized, and this patient remained free of disease 214 months after the original surgery. Both of these patients required instrumentation and fusion for spinal deformity at the level of surgery. Overall, many patients had worse or new symptoms at the last follow-up than at presentation (10, 41.7%); in one case, the tumor recurrence without symptoms was discovered on follow-up imaging. Thromboembolic complications occurred in 2 true astrocytoma cases (another occurred after the previously mentioned DLGT).

DISCUSSION

Spinal cord astrocytomas represent rare entities, and previous experiences in the literature are more often relegated to case reports and small case series. Here, we summarize our institutional



experience, existing studies, and current clinical recommendations for treatment.

WHO Grade I—Pilocytic Astrocytomas

In this cohort, 6 WHO grade I tumors had pilocytic histology; 1 was unspecified astrocytoma. Six presented with motor symptoms, 3 with sensory deficits, 1 with back pain, and 2 with bowel/bladder dysfunction. All were treated upfront with surgery (2 achieved GTR), and 2 received adjuvant chemotherapy. Four patients required discharge to a rehabilitation facility. Postoperative

complications were relatively mild with only one patient being diagnosed with a DVT, one with an easily corrected fluid leak, and one with both a cerebrospinal fluid leak and UTI. Five patients had symptomatic improvement, while 1 was stable and 1 worsened. There were no recurrences or deaths, and none suffered from mechanical spinal instability.

Pilocytic astrocytomas tend to have a greater incidence in younger patients.^{13,15} Outcomes are frequently better than those for high-grade lesions. One recent series of 16 patients with spinal cord pilocytic astrocytoma had a 37.5% recurrence rate during

Table 4. Patient-Specific Perioperative Characteristics

| Patient | WHO Grade | Extent of Resection | Reason for the Extent of Resection | Neuromonitoring | Other Treatment | Rationale for Other Treatment | Postoperative Course |
|---------|-----------|---------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | 3 | Subtotal | No distinct plane between tumor and spinal cord; loss of SSEPs | Loss of the SSEPs due to midline myelotomy | Radiotherapy | Felt that chemotherapy would not be effective for residual tumor, radiotherapy given to improve survival. | Worsened with paraplegia, needed spinal cord transection after recurrence; required fusion for stability due to extent of exposure during transection |
| 2 | 1 | Gross | N/A | No changes in the SSEPs | | N/A | Overall improvement with chronic left extensor hallucis longus |
| 3 | 2 | Subtotal | No distinct plane | Not used | | N/A | Improved numbness |
| 4 | 3 | Subtotal | After removal of significant tumor, stopped after small changes occurred in motor evoked potentials | Small changes in the MEPs | Radiotherapy, chemotherapy (temozolomide) | Given highly infiltrative tumor, fractionated radiotherapy offered. Chemotherapy added for additive survival benefit and continued for salvage. | Worsening LUE weakness, ambulatory problems; recurrence |
| 5 | 1 | Gross | N/A | Some reduction in SSEPs and in left MEPs | | N/A | Improved with full strength in right lower extremity, residual lower left extremity weakness |
| 6 | 2 | Subtotal | Loss of the plane in the middle of dissection | SSEPs lost early in dissection; loss of MEPs in lower extremities | Radiotherapy, chemotherapy (Temozolomide) | Salvage therapy | Worsened with coordination issues and spasticity; tumor recurrence, repeat surgery with fusion due to extend of exposure |
| 7 | 4 | Subtotal (biopsy) | Tumor infiltrated the entire cord including the dorsal columns, only biopsy performed. | Used, SSEPs were lost; MEPs preserved | Radiotherapy, chemotherapy (temozolomide) | Infiltrating tumor, radiotherapy and chemotherapy as the only options | Worsened, BLE weakness and decreased sensation; progression and death |
| 8 | 2 | Subtotal | Tumor infiltrated the cord | N/A | | N/A | Stable symptoms; later developed syrinx requiring repeated drainage, eventual syringopleural shunt |
| 9 | 1 | Subtotal | A plane between the tumor and cord could not be created. | MEPs and SSEPs stable at baseline with no changes intraoperatively | | N/A | Improved, BLE spasticity; required repeat surgery for cyst/syrinx expansion |

SSEP, somatosensory evoked potentials; MEP, motor evoked potentials; LUE, left upper extremity; BLE, bilateral lower extremities; OP, operative; RT, radiotherapy; CSF, cerebrospinal fluid; UTI, urinary tract infection.

Continues

Table 4. Continued

| Patient | WHO Grade | Extent of Resection | Reason for the Extent of Resection | Neuromonitoring | Other Treatment | Rationale for Other Treatment | Postoperative Course |
|---------|-----------|---------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| 10 | 3 | Subtotal (biopsy) | A plane between the tumor and cord could not be created, so only a biopsy was performed. | Stable throughout the case (no motors in the lower extremities). | Radiotherapy, chemotherapy (temozolomide) | Potential improvements in overall survival. | Worsened with paraplegia and continued loss of sensation and bowel and bladder dysfunction; death |
| 11 | 4 | Subtotal | A plane between the tumor and normal spinal cord could not be identified. | Stable at baseline throughout case | Radiotherapy, chemotherapy (temozolomide, bevacizumab, panobinostat) | To prolong survival; salvage after recurrence. | Worsened with quadriparesis right greater than left, nonambulatory. Tumor recurrence, death |
| 12 | 4 | Subtotal | Tumor was highly invasive, and only a biopsy was performed. A plane between the tumor and cord could not be identified. | During dissection, the lower extremity SSEP decreased to <50% of baseline recordings (but later returned to >50%) | Radiotherapy, chemotherapy (temozolomide) | To improve overall survival. | Worsened with respiratory failure; death |
| 13 | 2 | Subtotal (biopsy) | Biopsy performed only due to risk of neurologic deficits. Even after only a biopsy, neuromonitoring changes led to stop | Loss of MEP in right lower extremity. Motor signals robust in all other muscle groups. | Radiotherapy, chemotherapy (temozolomide) | Tumor type relatively resistant to temozolomide, radiotherapy only adjuvantly. Temozolomide added after growth | Worsened, weakness in all extremities. Tumor growth and death |
| 14 | 3 | Gross | N/A | Information about neuromonitoring not mentioned in chart or OP note | RT | Given aggressive nature of diagnosis, felt that adjuvant radiotherapy would improve local tumor control and potentially overall survival. | Improved pain |
| 15 | 1 | Subtotal | Lack of a plane between tumor and cord | No baseline neuromonitoring signals, no improvement in neuromonitoring signals at conclusion of the case. | | N/A | Worsened, distal right lower extremity greater than left lower extremity weakness |
| 16 | 3 | Subtotal (biopsy) | Biopsy only, no good plane found, malignant tumor from the frozen section, did not feel should attempt to perform resection | None used. | Chemotherapy (Cytoxan, vincristine, etoposide, irinotecan) | Survival benefit and tumor control | Improved, continued loss of sensation, possible subjectively improved gait. Tumor growth |
| 17 | 2 | Subtotal | Cord extremely swollen and difficult to develop a plane. | SSEPs and MEPs used. No SSEPs from lower extremity since beginning. After alloderm patch, change in MEPs on right side, reopened dura with no evidence of hematoma | Chemotherapy (unspecified) | Survival benefit and control of tumor. Plan to defer radiotherapy until no longer surgically accessible. | Symptoms resolved; required repeat surgery |

| | | | | | | | |
|----|---|-------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 18 | 1 | Subtotal | Debulked until tumor plane indistinct. | MEPs and SEPs used. Slight shift in SSEPs on right side, stopped shortly after | Chemotherapy (carboplatin, lomustine, procarbazine, temozolomide, vincristine, thioguanine) | Chemotherapy to prevent progression of tumor after noted growth | Improved symptoms |
| 19 | 4 | Subtotal | Due to the nature of tumor, stopped when the area well decompressed | N/A | Radiotherapy, chemotherapy (temozolomide) | Radiotherapy for palliation, chemotherapy for survival benefit. | Stable paraplegia, severe pain; lost to follow-up |
| 20 | 1 | Subtotal | N/A | N/A | | No mitosis and Ki-67 showed a low proliferation index and therefore did not require adjuvant therapy. | Improved, CSF leak, weakness, UTI; required re-exploration during postoperative months; repeated surgery for recurrence 116 months later |
| 21 | 3 | Subtotal (biopsy) | Biopsies performed, stopped after diagnosis of high-grade glioma | SSEP and MEPs used, good in arms but none in legs at baseline. Right lower extremity SSEPs somewhat improved throughout myelotomy. | Radiotherapy, chemotherapy (temozolomide) | Started with focal radiotherapy for symptoms, added temozolomide for survival. | Worsening left-sided weakness; death |
| 22 | 3 | Subtotal | No good plane between cord and tumor. Neuromonitoring changes led to stop. | SSEPs and MEPs used. While debulking the right side, decreased SSEPs of lower extremities and right arm. | Radiotherapy, chemotherapy (temozolomide, bevacizumab) | For survival benefit and edema. | Stable |
| 23 | 2 | Subtotal (biopsy) | Biopsy, whole spinal cord diffusely infiltrated | SSEPs and MEPs used with transient diminution of SSEPs during intramedullary biopsy | Radiotherapy | Given size and expansile nature of lesion, as well as age and comorbidities favored radiation therapy only | Improved |
| 24 | 1 | Subtotal | No clear plane of tumor, which infiltrated the brainstem. | SSEPs and MEPs used. Initial baseline SSEPs slightly decreased in left upper extremity and left lower extremity. | Chemotherapy (vincristine, carboplatin) | Short-term progression consistent with active growth | Stable |

SSEP, somatosensory evoked potentials; MEP, motor evoked potentials; LUE, left upper extremity; BLE, bilateral lower extremities; OP, operative; RT, radiotherapy; CSF, cerebrospinal fluid; UTI, urinary tract infection.

a mean follow-up of 40.4 months. Two of the patients with recurrence had STR, and 2 with GTR had genetic mutations (one H3-K27 M and one NF-1). There were no deaths. The PFS was 19 months.¹⁵ Another study reported a 5-year survival of 85.4% and a mean OS of 16 years.¹⁶ Reports for intracranial tumors suggest that ATRX loss and NF-1 and H3-K27 M mutations are considered poor prognostic factors in pilocytic astrocytomas.¹⁵

Maximal surgical resection alone is the preferred treatment for spinal cord pilocytic astrocytoma.¹⁵⁻¹⁷ RT is not currently supported in the treatment of these tumors, as the clinical course is a typical one of slow growth or stability; in addition, re-resection is generally the approach in recurrent tumors, and radiation changes can complicate these approaches.^{15,16} While chemotherapy is incompletely characterized, it is not routinely recommended for this slow-growing lesion as the risks are likely to outweigh any benefit.¹⁶

WHO Grade II Astrocytomas

Three of the 6 patients in this study with WHO grade II lesions were histologically identified as diffuse astrocytoma at the time of diagnosis (2 others were unspecified astrocytoma, 1 pleomorphic xanthoastrocytoma). Two patients presented with low-back pain, 3 had motor symptoms, and 3 had sensory deficits, while 2 were discovered during scoliosis evaluation. All were resected subtotally, 2 patients received adjuvant RT, and one patient received adjuvant chemotherapy. Three of the patients had recurrence or progression at a median of 36 months later. One patient died 16 months after surgery.

There is little information available in the literature regarding outcomes for spinal cord astrocytomas which are histopathologically specified as the diffuse type; most are reported in groups of low-grade (WHO grade III) gliomas.^{3,13,17-20} In a series that included 14 patients with WHO grade II tumors, the mean OS was 7.61 years.¹⁶ Another series reported a median PFS of 23 months in 24 low-grade tumors treated with surgery and radiation.²¹ RT has had mixed outcomes.^{1,21-24} Prognostic data are lacking for these tumors in the spine, but in supratentorial grade II astrocytomas, p53 mutations, age ≥ 4 years, size > 6 cm, tumor crossing midline, and preoperative neurologic deficit are poor prognostic factors.²⁵

While surgery is a preferred first-line treatment for this tumor, the use of adjuvant therapy is not well understood as sample sizes remain small.²³ Adjuvant RT may offer some benefit but may also increase the risk of complications such as postoperative deformity and dermatologic problems.^{1,21,22} As such, it can be considered for select cases (e.g., where resection is limited, older patients with a lower risk of long-term radiation effects) but should not be routinely employed for all grade II astrocytomas. Chemotherapy has not demonstrated efficacy for these tumors consistently and is currently not recommended for routine use in all cases.^{16,18,21}

WHO Grade II—Pleomorphic Xanthoastrocytomas

One patient with a WHO grade II lesion had histopathology suspicious for pleomorphic xanthoastrocytoma in our series. This patient presented with unilateral gastrocnemius atrophy and bilateral lower extremity numbness. The lesion was subtotally resected, and the patient was discharged to home with improvement of numbness and no recurrence at 2-month follow-up.

The literature on spinal cord pleomorphic xanthoastrocytomas is limited to case reports.^{26,27} In these cases, the lesion was treated with operative resection and adjuvant radiotherapy was only used sporadically.²⁶ GTR tended to yield improved PFS. In a review of the literature, the PFS ranged from 7 to 24 months, and the OS ranged from 6 to 62 months, with many patients remaining alive at the time of publication.²⁶

These tumors should be resected to the safest extent possible.^{26,28} Similar to diffuse astrocytomas, literature is mixed on adjuvant RT with recommendations generally limited to significant residual lesions, while chemotherapy results are equivocal.^{26,28} Both may be employed as salvage therapy.^{26,28}

WHO Grade III—Anaplastic Astrocytomas

Seven patients from our cohort had WHO grade III anaplastic astrocytomas. One patient had a history of NF1. Motor deficits occurred in 5 patients, sensory disturbances in 4, and back pain and bowel/bladder dysfunction in 2 each. One patient had a GTR, while the others underwent STRs. Two of these lesions were IDH wild type, while the others were resected before testing was routine. Five patients required discharge to rehabilitation, and 4 had worsened symptoms at the last follow-up, while 2 improved. Two received adjuvant RT, 1 received adjuvant chemotherapy, and 4 received combination RT and chemotherapy. Three lesions recurred; one of these was in a 9-year-old patient with total leg paresis treated with spinal cord transection above the lesion and resulting GTR, without recurrence. One patient demonstrated possible radiographic progression within a month after surgery and was managed with previously planned adjuvant therapy (RT and temozolomide), contributing to a lower PFS. While clinically considered recurrence in this case, a radiographic recurrence event within the month after surgery may also be due to evolution of postoperative changes, and this case is likely an outlier. The last patient was 10 years old and demonstrated radiographic progression 1 year after surgery with worsening symptoms and metastases to the brain, with loss to follow-up after the last discharge date. Of these, one patient developed a septic UTI 2 months after surgery, declined further therapy, and died, which caused the lower OS in this group.

In a series reporting outcomes for an individual group of grade III tumors, the mean OS was 19.2 months, and the median OS ranges from 33.8 to 72 months.^{16,29,30} Patients with anaplastic astrocytomas typically receive adjuvant RT and temozolomide, although specific chemotherapy protocols are not generally agreed upon and other agents are sometimes used.^{21-23,31} While data are limited for spinal cord tumors, increasing age and tumors lacking IDH and TERT mutations or 1p/19q codeletions had poorer OS for intracranial high-grade tumors.³²

Optimal operative resection and adjuvant chemoradiation are the standard of treatment for WHO grade III spinal gliomas. The chemotherapeutic agent utilized may differ based on molecular features of the tumor, but it generally consists of temozolomide as is used for intracranial anaplastic astrocytomas. Moreover, bevacizumab may also be used if the tumor has associated swelling and peritumoral cysts to aid in symptomatic management.

WHO Grade IV—Glioblastomas

Four patients in our cohort were diagnosed with glioblastomas. One had a history of NF1; 3 presented with motor symptoms, while sensory disturbance, back pain, and bowel/bladder dysfunction occurred in 2 patients each. All were subtotally resected, and 3 patients required admission to rehabilitation facilities. Three received adjuvant RT and temozolomide, while one only received chemotherapy. One patient with glioblastoma died less than a month after discharge due to respiratory failure, which is the reason the WHO grade IV group only had 2 instances of true radiographic recurrence. Three patients who were tracked died during follow-up at a median of 12 months. One patient was lost to follow-up after 12 months without any death or survival data recorded thereafter.

The median OS for this tumor is dismal across the literature, ranging from 9 to 32.5 months after diagnosis.^{29,33} Similar to intracranial glioblastoma, these tumors are often treated with optimal operative resection and chemoradiation.^{2-5,7,12,19,20,30,33,34} Radiation is most frequently utilized on residual tumors and is usually still implemented for high-grade lesions where GTR is achieved; it has been associated with improved outcomes in some series.^{4,12,13,21} Chemotherapy with temozolomide is also utilized as data have suggested it may provide modest benefit.^{2,35-37} Bevacizumab is another agent that has been employed in tumors with prominent cystic elements.^{13,14,36} Poor prognostic factors in spinal tumors include cervical location, out-of-field leptomeningeal seeding after RT, and worse preoperative functional status, while for intracranial tumors, worse prognosis has been noted for a lower extent of resection and for IDH wild-type tumors and those lacking TERT mutations or 1p/19q codeletions.^{7,10-12,20,32}

Patients with intracranial glioblastomas are at risk of developing thromboembolism such as DVT or PE; this occurs between 3% and 60% of cases.³⁸ It has previously been noted that IDH wild-type gliomas have a higher DVT risk than IDH-mutant tumors.³⁹ It is unclear whether this association holds true for gliomas in the spinal cord. One study noted the death of a patient from PE 2 months after surgery for a low-grade glioma, while another noted 2 pulmonary embolus deaths in the weeks following surgery (although the tumor grades in these patients were not reported).^{19,20} One of 4 patients in our cohort with glioblastomas (25%) ultimately experienced one of these events. In addition to IDH status, tumors in general (and especially high-grade gliomas) in the spinal cord naturally cause weakness and subsequent declines in patient functional status, facilitating thromboembolic events related to immobility. Although the sample size is small, these results should turn the clinician's attention to a possible heightened risk of thrombotic events in patients with spinal cord gliomas in a similar manner to intracranial gliomas.

The current clinical recommendation for these lesions is maximal surgery with adjuvant chemoradiation. As in WHO grade III lesions, bevacizumab may be considered if there is significant swelling and/or a peritumoral cystic component to the lesion. Significant predictors of PFS and functional outcomes include extent of resection, histopathology, age, and preoperative functional status.⁴⁰ Recent work has begun the process of predicting

survival with risk models, to which results from our study and future research will add statistical power.⁴¹

Limitations

Although a multicenter effort was undertaken, this is still a small cohort of rare tumors. In addition to the small sample size, the retrospective study design can introduce bias along the course of study from inconsistent patient care documentation to data collection and analysis. The recommendations provided here utilize existing literature and our institutional experiences since randomized trials are not available, as well as treatment paradigms for these tumors' intracranial counterparts as well. This case series illustrates the symptomatic profile, outcomes, and treatment experiences for our patients who underwent treatment for spinal cord gliomas. Systematic reviews and meta-analyses will likely be required to attain larger sample sizes, and these future studies may take advantage of this cohort and similar studies in the literature.

CONCLUSION

Spinal cord gliomas have often been treated in a similar manner to intracranial gliomas, although different neurologic, functional, and surgical considerations play a role due to the differences in surrounding anatomy. Functional outcomes remain a challenge in this patient cohort due to the high density of critical structures disrupted within the spinal cord, and patients frequently require both inpatient and outpatient rehabilitation. Patients with spinal cord glioblastomas may have a heightened risk of developing thromboembolic events as intracranial glioblastomas do, but a larger cohort would be required to confirm this. As spinal cord gliomas represent an entity that is rarely encountered by neurosurgeons, there is a need to meticulously document clinical outcomes and histological findings as one cannot always assume that they behave similarly to gliomas found intracranially.

CRedit AUTHORSHIP CONTRIBUTION STATEMENT

M. Harrison Snyder: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Andy Yu-Der Wang:** Data curation, Methodology, Writing – original draft, Writing – review & editing. **Leonel Ampie:** Conceptualization, Data curation, Writing – review & editing. **Danyas Sarathy:** Data curation, Writing – review & editing. **Ajay Chatrath:** Data curation, Writing – review & editing. **Ashok R. Asthagiri:** Supervision, Writing – review & editing. **Christopher I. Shaffrey:** Supervision, Writing – review & editing. **Justin S. Smith:** Supervision, Writing – review & editing. **Mark E. Shaffrey:** Supervision, Writing – review & editing. **Chun-Po Yen:** Supervision, Writing – review & editing. **Avery L. Buchholz:** Supervision, Writing – review & editing. **Hasan R. Syed:** Supervision, Writing – review & editing. **James Kryzanski:** Supervision, Writing – review & editing. **Julian K. Wu:** Supervision, Writing – review & editing. **Carl B. Heilman:** Supervision, Writing – review & editing.

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