World Neurosurgery: X 21 (2024) 100269

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Clinical presentation, role of surgery and prognosis in spinal astrocytoma: Cohort study

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ARTICLE INFO

Keywords:
Astrocytoma
Glioma
Intramedullary tumor
Spinal tumor
Prognosis

ABSTRACT

Spinal astrocytoma is a rare neoplasm with discouraging prognosis, which accounts for 6–8 % of total intramedullary spinal tumors. As this is a rare entity, details of the clinical and molecular features have not been fully unraveled. We evaluated the radiologic findings, perioperative clinical presentation, histopathological features and treatment response in a single institution series of 37 consecutive cases of spinal astrocytomas (WHO grades 1 to 4).

We identified 8, 16, 8, and 5 patients with grade 1, 2, 3, and 4 lesions, respectively, from 1988 to 2017. Peak ages were youngest in grade 1, followed in order by grades 4, 3 and 2. Whereas all cases of grade 1 and 4 enhanced with contrast, less than half of the cases of grade 2 tumors enhanced (44 %). Grade 3 tumors had a higher rate of multiplicity at presentation (50 %). A concomitant brain lesion at presentation was present in 14 % and 43 % of grade 2 and 3 lesions, respectively. Progression-free and overall survival were worse in grades 3 and 4 compared to grade 2 lesions but no significant difference was observed between grade 3 and 4. Many patients (16-of-36) experienced new neurological deficits postoperatively regardless of grade. Most patients (88 %) required postoperative rehabilitation, and 61 % were not discharged to home. Discharge destination closely correlated with age ($p = 0.002$). These clinical findings may be useful in understanding the clinical phenotype and improving the management of this rare disease.

1. Introduction

Spinal astrocytomas are rare intramedullary neoplasms accounting for 2–4 % of all central nervous system tumors, and 6–8 % of all spinal cord tumors.[10,12] While the cervical spine is most frequently involved, they occur along the entire neuraxis.[4,5] Peak incidence varies by age; pilocytic astrocytomas usually occur in pediatric or young adult patients,[7] grades 2–4 diffuse gliomas occur in children to adults (the mean ages were 31.9 and 37.5 years, respectively[10]). Spinal gliomas appear to be clinically and molecularly distinct from most supratentorial gliomas.[17] The optimal treatment strategy for spinal gliomas is unknown given the paucity of information regarding their clinical behavior, their defining molecular characteristics, and response to standard radiation and temozolomide.[1,2,8,10,15]

Herein, we analyzed the clinical and histopathological findings in 37 spinal astrocytomas (grades 1–4). We review perioperative functional status and complications, with the goal of contributing to the known clinical and biological features of these rare tumors, and also present a comprehensive review of their clinical profile.

2. Method

Retrospective review of Mayo Clinic Rochester neurosurgical cases from 1988 to 2017, revealed 37 patients with spinal astrocytoma. Clinical and demographic information including age, sex, race, symptoms, surgery, chemotherapy, radiation therapy, recurrence and death, imaging findings including location of the lesions, contrast enhancement, multiplicity and presence of concomitant intracranial lesion, histopathological diagnoses and molecular findings were collected from the clinical charts. The histopathological diagnosis was made at Mayo Clinic. This study was approved by the Mayo Clinic Institutional Review Board.

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https://doi.org/10.1016/j.wnsx.2023.100269
Received 24 February 2023; Accepted 28 November 2023
Available online 9 December 2023

2.1. Statistical analysis

Wilcoxon test was used to compare nonparametric values. Pearson's chi square test was used for categorical variables. Logistic regression analysis was used in multivariate analysis. The survival data were analyzed with the log-rank test and the multivariate Cox proportional hazard model. All statistical analyses were carried out using JMP® 14 (SAS Institute Inc., Cary, NC, USA). A p value below 0.05 was considered statistically significant.

3. Results

3.1. Demographics and histological diagnoses

Retrospective review of Mayo Clinic Rochester's surgical database of prior cases from 1988 to 2017 revealed 37 spinal cases for which pathology yielded astrocytomas. In 4 cases the upper part of the tumor existed in the medulla oblongata. All cases were treated and confirmed histopathologically in the single institution, and comprised 8 grade 1, 16 grade 2, 8 grade 3 and 5 grade 4 cases. These diagnoses were made based on the latest criteria at the time of diagnoses. The male-to-female ratio was 2.4:1. Median ages were 10.5, 55, 36.5 and 32 years for grades 1 through 4, respectively as summarized in Table 1 and Fig. 1A. Patients with grade 2 histology were significantly older (46.7 ± 5.1 years) than patients with grade 1 lesions (17.8 ± 7.2 years, $p = 0.04$) (Fig. 1A, right). Median duration between symptom onset and presentation was significantly longer in grade 2 cases (median 340.5 (4–3010) days) versus grade 3 cases (median 48 (10–232) days) ($p = 0.01$) (Fig. 1B). The proportion of patients with normal activity in daily life (Karnofsky performance status (KPS) ≥ 80) at presentation was significantly smaller in grade 3 (1-out-of-6, 16.7 %) cases compared with 2 (10-out-of-16, 62.5 %) ($p = 0.03$). This remained significant in multivariate analysis after controlling for age ($p = 0.0066$). The rate of KPS≥ 80 was 85.7 and 60 % in grade 1 and 4 cases, respectively. Demographic features are summarized in Table 1.

3.2. Imaging findings and CSF cytology

Radiologic features are summarized in Fig. 2 and Table 2. Grade 1 and 2 lesions more frequently affected the cervicothoracic region. All the 5 grade 1 cases and 5 grade 4 cases showed enhancement with contrast on MRI, whereas 7 out of 16 (43.7 %) grade 2 cases and 5 out of 7 (71.4 %) grade 3 cases enhanced on imaging. All the grade 1 and 4 lesions presented as a solitary lesion whereas 6.3 % (1-out-of-16) of grade 2 and 50.0 % (4-out-of-8) grade 3 cases showed multifocality at presentation (Fig. 2C). All grade 1 cases were limited to the spinal cord, whereas 18.2 % (2 out of 11) grade 2 and 14.3 % (1 out of 7) grade 3 had a concomitant brain lesion at presentation found by screening of the brain (Fig. 2D). For these 2 grade 2 cases, the brain lesions included brainstem/optic pathway (histopathology unknown), and the other included a cerebellar peduncle lesion for which attempted biopsy was non-diagnostic. A single grade 3 case, additionally revealed intracranial pial enhancement (biopsy was not undertaken). These findings suggested intracranial dissemination of spinal glioma or vice versa or multifocal occurrence.

The CSF was examined for cytology in 7 diffuse astrocytoma cases (3 grade 2 cases and 4 grade 3 cases) preoperatively, and was negative for malignant cells in 7/7 cases.

Representative MRI scans per WHO grades are presented in Fig. 3.

Table 1
Baseline demographic characteristics.

Clinical factor		WHO Grade				Total	p value
		1	2	3	4		
N		8	16	8	5	37	
Age							0.025*
	Range	1–58	1–73	11–63	27–48	1–73	
	Median	10.5	55	36.5	32	37	
	Mean	17.8	46.7	35.9	36.6	36.7	
Sex							0.11
	Female:Male	2:6	6:10	0:8	3:2	11:26	
Race							0.18
	White:Others	8:0	12:3	4:4	3:1	27:8	
Preoperative KPS							0.59
	50	0	1	1	0	2	
	60	0	2	1	0	3	
	70	1	3	3	2	9	
	80	4	7	1	3	15	
	90	2	3	0	0	5	

Abbreviations: KPS: Karnofsky performance scale.

3.3. Treatment

All patients with grade 1 lesions ($n = 8$) were treated with surgery alone. Subtotal resection (STR) was achieved in 7/8 cases and gross total resection (GTR) in one case (Table 3). Among patients with Grade 2 lesions ($n = 16$), 11 underwent biopsy, 4 underwent STR and 1 underwent near-total resection (NTR). No patients with grade 2 lesions underwent GTR. Four of 16 patients were treated with fractionated external beam radiation therapy (EBRT) combined with temozolomide (TMZ), 6 cases were treated with radiation alone, 1 case was treated with TMZ alone, three cases did not receive adjuvant therapies, and treatment data was missing for two cases. Among 8 patients with grade 3 lesions, 4 patients received both radiation and TMZ, one received radiation only, one patient received neither therapies and data were not available for two patients. Among 5 patients with grade 4 lesions, two underwent chemoradiation, two underwent radiation alone and one did not receive any therapy.

One grade 2 case with concomitant optic/brainstem lesions was diagnosed as neurofibromatosis type 1. The spinal cord lesion was controlled with surgical resection and TMZ; however, the brainstem lesion was recurred in spite of further chemotherapy with vincristine, CCNU and procarbazine, and the patient succumbed 8 years after presentation.

3.4. Postoperative clinical course

In most cases (29 out of 33 cases with available data, 87.9 %), patients needed rehabilitation postoperatively, regardless of the tumor grade, due to preexisting, worsened pre-operative, or newly-acquired postoperative deficits (Table 4). When acquired or worsened neurological deficits were analyzed with multivariate analysis involving age, tumor grade and extent of resection as cofactors, new weakness was associated with higher extent of resection (EOR) ($p = 0.0091$). EOR was categorized as gross total, near total or subtotal resection, or biopsy.

Patients who did not need rehabilitation were discharged from hospital earlier than those did (3.7 vs 7.5 days, $p = 0.02$). The length of hospital stay was not associated with the tumor grade, age or EOR.

Fewer than half of patients (12 out of 31) were discharged home after surgery; 50.0 % of grade 1, 31.3 % of grade 2, 42.9 % of grade 3 and 50.0 % of grade 4 cases. Most other patients were transferred to rehabilitation facilities. Two patients were transferred to skilled nursing facilities without rehabilitation (1 grade 2 and 1 grade 3). The discharge destination was not associated with tumor grade or EOR, but was significantly associated with increasing age on multivariate analysis ($p = 0.0022$) (Table 4).

3.5. Brain and spinal cord dissemination and metastasis

There were three cases (one grade 2 and two grade 3 lesions) wherein initial brain imaging was negative at presentation but new brain lesions emerged in or after the course of treatment for spinal glioma. The interval between imaging appearance on initial spinal and subsequent

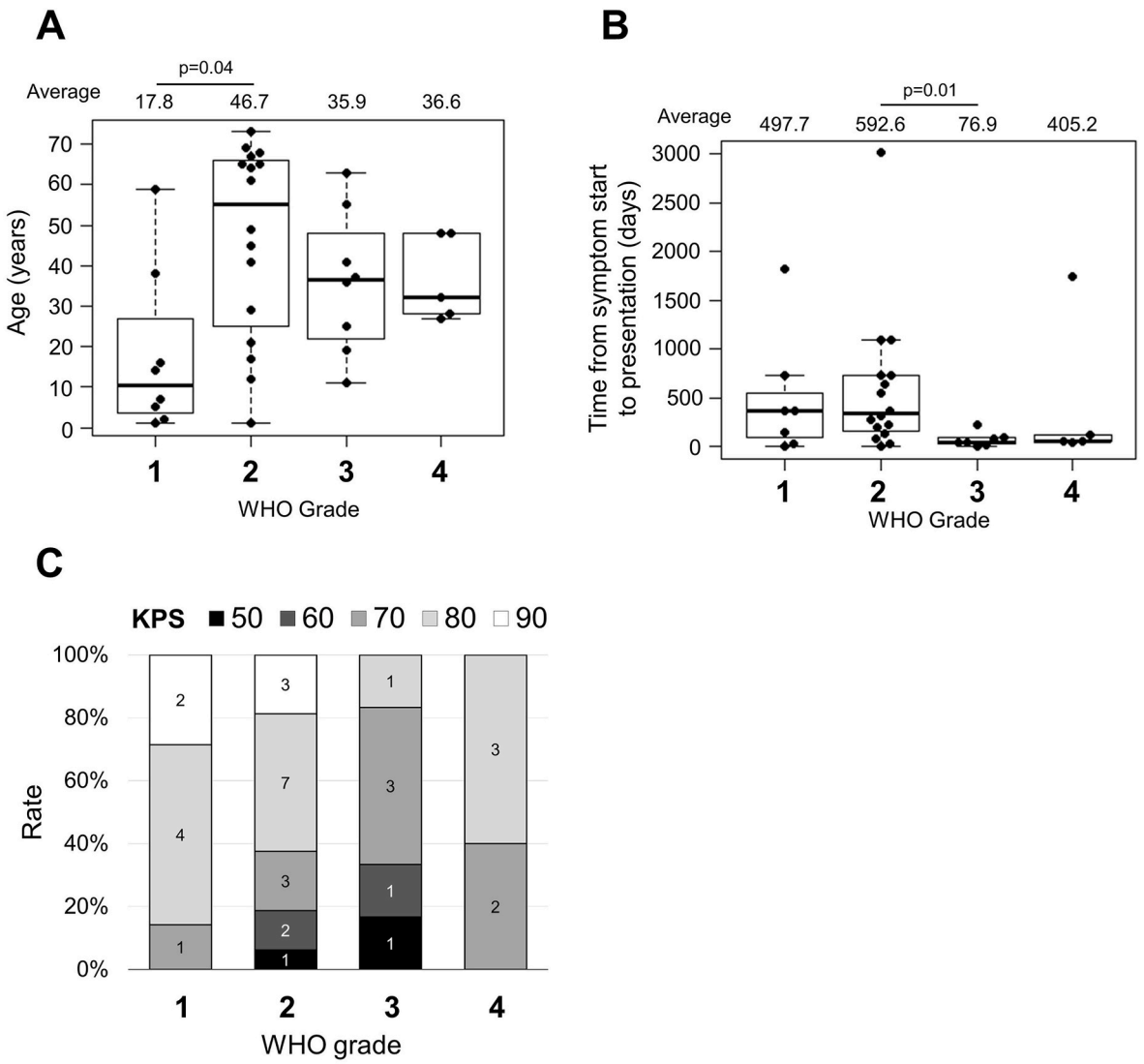

Fig. 1. (**A**) Age distribution is displayed according to the WHO grades, featuring the peak age (*Left*) and actual distribution in box plot (*Right*). Cases of grade 1 have a peak age at 1–10 years and significantly younger compared with grade 2, which has a peak age at 61–70 years. The average ages are shown at the top of the left figure for each grade (**B**) Time between symptom onset and presentation to hospital is displayed according to the tumor grade. Grade 2 showed an insidious onset, and the symptomatic duration was significantly longer compared with grade 3 ($p = 0.01$) (**C**) Karnofsky performance scale according to WHO grade of the tumors is displayed. The functionally independent rate (KPS $\geq$ 80) was significantly higher in grade 2 than grade 3 cases (62.5 vs 16.7 %, respectively, $p = 0.03$).

brain lesions was 742 days for the grade 2 lesion and 114 and 214 days for the grade 3 lesions. None of the cases underwent surgical resection of brain lesions.

3.6. Prognosis

Available records enabled follow-up after surgery for 4–8800 days (median 704 days). PFS and OS were significantly related to tumor grades ($p = 0.001$, <0.0001, respectively) (Fig. 4A and B). PFS and OS at 1, 3, and 5-year are listed in Table 5. Median PFS for grade 2–4 cases were 66.9, 7.0 and 10.7 months, respectively. Median OS for grade 2–3 cases were 77.8 and 10.9 months, respectively. No patient with a grade 1 lesion died during the follow-up (263–8800 days). Although PFS and OS were significantly different between grade 2 and 3/4, no difference was observed between grade 3 and 4 ($p = 0.93$ and 0.48, respectively for PFS and OS).

All patients with grade 1 ($n = 3$) and 2 ($n = 2$) lesions who experience recurrence within the follow-up period showed a recurrent lesion at the same region of previous surgery; whereas 3/5 patients with grade 3 lesions showed leptomeningeal dissemination rather than local recurrence, at 43, 114 and 214 days after surgeries.

Fifteen deaths were recorded. Among 6 patients with documented death following grade 2 lesions, 3 died of brain lesions, 1 died of gastrointestinal bleeding, and 2 died of unknown reasons. Among 8 deaths in patients with grade 3 lesions, three cases died of brain lesions, two cases of spinal cord disease, and three of unknown reasons. One patient with a grade 4 lesion died was of unknown reason.

3.7. Immunohistochemistry and molecular analysis

p53 IHC was mostly negative in grade 2 cases (8/9, 88.9 %), whereas most evaluated grade 3 lesions (3/4; 75.0 %) and all evaluated grade 4 lesions (4/4; 100.0 %), demonstrated p53 overexpression. No evaluated case was found to be positive for IDH1 R132H (0/12) or to have lost ATRX by IHC (0/7). H3K27me3 was negative in all grade 2 cases ($n = 2$), whereas all ($n = 4$) of the evaluated grade 4 cases were positive (Table 6).

Two grade 2 cases were analyzed for copy number analysis; one case showed chromothripsis at chromosome 6, and the other case showed gain of chromosome arm 3q and 7p/*q*, 12q amplification (*CDK4*) and

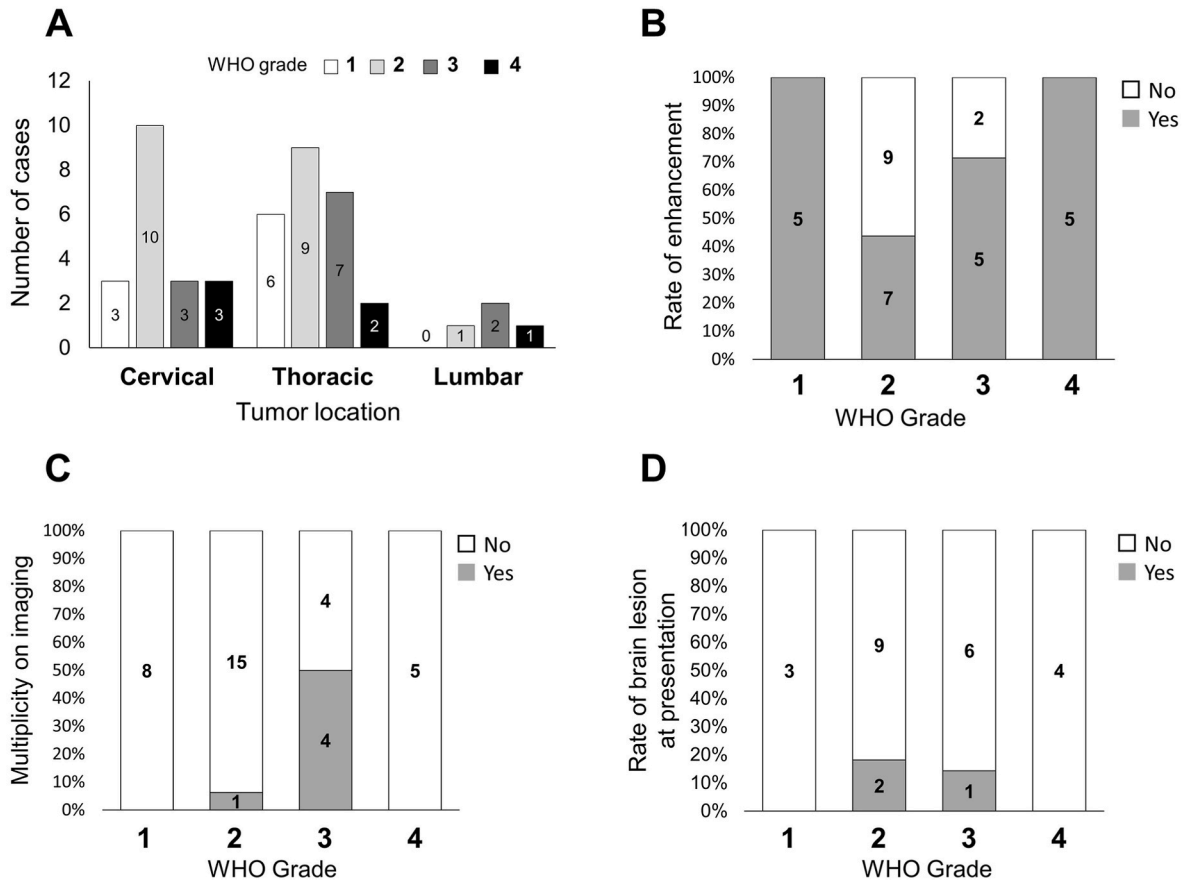

Fig. 2. (**A**) The location of the tumors in the spinal cord is displayed. Grade 1 and 2 lesions tended to arise in cervical and thoracic spinal cords (**B**) The rate of tumor enhancement is displayed according to the tumor grade. All the cases of grade 1 and 4 showed enhancement, whereas about half and majority of the grade 2 (43.7 %) and 3 tumors (71.4 %) enhanced, respectively (**C**) The rate of multiplicity according to the tumor grade is displayed according to the tumor grade (**D**) The rate of brain lesion at presentation according to the tumor grade is shown.

Table 2
Baseline imaging characteristics.

Imaging findings	WHO Grade					
	1	2	3	4	Total	*p* value
Location						0.03*
Cervical	2	7	0	2	11	
Cervical-thoracic	1	2	3	1	7	
Thoracic	5	6	2	1	14	
Thoracic-lumbar	0	0	2	0	2	
Lumbar	0	0	0	1	1	
Cervical-lumbar	0	1	0	0	1	
Number of lesions						0.008*
1	8	15	4	5	32	
2	0	1	2	0	3	
3	0	0	2	0	2	
Gd enhancement						0.03*
Positive	5	7	5	5	22	
Negative	0	9	2	0	11	
Cyst formation						0.82
Positive	0	3	1	1	5	
Negative	4	13	6	4	27	
Brain lesion						0.71
Positive	0	2	1	0	3	
Negative	3	9	6	4	22	

Abbreviations: Gd: gadolinium.

loss of heterozygosity of 17p (*TP53*). For the latter case, targeted sequencing was also performed, which showed *TP53*, *NF1* and *SUFU* mutations.

One grade 3 case was found to have 19q deletion on cytogenetic analysis, morphologically this case was diagnosed as anaplastic astrocytoma. *MGMT* methylation was analyzed in one of the grade 4 cases, and was negative.

4. Discussion

Spinal astrocytomas are rare and much about their biology and behavior remains unknown. This study affords an overview of this disease from multiple angles. Findings of note include higher age in grade 2 cases, long latency over a year before presentation in lower grade cases, high rate of neurological deficits and necessity of rehabilitation after surgery despite preoperative favorable KPS in lower grade cases, and molecular similarity to pediatric intracranial high grade glioma/diffuse midline glioma in the evaluated subset of grade 2–4 cases.

Whereas preoperative KPS was significantly better in low grade patients than grade 3 and 4 patients (functional independence rate: 62.5 % in grade 2 vs 16.7 % in grade 3/4, $p = 0.0066$ on multivariate analysis), many (44.4 %, motor deficits in 16.7 % and sensory deficits in 27.0 %) suffered neurological deficits postoperatively irrespective of tumor grade, and majority of patients (87.9 %) required postoperative rehabilitation. It was easily understandable that new weakness was associated with EOR ($p = 0.0091$), considering the eloquent location of spinal cord lesions. Babu et al reported a similar percentage of postoperative neurological worsening of 30.7 % and its association with EOR,[2] which

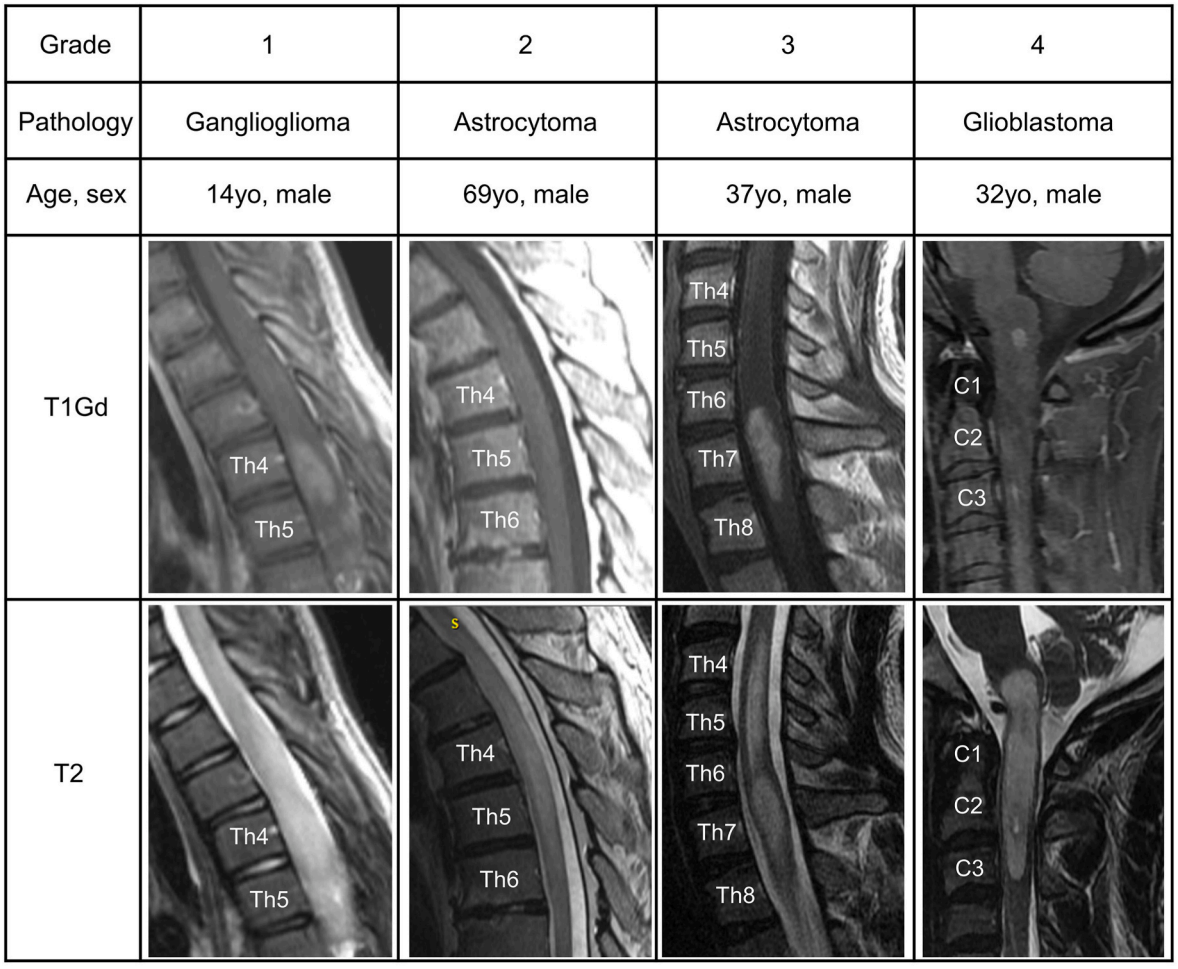

Fig. 3. MRI scans are presented for four representative cases, corresponding to each WHO grade.

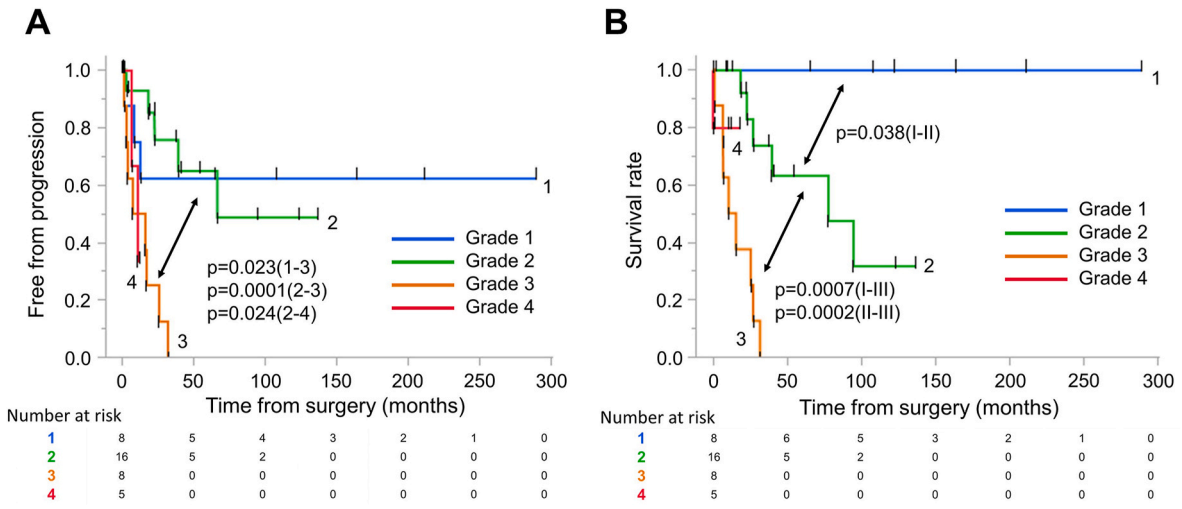

Fig. 4. The Kaplan–Meier curves of progression-free survival (PFS) (**A**) and overall survival (OS) (**B**) are shown.

corroborates our findings.

According to prior literature, median PFS and OS of spinal GBM were 5–8 months and 9–15 months, respectively.[1,3,8,9,14] Our result regarding grade 3–4 cases was mostly congruent with these results. The median OS was 10.9 months in our study ($n = 12$), which is worse than the median OS of 14.6 months reported for intracranial GBM.[16] A systematic review by Konar et al, revealed an OS benefit of 5 months[8] by these therapies (based on 53 patients; $p = 0.01$). As with brainstem gliomas, the optimal treatment for brainstem gliomas has remained uncertain, with most patients undergoing radiation, but use of empiric chemotherapy being less well accepted. We recently reported improved outcomes through analysis of the National Cancer Database with use of chemoradiation

Table 3
Surgical resection according to WHO grades.

WHO Grade	GTR	NTR	STR	Biopsy
1	1	0	7	0
2	0	1	4	11
3	1	0	0	7
4	0	1	1	3

Abbreviations: GTR: gross total resection, NTR: near total resection, STR: subtotal resection.

rather than radiation alone.[6] Further work will be needed to determine if the same result would be observed in spinal cord gliomas.

At the time of diagnosis of spinal glioma (2–4), 12.0 % of the cases (3/25) showed a brain lesion on MRI scans. Intracranial metastasis from spinal glioma were reported in 22.5 % of the cases in a prior systematic review study.[8] Furthermore, three additional cases in our series demonstrated new intracranial lesions after initial therapy (1 Grade 2 and 2 Grade 3) that were not present at diagnosis. One prior study reported that most of the recurrences in spinal glioma was outside of the original site, including brain, leptomeningeal, and even extraneural sites,[14] although a contradictory report suggested most of the recurrence was within the radiated field.[13] In our study, out of 9 clear causes of death of diffuse glioma cases, 6 cases (66.7 %) died of brain lesions. As such, in the management of spinal glioma, it is important to screen and monitor the entire neuro-axis.

This retrospective study has several inherent limitations. First, although the total number of the cases was large enough to analyze, since spinal glioma is a rare entity, the number of each grade was inevitably small. This limited the thorough and robust investigation on the effects of several clinical findings on prognosis in detail. Secondly, as the cases were collected from as far back as 1988, many of the cases did not undergo combinatory treatment with temozolomide and radiation. Furthermore, in these old cases immunohistochemistry or molecular investigations to reveal biological features were not performed. This should be the next investigation, considering that molecular findings can harbor a prognostic meaning, including a favorable prognostic effect in H3K27 M mutation in spinal GBM as indicated previously.[19] The combination of histopathological and molecular diagnosis according to the latest WHO 2021 classification would be worthwhile for a more thorough investigation.

The goal of surgery should be to establish an accurate diagnosis by getting an adequate tumor sample and cytoreduction.[11] The surgeon should use motor-evoked potentials and D-wave monitoring to guide cytoreductive surgery.[18] There is no role for aggressive surgery in the management of these lesions. If our experience with these lesions has taught us anything, it has been that aggressive surgery has no appreciable benefits and leads to more neurological morbidity.

Table 4
Postoperative clinical findings based on WHO grades.

Clinical findings	Result	WHO Grade				Total	Factors, *P*-value		
		1	2	3	4		Age (continuous)	Grade (ordinal)	EOR (ordinal)
New deficit, any	Yes	4	9	1	2	16	0.086	0.11	0.15
	No	4	7	6	3	20			
New weakness	Yes	2	3	0	1	6	0.45	0.66	0.0091*
	No	6	13	7	4	30			
New sensory deficit	Yes	2	6	0	2	10	0.47	0.18	0.86
	No	6	10	7	4	27			
New bladder symptom	Yes	1	0	1	0	2	0.31	0.51	0.90
	No	7	16	6	4	33			
Worsened deficit, any	Yes	3	7	1	4	15	0.81	0.20	0.40
	No	5	9	7	1	22			
Worsened weakness	Yes	3	7	1	3	14	0.82	0.55	0.39
	No	5	9	7	2	23			
Worsened sensory deficit	Yes	2	1	0	1	4	0.55	0.028*	0.66
	No	6	15	7	4	32			
Systemic complication	Yes	0	2	1	0	3	0.39	0.82	0.80
	No	8	14	6	5	33			
Wound complication	Yes	1	3	2	0	6	0.87	0.11	0.18
	No	7	13	5	5	30			
Hospital stay (days)	Range	4–17	4–8	2–16	4–7	2–17	0.78	0.032*	0.62
	Mean	11.0	5.9	7.9	5.3	7.1			
	Median	11.5	6	8	5	7			
Rehabilitation	Yes	3	15	6	5	29	0.73	0.20	0.49
	No	2	1	1	0	4			
Discharge destination	Home	2	5	3	2	12	0.0022*	0.16	0.83
	Rehab	2	10	3	2	17			
	SNF	0	1	1	0	2			

Abbreviations: Rehab: rehabilitation facility, SNF: skilled nursing facility.

Table 5
Progression free survival and overall survival based on WHO grades.

WHO Grade	PFS				OS			
	1 y	3 y	5 y	Median	1 y	3 y	5 y	Median
1	75.0	62.5	62.5	NR	100.0	100.0	100.0	NR
2	92.9	75.7	64.9	66.9	92.3	83.1	63.3	77.8
3	50.0	0	0	7.0	50.0	25.0	NR	10.9
4	33.3	NR	NR	10.7	80.0	NR	NR	NR

Abbreviations: PFS: progression free survival, OS: overall survival, NR: not reached, y: year.

Table 6
Immunohistochemistry and molecular markers identified in different WHO-grade cases.

Staining probes		WHO Grade				Total
		1	2	3	4	
TP53						
	Positive	0	1	3	3	9
	Negative	1	8	1	0	9
ATRX						
	Positive	0	0	0	0	0
	Negative	0	4	1	2	8
IDH1						
	Positive	0	0	0	0	0
	Negative	1	4	3	4	12
BRAF						
	Positive	0	0	0	0	1
	Negative	0	1	1	1	3
H3K27 M or H3K27me3 loss						
	Positive	0	0	0	4	4
	Negative	0	2	0	0	2

5. Conclusion

Spinal astrocytoma, is rare, but high grade lesions (Grade 3–4) demonstrate particularly rapid progression and poor prognosis. Surgical resection is associated with a high rate of expected neurological deficits. Further work will be needed to evaluate the impact of extent of resection on survival for spinal astrocytomas, Although higher extent of resection is known to improve survival for intracranial gliomas, neurological deficits are also inversely correlated with survival. In diffuse glioma, it is necessary to screen the whole neuraxis with imaging, as intracranial metastasis and spinal dissemination are not uncommon. Histopathological investigations revealed molecular similarity of grade 4 lesions to intracranial midline glioma with loss of H3K27 trimethylation. Data from these patients can add to the growing, but still very limited reported data regarding the biology and natural history of spinal astrocytomas.

Financial material & support

None.

Disclosures or conflicts of interest

None.

CRediT authorship contribution statement

Hirokazu Takami: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Investigation. **Desmond A. Brown:** Investigation, Writing - review & editing, Conceptualization, Formal analysis, Writing - original draft. **Joshua A. Spear:** Investigation, Writing - review & editing. **Yuki Shinya:** Investigation, Writing - review & editing. **Terry C. Burns:** Project administration, Supervision, Resources, Writing - review & editing. **Michelle J. Clarke:** Project administration, Writing - review & editing, Supervision. **William E. Krauss:** Project administration, Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

GTR: gross total resection
NTR: near-total resection
STR: subtotal resection
TMZ: temozolomide
WHO: World Health Organization