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Clinical Prognostic Factors and Molecular Characteristics of Spinal Cord Diffuse Midline Gliomas

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BACKGROUND AND OBJECTIVE: Spinal cord diffuse midline glioma (DMG) is an extremely rare and aggressive tumor, characterized by a poor prognosis. While sharing similarities with brain DMGs, spinal cord DMGs may exhibit distinct clinical and prognostic features. Recognizing these differences is crucial for developing effective treatment strategies tailored to spinal cord DMGs. The objective of this analysis was to evaluate the survival prognosis and the influencing factors associated with spinal cord DMGs.

METHODS: This study describes the clinical and molecular features of 46 patients with spinal cord DMG. The prognostic value of these clinical and molecular characteristics was investigated using Cox regression analysis and Kaplan-Meier curves.

RESULTS: The average age at diagnosis was 30 ± 14 years, with male-to-female ratio close to 2.1:1. The median survival time of patients was 16.5 months. Tumors predominantly occur in the thoracic spine, and they exhibited a notably superior prognosis than those in other locations ($P = .009$). The survival rate of patients undergoing radical resection tended to increase ($P = .003$). In addition, patients undergoing a second surgery demonstrated a significant increase in survival rates ($P = .022$). Median survival varied among histological grades: 43 months for grade II, 16 months for grade III, and 12 months for grade IV. Patients with histological grade IV had significantly worse prognosis than those with grades II and III ($P < .001$). Thoracic ($P = .001$) and thoracolumbar ($P = .017$) segments and gross total resection ($P = .018$) exhibited significantly higher survival rates for patients with histological grades II and III tumor, whereas none were observed for patients with histological grade IV tumor.

CONCLUSION: We conducted an analysis of the clinical and molecular features of 46 patients with spinal cord DMG, exploring their prognostic value. This study aims to provide evidence for evidence-based treatment strategies for spinal cord DMG.

KEY WORDS: , Cohort study, Spinal cord, Diffuse midline glioma, Neurosurgery, Histological grade, Prognosis

Spinal cord glioma is tumor originated from spinal glial cell and is the most common intramedullary spinal cord tumors.[1] The annual incidence is about 0.22~0.25/100 000 people.[2,3] Spinal cord glioma is common in young people and usually progress slowly, which can cause sensory, motor, and defecation dysfunction. Spinal cord glioma has different imaging and pathological characteristics.[4] Surgical treatment is the preferred treatment for spinal cord glioma, but the curative effect of comprehensive treatment based on surgery on high-grade spinal cord glioma is still not ideal.[1,5,6]

ABBREVIATIONS: DMG, diffuse midline glioma; **GTR,** gross total resection; **HR,** hazard ratio; **IDH,** isocitrate dehydrogenase; **OS,** overall survival; **PR,** partial resection; **STR,** subtotal resection; **WHO,** World Health Organization.

Diffuse midline glioma (DMG), H3 K27-altered (DMG), is a novel tumor of the central nervous system, primarily originating in the pontine, thalamic, and spinal cord, which is classified as the grade IV glioma, according to the 2021 World Health Organization (WHO) Classification.[7] Spinal cord DMG is more common in adults, and the average age of diagnosis is about 36 years.[8] The most common site of spinal cord DMG was the cervical enlargement and conus medullaris, and the average length of tumor was about 4 vertebral segments.[8] DMG is prone to leptomeningeal dissemination. An autopsy study showed that about 38.6% (17/44) of brain stem DMG had leptomeningeal dissemination.[9] Owing to its rarity, our understanding of spinal cord DMG largely relies on insights gained from its intracranial counterparts. However, tumor location often affects the clinical prognosis. Currently, specific features of spinal cord DMG remain undefined, leading to ongoing debates regarding its clinical characteristics and optimal treatment approaches.

We systematically analyzed the clinical and molecular characteristics of spinal cord DMG with the aim of determining the following: (1) the survival prognosis and influencing factors of spinal cord DMG; (2) the necessity and role of histological grading, while DMG is classified as the grade IV glioma according to the WHO Classification; and (3) the value of surgical resection of spinal cord DMG. Finally, we hope to have a more detailed understanding of spinal cord DMG and provide the basis for the precise treatment of spinal cord DMG. This cohort study has been reported in line with the Strengthening the Reporting of Observational Studies in Case Series Studies guidelines.[10]

METHODS

Patient Selection

This study followed the principles of the Declaration of Helsinki, and the Institutional Review Board of our hospital approved this study, and written informed consent was obtained from all the patients. We retrospectively reviewed the data obtained in 46 consecutive patients with spinal cord DMG resected between December 2014 and December 2021. These patients underwent their complete surgical treatment regimen at our institution, with the exclusion of cases where DMG originated in the brain and subsequently disseminated to the spinal cord.

Data Collection

Patients underwent continuous monitoring through regular follow-ups after surgery, with consultations or outpatient follow-up conducted every 3 months. The collected data encompassed fundamental clinical information for each patient, comprising age, gender, tumor location, segment length, preoperative McCormick Scale score,[11] extent of resection, adjuvant therapy (radiotherapy, chemotherapy, and targeted therapy), and histological grading, all of which were included for comprehensive analysis. All patients underwent surgery under neurophysiological monitoring, ensuring the maximal possible tumor resection. The extent of tumor removal was assessed postoperatively using MRI. Preoperative and postoperative MRI scans were conducted within 48 hours of surgery. The extent of resection was described previously,[1] with classified as gross total resection (GTR, resection of all visible tumor), subtotal resection (STR, residual tumor 20% of the initial size), and partial resection (PR, residual tumor >20% of the initial size) according to preoperative and postoperative MRI.

According to the 2021 WHO Classification, histological grading was systematically performed through microscopic evaluation of hematoxylin-eosin stained specimens prepared through formalin fixation and paraffin embedding, with criteria defined as: grade II (cytological atypia), grade III (focal/diffuse anaplastic features combined with elevated mitotic activity), and grade IV (characterized by either necrosis or microvascular proliferation or both).[12]

All samples were fixed in 10% neutral buffered formalin and paraffin-embedded immediately after surgical excision. Sections from these samples were used for immunohistochemical and molecular pathology tests, including assessments for H3 K27M mutation, isocitrate dehydrogenase 1 (IDH1) R132H mutation, α-thalassemia/mental retardation syndrome X-linked (ATRX), Ki-67, 06-methylguanine-DNA methyltransferase (MGMT) promoter methylation, and TP53. Based on the percentage of cells showing immunostaining, the Ki-67 index was classified as either high (≥10%) or low (less than 10%) for subsequent analysis.

Statistical Analysis

SPSS 26.0 (IBM) and GraphPad Prism 7 (GraphPad software) were used for statistical analysis. Univariate and multivariate Cox regression analysis was used to determine prognostic variables. The overall survival (OS) of all patients was analyzed from the date of surgery to the last follow-up or the date of death. Kaplan-Meier method was used to plot the survival curve, and the log-rank test was used to test the statistical significance. *P*-value <.05 was considered statistically significant.

RESULTS

Clinical Characteristics and Treatment Outcomes

The clinical characteristics of 46 patients are shown in Figure 1. The average age at diagnosis was 30 ± 14 years (range: 3-64 years), with 31 male (67.4%) and 15 female (32.6%), resulting in a male-to-female ratio close to 2.1:1. Of the total, 37 were adults (80.4%). The most common preoperative manifestations included motor dysfunction in 44 cases (96%), sensory abnormalities in 35 cases (76%), pain in 25 cases (54%), and sphincter dysfunction in 23 cases (50%). According to the preoperative McCormick Scale score, 3 patients were classified as Grade I, 11 as Grade II, 10 as Grade III, and 22 as Grade IV. Tumor locations included cervical in 8 cases (17.4%), cervicothoracic junction in 9 cases (19.6%), thoracic in 22 cases (47.9%), and thoracolumbar junction in 7 cases (15.2%). The tumors spanned an average of 4 ± 2 vertebral segments, with 21 (46.7%) patients exhibiting tumors extending over more than 5 segments in length.

All patients underwent surgical tumor resection, with 8 cases (17.3%) achieving GTR, 32(69.6%) achieving STR, and 6 (13.0%) undergoing PR. The median survival time for patients with GTR was 31 months (12-85 months), STR was 16 months (1-87 months), and PR was 15 months (4-17 months). Sixteen patients (34.8%) underwent reoperation to remove the recurrent tumor, and 36 patients (78.3%) received adjuvant therapy.

FIGURE 1. *A map of the characteristics of patients. C, cervical; C-T, cervicothoracic; F, female; GTR, gross total resection; M, male; MMS, Modified McCormick Scale; OS, overall survival; PR, partial resection; STR, subtotal resection; T, thoracic; T-L, thoracolumbar.*

Molecular Profiles

Of 46 patients, 22 underwent MGMT methylation testing, with 4 (18.2%) showing low methylation of the MGMT promoter. Among 28 tested for ATRX, 8 (28.6%) had loss of nuclear protein expression. In 29 patients screened for IDH1 mutation, only 2 (7%) were positive. Of 42 tested for TP53, 24 (57%) had TP53 gene mutations. Among all patients, 42 (91.3%) exhibited Ki-67 nuclear expression ≥10% (Figure 1). None of these molecular markers showed statistical significance.

Survival Analysis

The median OS of patients with DMG was 16.5 months (1-87 months), with median survival periods for histological grades II, III, and IV tumors being 43 months (20-87 months), 16 months (4-67 months), and 12 months (1-20 months), respectively. Univariate and multivariate Cox regression analyses showed that tumor location (P = .009; Figure 2A), extent of resection (P = .003; Figure 2B), reresection (P = .008; Figure 2C), and histological grade (P = .001; Figure 2D) were independent prognostic factors for OS (Table 1). Patients with thoracic tumor, GTR, reoperation, and histological grades II and III had a significantly better prognosis.

As illustrated in Figure 2D, although the Kaplan-Meier survival curve for patients with histological grade II tumors suggests a survival advantage over grade III patients, this difference was not statistically significant (P = .201). Subsequently, we stratified patients into two groups based on our histological grading study results (group I: patients with grade II and grade III tumors and group II: patients with grade IV tumors only). Multivariate Cox regression analysis revealed that among patients with grades II and III tumors, those with tumors located in the thoracic (hazard ratio [HR]: 0.024; 95% CI: 0.003-0.187; P = .001) and thoracolumbar segments (HR: 0.035; 95% CI: 0.002-0.543; P = .017) had a better prognosis (Figure 3A; Table 2). Moreover, patients who underwent GTR exhibited significantly higher survival rates compared with others (HR: 0.085; 95% CI: 0.011-0.654; P = .018; Figure 3B; Table 2). However, in patients with grade IV tumors, location and GTR did not achieve statistical significance (P > .05) (Figure 3C and 3D; Table 2).

DISCUSSION

Spinal cord DMG is a rare central nervous system tumor, characterized by its aggressive nature and poor prognosis.[13,14] There are many prognostic risk factors that affect spinal cord DMG, including age, tumor location, tumor size, preoperative neurological status, degree of surgical resection, adjuvant therapy, histological grading, Ki-67, and molecular features. In this study,

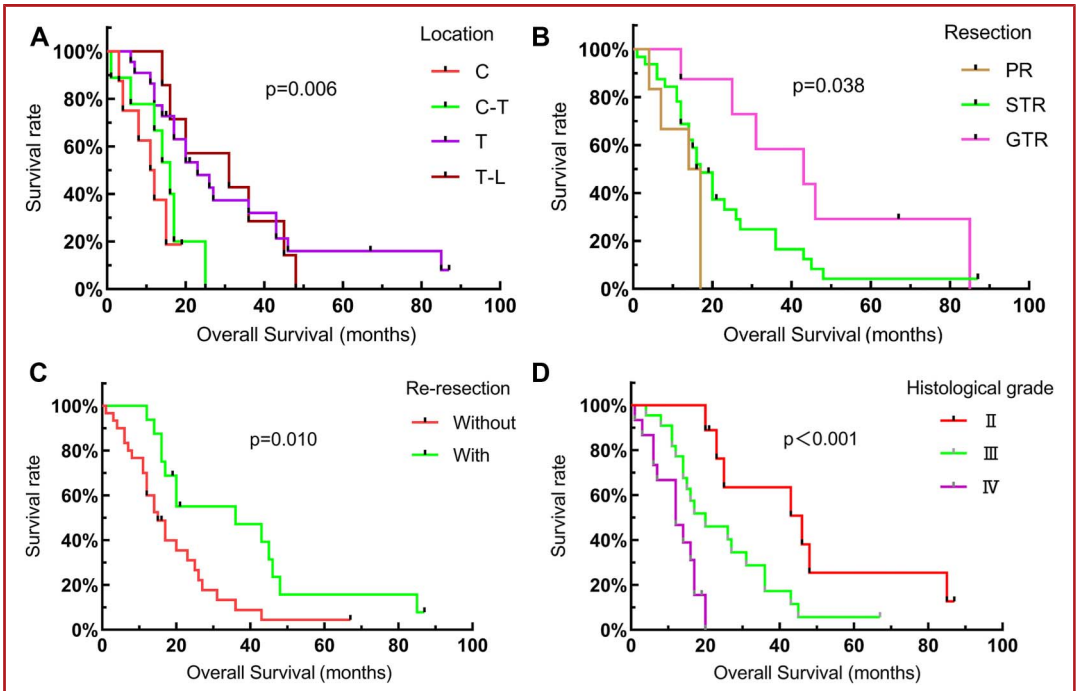

FIGURE 2. *Kaplan-Meier survival curves for factors influencing the prognosis of spinal cord diffuse midline glioma survival.* **A**, *Kaplan-Meier survival curves for tumor location;* **B**, *Kaplan-Meier survival curves for resection extent;* **C**, *Kaplan-Meier survival curves for reresection; and* **D**, *Kaplan-Meier survival curves for patients stratified by histological grade. GTR, gross total resection; PR, partial resection; STR, subtotal resection.*

TABLE 1. Independently Significant Risk Factors

Variable	All patients (n = 46)		Hazard ratio (95% CI)	*P* value
Location	C	8 (17.4%)		NA
	C-T	9 (19.6%)		NA
	T	22 (47.9%)	0.216 (0.069-0.681)	.009[a]
	T-L	7 (15.2%)		NA
Resection	PR	6 (13.0%)		NA
	STR	32 (69.6%)		NA
	GTR	8 (17.4%)	0.107 (0.024-0.471)	.003[a]
Reresection	With	16 (34.8%)	0.251 (0.090-0.699)	.008[a]
	Without	30 (65.2%)		NA
Histological grade	II	9 (19.6%)		NA
	III	22 (47.8%)		NA
	IV	15 (32.6%)	8.757 (2.515-30.488)	.001[a]

C, cervical; C-T, cervicothoracic; GTR, gross total resection; NA, not available; PR, partial resection; STR, subtotal resection; T, thoracic; T-L, thoracolumbar.
[a]Statistically significant.

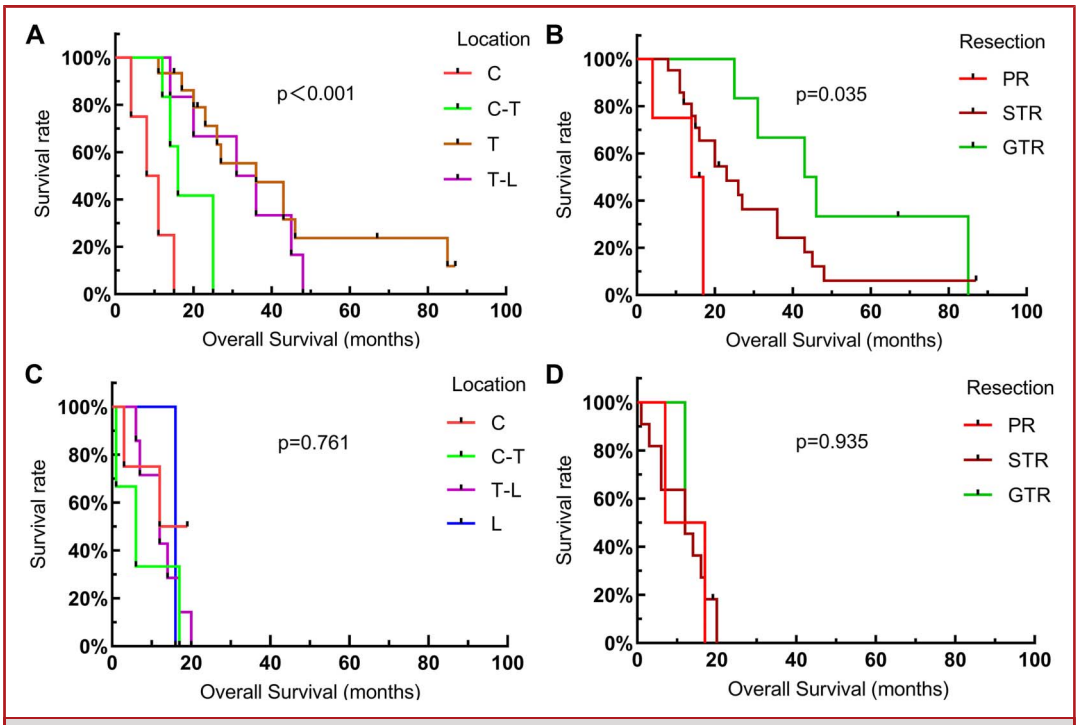

FIGURE 3. *Kaplan-Meier survival curves for prognostic factors in spinal cord diffuse midline glioma across various patient groups.* **A**, *Kaplan-Meier survival curves for patients with histological grades II and III regarding tumor location;* **B**, *Kaplan-Meier survival curves for patients with histological grade IV regarding tumor location;* **C**, *Kaplan-Meier survival curves for patients with histological grades II and III regarding the extent of surgical resection; and* **D**, *Kaplan-Meier survival curves for patients with histological grade IV regarding the extent of surgical resection. GTR, gross total resection; PR, partial resection; STR, subtotal resection.*

we conducted a comprehensive analysis of potential prognostic factors for spinal cord DMG and found that tumor location, surgical intervention, and histological grade were independent parameters for the prognosis of patients with spinal cord DMG. However, in clinical practice, we also found that the survival time span of spinal cord DMG is larger, and it is different from glioblastoma (WHO grade IV), but more like astrocytoma. Therefore, we analyzed the prognosis of DMG with different

TABLE 2. Multivariate COX Regression Analysis of Histological Grades II, III, and IV

		Histological grade II III			Histological grade IV		
Variable		**All patients (n = 31)**	**Hazard ratio (95% CI)**	***P* value**	**All patients (n = 15)**	**Hazard ratio (95% CI)**	***P* value**
Location	C	4 (12.9%)		NA	4 (26.7%)		NA
	C-T	6 (19.4%)		NA	3 (20.0%)		NA
	T	15 (48.4%)	0.024 (0.003-0.187)	.001[a]	7 (46.7%)		NA
	T-L	6 (19.4%)	0.035 (0.002-0.543)	.017[a]	1 (6.7%)		NA
Resection	PR	4 (12.9%)		NA	2 (13.3%)		NA
	STR	21 (67.7%)		NA	11 (73.3%)		NA
	GTR	6 (19.4%)	0.085 (0.011-0.654)	.018[a]	2 (13.3%)		NA

GTR, gross total resection; NA, not available; PR, partial resection; STR, subtotal resection.
[a]Statistically significant.

histological grades according to the grading criteria for astrocytoma.[12] GTR, thoracic, and thoracolumbar segments exhibited significantly higher survival rates for patients with histological grades II and III tumor, while none were observed for patients with histological grade IV tumor.

Tumor location is an important factor affecting the prognosis of patients. Wang et al[8] analyzed clinicopathological features and prognosis in 44 patients with spinal cord DMG and found that tumors located at T2 to T11 had better survival compared with those located at other segments (26.3 vs 18.1 and 13.9 months). Our research indicates that the thoracic segment was the most common site of tumor occurrence and exhibited a significantly better prognosis compared with tumors in other locations. The prognosis of patients with thoracic and thoracolumbar DMG is better, when we further analyzed according to histological grading. Histological grades II and III tumors were relatively common in the thoracic and thoracolumbar segments (72.4%), and tumor infiltrative growth or leptomeningeal dissemination to the life-threatening central nervous system took a longer time than other segments.

In the 2021 WHO classification, DMG at any location was defined as a grade IV glioma, irrespective of histopathological grading.[7] Research has shown that the higher the WHO histological grade of spinal cord gliomas, the higher the proportion of H3 gene mutations,[15] and H3 gene mutations are closely related to poor prognosis in patients with DMG.[16] However, some studies reported that H3.3K27M mutation is not the main factor affecting poor prognosis in patients with spinal cord DMG.[15,17] The OS of patients with DMG is significantly longer than that of other WHO histological grade IV spinal cord gliomas, which may be since the DMG group contains some WHO histological grades II and III tumors. Chai et al further analyzed the prognosis of patients with DMG with different histological grades, and the results showed that the OS of patients with DMG with histological grades II and III was longer than that of patients with histological grade IV (24 and 12 months, respectively). H3K27M mutation was only associated with low survival rate in tumors with histological grade II, but not in tumors with histological grades III and IV. Another study further showed that the prognosis of patients with spinal cord DGM with different histological grades is not consistent and highlighted the significance of histopathological grading as a determinant of the prognosis for spinal cord DMG. The median OS of patients with DMG with histological grade IV is only 8.6 months, and the 1-year and 5-year survival rates are 33% and 0, respectively, which is significantly shorter than that of patients with histological grades II (23.9 months) and III (26.3 months).[8] This finding stands out as it contrasts with the behavior of DMGs located in the brainstem and thalamus.[18] Unlike these areas, the grading of spinal cord DMGs has been identified as a pivotal factor in predicting disease progression and outcome. Histological grading stratifies the OS of spinal cord DMG, with grade II/III gliomas showing significantly higher survival rates than all grade IV gliomas. In our study, we analyzed 9 cases of histological grade II, 22 cases of grade III, and 15 cases of grade IV spinal cord DMG and found that patients with grade IV histology had significantly worse survival outcomes than those with lower-grade tumors. This emphasizes the critical impact of histopathology on the prognosis of spinal cord DMG, although there was no statistically significant difference in survival between patients with grades II and III tumors (P = .201).

Owing to the rarity of spinal cord DMG, there is currently no standardized treatment protocol. Surgical treatment is the preferred treatment for spinal cord gliomas, with the primary goals of preserving spinal cord function to the greatest extent possible, reducing tumor compression on the spinal cord, and clarifying pathological diagnosis.[6] In prior research, Yi et al[15] performed surgery on 25 individuals with spinal cord astrocytoma, of which 20 harbored H3 K27M mutation, and determined that surgery did not significantly influence patient outcomes. Wang et al[8] observed a nonsignificant trend toward improved survival with more extensive resections. Conversely, Garcia et al[19] demonstrated a markedly reduced OS in patients who underwent biopsy compared with those who received GTR. Our study findings suggested that patients with spinal DMG may derive greater survival benefits from more aggressive surgical resection strategies. A critical distinction among these studies is the criteria used to define GTR. In the investigations led by Yi[15] and Wang,[8] GTR was characterized as the removal of 90% of the tumor mass. By contrast, Garcia[19] and colleagues defined GTR as the complete excision of all neoplastic tissue, which was verified by surgical documentation or postoperative MRI that confirmed the absence of any residual tumor. Therefore, the divergence in the definition of tumor resection may influence the assessment of surgical efficacy in the context of spinal cord DMG. In addition, the patient with spinal cord transection exhibited no tumor recurrence for 4 years postoperatively, which illustrated the potential impact of GTR on the postoperative survival prognosis.[20] Given the distribution characteristics of spinal cord functions and the current poor clinical outcomes of spinal cord DMG, it may be warranted to consider more aggressive tumor resection for DMG located in the lower thoracic spinal cord.

Our study further demonstrated that as the histological grade of the tumor increases, the survival benefits derived from surgery for patients progressively diminish. We hypothesize that this correlation may be attributed to the heightened malignancy and more aggressive invasive growth characteristic of high-grade tumors. Tumors of a higher grade are often refractory to complete resection and are associated with rapid progression. Consequently, this could result in the survival benefits obtained from surgery in patients with lower-grade tumors being offset by the unfavorable prognosis of higher-grade tumors. This observation underscores the significance of histological grading in predicting treatment outcomes.

Limitations

The major limitations of this study are its retrospective and observational nature. Given the rarity of this disease, only some medical centers have a considerable amount of patient information available for research. Spinal cord DMG is usually

associated with TP53 gene mutations. ATRX deletions/mutations, NF1, IDH1/2 mutations, PDGFRA amplification, ACVR1 mutations, PIK3CA mutations, FGFR1 mutations, PPM1D mutations, TERT promoter mutations, MGMT promoter methylation, and BRAF V600E mutations are less common.[21-24] Therefore, there are insufficient data to clarify their relationship with prognosis. It is hoped that in the future, clinical and molecular data can be shared with other centers to increase sample size, obtain more comprehensive and accurate information, and facilitate precise treatment of spinal cord DMG.

CONCLUSION

The study demonstrates that although spinal cord DMG is classified as a WHO grade IV tumor, significant prognostic stratification exists based on histopathological criteria. Lower histological grades may experience even greater survival advantages with location and surgical interventions. Future treatment strategies for spinal cord DMG should therefore consider distinct therapeutic approaches tailored to different histological grades. This research aims to support evidence-based treatment strategies for spinal cord DMG, enhancing therapeutic efficacy and extending patient survival.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENTS

The retrospective case series "Clinical Prognostic Factors and Molecular Characteristics of Diffuse Midline Gliomas in the Spinal Cord" aims to address survival prognostic factors of DMG. The authors analyzed several possible prognostic factors, including recently introduced molecular factors.

While recent publications have addressed that DMGs should be considered grade IV glial lesions, the authors found that spinal DMGs have longer survival than the cerebral counterpart. This adds significant value to the management of spinal DMGs. Moreover, this enabled authors to stratify the tumors based on histological features.

Tumor location, extent of resection, reresection, histological grade were analyzed as possible prognosticators, as well as MGMT, ATRX, IDH1, TP53 and Ki67 >10%. Among these, thoracic location, GTR, reoperation for recurrence and histological grades II and III were favorable prognosticators. No molecular factor reached significance. In grades II and III, thoracic and thoracic-lumbar location had a better prognosis. The

survival advantage based on location seems to correlate with less local infiltration and leptomeningeal invasion; this should lead surgeons to treat suspicious DMGs aggressively when found in these locations.

Interestingly, in patients with grade IV tumors, GTR did not show a significant benefit. This reduces the impact of surgical resection in this specific context and future research should be conducted to investigate possible radiological predictors of grade IV DMGs.

In conclusion, this case series adds three important concepts to the knowledge of spinal DMGs: longer survival than cerebral DMGs, favorable survival for grade II and III thoracic DMGs, low impact of aggressive resection on grade IV DMGs.

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