Spinal Cord Diffuse Midline Gliomas With H3 K27m-Mutant: Clinicopathological Features and Prognosis

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The current data included some cases included in previous reports (Chai RC et al. Acta Neuropathol Commun, 2020; 8:40; Zhang YW et al. Cancer Med. 2020; 9: 6996–7006). The current study enrolled new cases and further comprehensive analysis focusing on grade IV diffuse midline gliomas with H3 K27M-mutant located in the spinal cord.

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BACKGROUND: "Diffuse midline glioma, H3 K27M-mutant" (DMG) mainly arises within the pontine, thalamic, and spinal cord regions. Because of the rarity of spinal cord gliomas, the general knowledge surrounding DMGs is mainly based on pontine and thalamic gliomas, whereas tumor location tends to influence the clinicopathological features and prognosis.
OBJECTIVE: To determine the clinicopathological characteristics and molecular profiles of DMGs located in the spinal cord.
METHODS: The clinical and molecular pathologic features and prognosis were comprehensively analyzed in a series of 44 patients with spinal cord DMGs.
RESULTS: The median age was 36 yr, and 88.7% of patients (39/44) were adults (≥18 yr). Histopathologically, malignant grades included grade II (16 cases), grade III (20 cases), and grade IV (8 cases). Compared with patients with histological grade IV, patients with lower histological grade (grade II/III) were older (37 vs 24 yr, $P = .020$) and were associated with longer overall survival (24.1 vs 8.6 mo, $P = .007$). All 30 tested tumors were isocitrate dehydrogenase (IDH) wild type, and 96% of cases (22/23) presented with unmethylated O^6-methylguanine-DNA methyltransferase. Univariate and multivariate analyses showed that histological grade and presurgery McCormick Scale scores were independent prognostic factors for overall survival, whereas extensive surgical resection and chemoradiotherapy were not significantly associated with improved survival. The most frequent anatomic locations were the cervical enlargement (C4-T1, n = 16) and conus medullaris (T12-L1, n = 13), which exhibited distinctive clinical characteristics and molecular features.
CONCLUSION: The findings provide guidelines for the evidence-based practice of the specialized management of spinal cord DMGs.

KEY WORDS: Astrocytoma, Spinal cord, Intramedullary tumor, Diffuse midline glioma, H3 K27M mutation

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Diffuse midline glioma, H3 K27M-mutant (DMG), which mainly arises within the pontine, thalamic, and spinal regions, is defined as a grade IV glioma independent of the histological signs of anaplasia in the 2016 World Health Organization (WHO) Classification.[1] The tumor is mainly prevalent in children and young adults, characterized by astrocytic differentiation, and K27M mutation in the histone H3 gene *H3F3A* (or in *HIST1H3B/C*), and it mainly occurs in midline structures including the thalamus, brain stem, and spinal cord.[2-4]

Compared with a K27M mutation rate of over 80% in diffuse intrinsic pontine gliomas (DIPGs), the mutation rate in spinal gliomas is much lower at approximately 38%.[5,6] Because of the rarity of spinal cord gliomas, the general knowledge regarding DMGs is mainly based on the pontine and thalamic gliomas.[7-14] However, tumor location tends to influence clinicopathological features and prognosis.[15] The features of spinal cord DMG have not been specifically described.

ABBREVIATIONS: DIPG, diffuse intrinsic pontine glioma; **DMG,** diffuse midline glioma, H3 K27M-mutant; **ER,** extensive resection; **FFPE,** formalin fixed/paraffin embedded; **HR,** hazard ratio; **IDH,** isocitrate dehydrogenase; **MMS,** McCormick Scale; **OB,** open biopsy; **OS,** overall survival; **STR,** subtotal resection; **TMZ,** temozolomide; **WHO,** World Health Organization

Although the characteristics of H3 K27M-mutant gliomas have been reported in several studies, tumors located in the spinal cord are rarely reported.[2,3,15-18] Yi et al[19] first reported the prognosis and survival of 25 patients with 2016 WHO grade IV spinal cord gliomas (including 20 patients with H3 K27M mutation), but the risk stratification and treatment optimization of patients with H3 K27M mutation have not been analyzed. In our previous studies, we suggested that spinal cord gliomas are different from DIPGs in terms of their clinicopathological features and that histological grade should be considered when assessing the prognosis of DMGs.[6,20]

Herein, we specifically describe the clinicopathological characteristics and molecular profiles of spinal cord DMGs. We performed a comprehensive analysis of clinical characteristics and molecular pathology to acquire more comprehensive understanding of spinal cord DMGs and provide evidence-based practice for their management.

METHODS

Patients

We identified 44 patients who underwent spinal cord tumor surgery and were pathologically diagnosed with DMGs based on the 2016 WHO Classification between 2011 and 2019. Clinical data including histological type, age, sex, tumor location, presurgery McCormick Scale (MMS), extent of resection, radiotherapy, and chemotherapy were collected from the medical records, as shown in Table 1.

This study followed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of our institute. Informed consent had been obtained from all participants.

Therapy

The aim and consensus of all neurosurgeons was to achieve maximal tumor resection and decompression while preserving neurological function. In the present study, all patients underwent surgical resection with neurophysiological monitoring. The extent of resection was defined as extensive resection (ER: ≥90%), subtotal resection (STR: ≥50% and <90%), and open biopsy (OB: <50%) according to the postoperative magnetic resonance imaging.

The postsurgery conventional adjuvant radiotherapy total dose was 40 to 50 Gy, which was administered at a dose of 1.8 to 2.0 Gy per fraction per day for 5 d per treatment week over 5 consecutive weeks. The chemotherapy consisted of temozolomide (TMZ) following the Stupp regimen.[21] In brief, a daily dose of 75 mg/m^2 was given during radiotherapy or a daily dose of 150 to 200 mg/m^2 for 5 consecutive days per treatment week and 4 wk per cycle.

Molecular Neuropathology

According to the 2016 WHO Classification, formalin fixed/paraffin embedded (FFPE) samples with hematoxylin and eosin staining were routinely evaluated to determine the histopathological grade. The histological grade was defined as follows: (1) histological grade II (include 16 cases), features by tumor cells with cytological atypia alone; (2) histological grade III (include 20 cases), features by anaplasia and mitotic activity; and (3) histological grade IV (include 8 cases), features by microvascular proliferation and/or necrosis (including focal microvascular proliferation and/or necrosis). The

TABLE 1. Clinical Characteristics and Molecular Profiles for 44 Patients in the Present Study

		Histological grade		
	Total	II (n = 16)	III (n = 20)	IV (n = 8)
Age (yr)				
Median (range)	36 (9-52)	38 (10-51)	38 (9-52)	24 (13-36)
Mean (±SD)	34 ± 12	35 ± 12	38 ± 11	25 ± 9
Sex				
Male	23 (52%)	8 (50%)	13 (65%)	2 (25%)
Female	21 (48%)	8 (50%)	7 (35%)	6 (75%)
Location				
C	12 (27%)	5 (31%)	5 (25%)	2 (25%)
C-T	7 (16%)	2 (13%)	3 (15%)	2 (25%)
T	19 (43%)	8 (50%)	8 (40%)	3 (38%)
T-L	6 (14%)	1 (6%)	4 (20%)	1 (13%)
Segment length				
Median (range)	4 (1-9)	4 (2-8)	3 (1-7)	5 (2-9)
Presurgery MMS				
1	1 (2%)	1 (6%)	0 (0%)	0 (0%)
2	9 (20%)	3 (19%)	4 (20%)	2 (25%)
3	23 (52%)	9 (56%)	12 (60%)	2 (25%)
4	11 (25%)	3 (19%)	4 (20%)	4 (50%)
Resection				
ER (≥90%)	18 (41%)	4 (25%)	10 (50%)	4 (50%)
STR (50%-90%)	8 (18%)	3 (19%)	3 (15%)	2 (25%)
OB (<50%)	18 (41%)	9 (56%)	7 (35%)	2 (25%)
Re-resection				
With	9 (20%)	4 (25%)	4 (20%)	1 (13%)
Without	35 (80%)	12 (75%)	16 (80%)	7 (88%)
Radiotherapy				
Yes	28 (78%)	10 (77%)	14 (78%)	4 (80%)
No	8 (22%)	3 (23%)	4 (22%)	1 (20%)
NA	8	3	2	3
TMZ chemotherapy				
Yes	20 (56%)	5 (38%)	12 (67%)	3 (60%)
No	16 (44%)	8 (62%)	6 (33%)	2 (40%)
NA	8	3	2	3
Ki-67				
<10%	7 (16%)	6 (38%)	1 (5%)	0 (0%)
≥10%	37 (84%)	10 (63%)	19 (95%)	8 (100%)
IDH				
Mutant	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wild type	30 (100%)	11 (100%)	13 (100%)	6 (100%)
NA	14	5	7	2
MGMT promoter				
Methylation	1 (4%)	0 (0%)	0 (0%)	1 (33%)
Unmethylation	22 (96%)	9 (100%)	11 (100%)	2 (67%)
NA	21	7	9	5
TERT promoter				
Mutant	4 (14%)	1 (9%)	2 (15%)	1 (20%)
Wild type	25 (86%)	10 (91%)	11(85%)	4 (80%)
NA	15	5	7	3
BRAF V600E				
Mutant	1 (4%)	0 (0%)	1 (9%)	0 (0%)
Wild type	23 (96%)	9 (100%)	10 (91%)	4 (100%)
NA	20	7	9	4

C, cervical; C-T, cervicothoracic; T, thoracic; T-L, thoracolumbar; ER, extensive resection; IDH, isocitrate dehydrogenase; STR, subtotal resection; OB, open biopsy; TMZ, temozolomide; MMS, McCormick Scale; NA, not available.

H3 K27M mutant (ABE419; Millipore, Billerica, Massachusetts; 1:800) and Ki-67 expression (MIB-1; Labvision, Fremont, California; 1:50) were evaluated using immunohistochemistry and corresponding antibodies; neuropathologists manually calculated the proportion of Ki-67-positive nuclei. After sufficient DNA was extracted from FFPE samples, isocitrate dehydrogenase (IDH1) R132H, TERT promoter C228T and C250T, and BRAF V600E mutations were determined using pyrosequencing after PCR amplification. The PyroMark Q24 MGMT kit (Qiagen) was used to evaluate O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation following pyrosequencing.[20]

Statistical Analysis

All statistical analyses were conducted using GraphPad Prism 7 (GraphPad Software, La Jolla, California) and SPSS (IBM, Armonk, New York). The Chi-square test was used for comparisons of categorical data, and the t-test was used to compare quantitative variables. Overall survival (OS) was measured from the date of surgery to the date of last follow-up or death, whichever occurred first. The Kaplan-Meier method was used to estimate survival rates, and the log-rank test was used to assess differences between curves. Univariate Cox regression analyses were performed to determine prognostic variables. For all analyses, $P < .05$ was considered statistically significant.

RESULTS

Presentation Characteristics

Patient demographics and baseline characteristics are summarized in Table 1. Of all 44 patients with spinal cord DMG, 39 patients (88.7%) were adults (age at diagnosis ≥18 yr). Histopathologically, these tumors comprised 16 grade II diffuse astrocytomas, 20 grade III anaplastic astrocytoma, and 8 grade IV glioblastomas. The median age at diagnosis of all patients was 36 yr (range: 9-52 yr); the patients with lower histological grade (grade II/III) were older than patients with histological grade IV (37 vs 24 yr, $P = .020$). The male-to-female ratio of 1.1:1 (23 vs 21), which means there was no significant sex bias. The tumors usually invaded extensively, and the median span was 4 vertebral segments.

Molecular Profiles

All 30 tested patients lacked mutations in IDH1 R132H, regardless of their histological grade. MGMT promoter methylation was present in only 1 out of 23 tested patients (4%) who had grade IV glioblastoma histologically. TERT promoter mutations were present in 14% of patients (4 out of 29 tested) and were present across all histological grades. BRAF V600E mutation was present in 1 of 24 tested patients who had histological grade III. A high percentage of Ki-67-positive nuclei (≥10%) were observed in almost all high histological grade tumors (grade III/IV) and only 63% of grade II tumors ($P < .01$). Notably, however, none of the molecular markers showed any prognostic value for OS (all $P > .05$, Kaplan-Meier analysis; data not shown).

Treatment Outcomes

The median follow-up was 42.7 mo; 32 patients (72.7%) died, and 1 patient (2.3%) was lost to follow-up. Of all cases of surgical resection, only 41% of patients underwent ER (≥90%), whereas 41% of patients had undergone OB (<50%). Although greater resection could achieve a slight survival advantage, the difference in survival was not statistically significant ($P = .687$; Figure 1A). In cases of recurrence more than 6 mo after the initial treatment, re-operation was preferred if the tumor was resectable.[19] There were 20% of patients who underwent tumor re-resection but had no statistically significant survival benefit ($P = .344$, data not shown). Adjuvant radiotherapy was performed in 78% of patients, and TMZ chemotherapy was adopted in 56% of patients. However, radiotherapy, chemotherapy, or their combination did not have statistically significant improvement in OS (all $P > .05$; Figure 1B-1D).

Survival Analysis

The median OS was 23.9 mo for patients with spinal cord DMG, and the 1-, 3-, and 5-yr OS rates were 73%, 32%, and 8%, respectively. Survival times based on different histological grades are shown in Table 2. The median OS of histological grades II, III, and IV were 23.9, 26.3, and 8.6 mo, respectively. Histological grade was significantly associated with OS ($P = .027$), and low histological grade showed a better prognosis than in grade IV ($P = .007$). Of note, patients with histological grade IV had a 1-yr OS rate of 33% and a 5-yr OS rate of 0. Histological grades II and III possessed similar prognoses ($P = .865$, data not shown).

Univariate and multivariate Cox regression analyses showed that histological grade (hazard ratio [HR] 1.637; 95% confidential interval [CI] 1.057-2.537; $P = .027$) and presurgery MMS (HR 1.939; CI 1.110-3.386; $P = .020$) were independent prognostic factors for OS. However, age at diagnosis, sex, segment length, extent of resection, radiotherapy, and TMZ chemotherapy did not statistically affect survival (Table 3).

The Clinical and Biological Characteristics Based on Anatomic Locations

We noticed that the most frequent tumor locations were C4-T1 and T12-L1, which correspond to 2 anatomic locations of the medulla spinalis: the cervical enlargement and conus medullaris (Figure 2). Therefore, we further analyzed the clinical and molecular characteristics of these 2 anatomic locations compared with those of other locations. There were 2 peak ages of 25 to 35 yr and 40 to 50 yr for the tumors affecting the cervical enlargement, whereas the susceptibility age was 40 to 50 yr for tumors of the conus medullaris. Thoracic tumors demonstrated no age bias. Conus tumors were more common in women, with a male-to-female ratio of 1:3.3, whereas thoracic tumors were more common in men, with a male-to-female ratio of 3:1. The tumors located at the cervical enlargement were equally common in both

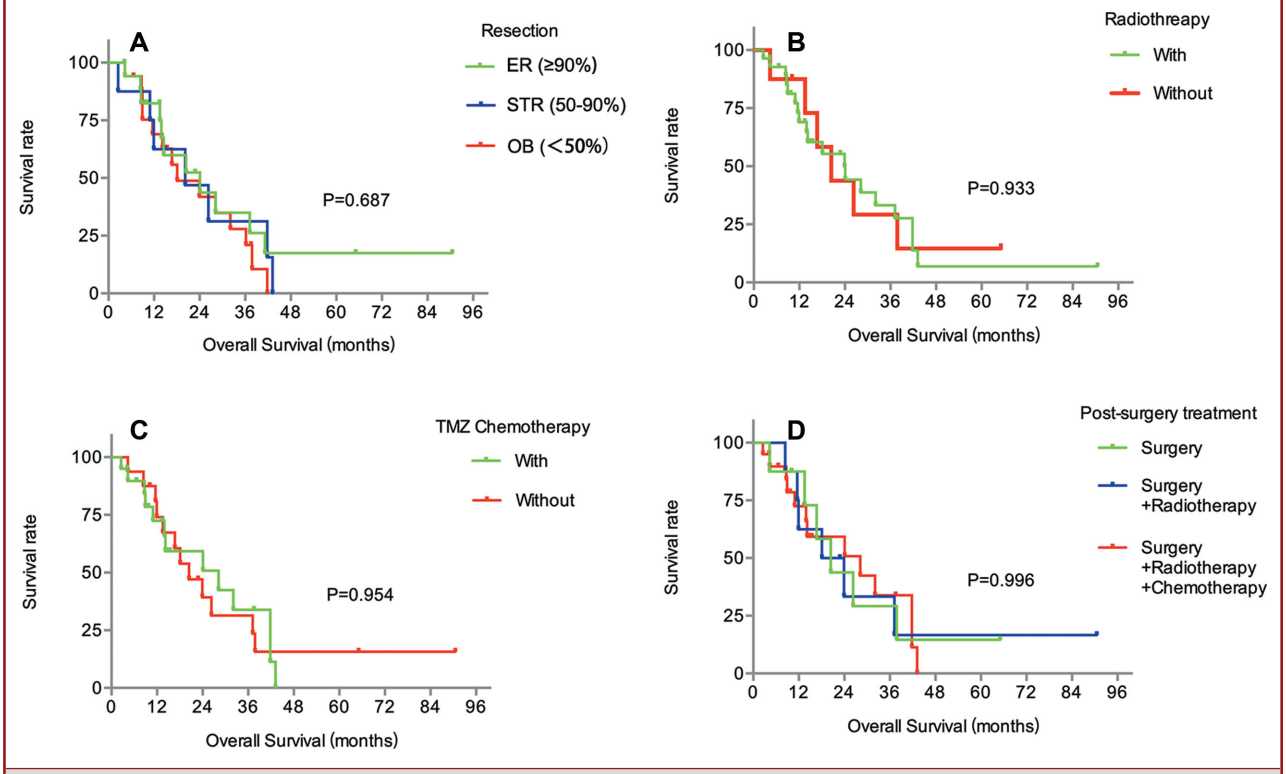

FIGURE 1. *Kaplan-Meier survival curves for treatment modalities.* **A**, *Kaplan-Meier survival curves for resection extent.* **B**, *Kaplan-Meier survival curves for radiotherapy.* **C**, *Kaplan-Meier survival curves for chemotherapy.* **D**, *Kaplan-Meier survival curves for combined treatment.*

TABLE 2. Overall Survival (OS) of Spinal Cord Diffuse Midline Glioma With Different Histological Grades

		OS rate (yr)				
	N	1	3	5	Median OS (mo) 95%	*P*-value
Total	43	73%	32%	8%	23.9 (15.9-31.9)	.027[a]
Histological grade II	15	87%	42%	8%	23.9 (4.7-43.1)	
Histological grade III	20	78%	29%	13%	26.3 (16.3-36.2)	
Histological grade IV	8	33%	17%	0%	8.6 (0.0-17.5)	.007[b]

[a] *P*-value for 3 histological grades.
[b] *P*-value for histological lower-grade (grade II/III) vs grade IV.

sexes. Histopathologically, of the tumors in the thoracic region, 11 out of 12 tumors (91.7%) were of lower grade, and only 1 patient (8.3%) had a grade IV tumor. In contrast, regarding tumors in the cervical enlargement and conus, a quarter of cases were grade IV glioblastomas. The tumors of the cervical enlargement had no TERT promoter mutation or BRAF V600E mutation. In contrast, 17% of the tumors at T2-11 and 33% of tumors at the conus carried TERT promoter mutations.

The median OSs of cervical enlargement, T2-T11, and conus medullaris tumors were 13.9, 26.3, and 18.1 mo, respectively (Figure 2). The Kaplan-Meier survival curve showed that tumors located at the cervical enlargement and conus medullaris had similarly poor survival compared with those located at T2-T11 (Figure 3).

DISCUSSION

Herein, we performed a comprehensive analysis of spinal cord DMGs in a relatively large sample single-institution series. Our findings suggest that histological grade significantly affects the

TABLE 3. Univariate and Multivariate Analysis of Variables Associated With Overall Survival

	Univariate		Multivariate	
Variables	**Hazard ratio (95% CI)**	***P***	**Hazard ratio (95% CI)**	***P***
Age (yr)	1.009 (0.980-1.039)	.562	–	–
Sex (male)	0.586 (0.290-1.183)	.136	–	–
Location (CE, CM, C, T)	0.776 (0.586-1.026)	.075	–	–
Segment length	1.128 (0.926-1.374)	.230	–	–
Histological grade (II/III, IV)	1.754 (1.138-2.701)	**.011**	1.637 (1.057-2.537)	**.027**
Presurgery MMS (1-4)	2.015 (1.171-3.468)	**.011**	1.939 (1.110-3.386)	**.020**
Resection (ER, STR, OB)	1.193 (0.799-1.781)	.389	–	–
Radiotherapy	1.040 (0.414-2.610)	.934	–	–
TMZ chemotherapy	1.024 (0.464-2.255)	.954	–	–

CE, cervical enlargement; CM, conus medullaris; C, C1-3; T, T2-11; ER, extensive resection; STR, subtotal resection; OB, open biopsy; MMS, McCormick Scale; TMZ, temozolomide. $P < .05$ was considered statistically significant. Significant *P*-values are shown in bold.

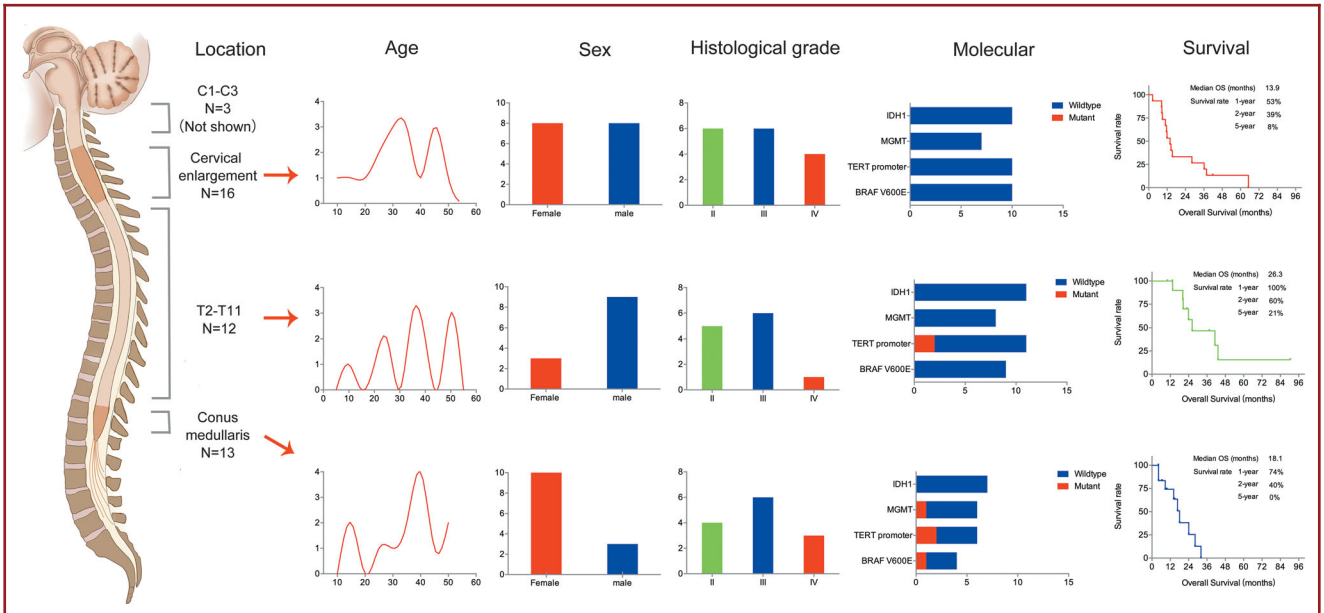

FIGURE 2. *Overview of the clinical characteristics, molecular profiles, and survival corresponding to anatomical locations of the spinal cord for diffuse middle gliomas.*

clinical features and prognosis for the type of DMG located in the spinal cord. The data show that spinal cord DMGs mainly occur in adults. The patients with histological grade IV are younger than those with grade II/III, and a lower histological grade is associated with a longer survival than grade IV. The most frequent anatomic locations are the cervical enlargement and conus medullaris, and tumors found at these locations exhibit distinctive clinical characteristics and molecular features. The histological grade and presurgical MMS score were independent prognostic factors for OS; however, extensive surgical resection, radiotherapy, and TMZ chemotherapy were not associated with improved survival.

In the 2016 WHO Classification, DMGs were defined as grade IV gliomas independent of the histological grade. It is worth noting that this concept is mainly based on pontine and thalamic gliomas, but tumor location tends to influence clinicopathological features and prognosis. In the present series, the median age at diagnosis was 36 yr, and the median OS was almost 2 yr, which is markedly different from those of pontine DMGs, which mostly occurred in young children and median OS was less than 1 yr.[11] In a study of 56 cases (only 6 spinal cord gliomas), histopathological grade had no influence on survival.[2] However, the present study focused on 44 spinal cord DMGs and found that histological grade was an important stratification factor for

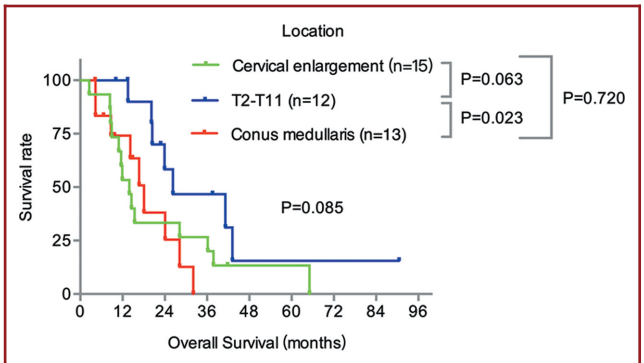

FIGURE 3. *Kaplan-Meier survival curves for anatomical locations in the spinal cord for diffuse middle gliomas.*

survival; patients with a histological grade of IV had poorer survival. The patients with lower histological grade tumors were older than those with grade IV tumors. These findings suggest that the DMGs located in the spinal cord are different from those located in the brainstem.

The current consensus on the treatment of spinal cord DMG has not been clearly determined because of the lack of adequate evidence-based practice. Here, we present a comprehensive analysis of available treatments; the results show that the extent of surgical resection, radiotherapy, and TMZ chemotherapy did not significantly improve survival outcomes. This conclusion is consistent with a recent study by Yi et al,[19] which reported 25 patients with spinal cord astrocytomas (including 20 patients with H3 K27M mutation). Low methylation of MGMT promoter is a key indicator of poor response to TMZ chemotherapy.[22,23] In the present study, only one patient showed MGMT promoter methylation, which probably explains why chemotherapy did not improve the prognosis of spinal cord DMG.

Advances in molecular neuropathology have revolutionized the diagnosis and classification of gliomas.[24] However, the molecular characteristics of spinal cord DMGs remain poorly known.[2,3,25-27] In the present study, the molecular profiles of IDH1 mutation, TERT promoter, BRAF V600E, and MGMT promoter methylation were identified. The results showed that all the tumors presented with wild-type IDH, which is consistent with previous reports.[3,15,28,29] This suggests that the H3 K27M mutation is mutually exclusive to the IDH mutation. TERT promoter mutations appear to be a biomarker for poor survival prognosis in wild-type IDH brain gliomas.[24,30,31] In a study involving 116 patients with midline diffuse gliomas, TERT promoter mutations were associated with poor survival and occurred in 40% of patients with spinal cord DMGs.[27] The present study showed that TERT promoter mutations occurred in only 14% of patients and did not correlate with survival. BRAF V600E mutations are frequent in pleomorphic xanthoastrocytoma, ganglioglioma, and extracerebellar pilocytic astrocytoma and are a significant prognostic factor for the tumor regrowth rate of brainstem gangliogliomas.[32,33] Examples of BRAF V600E and H3 K27M double mutations have rarely been reported. Here, only one patient with a tumor located in the conus was tested for BRAF V600E mutations and histologically presented with anaplastic astrocytoma. The patient received radiation and TMZ chemotherapy after OB and had an OS of only 7 mo.

The most frequent tumor location corresponded to 2 anatomic locations in the spinal cord: the cervical enlargement (C4-T1, 36%) and conus medullaris (T12-L1, 30%). Therefore, we further analyzed the tumors from these 2 anatomic locations compared with those in other locations and found that they presented with distinct clinical characteristics and molecular features. The sex distribution was inconsistent. Conus DMGs were more common in women, and the thoracic DMGs were more common in men, whereas cervical enlargement DMGs were equally common among both sexes. Histological grade IV was relatively rare in the T2-11 segments, accounting for only 8% of tumors, which probably explains their relatively favorable prognosis. Compared to tumors located in the T2-11 segments, tumors in the cervical enlargement and conus medullaris showed a similar unfavorable prognosis. The distribution of molecular profiles depended on tumor location. Conus DMGs possibly have a molecular phenotype involving TERT promoter mutation, BRAF V600E mutation, and MGMT promoter methylation, but none of these were present in DMGs located at the cervical enlargement.

Limitations

The limitations of present study include a retrospective design, and only the basic molecular features of the tumors were analyzed based on the available samples. In addition, because of the rarity of the disease, the sample size was still relatively small. Postoperative adjuvant chemoradiotherapy regimens and cycles vary according to the individual disease status and progression of patients, which may introduce treatment parameters bias. Future studies include next extensive generation sequencing should be performed to investigate the specificity of the disease.

CONCLUSION

Our findings suggest that DMGs originating from the spinal cord differ from those located in the brainstem in terms of their clinicopathological features and prognosis. Histological grade was an important stratification factor for the survival of spinal cord DMGs. Conventional therapies for gliomas, such as extensive surgical resection, radiation, and TMZ chemotherapy regimens, could not significantly improve survival outcomes. Therefore, special diagnosis and management guidance should be made for spinal cord DMGs.

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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

Spinal cord DMG is a rare tumor and, therefore, literature on it is limited; this study contributes significantly to our knowledge on this topic. Two interesting points are raised in this manuscript. First, the prognostic impact of histopathological grade suggests that perhaps this parameter should be taken into consideration for staging. Second, this study brings to the surface our lack of robust evidence to guide treatment decisions. The lack of significant differences in overall survival between treatment groups should not be interpreted as proof of futility of adjuvant therapeutic modalities; rather it should trigger further investigation, perhaps as a multi-institutional study given the rarity of the pathology.

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The authors present a very nice review of 44 patients with spinal cord DMG. This is a large cohort of a relatively uncommon entity. They provide some new insights in that these DMG's of the spinal cord behave

differently than those of the pontine and thalamic regions. Unlike their intracranial counterparts for the spinal cord DMG the World Health Organization (WHO) grade seems to have a greater prognostic value. The authors further characterize some of the features of these tumors including the predominance in the cervical enlargement and in the conus medullaris. The authors report that the spinal cord DMGs occurred mainly in adults. It is not clear if the authors' institution provides care for a significant pediatric population or could this adult predilection be an institutional bias? This is an excellent study that provides additional understanding of the behavior and prognosis for these relatively rare tumors.

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