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CLINICAL ARTICLE

Clinicoradiological characteristics of primary spinal cord H3 K27M-mutant diffuse midline glioma

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OBJECTIVE Primary spinal cord H3 K27M-mutant diffuse midline glioma (DMG) is a rare and devastating pathological entity. However, little attention has been paid to this disease. As a result, its clinicoradiological characteristics have yet to be described. The aim of this study was to describe the clinicoradiological characteristics of primary intramedullary H3 K27M-mutant DMG and to compare this tumor with the H3 K27 wild-type to explore potential features that could differentiate the two.

METHODS A total of 59 patients with pathologically confirmed intramedullary astrocytoma were included in this study. The cohort was divided into an H3 K27M-mutant group and H3 K27 wild-type group based on the status of H3 K27M according to an immunohistochemistry method. Demographic data, MRI features, and molecular information were collected. Multivariate logistic regression was conducted to investigate variables that might have a role in differentiating an H3 K27M DMG from an H3 K27 wild-type tumor.

RESULTS Only symptom duration showed an independent association with the H3 K27M mutation (OR 0.82, 95% CI 0.68–0.94, p = 0.016). Patients with spinal cord H3 K27M-mutant DMG had a shorter symptom duration than patients with H3 K27 wild-type glioma. No significant difference was found in terms of MRI features between the H3 K27M-mutant and H3 K27 wild-type groups. Additionally, H3 K27M-mutant DMG frequently demonstrated overexpression of p53. Survival outcome did not show a statistical difference between the H3 K27-mutant subgroup and H3 K27 wild-type subgroup in histologically high-grade astrocytoma.

CONCLUSIONS Symptom duration was associated with an H3 K27M mutation in intramedullary astrocytoma. MRI features were heterogeneous, and no imaging feature was able to predict the H3 K27M mutation. The H3 K27M mutation did not impact survival outcome in spinal histologically high-grade astrocytoma.

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KEYWORDS spinal cord; diffuse midline glioma; H3 K27M; radiology; oncology

Primary spinal cord glioma is a rare disease, accounting for 2%–4% of all primary central nervous system (CNS) tumors, and intramedullary ependymoma and astrocytoma compose approximately 60%–70% and 30%–40% of all primary spinal cord glioma, respectively.[1,2] The H3 K27M-mutant diffuse midline glioma (DMG), a subtype of astrocytoma characterized by an H3 K27M mutation in either the *H3F3A* or *HIST1H3B* gene, was considered a novel entity and was classified as a grade IV tumor regardless of its histological grade in the updated fourth edition of the World Health Organization (WHO) 2016 classification of CNS tumors, which integrates molecular features into a traditional histopathological diagnosis modality.[3] Nevertheless, given the paucity of primary spinal cord astrocytomas, the characteristics of primary spinal cord H3 K27M-mutant DMG have been seldomly reported. In this study, we evaluated the clinicoradiological characteristics of primary spinal cord H3 K27M-mutant DMG and compared this tumor with the H3 K27 wild-type tumor.

Methods

Study Population

Demographic and radiological data on all patients

ABBREVIATIONS CNS = central nervous system; DMG = diffuse midline glioma; EOR = extent of resection; GBM = glioblastoma; GTR = gross-total resection; MMS = modified McCormick scale; PR = partial resection; TMZ = temozolomide; WHO = World Health Organization.

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with a pathologically diagnosed spinal cord astrocytoma at our institution from 2016 to 2020 were retrospectively reviewed. Patients with a diagnosed metastatic tumor were excluded. Preoperative neurological function was evaluated using the modified McCormick scale (MMS).[4] Moreover, the status of H3 K27M, ATRX, p53, *IDH1* R132H, and Ki-67 was evaluated using immunohistochemistry. A cutoff of 20% was used to dichotomize Ki-67 into a Ki-67 < 20% group and ≥ 20% group based on the previous literature.[5] Based on a final integrated diagnosis, this cohort was divided into an H3 K27M-mutant DMG group and H3 K27 wild-type group. Additionally, the initial neuropathological diagnosis and grade based on the 2007 WHO classification of CNS tumors were also evaluated. Preoperative contrast-enhanced MRI was reviewed by two independent neuroradiologists, and the following features were recorded: tumor site, involved segments, tumoral enhancement, pial enhancement, margin, edema, hemorrhage, cyst, necrosis, and syrinx. Tumoral enhancement was rated as none, partial, or diffuse; tumor margin was classified as an ill-defined margin or a well-defined margin based on the margin pattern on a T2-weighted image; and the presence of pial enhancement, edema, intratumoral hemorrhage, cyst, necrosis, and syrinx was also noted. Extent of resection (EOR) was categorized as biopsy (< 50%), partial resection (PR; 50%–90%), and gross-total resection (GTR; ≥ 90%) and was determined with postoperative MRI. The chemotherapeutic agent used in our cohort was temozolomide (TMZ). Agreement on imaging findings between the two neuroradiologists was reached by consensus. Symptom duration was defined as the time from reported onset to radiological diagnosis. Survival time was defined as the time span from the date of initial symptom onset to death or the time of the last follow-up. This study was approved by Xuanwu Hospital ethics board, and written informed consent was obtained from all the patients at the time of treatment.

Statistical Analysis

Continuous variables were presented as the mean ± standard deviation or median and interquartile range, and categorical variables were presented as the frequency (percentage). A two-tailed t-test or nonparametric test was used for continuous variables and the chi-square test or Fisher's test for categorical variables to compare differences in the appropriate situation. Kaplan-Meier curves were constructed for survival and were compared using the log-rank test. Multivariate logistic regression was conducted to investigate potential variables that were independently associated with H3 K27M DMG, and with the aim of differentiating H3 K27M DMG from the H3 K27 wild-type tumor, variables with p values < 0.25 or previously established clinical importance were included in the model.[6] More specifically, age, symptom duration, preoperative MMS grade, tumoral enhancement, margin, edema, necrosis, and syrinx were included in the final multivariate logistic model. A p value < 0.05 was defined as statistically significant. All statistical analysis was performed using R language software (version 3.6.1, R Foundation for Statistical Computing).

Results

Study Cohort Characteristics and Outcomes

Demographic, imaging, and molecular characteristics are listed in Table 1. A total of 59 patients with neuropathologically confirmed spinal cord astrocytoma were included, 28 of whom (47.5%) had a diagnosis of H3 K27M-mutant DMG and 31 of whom had a diagnosis of H3 K27 wild-type astrocytoma, based on integrated neuropathology. Overall, the mean age at diagnosis was 29.5 ± 15.6 years, and 62.7% of the entire cohort was male. The main tumor burden presented in the cervical spine in 23.7% of cases, thoracic spine in 42.4%, thoracolumbar spine in 18.6%, cervicothoracic spine in 11.9%, and lumbar spine in 1.7%, and 1 patient with DMG presented with holocord involvement. The median symptom duration was 3.0 months (IQR 2.0–11.0). The median tumor span was 3.0 segments (IQR 2.0–5.0). Histological classification and grade according to the 2007 WHO classification of CNS tumor revealed that 45.8% of cases were diffuse astrocytoma grade II, followed by glioblastoma (GBM) grade IV (23.7%), anaplastic astrocytoma grade III (23.7%), and pilocytic astrocytoma grade I (6.8%); histologically low-grade tumors accounted for 52.5% of all cases. The histological spectrum presented a significant difference between the H3 K27M-mutant and H3 K27 wild-type groups (p = 0.012; Fig. 1). On contrast-enhanced T1-weighted MR images, 24 patients (40.7%) showed partial enhancement, 28 (47.5%) demonstrated diffuse enhancement, and the remaining 7 (11.9%) showed no enhancement. Fifty-four patients demonstrated pial enhancement. An ill-defined margin was observed in 48 cases. Edema was identified in 37 patients, whereas hemorrhage and cyst occurred in only 9 and 5 patients, respectively. Seventeen and 22 cases manifested necrosis and a syrinx on MRI, respectively. In terms of molecular features, only 2 cases presented with an *IDH1* R123H mutation. p53 overexpression was observed in 30 cases, whereas ATRX loss occurred in 17 cases. Twenty-seven cases presented with Ki-67 ≥ 20%. As regards treatment modality, the majority of patients underwent PR (74.6%), and biopsy and GTR were performed in 11 (18.6%) and 4 (6.8%) patients, respectively. Twenty-three and 23 patients received postoperative radiotherapy and chemotherapy, respectively.

Thirty-one patients had died by the last follow-up, with a median survival time of 29 months in the entire cohort (Supplementary Fig. 1). Patients with WHO grade III/IV glioma had worse survival outcomes than those with WHO grade II glioma (p < 0.05; Fig. 2). With respect to the role of EOR in primary intramedullary astrocytoma, subgroup analysis stratified by tumor grade revealed that EOR did not significantly impact survival outcome in low-grade and high-grade glioma (Fig. 3).

Comparison of H3 K27M-Mutant and H3 K27 Wild-Type Astrocytomas

In terms of demographic, MRI, and molecular features, only symptom duration, syrinx, p53 expression, and Ki-67 ≥ 20% showed a significant difference between H3 K27M-mutant and H3 K27 wild-type astrocytoma. Patients with H3 K27M-mutant DMG exhibited a shorter symptom duration than patients with H3 K27 wild-type astrocytoma

TABLE 1. Comparison of clinicoradiological features between primary spinal cord H3 K27M-mutant and H3 K27 wild-type astrocytoma

Variable	Total	H3 K27M Mutant	H3 K27 Wild-Type	p Value
No. of patients	59	28	31	
Mean age at diagnosis in yrs (SD)	29.5 (15.6)	28.7 (14.0)	30.3 (17.1)	0.702
Sex, no. (%)				0.437
Male	37 (62.7)	19 (67.9)	18 (58.1)	
Female	22 (37.3)	9 (32.1)	13 (41.9)	
Median symptom duration in days (IQR)	3.0 (2.0–11.0)	2.0 (1.0–5.3)	6.0 (2.0–12.0)	**0.006**
Site				0.924
Cervical	14 (23.7)	7 (25.0)	7 (22.6)	
Cervicothoracic	7 (11.9)	4 (14.3)	3 (9.7)	
Thoracic	25 (42.4)	11 (39.3)	14 (45.2)	
Thoracolumbar	11 (18.6)	5 (17.9)	6 (19.4)	
Lumbar	1 (1.7)	0 (0.0)	1 (3.2)	
Holocord	1 (1.7)	1 (3.6)	0 (0.0)	
Median no. involved segments (IQR)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.631
Preop MMS grade, no. (%)				0.107
I	7 (11.9)	1 (3.6)	6 (19.4)	
II	24 (40.7)	9 (32.1)	15 (48.4)	
III	12 (20.3)	8 (28.6)	4 (12.9)	
IV	12 (20.3)	8 (28.6)	4 (12.9)	
V	4 (6.8)	2 (7.1)	2 (6.5)	
Histological type, no. (%)*				**0.012**
PA, grade I	4 (6.8)	0 (0.0)	4 (12.9)	
DA, grade II	27 (45.8)	9 (32.1)	18 (58.1)	
AA, grade III	14 (23.7)	10 (35.7)	4 (12.9)	
GBM, grade IV	14 (23.7)	9 (32.1)	5 (16.1)	
Tumoral enhancement, no. (%)				>0.99
None	7 (11.9)	3 (10.7)	4 (12.9)	
Partial	24 (40.7)	12 (42.9)	12 (38.7)	
Diffuse	28 (47.5)	13 (46.4)	15 (48.4)	
Pial enhancement, no. (%)	54 (91.5)	24 (85.7)	30 (96.8)	0.291
Ill-defined margin, no. (%)	48 (81.4)	25 (89.3)	23 (74.2)	0.137
Edema, no. (%)	37 (62.7)	16 (57.1)	21 (67.7)	0.401
Hemorrhage, no. (%)	9 (15.3)	4 (14.3)	5 (16.1)	>0.99
Cyst, no. (%)	5 (8.5)	4 (14.3)	1 (3.2)	0.291
Necrosis, no. (%)	17 (28.8)	10 (35.7)	7 (22.6)	0.266
Syrinx, no. (%)	22 (37.3)	6 (21.4)	16 (51.6)	**0.017**
Molecular alteration, no. (%)				
IDH1 R132H mutation	2 (3.4)	0 (0.0)	2 (6.5)	0.493
p53 overexpression	30 (50.8)	20 (71.4)	10 (32.3)	**0.003**
ATRX loss	17 (28.8)	8 (28.6)	9 (29.0)	0.969
Ki-67 ≥20%	27 (45.8)	18 (64.3)	9 (29.0)	**0.007**
EOR, no. (%)				**0.036**
Biopsy	11 (18.6)	8 (28.6)	3 (9.7)	
PR	44 (74.6)	20 (71.4)	24 (77.4)	
GTR	4 (6.8)	0 (0.0)	4 (12.9)	
RT, no (%)	23 (39.0)	17 (60.7)	6 (19.4)	**0.001**
Chemo, no. (%)	23 (39.0)	16 (57.1)	7 (22.6)	**0.007**

AA = anaplastic astrocytoma; Chemo = chemotherapy; DA = diffuse astrocytoma; PA = pilocytic astrocytoma; RT = radiotherapy.
Boldface type indicates statistical significance.
* 2007 WHO grade.

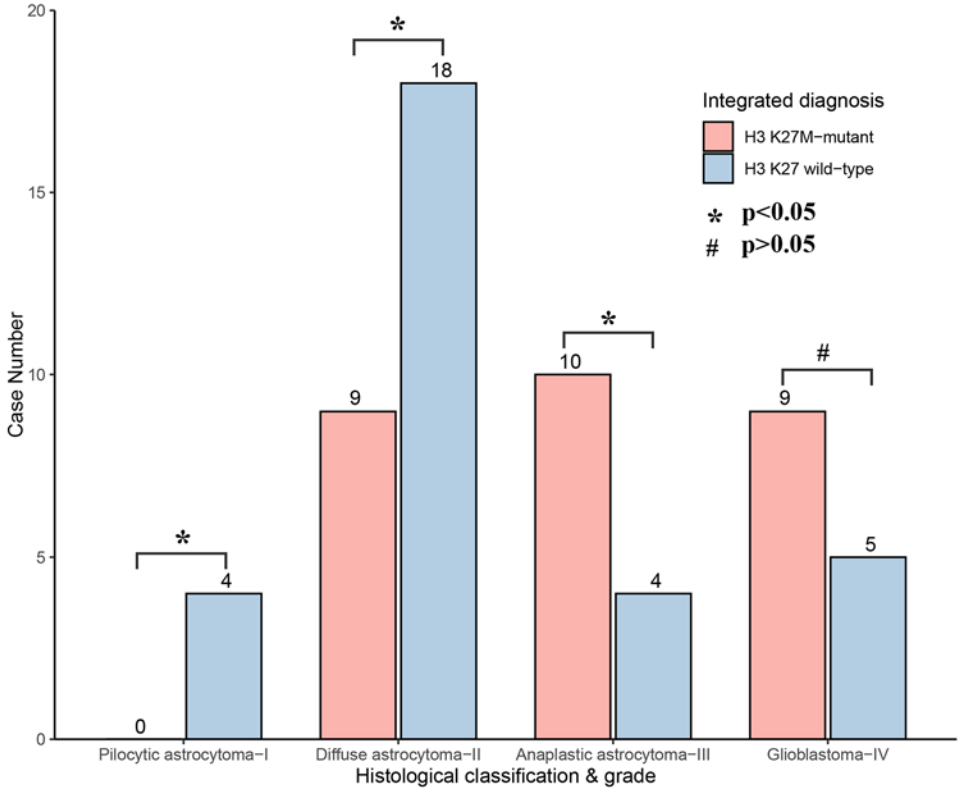

FIG. 1. Histological classification and grading of 59 intramedullary astrocytomas according to the 2007 WHO classification criteria for CNS tumors. Figure is available in color online only.

(2.0 vs 6.0 months, p = 0.006). Additionally, both p53 overexpression and Ki-67 ≥ 20% were more frequently found in patients with H3 K27M-mutant DMG (20 vs 10, p = 0.003; 18 vs 9, p = 0.007, respectively). In contrast, patients with H3 K27 wild-type tumor more frequently exhibited a syrinx on T2-weighted imaging than the patients with H3 K27M-mutant DMG (16 vs 6, p = 0.017).

Generally, overall survival at 1, 3, and 5 years was 56.5%, 13.8%, and 0% in the H3 K27M-mutant DMG group and 85.5%, 72.5%, and 66.5% in the H3 K27 wild-type group, respectively (Fig. 4A). Patients with H3 K27M-mutant DMG had worse overall survival than the patients with the H3 K27 wild-type tumor (log-rank test, p = 0.013). To address the confounding effect of histological grade on the results of a survival comparison between the H3 K27M-mutant group and H3 K27 wild-type group, we performed subgroup analysis stratified by histological grade, which revealed that patients with histological grade II tumor with the H3 K27M mutation had poorer survival than those with histological grade II tumor without the H3 K27M mutation (p = 0.018; Fig. 4B), whereas no significant difference was observed in histological grade III astrocytoma with and without the H3 K27M mutation (p = 0.9) or in histological grade IV tumor with and without the H3 K27M mutation (p = 0.9; Fig. 4C–E).

Multivariate logistic regression analysis revealed that only symptom duration was independently associated with the H3 K27M mutation (OR 0.82, 95% CI 0.68–0.94, p = 0.016).

A comparison of clinicoradiological characteristics between the H3 K37M-mutant subgroup and H3 K27 wild-type subgroup stratified by histological grade was performed. Preoperative MMS grade, syrinx, Ki-67 index, and radiotherapy demonstrated a significant difference between the H3 K37M-mutant subgroup and H3 K27 wild-type subgroup in histological grade II astrocytoma, whereas no variables were statistically significantly different between the H3 K37M-mutant and wild-type subgroups in histological grade III/IV astrocytoma (Tables 2 and 3). Illustrative cases are presented in Fig. 5.

Discussion

Primary spinal cord H3 K27M-mutant DMG is a rare and devastating disease. The clinicoradiological characteristics of intracranial H3 K27M-mutant DMG have been reported in previous studies,[7–9] but primary spinal cord H3 K27M-mutant DMG has been rarely investigated. The present study reveals the clinicoradiological characteristics of primary spinal cord H3 K27M-mutant DMG in the largest sample size to date. In our cohort, the H3 K27M mutation occurred in 47.5% of cases. Of those cases, the majority were classified as histologically high-grade (grade III–IV) tumors based on the 2007 WHO CNS tumor classification. Similarly, Zhang et al.[10] found that 38% of cases harbored the H3 K27M mutation in a cohort of 108 intramedullary astrocytomas, whereas Lebrun et al.[11] reported that 11 (18.0%) of 61 patients with intramedullary

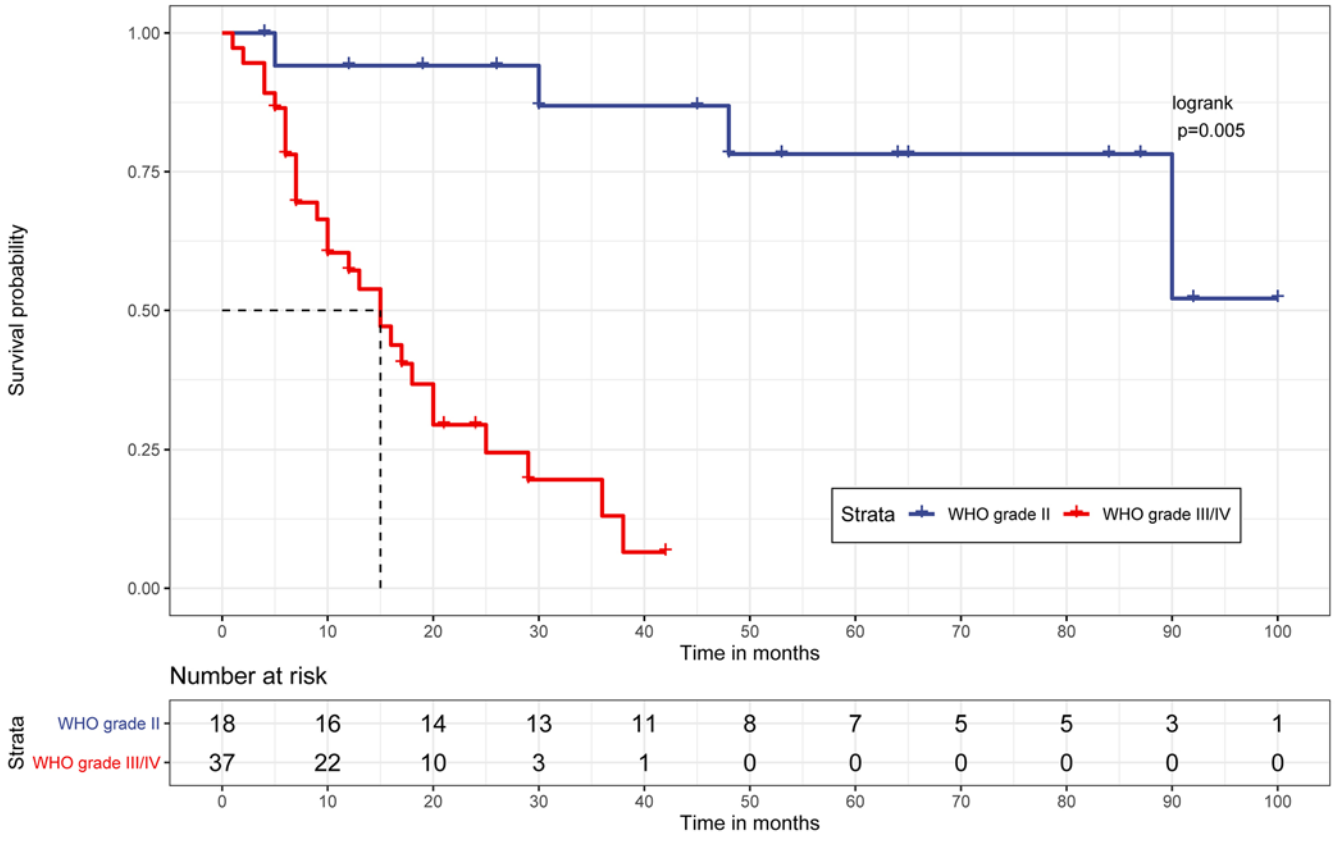

FIG. 2. Comparison of survival outcomes between WHO grade II and III/IV gliomas. Figure is available in color online only.

astrocytoma had the H3 K27M mutation. The study by Gessi et al.[12] revealed that spinal high-grade astrocytoma frequently harbored the H3 K27M mutation. Thus, considering the high incidence of high-grade tumor in primary spinal cord astrocytoma,[13,14] it is likely reasonable to suppose that the incidence of an H3 K27M mutation in primary intramedullary astrocytoma is not low. Additionally, in our cohort, the H3 K27M mutation did not show an increasing trend as the histological grade of the glioma increased. Similarly, the study by Chai et al.[15] demonstrated that 35 cases harbored the H3 K27M mutation in a cohort of 83 primary intramedullary astrocytomas. And in those cases, 40% of the H3 K27M mutations occurred in histological grade II and III tumors, respectively, whereas the remaining 20% of mutations were identified in histological grade IV tumors. Wang et al.[16] found that 61 of 120 patients with DMG harbored an H3 K27M mutation and that 36.1%, 39.3%, and 24.6% of the mutations were identified in histological grade II, III, and IV tumors, respectively. No propensity for histological phenotype potentially validates the notion that the H3 K27M mutation is a trunk event rather than a passenger mutation in primary spinal cord astrocytoma. Interestingly, our study demonstrated that the H3 K27M mutation did not significantly worsen survival outcome in histologically high-grade astrocytoma. Similarly, the study by Yi et al.[17] revealed that the H3.3 K27M mutation was not a major poor prognostic factor for spinal GBM in a cohort of 25 cases. Of note, the sample size of high-grade tumors in both our study and that of Yi and colleagues' was too small; therefore, the effect of the H3 K27M mutation on survival outcome in spinal high-grade glioma should be confirmed in a study with a larger sample size.

In the present study, patients with an H3 K27M-mutant tumor manifested a shorter symptom duration than the patients with an H3 K27 wild-type tumor, and only symptom duration showed a significant difference in the multivariate logistic model. This finding was consistent with our daily clinical practice and may play a potential role in the differentiation of H3 K27M-mutant and H3 K27 wild-type astrocytoma. Moreover, it could serve as a clue to identify candidates for further CSF-based mutation analysis of H3 K27M to define the diagnosis.[18,19] As for MRI features, a syrinx more frequently occurred in the H3 K27 wild-type cohort than in the H3 K27M-mutant cohort, and this difference was especially apparent in histological grade II astrocytomas. The syrinx usually presented in a chronic and relatively benign entity, such as ependymoma, Chiari malformation, etc.[20] Hence, intramedullary astrocytoma with a syrinx may indicate a relatively benign pathological type. However, this difference did not show statistical significance in the multivariate logistic model. This finding likely could be ascribed to the limited sample size, which could not provide sufficient statistical power to identify the difference. H3 K27M-mutant glioma presents varying histological spectrums.[16,21] Subgroup analy-

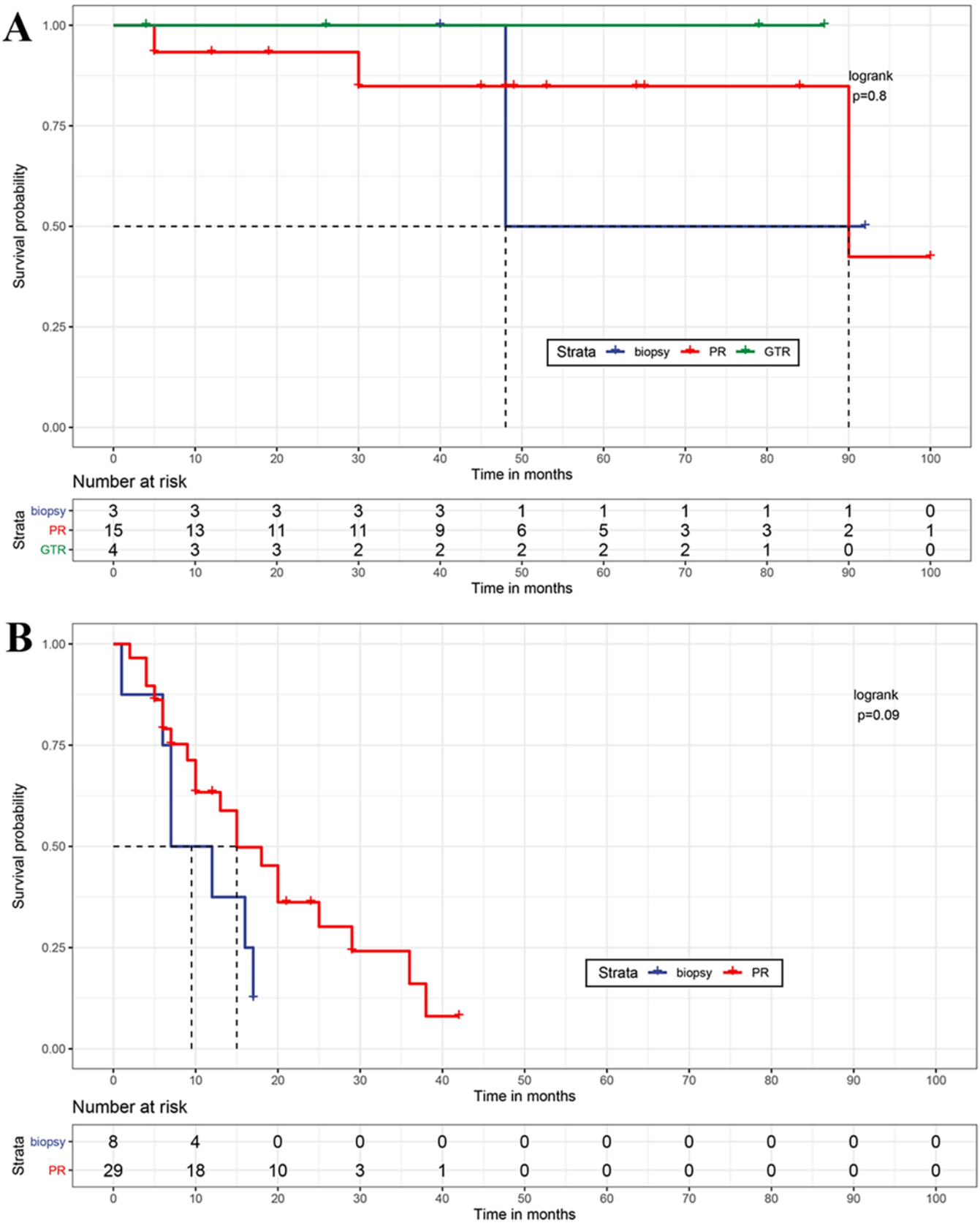

FIG. 3. The effect of EOR on survival outcome for patients with low-grade (**A**) and high-grade (**B**) glioma, respectively. Figure is available in color online only.

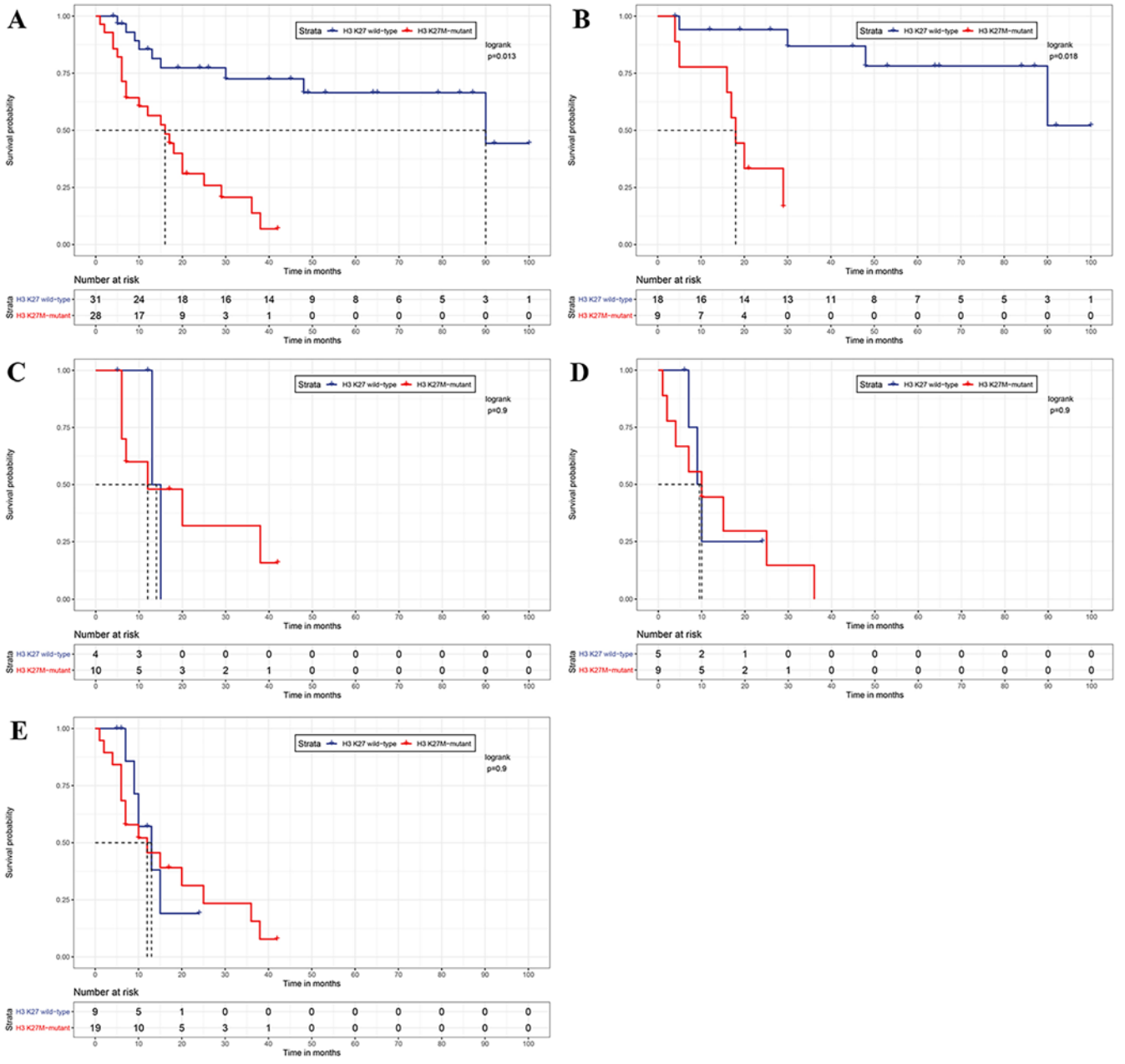

FIG. 4. Kaplan-Meier survival curves stratified by status of H3 K27M mutation overall (**A**); for histological grade II (**B**); histological grade III (**C**); and histological grade IV (**D**) with and without the H3 K27M mutation; and for histologically high-grade astrocytoma with and without the H3 K27M mutation (**E**). Figure is available in color online only.

sis of histological grade II or III/IV with and without the H3 K27M mutation did not reveal a difference in terms of MRI, which likely suggests that the H3 K27M mutation did not induce an extra radiological phenotype. Similarly, Aboian et al.[7,22] found that H3 K27M-mutant glioma did not present with MRI features distinct from those of wild-type tumors.

In our cohort, only 2 cases harbored the *IDH1* R132H mutation, which is common in adult brain glioma. Similarly, Lebrun et al.[11] found 1 case that harbored the *IDH1* R132S mutation and 1 that harbored *IDH2* R172M in a cohort of 61 intramedullary astrocytomas. Several case studies have reported the *IDH1* mutation in addition to the hotspot R132H mutation in spinal cord glioma.[23,24] Given the very small number of *IDH1*-mutant spinal cord astrocytomas, the association between *IDH* mutation and prognosis needs be investigated in a study with a larger sample size. Besides the H3 K27M mutation, *TP53* and *ATRX* have been reported to be the most frequent mutations in spinal cord astrocytoma.[11] In the present study, 50.8% and 28.3% of cases presented with p53 overexpression and ATRX loss, respectively. Investigators have validated p53

TABLE 2. Comparison of clinicoradiological features between diffuse astrocytoma grade II with H3 K27M mutation and H3 K27 wild-type tumor*

Variable	Total	H3 K27M Mutation	H3 K27 Wild-Type	p Value
No. of patients	27	9	18	
Mean age at diagnosis in yrs (SD)	31.3 (16.3)	33.8 (15.1)	30.1 (17.1)	0.586
Sex, no. (%)				>0.99
Male	18 (66.7)	6 (66.7)	12 (66.7)	
Female	9 (33.3)	3 (33.3)	6 (33.3)	
Median symptom duration in days (IQR)	7.0 (3.0–12.0)	4.0 (2.0–8.0)	12.0 (6–16.5)	0.651
Site				>0.99
Cervical	5 (18.5)	1 (11.1)	4 (22.2)	
Cervicothoracic	2 (7.4)	1 (11.1)	1 (5.6)	
Thoracic	14 (51.9)	5 (55.6)	9 (50.0)	
Thoracolumbar	5 (18.5)	2 (22.2)	3 (16.7)	
Lumbar	1 (3.7)	0 (0.0)	1 (5.6)	
Median no. involved segments (IQR)	3.0 (2.0–3.6)	4.0 (2.0–5.0)	3.0 (2.3–4.0)	0.753
Preop MMS grade, no. (%)				**0.042**
I	5 (18.5)	0 (0.0)	5 (27.8)	
II	13 (48.1)	3 (33.3)	10 (55.6)	
III	3 (11.1)	2 (22.2)	1 (5.6)	
IV	4 (14.8)	2 (22.2)	2 (11.1)	
V	2 (7.4)	2 (22.2)	0 (0.0)	
Tumoral enhancement, no. (%)				0.857
No	4 (14.8)	2 (22.2)	2 (11.1)	
Partial	14 (51.9)	4 (44.4)	10 (55.6)	
Diffuse	9 (33.3)	3 (33.3)	6 (33.3)	
Pial enhancement, no. (%)	25 (92.6)	8 (88.8)	17 (94.4)	0.485
Ill-defined margin, no. (%)	23 (85.2)	9 (100.0)	14 (77.8)	0.268
Edema, no. (%)	17 (63.0)	5 (55.6)	16 (88.9)	0.683
Hemorrhage, no. (%)	3 (11.1)	1 (11.1)	2 (11.1)	>0.99
Cyst, no. (%)	3 (11.1)	2 (22.2)	1 (5.6)	0.250
Necrosis, no. (%)	5 (18.5)	3 (33.3)	2 (11.1)	0.295
Syrinx, no. (%)	9 (33.3)	0 (0.0)	9 (50.0)	**0.012**
Molecular alteration, no. (%)				
IDH1 R132H mutation	2 (7.4)	0 (0.0)	2 (11.1)	0.539
p53 overexpression	9 (33.3)	4 (44.4)	5 (27.8)	0.423
ATRX loss	6 (22.2)	1 (11.1)	5 (27.8)	0.628
Ki-67 ≥20%	5 (18.5)	4 (44.4)	1 (5.6)	**0.030**
EOR, no. (%)				0.545
Biopsy	4 (14.8)	2 (22.2)	2 (11.1)	
PR	20 (74.1)	7 (77.8)	13 (72.2)	
GTR	3 (11.1)	0 (0.0)	3 (16.7)	
RT, no. (%)	5 (18.5)	4 (44.4)	1 (5.6)	**0.030**
Chemo, no. (%)	6 (22.2)	4 (44.4)	2 (11.1)	0.136

Boldface type indicates statistical significance.
* 2007 WHO grade II.

expression and ATRX loss as surrogates for *TP53* and *ATRX* mutation analysis.[25,26] *TP53* is a tumor suppressor gene and encodes the p53 protein, a transcription factor regulating cell cycle to prevent proliferation of genetically damaged cells with oncogenic properties; *TP53* mutation frequently results in an increase of p53 expression.[27] ATRX mediates chromatin modification through interaction with H3.3, and the *ATRX* mutation is associated with the presence of alternative lengthening of telomeres, which is a mechanism of maintaining telomere length by cancer

TABLE 3. Comparison of clinicoradiological features between grade III/IV astrocytoma with H3 K27M mutation and H3 K27 wild-type tumor*

Variable	Total	H3 K27M Mutant	H3 K27 Wild-Type	p Value
No. of patients	28	19	9	
Mean age at diagnosis in yrs (SD)	28.3 (14.9)	26.3 (13.2)	32.6 (18.2)	0.372
Sex, no. (%)				0.678
Male	18 (64.3)	13 (68.4)	5 (55.6)	
Female	10 (35.7)	6 (31.6)	4 (44.4)	
Median symptom duration in days (IQR)	7.0 (3.0–12.0)	4.0 (2.0–8.0)	12.0 (6–16.5)	0.651
Site				0.898
Cervical	8 (28.6)	6 (31.6)	2 (22.2)	
Cervicothoracic	4 (14.3)	3 (15.8)	1 (11.1)	
Thoracic	9 (32.1)	6 (31.6)	3 (33.3)	
Thoracolumbar	6 (21.4)	3 (15.8)	3 (33.3)	
Lumbar	1 (3.6)	1 (5.3)	0 (0.0)	
Median no. involved segments (IQR)	2.0 (2.0–4.3)	2.0 (2.0–4.0)	2.0 (2.0–4.0)	0.817
Preop MMS grade, no. (%)				0.085
I	1 (3.6)	1 (5.3)	0 (0.0)	
II	10 (35.7)	6 (31.6)	4 (44.4)	
III	9 (32.1)	6 (31.6)	3 (33.3)	
IV	6 (21.4)	6 (31.6)	0 (0.0)	
V	2 (7.1)	0 (0.0)	2 (22.2)	
Tumoral enhancement, no. (%)				0.269
No	2 (7.1)	1 (5.3)	1 (11.1)	
Partial	9 (32.1)	8 (42.1)	1 (11.1)	
Diffuse	17 (60.7)	10 (52.6)	7 (77.8)	
Pial enhancement, no. (%)	25 (89.3)	16 (84.2)	9 (100.0)	0.530
Ill-defined margin, no. (%)	23 (82.1)	16 (84.2)	7 (77.8)	>0.99
Edema, no. (%)	17 (60.7)	11 (57.9)	6 (66.7)	>0.99
Hemorrhage, no. (%)	4 (14.3)	3 (15.8)	1 (11.1)	>0.99
Cyst, no. (%)	2 (7.1)	2 (10.5)	0 (0.0)	>0.99
Necrosis, no. (%)	12 (42.9)	7 (36.8)	5 (55.6)	0.432
Syrinx, no. (%)	10 (35.7)	7 (36.8)	3 (33.3)	>0.99
Molecular alteration, no. (%)				
IDH1 R132H mutation	0 (0.0)	0 (0.0)	0 (0.0)	
p53 overexpression	20 (71.4)	16 (84.2)	4 (44.4)	0.068
ATRX loss	17 (60.7)	12 (63.2)	5 (55.6)	>0.99
Ki-67 ≥20%	22 (78.6)	14 (73.7)	8 (88.9)	0.630
EOR, no. (%)				0.136
Biopsy	6 (21.4)	6 (31.6)	0 (0.0)	
PR	22 (78.6)	13 (68.4)	9 (100.0)	
GTR	0 (0.0)	0 (0.0)	0 (0.0)	
RT, no. (%)	18 (64.3)	13 (68.4)	5 (55.6)	0.678
Chemo, no. (%)	17 (60.7)	12 (63.2)	5 (55.6)	>0.99

* 2007 WHO grade.

cells.[28] The *ATRX* mutation frequently causes diffuse loss of ATRX immunostaining in diffuse glioma.[29] Both *TP53* and *ATRX* were diagnostic markers for glioma,[3,30] but their prognostic relevance with brain and spinal cord glioma are undetermined. Comprehensive genetic evaluation of intramedullary astrocytoma is essential to molecular classification, prognostic prediction, and the development of new treatment modalities. Unfortunately, given the rarity of primary spinal cord astrocytoma and insufficient specimens available for sequencing analysis, few studies have depicted the genomic landscape of intramedullary astrocytoma in an in-depth, comprehensive manner with a suf-

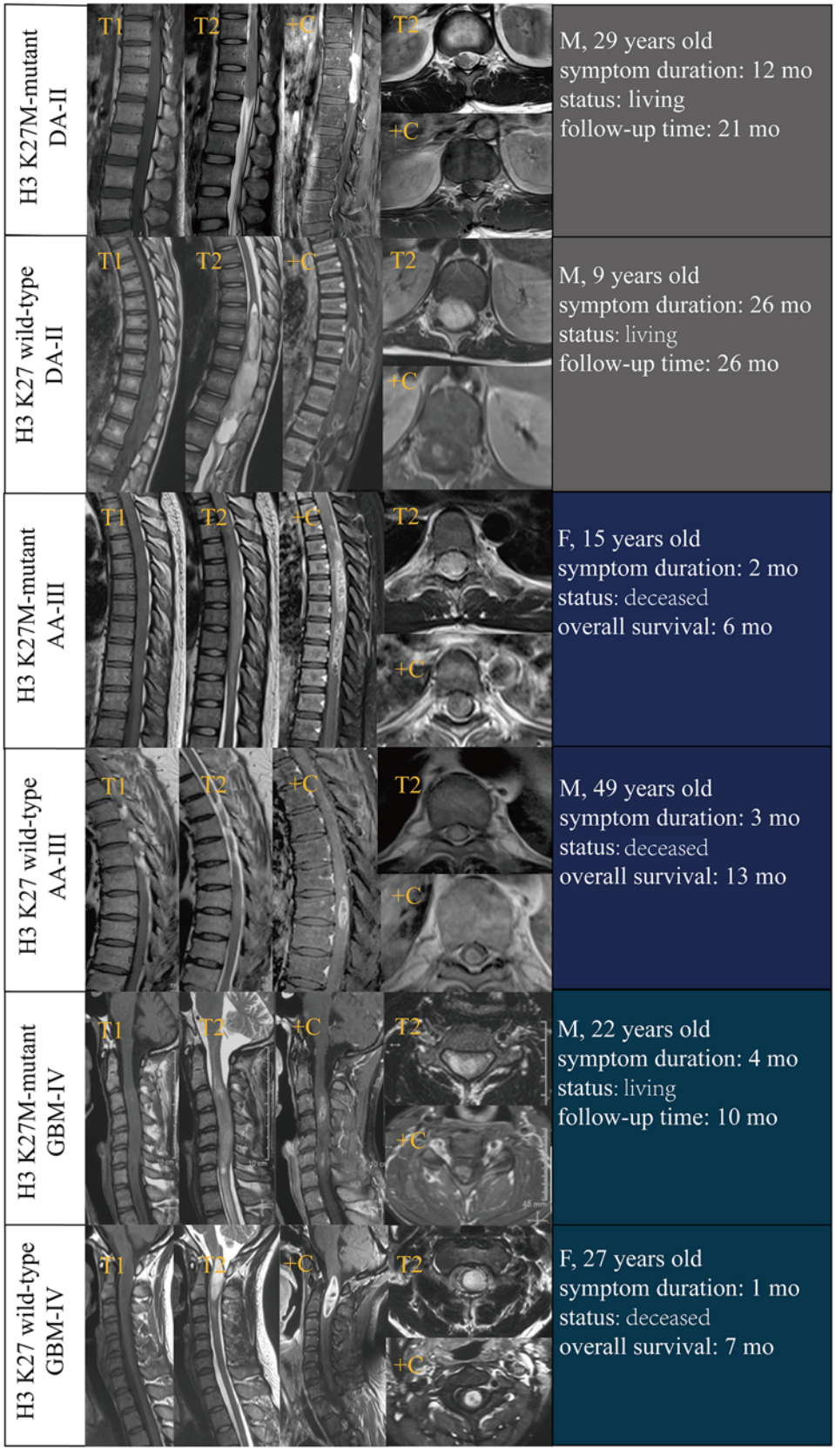

FIG. 5. MRI for illustrative cases of different histological types in the H3 K27M-mutant and H3 K27 wild-type groups. AA = anaplastic astrocytoma; DA = diffuse astrocytoma. Figure is available in color online only.

ficiently sized sample;[12,15,31–35] thus, a large study focusing on molecular analysis conducted by a collaborative multi-institutional group is needed.

Currently, there are no guidelines that standardize the treatment of primary spinal cord astrocytoma. And it seems unreasonable to arbitrarily repurpose the treatment for brain glioma to treat patients with intramedullary glioma given the distinct molecular features of these two entities.[36] GTR without major neurological functional impairment is a great challenge for intramedullary astrocytoma because no defined margin exists between tumor and normal tissue. As for adjuvant treatment, radiotherapy was routinely offered to patients with high-grade intramedullary glioma at our institution, and our previous work demonstrated that radiotherapy could provide a short-term survival advantage for patients with high-grade intramedullary glioma;[37] however, the role of chemotherapy in intramedullary astrocytoma, such as TMZ, bevacizumab, etc., is unknown.[38,39] The study by Banan et al.[40] revealed that MGMT promoter methylation, which is predictive of a response to TMZ for GBM, was a rare event in patients with DMG. Given the high frequency of the H3 K27M mutation in intramedullary astrocytoma, high-grade intramedullary glioma is likely not as sensitive to TMZ as its intracranial counterpart.

Several study limitations should be noted. First, the sample size of each group was too small to perform a prediction model using machine learning methods to differentiate H3 K27M-mutant tumor from H3 K27 wild-type tumor. In particular, after the mutant and wild-type groups were stratified by variables, the smaller sample sizes in each subgroup may have contributed to the too-low power to identify significant differences between subgroups. For example, EOR was not identified as protective in low-grade glioma, and we supposed that this finding resulted from the small sample size in each subgroup. Second, H3 K27M status was assessed by immunohistochemistry in our study; however, this method is not competent enough to detect non-hotspot mutations, such as H3 G34W/V. Additionally, other molecular markers, such as *MGMT* methylation, *BRAF* V6600E, *TERT* promoter, *EGFR*, etc., were not assessed in our cohort. Finally, other imaging modalities evaluating intramedullary astrocytoma, especially PET-CT or PET-MRI, were not performed in this study.[41,42]

Conclusions

Primary spinal cord astrocytoma with an H3 K27M mutation was characterized by a shorter symptom duration than the H3 K27 wild-type astrocytoma. No MRI-based radiological features that could differentiate the H3 K27M-mutant glioma from the H3 K27 wild-type glioma were found. The H3 K27M mutation did not impact survival outcome in spinal histologically high-grade astrocytoma.

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Disclosures

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

Author Contributions

Conception and design: Jian. Acquisition of data: Cheng, L Wang, Yao, Ma, Duan, Guan, Zhang, K Wang, Liu, X Wang, Z Wang, Wu, Chen. Analysis and interpretation of data: Cheng. Drafting the article: Cheng. Critically revising the article: Jian. Approved the final version of the manuscript on behalf of all authors: Jian. Administrative/technical/material support: Jian. Study supervision: Jian, X Wang, Z Wang, Wu, Chen.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Figure 1. https://thejns.org/doi/suppl/10.3171/2021.4.SPINE2140.

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