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CLINICAL ARTICLE

Central nervous system dissemination in spinal cord astrocytomas: association with H3 K27M mutation

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OBJECTIVE Patients with spinal cord astrocytomas (SCAs) are at high risk for CNS dissemination, yet comprehensive data on characteristics of dissemination are lacking. This study depicts the exact incidence and patterns of dissemination by analyzing data from a large-scale dataset of SCA.

METHODS The authors included 94 patients with SCA based on the 2021 WHO classification from 2011 to 2022, retrospectively collected their clinical and pathological characteristics, and analyzed factors influencing SCA dissemination.

RESULTS CNS dissemination, encompassing leptomeningeal spreading and/or subarachnoid seeding, was evaluated in 94 patients with and without H3 K27 alterations, with an overall dissemination rate reaching 85.0% at 5-year follow-up. Patients with altered H3 K27 had a significantly higher 5-year CNS dissemination rate than patients with H3 K27 wildtype status (95.2% vs 68.0%, p = 0.002). The median dissemination-free survival in H3 K27–altered patients was 14.37 (95% CI 2.84–25.89) months, significantly shorter than those with H3 K27 wildtype (statistics not calculated; p < 0.001). Based on univariate Cox regression analysis, H3 K27M alteration, higher histopathological grade, Ki-67 index (≥ 10%), and tumor length (≥ 4 segments) were identified as potential factors associated with CNS dissemination in SCAs. Multivariate Cox regression analysis revealed that H3 K27M alteration appeared to be a risk factor for this phenomenon (HR 2.089, 95% CI 0.940–4.642, p = 0.070). Following dissemination, H3 K27–altered patients had a median postdissemination survival of 8.83 (95% CI 7.13–10.54) months, which was significantly shorter than the 13.40 (95% CI 3.98–34.26) months in those with H3 K27 wildtype (p = 0.008).

CONCLUSIONS Factors indicative of higher SCA malignancy, such as H3 K27M alteration, higher histopathological grade, Ki-67 index (≥ 10%), and tumor length (≥ 4 segments), were similarly suggestive of higher rates of dissemination. The occurrence of dissemination is closely associated with the outcome events in patients with SCA.

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KEYWORDS CNS dissemination; spinal cord astrocytoma; diffuse midline glioma; H3 K27M; tumor; oncology

Spinal cord astrocytomas (SCAs) constitute 20%–40% of all intramedullary tumors.[1] The diffuse invasive nature of SCAs is a distinct characteristic, contributing to recurrence and morbidity.[2,3] Moreover, nearly all patients with SCA experience central respiratory depression during the terminal stage, regardless of whether the tumor originated in the cervical section or conus medullaris. This phenomenon could be attributed to the CNS dissemination of the tumor.

Empirically, brain gliomas rarely exhibit CNS metastasis.[4] It is estimated that the incidence of dissemination in glioblastoma, a common brain glioma, ranges between 3.8% and 6.9%.[5] In the case of gliomas growing on midline structures, approximately 20% of patients with diffuse intrinsic pontine gliomas experience the spread of tumor cells to distant areas of the brain, spine, or meninges.[6–8] Although numerous cases of CNS dissemination in patients with SCA have been reported, a comprehensive description of the prevalence of this phenomenon has yet to be established.[9–14] In patients with SCA, CNS dissemination is a predictor of poor prognosis, underscoring the importance of elucidating factors that impact dissemination.[15]

In this retrospective analysis, we collected clinical, radiological, and basic pathological features of 94 patients

ABBREVIATIONS FFPE = formalin-fixed, paraffin-embedded; HR = hazard ratio; IDH1 = isocitrate dehydrogenase 1; MGMT = O^6-methylguanine-DNA methyltransferase; MMS = McCormick Scale; OS = overall survival; SCA = spinal cord astrocytoma; TERT = telomerase reverse transcriptase; TMZ = temozolomide.

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with SCA diagnosed at Beijing Tiantan Hospital between 2011 and 2022. We examined CNS dissemination in this extensive SCA cohort and calculated its incidence. Subsequently, we analyzed factors that could impact dissemination and evaluated their prognostic significance.

Methods

Standard Protocol Approval, Registration, and Patient Consent

The study protocol, including the research question, study design, sample collection, and implementation scheme, was prepared prior to study commencement through a project authorization request for ethics committee approval. The study protocol was approved by the IRB and ethics committee of Beijing Tiantan Hospital. This study followed the principles of the Declaration of Helsinki, and all patients provided written informed consent.

Study Criteria and Data Collection

We retrospectively collected data from patients who were diagnosed with diffuse astrocytoma in the spinal cord in our institute. Patients who met the following criteria were included: 1) spinal location of the tumor; 2) histopathological diagnosis of diffuse astrocytoma according to the WHO classification, version 2021 (prevailing classification during the study); 3) surgical management between March 2011 and November 2022; and 4) formalin-fixed, paraffin-embedded (FFPE) samples available when molecular marker staining information was lacking in the postoperative pathological diagnosis. Exclusion criteria were as follows: 1) lack of consent to participate in the study; 2) missing basic data or follow-up information; and 3) glioma other than SCA. Based on the above exclusion criteria, patients who were lost to follow-up (n = 14) or lacked definitive radiological evidence of disease (n = 46) were excluded (Supplementary Fig. 1). Data collection was performed by a neurosurgeon specialized in neurooncology. Demographics, clinical data, imaging features, surgical details, postoperative course, type of adjuvant treatment, and follow-up data were locally extracted from medical records using a chart designed for the study.

Determination of Molecular Features

In the present study, all patients underwent resection with neurophysiological monitoring to achieve maximal tumor resection and decompression while preserving neurological function. Sufficient samples of tumor were resected, embedded, and stored for pathological diagnosis and subsequent supplementary staining. The histopathological grade was determined by routine evaluation of FFPE samples with H & E staining based on the 2021 WHO classification. The proportion of Ki-67–positive nuclei was calculated manually by neuropathologists, and immunohistochemical analysis with corresponding antibodies was used to evaluate the H3 K27M–mutant status (ABE419, 1:800; Millipore), isocitrate dehydrogenase 1 (IDH1)–mutant status (ab230949, 1:1000; Abcam), and Ki-67 expression status (MIB-1, 1:50; Labvision) in all 94 patients, particularly for some cases prior to the implementation of the 2016 and 2021 WHO classifications (n = 33).

Detailed molecular pathological information was obtained from 73 patients. Molecular features were determined for 22 cases with targeted sequencing data. Detailed methods for next-generation sequencing have been reported previously.[16] For the other 51 cases, following the extraction of sufficient DNA from FFPE samples (QIAmp DNA Mini Kit, Qiagen), IDH1 R132H, IDH2 R172K, telomerase reverse transcriptase (TERT) promoter C228T and C250T, and BRAF V600E mutations were determined using pyrosequencing after polymerase chain reaction amplification. We also assessed O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation using pyrosequencing with the PyroMark Q24 MGMT kit on a PyroMarker Q24 instrument (Qiagen).[17–19]

Dissemination Measures

Based on previous studies and our clinical setting, two CNS dissemination patterns could be identified: 1) tumor infiltration into the surrounding leptomeningeal space, and 2) subarachnoid seeding in CSF flow channels (Fig. 1).[20–24] According to visualization on MRI, CNS dissemination was defined as the enhanced leptomeningeal area beyond the primary tumor locus (or discontinuous) or newly enhanced subarachnoid areas of the tumor along the spinal canal. Two independent reviewers (S.A., H.L.) confirmed the imaging findings. In cases of discordance, a third senior neuroradiologist with more than 20 years of experience re-evaluated the image and made the final decision. The date of dissemination diagnosis was defined as the earliest date of imaging on which CNS dissemination was noted. All collectors and evaluators of CNS dissemination were blinded to the patient's pathological diagnoses.

Statistical Analysis

Using the life table method, actual CNS dissemination occurrence rates at diagnosis and at 1-, 3-, and 5-year follow-up evaluations were calculated based on the number of patients in each stage of follow-up. The p values were reported as 2-sided, with statistical significance defined as $p < 0.05$. Categorical variables (sex, treatment, histopathology, location, and medical history) are presented as frequencies and percentages. Stratification was performed based on categories for categorical variables, and the cutoff for quantitative variables was determined as previously reported.[17–19] When addressing missing values, observations containing missing data were excluded, and the analysis was performed using complete data. The Student t-test was used to compare all continuous variables, whereas the chi-square test (or Fisher exact test when appropriate) was used to compare all categorical variables. Uni- and multivariable analyses were conducted separately for each diagnosis, and the Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs. Overall survival (OS) was measured from the date of histopathological diagnosis to the date of death. Similar to progression-free survival time, dissemination-free survival time was defined as the duration between the time of SCA diagnosis and the date of dissemination. Postdissemination survival was defined as the duration between the date of dissemination and the time of death or last follow-

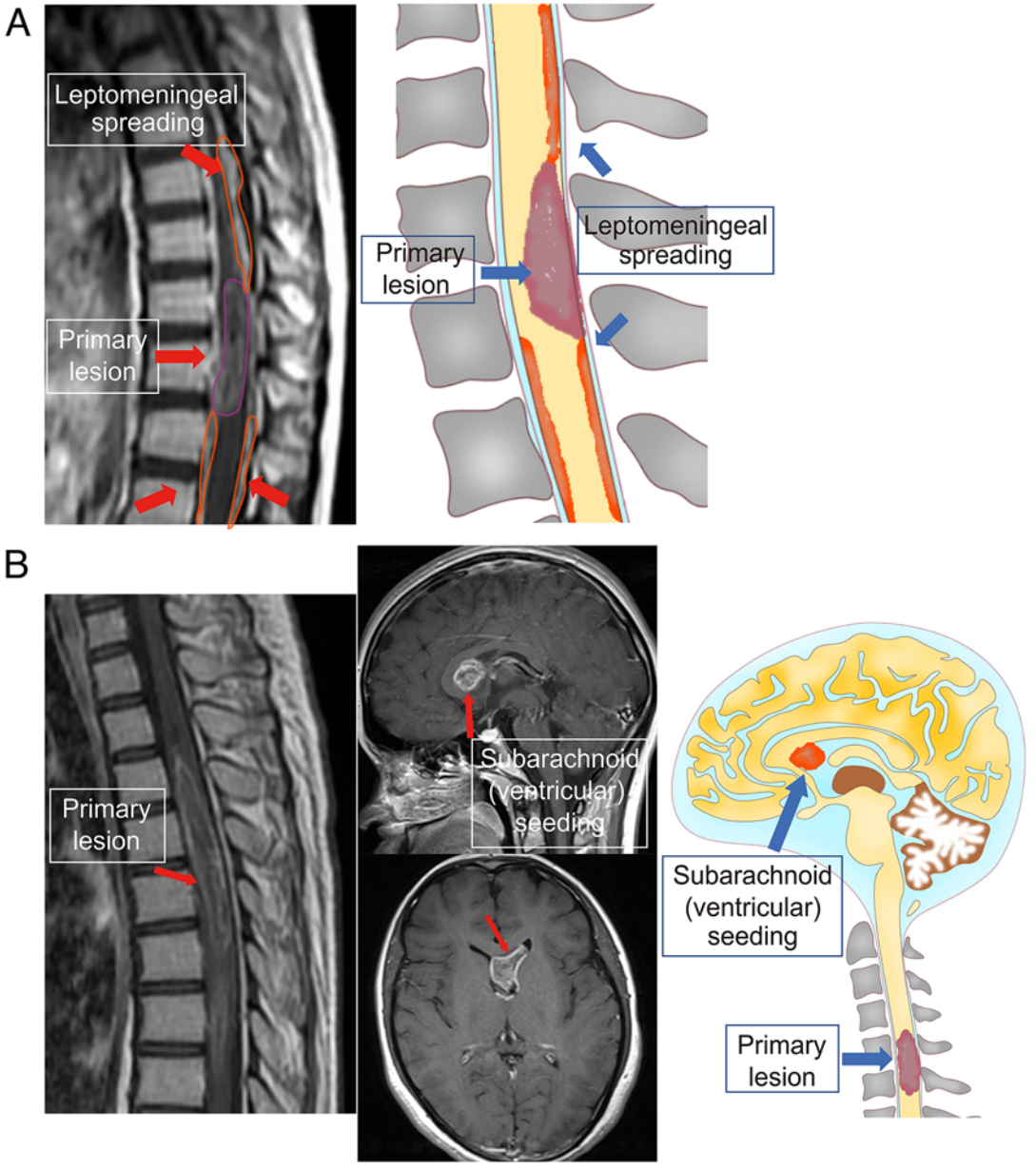

FIG. 1. Different dissemination patterns in patients with SCAs diagnosed with dissemination. **A:** Leptomeningeal spreading (*red outline*). A tumor infiltrate locus surrounding the leptomeningeal space and enhancing the leptomeningeal area beyond the primary tumor locus was found on gadolinium-enhanced T1-weighted MRI sequences. **B:** Subarachnoid seeding. The tumor metastasized in CSF flow channels, and discontinuous newly enhancing subarachnoid areas of tumor were found along the spinal canal. Figure is available in color online only.

up. Kaplan-Meier curves were generated to estimate the OS, dissemination-free survival, and postdissemination survival. Statistical analysis was performed using SPSS (IBM Corp.).

Results

Epidemiological and Clinical Data

The study included 94 patients, with 48 males (51.1%) and 46 females (48.9%). The median age of the study population was 30.5 (range 0.5–75) years. Tumors were most commonly located in thoracic segments (33/94, 35.1%), followed by cervical segments (28/94, 29.8%), thoracic-to-lumber spinal cord (15/94, 16.0%), and high cervical-to-thoracic lesions (11/94, 11.7%). Seven patients (7/94, 7.4%) had multiple loci of lesions. In addition, long tumor length (≥ 4 segments) was noted in 51.1% of patients, while short tumor length (< 4 segments) was detected in 48.9% (Table 1).

Tumor Histology and Molecular Profile

After resection of the lesions, pathological analysis

TABLE 1. Clinical characteristics of 94 patients in the study

Variable	Total (%)	H3 K27 Wildtype (%)	H3 K27M Mutant (%)	p Value
Age, yrs				0.697
<18	25 (26.6)	12 (28.6)	13 (25.0)	
≥18	69 (73.4)	30 (71.4)	39 (75.0)	
Sex				0.289
Female	46 (48.9)	18 (42.9)	28 (53.8)	
Male	48 (51.1)	24 (57.1)	24 (46.2)	
Location				0.262
C	28 (29.8)	15 (35.7)	13 (25.0)	
C-T	11 (11.7)	5 (11.9)	6 (11.5)	
T	33 (35.1)	14 (33.3)	19 (36.5)	
T-L	15 (16.0)	4 (9.5)	11 (21.2)	
Multiple	7 (7.4)	4 (9.5)	3 (5.8)	
Length (vertebral segments)				0.853
<4	46 (48.9)	21 (50.0)	25 (48.1)	
≥4	48 (51.1)	21 (50.0)	27 (51.9)	
Preop MMS grade				0.247
I	23 (24.5)	11 (26.2)	12 (23.1)	
II	35 (37.2)	19 (45.2)	16 (30.8)	
III	23 (24.5)	9 (21.4)	14 (26.9)	
IV	13 (13.8)	3 (7.1)	10 (19.2)	
Postop MMS grade				0.247
I	17 (18.1)	7 (16.7)	10 (19.2)	
II	27 (28.7)	15 (35.7)	12 (23.1)	
III	31 (33.0)	15 (35.7)	16 (30.8)	
IV	19 (20.2)	5 (11.9)	14 (26.9)	
Resection				**0.030**
<50%	43 (45.7)	14 (33.3)	29 (55.8)	
≥50%	51 (54.3)	28 (66.7)	23 (44.2)	
Radiotherapy				**0.040**
No	32 (34.0)	19 (45.2)	13 (25.0)	
Yes	62 (66.0)	23 (54.8)	39 (75.0)	
TMZ				**0.003**
No	49 (52.1)	29 (69.0)	20 (38.5)	
Yes	45 (47.9)	13 (31.0)	32 (61.5)	
Histopathological grade				**<0.001**
II	40 (42.6)	29 (69.0)	11 (21.2)	
III	22 (23.4)	7 (16.7)	15 (28.8)	
IV	32 (34.0)	6 (14.3)	26 (50.0)	
Ki-67 index				**<0.001**
<10%	35 (37.2)	26 (61.9)	9 (17.3)	
≥10%	59 (62.8)	16 (38.1)	43 (82.7)	

C = cervical; C-T = cervicothoracic; T = thoracic; T-L = thoracolumbar.
Boldface type indicates statistical significance.

revealed that SCA histopathological grades 2, 3, and 4 accounted for 42.6% (40/94), 23.4% (22/94), and 34.0% (32/94), respectively. High Ki-67 expression (≥ 10%) was detected in 62.8% (59/94) of patients (Table 1). The H3 K27M status was also evaluated, with 52 patients (55.3%) recognized as H3 K27M–positive (Table 2). Immunohistochemistry variation of IDH was investigated in all patients, and all patients had an IDH wildtype tumor. MGMT promoter methylation status was examined in 53 of 94 patients, with methylation identified in only 10 patients. TERT sequence variation was investigated in 72 patients, and 9 patients exhibited this variation. BRAF V600E sta-

TABLE 2. Molecular profiles for the 94 patients in the study

Molecular Marker	Total (%)	H3 K27 Wildtype (%)	H3 K27M Mutant (%)	p Value
IDH				—
Wildtype	94 (100.0)	42 (100.0)	52 (100.0)	
Mutant	0 (0)	0 (0)	0 (0)	
MGMT promoter				0.408
Unmethylation	43 (45.7)	16 (38.1)	27 (51.9)	
Methylation	10 (10.6)	5 (11.9)	5 (9.6)	
Unknown	41 (43.6)	21 (50.0)	20 (38.5)	
TERT promoter				0.069
Wildtype	63 (67.0)	24 (57.1)	39 (75.0)	
Mutant	9 (9.6)	7 (16.7)	2 (3.8)	
Unknown	22 (23.4)	11 (26.2)	11 (21.2)	
BRAF V600E				0.144
Wildtype	64 (68.1)	27 (64.3)	37 (71.2)	
Mutant	3 (3.2)	3 (7.1)	0 (0)	
Unknown	27 (28.7)	12 (28.6)	15 (28.8)	

tus was determined in 67 patients, and 3 patients carried the BRAF V600E mutation (Supplementary Fig. 2).

Oncological Therapy

Regarding treatment, most patients (51/94, 54.3%) underwent gross-total or subtotal resection (resection ≥ 50%), and biopsy (resection < 50%) was performed in 43 patients (45.7%; Table 1). Sixty-two patients (66.0%) received spinal radiation therapy alone, along with concurrent adjuvant temozolomide (TMZ) chemotherapy, according to the Stupp protocol (41/94, 43.7%). Four patients (4.3%) received chemotherapy with TMZ alone. Three patients (3.2%) received an alternate therapy regimen (methotrexate or anlotinib). Finally, 26 patients (27.7%) did not receive chemotherapy or radiation therapy and instead underwent supportive care management.

Dissemination Rate in SCA

Our cohort had a median follow-up duration of 84.93 (range 0.97–142.53) months, with a high occurrence of CNS dissemination in SCA. As many as 60.6% (57/94) of patients exhibited CNS dissemination, as determined based on clinical radiological evidence during follow-up. Among 57 patients with dissemination, 19 (33.3%) with SCA had CNS dissemination at initial diagnosis, whereas 38 patients (66.7%) developed CNS dissemination at the time of recurrence during regular follow-up visits. Over follow-up periods, patients with SCA experienced dissemination at a median of 35.07 (95% CI 16.86–53.27) months, and the 1-, 3-, and 5-year CNS dissemination rates were 46.0%, 74.3%, and 85.0%, respectively (Fig. 2A).

Given the prognostic disparity observed in previous studies between the H3 K27–altered and H3 wildtype groups, we conducted a more in-depth analysis of the dissemination characteristics within each group. Interestingly, 95.2% of patients (40/42) with H3 K27M mutation experienced CNS dissemination, a significantly higher proportion than the H3 wildtype group (68.0%, 17/25) at the 5-year follow-up period ($p = 0.002$; Fig. 2B). Dissemination rates during other periods are presented in Supplementary Fig. 3. The median dissemination-free survival of patients with H3 K27M mutation was 14.37 (95% CI 2.84–25.89) months, which was a significantly shorter duration than that of the H3 K27 wildtype group ($p < 0.001$; Fig. 2C).

Factors Impacting CNS Dissemination in SCA

To gain further insight into the factors that impact CNS dissemination, we conducted both uni- and multivariate Cox regression analyses on this SCA cohort using their dissemination-free survival period. Various clinical and pathological features were examined, including age, pre- and postoperative McCormick Scale (MMS) grade, tumor location and length, histopathological grade, Ki-67 index, H3 K27M status, MGMT promoter (methylation or unmethylation, n = 53), TERT promoter (mutation or not, n = 72), BRAF V600E (mutation or not, n = 67), resection, chemotherapy, and radiotherapy (Tables 2 and 3). Univariate analysis revealed that pre- and postoperative MMS grade, higher histopathological grade, chemotherapy, Ki-67 index (≥ 10%), and H3 K27M mutation were associated with CNS dissemination. In the multivariate analysis, H3 K27M mutation emerged as a marginally significant risk factor for the occurrence of long-term CNS dissemination (HR 2.089, 95% CI 0.940–4.642, $p = 0.070$; Table 3).

Dissemination Survival

Considering the prognostic implications of CNS dissemination reported previously, we further analyzed the OS of our patients with SCA, as well as postdissemination survival. The objective was to better understand the influence of CNS dissemination on SCA prognosis. A significantly higher proportion of patients in the dissemination group (80.1%, 46/57) succumbed to the disease during the follow-up period. The median OS time for patients with CNS dissemination of SCA was 18.37 (95% CI 16.82–

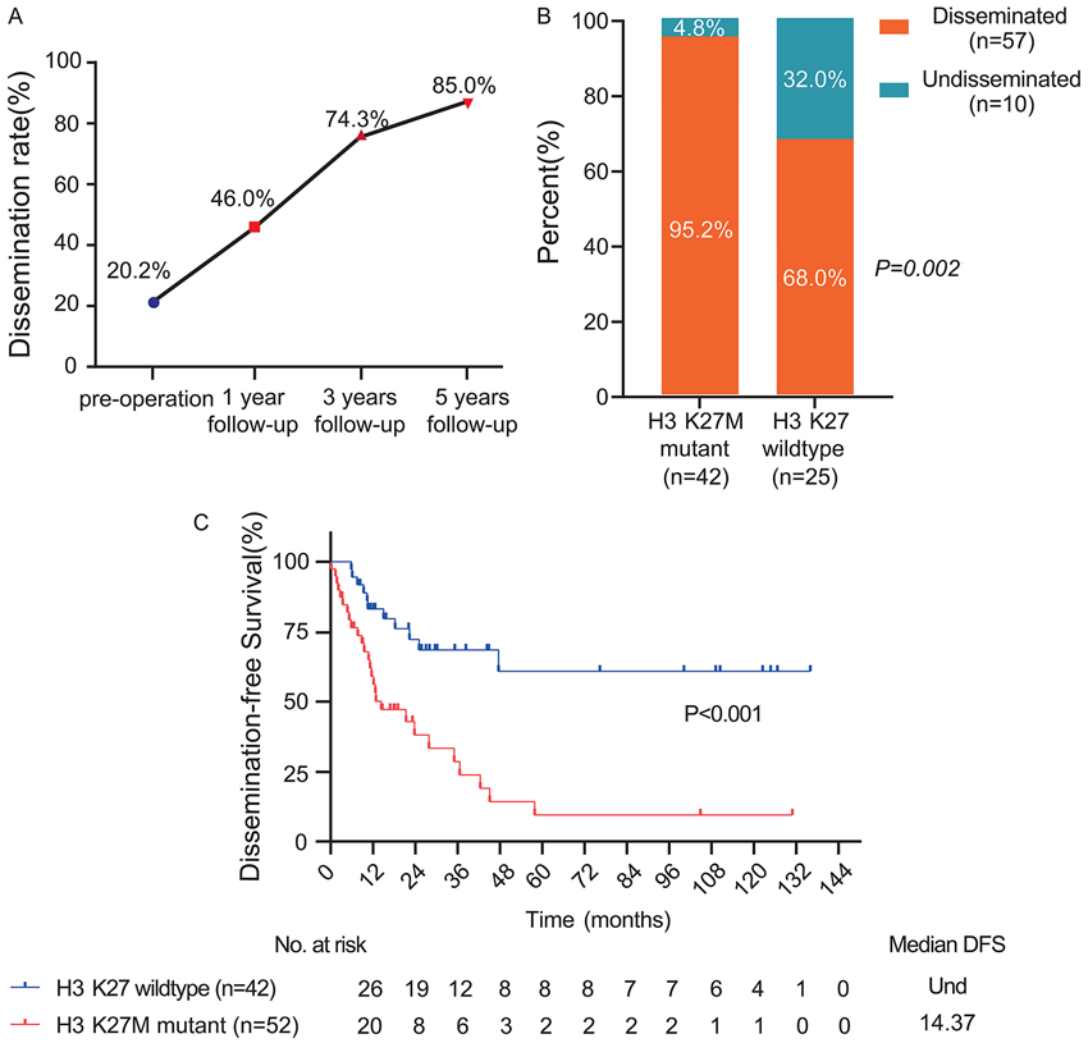

FIG. 2. Characteristics of CNS dissemination in SCA cases. **A:** Preoperative and 1-, 3-, and 5-year dissemination rates of patients with SCA in our cohort. **B:** Dissemination distribution in SCA patients. The dissemination rate of H3 K27M mutant cases was higher than that of H3 K27 wildtype cases. **C:** The association between dissemination-free survival (DFS) time and H3 K27 altered status. The median dissemination-free survival time of patients with SCA was 35 months. The median dissemination-free survival time of H3 K27M mutant cases was 14.37 months. Und = statistics undefined. Figure is available in color online only.

59.51) months, while patients without CNS dissemination were all alive to date ($p < 0.001$; Fig. 3). Regarding postdissemination survival time, the median postdissemination survival time for all patients was 8.97 (95% CI 6.84–11.09) months. H3 K27–altered status significantly impacted the postdissemination survival period. Patients with H3 K27M mutant status exhibited shorter postdissemination survival than those with H3 wildtype status (8.83 [95% CI 7.13–10.54] vs 13.40 [95% CI 3.98–34.26] months, $p = 0.008$; Fig. 4). Regarding other molecular features, no significant trends were detected in terms of postdissemination survival, except for MGMT promoter methylation (Supplementary Fig. 4).

Discussion

Given the rare occurrence of SCA, a comprehensive understanding of its clinical characteristics and biological behavior remains limited. Existing literature on SCA dissemination is scarce, mainly comprising individual reports, small case series, or literature reviews, contributing to insufficient evidence levels.[11,13,14] To the best of our knowledge, the current study represents the first exploration of SCA dissemination and its impact on prognosis. During extended follow-up, we found that the 5-year CNS dissemination rate of SCA reached as high as 85%, exceeding rates observed in brain gliomas (< 5%) and comparable to those of medulloblastoma (approximately 70%).[23,25] This CNS dissemination often portends a lethal outcome for patients.

Two dissemination patterns were identified in our cohort, exhibiting diverse clinical behaviors and MRI features: leptomeningeal infiltrating and subarachnoid seeding groups, each constituting approximately half of the disseminated cases. However, the sample size in our study was insufficient to establish accurate evidence, necessitat-

TABLE 3. Uni- and multivariate analysis of variables associated with dissemination-free survival

Variable	Univariate Cox Regression Analysis		Multivariate Cox Regression Analysis	
	HR	p Value	HR	p Value
Age, >20 yrs	1.000 (0.495–2.020)	0.999		
Preop MMS grade	1.451 (1.033–2.038)	**0.032**	0.925 (0.396–2.316)	0.867
Postop MMS grade	1.499 (1.066–2.107)	**0.020**	1.737 (0.696–4.334)	0.236
Tumor location, cervical	0.965 (0.737–1.264)	0.798		
Segment length, ≥4 segments	1.554 (0.767–3.149)	0.221		
Histopathological grade	2.303 (1.536–3.453)	**<0.001**	1.478 (0.828–2.641)	0.186
Ki-67 index, ≥10%	4.170 (1.866–9.318)	**<0.001**	2.028 (0.674–6.104)	0.209
H3 K27, mutation	3.637 (1.792–7.382)	**<0.001**	2.089 (0.940–4.642)	0.070
MGMT promoter, methylation	0.531 (0.152–1.848)	0.327		
TERT promoter, mutation	1.397 (0.483–4.039)	0.537		
BRAF V600E, mutation	1.374 (0.322–53877)	0.668		
Resection, ≥50%	0.722 (0.381–1.369)	0.319		
Chemotherapy, TMZ	2.494 (1.283–4.848)	**0.007**	0.898 (0.385–2.091)	0.802
Radiotherapy, postop	1.436 (0.696–2.964)	0.327		

Boldface type indicates statistical significance.

ing larger cohorts. Moreover, the mechanisms underlying the observed patterns remain poorly reported, emphasizing the need for in-depth studies.

Various factors can impact CNS dissemination of SCAs. In our cohort, H3 K27 altered status suggestively impacted the CNS dissemination of SCAs when compared with other clinical features and case characteristics, suggesting possible influence of molecular profiling on tumor malignant potential.[7,18,26] Patients with SCAs and H3 K27 alteration reportedly exhibit higher malignancy and poorer prognosis. Moreover, H3 K27 alteration has been implicated in the invasion, shedding, and implanting of SCA.[27,28] When combined with germline variants, H3 K27 alteration activates multiple oncogenic pathways and upregulates diverse oncoproteins across multiple foci, possibly contributing to enhanced tumor invasiveness.[29] Therefore, patients with diffuse midline glioma, H3 K27–altered, appear to exhibit a greater tendency for CNS dissemination than those with H3 K27 wildtype.

Notably, even patients with H3 K27 wildtype exhibit a substantial dissemination rate (approximately 40%), suggesting additional factors can impact SCA dissemination. Moreover, the tumor microenvironment reportedly differs between the brain and spinal cord.[30,31] In contrast to glioblastomas, diffuse intrinsic pontine gliomas, with similar gene features and midline position, exhibit less T

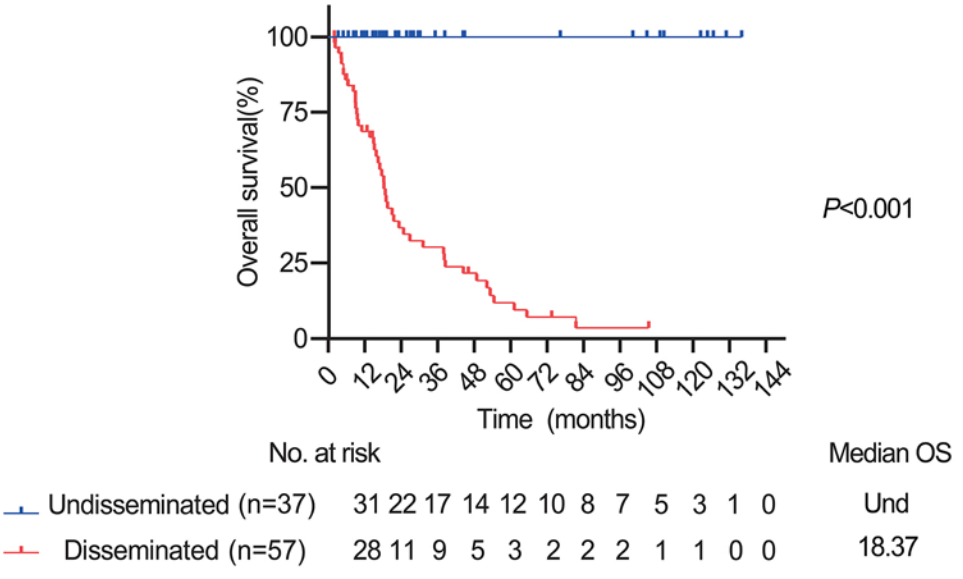

FIG. 3. Kaplan-Meier survival curves showing the association between dissemination with OS in patients with SCA. The median OS of disseminated cases was 18.37 months. Figure is available in color online only.

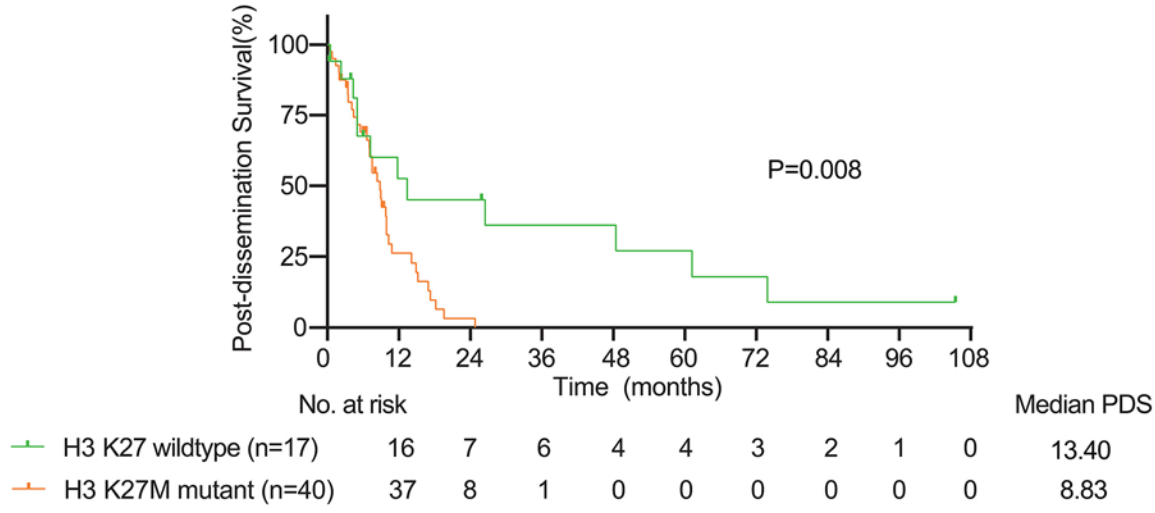

FIG. 4. Kaplan-Meier survival curves demonstrating the association between postdissemination survival (PDS) period and H3 K27 altered status in our cohort. The median postdissemination survival time of H3 K27 wildtype cases was 13.40 months compared with 8.83 months in H3 K27M mutant cases. Figure is available in color online only.

cell infiltration, more macrophage/microglial infiltration, and limited expression of cytokines and chemokines.[30,32] Therefore, the tumor microenvironment of the spinal cord likely impacts the unique CNS dissemination behavior of SCAs when compared with their brain counterparts.[33,34]

Consistent with prior reports, patients with SCA experiencing CNS dissemination exhibit higher mortality rates than those without dissemination in this study.[35] Notably, 80% of patients with SCA succumbed to post-CNS dissemination, with no deaths observed among patients without dissemination. This finding explains why extensive resection fails to enhance survival in patients with high-grade SCA.[17] Therefore, it is crucial to pay close attention to the clinical symptoms and neurological deficits beyond primary tumor sites in a timely manner. Comprehensive assessments, including whole-neuraxis imaging, are vital for managing SCA.[36] Initial diagnostic evaluations for suspected SCAs should encompass complete CNS imaging and CSF examination to detect potential tumor progression. Advancements in technology enable circulating-tumor DNA from CSF to predict minimal residual disease earlier than regular imaging tests, offering a novel approach for monitoring CNS dissemination.[37–39]

Despite current treatments mirroring those for intracranial gliomas, offering radiation with or without TMZ based on tumor grades, the OS of patients with SCA was not substantially prolonged. Extensive resection is not feasible and does not confer better survival, even postdissemination survival.[17,40] Adjuvant therapy, combining local radiotherapy with TMZ-based chemotherapy, fails to extend OS or dissemination-free survival, possibly due to rapid progression in nonirradiated areas.[41,42] Craniospinal irradiation is often used for high-risk leptomeningeal tumor dissemination and is highly successful in medulloblastoma and CNS germinoma, but it carries risks of acute and delayed brain injury and endocrine deficiencies.[43] Furthermore, SCA appears to exhibit low sensitivity to TMZ therapy, leading to chemotherapy failure. Alternative treatments for leptomeningeal dissemination are being considered, with intrathecal drug delivery at lower doses able to cross the blood-brain barrier and reduce drug-related adverse events. Published studies reported that methotrexate and cytarabine comprise the most common agents administered intrathecally in leptomeningeal dissemination of somatic, hematological, and primary CNS malignancies.[44,45] However, the applicability of craniospinal irradiation and intrathecal therapy to patients with SCA is uncertain, and the therapeutic effects and toxicity profiles of these exploratory treatments in patients with SCA and leptomeningeal dissemination should be analyzed and compared with standard therapies. In addition, novel treatment options, potentially guided by molecular testing, are crucial for exploring targeted treatments and/or immunotherapy.

Conclusions

This study showed more comprehensive evidence of CNS dissemination of SCA. Several potential clinical factors were found to be associated with dissemination, such as H3 K27M alteration, higher histopathological grade, Ki-67 index (≥ 10%), and tumor length (≥ 4 segments). Due to the high dissemination rate of SCA and its substantial strong association with patient survival, clinicians should pay careful attention to prevent and monitor the occurrence of dissemination. Further studies are needed to elucidate the mechanism of CNS dissemination and examine specific therapeutic strategies.

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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: Y Wang, An, Chai. Acquisition of data: Y Wang, An, Lin, Zhang, Pang, Yan, Liu, L Wang, Wu. Analysis and interpretation of data: Y Wang, An, Lin, Zhang, Chai. Drafting the article: An, Lin, Yan. Critically revising the article: Y Wang, Lin, Pang, Chai, Jia. Reviewed submitted version of manuscript: Y Wang, An, Lin, Chai. Approved the final version of the manuscript on behalf of all authors: Y Wang. Statistical analysis: An, Lin, Zhang. Administrative/technical/material support: Y Wang, Jia. Study supervision: Y Wang, Yan, Chai, Jia.

Supplemental Information

Online-Only Content

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

Supplementary Figs. 1–4. https://thejns.org/doi/suppl/10.3171/2024.6.SPINE24233.

Data Availability

More details of the current study are available from the corresponding author upon reasonable request.

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