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# Advances in Molecular Pathology, Diagnosis and Treatment of Spinal Cord Astrocytomas

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## Abstract

Spinal cord astrocytoma (SCA) is a rare subtype of astrocytoma, posing challenges in diagnosis and treatment. Low-grade SCA can achieve long-term survival solely through surgery, while high-grade has a disappointing prognosis even with comprehensive treatment. Diagnostic criteria and standard treatment of intracranial astrocytoma have shown obvious limitations in SCA. Research on the molecular mechanism in SCA is lagging far behind that on intracranial astrocytoma. In recent years, huge breakthroughs have been made in molecular pathology of astrocytoma, and novel techniques have emerged, including DNA methylation analysis and radiomics. These advances are now making it possible to provide a precise diagnosis and develop corresponding treatment strategies in SCA. Our aim is to review the current status of diagnosis and treatment of SCA, and summarize the latest research advancement, including tumor subtype, molecular characteristics, diagnostic technology, and potential therapy strategies, thus deepening our understanding of this uncommon tumor type and providing guidance for accurate diagnosis and treatment.

## Keywords

spinal cord, astrocytoma, diagnosis, oncology, treatment strategy

## Abbreviations

3DCRT, three-dimensional conformal radiation therapy; ADC, apparent diffusion coefficient; CNS, central nervous system; CNV, copy number variation; CPS, cancer predisposition syndrome; CSF, cerebral spinal fluid; CSI, craniospinal irradiation; CT, computed tomography; CTC, circulating tumor cell; ctDNA, circulating tumor DNA; DIPG, diffuse intrinsic pontine glioma; DMG, diffuse midline glioma; DTI, diffusion tensor imaging; EZH2i, enhancer of zeste homolog 2 inhibitor; GBM, glioblastoma multiforme; GTR, gross total resection; HDACi, histone deacetylase inhibitor; HGAP, high-grade astrocytoma with piloid features; IDH, isocitrate dehydrogenase; IMRT, intensity modulated radiation therapy; LP, lumbar puncture; MAPK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NGS, next-generation sequencing; OS, overall survival; PA, pilocytic astrocytoma; PBRT, proton beam radiation therapy; PCA, principal component analysis; PCV, procarbazine, lomustine, and vincristine; PET, positron emission tomography; PT, proton therapy; PXA, pleomorphic xanthoastrocytoma; RT, radiation therapy; SCA, spinal cord astrocytoma; SNV, single nucleotide variation; SWI, susceptibility weighted imaging; T1WI, T1 weighted imaging; T2WI, T2 weighted imaging; TMZ, temozolomide; t-SNE, t-distributed stochastic neighbor embedding; UMAP, Uniform Manifold Approximation and Projection; VEGF, vascular endothelial growth factor; VMAT, volumetric modulated arc therapy; VP, ventriculoperitoneal.

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## Introduction

Spinal cord astrocytoma (SCA), a subset of central nervous system (CNS) tumors, represents a rare and complex challenge in neuro-oncology. SCA accounts for about one-third of intramedullary tumors and 2% to 4% of CNS tumors, with an incidence rate lower than 0.1 per 100,000 persons per year; the average age of onset is 35 years, with a slightly higher incidence in men than in women.[1–4] Because of its extremely low incidence rate, our understanding of SCA lags far behind that of intracranial astrocytoma. Pilocytic astrocytoma (PA, grade 1) and diffuse astrocytoma (grade 2) are the common types of SCA, which almost always occur in young patients.[5] High-grade SCA (grade 3 and grade 4) accounts for about 25% of SCA.[6]

Clinical presentations of SCA are primarily influenced by the tumor location and growth patterns. These tumors are frequently observed in the cervical and thoracic segments, while their occurrence in the lumbar segment is less frequent. This phenomenon may be attributed to the gradual reduction in the diameter of the spinal cord from the cranial to caudal regions, and the absence of medulla in most lumbar regions. Initial symptoms often involve diffuse, nonspecific axial pain, encompassing back pain, nerve root pain, and central pain. Other common symptoms of the disease are slow progressing motor or sensory deficits. Bladder or gastrointestinal dysfunction, although less frequent, could also be the first symptom of SCA.[7] Notably, in some high-grade SCAs with intracranial dissemination, spinal cord compression may not be the initial symptom. Chen et al described an adult case initially thought to be a CNS infection but was ultimately diagnosed as spinal cord diffuse midline glioma (DMG) with H3 K27 alteration.[8] Liu et al reported a 7-year-old patient with intracranial hypertension and negative results in cerebral spinal fluid (CSF) and cranial imaging examinations, which was also identified as spinal cord DMG with H3 K27 alteration.[9]

The diagnosis of SCA has traditionally relied heavily on histological tests, including immunohistochemistry and ultrastructure. The majority of high-grade SCAs were diagnosed as glioblastoma multiforme (GBM) or anaplastic astrocytoma in the past. In recent years, molecular markers have become increasingly important in offering auxiliary diagnosis and enhancing diagnostic information. The 2021 WHO Classification of Tumors of the Central Nervous System emphasized the significance of molecular diagnosis in categorizing CNS tumors. In this version, astrocytomas are divided into adult-type diffuse gliomas (astrocytoma, isocitrate dehydrogenase [IDH] mutant; GBM, IDH wild-type), pediatric-type diffuse low-grade gliomas (diffuse astrocytoma, MYB/MYBL1-altered; diffuse low-grade glioma, mitogen-activated protein kinase [MAPK] pathway-altered) and pediatric-type diffuse high-grade gliomas (diffuse midline glioma, H3 K27-altered; diffuse hemispheric glioma, H3 G4-mutant; diffuse pediatric high-grade gliomas, H3-wildtype, and IDH-wildtype).[10] However, the new classification of astrocytoma is mainly based on the findings of intracranial astrocytomas. Except for DMG (H3 K27-altered) and PA, the diagnosis for other types of SCA remains a challenging work. Even in DMG (H3 K27-altered), spinal cord DMGs have multiple differences with intracranial DMG in the clinicopathological parameters and tumor microenvironment.[11,12] It was reported that the incidence of H3 K27 M mutations in SCA was much lower than that of diffuse intrinsic pontine glioma (DIPG).[13,14] The common molecular features of intracranial astrocytoma, including IDH mutation and 1p/19q codeletion, are rarely observed in SCA.[15,16] These evidence suggest that SCA seems to have unique molecular pathological features.

Magnetic resonance imaging (MRI) is the best noninvasive method for SCA diagnosis due to its spatial resolution and superb soft tissue contrast.[17] On T1 weighted imaging (T1WI), SCAs are usually isointense or hypointense, and on T2 weighted imaging (T2WI), they are hyperintense. On post-contrast images, most SCAs exhibit a degree of enhancement.[18] The presence of enhancement is often associated with a higher tumor grade and lower 5-year survival rates. Diffusion weighted imaging (DWI) is a technique that utilizes water diffusion properties to create contrast between normal tissue and pathology, providing functional and physiological information about CNS tumors and the tumor microenvironment. The movement of water molecules is limited in areas with high cell density or protein content, leading to an increase in the DWI signal and a decrease in apparent diffusion coefficient (ADC) values. The ADC atlas also offers quantitative data to distinguish tumor types and grades. Diffusion tensor imaging (DTI) applies the diffusion tensor model to DWI data to determine diffusion along three axes of a voxel, generating fractional anisotropic images that depict white matter tracts. Preoperative white matter mapping helps neurosurgeons remove tumors while preserving important white matter tracts, improving patient quality of life and survival. Magnetic susceptibility weighted imaging (SWI) is a high-resolution MRI technique that highlights the magnetism of substances like blood and calcification. SWI is sensitive in detecting microbleeds and can demonstrate abnormal blood vessels within tumors, aiding in tumor grading evaluation. Calcification is a feature of low-grade tumors, while bleeding and increased blood vessels are common in high-grade tumors. Magnetic resonance spectroscopy (MRS) aids in tumor evaluation by providing metabolic information for neuro-oncology imaging. N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr) are the dominant peaks in our multi-voxel long time-to-echo (TE) MRS for neuro-oncology imaging. Semiquantitative analysis of metabolite ratios, such as Cho/Cr, Cho/NAA, and NAA/Cr, helps to predict tumor grade. For high-grade astrocytoma, the Cho/Cr and Cho/NAA ratios typically show an increase, and NAA/Cr is decreased. Wang et al[19] found the Cho/NAA ratio to have the highest accuracy (0.87) in predicting glioma malignancy, followed by Cho/Cr (0.83) and NAA/Cr (0.78). In conventional MRI, infiltrative SCAs are sometimes difficult to diagnose because their imaging pattern may overlap with those of neurosarcoidosis and neuromyelitis optica. The prediction for the H3 K27-altered status of SCAs seems unlikely only using MRI.

Recently, the emergence of radiomics has been effectively compensating for the shortcomings of traditional imaging diagnosis that relies on human eye recognition of signs and empirical judgment. Multiple predictive models have been developed for evaluating the prognosis and H3 K27 M mutation status of SCA.[20,21]

Tumor grade is the main factor affecting the prognosis of SCA. Low-grade SCAs usually have a long-term survival after tumor resection, while the prognosis for high-grade SCA is extremely poor. Although high-grade SCAs tend to display varying molecular pathological features in pediatric and adult populations, the median survival time for individuals with high-grade SCA is mostly less than 3 years across different age groups based on several published studies.[22–26] According to the previous clinical research, the removed degree of tumor is the most significant prognostic factor for lower-grade SCA, and total resection can achieve effective control of SCA.[27,28] High-grade SCA cannot be completely removed by surgery for severe local infiltration. Positive surgical treatments are unable to extend the survival time of high-grade SCAs for tumor metastasis.[29–31] Even some views consider that tumor resection may facilitate the dissemination of SCA cells into the spinal subarachnoid space via the CSF, leading to intracranial metastasis. Brain and bone are the common sites of metastasis from high-grade SCA, according to the reports of spinal cord DMG.[32–34] Tumor location and age are also acknowledged as potential factors affecting the prognosis of SCA, especially for high-grade SCA. It was reported that tumor located at thoracic segments and adult patient had relatively better prognosis.[26,30,35]

Overall, compared with intracranial astrocytoma, SCA has unique clinical, pathological, and molecular genetic characteristics. The guidelines of intracranial astrocytoma have exhibited multiple limitations in diagnosis and treatment process of SCA. High-grade SCA patients are difficult to benefit from the standard treatment (surgery combined with chemoradiotherapy) for intracranial astrocytoma. Given these challenges, novel treatment approaches for SCA have attracted growing interest in research and clinical trials. As a result of advances in molecular profiling and genetic sequencing, new therapies and diagnostic criteria could be developed based the unique genetic characteristics of SCAs. Various novel treatment methods are being investigated in clinical trials with the goal of improving outcomes for people with high-grade SCA. This article aims to provide a comprehensive overview of the diagnosis, molecular pathology, and therapy strategies of SCAs.

## Classification of Spinal Cord Astrocytoma Based on DNA Methylation Profiling

In the past, tumor grading based on tissue morphology did not provide good prognostic guidance for astrocytoma. The 2021 WHO Classification of Tumors of the Central Nervous System offered recommendations for risk stratification of astrocytoma based on recent findings and incorporated molecular markers associated with clinical prognosis into the updated grading criteria for astrocytoma. These molecules include CDKN2A/B homozygous deletion in IDH-mutant astrocytoma[36]; combined gain of entire chromosome 7 and loss of entire chromosome 10 [+7/−10]; TERT promoter mutation; and EGFR gene amplification in IDH-wildtype astrocytoma.[37,38] The new WHO classification incorporated these molecular features along with traditional histological criteria (anaplastic histological features, mitotic images, microvascular proliferation, and necrosis) into the tumor grading system of astrocytoma. When these molecular events occur, regardless of the histological manifestation of tumors astrocytomas should be graded as grade 4.[10] Low-grade astrocytoma often occurs in children and adolescents. The histology of pediatric astrocytoma is nonspecific, lacking IDH mutations, and exhibiting specific genetic changes. Except for subtypes with histone H3 mutation, pediatric diffuse astrocytomas typically have a good prognosis. Therefore, the adult-type grading system is not suitable for pediatric astrocytoma. In addition, the new WHO classification emphasizes the role of genome-wide DNA methylation analysis in the diagnosis of CNS tumors. DNA methylation is relatively stable during the development of cancer, and analyzing the genome-wide DNA methylation profile of tumors is more helpful in accurately identifying tumor types and molecular subtypes than histological characteristics. DNA methylation and next-generation sequencing (NGS) have shown that the driver genes of pediatric IDH wild-type astrocytoma are usually associated with the MAPK pathway.[39] The majority of grade 2 and grade 3 tumors in IDH wild-type astrocytoma progress rapidly, with a clinical prognosis similar to GBM. DNA methylation analysis revealed that the presence of TERT promoter mutation, EGFR amplification, and +7/−10 signature in IDH wild-type astrocytoma, even when histologically resembling low-grade astrocytoma, results in a biological behavior similar to that of IDH wild-type GBM.[40–42]

In 2012, Fernandez et al analyzed and summarized DNA methylation data from 1628 tissue samples (including 424 normal tissues, 1054 tumor samples, and 150 nontumor samples). They found that DNA methylation patterns were related to histological types, and different tumor types had their own unique DNA methylation profiles.[43] In 2018, Capper et al collected DNA methylation data from nearly 3000 tumor samples, and finally acquired 82 types of CNC tumors, covering almost all types in the 2016 WHO classification of CNS tumors.[44] Moreover, they established an online diagnostic tool (the Heidelberg "Classifier," https://www.molecularneurop athology.org/mnp) based on DNA methylation data from 3000 CNS tumor samples and found that the diagnostic accuracy of the online tool was 92.81% in prospective analysis. DNA methylation profiling is a crucial technique in the classification of CNS tumors, enabling their categorization into distinct subgroups based on clinical phenotype.

The molecular pathology diagnosis for SCA still encounters challenges due to molecular characteristic differences with intracranial astrocytomas. It is unclear whether the molecular

markers of intracranial astrocytoma can apply to SCA. Genome-wide DNA methylation analysis is a valuable tool for categorizing CNS tumors, offering significant advantages in the diagnosis of rare tumor types and the identification of novel tumor subtypes. This approach facilitates comprehensive diagnosis in cases where molecular diagnosis encounters challenges. The fifth edition classification of CNS tumors proposed multiple tumor types and subtypes based on DNA methylation analysis (such as high-grade astrocytoma with piloid features and myxoid glioneuronal tumor).

This technique demonstrates stability and reproducibility, rendering it applicable to both fresh/frozen and formaldehyde-fixed paraffin-embedded (FFPE) tumor specimens.[45] The prevailing methods for detecting methylation involve the utilization of DNA and microarray technology treated with bisulfite. The Illumina microarray chip for CpG methylation relies on the hybridization of fragmented whole genome amplification products with oligonucleotide bead arrays containing oligomers linked to particular CpG sites.[46,47] After extraction, DNA from tumor tissues is treated with bisulfite conversion and hybridized to the BeadChip. Fluorescence signals are then read independently with the NextSeq 550 readers or iScan. After these preprocessing procedures, methylation data, typically represented as beta values, can be utilized for clustering analysis or visualization. The popular R packet used for processing methylated array data is Minfi[48], and a commonly used and practical method for describing tumor types through methylated data is dimensionality reduction. Similar to principal component analysis (PCA), these unsupervised algorithms aim to reduce high-dimensional data, such as thousands of CNS tumor samples with approximately 20,000 to 30000 data points each, to lower dimensions (2 or 3) for visualization. Among the most commonly utilized techniques are t-distributed stochastic neighbor embedding (t-SNE) and uniform manifold approximation and projection (UMAP), with UMAP being recognized for its ability to better preserve the overall structure compared to t-SNE.[49] The clustering analysis can also be performed in an online platform (Heidelberg "Classifier"), which allows users to upload their data without any additional onsite data processing.[44] The clustering of samples in close proximity to defined tumor types indicates similarities in both pathology and molecular characteristics (Sample 1 in Figure 1B). Samples that do not align with any defined tumor types may be classified as novel tumor types (Sample 2 in Figure 1B). Moreover, the sum of methylation and nonmethylation signal intensities can be used to detect the key molecular events of astrocytoma (Figure 1C), such as EGFR amplification, + 7/−10 signature, 1p/19q codeletion, and CDKN2A/B homozygous deletion.[49,50]

Although potentially useful for diagnosis, DNA methylation analysis has not been incorporated into clinical medicine due to the high costs of performing the assay. In published works, several studies reported SCA cases diagnosed by DNA methylation analysis.[29,51–53] The identified types of SCA by DNA methylation analysis included PA, high-grade astrocytoma with piloid features (HGAP), pleomorphic xanthoastrocytoma (PXA), astrocytoma (IDH-mutant), DMG (H3 K27-altered), DMG (H3 K27 and BRAF/FGFR1 co-altered), and GBM_MID (IDH wildtype, subclass midline). It should be noted that HGAP, GBM_MID (IDH wildtype, subclass midline) and DMG (H3 K27 and BRAF/FGFR1 coaltered) are the tumor types defined by methylation characteristics, and the latter two types are not included in the 2021 WHO classification of CNS tumors. Table 1 summarizes the molecular characteristics, prognosis, tumor subclass, and potential therapy of the 7 tumor types.

## GBM_MID

GBM_MID refers to tumors with locations in the midline structure and histological diagnosis of glioblastoma. It was reported that the epigenetic characteristic of GBM_MID was similar to that of DMG (H3 K27-altered) according to DNA methylation analysis.[54] This type of tumor exhibits the loss of H3K27me3 and EZHIP proteins but is lacking histone mutations.[55] The prognosis of GBM_MID is similar to that of adult GBM (IDH wildtype). PDGFRA amplification and mutations of the mismatch repair genes and TP53 were the common molecular characteristics of GBM_MID.[55,56] Chromosome 7p gain/amplification and 10q loss, EGFR amplification, and TERT promoter mutation, which serve as the diagnostic molecular criteria of adult GBM, were rarely seen in GBM_MID.[55] Although GBM_MID was originally discovered in the midline structure, it also widely occurs in other nonmidline structures.[55–57] These facts suggest that "GBM_MID" may not be a suitable term of this tumor type as GBM_MID describes a group of tumors with similar epigenetic features rather than clinical characteristics. Currently, a systematic analysis of GBM_MID is lacking, and the conclusions about its molecular and clinical features are mainly based on several small sample studies.

## HGAP

HGAP represents a recently delineated group of astrocytoma and is distinguished predominantly through DNA methylation profiling. HGAP is most common in young people (median age of 40) and can occur throughout the entire neuraxis, but mainly in the posterior cranial fossa.[58] The histopathological manifestations of HGAP can exhibit high-grade or low-grade characteristics, sharing the features of GBM or PA.[58,59] It is characterized by alterations in the MAPK pathway, often accompanied by CDKN2A/B homozygous deletion and ATRX mutation.[49] The outcome of HGAP is significantly poorer than of PA, with a median overall survival (OS) of about 4 years, which is similar to that of IDH-mutant GBM.[58] An in-depth analysis of a cohort of 144 patients, identified three distinct subgroups of HGAP (gNF1, g1, and g2) through the DNA methylation-based clustering analysis.[60] Each subgroup presents unique epigenetic and clinical features. The gNF1 subgroup is particularly noteworthy for its association with neurofibromatosis type 1 (NF1), marked hypermethylation in the NF1 enhancer region, and an observed trend toward decreased progression-free survival (PFS).

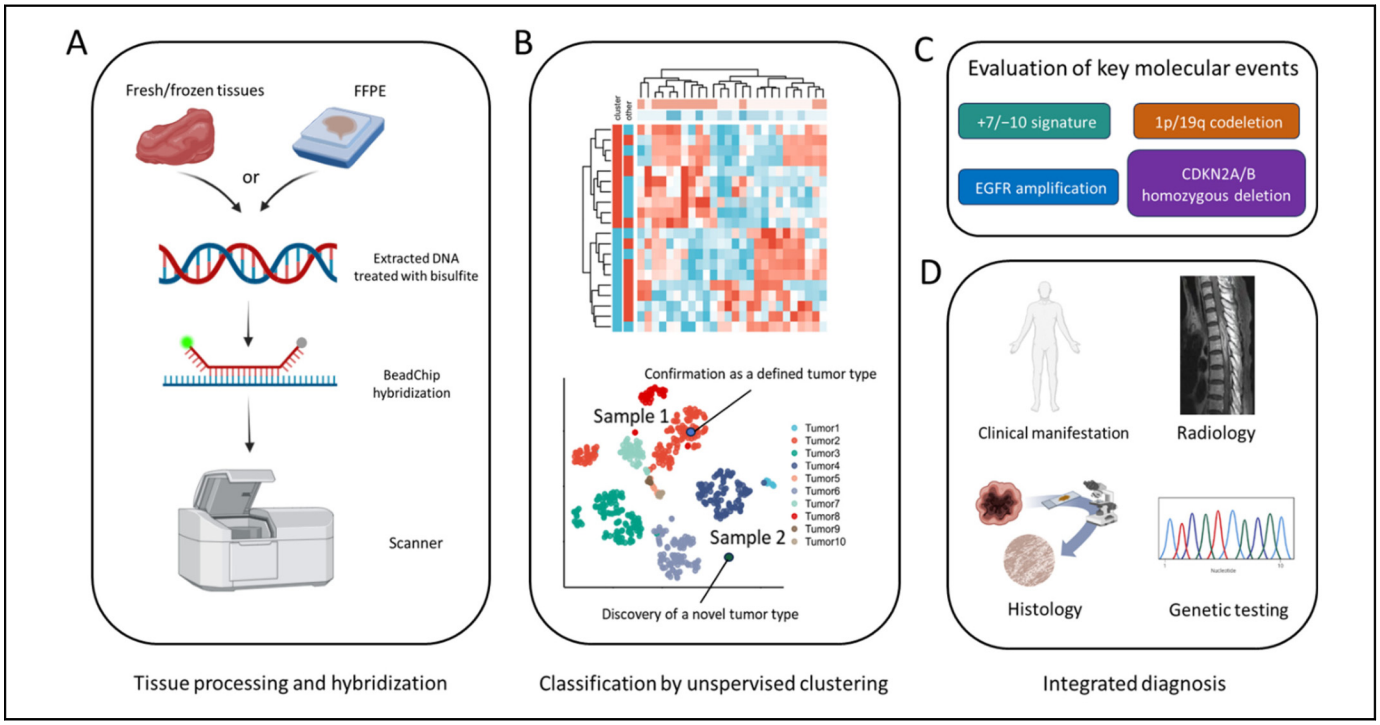


**Figure 1.** The flow chart of DNA methylation analysis for accurate diagnosis of spinal cord astrocytoma. (A) The DNA extracted from fresh/frozen tissues or FFPE is subjected to bisulfite treatment, followed by hybridization to the BeadChip and scanning to obtain methylation data. (B) The classification of spinal cord astrocytoma can be achieved through unsupervised clustering using methylation data. (C) Utilizing DNA methylation data allows for the assessment of key molecular events in astrocytoma, such as EGFR amplification, + 7/−10 signature, 1p/19q codeletion, and CDKN2A/B homozygous deletion. (D) The integration of DNA methylation analysis with clinical manifestation, radiology, histology and genetic testing is essential for a comprehensive diagnosis of spinal cord astrocytoma.

## *PA*

PA is a type of benign astrocytoma with typical histologic characteristics including piloid cytology, low proliferative activity, and biphasic growth pattern.[61] PA is associated with genetic alterations involved in the MAPK pathway, most commonly with the KIAA1549-BRAF gene fusion and is graded as grade 1 according to WHO classification[62]. This type of astrocytoma constitutes approximately 5% of gliomas and 17.6% of primary intracranial tumors, predominantly affecting pediatric and adolescent populations.[63] The prognosis of PA is good, with a 10-year survival rate of over 90%, generally requiring surgical resection only.[64]

## *PXA*

PXA is a rare type of circumscribed astrocytoma, mostly located above the tentorium, such as the temporal and frontal lobes.[65] The diagnosis of PXA poses a significant challenge due to the absence of specific molecular alterations. In the current WHO classification, the main molecular alterations of PXA include homozygous deletion of CDKN2A/B and BRAF mutation, while the specific histologic characteristics include eosinophil granules, xanthoma cells, pleomorphism, and multinucleated and spindle cells.[10,66] Currently, it is proposed that the favorable criteria of diagnosing PXA should include the methylome profile of PXA, which is because tumors with typical histologic characteristics of PXA often exhibit molecular features of other CNS tumors, and most PXAs diagnosed by methylome analysis do not display the typical histologic characteristics of PXA.[67–69] There is a relatively good prognosis for PXA, with 5-year PFS rate above 60% and 5-year OS rate above 75%.[70] The majority of PXAs are WHO grade 2, often effectively treated with just surgery, while grade 3 PXAs have a relatively bad prognosis for recurrence and metastasis.[71–73]

## *DMG (H3 K27-Altered)*

DMGs (H3 K27 M mutant) harboring somatic mutations in the HIST1H3B/C or H3F3A genes are classified as a unique entity characterized by lysine to methionine substitution at amino acid residue 27 (K27 M) in the histone H3 variants H3.3 or H3.1, which was first put forward in the 2016 WHO classification of CNS tumors.[74] In the 2021 WHO classification, DMGs (H3 K27 M mutant) are renamed as "diffuse midline glioma, H3 K27-altered" due to the fact that H3 K27 alteration also occurs in H3-wildtype DMG with other molecular events (such as EZHIP overexpression). DMGs are seen mainly in midline sites (including the brainstem, thalamus, and spinal cord), and the histologic appearance of DMG can be any form from grade 2 to grade 4. The prognosis of DMG is very poor, with a 2-year survival

**Table 1.** Summary of Molecular Characteristics, Prognosis, Tumor Subclass, and Potential Therapy of the 7 Tumor Types.

| Tumor Type | Molecular Characteristics | Subclass | Prognosis | Target Therapy or Immunotherapy |
|---|---|---|---|---|
| GBM_MID (IDH-wildtype, subclass midline) | PDGFRA amplification/ mutation, H3K27me3 and EZHIP loss | Not available | Median OS about 1 year | Inhibitors of PDGFR signaling pathway (dasatinib[189], crenolanib[190]) |
| High-grade astrocytoma with piloid features | MAPK pathway alteration, CDKN2A/B homozygous deletion and ATRX mutation | gNF1, g1 and g2 | Median OS about 4 years | Inhibitors of MAPK pathway (trametinib[191], cobimetinib[192]), CDK 4/6 inhibitor (abemaciclib)[193] |
| Pilocytic astrocytoma | MAPK pathway alteration and KIAA1549-BRAF gene fusion | Not available | 10-year survival rate over 90% | Inhibitors of MAPK pathway (trametinib[191], cobimetinib[192]) |
| Pleomorphic xanthoastrocytoma | CDKN2A/B homozygous deletion and BRAF mutation | Not available | 5-year survival rate over 75% | CDK 4/6 inhibitor (abemaciclib)[193] and BRAF inhibitors (dabrafenib, vemurafenib and trametinib)[194] |
| DMG (H3 K27-altered) | H3 K27 M mutation, EZHIP overexpression, H3K27me3 loss and EGFR alteration | H3 K27M-mutant, H3-wildtype with EZHIP overexpression, and H3-wildtype with EGFR mutation | Median OS about 2 years | Epigenetic therapies (panobinostat and tazemetostat) and immune checkpoint inhibitors (pembrolizumab and ipilimumab)[184] |
| DMG (H3 K27 and BRAF/FGFR1 coaltered) | H3 K27 and BRAF/FGFR1 coalteration | Ganglioglioma-like, DMG (H3 K27 M mutant)-like and HGAP-like | Median OS over 3years | BRAF inhibitors (dabrafenib, vemurafenib and trametinib)[194] |
| Astrocytoma (IDH-mutant) | IDH mutation | IDH-R82 K and IDH-176 T mutant | Not available | Inhibitors of mutant IDH enzymes (vorasidenib[179] and ivosidenib[180]) |

rate lower than 10% and median OS from 9 to 12 months.[75–77] Notably, survival data available for H3K27M-mutant DMG are mainly derived from pediatric DIPG, which only represents a subgroup of DMG. Some retrospective studies reported that adult DMG had better prognosis than pediatric DMG, and spinal cord DMG had better prognosis than brainstem DMG.[12,30,78,79] Chai et al reported that the median OS of spinal cord DMGs (H3 K27M-mutant) was approximately 2 years, based on a cohort of 77 cases.[29] DMGs with different locations might be different subgroups according to DNA methylation analysis.[11,80] In 2022, Liu et al explored the cellular heterogeneity of H3-K27 M mutant DMG across time and space, and found that mesenchymal-like cells increased with age; lineage-committed oligodendrocyte precursor cells were more mature in thalamic DMG than in pontine DMG.[11] TP53 mutation is the major molecular event in DMG besides H3 K27 M mutation. It was reported that TP53 mutations had a higher frequency in pontine DMG than medulla DMG, while PPM1D and NF1 were more frequent in medulla DMG than that of medulla DMG.[80] In spinal cord DMGs, higher numbers of copy number variations (CNVs) were discovered in TP53-mutant cases, such as Chr 19q deletion, Chr 10q deletion, Chr 7p amplification, CDK6 amplification, and KIT/PDGFRA amplification, suggesting the different mechanisms between TP53-wildtype and TP53-mutant DMGs.[29] Noor et al revealed that mutations in TP53 codon 273 were associated with a more favorable prognosis compared to TP53 wildtype patients in low-grade astrocytoma, suggesting a potential influence of TP53 on chemotherapy efficacy through YAP1.[81] A bioinformatics analysis indicated that TP53 mutations were linked to the TGF-β pathway, NOTCH signaling pathway, and cAMP signaling pathway in lower-grade astrocytoma of the brain.[82]

## DMG (H3 K27 and BRAF/FGFR1 Coaltered)

DMG (H3 K27 and BRAF/FGFR1 coaltered) was once regarded as a special subclass of H3 K27 M mutant DMGs for its better prognosis.[83] The mutations of FGFR1 and BRAF are commonly observed in low-grade glioma, including PA and ganglioglioma. Consequently, the simultaneous occurrence of these MAPK alteration and H3-K27 M mutation poses challenges in terms of grading and diagnosis.[84] Recently, DNA methylation analysis showed that DMG with H3 K27 and BRAF/FGFR1 coalteration was a new subtype of DMG, which had different epigenetic and histological characteristics with H3 K27 M mutant DMG and other others adult/pediatric diffuse gliomas.[52,85] Among this new subtype of DMG, there is calcification or a solid tumor component, as well as atypical radiological and pathological characteristics. According to histological criteria, DMG (H3 K27 and BRAF/FGFR1 co-altered) can be generally divided into three types: ganglioglioma-like, DMG (H3 K27 M mutant)-like, and HGAP-like[52]. Different from H3 K27-altered DMG, the prognosis of this DMG subtype is better, with a median OS over 3 years.[52]

## Astrocytoma (IDH-Mutant)

IDH mutant astrocytoma is the common type of supratentorial glioma, which are usually found in younger adult patients and typically indicate a better prognosis compared to gliomas

without IDH mutations. Previous research demonstrated that over 80% of IDH-mutant supratentorial astrocytoma were IDH1-R132H type, while IDH1-R132H-mutant type accounted for only 20% in infratentorial astrocytoma.[86,87] Compared to supratentorial astrocytomas, infratentorial astrocytomas exhibit significantly lower frequencies of MGMT promoter methylation and ATRX-loss.[87] Several rare mutation types (such as IDH-R82 K and IDH-I76 T) discovered in IDH-mutant spinal cord astrocytoma had never been reported in supratentorial astrocytoma before.[88] DNA methylation profiling showed the epigenetic differences between supratentorial and infratentorial IDH-mutant astrocytomas.[87] This differentiation is associated with the tumor grade, but not contingent upon the IDH mutation type.[87]

## Novel Diagnostic Techniques

### *Radiomics*

The diagnosis of solid tumors heavily relies on imaging studies, including computed tomography (CT), MRI, and positron emission tomography (PET). Among these, MRI is the most commonly used imaging modality for CNS tumor patients to date.[89] However, traditional structure-based medical imaging is subjective and represents a qualitative assessment, which means these conventional radiological techniques are beset with some of inherent limitations. In contrast to conventional imaging techniques, radiomics offers notable benefits. Primarily, radiomics can provide a more comprehensive array of imaging features, as many characteristics are not discernible to the unaided eye. Additionally, the reliance on individual physician interpretation in radiomics analysis is diminished, enabling the utilization of big data analysis and fostering greater objectivity in the evaluation of imaging data, thereby minimizing discrepancies among various operators.[90] Radiomics combines principles from computer science and medicine to extract a vast amount of image data from various imaging modalities (such as CT, MRI, and PET) for the purposes of tumor segmentation, feature extraction, and model development. Through comprehensive analysis, prediction, and interpretation of this extensive image data, radiomics aids healthcare professionals in achieving precise diagnostic outcomes. The workflow of radiomics can be succinctly delineated as follows: (1) acquisition of imaging data; (2) calibration of tumor areas; (3) segmentation of tumor areas; (4) feature extraction and quantification; (5) the establishment of an image database; and (6) classification and prediction. Recent studies have demonstrated that radiomics has a wide range of applications, including the identification of primary tumors, differential diagnosis, tumor grading, and assessment of genetic mutation status, as well as evaluation of infiltration and heterogeneity, prediction of treatment response, prognostic assessment, and in the context of recurrence.[91,92]

At present, multiparametric MRI (MP-MRI) is the primary modality utilized for the diagnosis of astrocytoma, monitoring of tumor progression, and assessment of therapeutic effectiveness. The common sequences used for astrocytoma include precontrast T1- and postcontrast T1-weighted images (T1, T1 + C), FLAIR, and DWI images.[93] Radiomics has the capability to measure multiple characteristics of MP-MRI images, including texture heterogeneity, spatial relationships, and intensity distribution for the purpose of precise tumor assessment. The application of radiomics in astrocytoma can be divided into the following aspects: (1) Predicting molecular subtypes of astrocytoma: Utilizes radiomics to non-invasively predict astrocytoma subtypes, integrating digital analysis of brain histopathology images with molecular features. This includes predicting IDH mutations, MGMT methylation status, and astrocytoma grades using MRI radiomics[94–97]; (2) Survival prediction in astrocytoma: Focuses on using radiomics for more accurate survival rate predictions in astrocytoma patients, potentially leading to better treatment plans. This includes combining radiomic features with clinical and genetic information to improve OS and PFS predictions[98,99]; (3) Differential diagnosis of astrocytoma: Discusses the use of radiomics in distinguishing astrocytoma from other conditions like lymphoma and brain metastases, as well as differentiating between pseudoprogression and tumor progression.[100–102] It highlights the potential of radiomics in guiding treatment decisions and reducing adverse events. (4) Individualized treatment of astrocytoma: Highlights the significant role of radiomics in advancing precision medicine for astrocytoma treatment. It emphasizes its use in personalized diagnosis and treatment planning, especially in recurrence prediction and therapy stratification based on various radiomic, molecular, and clinical features.[103,104]

In SCA, Li et al developed a radiomics-based logistic regression model using preoperative T2-weighted MR imaging to accurately predict H3 K27-altered status in SCA.[20] This model demonstrated high accuracy and robustness in both test and prospective patient sets, offering significant potential for improving clinical management. Sun et al developed an automated deep learning pipeline using preoperative MR images for tumor segmentation and stratified overall survival prediction in spinal cord astrocytoma patients, achieving high accuracy and effectively addressing the lack of prognostic models for this rare disease.[21] Currently, due to the low incidence rate of SCA, research related to the radiomics of SCA is notably scarce. In the realm of assisting the diagnosis of SCA through radiomics, there is a significant reliance on referencing the research findings and methodologies from supratentorial astrocytoma.

Despite much progress in radiomics, there remains a notable deficiency in large-scale, multicenter validations of exploratory studies, with most validation cohorts relying on retrospective data from individual units. The forthcoming pivotal advancement in radiomics is expected to be the creation of models for clinical decision support. Realizing this objective demands the formulation of universally accepted standards and the construction of an extensive, detailed common database. The initiation of a database necessitates the comprehensive collection and systematic organization of a substantial volume of tumor patient imaging data on a global scale. The samples should encompass tumors originating from diverse anatomical sites

and exhibiting various histological characteristics, while also encompassing patients across different age cohorts and pathological profiles. Concurrently, the acquisition of pertinent clinical data, such as the patient's medical background, clinical presentations, and therapeutic interventions, is imperative. Rigorous quality control measures, including assessments of image quality and verification of data consistency, must be also implemented to ensure the reliability and accuracy of the collected data. Upon the establishment of the database, researchers can utilize the data to engage in research across various facets. Primarily, through the analysis of images pertaining to a substantial cohort of tumor patients, the morphological, density, and vascular characteristics of diverse tumors can be investigated. These research findings may offer insights for the diagnosis and differential diagnosis of tumors, aiding medical professionals in accurately discerning the nature and pathological subtype of tumors, as well as formulating rational treatment strategies. Additionally, databases can be leveraged to examine the growth trends and prognostic determinants of tumors. Through the utilization of time series analysis on patient images, it is possible to observe the growth rate and characteristics of tumors, predict the progression of tumors, and study factors related to tumor prognosis (such as tumor size, metastasis) and make the treatment plan by integrating clinical data of patients. These research findings can offer a scientific foundation for the prognosis assessment of tumors and serve as a valuable resource for healthcare professionals and patients in devising personalized treatment approaches.

## *Biopsy*

Biopsy plays a pivotal role in the confirmation of SCA diagnosis and the acquisition of molecular data that can provide valuable insights for treatment decisions. Biopsies are indispensable in ruling out other types of lesions, such as ependymoma, hemangioblastoma, and non-neoplasm diseases. Moreover, biopsies are imperative in validating the existence of the H3 K27 M, IDH mutation, and KIAA1549-BRAF fusion, which are crucial for accurate diagnosis for DMG, IDH mutant astrocytoma, and PA.[105] Other genetic alterations (such as TP53, ATRX mutations, or PDGFRA gene amplification), which can influence the prognosis and provide guidance for target therapies, are also the main detection indicators in biopsy.[10]

Numerous research groups have conducted investigations into a range of biopsy techniques for CNS tumors, with a specific emphasis on their practicality and effectiveness. The advent of liquid biopsy has introduced a less invasive method for tumor sampling, facilitating easier and ongoing monitoring. This innovative approach provides a quicker means of obtaining vital information for molecular pathological diagnosis, prognosis prediction and recurrence assessment. Tumors release a variety of distinct components, including cells, fragments, DNA, and RNA, into bodily fluids. These components originating from tumors display molecular profiles that significantly deviate from those observed in healthy tissue, facilitating their identification and examination. Digital PCR has emerged as the predominant and efficacious method for liquid biopsy of astrocytoma,[106] demonstrating superior sensitivity and specificity compared to Sanger sequencing, qPCR, and NGS.[107] Particularly adept at detecting known single nucleotide variations (SNVs), this technique is well suited for identifying driver mutations in key genes such as IDH1/2, pTERT, histone H3 variants, and BRAF within astrocytoma. Digital PCR has the capability to identify variant alleles with a sensitivity ranging from 70% to100% in GBM and 80% to 100% in DMG.[106] Nevertheless, when utilizing cerebrospinal fluid for digital PCR, the detection sensitivity of low-grade astrocytoma falls below 50%.[106] At present, liquid biopsy cannot replace tissue biopsy in the diagnosis of astrocytoma, and liquid biopsy is only an alternative solution when tumor tissue cannot be obtained through surgery.

Compared to other biological fluids, including blood, urine, and pleural effusion, CSF has significant advantages in diagnosing CNS tumors. The blood–brain barrier restricts the translocation of circulating tumor DNA (ctDNA), resulting lower plasma ctDNA concentrations in patients with CNS tumors than those with other solid tumors. Conversely, the CSF, which circulates around the brain parenchyma in various anatomical spaces, serves as a rich source of ctDNA in CNS tumors.[108,109] Although circulating tumor cells (CTCs) are the direct evidence of tumor occurrence and development, their detection rate is not high for technical limitations.[110] CtDNAs offer a wider range of applications in astrocytoma diagnosis by CSF biopsy. CSF-derived ctDNAs can reflect tumor heterogeneity, capturing the spatial diversity of tumors and presenting a more comprehensive view of tumor mutations.[111–113] Cheng et al explored the application of CSF biopsy for molecular analysis of SCA, utilizing ctDNA sequencing to explore its genomic landscape. The main genetic alterations occurred both in CSF-derived ctDNA and tumor biopsy, including H3F3A K27 M, TP53 and ATRX mutation, often displayed at higher average mutant allele frequency in CSF compared to tumor tissues. Nevertheless, the clinical utility of ctDNA genomics is constrained by the low specificity of known mutations in different tumor subtypes, which may not be definitive in ruling out other significant differential diagnoses. To address this limitation, ctDNA methylation analysis can be employed. Zuccato et al classified malignant brain tumors based on liquid biomarkers using the ctDNA methylation analysis in 57 patients including brain metastases, GBM, CNS lymphomas, and nontumor cases.[114] Their findings indicated that the methylation feature classifier utilizing CSF effectively differentiated various tumor types and nontumor lesions. In comparison to tissue biopsy, the procedure poses a lower risk to patients as only 0.5 to 2 mL of CSF is required and can be obtained through lumbar puncture (LP). Li et al demonstrated in their study on medulloblastoma that the DNA methylation patterns of ctDNA in CSF can identify the presence and subtype of medulloblastoma, indicate response to treatment and tumor recurrence, and potentially serve as prognostic biomarkers for medulloblastoma.[115]

Multiple studies have demonstrated that the presence of ctDNA in CSF is associated with shorter survival of patients with CNS tumors, suggesting that dynamic monitoring the alterations of ctDNA in CSF may become an effective method in predicting prognosis and therapeutic response of CNS tumors and during treatment.[116–118] In a study on patients with brain metastasis from nonsmall cell lung cancer, Chen et al observed that individuals who experienced a reduction in CSF ctDNA concentration exceeding 50% compared to baseline exhibited extended intracranial PFS.[116] Miller et al conducted a study to assess ctDNA genomics in the CSF of 85 patients diagnosed with glioma.[118] Their findings revealed that 49.4% of the glioma patients exhibited at least one tumor-related genetic alteration in CSF ctDNA. Additionally, 6 patients underwent ventriculoperitoneal shunt (VP shunt) treatment for hydrocephalus within 3 weeks following the initial LP. Notably, the sequencing results indicated a high level of consistency in the genomic profiles detected in CSF obtained from different anatomical positions (LP and VP shunt). Five patients underwent tumor resection within 3 weeks of CSF collection, with sequencing results demonstrating a high degree of genetic profile consistency between the CSF and tumor tissue.[118] Therefore, for patients with CNS tumors, CSF ctDNA analysis can offer a dynamic, comprehensive, and dependable representation of the tumor genomics, and serve as a valuable prognostic tool. LP is deemed to be a highly safe procedure, particularly advantageous for patients with recurrent tumors as it presents a simpler and safer alternative to undergoing a second craniotomy surgery. Furthermore, this approach enables the identification of emerging genetic alterations and drug resistance mechanisms, thereby providing valuable guidance for treatment decision-making.[119] These findings suggested that CSF biopsy is a promising method for diagnosis, offering prognostic insights for SCA. CSF biopsy combined with radiomics presents a potentially fruitful approach for less-invasive diagnosis and offering novel insights for treatment strategies.

## Prognostic Factors

For individualized therapies and accurate survival prediction in SCA patients, multiple prognostic factors have been identified. Age, tumor grade, extent of surgical resection, and H3 K27 M mutation status are the main prognostic factors in the entire population of SCA.[13,23,35,120] The published research establishes a clear correlation between tumor grade and prognosis in SCA. A higher tumor grade is consistently associated with shorter survival time.

There were inconsistent results reported in early studies of SCA that utilized age as a prognostic factor.[3,121] In a large study with over 600 SCA cases, age had obvious prognostic significance in low-grade SCA, but had no prognostic significance in high-grade SCA.[23] Considering the lack of definitive pathologic diagnosis in these SCA samples, we speculate that pediatric low-grade SCA are mostly PAs, which account for their better prognosis compared to adult low-grade SCA. No prognostic significance of age was also found in a retrospective study containing 494 high-grade SCAs and a spinal cord DMG (H3 K27M-mutant) cohort.[29,122] However, it is important to note that low-grade or high-grade SCA are composed of various astrocytoma subtypes with different outcomes and molecular pathologies. In this situation, investigating prognostic significance of age in the entire SCA group without subtype analysis is inappropriate. Regrettably, while the diagnostic criteria for intracranial astrocytoma do not entirely align with those for SCA, the current pathological diagnosis still depends on histological and molecular markers associated with intracranial astrocytoma. Most published studies on SCA lacked data on molecular pathology and DNA methylation. Despite being recommended in the new WHO classification, the integrated diagnosis based on DNA methylation analysis is not widely implemented due to the high cost. The limited number of published studies with small sample sizes precludes definitive conclusions regarding disparities in tumor molecular profiles and prognostic outcomes between adult and pediatric SCA. It is imperative to conduct extensive research on the utilization of DNA methylation analysis as a diagnostic tool in SCA. By collecting an adequate number of cases, investigate the molecular mechanisms underlying various subtypes of SCA and devise appropriate therapeutic interventions.

So far, the most commonly used treatment method for SCA is surgical intervention, and the extent of surgical resection is also the key factor affecting the prognosis of SCA, especially in low-grade SCA.[22] Gross total resection (GTR) significantly improved OS in comparison with biopsy and incomplete resection.[24,35,120] In high-grade SCAs, most of the published studies showed that aggressive resection did not improve the prognosis.[22,23,29,123] Despite the advancements in neurosurgery in the past decades, there has been no notable improvement in the prognosis of high-grade SCAs. It is also found that the McCormick score in preoperation and postoperation is associated with the OS of SCA.[22,35] Other factors, such as tumor location and tumor length, have exhibited potential prognostic value and should be validated in a large-scale cohort of SCA.

In the past, H3 K27 M mutation was considered the marker of poor prognosis in SCA, perhaps because a substantial part of H3 K27 wild-type SCA were low-grade SCA, such as PA. The situation becomes interesting when analyzing the prognostic significance of H3 K27 M mutation in high-grade SCA. Some studies suggested that H3 K27 M mutant high-grade SCA had longer OS than H3 K27 wild-type high-grade SCA,[124,125] while others indicated that H3 K27 M mutation had no prognostic value in high-grade SCA.[13,26,126] The problem is that H3 K27 wild-type high-grade SCA is not an independent tumor entity, and it may consist of various astrocytoma subtypes (such as HGAP, GBM_MID, and PXA) with different prognosis. The different proportions of the astrocytoma subtypes can influence the overall survival of H3 K27 wild-type high-grade SCA in these published studies. Therefore, it is imperative to consider the variations in prognosis among different subtypes of SCA when examining the prognostic implications of H3 K27 M mutation.

The majority of SCA cases are considered sporadic; however, few cases occur as a result of germline mutation, particularly for

individuals with cancer predisposition syndromes (CPS), such as Lynch syndrome (LS), Li–Fraumeni syndrome, NF1, and NF type 2 (NF2). Except standard treatment, targeting the characteristic molecular changes of the syndrome may present an alternative therapeutic approach for CPS-associated astrocytoma.[127] Specifically, targeting the MEK-ERK/mTOR pathway has shown promise in the treatment of NF1-associated astrocytoma.[128] Immunotherapy presents a promising treatment modality for astrocytomas associated with LS, as these tumors exhibit a propensity for generating novel antigens as a result of their high mutational burden.[129] Nevertheless, the presence of tumor suppressor gene deficiencies in CPS-associated astrocytomas raises concerns regarding the potential for radiotherapy and chemotherapy to exacerbate the risk of secondary malignancies.[130,131]

## Treatment

### Surgery

Surgical resection of tumors is still the main treatment for SCA. Low-grade SCA patients can achieve long-time survival after tumor resection, while high-grade SCA patients benefit low from surgery treatment. Influenced by treatment options in intracranial astrocytoma, neurosurgeons often ignore the use of cordectomy in SCA. Cordectomy, introduced in 1916, is a radical neurosurgical treatment involving the amputation of the spinal cord rostrally to the lesion and closure of the thecal sac.[132] Cordectomy was initially used for spinal cord glioblastoma in 1949, which lead to a survival time of 6.5 months after surgery.[133] The objective of the procedure is to impede the tumor dissemination through CSF and nerve fibers. Cordectomy is particularly considered for patients with severe dysfunction of spinal cord below the planned operative level. It was reported that a spinal cord GBM patient survived 135 months after cordectomy, which suggest the potential favorability in selected instances.[134] Despite theoretical benefits, including prolonged survival without tumor recurrence in some cases, cordectomy is not widely adopted due to the risk of total neurological function loss below the transected level and the absence of clear criteria for patient selection. Based on the publishes cases, tumor location appears crucial for postcordectomy prognosis, with upper thoracic level tumors (T2–T3) showing earlier dissemination than lower thoracic tumors (T5–T12).[135–137] Timmons et al highlighted a better prognosis for thoracic cord GBM compared to cervical ones, which might be attributable to the feasibility of more aggressive treatment in the lower spinal cord.[138] Successful cases typically had tumors in the lower thoracic region, allowing for sufficient margins over 3 spine levels in cordectomy. Moreover, evaluation of tumor metastasis is also important when considering cordectomy in SCA. However, accurate judgment of tumor metastasis in high-grade SCA is still challenging based on current imaging and biopsy techniques. In brief, cordectomy application remains rare, and each case requires careful consideration of patient neurological status, tumor location, and metastasis, as well as the feasibility of achieving an adequate surgical margin.

### Chemotherapy

Currently, the chemotherapy options available for treating astrocytomas include temozolomide (TMZ), nitrosourea agents (such as nimustine, carmustine, lomustine, and ranimustine), and platinum-based agents (cisplatin, carboplatin, and oxaliplatin). Some studies supported the use of drugs initially designed for brain astrocytoma for treating SCA, such as the PCV (procarbazine, lomustine, and vincristine) regimen, which has shown effectiveness in certain cases.[6,139] TMZ treatment has been proved effective in a 2-year multiinstitutional retrospective study for recurrent grade 2 and grade 3 SCA,[140] while it had poor results in H3 K27-altered DMG.[141–143] The effectiveness of single chemotherapy drug for the treatment of astrocytoma is constrained, prompting the exploration of combination therapies to enhance efficacy and mitigate issues such as systemic toxicity and drug resistance. Combining TMZ with other agents can augment its antitumor properties, as evidenced by studies demonstrating prolonged survival in mice treated with a combination of TMZ and bevacizumab.[144] Furthermore, synergistic effects in inhibiting astrocytoma cell growth were observed with combinations of TMZ and doxorubicin, proteasome inhibitors, fumoxetine, and amlotinib.[145] Molecular targeted therapy, such as combining TMZ with small interfering RNA targeting PLK1, also enhanced the antitumor effect of TMZ.[146]

Other strategies include using nanocarriers to effectively deliver chemotherapy drugs to tumor regions and reduce drug resistance. A study demonstrated the efficacy of synthesized carmustine loaded onto metal nanoparticles in inhibiting cell tumor proliferation and reducing survival rates of astrocytoma cells.[147] This nanocomposite can be delivered to the brain without causing damage to normal brain tissue and accumulating in astrocytoma cells. These methods have the potential to overcome drug resistance, mitigate adverse effects, and enhance therapeutic outcomes. However, the role of chemotherapy in SCA is less well defined. Chemotherapy is mainly used for refractory SCA, and its application as a postoperative adjunctive treatment is increasing.

The separate use of chemotherapy is usually not effective for malignant astrocytoma. Combination therapy includes surgery, radiation and chemotherapy, is a better choice for high-grade SCA. Shen et al observed that the average survival was reduced for patients receiving surgery and radiation therapy without chemotherapy, compared to cases receiving surgery, radiation and chemotherapy.[148] Raco et al reported that high-grade SCA had nearly 12 months longer OS for those receiving combination therapy subsequent to surgery, compared to surgery alone.[149]

### Radiation Therapy

The initiation of adjuvant radiation therapy (RT) following resection for SCA typically occurs within 4 to 6 weeks. For high-grade SCA, RT treatment may start earlier. Common RT modalities for SCA include intensity modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3DCRT), and proton therapy (PT). The prescribed

radiation dose for SCA patients is typically 45 to 54 Gy and 1.8 to 2 Gy/fraction.[150] In cases of large tumor volumes, tumors situated in critical anatomical regions or low-grade tumors, the total radiation therapy dose can be appropriately reduced. In the specified dose ranges, the incidence of treatment-induced spinal cord damage is low (1% to 6% at 60 Gy and 0.2% to 0.5% at 50 Gy).[151,152] While IMRT and 3DCRT allow for escalated radiation doses to the target site and reduced irradiation volume, the efficacy of dose escalation remains unverified.

Volumetric modulated arc therapy (VMAT), as a more advanced version of IMRT, enables faster radiation dose delivery while maintaining accuracy in complex brain tumors.[153] The unique advantage of VMAT is that it can deliver complex treatments with coplanar or nonplanar single or multiple arcs, thereby spreading a low dose over a wide area of normal tissue. In comparison to IMRT, VMAT typically uses fewer monitor units (MUs), which can decrease the risk of secondary malignancy.[154] Navarria et al found that VMAT has superior dose conformity compared to 3DCRT and spares the healthy brain at medium to high doses in high-grade astrocytoma.[155] In low-grade astrocytoma, inhomogeneity and conformity did not differ significantly between VMAT and IMRT, while VMAT was related to a significant reduction of Mus.[156] Unfortunately, the wide use of VMAT is currently limited by the high cost of equipment and related software.

Regular monitoring of blood cell counts is recommended during RT treatment. In cases of extended length of the spine, PT may be a preferable alternative. PT has increasingly been utilized for the treatment of CNS tumors in patients since the onset of the 21st century.[157] In contrast to conventional photon-based RT, proton therapy offers the advantage of confining radiation exposure to a more localized area, suggesting that proton therapy enables precise targeting of deep cerebral tumors while mitigating harm to surrounding healthy brain tissue.[158] This approach has the potential to mitigate the adverse effects associated with radiation exposure to healthy tissues, such as cognitive dysfunction, lymphocyte depletion, and sensory and motor impairments. Furthermore, patients may benefit from the ability to receive higher doses of radiation in more precise beams, leading to enhanced treatment efficacy and precision.[159] Research findings indicated that PT, when compared to proton beam radiation therapy (PBRT) at standard doses in GBM, significantly reduced rates of fatigue and the incidence of grade 2 or higher toxicities.[160] No significant difference was shown in the primary endpoint of time to cognitive failure between PT and PBRT, probably because the advantage of PT in reducing damage to normal tissues is overshadowed by the rapid progression of GBM.[160] A prospective cohort study demonstrated that patients diagnosed with low-grade astrocytoma exhibited sustained cognitive, emotional, and performance stability following PT treatment.[161] The 5-year PFS rate and overall survival rate were reported as 40% and 84%, respectively.[162] Regrettably, most patients with astrocytoma continue to be treated with conventional PBRT, and the lack of direct comparative data between PT and PBRT persists as a result of challenges in accruing patients for clinical trials.

As the adjuvant therapy for SCA patient following a surgical biopsy or resection, traditional RT has limited impact on overall survival for SCA.[22,23,122] Craniospinal irradiation (CSI) is a promising therapeutic intervention for individuals afflicted with tumor leptomeningeal metastasis.[163] The efficacy of CSI in improving prognosis outcomes has been demonstrated in various pediatric brain tumors with metastatic capabilities, including intracranial germ cell tumors and medulloblastoma.[164,165] Given that leptomeningeal metastasis is the main cause of poor prognosis in SCA, CSI may be a sensible treatment option for high-grade SCA. There was evidence that metastatic tumor often appeared at first diagnosis of DMG based on some sensitive methods, such as CSF ctDNA, which suggested the early implantation of metastatic tumor rather than gradual dissemination from the primary tumor.[166–168] Knox et al determined the efficacy of CSI treatment at initial stages of DMG, and proposed that CSI should be applied in the time of diagnosis, even without MRI evidence of metastatic tumor.[168] Blood toxic side effect is the critical issue for CSI, and CSI doses for clinical practice should be further explored to balance survival and treatment efficacy in SCA.

## *Targeted Therapy and Immunotherapy*

With the development of tumor molecular biology and molecular immunology in recent years, targeted therapy and immunotherapy have made major breakthroughs in tumor treatment. Targeted therapy is an efficacious treatment modality that focuses on specific molecular targets, thereby facilitating the development of corresponding drugs to impede the proliferation and dissemination of tumors. Bevacizumab is a type of vascular endothelial growth factor (VEGF) inhibitor, which has been approved as a standard of care for recurrent GBM. Although effective for extension of PFS, bevacizumab has failed to improve the OS of newly diagnosed GBM.[169,170] In SCA, Yabuno et al reported 2 spinal cord DMGs had drastic symptom improvement and tumor regression after bevacizumab administration.[171] The presence of the BRAF V600E mutation results in the continuous activation of the MAPK signaling pathway, which is thought to be one of the mechanisms of glioma tumorigenesis. A VE-BASKET study revealed the antitumor effect of vemurafenib (a BRAF V600 inhibitor) in BRAF V600E-mutant glioma, while the effect seemed to be influenced by pathologic subtypes.[172] A phase II clinical trial combining the BRAF inhibitor dalafinib and the MEK inhibitor trametinib showed promising results in treating 45 glioma patients with the BRAF V600E mutation.[173] The trial achieved objective remission in 15 patients and complete remission in 3 patients, with a median PFS of 3.8 months and an OS of 17.6 months. Paxalisib, a PI3 K/AKT/mTOR pathway inhibitor with the ability to traverse the blood–brain barrier, exhibited enhanced effectiveness compared to conventional treatment in patients with GBM without methylated MGMT promoter.[174] Notably, the paxalisib administration as an adjuvant therapy resulted in a PSF of 8.4 months and an OS of 17.7 months. ONC201, a dopamine receptor D2 antagonist, demonstrates encouraging outcomes in the

treatment of H3K27M-mutant DMG. Clinical trials elucidated the effectiveness of ONC201 in enhancing survival rates and eliciting radiographic response by blocking metabolic and epigenetic pathways within these tumors.[175] Moreover, it counteracted the customary decline of H3 K27me3, a pivotal epigenetic marker in DMG, thereby implying its potential as monotherapy to treat H3 K27M-mutant DMG.

The investigation of the epigenetic characteristics in glioma has revealed multiple modifications associated with the advancement of tumors,[176] which include the changes in IDH mutation methylation, histone methylation/acetylation, and DNA methylation. The inhibition of tumor development in glioma can be achieved by targeting the aberrant epigenetic patterns that sustain tumors. Ongoing clinical trials are assessing the efficacy of IDH inhibitors, Enhancer of zeste homolog 2 inhibitor (EZH2i), histone deacetylase inhibitors (HDACi) and DNA methyltransferase inhibitors.[177] Additionally, the impact of epigenetic characteristics on immune responses in glioma cells implies that interventions focusing on epigenetic mechanisms might augment anti-tumor immunity.[178] Inhibitors of mutant IDH enzymes, such as vorasidenib and ivosidenib, have been reported to significantly prolong the PFS and time to next treatment in IDH-mutant astrocytoma.[179,180] Panobinostat is a HDACi which has antitumoral effect in H3 K27M-mutant DMG.[181,182] Neth et al found good tolerance of panobinostat, and prolonged OS of spinal cord DMG after panobinostat treatment compared to that in similar patients reported previously.[183] Recently, Zhang et al utilized epigenetic therapies (HDACi panobinostat and EZH2i tazemetostat) combined with immune checkpoint inhibitors (pembrolizumab and ipilimumab) to treat spinal cord DMG with extensive leptomeningeal metastasis and/or recurrence, and achieved significant clinical efficacy.[184] Their research also suggested that epigenetic therapy can enhance antitumor immunity, transforming DMG from immune "cold" to immune "hot."

Significant advancements in immunotherapy for intracranial astrocytomas, including immune checkpoint inhibitors like nivolumab and pembrolizumab, adoptive T-cell transfer methods like TIL, TCR T-cells, and CAR T-cells, and various vaccine strategies, have shown efficacy. However, translating these therapies to SCA has its unique challenges, including low incidence, limited antigenic targets, the blood–spinal cord barrier, an immunosuppressive tumor microenvironment, and neurotoxic treatment effects.[185] Despite these challenges, there have been promising case reports and clinical trials demonstrating the efficacy of immunotherapies in treating SCA. For instance, nivolumab showed effectiveness in treating spinal cord metastasis from non-small cell lung cancer,[186] and CAR T-cell therapy led to tumor regression in spinal GBM metastases.[187] Additionally, H3.3K27M-specific vaccine responses in DMG, including spinal cord DMG, suggested potential in SCA treatment.[188]

The summary of treatment strategies for SCA is shown in Figure 2.

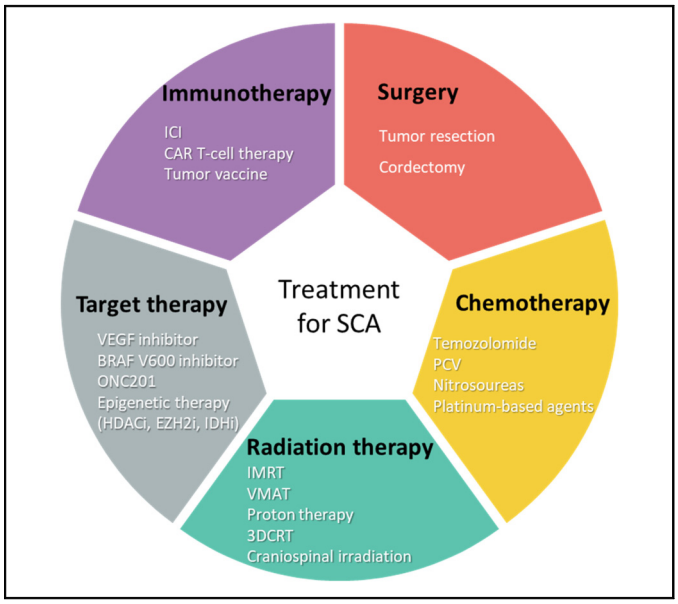


**Figure 2.** Summary of treatment for SCA. SCA: spinal cord astrocytoma; ICI: immune checkpoint inhibitor; PCV: procarbazine, lomustine, and vincristine; HDACi: histone deacetylase inhibitors; EZH2i: enhancer of zeste homolog 2 inhibitor; IDHi: isocitric dehydrogenase inhibitor. IMRT: intensity modulated radiation therapy. VMAT: volumetric modulated arc therapy. 3DCRT: three-dimensional conformal radiation therapy.

## Conclusions

SCAs represent a small fraction of astrocytomas in central nervous system. Though SCAs share some characteristics with their cerebral counterparts, they exhibit unique molecular features, clinical presentations, and treatment responses. The absence of viable molecular markers in SCA caused considerable difficulty in diagnosis and treatment. Nevertheless, continuous research endeavors are currently revealing encouraging novel perspectives regarding the biology of these tumors. The advancement in molecular pathology and DNA methylation analysis promoted the precise diagnosis in this rare group of tumors. The emergence of radiomics and CSF biopsy has important implications for less-invasive diagnosis in SCA.

There is currently a lack of effective treatment methods for high-grade SCAs due to tumor metastasis. Craniospinal irradiation might be a better therapeutic intervention for individuals afflicted with tumor leptomeningeal metastasis compared to local radiation therapy. Surgical resection has been shown to have limited effect in improving high-grade SCA prognosis. In exceptional circumstances, such as patients with no evidence of tumor metastasis, cordectomy is an optional approach to block tumor dissemination and prolong survival for high-grade SCAs. Immunotherapy and target therapy have also demonstrated great potential in improving survival of patients with SCA.

In the future, data sharing and interdisciplinary collaboration should be promoted to accelerate the progress of SCA research. By gathering experts from diverse disciplines, researchers can

synergistically amalgamate their expertise and resources to effectively tackle intricate challenges and foster the development of pioneering solutions.

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