





## Review Articles

## The CGCG response assessment criteria for spinal cord gliomas

Yongzhi Wang<sup>a,b,c,1</sup>, Wenqing Jia<sup>a,c,1</sup>, Ruichao Chai<sup>b,c,1</sup>, Wenhao Xia<sup>a,c,1</sup>,  
Liang Wang<sup>e</sup>, Xiaoguang Qiu<sup>c,f</sup>, Yaou Liu<sup>c,f</sup>, Wei Zhang<sup>a,c</sup>, Chunsheng Kang<sup>g</sup>, Yinyan Wang<sup>a,c</sup>,  
Yanwei Liu<sup>c,f</sup>, Songyuan An<sup>a,c</sup>, Ting Sun<sup>c,f</sup>, Yupeng Zhang<sup>a,c</sup>, Yun Liu<sup>a,c</sup>, Bo Pang<sup>b,c</sup>,  
Nannan Li<sup>c,f</sup>, Zhong Zhang<sup>a,c</sup>, Hao Yan<sup>a,c</sup>, Yaowu Zhang<sup>a,c</sup>, Yuzhou Chang<sup>b,c</sup>, Wenhua Fan<sup>a,c</sup>,  
Long Wang<sup>a,c</sup>, Bing Sun<sup>a,c</sup>, Tao Jiang<sup>a,b,c,d,\*</sup>, on behalf of the Chinese Glioma Cooperative Group (CGCG)

<sup>a</sup> Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, China

<sup>b</sup> Beijing Neurosurgical Institute, Capital Medical University, Beijing, 100070, China

<sup>c</sup> China National Clinical Research Center for Neurological Diseases, Beijing, 100070, China

<sup>d</sup> Center of Brain Tumor, Beijing Institute for Brain Disorders, Beijing, 100070, China

<sup>e</sup> Department of Neurosurgery, Tangdu Hospital, The Fourth Military Medical University, Xi'an, 710038, China

<sup>f</sup> Department of Radiotherapy, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, China

<sup>g</sup> Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin, 300052, China

## ARTICLE INFO

## Keywords:

CGCG  
Spinal cord glioma  
Diffuse midline glioma  
Response assessment  
Central nervous system dissemination

## ABSTRACT

The RANO criteria remain the cornerstone for evaluating adult gliomas; however, they often fail in spinal cord gliomas due to anatomical constraints, molecular heterogeneity, and distinct biological behavior. Firstly, central nervous system (CNS) dissemination is a hallmark feature of spinal cord gliomas and a critical driver of mortality, distinguishing them from their brain counterparts where such spread is rare. Moreover, T1-weighted contrast-enhanced MRI typically reveals non-enhancing primary lesions, a characteristic feature of H3 K27M-mutant diffuse midline gliomas (DMG) that constitute over 40% of spinal cord gliomas, while non-contrast T2-weighted imaging demonstrates sensitivity and reproducibility. Given the narrow and elongated anatomy of the spinal cord and the unique surgical strategy required for spinal cord gliomas, we advocate for volumetric assessment as the primary evaluation method, utilizing millimeters (mm) rather than centimeters (cm) as the measurement unit, and consider all visually identifiable lesions as measurable. Furthermore, the spinal cord exhibits super-functional integration across motor, sensory, and reflex pathways, thereby accentuating the importance of clinical manifestations and neurological functional assessment in accurately and promptly tracking disease progression. Our objective is to develop the specialized response assessment criteria for spinal cord gliomas to serve clinical trials.

## 1. Introduction

Spinal cord gliomas constitute one of the prevalent types of intramedullary spinal cord tumors [1,2], and account for less than 10% of all glioma cases [3–6]. The Fifth edition (2021) of the WHO Classification of Central Nervous System (CNS) Tumors emphasizes the importance of incorporating histological and molecular features in gliomas [2]. Consequently, the traditional distinction high- and low-grade gliomas

may not be entirely appropriate for spinal cord gliomas. Specifically, spinal cord gliomas with H3 K27M mutation should be diagnosed as “diffuse midline gliomas, H3 K27-altered, grade 4,” regardless of histological grading [2]. Given the characteristics of spinal cord gliomas, we propose that differentiation based on H3 K27 alteration status may be more clinically relevant [5,7].

Spinal cord gliomas are typically associated with significant symptom burden and poor prognosis. The advancement in formulating

\* Corresponding author. Beijing Neurosurgical Institute; Beijing Tiantan Hospital, Capital Medical University; China National Clinical Research Center for Neurological Diseases, No. 119 South 4th Ring West Road, Fengtai District, Beijing, 100070, China.

E-mail address: [taojiang1964@163.com](mailto:taojiang1964@163.com) (T. Jiang).

<sup>1</sup> These authors contributed equally to this work.

efficacious therapies has been unacceptably sluggish, and the effectiveness of surgery-based comprehensive treatment for diffuse spinal cord gliomas continues to be suboptimal [8–12]. Consequently, an increasing number of clinical trials have been conducted in recent years to develop novel therapies for patients with spinal cord gliomas. However, at present, there are no standardized criteria for evaluating responses to spinal cord gliomas.

Over the past decade, the RANO working group has published a series of response evaluation criteria for assessing clinical trials of adult gliomas [13–17]. These criteria provide support for evaluating treatment responses in gliomas, offering objective radiological standards for tumor response, including contrast-enhanced and non-enhanced lesions, while also considering the use of corticosteroids and changes in patients' clinical status. Currently, these criteria have been widely accepted and incorporated into most clinical trials for gliomas. However, due to the unique anatomical structure, imaging characteristics, clinical and molecular features of spinal cord gliomas, as well as distinct treatment approaches such as surgery and radiotherapy compared to brain gliomas [7,18–24], the RANO and other gliomas response assessment criteria are not entirely applicable to spinal cord gliomas. Therefore, we define the CGCG Response Assessment for Spinal Cord Gliomas (for short: C-RAS) for response assessment of spinal cord gliomas, excluding ependymomas.

## 2. The limitations of the RANO criteria in evaluating spinal cord gliomas

The RANO criteria for gliomas demonstrate substantial limitations when applied to spinal cord gliomas. Firstly, CNS dissemination is a prevalent feature and manifests in two dissemination patterns: tumor infiltration into the surrounding leptomeningeal space and subarachnoid seeding in CSF flow channels, which is distinct from brain gliomas [5,25–29] (Fig. 1 [28]). Notably, tumor dissemination is significantly associated with poorer survival. The RANO criteria define the appearance of definite leptomeningeal disease as a sign of progressive disease. However, in addition to the appearance of definite leptomeningeal disease, subarachnoid seeding in CSF flow channels is also a characteristic of CNS dissemination.

Another challenge in evaluating patients with spinal cord gliomas using the RANO criteria is the inapplicability of MRI-based measurement methods. On imaging, T1-weighted contrast-enhanced imaging of diffuse spinal cord gliomas frequently reveals non-enhancement of the

lesions [30]. Relying on enhanced lesions is inadequate as a reliable indicator for evaluating tumor progression [31]. Some spinal cord gliomas demonstrate enhancement, yet the majority are of circumscribed spinal gliomas [5,30,31]. Owing to the distinctively narrow anatomical structure of the spinal cord, volume assessment is likely better suited to delineate spinal cord tumor shapes and their changes compared to simplified two-dimensional tumor assessments. Furthermore, there is no functional redundancy in the spinal cord, and even 1 mm of tissue loss produces irreversible deficits. Therefore, neurological deterioration is a critical and direct clinical manifestation of disease progression in spinal cord gliomas [10].

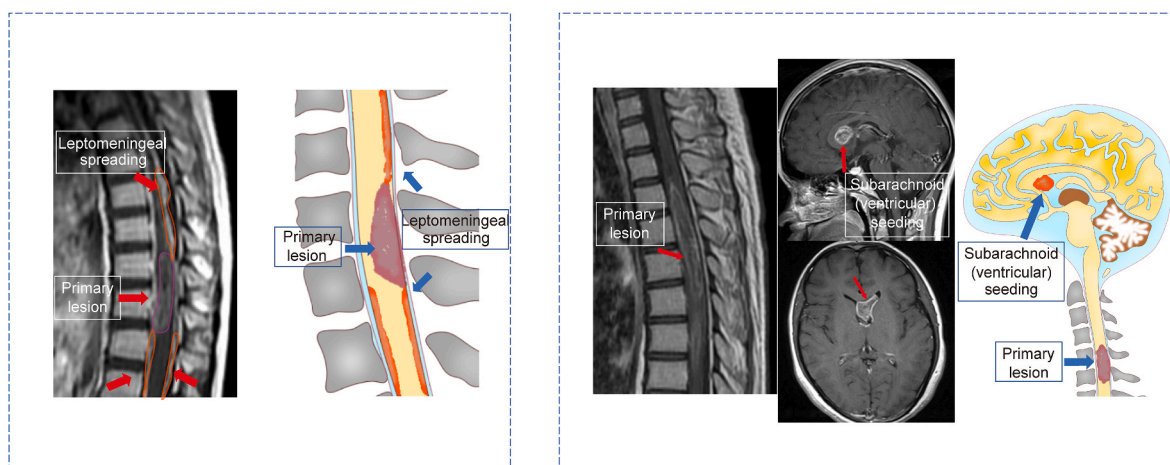
Overall, these limitations encompass the lack of evaluation for the CNS dissemination in spinal cord gliomas, challenges in measuring spinal cord tumors, difficulties in determining tumor progression or remission, and the absence of precise assessment for the clinical manifestations and neurological function of patients with spinal cord gliomas. Therefore, there is an urgent requirement for dedicated response assessment criteria specifically designed for spinal cord gliomas. The following sections outline these issues and propose response criteria.

## 3. Dissemination tendency

Over the 5-year follow-up period, the dissemination rate within the CNS for all spinal cord gliomas reached as high as 85.0%, and even 95.2% in H3K27-altered gliomas [28]. However, in stark contrast to brain gliomas, which exhibit a dissemination rate consistently below 5% [27]. Following dissemination, H3 K27-wildtype patients had a median post-dissemination survival of 13.4 months, and only 8.8 months in H3 K27-altered diffuse gliomas [28]. The CNS dissemination is a prevalent feature and a key determinant of lethality in patients with spinal cord gliomas [5,28]. Therefore, the response assessment criteria for spinal cord gliomas will regard the CNS dissemination as an indicator of tumor progression.

## 4. Distinctive surgical strategy

For brain gliomas, supramaximal resection (SMR), which deliberately exceeds the enhanced boundaries, has gained significant momentum in recent years [32,33]. However, in spinal cord gliomas, the super-functional integration of the spinal cord in motor, sensory, and reflex processing renders complete resection challenging and less amenable to SMR [34]. The relationship between the extent of resection



**Fig. 1.** Different dissemination patterns in patients with spinal cord gliomas diagnosed with dissemination (left) Leptomeningeal spreading (red outline). A tumor infiltrate locus surrounding the leptomeningeal space and enhancing leptomeningeal area beyond the primary tumor locus was found on gadolinium-enhanced T1-weighted MRI sequences. (right) Subarachnoid seeding. The tumor metastasized in CSF flow channels, and discontinuous newly enhancing subarachnoid areas of tumor were found along the spinal canal. Figure Reprinted from Ref. [28]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and prognosis of diffuse spinal cord gliomas remained a topic of debate [8,9,11,19,35–39]. However, the choice of surgical strategy has a great impact on the long-term survival and quality of life of patients with spinal cord glioma because of the super-functional integration of the spinal cord in the processing of motor, sensory and reflex. Therefore, the primary goal of surgical resection for spinal cord gliomas is to maximize tumor removal while minimizing damage to spinal cord function [40]. This necessitates intraoperative neurophysiological monitoring (INM), encompassing somatosensory evoked potentials (SEP), muscle motor evoked potentials (MEP) and D-wave, to provide assistance during spinal cord tumor surgery [41–43].

In particular, the pia mater exerts a restrictive influence on the spinal cord and significantly contributes to intraparenchymal pressure [44]. Thus, the extensive opening of the pia mater is the key to spinal cord decompression. However, post-operative spinal cord deformation following pial opening complicates the measurement of gliomas. In summary, the distinctive surgical strategy for spinal cord glioma renders it challenging to measure the tumor size, which diverges from the measurement methodologies employed for brain tumors.

## 5. New MRI-based measurements for spinal cord gliomas

The standardized spinal cord MRI protocol must include at least the following three sequences: sagittal T1-weighted sequences, T2-weighted sequences, and contrast-enhanced T1-weighted sequences. For patients with primary lesions, T2-weighted images will be used to measure the size of the lesions. This phenomenon can be attributed to the fact that non-enhanced T2-weighted imaging demonstrates sensitivity and reproducibility in the assessment of diffuse spinal cord glioma, whereas contrast-enhanced T1-weighted imaging does not [45,46]. For patients with disseminated lesions, enhanced scanning should be used to identify disseminated lesions, and whole brain and spinal cord MRI will be performed. This occurs because CNS dissemination is generally recognized as involving the leptomeningeal area beyond the primary tumor site (either continuously or discontinuously) or as newly enhancing subarachnoid areas along the spinal cord [28].

We propose volumetric assessment as the preferred method rather than RANO 2.0's two-dimensional (2D) measurements for evaluating spinal cord tumors. This recommendation stems from the characteristic elongated volume patterns of these tumors, which render the product of maximal cross-sectional diameters potentially misleading for tracking disease progression [46]. To ensure accuracy, 1 mm isotropic 3D imaging is recommended. For primary lesions, examination should encompass all affected spinal cord segments and those with high clinical

suspicion of involvement. In cases where tumor dissemination is highly suspected, whole-brain and spinal cord enhanced MRI is warranted. If circumstances permit, it is reasonable to initiate brain MRI from baseline MRI. Moreover, unlike brain gliomas, spinal cord gliomas cannot be assessed by 1 cm minimum dimension criteria because of the spinal cord's slender anatomy (~1.0–1.4 cm transverse diameter) and the tumors' ill-defined borders. Therefore, millimeter-scale evaluation of all visible lesions is more rational (Fig. 2).

## 6. Clinical manifestations and neurological function assessment

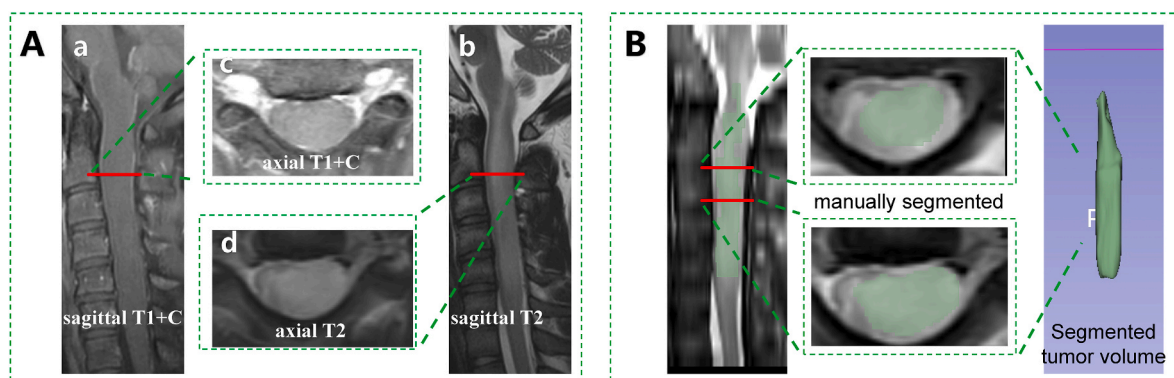
Clinical and neurological deterioration is a critical component of response assessment, particularly for identifying disease progression. While the Karnofsky Performance Status (KPS) serves as a clinical deterioration assessment tool for brain gliomas, it may be inadequate for evaluating clinical manifestations or neurological functional decline in spinal cord gliomas. This limitation stems from the spinal cord's critical integrative role in motor, sensory, and reflex processing, underscoring the need for precise assessment of clinical and neurological status. The modified McCormick Scale (MMS) is currently the recommended assessment instrument. MMS scores correlate strongly with prognosis, where higher grades are associated with reduced survival [10]. Alterations in MMS grades signify neurological deterioration.

The American Spinal Injury Association (ASIA) scale is an internationally standardized tool for evaluating spinal cord injury severity and functional prognosis [47]. It systematically defines the lowest neurologically intact level through bilateral sensory and motor testing and classifies injury completeness. In patients with spinal cord glioma, the ASIA scale offers a structured, clinically granular framework for serial neurological assessment, capturing deficits that may be inadequately reflected by other scoring systems. Although this tool is being used increasingly in clinical trials to assess response, its formal incorporation into the C-RAS will require further validation studies.

## 7. Definitions

### 7.1. Measurable disease and target lesions

Measurable lesions are defined as all lesions visible on MRI scans. All measurable lesions should be considered target lesions, and the sum of their three-dimensional volumes is regarded as the target lesion volume.



**Fig. 2.** Radiographic Evaluation Utilizing T2-Weighted Imaging and Volumetric Measurements with Volumetric Analysis Software (A) MRI imaging. a) sagittal contrast-enhanced T1-weighted sequences; b) sagittal T2-weighted sequences; c) axial contrast-enhanced T1-weighted sequences; d) axial T2-weighted sequences. a) and c): T1-weighted contrast-enhanced images reveal non-enhancement of the lesions; b) and d): T2-weighted images can distinguish abnormal tumor signals. (B) Volumetric Measurements Conducted Using 3D slicer Software. Tumor margins were manually segmented using 3D slicer Software by delineating the tumor ROI region on axial T2-weighted images. (Red line: The position of the axial T2-weighted images corresponding to the sagittal T2-weighted images). The segmented tumor volume was automatically obtained from the outlined tumor. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

## 7.2. Baseline MRI and follow-up schedule

For postoperative evaluation, immediate MRI is the gold standard for complication detection and resection assessment. Baseline MRI should ideally be obtained within 48 h postoperatively, consistent with brain glioma protocols. When immediate postoperative MRI is not feasible due to patient factors or clinical stability, postradiotherapy MRI (21–35 days post-treatment) serves as the baseline for newly diagnosed spinal cord gliomas. In non-radiotherapy patients with circumscribed tumors, baseline MRI at 3 months postoperatively is recommended if 48-h imaging is unavailable. Follow-up intervals should be predefined (e.g., every 2 months for grade 4 SCG). Significant disease progression before baseline MRI warrants study withdrawal.

## 7.3. Definitions of radiological response and progression

Radiological response is determined by comparing tumor measurements from baseline scans. Partial response (PR) requires  $\geq 65\%$  reduction in the 3D volume of measurable target lesions from baseline, maintained for  $\geq 4$  weeks with stable/improved clinical status. Progressive disease (PD) is defined as  $\geq 40\%$  increase in 3D volume of measurable lesions compared to baseline or post-treatment nadir, or appearance of new disseminated lesions. For patients with CNS dissemination, contrast-enhanced imaging should be used for identification. If imaging changes are ambiguous, continued treatment with close surveillance (e.g., every 4 weeks) is permitted. Confirmed progression retroactively assigns the date of progression to the initial measurement time (Table 1).

**Table 1**  
Response Criteria for Spinal cord gliomas.

CR
<p>Complete remission (CR) requires all the following criteria compared with the baseline scans</p> <ol style="list-style-type: none"> <li>(1) Complete disappearance of all target lesion(s) on T2 imaging, sustained for at least 4 weeks</li> <li>(2) No new lesions or disseminated lesions</li> <li>(3) Patients must be off corticosteroids or only on physiologic replacement doses</li> <li>(4) Clinical manifestations and neurological function are stable or improved, with stable or improved McCormick grades</li> </ol> <p>Before completing the confirmatory scan after 4 weeks to verify the durability of the treatment response, the treatment response evaluation can only be determined as SD. Patients without target lesions at baseline scans cannot be evaluated as CR; the best possible evaluation is SD.</p>
<p><b>PR</b></p> <p>Partial remission (PR) requires all the following criteria compared with the baseline scans</p> <ol style="list-style-type: none"> <li>(1) <math>\geq 65\%</math> decrease in total volume of the target lesion(s) on T2 imaging, sustained for at least 4 weeks</li> <li>(2) No new lesions or disseminated lesions</li> <li>(3) Patient must be on a corticosteroid dose that is not greater than the dose at the time of baseline scan</li> <li>(4) Clinical manifestations and neurological function are stable or improved, with stable or improved McCormick grades</li> </ol> <p>Before completing the confirmatory scan after 4 weeks to verify the durability of the treatment response, the treatment response evaluation can only be determined as SD. Patients without target lesions at baseline scans cannot be evaluated as PR; the best possible evaluation is SD.</p>
<p><b>SD</b></p> <p>Stable disease (SD) requires all the following criteria compared with the baseline scans (only if the changes do not qualify CR, PR, or PD criteria)</p> <ol style="list-style-type: none"> <li>(1) No new lesions or disseminated lesions.</li> <li>(2) Corticosteroid usage is stable at doses no higher than those at baseline scans. If a patient requires increased corticosteroid doses due to worsening clinical symptoms or signs without imaging-confirmed disease progression, but subsequent MRI confirms disease progression, the SD timepoint should be the last imaging scan confirming stable disease while corticosteroid doses matched the baseline phase.</li> <li>(3) Clinical manifestations and neurological function are stable or improved, with stable or improved McCormick grades</li> </ol>
<p><b>PD</b></p> <p>Progressive disease (PD) is defined by any of the following compared with baseline or best response after initiation of therapy if there has been a reduction from baseline</p> <ol style="list-style-type: none"> <li>(1) <math>\geq 40\%</math> increase in total volume of the T2 imaging target lesion(s) on stable or increasing doses of corticosteroids not attributable to radiation effect, edema, or comorbid events</li> <li>(2) Appearance of new lesions or disseminated lesions.</li> <li>(3) Clear clinical manifestations or neurological function deterioration, as indicated by worsening McCormick grades, excluding reductions in corticosteroid doses or non-tumor-related causes.</li> <li>(4) Failure to return for follow-up due to death or clinical deterioration should also be considered progression unless confirmed to be due to unrelated conditions.</li> </ol> <p>Isolated increases in corticosteroid doses without tumor-related clinical deterioration are not sufficient to determine PD. For patients with stable imaging findings, corticosteroid dose increases due to non-tumor-related clinical deterioration are insufficient to classify as SD or PD; close observation is required. If corticosteroid doses can be reduced to baseline levels, the patient is classified as SD; if tumor-related clinical deterioration becomes evident, the patient is classified as PD. The PD date should be defined as the timepoint of the first corticosteroid dose increase.</p>

## 8. Knowledge gaps and further directions

We propose a standardized response evaluation framework for spinal cord gliomas (C-RAS), designed for clinical and research applications. While these criteria adapt established glioma standards through expert consensus, they require validation and refinement. Specifically, future research ought to prioritize the evaluation of the assessment efficacy of tumor growth via comparative analysis of diverse measurement methods, encompassing 2D, 3D, and volumetric measurements. Considering that the growth pattern of spinal cord gliomas does not conform to spherical mathematical models, the 40% threshold founded on the three-dimensional spherical volume hypothesis might not be applicable. It is imperative to validate the classification results of different measurement methods with varying thresholds, as well as to assess the accuracy of disease progression detection and the reliability of clinical outcome prediction among these methods. Confirming whether the ASIA scale is associated with high inter-observer consistency is a prerequisite for its use as a meaningful and reproducible measure of neurological function. The specific plan includes incorporating the ASIA scale in clinical trials alongside the C-RAS criteria, with a prospective evaluation of its efficacy and utility relative to radiological and survival. Prospective studies are critical for framework validation. Additionally, emerging therapies (e.g., immunotherapy) may necessitate updates to response criteria.

Advanced imaging techniques, such as perfusion imaging, diffusion imaging, magnetic resonance spectroscopy, and amino acid PET, show promise in predicting tumor response [48–50]. Artificial intelligence (AI) offers potential for automating lesion detection, tumor segmentation, and response assessment [51]. These techniques are undergoing validation and may be integrated into future C-RAS, which will incorporate novel developments, advanced imaging, and validated endpoints.

Spinal cord gliomas pose a critical unmet clinical challenge, with clinical trial activity accelerating. The CGCG Response Assessment Criteria for Spinal Cord Gliomas (C-RAS) aims to enhance next-generation clinical trial design and improve patient outcomes.

#### CRedit authorship contribution statement

**Yongzhi Wang:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Conceptualization. **Wenqing Jia:** Writing – review & editing, Funding acquisition, Conceptualization. **Ruichao Chai:** Writing – review & editing, Funding acquisition, Conceptualization. **Wenhao Xia:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation. **Liang Wang:** Resources. **Xiaoguang Qiu:** Resources. **Yaou Liu:** Resources. **Wei Zhang:** Resources. **Chunsheng Kang:** Resources. **Yinyan Wang:** Resources. **Yanwei Liu:** Resources. **Songyuan An:** Resources. **Ting Sun:** Resources. **Yupeng Zhang:** Resources. **Yun Liu:** Resources. **Bo Pang:** Resources. **Nannan Li:** Resources. **Zhong Zhang:** Resources. **Hao Yan:** Resources. **Yaowu Zhang:** Resources. **Yuzhou Chang:** Resources. **Wenhua Fan:** Resources. **Long Wang:** Resources. **Bing Sun:** Resources. **Tao Jiang:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

#### Funding

This work was supported by grants from the National Key Research and Development Program of China (2019YFE0108100), the National Natural Science Foundation of China (82573703, 82272867), the Non-communicable Chronic Diseases-National Science and Technology Major Project (2024ZD0525300), Beijing Key Laboratory of Drug Innovation for Neuro-Oncology (Z241100009024044), Beijing Municipal Health Commission (No. BRWEP2024W032040203), the Natural Science Foundation of Beijing, China (J230003), and Beijing Neurosurgical Institute (11000025T000003319495).

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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