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Review Articles

The CGCG response assessment criteria for spinal cord gliomas

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

[a] Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, China
[b] Beijing Neurosurgical Institute, Capital Medical University, Beijing, 100070, China
[c] China National Clinical Research Center for Neurological Diseases, Beijing, 100070, China
[d] Center of Brain Tumor, Beijing Institute for Brain Disorders, Beijing, 100070, China
[e] Department of Neurosurgery, Tangdu Hospital, The Fourth Military Medical University, Xi'an, 710038, China
[f] Department of Radiotherapy, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, China
[g] Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin, 300052, China

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Highlights

- TheC-ARScriteria regard CNS dissemination as an indicator of progressive disease.
- Volumetric assessment should be performed on T2-weighted images.
- A millimeter-scale assessment of all visible lesions is more appropriate.
- Clinical and neurological deterioration is a critical component of response assessment.

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.

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], [4], [5], [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 efficacious therapies has been unacceptably sluggish, and the effectiveness of surgery-based comprehensive treatment for diffuse spinal cord gliomas continues to be suboptimal [[8], [9], [10], [11], [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], [14], [15], [16], [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], [19], [20], [21], [22], [23], [24]], the RANO and other gliomas response assessment criteria are not entirely applicable to spinal cord gliomas. Therefore, we define the **C**GCG **R**esponse **A**ssessment for **S**pinal Cord Gliomas (for short: C-RAS) for response assessment of spinal cord gliomas, excluding ependymomas.

Section snippets

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], [26], [27], [28], [29]] (Fig. 1 [28]). Notably, tumor dissemination is significantly associated with poorer survival. The RANO criteria define the …

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 …

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 and prognosis of diffuse spinal cord gliomas remained a topic of debate [8,9,11,19,[35], [36], …

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 …

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 …

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. …

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 …

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 …

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** …

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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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