Journal Pre-proof

Updated Clinical practice guidelines for the management of adult diffuse gliomas

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PII: S0304-3835(25)00757-8

DOI: https://doi.org/10.1016/j.canlet.2025.218185

Reference: CAN 218185

To appear in: *Cancer Letters*

Received Date: 3 September 2025

Revised Date: 19 November 2025

Accepted Date: 27 November 2025

Please cite this article as: T. Jiang, D.-H. Nam, Z. Ram, W.-s. Poo, J. Wang, D. Boldbaatar, Y. Mao, W. Ma, Q. Mao, Y. You, C. Jiang, X. Yang, V. Tergaonkar, W. Zhang, Z. Wang, C. Kang, X. Qiu, S. Li, L. Chen, X. Li, Z. Liu, H. Bai, Y. Yao, S. Li, A. Wu, Y. Mou, K. Sai, G. Li, X. Wei, X. Liu, Z. Zhang, Y. Dai, S. Lv, L. Wang, Z. Lin, J. Dong, G. Xu, X. Ma, R. Yu, D. Kang, Y. Liu, G. Li, S. Zhang, Y. Qu, Y. Wang, C. Zhang, B. Chen, G. You, Y. Wang, Y. Wang, Z. Bao, X. Fan, X. Liu, Z. Zhao, Y. Li, Z. Wang, G. Li, S. Fang, Y. Liu, X. Shan, Y. Liu, R. Chai, H. Hu, J. Chen, W. Yan, J. Cai, Y. Wang, on behalf of the Chinese Glioma Cooperative Group (CGCG), Society for Neuro-Oncology of China (SNOChina), Chinese Brain Cancer Association (CBCA), Chinese Glioma Genome Atlas (CGGA), Asian Glioma

Genome Atlas (AGGA) network, Updated Clinical practice guidelines for the management of adult diffuse gliomas, *Cancer Letters*, https://doi.org/10.1016/j.canlet.2025.218185.

Updated Clinical practice guidelines for the management of adult diffuse gliomas

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Keywords: Molecular diagnostics, Surgery, Chemoradiation, Immune therapy, Target therapy

Abstract

It has been five years since the last version of the clinical practice guidelines for the management of adult diffuse gliomas was published by the Asian Glioma Genome Atlas (AGGA). Significant progress and revisions have occurred in the diagnosis and treatment of adult diffuse gliomas in recent years. In response to these updates, the joint guideline committee of the Chinese Glioma Cooperative Group (CGCG), the Society for Neuro-Oncology of China (SNO-China), and the Chinese Brain Cancer Association (CBCA) has revised the clinical practice guidelines. This updated guideline emphasizes molecular and pathological diagnostics, as well as the primary treatment modalities of surgery, radiotherapy, chemotherapy, and targeted therapy. Additionally, we have incorporated findings from recent clinical trials of new therapies to align with cutting-edge treatment strategies. This guideline is designed to serve as a practical resource for all professionals involved in managing adult diffuse glioma patients, while also providing valuable information for insurance companies and other institutions responsible for regulating cancer care costs in China and beyond.

1. Introduction

According to the 2021 World Health Organization (WHO) classification of tumors of the central nervous system (CNS), diffuse gliomas have been reclassified into two major types, adult-type diffuse glioma and pediatric-type diffuse glioma based on combined molecular and histopathological information. In the new classification scheme, common adult-type diffuse gliomas are simplified into three subtypes: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype. Pediatric-type diffuse gliomas are further grouped into high-grade and low-grade gliomas mainly based on molecular features.

To follow these new updates, the joint guideline committee of Chinese Glioma Cooperative Group (CGCG), Society for Neuro-Oncology of China (SNO-China) and Chinese Brain Cancer Association (CBCA) update the clinical practice guideline for gliomas. This guideline focuses on molecular and pathological diagnostics, and the main treatment modalities of surgery, radiotherapy, chemotherapy, and targeted therapy. In this guideline, we also integrated the results of some clinical trials of new therapies, keeping in pace with the frontier treatment strategies. The guideline should serve as an application for all professionals involved in the management of patients with adult diffuse glioma and a source of knowledge for insurance companies and other institutions involved in the cost regulation of cancer care in China and other countries.

2. Epidemiology and survival

According to the latest global statistics, the incidence rate of central nervous system (CNS) tumors was approximately 24.83 per 100,000 population from 2016 to 2020[1]. China is one of the three countries with the highest incidence and mortality of CNS tumors[2]. According to the investigation and statistics of the Chinese National Cancer Center, in 2022, the estimated new cases of malignant brain tumors in China were about 87,500, and the estimated deaths were about 56,600, with age-standardized incidence and mortality rates of 4.21 per 100,000 and 2.52 per 100,000, respectively[3]. The age-standardized incidence rate of brain tumors in China is lower than that in the

United States, Europe, and North America[4]. Glioma is the most common histological type of primary malignant CNS tumors, originating from astrocytes, oligodendrocytes, and ependymal cells, with an annual incidence of approximately 5-6 cases per 100,000 population worldwide[1, 5]. The incidence rate in males is approximately 1.5-1.6 times higher than that in females.

Patient age, KPS (Karnofsky Performance Scale) status, degree of tumor malignancy, extent of resection are well established prognostic factors for diffuse gliomas. The median overall survival (OS) times were 78.1, 37.6 and 14.4 months for CNS WHO grade 2, grade 3 and grade 4, respectively[6]. Moreover, molecular genetic features, such as isocitrate dehydrogenase 1 (IDH1) or IDH2 mutation, chromosomal 1p/19q codeletion and MGMT promoter methylation, confer a much favorable prognosis.

3. Imaging diagnosis

Routine neuroimaging for glioma primarily includes CT and MRI. These modalities provide clear and accurate visualization of brain anatomy and tumor morphology, including features such as lesion location, size, peritumoral edema, intralesional tissue homogeneity, mass effect, the degree of blood-brain barrier disruption, and other associated findings. MRI offers superior imaging detail compared to CT. CT primarily demonstrates density differences between glioma tissue and normal brain parenchyma, with characteristic features such as calcification, hemorrhage, and cystic changes. Conventional MRI reveals signal intensity variations in hemorrhage, necrosis, and edematous tissue, along with mass effect, while also delineating tumor location and invasion extent. Additionally, multimodal MRI can assess the tumor's functional and metabolic status, as well as its spatial relationship with surrounding functional fiber tracts[7, 8].

Conventional MRI scanning mainly acquires T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences, and contrast-enhanced scans. Gliomas can occur in various brain regions, with indistinct boundaries, presenting as long T1 and T2 signal abnormalities, often with heterogeneous signal, and varying

degrees of surrounding edema. Due to different degrees of blood-brain barrier disruption by the tumor, the contrast enhancement pattern varies. Low-grade gliomas typically show long T1 and T2 signal abnormalities on conventional MRI, with indistinct boundaries and mild surrounding edema, mild mass effect, such as slight compression of adjacent ventricles and minimal midline shift, with normal cerebrospinal fluid spaces; hemorrhage, necrosis, and cystic changes are rarely seen within the lesion, and only a small proportion show mild abnormal enhancement after contrast administration. High-grade gliomas show clearly heterogeneous MRI signals, with mixed T1 and T2 signal abnormalities and significant surrounding infiltrative edema; obvious mass effect, with compression and deformation of adjacent ventricles and midline shift, as well as compression of sulci and cisterns; and significant ring-like or nodular abnormal enhancement on contrast-enhanced scans.

DWI hyperintense regions indicate high cell density, representing high-grade lesions; PWI hyperperfusion regions suggest increased blood volume, often indicating high-grade lesions; and elevated choline (Cho) and Cho/N-acetyl-aspartate (NAA) ratios on MRS correlate positively with tumor grade.

Diffusion tensor imaging (DTI) and blood oxygenation level dependent (BOLD) fMRI sequences can clearly delineate the relationship between the tumor and important functional cortices and subcortical fiber tracts, providing evidence to support brain function protection during surgical resection. Multimodal MRI is an important complement to morphological imaging diagnosis, with significant value in differential diagnosis of gliomas, defining surgical boundaries, prognosis assessment, treatment response monitoring, and detection of recurrence.

4. Recommended molecular biomarkers

The diagnosis of gliomas has historically been based on histopathological features, including microscopic resemblance to putative cells of origin and presumed differentiation levels. However, advances in understanding the genetic underpinnings of tumorigenesis have revealed that molecular characteristics may be crucial for precise glioma classification. Detailed information about these molecular markers and their clinical relevance are presented in Table 1.

Table 1. Recommended molecular markers

Markers	Variation	Detection methods	Clinical significance
IDH	IDH1 Mutation (R132)	IHC, Sanger sequencing, pyrosequencing, NGS	**Diagnosis**: Key markers for the classification of adult-type diffuse gliomas. [9] **Prognosis**: Indicates a relatively favorable prognosis; often used as an important stratification factor in clinical trials; closely associated with MGMT promoter methylation; relatively sensitive to radiotherapy and alkylating agents; therapeutic target. [10-12]
	IDH2 Mutation (R172)	Sanger sequencing, pyrosequencing, NGS	
Chr 1p/19q	Co-deletion	FISH, PCR, array or NGS-based methods	**Diagnosis:** Key markers for the diagnosis of *oligodendroglioma, IDH-mutant and 1p/19q-codeleted*. [13, 14] **Prognosis:** Indicates a relatively favorable prognosis; relatively sensitive to radiotherapy and alkylating agents. [15, 16]
TP53	Mutation	IHC, Sanger sequencing, NGS	**Diagnosis:** Diagnostic marker for astrocytic glioma; Used to distinguish low-cellularity diffuse astrocytic gliomas from reactive gliosis. Also observed in glioblastoma (especially giant cell glioblastoma) and some other pediatric diffuse glioma. [17]
ATRX	Mutation	IHC, Sanger sequencing, NGS	**Diagnosis:** Loss of nuclear ATRX expression can be used to diagnose IDH-mutant astrocytic gliomas, without the need for additional 1p/19q codeletion testing. This ATRX loss is also a characteristic finding in other glioma subtypes, including diffuse midline gliomas, diffuse hemispheric gliomas, high-grade astrocytomas with piloid features, and pleomorphic xanthoastrocytomas. [18, 19]

CDKN2A/B	Homozygous deletion	NGS	**Diagnosis:** Grading molecular marker for "astrocytoma, IDH-mutant" and "oligodendroglioma, IDH-mutant and 1p/19q-codeleted". Can be observed in pleomorphic xanthoastrocytoma, high-grade astrocytoma with piloid features, and glioblastoma. To diagnose "diffuse low-grade glioma, MAPK pathway-altered", CDKN2A/B homozygous deletion must be ruled out. [20-22]
TERT	Promoter mutation (C228T/C250T)	NGS	**Diagnosis:** In the absence of histological necrosis and microvascular proliferation, it is one of the diagnostic molecular markers for "glioblastoma, IDH-wildtype". Can be observed in oligodendroglioma, glioblastoma, pleomorphic xanthoastrocytoma, and diffuse pediatric high-grade gliomas, H3-wildtype and IDH-wildtype. [23-25]
chr7/10	+7/-10	NGS	**Diagnosis**: In the absence of histological necrosis and microvascular proliferation, it is one of the diagnostic molecular markers for "glioblastoma, IDH-wildtype" **Prognosis**: Indicates worse prognosis in IDH wild-type diffuse glioma[26, 27].
PTEN	Mutation/ Deletion	NGS	**Prognosis:** Indicates worse prognosis in IDH wild-type diffuse glioma. [28, 29]
EGFR	Mutation/Amplification	NGS	**Diagnosis:** In the absence of histological necrosis and microvascular proliferation, EGFR amplification is one of the diagnostic molecular markers for "glioblastoma, IDH-wildtype".[28, 30]
	EGFRvIII mutation	NGS	**Prognosis:** EGFRvIII occurs in approximately 20–30% of primary GBM and is a potential therapeutic target. [31-33]

MGMT	Promoter methylation	pyrosequencing, array-based methods	**Prognosis:** MGMT promoter methylation is associated with a favorable prognosis in patients with glioblastoma. Patients with MGMT promoter-methylated glioblastomas tend to have a better response to temozolomide chemotherapy. MGMT promoter methylation is associated with IDH mutations and the G-CIMP molecular subtype in glioblastoma. [34-36]
MET	Gene fusion (PTPRZ1::MET), mutation (METex14), amplification, over-expression	NGS	**Diagnosis:** MET alteration is one of the diagnostic molecular markers for "infant-type hemispheric glioma". It can also be seen in high-grade "astrocytoma, IDH-mutant".[37, 38] **Prognosis:** In IDH-mutant astrocytomas, MET gene fusion is associated with a poorer prognosis. MET inhibitors (such as Vebreltinib) has showed promising clinical practice.[39]

5. Integrated pathological diagnosis

Gliomas are a group of neuroepithelial tumors characterized by glial cell phenotypes. With the development of pathology and the advancement of pathological detection techniques, especially the improvement of second-generation sequencing and genomic technologies such as DNA methylation profiling, the genetic background and pathogenic mechanisms of gliomas are becoming increasingly clear. More and more molecular biomarkers have been proven to play important roles in the classification, subtyping, grading, prognosis, and treatment of gliomas. The 5th edition of the WHO Classification of Tumors of the Central Nervous System published in 2021 integrated the histological features and molecular phenotypes of tumors, and proposed new tumor classification criteria, emphasizing the application of molecular diagnostics in the classification of central nervous system tumors. This classification system is currently an important basis for the diagnosis and grading of cerebral gliomas. Integrated diagnosis scheme for diffuse glioma is summarized in **Figure 1**.

The new classification system for the first time divides diffuse gliomas into two major categories: adult-type and pediatric-type diffuse gliomas. It is important to note that this diagnostic classification is not based solely on the age of tumor onset, but rather on the predominant molecular alterations and the clinical characteristics of these tumors in different age groups. Adult-type diffuse gliomas are the main type of adult gliomas, but they can also occur in children, while pediatric-type diffuse gliomas primarily occur in children, but can also be seen in adults, especially in young adults.

Isocitrate dehydrogenase (IDH) mutation is an important diagnostic biomarker for adult-type diffuse gliomas. Diffuse gliomas with IDH mutation, if accompanied by 1p/19q co-deletion, can be diagnosed as *oligodendroglioma, IDH-mutant and 1p/19q-codeleted*; if without 1p/19q co-deletion but with ATRX mutation, they can be diagnosed as *astrocytoma, IDH-mutant*. CDKN2A/B homozygous deletion is a grading indicator for these tumors. For *astrocytoma, IDH-mutant*, either necrosis, microvascular proliferation or CDKN2A/2B would be adequate to diagnose as *astrocytoma, IDH-mutant, grade 4*.

For *glioblastoma, IDH-wildtype*, except for histopathological features such as necrosis and microvascular proliferation, genetic alteration, such as EGFR amplification, mutation at TERT promoter area, and chromosome 7 gain & 10 loss, are also encompassed as the key diagnostic marker.

For *glioblastoma, IDH-wildtype*, in addition to histopathological features (e.g., necrosis and microvascular proliferation), key diagnostic markers also include key genetic alterations such as EGFR amplification, TERT promoter mutations, and combined chromosome 7 gain with chromosome 10 loss.

For the pediatric-type diffuse gliomas, the classification scheme is a little bit complicated than that of adult-type diffuse gliomas, because more genetic/epigenetic alterations are involved. In principle, pediatric-type diffuse gliomas are classified into two major categories, including pediatric-type low grade glioma and pediatric-type high grade glioma based on histological features.

Diffuse gliomas that are IDH-wildtype and histone H3-wildtype, if presenting with necrosis or microvascular proliferation, or having one of the three molecular alterations (EGFR amplification, +7/-10, TERT promoter mutation), can be diagnosed as *glioblastoma, IDH-wildtype*.

Pediatric-type diffuse low-grade gliomas are mainly characterized by MYB/MYBL1 alterations and mitogen-activated protein kinase (MAPK) pathway alterations. MYB/MYBL1 gene structural variations and gene fusions are important molecular markers for diagnosing *diffuse astrocytoma, MYB or MYBL1-altered* and *angiocentric glioma*. MAPK pathway-related gene alterations, including BRAF, FGFR1, etc., are important diagnostic indicators for *diffuse low-grade glioma, MAPK pathway-altered* and *pediatric-type high-grade neuroepithelial tumor with MAPK alteration*.

Pediatric-type diffuse high-grade gliomas are mainly characterized by histone H3 mutations, including *diffuse midline glioma, H3 K27-mutant* with H3 K27 mutation and loss of H3 K27me3 nuclear expression in the midline, and *diffuse hemispheric glioma, H3 G34-mutant* with H3 G34 R/V mutation in the hemispheres.

For diffuse gliomas lacking IDH and H3 mutations, commonly occurring in infants,

children, and young adults, with high-grade histological features, they can be diagnosed as *diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype* or *infant-type hemispheric glioma* based on their molecular alterations and methylation profiles.

Glioma pathology reports should follow a standardized, integrated, and tiered format in accordance with the current classification system. The content should include: (1) Integrated diagnosis; (2) Histopathological classification; (3) CNS WHO grade; (4) Molecular information, with details on specimen type, detection method, and variant type. Additionally, the report should document the patient's clinical background, tumor location, and any relevant diagnostic notes or interpretive comments.

In summary, the standardized glioma pathology report should provide a comprehensive diagnosis by integrating histopathological classification, WHO grading, and detailed molecular profiling, along with relevant clinical information. This facilitates consistent and accurate diagnosis and classification of gliomas according to the updated guidelines.

6. Disease management

6.1 General recommendations

The management of gliomas requires a multidisciplinary strategy integrating surgical resection, radiotherapy, systemic therapies, and supportive care, as outlined in the treatment algorithm (Figure 2). For optimal therapeutic decision-making - whether for newly diagnosed or recurrent disease - clinicians must carefully evaluate critical patient-specific factors including age, functional status, and the tumor's molecular profile.

6.2 Neurosurgical resection

MRI, including T2-weighted and FLAIR sequences, as well as T1-weighted sequences before and after contrast enhancement, is the standard method for detecting and monitoring gliomas. Prior to surgery, a neuropsychological assessment and functional imaging studies should be conducted for a comprehensive evaluation of neurological status, particularly in patients with tumors located in the eloquent areas

(e.g., speech or motor cortex), or when presenting with related neurological deficits. Surgical strategies for diffuse glioma patients are summarized in **Figure. 2**. To achieve the goal of maximal safe resection—removing as much of the tumor as safely as possible to improve neurological function—microsurgical techniques are currently the standard practice. To optimize resection outcomes, surgeons increasingly utilize adjunct technologies including: neuronavigation systems, intraoperative MRI and ultrasound, functional monitoring, and 5-aminolevulinic acid fluorescence guidance. These advanced techniques collectively enhance resection extent while reducing the risk of postoperative neurological deficits. An early imaging study (MRI or CT, if MRI is not feasible) within 48-72 hours is strongly recommended for assessing the extent of resection (EOR). According to the updated RANO 2.0 criteria[40] for assessing treatment outcomes in neuro-oncology, the initial MRI (non-contrast and contrast-enhanced) after radiation therapy is recommended as the baseline imaging data for postoperative glioma assessment. For patients who did not receive radiation therapy, preoperative MRI or MRI performed within 24 to 72 hours post-surgery (non-contrast and contrast-enhanced) can be used as the baseline imaging data.

Blood oxygen level-dependent (BOLD) fMRI is a preoperative technique for mapping functional regions of the brain, allowing for the assessment of both cortical and subcortical functions[41]. This method aids neurosurgeons in determining surgical strategies prior to surgery[42, 43]. A recent cohort study highlighted a novel imaging technique called zoomed imaging with parallel transmission (ZOOMit)-BOLD, which offers high spatial resolution within a relatively small field of view and may serve as a potential replacement for conventional BOLD imaging in identifying the hand motor cortex, especially in cases where gliomas directly invade the hand-knob region[44]. The accuracy of fMRI is influenced by the distance between the tumor and the motor cortex[45]. Preoperative fMRI data should be interpreted with caution when the shortest distance from the tumor to the hand-knob is $\leqslant$ 4 mm; in such cases, an awake craniotomy is strongly recommended. Additionally, the functional outcomes of patients have been found to correlate with tumor location[46, 47].

In the era of molecular neuropathology, an increasing number of studies have

confirmed the value of molecular markers in guiding the extent of resection (EOR) in diffuse gliomas [48, 49]. With advances in preoperative radiomics-based molecular subtyping[50] and intraoperative molecular pathology techniques[51-53], it is now possible to make diagnoses pre- or intra-operation. For certain molecular pathological types, gross total resection (GTR) or even supra-total resection is essential, while for others, GTR may not confer survival benefits and can increase the risk of postoperative complications. A retrospective study of WHO grade 2 glioma patients stratified by IDH status demonstrated that greater EOR independently prolonged survival in diffuse gliomas with IDH mutations and 1p/19q codeletion[54]. It is generally inadvisable to pursue total resection at the expense of functional impairment. To further enhance surgical outcomes, achieving a more significant reduction in residual glioma cells through supra-total resection (i.e., extending resection beyond MRI abnormalities) has been suggested, particularly in IDH-wildtype astrocytomas[55-57].

For WHO grade 3-4 gliomas, maximal resection of contrast-enhanced (CE) tumors on T1-weighted MRI has consistently been associated with longer survival[58, 59]. A study conducted by Molinaro et al. showed that maximal resection of CE tumor would lead to longer OS in patients with glioblastoma irrespective of subgroups, and maximal resection of NCE tumor was associated with longer OS in younger (< 65y) patients, regardless of *IDH* status[60].

After surgery, optimal management for glioma patients is often through clinical trials, and participation in these trials is strongly encouraged. Postoperative radiotherapy and chemotherapy are standard components of care for most glioma patients. Therapeutic regimens vary significantly based on tumor grade and specific molecular features. A scheme of surgical treatment strategies for adult diffuse glioma is provided in Figure 2.

6.3 Adjuvant management based on new classification scheme.

The implementation of adjuvant therapy plays a pivotal role in improving clinical outcomes for patients with diffuse glioma, particularly in high-risk populations. Traditionally, patients with favorable prognostic factors—including age ⩽40 years, Karnofsky Performance Scale (KPS) ⩾70, minimal or absent neurological deficits, and tumor diameter <6 cm—have been regarded as low-risk and may require less aggressive treatment. However, emerging evidence underscores the critical importance of tailored adjuvant therapies for high-risk patients, such as those with *glioblastoma, IDH wild-type*, subtotal resection, or poor functional status, as these individuals face significantly worse survival outcomes without intensive multimodal intervention. A scheme of adjuvant treatment strategies for adult diffuse glioma is provided in Figure 3.

6.3.1 Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted

For CNS Grade 2 tumors, if the tumor is grossly totally removed and the patient has a good functional status (KPS ⩾ 60), regular follow-up is essential for those undergoing observation alone. Final decision-making should involve discussions with the patients and their families, considering the potential need for adjuvant therapy at a later stage if a "watch and wait" strategy is adopted. If the tumor is not completely removed or if the patient presents other high-risk features, a treatment regimen consisting of standard radiotherapy plus adjuvant PCV or TMZ is recommended. Additionally, IDH inhibitors have shown promising results in the clinical trial NCT04164901 for patients with residual or recurrent grade 2 IDH-mutant gliomas[61]. Therefore, IDH inhibitors are recommended for patients with high risk or residual tumors. For patients with poor functional status (KPS < 60), hypofractionated radiotherapy (40 Gy in 15 fractions), with or without concurrent and/or adjuvant TMZ treatment, is advised.

For CNS Grade 3 tumors, if the patient is in good performance of functional status (KPS ⩾ 60), standard radiotherapy plus neoadjuvant or adjuvant PCV regimen is

recommended. Alternatively, the patient also can choose to receive standard radiotherapy plus concurrent and adjuvant TMZ. Standard radiotherapy plus adjuvant TMZ is also an alternative plan for these patients. For patient with PFS < 60, hypofractionated radiotherapy with or without concurrent and/or adjuvant TMZ can be recommended. Regimen with TMZ alone also shows some potential benefit for these patients (category 2 recommendation). Otherwise, for patients with very bad physical condition, best supportive care is the last plan to choose.

6.3.2 Astrocytoma, IDH-mutant

For CNS Grade 2 tumors, similar to the treatment strategy for grade 2 Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, if the tumor is gross totally removed and the patient is also performing well in functional status (KPS ⩾ 60), regular follow-up is essential for these patients receiving observation alone. For patients with high risk or a residual tumor, standard radiotherapy plus adjuvant PCV/TMZ can be applied. Standard radiotherapy plus concurrent and adjuvant therapy is also an alternative choice for these patients. Besides, IDH inhibitor also shows inspiring effects for grade 2 IDH-mutant astrocytoma, especially those with residual or recurrent tumor after resection. For patients with low performance status, hypofractionated radiotherapy is preferred with or without concurrent and/or adjuvant TMZ. IDH inhibitor is also alternatively recommended because of its low-grade toxic effects. TMZ alone is recommended as a category 2B plan for these patients. And for patients with very bad physical condition, best supportive care is also recommended as the last plan.

For CNS Grade 3 and Grade 4 tumors, if the patient has a good performance status, the recommended treatment is standard radiotherapy plus adjuvant temozolomide (TMZ) chemotherapy, or standard radiotherapy plus concurrent and adjuvant TMZ. Furthermore, for CNS Grade 4 tumors, an alternative treatment option is radiotherapy plus concurrent and adjuvant TMZ, in combination with tumor treating fields therapy. If the patient has a KPS < 60, hypofractionated radiotherapy with or without concurrent and/or adjuvant TMZ is preferred. Best supportive care only can be provided to patients with very poor physical conditions.

6.3.3 Glioblastoma, IDH-wildtype

Maximal safe resection, followed by radiotherapy with concomitant and adjuvant TMZ, has been widely considered as the standard of care (Stupp regimen) for newly diagnosed GBM patients since the EORTCNCIC trail-a randomized phase III study on the comparison of radiotherapy with concomitant and adjuvant TMZ versus radiotherapy alone on survival in GBM[58]. In elderly GBM patients, a randomized clinical trial (patient age: 65–90 years) also demonstrated that the addition of TMZ to short-course radiotherapy (40 Gy in 15 fractions) resulted in longer survival (9.3 months vs. 7.6 months) than short-course radiotherapy alone[62]. Up till now, dose-dense TMZ regimens, extending use of adjuvant TMZ beyond 6 cycles, and the addition of bevacizumab have all been proved to offer no additional survival benefit[63-66].

The standard dose of radiotherapy for GBM patients is 60 Gy in 1.8–2.0 Gy fractions. Radiotherapy (50 Gy in 1.8 Gy fractions) also results in a modest improvement in survival (median survival: 29.1 weeks vs. 16.9 weeks), without reducing the quality of life or cognition, in elderly patients with glioblastoma (age $\geqslant$ 70 years and KPS $\geqslant$70)[67]. Hypofractionated radiotherapy (40 Gy in 15 fractions) is the standard radiotherapy regimen for elderly GBM patients, especially when MGMT status is unknown or unmethylated[68].

Tumor treating fields (TTFs) are low-intensity electric fields alternating at an intermediate frequency (200 kHz), producing antimitotic effects for dividing tumor cells with limited toxicity. It has been evaluated in a randomized phase III trial in newly diagnosed GBM and demonstrated to prolong progression-free survival (PFS) and OS when administered during adjuvant TMZ in comparison with the standard Stupp regimen[69].

6.3.4 Tumor recurrence/progression

Generally, the standards of care for managing tumor recurrence or progression are less well-established. In such cases, clinicians may consider a range of treatment options, including further surgical resection, re-irradiation, systemic therapies such as lomustine or bevacizumab, or supportive care. The choice of treatment approach

depends on various factors, such as the patient's age, neurological status, Karnofsky Performance Status (KPS), the pattern of recurrence or progression, and the patient's previous therapies. A second surgical intervention will be considered when the patient's condition and clinical profile are appropriate for these conditions: 1) for a symptomatic but well-circumscribed lesion; or 2) for recurrence or progression occurring more than 6 months after the first surgery, or in cases where the initial surgery was inadequate. After a second surgery (or when a second surgery is not feasible), radiotherapy may be an option for previously non-irradiated patients, or if the new lesion is outside the target area of the prior radiation therapy. A minimum interval of 12 months from the first radiotherapy course is typically required for this approach.

For chemo-naive tumors that recur or progress after radiotherapy, chemotherapy with alkylating agents, such as temozolomide (TMZ) or nitrosoureas, may be considered. For patients previously treated with TMZ, a rechallenge with altered dosing regimens could be an option, although the effectiveness of this approach is likely limited to tumors with MGMT promoter methylation [70, 71]. Nitrosoureas, including carmustine (BCNU) [72], lomustine (CCNU) [73], and fotemustine[74], have also been reported as treatment options for recurrent gliomas.

Among the various molecular-targeted drugs investigated in clinical trials for recurrent glioma patients, bevacizumab (a vascular endothelial growth factor inhibitor) is approved for recurrent glioblastoma (GBM) in North America, although its impact on survival is limited[66, 75].

6.4 Best supportive care

Glioma patients often experience significant and progressive neurological dysfunction throughout the course of their disease. As the disease advances, these patients typically require increasing levels of nursing and social support. Supportive and palliative care approaches are especially appropriate for those with large or multifocal lesions and a low Karnofsky Performance Status (KPS), particularly if they are unable to consent to further active therapy following a biopsy[76].

Seizures are a common symptom both before and after surgery, often necessitating

long-term antiepileptic therapy[77]. The principles of antiepileptic management should focus on using the lowest effective dose to control seizures, thereby minimizing side effects and potential drug-drug interactions[78]. Levetiracetam is now commonly recommended for glioma patients due to its favorable safety profile and minimal interactions with other frequently used medications[79, 80]. Routine prophylactic use of antiepileptic drugs in patients without a history of seizures is generally not recommended, although temporary use may be appropriate during the perioperative period[81].

Corticosteroids are commonly prescribed to manage tumor-associated edema and improve clinical symptoms. However, it is not necessary for patients without increased intracranial pressure or edema-related neurological deficits, as corticosteroids have been reported to have negative effects on patient survival[82-84]. A rapid tapering and discontinuation of corticosteroids is recommended to avoid the toxicities associated with prolonged exposure, such as lymphopenia, increased infection risk, osteoporosis, and Cushing's syndrome. Therefore, the lowest effective dose for the shortest duration is preferred.

Glioma patients are at an increased risk of thromboembolic events, with up to 20% experiencing these complications within the first year[85]. Multiple factors contribute to this elevated risk, including neurological deficits, steroid use, radiotherapy, chemotherapy, and the release of vasoactive molecules from glioma cells. While prophylactic anticoagulation is not routinely recommended, a low threshold for excluding deep vein thrombosis (DVT) and pulmonary embolism (PE) is advised when suspicious symptoms arise. Treatment for venous thromboembolism (VTE) is generally lifelong with low-molecular-weight heparin, unless contraindications are present, as there is insufficient evidence to support the use of newer oral anticoagulants.

Integrating palliative care early in the disease course is crucial, and best supportive care may be the most appropriate approach for some patients. Addressing symptoms such as fatigue, mood and behavioral disorders, and impaired cognition, as well as engaging in advanced care planning, should all be considered to enhance quality of life and reduce symptom burden.

Cognitive impairment is a common and debilitating sequela of glioma and its treatments, significantly impacting patients' quality of life. Therefore, integrating cognitive rehabilitation as a core component of multidisciplinary supportive care is strongly recommended[86]. Neuropsychological assessment is foundational, providing objective characterization of cognitive strengths and deficits across domains like memory, executive function, and attention. Based on this assessment, neuropsychologists guide the delivery of evidence-based interventions, which may include compensatory strategy training, cognitive exercises, and psychoeducation. Through this process, neuropsychology plays a critical role in helping patients manage cognitive challenges, optimize functional independence, and improve overall well-being throughout the disease trajectory.

6.5 Response evaluation and follow-up

The Response Assessment in Neuro-Oncology (RANO) working group was established to improve the assessment of tumor response and the selection of endpoints, specifically in the context of clinical trials[87]. RANO2.0 has been published with integrating features of the modified RANO (mRANO) and the immunotherapy RANO (iRANO) criteria. In the new version, postradiotherapy MRI, rather than the post-surgical MRI, is recommended as the baseline for comparison with subsequent scans[40]. MRI should be utilized to evaluate the efficacy of treatment after completion of treatment, at intervals of 3-6 months. Contrast enhancement and presumed tumor progression on imaging 4-8 weeks after the end of radiotherapy may be a reactive process following radiotherapy (pseudo-progression)[88]. Accurate determination of response and progression remains a challenge. Due to the difficulty in differentiating pseudo-progression from true progression, the RANO working group has recommended avoiding enrolling patients within 3 months of completing radio-chemotherapy into clinical trials for recurrent disease, unless the recurrence is mainly outside the radiotherapy field or there is tissue confirmation of progression[89].

For immunotherapies, the assessment of radiological changes presents unique challenges due to the potential for delayed responses or therapy-induced inflammation.

The Immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria suggest that confirmation of radiographic progression on follow-up imaging is required among patients who demonstrate imaging findings meeting RANO criteria for progressive disease within 6 months of initiating immunotherapy, including the development of new lesions, provided that the patient is not significantly worse clinically[89].

7. Novel therapies

7.1. Molecular targeted therapies

Molecular targeted therapy is an important attempt at precision treatment for gliomas. Numerous new targeted drugs have been developed and are continuously being applied in clinical trials to test their efficacy against gliomas. Although only a small portion of these drugs ultimately make it to clinical use, research into molecular targeted therapy for gliomas has not ceased[90, 91].

Microvascular proliferation is one of the key pathological characteristics of gliomas, particularly glioblastomas[92]. Vascular endothelial growth factor (VEGF) is a major driver of angiogenesis[93, 94]. Bevacizumab, a humanized monoclonal antibody, specifically binds to VEGF molecules and blocks their activity. Several clinical trials have shown that Bevacizumab can improve the quality of life at short term for patients with recurrent glioblastoma and extend progression-free survival; however, it does not significantly improve overall survival[66, 95, 96]. Clinically, its use is therefore primarily for symptom control and reducing corticosteroid dependence in the recurrent tumors.

Another agent targeting VEGF pathway, regorafenib, a VEGF receptor 2 and multi-kinase inhibitor, was proven to increase survival in patients with recurrent glioblastoma compared to lomustine (CCNU) in a randomized phase II trial[97].

Fusion genes and proteins typically arise from chromosomal translocations and can execute novel functions that cannot be reconstituted by the expression of either

parental gene or protein. Since the initial report of the FGFR3-TACC3 fusion[98, 99] an increasing number of oncogenic fusions have been identified in gliomas, with some preclinical and early clinical trials demonstrating the therapeutic potential of these gene fusions. FGFR-TACC fusions are present in 3.5% of IDH-wildtype grade 2 or 3 gliomas and 2.9% of glioblastomas (GBMs). These fusions are mutually exclusive with IDH1/2 mutations and EGFR amplification but can co-occur with CDK4 amplification[100]. A clinical trial targeting FGFR-TACC fusions with Infigratinib have been conducted and durable disease control lasting >1 year was observed in a patient subset with activating FGFR1 or FGFR3 point mutations or FGFR3 fusions, although further trials with refined biomarker inclusion are warranted[101].

MET fusions, including TFG-MET, CLIP2-MET, and PTPRZ1-MET, are found in approximately 10% of pediatric GBMs[102] and 15% of adult secondary GBMs (specifically PTPRZ1-MET)[103, 104]. Results of phase I and phase II/III clinical trials (NCT02978261, NCT06105619) of vebreltinib in the treatment of adult glioma bearing PTPRZ1-MET fusion, showed that the median overall survival of the vebreltinib monotherapy group was 6.31 months, compared to 3.38 months in the control group receiving the TMZ dose-dense regimen or the cisplatin plus etoposide regimen, representing a 48% reduction in the risk of death[103, 105]. Based on these results, in April 2024, the National Medical Products Administration of China approved vebreltinib enteric-coated capsules for the treatment of patients with recurrent IDH-mutant WHO grade 4 astrocytomas or with a history of lower-grade gliomas bearing PTPRZ1-MET fusion gene.

While current targeted therapies have not yet demonstrated a significant impact on survival, a multimodal approach combining standard-of-care treatments and novel targeted therapies may hold promise for improving survival outcomes and quality of life for glioma patients.

7.2. IDH-targeted therapy

Mutations in the IDH1/2 gene are commonly found in human glioma, with the majority of low-grade gliomas harboring recurrent point mutations (IDH1 R132 and

IDH2 R172 sites)[10, 106] [11]. The mutated IDH1 leads to the synthesis of 2-hydroxyglutarate, and that this metabolite elicits a significant impact on tumors by regulation of cell death, the epigenome, and metabolism[107, 108]. Blocking the activity by several IDH1/IDH2 inhibitors has proven to be promising in preclinical models. A phase 3 study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation (NCT04164901) indicated that vorasidenib significantly improved progression-free survival and delayed the time to the next intervention[61]. The latest results further indicate that vorasidenib offers superior seizure control compared to placebo, all while having no observed adverse effects on HRQOL or neurocognition[109]. This outcome solidifies the case for the IDH-targeted treatment strategy. Consequently, we recommend administering IDH inhibitor therapies as early as possible, especially for patients presenting with high-risk factors.

7.3. Immunotherapy

A variety of immunotherapies, including vaccination, oncolytic viruses, and immune checkpoint inhibitors, are currently under active investigation for patients with GBM.

Vaccination aims to induce an active immune microenvironment and enhance the anti-glioma activity of the adaptive immune system in glioma patients. This approach relies on dendritic cell (DC)-mediated presentation of antigens derived from tumor lysates to T cells. Several peptide mimics, including EGFRvIII, IDH1-R132H, and TERT, have completed or are currently being studied in phase II or III clinical trials. Some phase II trials of the EGFRvIII vaccine (ACTIVATe, NCT00643097; HeatShock, NCT00905060) demonstrated superior results compared to controls. Additionally, a randomized phase II trial involving recurrent EGFRvIII-positive GBM patients treated with rindopepimut plus bevacizumab, compared to bevacizumab plus control, showed a potential progression-free survival (PFS) benefit, suggesting that the timing of therapy or combination approaches may be crucial[110].

Oncolytic viruses can activate the immune system through pathogen-associated

molecular patterns and pattern recognition receptors, stimulating macrophages via their receptors. A completed phase II clinical trial (BrTK02, NCT00589875) of oncolytic viral therapies indicated favorable prognostic outcomes. A recently published study on recurrent GBMs treated with recombinant poliovirus showed that intratumoral infusion of the recombinant nonpathogenic polio-rhinovirus chimera (PVSRIPO) confirmed the absence of neurovirulent potential. Patients receiving PVSRIPO immunotherapy exhibited higher survival rates at 24 and 36 months compared to historical controls[111].

Immune checkpoint inhibitors are antibodies that reduce the activity of endogenous negative regulatory pathways that limit T cell activation. These inhibitors have significantly advanced immune therapies for several critical cancers in recent years. In gliomas, higher expression of PD-1/PD-L1 in glioblastoma has been correlated with poorer patient prognosis in some studies[112, 113], likely due to increased suppression of anti-tumor immunity. Trials of immune checkpoint inhibitors, primarily targeting PD-1/PD-L1 and/or CTLA-4, have been conducted in both newly diagnosed and recurrent GBM, although initial results have been disappointing. An interesting approach is the use of neoadjuvant anti-PD-1 treatment prior to surgery; two recent studies indicated a favorable local immune response and improved survival in recurrent GBM patients [114].

Chimeric antigen receptor (CAR) T cell therapy employs engineered T cells that express chimeric antigen receptors, which combine antigen recognition domains of antibodies with T cell activation domains. A recent study reported that a patient with recurrent multifocal glioblastoma received CAR T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2) [115]. This clinical response persisted for 7.5 months following the initiation of CAR T cell therapy. CAR T cells targeting multiple antigens have been demonstrated to be an effective strategy to overcome antigen escape, a recent study reported a tandem chimeric antigen receptor (CAR)-T cell targeting CD44 and CD133 (PROM1), showed robust antitumor activity against glioblastoma organoids, though further clinical trials are warranted. Currently, several CAR T cell therapy targets have been investigated for glioma treatment, including EGFRvIII, HER2, EphA2, CD70, GD2, and B7H3[116-118]. Clinical trials

have shown that CAR T cells can infiltrate tumor tissues and become activated. However, further studies are needed to identify critical targets for gliomas and to understand the potential efficacy of CAR T cell therapy[119].

Dendritic cell vaccination uses patient-specific dendritic cells pulsed with tumor lysate, offering a tailored immunotherapy targeting individual tumor antigens. A recent study[120] reported that by adding autologous tumor lysate-loaded dendritic cell vaccine (DCVax-L) to standard of care (SOC) extends survival among patients with glioblastoma, shedding new light on the treatment of GBM with DC vaccines.

In summary, significant strides have been made in immunotherapy for glioma. Among various modalities, CAR-T cell therapy stands out as a particularly promising strategy, with clinical studies demonstrating its ability to infiltrate tumors and elicit sustained anti-tumor responses. Looking forward, key research directions will likely focus on combining different immunotherapies or integrating them with conventional radiotherapy and chemotherapy to achieve synergistic efficacy and overcome current therapeutic limitations.

Note

This guideline was prepared by a joint committee of Chinese Glioma Cooperative Group (CGCG), Society for Neuro-Oncology of China (SNOChina) and Chinese Brain Cancer Association (CBCA). The manuscript was critically revised by experts at home and abroad. We used PubMed to retrieve references for articles published in English since Jan 1st, 1990. The search was completed in January 2025.

Funding

This work was supported by grants from 1. National Natural Science Foundation (82192894, 82261160578, 81761168038, 2019YFE0109400).

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Declaration of interests

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.

Acknowledgements

The Expert Panel of the joint guideline committee wishes to express its gratitude to Jizong Zhao (Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University), Liangfu Zhou (Department of Neurosurgery, Huashan Hospital, Fudan University), and Renzhi Wang (Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College) for their help and thoughtful review of the updated version of the guidelines.

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Figure Legends

Fig 1. Classification Scheme for Diffuse Glioma

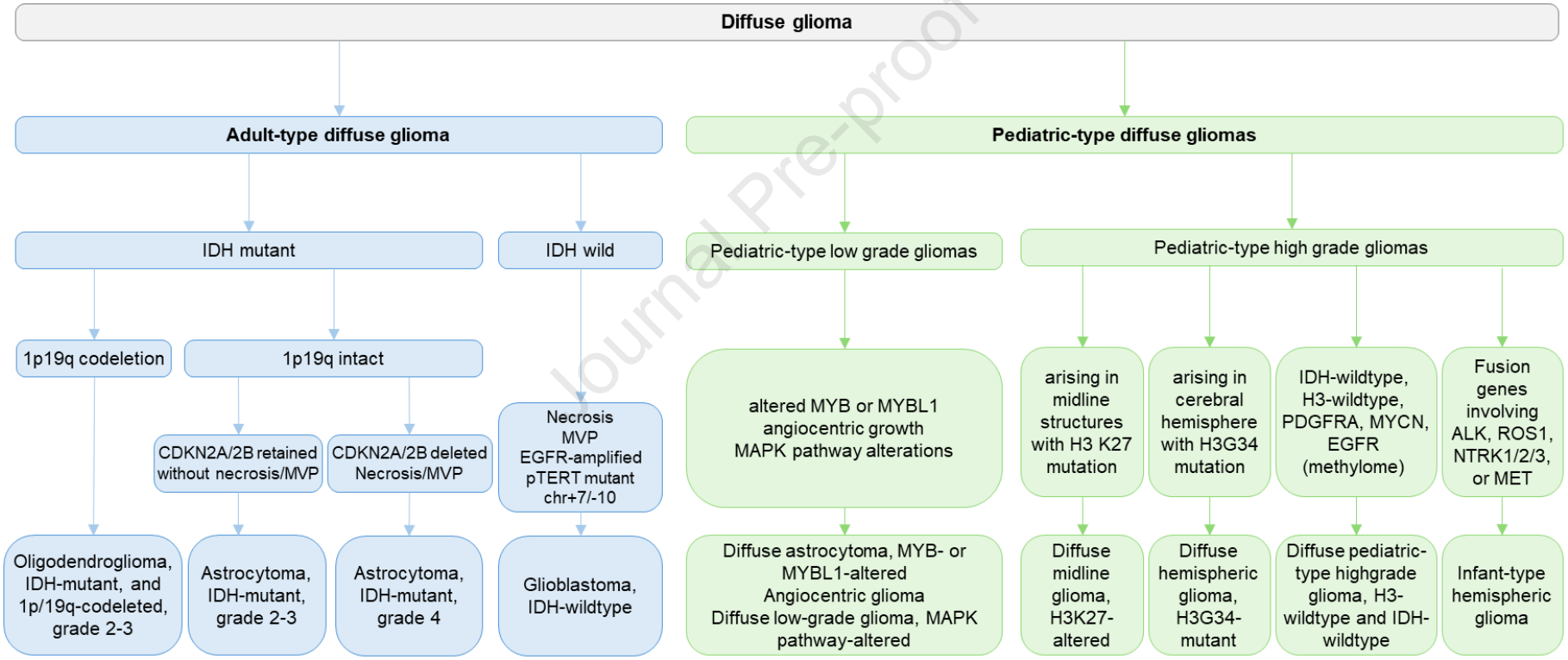


Fig 2. Surgical Treatment Strategy for Adult Diffuse Glioma

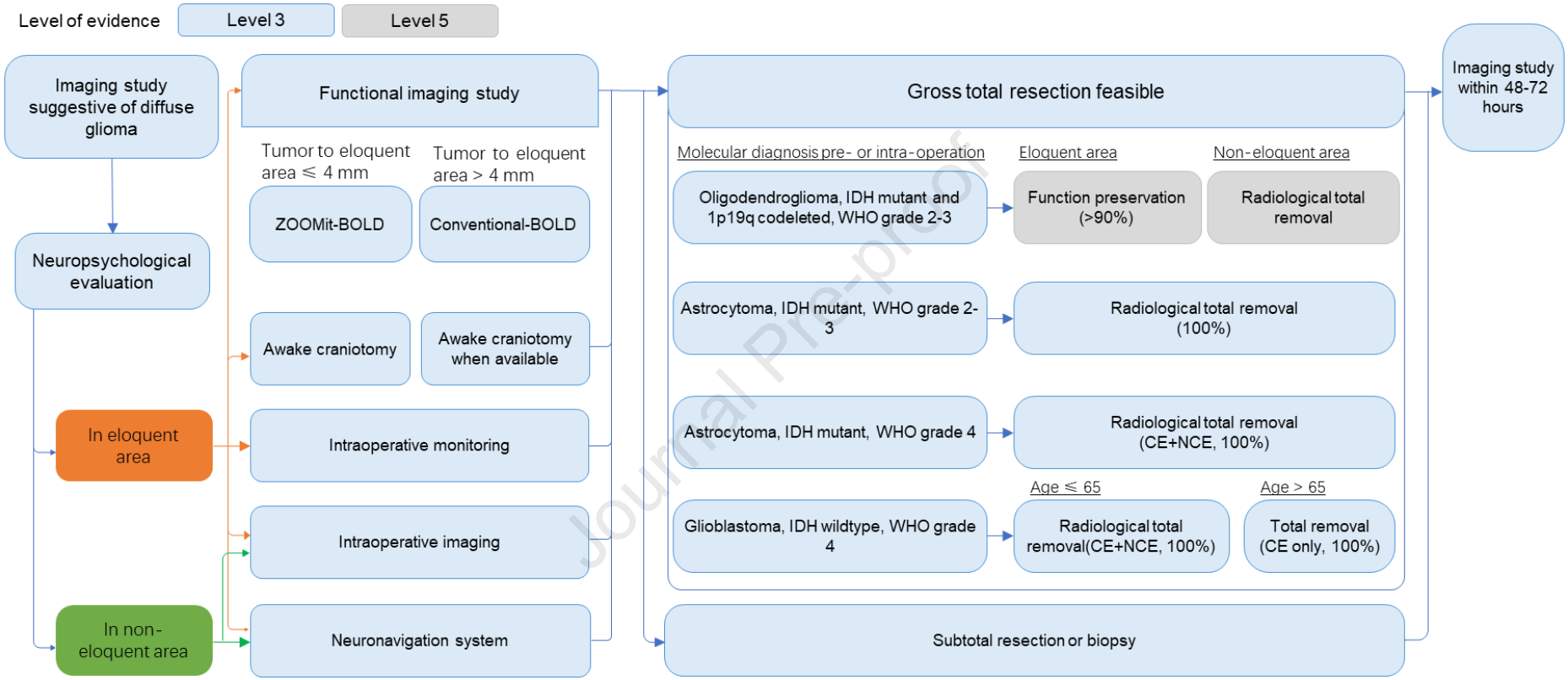
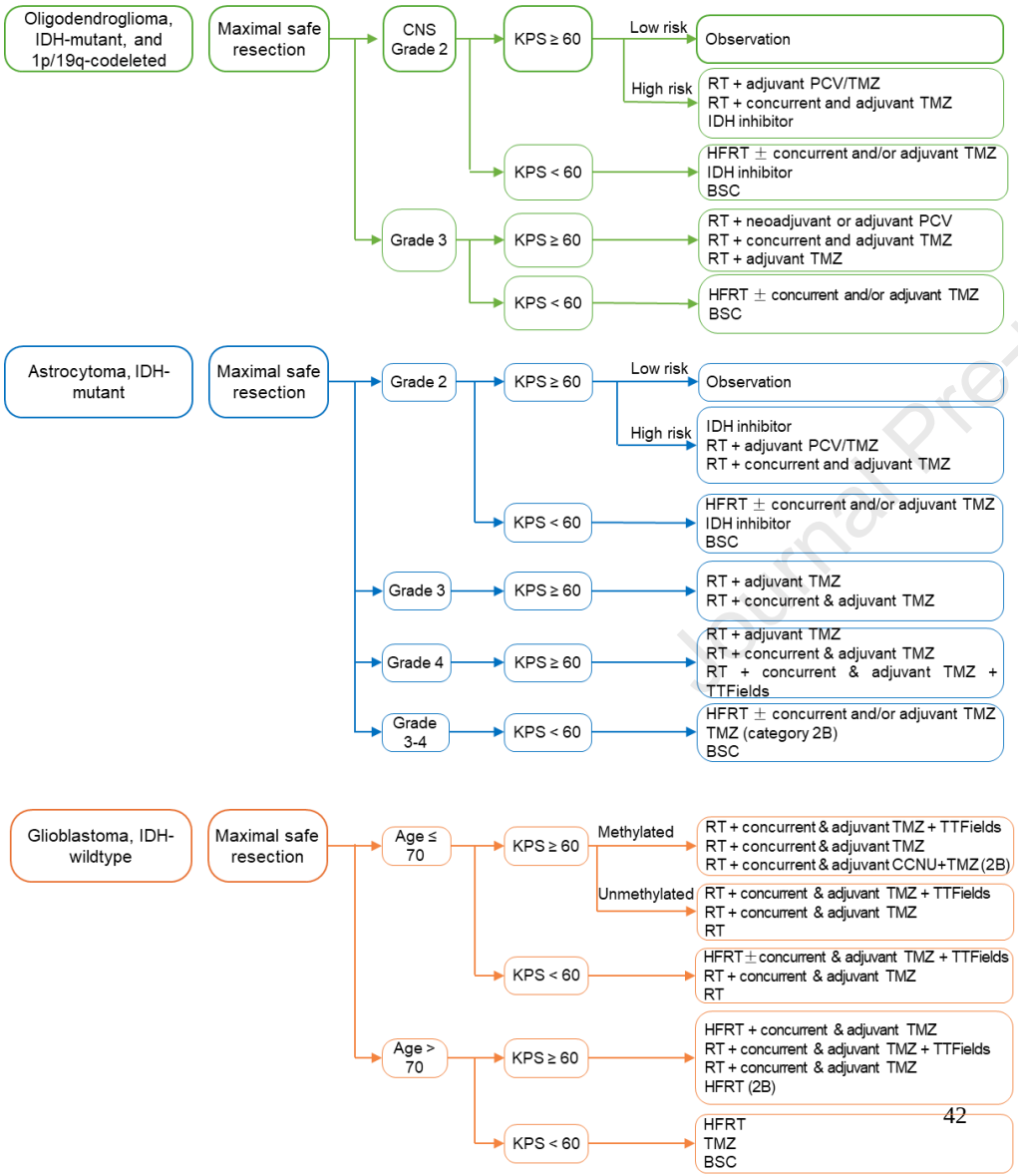
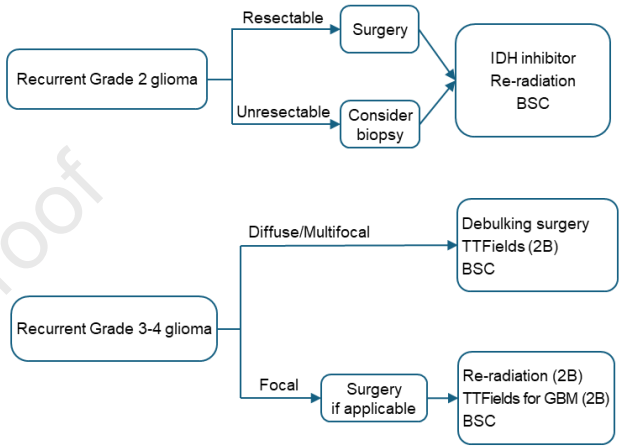


Fig 3. Adjuvant Treatment Strategy for Adult Diffuse Glioma





Tips:

Maximal resection remains the basic surgical principle of removing a glioma

Unless otherwise noted, all recommendations are Class 2A or Class I recommendations.

High risk: Age ≥ 40 years, not gross total resected, tumor size > 6 cm in diameter, neurological defects before surgery

Low risk： Age < 40 years, gross total resected, tumor size < 6 cm in diameter, neurological intact

RT, radiotherapy; PCV, procarbazine, lomustine and vincristine regimen; TMZ, temozolomide; BSC, best supportive care; HFRT, hypofractionated radiotherapy; KPS, Karnofsky performance status; TTF, tumor-treating fields

Glioma is the most common primary malignant intracranial tumor, and its treatment protocols are continuously evolving. Updated guidelines promote standardized, evidence-based approaches to the diagnosis and management of glioma in clinical practice.

Five years have passed since the Asian Glioma Genome Atlas (AGGA) published last version clinical practice guideline for adult diffuse gliomas. During this period, significant advancements have been made in the diagnosis and treatment of these tumors. To reflect these developments, the Chinese Glioma Cooperative Group (CGCG), the Society for Neuro-Oncology of China (SNO-China), and the Chinese Brain Cancer Association (CBCA) have jointly updated the clinical practice guidelines.

This revision prioritizes molecular and pathological diagnostics, along with standard treatment modalities including surgery, radiotherapy, chemotherapy, and targeted therapy. Furthermore, emerging evidence from recent clinical trials on novel therapies has been integrated to ensure alignment with contemporary therapeutic approaches. The updated guideline aims to serve as a comprehensive reference for clinicians managing adult diffuse glioma patients while also providing valuable information for insurance companies and other institutions responsible for regulating cancer care costs in China and internationally.

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.