Clinical practice guidelines for the management of adult diffuse gliomas

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Clinical Practice Guidelines for the Management of Adult Diffuse Gliomas

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Abstract

To follow the revision of the fourth edition of WHO classification and the recent progress on the management of diffuse gliomas, the joint guideline committee of Chinese Glioma Cooperative G oup (CGCG), Society for Neuro-Oncology of China (SNO-China) and Chinese Brain Cancer Association (CBCA) updated the clinical practice guideline. It provides recommendations for diagnostic and management decisions, and for limiting unnecessary treatments and cost. The recommendations focus on molecular and pathological diagnostics, and the main treatment modalities of surgery, radiotherapy, and chemotherapy. In this guideline, we also integrated the results of some cl nical trials of immune therapies and target therapies, which we think are ongoing future directions. The guideline should serve as an application for all professionals involved in the management of patients with adult diffuse glioma and also a source of knowledge for insurance companies and other institutions involved in the cost regulation of cancer care in China and other countries.

Keywords: molecular diagnostics, surgery, chemoradiation, immune therapy, target therapy

1. Introduction

According to the 2016 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) and the recent updates from the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) [1], molecular parameters in addition to histology are recommended to define many tumor entities, thus formulating an integrated pathological diagnostics for CNS tumor in the molecular era. To follow the revision of the fourth edition of WHO classification and the recent progress on the management of gliomas, the joint guideline committee of Chinese Glioma Cooperative Group (CGCG), Society for Neuro - Oncology of China (SNO-China) and Chinese Brain Cancer Association (CBCA) updated the clinical practice guidelines for the management of adult diffuse gliomas[2]. The guideline covers adult astrocytic and oligodendroglial tumors of WHO grades II–IV, and variants of these tumors, and discusses histological and molecular diagnostics, state-of-the-art treatment strategies and novel therapies.

2. Epidemiology and survival

According to the latest global statistics, there were 330,000 incident cases of CNS cancer and 227,000 deaths globally in 2016[3]. And China was one of the top three countries with the largest incident cases and the most deaths of CNS cancer[3, 4]. The most common histological type of primary CNS cancer is glioma, which is derived from glial cells of astrocytic, oligodendroglia and ependymal origin, with the annual incidence of 5 6 cases per 100,000 individuals worldwide[5, 6].

The signs and symptoms associated with diffuse gliomas are dependent on histopathology and affected anatomical regions, which include headaches, speech disturbance, cognitive impairment, seizures, and paralysis. The overall prognosis of malignant glioma remains poor, due to the high rates of mortality and inherently disabling effects it has on patients. Patient age, performance 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 low grade gliomas, anaplastic gliomas and glioblastomas, respectively[7]. Moreover, molecular genetic features, such as isocitrate dehydrogenase 1 (IDH1) or IDH2 mutation, chromosomal 1p/19q codeletion and MGMT promoter methylation, confer a favorable prognosis, which will be discussed in more detail below.

3. Diagnosis and pathology

The diagnosis of gliomas has long been largely based on their microscopic similarities with different putative cells of origin and their presumed levels of differentiation. However, as the expansion of knowledge on the genetic basis of tumorigenesis, accumulating evidences have shown the possibility that the molecular features may contribute to classification of gliomas. The detailed information of these molecular markers and their clinical relevance[8-45] are listed in **Table 1**.

The current recommended glioma diagnostic process, summarized in **Figure 1**, is the integration of histological typing and molecular characteristics. The application of molecular features is currently recommended in clinical practice and considered to provide more information about the biological behavior of tumors and consequently the patient's prognosis and outcome. Not other-wise specified (NOS) diagnoses refer to the following situations: 1)

diagnostic testing necessary for reaching a specific WHO diagnosis cannot or will not be performed; 2) necessary diagnostic testing has failed. Not elsewhere classified (NEC) diagnoses reflect the situations in which the necessary assays (molecular testing such as IDH1/2 and 1p/19q status) are performed, but the results do not allow for a specific entity in the current WHO classification [46].

For IDH1/2, If immunohistochemistry for mutant R132H IDH1 protein and sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations are both negative, or if sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations alone is negative, then the lesion can be diagnosed as IDH-wildtype. Particularly, it is near absence of non-R132H IDH1 and IDH2 mutations in glioblastomas from patients over about 55 years of age[47], thus, sequencing may not be needed in the setting of negative R132H IDH1 immunohistochemistry in such patients.

Oligodendroglioma/Anaplastic oligodendrogliomas are characterized by IDH mutation and chromosome 1p/19q codeletion. Other diagnostic biomarkers include TERT promoter mutation, CIC and/or FUBP1 mutation. These patients showed the most favorable prognosis of all the diffuse gliomas (**Figure 2**).

Diffuse/Anaplastic astrocytomas are classified into two categories according to the IDH mutational status. The IDH-mutant tumors also harbor frequent ATRX and TP53 mutations, accompanied by 17p loss of heterozygosity (LOH), a second TP53 mutation or complete loss of TP53 expression, suggesting biallelic TP53 inactivation These patients had more favorable survival in comparison to the latter type(**Figure 2**). The IDH-wildtype diffuse/anaplastic astrocytomas are characterized by the presence of 'glioblastoma (GBM)-like' mutations and CNVs, such as amplification of EGFR, PDGFRA, CDK4, MDM2 and MDM4, deletion or mutation of PTEN, NF1, RB1, CDKN2A/B, 10q, and amplification or mutation of PI3K genes, which were much less frequent in other WHO grade II-III gliomas.

GBMs are divided into (1) glioblastoma, IDH-wildtype, accounting for about 90% of GBM cases, have a worst survival (**Figure 2**), predominately in patients over 55 years. Other genomic alterations include TERT promoter mutation, EGFR amplification/mutation and PTEN loss/mutation. Epithelioid glioblastoma (a new variant of glioblastoma), giant cell glioblastoma and gliosarcoma are under the umbrella of IDH-wildtype GBM. (2) glioblastoma, IDH-mutant (about 10% of GBM cases) is often considered as secondary GBMs with a history of prior lower grade diffuse glioma and preferentially arises in younger patients. TP53 and ATRX mutations are the most common coexisted genomic alterations in IDH-mutant GBMs.

IDH-wildtype diffuse astrocytic tumors would follow an aggressive clinical course and considered as an entity equivalent to glioblastoma if they have the genotype of epidermal growth factor receptor (EGFR) amplification and/or combined whole chromosome 7 gain and whole chromosome 10 loss (+7/−10) and/or TERT promoter mutation[29, 34]. Although these tumors possess "GBM like" genotypes, it is not appropriate to designate the tumor as a glioblastoma in the absence of histological features including palisading necrosis and microvascular proliferation. Thus, the diagnosis of "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV" is the most appropriate entity. The overall survival of these patients was more similar to that of GBMs.

The overall survival of IDH-mutant diffuse astrocytic tumors were associated with the status of CDKN2A/2B homozygous deletion[28]. Patients with CDKN2A/2B homozygous deletion without necrosis, graded as WHO grade III anaplastic astrocytoma exhibited similar overall

survival to those with WHO grade IV glioblastoma, IDH-mutant with CDKN2A/2B homozygous deletion and necrosis[48]. In addition, the glioma cases with necrosis and no CDKN2A/2B homozygous deletion survive significantly longer than those with CDKN2A/2B homozygous deletion and no necrosis. Therefore, IDH-mutant astrocytomas with microvascular proliferation or necrosis or CDKN2A/B homozygous deletion, or any combination of these features are clinically and genetically distinct from glioblastoma, IDH-wildtype, and more closely related to WHO grade 2 or 3 IDH-mutant astrocytomas. cIMPACT-NOW suggested to diagnose these tumors as "Astrocytoma, IDH-mutant, WHO grade 4"(**Figure 1**)[28].

Diffuse midline gliomas involve thalamic, spinal, and diffuse brainstem gliomas, which usually occur in children (but sometimes in adults too). This entity includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG). One specifically defined group of these tumors, termed as diffuse midline glioma, H3 K27M-mutant, is characterized by K27M mutations in either H3F3A or HIST1H3B/C. H3 K27M mutations were first described in DIPGs, but soon thereafter were found in midline gliomas in adults. The presence of H3 K27M mutation in these tumors was recognized to portend an adverse prognosis regard ess of the histology and thus WHO grade IV was assigned by the 2016 WHO Classification criterion. H3 K27M mutation also exist in other brain tumors, including ependymomas, pilocytic astrocytomas, pediatric diffuse astrocytomas, and gangliogliomas. Thus, the term diffuse midline glioma, H3 K27M-mutant should be reserved for tumors that are diffuse (i e infiltrating), midline (e.g., thalamus, brain stem, spinal cord, etc.), gliomas and H3 K27M-mutant, and should not be applied to other tumors that are H3 K27M-mutant (**Figure 1**)[18].

IDH-wildtype gliomas in pediatric or young adult patients generally have a prolonged disease course and good overall survival. These umors are genetically featured with either BRAF V600E mutation, FGFR1 alteration, or a MYB or MYBL1 rearrangement, or other MAPK pathway alterations[49]. Thus, the diagnosis of "Diffuse glioma, MYB-altered/MYBL1-altered/FGFR1 TKD duplicated/FGFR1-mutant/BRAFV600E-mutant (but without CDKN2A/B deletion)/other MAPK pathway alteration" should be made in these situations (**Figure 1**).

4. Disease management

4.1 General recommendations

Management of gliomas requires a multidisciplinary approach, including surgical resection, irradiation, systemic therapies, and supportive care. A therapeutic treatment algorithm is provided in **Figure 3**. In both the newly diagnosed and recurrent glioma, consideration of factors such as patient age, performance status, and tumor molecular features is of critical importance.

4.2 Neurosurgical resection

MRI, including T2-weighted and FLAIR sequences, and T1-weighted sequences before and after contrast enhancement, is the standard method for the detection and follow-up of a glioma. Before surgery, neuropsychological assessment and functional imaging study should be applied for comprehensive evaluation of neurological status, especially for patients with tumor in speech/motor area or with speech/motor symptoms.

Surgical strategies for diffuse glioma patients are summarized in **Figure 4**. To meet the goal of maximal safe resection (remove as much of the tumor as safely as possible to improve neurological function), microsurgical techniques are current standard procedures. Some other

techniques, including neuronavigation system, intraoperative MRI, ultrasound, intraoperative functional monitoring, and the fluorescent dye 5-aminolevulinic acid, are becoming more popular in order to increase the extent of surgical resection, while minimizing the risk of new neurological deficits. An early imaging study (MRI or CT if MRI is not feasible) is strongly recommended within 72 hours for the assessment of the extent of resection (EOR), which is also part of the standard of care for diffuse gliomas.

Blood oxygen level-dependent (BOLD) fMRI is a preoperative method for mapping functional regions of the brain that allows assessment of the function of cortical and subcortical regions[50]. BOLD fMRI helps neurosurgeons determine surgical strategy before an operation[51, 52]. A recent cohort study reported a zoomed imaging technique with parallel transmission (ZOOMit)-BOLD (a novel sequence allowing high spatial resolution with a relatively small field of view that may solve this problem) may potentially replace conventional-BOLD to identify the hand-motor cortex, particularly in cases in which gliomas directly invade the hand-knob[53]. The accuracy of fMRI is affected by the tumor to the motor cortex distance[54]. Preoperative fMRI data for surgical planning should be used cautiously when the shortest distance from the tumor to the hand knob is $\leq$4 mm, and an awake craniotomy is strong y recommended in this situation. Functional outcome of patient is found to be associated with tumor location[55-58].

In the era of molecular neuropathology, recent studies have confirmed the interaction effect between molecular biomarkers and EOR in diffuse gliomas[59]. As the development of pre-operation radiomics based molecular subtyping[60] or intra-operation molecular pathology techniques (e.g., rapid immunohistochemistry high-resolution melting)[61], it is now possible to make a diagnosis before or during operations. For some molecular pathological types, gross total resection (GTR) or even supra-total resection was essential, while for the others, GTR had no survival benefit but increased the risk for postoperative complications.

In a retrospective study of WHO grade II glioma patients, stratifying by IDH status demonstrates that greater EOR independently prolonged survival for IDH-wildtype patients, but not for IDH-mutant patients[62]. For IDH-mutant patients, this might due to the complication of oligodendroglioma with IDH mutation and 1p/19q codeletion, as in some studies, increased EOR resulted in better survival for diffuse astrocytoma but not for oligodendroglioma[63] nor specially (anaplastic) oligodendroglioma with IDH mutation and 1p/19q codeletion[64-66]. The prognostic impact of postoperative tumor volume was particularly strong in IDH-mutant astrocytoma patients[65] or in anaplastic astrocytoma/oligoastrocytoma[67] patients. Thus, the surgical treatment for diffuse gliomas with IDH mutation and 1p/19q codeletion should consider the tumor location and comprehensively functional protection. It is commonly inadvisable to achieve total resection at the expense of function impairment. To further strengthen the impact of surgery, a more significant reduction of the number of residual glioma cells by achieving a supra-total resection (i.e. resection extended beyond the MRI abnormalities) has been suggested[68, 69], especially in IDH-wildtype astrocytoma[61].

For WHO grade III-IV gliomas, maximum resection of contrast-enhanced (CE) tumor on T1-weighted magnetic resonance imaging has been consistently associated with longer survival[70, 71]. In a cohort study of patients with newly diagnosed glioblastoma, reduction of CE tumor was significant regardless of IDH status and MGMT methylation status. Reduction of non-contrast-enhanced (NCE) tumor was significant in younger (<65 years) patients with IDH-wildtype tumors, regardless of MGMT status, and in all patients with IDH-mutant tumors.

Thus, for newly diagnosed glioblastoma, it is suggested to perform maximal resection of the CE tumor for all patients, with the additional maximum resection of the NCE tumor in patients younger than 65 years, when safely feasible[72].

After surgery, the optimal management for a glioma patient is in a clinical trial, thus participation in clinical trials is especially encouraged. Post-operation radio- and chemotherapies are parts of the standard of care for most patients with glioma. The therapeutic regimens are notably different according to the grading of the tumor with certain molecular features.

4.3 IDH-mutant grade II glioma

Traditionally, patients with the following features are considered as low risk: age≤40 years, Karnofsky Performance Status (KPS) ≥70, minor or no neurological deficit, oligodendroglioma or oligoastrocytoma, tumor dimension <6cm, 1p and 19q co-deleted, and IDH1/2 mutation. Regular follow-up is essential for low-risk patients receiving observation alone after gross total resection, and final decision-making should be done after due discussion wi h the patients and their families bearing in mind the need for adjuvant therapy at a later stage if the wait and see policy is applied.

The postoperative treatment strategies for high-risk grade I gliomas are including utilized for high risk low-grade gliomas, i.e., RT along with chemotherapy, either with adjuvant “PCV” [procarbazine-CCNU (lomustine)-vincristine] regimen or oncurrent and adjuvant temozolomide (TMZ).

4.4 IDH-wildtype grade II glioma

After exclusion of other entities (such as pediatric-type diffuse gliomas), IDH-wildtype grade II gliomas should offer protocols similar to that utilized for high risk low-grade gliomas Postoperative radiotherapy, or adjuvant temozolomide (TMZ) or PCV chemotherapy is usually recommended, and timing of radiation typically depends on several variables such as age and EOR. In the RTOG 9802 trial, grade II glioma patients who were younger than 40 years of age and had undergone subtotal tumor resection or who were 40 years of age or older, progression free survival and overall survival were longer among those who received combination chemotherapy (PCV) in addition to radiation therapy than among those who received radiation therapy alone[73]. The NRG Oncology/RTOG 0424 trial demonstrated a 3-year overall survival benefit with the addition of TMZ to radiotherapy compared with a historical control[74]. The following study also demonstrated that MGMT promoter methylation was an independent prognostic biomarker of high-risk low-grade glioma treated with TMZ and radiotherapy[75].

4.5 IDH-mutant and 1p/19q-codeleted grade III glioma

Standard treatment for anaplastic (grade III) glioma patients includes maximal safe surgical removal or biopsy followed by radiotherapy (60Gy in 1.8~2.0 Gy fractions) and adjuvant chemotherapy. The chemotherapy regimens vary according to the patients’ characteristics, such as KPS, 1p/19q codeletion or MGMT promoter methylation. For 1p/19q-codeleted anaplastic oligodendroglial tumors, two large randomized clinical trials (European Organization for Research and Treatment of Cancer (EORTC) 26951 and RTOG 9402) showed that patients treated with PCV chemotherapy, either before or after radiotherapy, in first-line treatment had longer overall survival compared with patients treated with radiotherapy alone[76, 77]. The modified CODEL

trial is ongoing as a two-arm comparison of radiotherapy plus adjuvant PCV vs. radiotherapy plus concomitant/adjuvant TMZ.

4.6 IDH-mutant and 1p/19q non-codeleted grade III glioma

For 1p/19q intact anaplastic gliomas, an interim analysis the EORTC 26053 trial (CATNON) suggested that patients treated with 12 cycles of maintenance TMZ to radiotherapy had longer overall survival than patients not treated with maintenance TMZ[78]. Maintenance TMZ has since been introduced as the standard of care for grade III gliomas, whereas the value of concomitant TMZ remains unclear.

4.7 IDH-wildtype GBM

IDH-wildtype GBM accounts for the vast majority (~90%) of GBMs. Three morphological variants of giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma are also included in this diagnosis, although no specific treatment recommendations exist according to glioblastoma variants. However, about 50% of the epithelioid glioblastoma have a targetable $BRAF^{V600E}$ mutation, the therapeutic role of which needs to be evaluated systematically.

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 EORTC-NCIC trail- a randomized phase III study on the comparison of radiotherapy with concomitant and adjuvant TMZ versus radiotherapy alone on survival in GBM [79]. 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[80]. 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[81-83].

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 ≥70 years and KPS ≥70)[84]. Hypofractionated radiotherapy (40 Gy in 15 fractions) is the standard radiotherapy regimen for elderly GBM patients, especially when MGMT status is unknown or unmethylated[85].

Tumor treating fields (TTFs) are low-intensity electric fields alternating at an intermediate frequency (200kHz), 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 [86].

4.8 IDH-mutant GBM

IDH-mutant GBM (astrocytoma, IDH-mutant, grade 4) correspond to secondary GBM with a longer history or a history of prior lower grade diffuse glioma, and arises in relatively younger patients. Although these patients showed more favorable prognosis than IDH-wildtype GBMs, they commonly been treated in a similar approach.

4.9 Tumor recurrence/progression

Generally, standards of care for tumor recurrence/progression are less well defined. Treatment options include further surgical resection, re-irradiation, systemic therapies such as lomustine or bevacizumab, or supportive care, which depends on age, neurological status, KPS, pattern of recurrence/progression and previous therapies. A second surgery will be considered when the patient is in these conditions: 1) a symptomatic but circumscribed lesion; 2) >6 months after the first surgery or early recurrence/progression when the first surgery was not adequate. After a second surgery (or a second surgery is not available), radiotherapy in previously non-irradiated patients, or if new lesion is outside target of prior radiation, is usually an option, with a minimum interval of 12 months from the first radiotherapy course. Chemotherapy with alkylating drugs (usually TMZ or nitrosoureas) could be considered for chemonaive tumors which recur or progress after radiotherapy. TMZ rechallenging with altered dosing regimens is an option for patients pre-treated with TMZ, although the activity is probably limited to tumors with MGMT promoter methylation. Nitrosoureas, including carmustine (BCNU), lomustine (CCNU) and fotemustine have also been reported to be used for the treatment of recurrent gliomas. Of the various molecular targeted drugs investigated in clinical trials or recurrent glioma patients, bevacizumab (vascular endothelial growth factor inhibitor), is approved for recurrent GBM in North America, although the effect of bevacizumab on surv val improvement is limited. However, there is no evidence to suggest that TMZ rechallenge, nitrosoureas, bevacizumab, or re-irradiation, TTFs could prolong survival of recurrent GBMs in randomized trials.

4.10 Supportive care

Glioma patients often experience significant and progression neurological disfunctions throughout the disease course. As the disease advancing, the patients require greater levels of nursing and social support[87]. Supportive and palliative care are also appropriate for patients with large or multifocal lesions with a low KPS, especially if patients are unable to consent to further therapy after biopsy.

Seizure is a common symptom before administration or after surgery, and many require long-term antiepileptic therapy. The principles of antiepileptic therapy should aim for the lowest dose possible for seizure control to avoid side effects and minimize drug-drug interactions[88, 89]. Levetiracetam is now commonly recommended for glioma patients for its safety and relatively few interactions with other commonly used drugs[90]. The routine prophylactic use of antiepileptic drugs in patients with no history of seizures is not recommended, although they may be used temporarily in the perioperative period[91].

Corticosteroids are often prescribed to patients for control of tumor-associated edema and improving clinical symptoms. Steroids are not necessary in patients without increased intracranial pressure or in the absence of edema-associated neurological deficits. There is no need for prolonged steroid therapy after tumor resection or for prophylaxis during radiotherapy in asymptomatic patients. Rapid tapering and discontinuation of corticosteroids is recommended in order to avoid toxicity associated with prolonged exposure to steroids, e.g. lymphopenia and risk of infection, osteoporosis, and Cushing syndrome. Therefore, the lowest dose for the shortest time possible is recommended[92].

Patients with gliomas are at increased risk of thromboembolic events (up to 20% of patients at 1 year[93]). Multiple factors contribute to this increased risk, including neurological deficits, steroid use, radiotherapy, chemotherapy, and release of vasoactive molecules from glioma cells.

Prophylactic anticoagulation is not recommended. However, a low threshold for excluding deep vein thrombosis and pulmonary emboli is indicated when suspicious symptoms occur. Treatment of VTE is generally lifelong with low-molecular-weight heparin unless there are contraindications, and there is a lack of evidence for newer oral anticoagulants[94].

Integration of palliative care early in the course of the disease is important, and best supportive care may be the most appropriate course in some patients[95]. The management of symptoms, such as fatigue, mood and behavioral disorders, and impaired cognition, and advanced care planning should all be considered in improving quality of life and reducing symptom burden[94].

4.11 Response evaluation and follow-up

The Response Assessment in Neuro-Oncology (RANO) working group was established to improve the assessment of tumor response and selection of end points, specifically in the context of clinical trial[96]. MRI should be utilized to evaluate the efficacy of treatment after completion of treatment at an interval 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)[97]. Accura e determination of response and progression remains a challenge. Because of the difficulty in differentiating pseudoprogression from progression, the RANO working group has recommended avoiding enrolling patients within 3 months of completion of radiochemotherapy into clinical trials for recurrent disease, unless the recurrence is mainly outside the radiotherapy field or there is tissue confirmation of progression[98]. For immunotherapies, because of the delayed responses or therapy-induced inflammation, it has unique challenges associated with the assessment of radiological changes. The immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria suggest to have confirmation of radiographic progression on follow-up imaging 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[99].

5. Novel therapies

5.1 Molecular targeted therapies

The growing knowledge of tumor genomics has led to great advances in medical oncology. Receptor tyrosine kinase (RTK)-PI3K, TP53 and RB pathways have long been considered as the most mutated oncolytic pathways[100]. Some well-known oncogenes, RTKs for example, have been used as therapeutic targets for gliomas in clinical trials, but there are very few positive results.

Targeting EGFR with tyrosine kinase inhibitors (TKIs) have been explored. Depatuxizumab mafodotin (Depatux-M) is a tumor-specific antibody-drug conjugate consisting of an antibody (ABT-806) directed against activated EGFR and the toxin monomethylauristatin-F. A phase II trial showed a promising result in combination with TMZ in recurrent EGFR amplified glioblastoma[101]. However, a phase III trial of Depatux-M in combination with standard therapy for newly diagnosed, EGFR-amplified glioblastoma was stopped early because of futility, and no OS benefit was observed at an interim analysis[102]. Other RTK-PI3K pathway inhibitors also showed limited roles in unselected population in phase II/III clinical trials[103-107]. Regorafenib,

a VEGF receptor 2 and multikinase inhibitor, was proved to increase survival in patients with recurrent GBM compared to CCNU from a randomized phase II trial[105].

A fusion gene/protein typically resulted from chromosomal translocations and executed novel functions that cannot be reconstituted by the expression of either parental gene/protein. Accumulating oncogenic fusions have been reported in gliomas since the first report of FGFR3-TACC3 fusion[43, 108]. Some preclinical or early clinical trials have found the therapeutic potential of these gene fusions. FGFR-TACC fusions are found in 3.5% IDH-wildtype grade II or III gliomas and 2.9% GBMs. They are mutually exclusive with IDH1/2 mutations and EGFR amplification, whereas they co-occur with CDK4 amplification[109]. The clinical response observed in the two FGFR3-TACC3–positive patients treated with an FGFR inhibitor supports clinical studies of FGFR inhibition in FGFR-TACC–positive patients[42]. MET fusions (TFG-MET, CLIP2-MET and PTPRZ1-MET) exists in about 10% pediatric GBMs[110] and about 15% adult secondary GBMs (PTPRZ1-MET)[45]. MET inhibitors could suppress MET tumor growth in xenograft models. A pediatric patient bearing a MET-fusion-expressing GBM was treated with the targeted inhibitor crizotinib. This therapy led to substantial tumor shrinkage and associated relief of symptoms, but new treatment-resistant lesions appeared, indicating that combination therapies are likely necessary to achieve a durable clinical response. EGFR fusions (EGFR-SEPT14, 3.7%; EGFR-PSPH, 1.9%) are also frequent in GBMs[111]. EGFR-SEPT14 fusions activate STAT3 signaling and confer mitogen independence and sensi ivity to EGFR inhibition in preclinical studies. Other targetable involving NTRK, BRAF and PDGFRA also have been found in gliomas. MGMT fusions (NFYC-MGMT, BTRC-MGMT and SAR1A-MGMT) were reported in recurrent GBMs[112], which might contribute to the tumor clonal evolution and therapeutic target.

Although the current targeted therapies have not demonstrated a significant impact on survival, a multimodality approach by combinations of current standard of care and novel therapies might improve survival outcomes and quality of life for glioma patients.

5.2 Immunotherapy

A series of different immunotherapies, including vaccination, oncolytic viruses, immune-checkpoint inhibitors, etc. are currently being actively investigated in GBM patients.

To induce an active immune microenvironment and strengthen the anti-glioma activity of adaptive immune system in glioma patients, vaccination has been considered as pursued a promising path forward. Vaccination relies on dendritic cell (DC)-mediated antigen (GBM-associated peptides, antigens, or epitopes derived from tumor lysates) presentation to T cells of the adaptive immune system. Several peptide mimics, such as EGFRvIII, IDH1-R132H and TERT, or a combination of peptides, have completed or are being studied in phase II or III clinical trials. A large phase III clinical trial of EGFRvIII vaccine[113] (n=745, ACT IV, NCT01480479) showed negative outcome, but some phase II clinical trials (ACTIVATe, NCT00643097[114]; HeatShock, NCT00905060) showed superior outcomes comparing to controls. A randomized phase II trial in recurrent, EGFRvIII positive GBM patients of rindopepimut plus bevacizumab, compared with bevacizumab plus control, showed a potential PFS benefit, indicating that the timing of therapy or combination approaches may be important[37].

Oncolytic viruses can activate the immune system through pathogen-associated molecular patterns and pattern recognition receptors, and activate macrophages through receptors. A completed phase II clinical trials (BrTK02, NCT00589875[115] of oncolytic viral therapies showed

favorable prognosis. To date, there is no large phase III trials focusing on viral therapies. A recently published study of recurrent GBMs treated with recombinant poliovirus showed that intratumoral infusion of the recombinant nonpathogenic polio-rhinovirus chimera (PVSRIPO) confirmed the absence of neurovirulent potential. The survival rate among patients who received PVSRIPO immunotherapy was higher at 24 and 36 months than the rate among historical controls[116].

Immune checkpoint inhibitors are antibodies that reduce the activity of endogenous, negative regulatory pathways limiting T cell activation. The immune checkpoint inhibitors have achieved a major improvement of immune therapies in some vital cancers in the past years. In gliomas, higher PD-1/PD-L1 expression in glioblastoma has been correlated with poorer patient prognosis in some studies[117], which might be the result of increased suppression of anti-tumor immunity. Trials of immune checkpoint inhibitors, predominantly targeting PD-1/PD-L1 and/or CTLA-4, have been ongoing in newly diagnosed and recurrent GBM, although initial results have been disappointing. Due to the cold immunological microenvironmen of GBM tumors, phase III studies of PD-1 inhibitor nivolumab were both negative in patients with recurrent (CheckMate-143) and MGMT unmethylated, newly diagnosed (CheckMate-498) GBM. A recent phase III trial of nivolumab versus bevacizumab in recurrent GBM demonstrated no improvement in patient OS[118]. Another interesting attempt is neoadjuvant anti-PD-1 treatment prior to surgery, and two recent studies indicated favorable local immune response and improved survival in recurrent GBM patients[119, 120].

Chimeric antigen receptor (CAR) T cell therapy used engineered T cells expressing chimeric antigen receptors, which lined antigen recognition domains of antibodies to T cell activation domains. A recent case study reported that a patient with recurrent multifocal glioblastoma received CAR T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2)[121]. No toxic effects of grade 3 or higher were observed, while, the regression of all intracranial and spinal tumors was observed. This clinical response continued for 7.5 months after the initiation of CAR T cell therapy. At present, a number of CAR-T cell therapy targets have been used in glioma treatment, such as EGFRvIII, HER2, EphA2, CD70, GD2, and B7H3[122]. Clinical trials have shown that CAR T cells could infiltrate into tumor tissues and become activated. But further studies are required to identify critical targets for gliomas and understand its potential efficacy in CAR-T cell therapy[123].

Although several negative results of immune therapy are disappointing for malignant gliomas, using combination approaches, and reversing local immunosuppression in the microenvironment, might be a promising strategy in the future.

5.3 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)[8, 124-127]. The discovery of IDH1 R132H in gliomas remains an important finding in biomedical research. 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. Blocking the activity by several IDH1/IDH2 inhibitors has proven to be promising in preclinical models. In a phase I study, ivosidenib (AG-120) 500 mg once per day was associated with a favorable safety profile, prolonged disease control, and reduced growth of nonenhancing tumors

in patients with IDH-mutant advanced glioma[12]. Thus, the evaluation of efficacy of these molecules (e.g. AG-120, AG-221, AG-881, BAY1436032, and DS-1001b) is still in early clinical development and the results of ongoing and subsequent clinical trials will provide pivotal insight about the efficacy and toxicity of these compounds in patients[128].

Note

This guideline was prepared by a joint committee of Chinese Glioma Cooperative Group (CGCG), Society for Neuro-Oncology of China (SNO-China) 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, 2000. The search was completed in July 2020.

The joint committee covered all fields of expertise in neuro-oncology, including neurosurgeons, neurologists, neuropathologists, neuroradiologists, radiation and medical oncologists and clinical trial experts. The scientific evidence of papers collected from the lit rature was evaluated and graded (summarized in **Table 2**) according to the Oxford Centre for Evidence-based Medicine Levels of Evidence and Grades of Recommendation.

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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.

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Figure captions

Figure1. The current integrated diagnostic algorithm for diffuse gliomas according to 2016 WHO classification and cIMPACT-NOW updates. (Abbreviations: NOS, not other-wise specified; NEC, not elsewhere classified; WHO, World Health Organization; cIMPACT-NOW, the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy)

Figure 2. The overall survival curve for adult diffuse gliomas from CGGA (A) and TCGA (B) database according to 2016 WHO Classification. (Abbreviations: LGG, lower grade glioma; GBM, glioblastoma; NA, not arrived)

Figure 3. The therapeutic treatment algorithm for diffuse gliomas. (Abbreviations: 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)

Figure 4. The surgical strategies and extent of resection for diffuse gliomas. (Abbreviations: ZOOMit, zoomed imaging technique with parallel transmission; BOLD, blood oxygen level-dependent; WHO, World Health Organization; CE, contrast-enhanced; NCE, non-contrast-enhanced)

Table 1. Molecular markers and their clinical relevance in gliomas.

Markers	Genetic alterations	Detection methods	Clinical importance
IDH1[8-13]	Mutations (R132H/C/L/S/G)	IHC, Sanger sequencing, pyrosequencing, NGS	*Diagnostic value* Molecular parameters for glioma classification; Differential diagnosis between diffuse and non-diffuse gliomas (WHO grade 1) or gliosis.
IDH2[8-11, 13]	Mutations (R172K/M/G/W)	Sanger sequencing, pyrosequencing, NGS	*Prognostic value* Relatively favorable prognosis; Important in stratification for clinical trials; Associated with *MGMT* promoter methylation; Benefit from radiation or alkylating chemotherapy; Potential parameters for target therapy (e.g., Ivosidenib).
Chromosome 1p/19q[14-17]	codeletion	FISH, PCR, array- or NGS-based methods	*Diagnostic value* Essential for diagnosis of oligodendroglioma. *Prognostic value* Relatively favorable prognosis; Predictive of response to alkylating chemotherapy and combination of radiation and alkylating chemotherapy.
H3 K27[13, 18-21]	Mutation (K27M)	IHC, Sanger sequencing, NGS	*Diagnostic value* Diagnostic parameters for Diffuse midline glioma, H3 K27M-mutant. *Prognostic value* Relatively worse prognosis than that of wildtype diffuse midline gliomas; Potential parameter for target therapy (e.g., EZH2 inhibitors).
H3 G34[13, 22-24]	Mutations (G34R/V)	IHC, Sanger sequencing, NGS	*Diagnostic value* Diagnostic parameters for Diffuse glioma, H3.3 G34-mutant. *Prognostic value* Slightly longer survival time than IDH-wildtype glioblastoma, but shorter than IDH-mutant astrocytoma, WHO grade 4.
ATRX[13, 25, 26]	Loss of function mutations	IHC, Sanger sequencing, NGS	*Diagnostic value* IDH-mutant astrocytomas, with loss of ATRX nuclear expression and/or strong, diffuse

			p53 immunopositivity, could be diagnosed without 1p/19q testing. *Prognostic value* Relatively favorable prognosis in IDH-wildtype glioblastoma.
TP53[13, 27]	Mutations	IHC, Sanger sequencing, NGS	*Diagnostic value* IDH-mutant astrocytomas, with loss of ATRX nuclear expression and/or strong, diffuse p53 immunopositivity, could be diagnosed without 1p/19q testing. Differential diagnosis between diffuse and no diffuse gliomas (WHO grade 1) or gliosis.
CDKN2A/B[13, 28-31]	Homozygous deletion	FISH, qPCR, MLPA, array- or NGS-based methods	*Diagnostic value* Diagnostic parameters for IDH-mutant astrocytoma, grade 4, in the absence of necrosis and/or microvascular proliferation; Frequent in high-grade astrocytoma with piloid features. *Prognostic value* Relatively poor prognosis in patients with IDH-mutant diffuse astrocytic gliomas
TERT[25, 29, 32-35]	Promoter mutations (C228T/C250T)	Sanger sequencing, pyrosequencing, NGS	*Diagnostic value* Frequent in oligodendroglioma and glioblastoma; diagnostic parameters for diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade 4. *Prognostic value* Relatively worse prognosis in IDH-wildtype glioma; Relatively favorable prognosis in IDH-mutant gliomas.
Chromosome 7/10 [29, 30, 35, 36]	7 gain/10 loss	FISH, array- or NGS-based methods	*Diagnostic value* Diagnostic parameters for diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade 4 *Prognostic value* Relatively worse prognosis in IDH-wildtype glioma.
EGFR[13, 29, 36]	Amplification	FISH, digital PCR, array- or NGS-based methods	*Diagnostic value* Diagnostic parameters for IDH-wildtype astrocytoma, with molecular features of

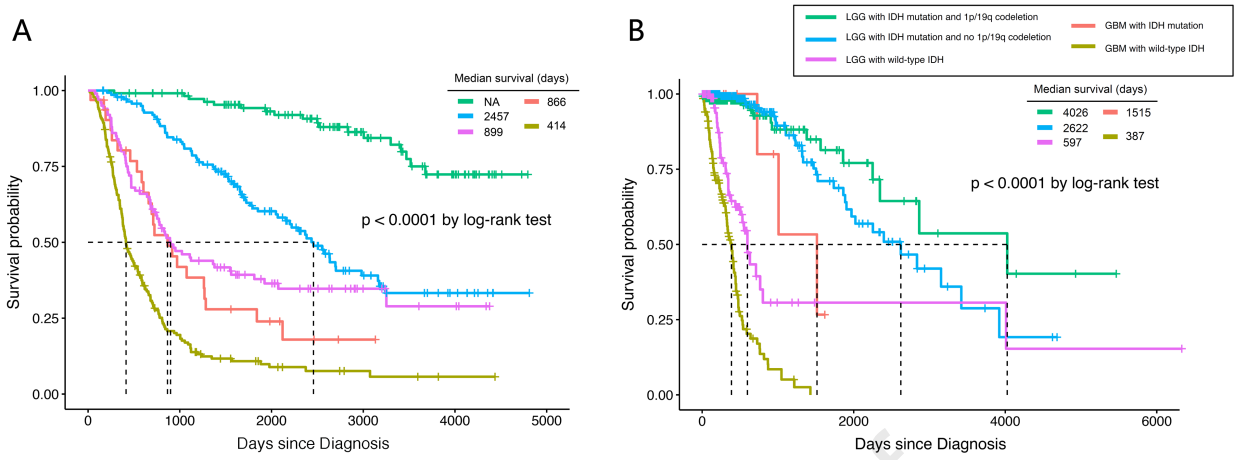
			glioblastoma, grade 4; High copy number amplification frequent in IDH-wildtype glioblastomas.
	EGFRvIII[37]	RT-PCR, digital PCR, IHC, MLPA, NGS	*Prognostic value* EGFRvIII present in about half of EGFR-amplified glioblastomas. Potential parameter for target therapy.
BRAF[19, 38, 39]	Activating mutation (*BRAF* V600E)	IHC, Sanger sequencing, pyrosequencing, NGS	*Diagnostic value* Presented in a variety of gliomas, including epithelioid glioblastoma. *Prognostic value* Potential parameter for target therapy (e.g., vemurafenib).
MGMT[40, 41]	Promoter methylation	pyrosequencing, MSP, array-based methods	*Prognostic value* Relatively favorable prognosis in glioblastoma; Benefit from temozolomide treatment for high-grade gliomas; associated with IDH mutation and G-CIMP phenotype
FGFR[42, 43]	Fusion (FGFR-TACC)	Sanger sequencing, qPCR, NGS	*Diagnostic value* Occurred in glioblastoma and IDH-wildtype astrocytoma. *Prognostic value* Potential parameter for target therapy (e.g., FGFR inhibitors).
MET[44, 45]	Fusion (PTPRZ1-MET) Mutation (METex14)	Sanger sequencing, qPCR, NGS	*Diagnostic value* Occurred in glioblastoma and IDH-mutant astrocytoma. *Prognostic value* Relatively worse prognosis in secondary glioblastoma; Potential parameter for target therapy (e.g., MET inhibitors).

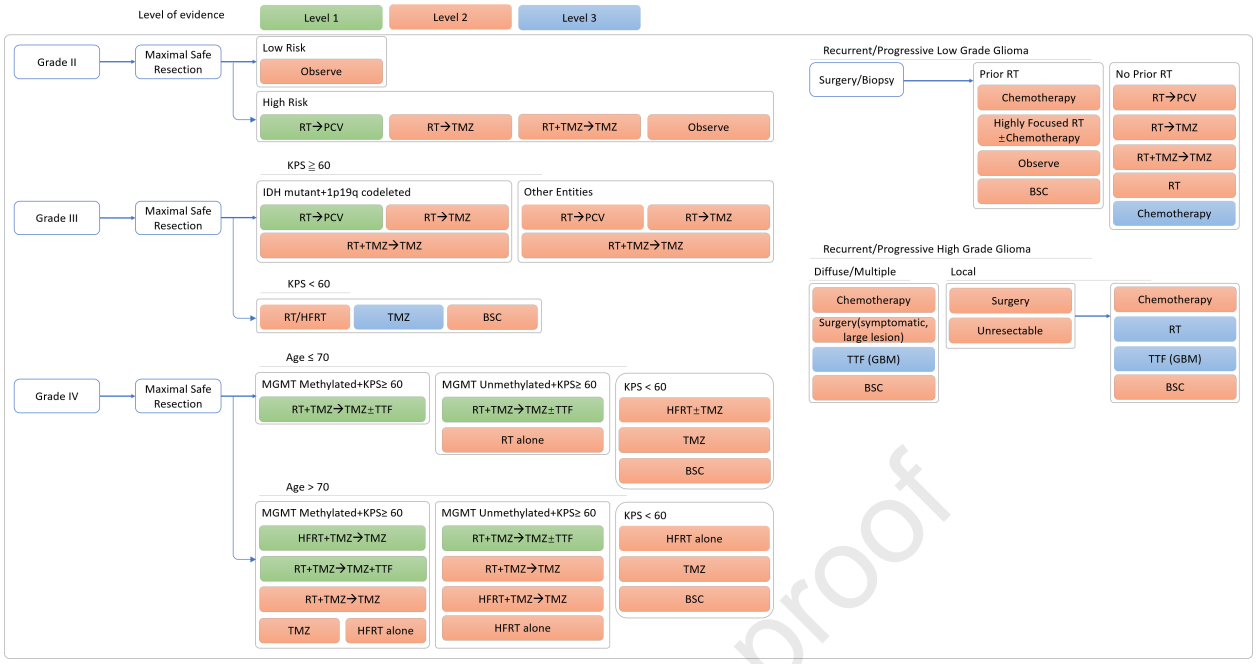
Abbreviations: IHC, immunohistochemistry; NGS, next-generation sequencing; FISH, fluorescence in-situ hybridization; PCR, polymerase chain reaction; MSP, methylation-specific PCR; RT-PCR, real-time PCR; qPCR, quantitative PCR; MLPA, multiplex litigation-dependent probe amplification.

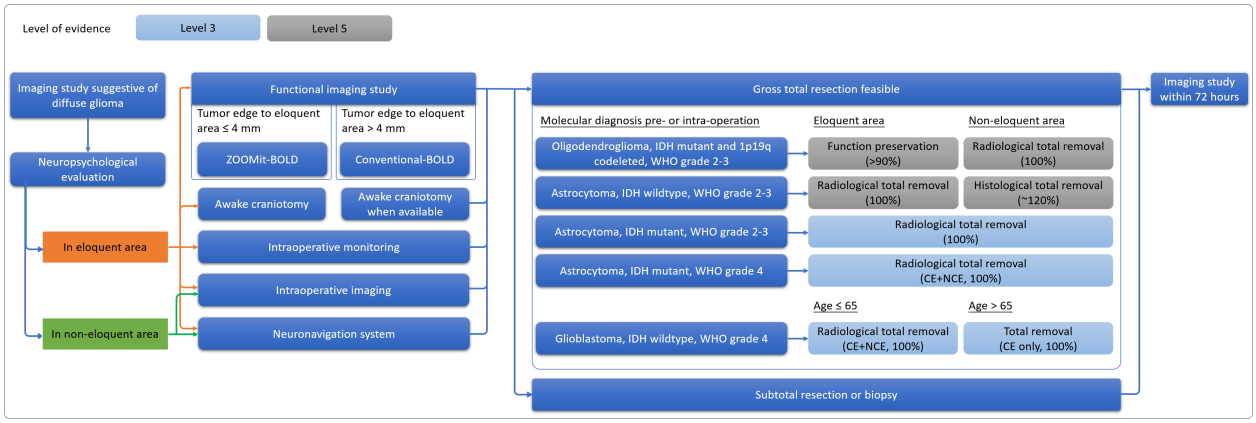
Table 2. Conclusion and recommendations.

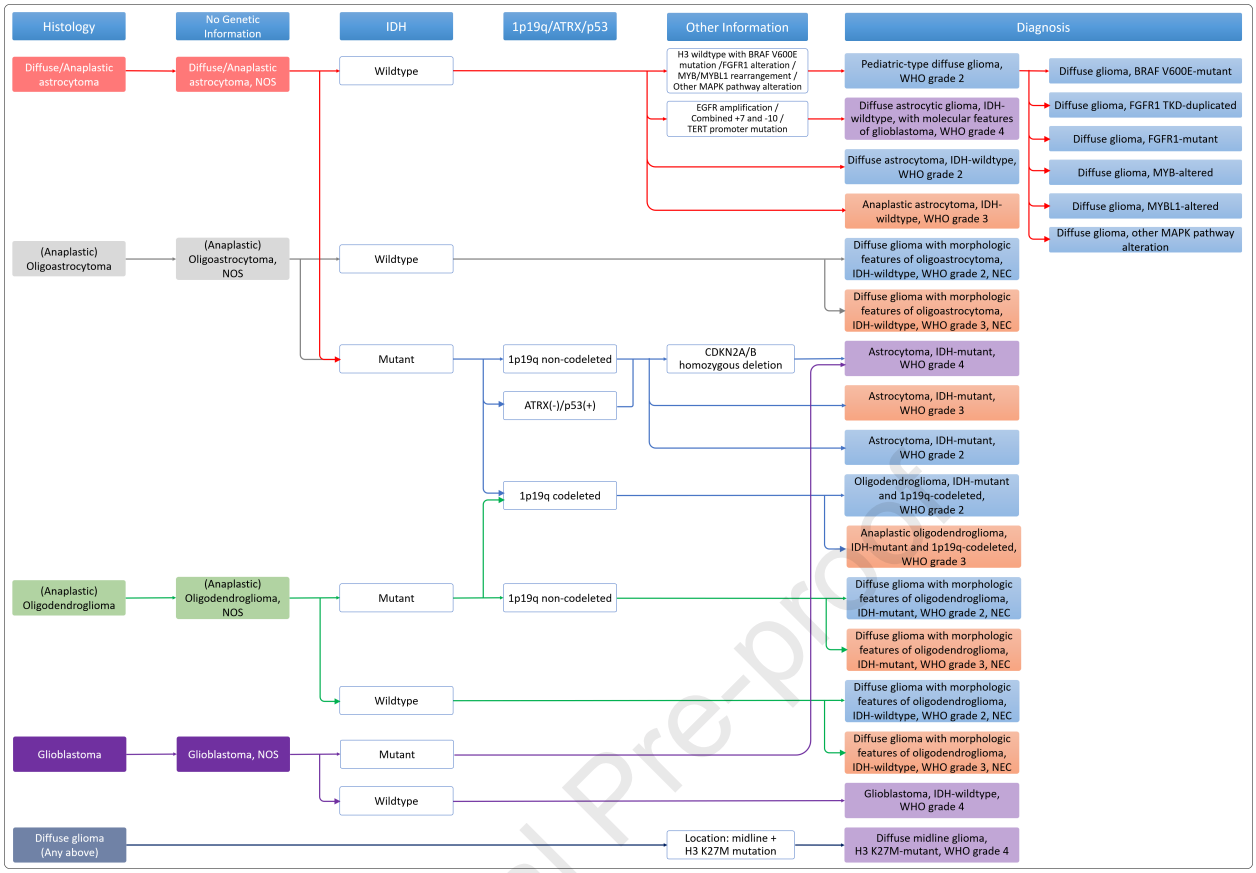
	Level of evidence	Grade of recommendation
General recommendations		
Gliomas are diagnosed using morphological and molecular criteria according to 2016 WHO classification.	1a	A
Karnofsky performance score, neurological function, and age need to be considered in clinical decision making in neuro-oncology.	1b	A
Magnetic resonance imaging can be used to detect the presence of tumor and guide managements such as biopsy, surgery and radiation.	2b	B
Maximal safe resection is the first option for all gliomas, while minimizing the postoperative morbidity.	2a	B
Molecular biomarkers can inform the design of surgical strategies for diffuse gliomas.	3b	B
When surgery is not feasible, a biopsy should be performed to ob ain a histological diagnosis.	4	C
Immunohistochemistry for mutant IDH1 R132H protein and nuclear expression of ATRX should be performed routinely in the diagnosis of diffuse gliomas.	1b	A
IDH mutation status should be assessed by immunohistochemistry for IDH1 R132H. If negative, immunohistochemistry should be followed by sequencing of IDH1 codon 132 and IDH2 codon 172 in all WHO grade II and III diffuse gliomas and in all glioblastomas of patients younger than 55 years to allow for integrated diagnoses according to the 2016 WHO cla sification and to guide treatment decisions.	1b	A
Chromosome 1p/19q codeletion status should be determined in all IDH-mutant gliomas with retained nuclear expression of ATRX.	1b	A
MGMT promoter me hylation status should be determined in elderly patients with glioblastoma and in IDH-wildtype WHO grade II and III diffuse gliomas to guide decision for the use of temozolomide instead of or in addition to radiotherapy.	1b	A
Grade II diffuse gliomas		
Younger patients (≤40 years of age) with gross total resection can be observed after surgery, but close follow-up is needed.	1b	B
For patients with high risk (age >40 years or none receiving gross total resection), an adjuvant treatment is indicated at any time.	1b	B
Radiotherapy may be selected for high risk patients (age >40 years or gross total resection not received).	1b	A
Chemotherapy is an option as initial treatment for patients with large residual tumors after surgery or unresectable tumors.	1b	B
Standard of care for WHO grade II astrocytomas (IDH-mutant and 1p/19q non-codeleted) and oligodendrogliomas (IDH-mutant and 1p/19q-codeleted) that require further treatment includes resection or biopsy followed by involved field radiotherapy and maintenance procarbazine, lomustine, and vincristine	1b	B

chemotherapy		
Grade III diffuse gliomas		
Patients with 1p/19q-codeleted anaplastic oligodendroglial tumours should be treated with radiotherapy plus procarbazine, lomustine, and vincristine chemotherapy.	1b	B
Standard of care for 1p/19q non-codeleted anaplastic astrocytoma includes resection or biopsy followed by involved field radiotherapy and maintenance temozolomide.	1b	B
MGMT promoter methylation could be a predictive marker for response to alkylating chemotherapy in IDH-wildtype anaplastic gliomas.	2b	B
Temozolomide chemotherapy is standard treatment at progression after surgery and radiotherapy.	1b	A
Glioblastoma (Grade IV)		
Standard of care for newly diagnosed glioblastoma includes resection or biopsy followed by involved-field radiotherapy and concurrent and adjuvent temozolomide with or without alternating electric field therapy.	1b	A
Temozolomide is particularly active in patients with MGMT promoter methylation whereas its activity in patients with MGMT promoter-unmethylated tumours is marginal.	1b	B
In elderly patients with IDH-wildtype and MGMT promoter methylation, temozolomide chemotherapy may be considered, while radiotherapy is the treatment of choice for patients with an unmethylated gene promoter.	1b	B
Standards of care are not well defined at recurrence. Temozolomide rechallenge, bevacizumab are pharmacological options, but an effect on overall survival remains unproven. When available, recruitment into appropriate clinical trials should be considered.	2b	B









Highlights

The guideline provides diagnostic and management recommendations for diffuse gliomas.

The guideline focuses on molecular diagnostics, and the main treatment modalities.

The guideline includes clinical trials of immune therapies and target therapies.

The guideline should serve as an application for all medical professionals.

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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: