

European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas

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Abstract

The European Association for Neuro-Oncology guideline provides recommendations for the clinical care of adult patients with astrocytic and oligodendroglial gliomas, including glioblastomas. The guideline is based on the 2016 WHO classification of tumours of the central nervous system and on scientific developments since the 2014 guideline. The recommendations focus on pathological and radiological diagnostics, and the main treatment modalities of surgery, radiotherapy, and pharmacotherapy. In this guideline we have also integrated the results from contemporary clinical trials that have changed clinical practice. The guideline aims to provide guidance for diagnostic and management decisions, while limiting unnecessary treatments and costs. The recommendations are a resource for professionals involved in the management of patients with glioma, for patients and caregivers, and for health-care providers in Europe. The implementation of this guideline requires multidisciplinary structures of care, and defined processes of diagnosis and treatment.

Introduction

The European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas follows the revision of the fourth edition of WHO classification of tumours of the central nervous system¹ and builds on previous guidelines.^{2,3} The guideline covers adult astrocytic and oligodendroglial gliomas of WHO grades II–IV, including glioblastomas, and variants of these tumours, and discusses prevention, early diagnosis and screening, histological and molecular diagnostics, therapy, and follow-up. However, the guideline does not address differential diagnosis, adverse effects of treatment, or supportive or palliative care.

Diagnostics

Prevention, early diagnosis, and screening

The annual incidence of gliomas, including glioblastoma, is around six cases per 100 000 individuals worldwide. Serum markers for early detection have not been identified. Brain MRI has the highest sensitivity for the detection of small tumours. Gliomas can evolve rapidly over several weeks or months, presenting

challenges for population-based prevention or early intervention. Screening is therefore limited to individuals at genetic risk—eg, patients with neurofibromatosis type I, Turcot syndrome, and Li Fraumeni syndrome. Repeat scans are not recommended in such individuals unless clinically justified. A particular challenge is the counselling and screening of relatives of patients who carry germline mutations associated with gliomagenesis, given that prevention strategies are not available.⁴

History and clinical examination

The evolution of neurological symptoms and signs enables the growth dynamics of gliomas to be estimated: tumours that cause symptoms for weeks are probably fast-growing, whereas tumours that cause symptoms for years before being diagnosed are probably slow-growing. Patient history might also reveal familial risk or exogenous risk factors, including exposure to radiation or other conditions associated with brain tumours. Discussion with relatives might be required to obtain a reliable history. Characteristics of clinical presentation are new onset epilepsy, focal deficits, including neurocognitive impairment, and indicators of intracranial mass effect, such as headache, vomiting, and altered consciousness. Physical examination focuses on the detection of systemic cancer and contraindications for neurosurgical procedures. Neurocognitive assessment beyond documenting the Karnofsky performance score or the WHO performance status, and the performance of a Mini-Mental State Examination⁵ or a Montreal Cognitive Assessment,⁶ has become increasingly common.^{7,8} The Mini-Mental State Examination is widely used as a screening tool across Europe and remains freely available for individual use—eg, outside of clinical trials.

Ancillary studies

MRI, including T2-weighted and fluid-attenuated inversion recovery sequences, and T1-weighted sequences before and after gadolinium use, in at least one plane, is the standard method for the detection of a glioma.⁹ Additionally, cranial CT shows calcifications, intra-arterial angiography can aid the surgical strategy, and aminoacid PET helps define metabolic hotspots for biopsy.¹⁰ Standardised MRI sequences are also recommended to assess the efficacy of therapeutic interventions.¹¹ Cerebrospinal fluid studies have no major role in the diagnostic work-up of gliomas and lumbar punctures carry the risk of neurological deterioration in patients with large space-occupying tumours. Electroencephalography is useful for monitoring tumour-associated epilepsy and in determining causes of altered consciousness.

Preoperative management

Management should follow documented local standard operating procedures and multidisciplinary discussion in a brain tumour board review that ideally should include dedicated neuroradiologists and neuropathologists, in addition to neurosurgeons, radiation oncologists, and neurooncologists. Before surgery, unless contraindications are present or primary cerebral lymphoma or inflammatory lesions are suspected, corticosteroids should be administered to decrease tumour-associated oedema. Additional pharmacological interventions, such as osmotic drugs, are rarely necessary. Patients with glioma who have epileptic seizures

should receive anticonvulsant drugs preoperatively; however, evidence shows that primary prophylaxis does not reduce the risk of a first seizure in patients with glioma without a history of seizures.¹²

Biopsy or resection

Treatment decisions in patients with glioma are dependent on tissue diagnosis and the assessment of selected molecular markers. Thus, surgery is commonly performed with diagnostic and therapeutic objectives. The surgical management of patients with glioma should take place in high-volume specialist centres, where high-volume refers to the high volume of patients individual surgeons specifically treat.¹³ A decision to initiate palliative care without histological diagnosis should be avoided unless the risk of the biopsy is considered too high or the prognosis is likely to be unfavourable even with treatment—eg, in patients with large tumours who are at risk of rapid clinical decline. Stereotactic biopsies under local anaesthesia are associated with low morbidity¹⁴ and an integrated diagnosis can be used to counsel patients and relatives even when no further tumour-specific therapy is recommended. Serial samples from the tumour mass along the trajectory of the biopsy needle should be acquired during the stereotactic procedure, which requires an experienced team of neurosurgeons and neuropathologists.

Histological classification and molecular diagnostics

Intraoperative assessment of cytological specimens or frozen sections before the surgical procedure is terminated helps to ensure that sufficient tissue is obtained to establish a diagnosis. Tumour tissue is formalin-fixed and embedded in paraffin for conventional histological staining, including routine haematoxylin-eosin staining and additional immunohistochemical and molecular analyses. If possible, part of the tissue should be cryopreserved for future molecular marker studies. The diagnostic process follows the WHO classification¹ and integrates histological tumour typing, tumour grading using the four-tiered WHO grading scheme (WHO grade I–IV)—designed to provide clinicians with information about the biological behaviour of tumours and consequently the patient's prognosis and outcome—and tissue-based molecular biomarkers (figure 1). The 2016 WHO classification¹ specifies the major diagnostic role of isocitrate dehydrogenase 1 (*IDH1*) codon 132 or *IDH2* codon 172 missense mutations and defines diffuse and anaplastic astrocytic gliomas and oligodendroglial gliomas as IDH-mutant tumours.¹

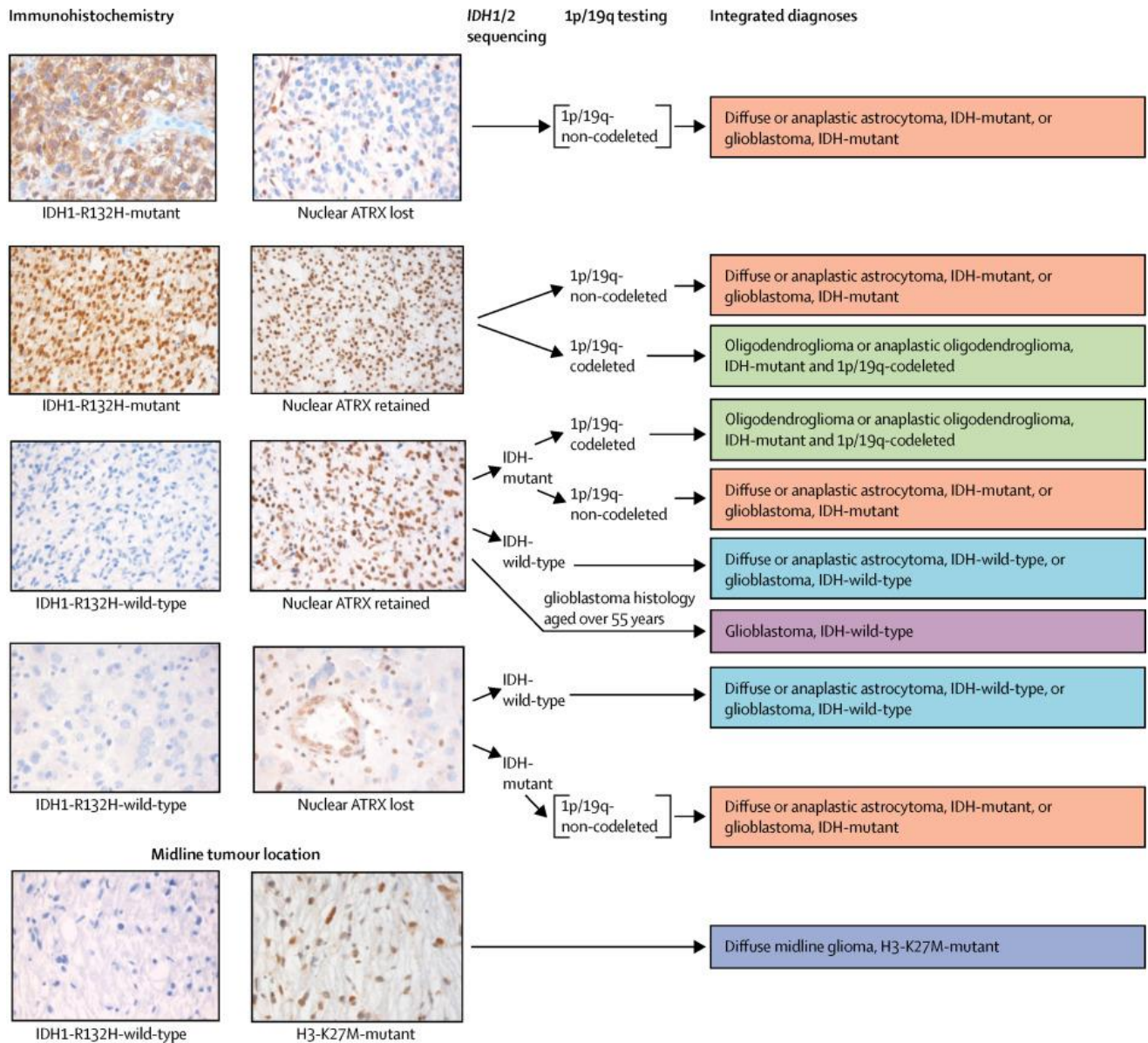


Figure 1. Diagnostic algorithm for integrated classification of diffuse astrocytic and oligodendroglial gliomas, including glioblastoma

Oligodendroglial tumours also have 1p/19q codeletions. IDH-wild-type diffuse astrocytomas and anaplastic astrocytomas are considered provisional entities. Not otherwise specified categories have been introduced for gliomas and are defined as those that cannot be tested for the diagnostically relevant markers, or for which testing remains inconclusive. Table 1 shows the management recommendations for these not otherwise specified categories, but evidence on how to manage these tumours best is scarce. Oligoastrocytomas and gliomatosis cerebri do not have distinctive genetic and epigenetic profiles^{24,25} and thus are not considered distinct glioma entities.¹ Diffuse midline glioma, histone H3-K27M-mutant, has been introduced as a new entity characterised by midline tumour location and the presence of a mutation at codon 27 that results in a lysine to methionine change in histones H3-3 or H3-1.¹

Table 1. Key treatment recommendations for patients with diffuse astrocytic and oligodendroglial tumours according to the new WHO classification¹

	First-line treatment*	Salvage therapies**	Comments and references
Diffuse astrocytic and oligodendroglial tumours			
Diffuse astrocytoma, IDH-mutant	Watch-and-wait or radiotherapy followed by PCV (or temozolomide plus radiotherapy followed by temozolomide)	Nitrosourea (or temozolomide rechallenge or bevacizumab [§])	RTOG 9802 trial ¹⁵ and extrapolation from WHO grade III tumours ¹⁶
Gemistocytic astrocytoma, IDH-mutant	Watch-and-wait or radiotherapy followed by PCV (or temozolomide plus radiotherapy followed by temozolomide)	Nitrosourea (or temozolomide rechallenge or bevacizumab [§])	..
Diffuse astrocytoma, IDH-wild-type	Watch-and-wait (remains controversial), radiotherapy, radiotherapy followed by PCV, or temozolomide and radiotherapy followed by temozolomide (according to <i>MGMT</i> status [remains controversial])	Temozolomide, or nitrosourea (or temozolomide rechallenge) or bevacizumab [§]	Extrapolation from IDH-wild-type glioblastoma ¹⁷
Diffuse astrocytoma, not otherwise specified	Watch-and-wait or radiotherapy followed by PCV (or temozolomide plus radiotherapy followed by temozolomide)	Nitrosourea (or temozolomide rechallenge or bevacizumab [§])	..
Anaplastic astrocytoma, IDH-mutant	Radiotherapy followed by temozolomide	Nitrosourea or temozolomide rechallenge or bevacizumab [§]	¹⁶
Anaplastic astrocytoma, IDH-wild-type	Radiotherapy or temozolomide plus radiotherapy followed by temozolomide, according to <i>MGMT</i> status (remains controversial)	Temozolomide, or nitrosourea (or temozolomide rechallenge) or bevacizumab [§]	Extrapolation from IDH-wild-type glioblastoma ^{17,18}
Anaplastic astrocytoma, not otherwise specified	Radiotherapy followed by temozolomide and radiotherapy followed by temozolomide, according to <i>MGMT</i> status (remains controversial)	Nitrosourea or temozolomide rechallenge or bevacizumab [§]	..
Glioblastoma, IDH-wild-type (including giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma)	Temozolomide plus radiotherapy followed by temozolomide for patients aged 70 years or younger; radiotherapy alone (<i>MGMT</i> unmethylated) or temozolomide plus radiotherapy followed by temozolomide or temozolomide alone (<i>MGMT</i> methylated) for patients older than 70 years	Nitrosourea or temozolomide rechallenge or bevacizumab [§] , radiotherapy for radiotherapy-naive patients	^{17,19–21}
Glioblastoma, IDH-mutant	Radiotherapy with or without temozolomide followed by temozolomide	Nitrosourea or temozolomide rechallenge or bevacizumab [§]	Extrapolation from IDH-mutant anaplastic astrocytoma ¹⁶
Glioblastoma, not otherwise specified	Temozolomide plus radiotherapy followed by temozolomide for patients aged 70 years or younger; radiotherapy alone (<i>MGMT</i> unmethylated) or temozolomide plus radiotherapy	Nitrosourea or temozolomide rechallenge or bevacizumab [§] , radiotherapy for radiotherapy-naive patients	¹⁷

	First-line treatment*	Salvage therapies†‡	Comments and references
	followed by temozolomide or temozolomide alone (<i>MGMT</i> methylated) for patients older than 70 years		
Diffuse midline glioma, H3-K27M mutant	Radiotherapy or temozolomide plus radiotherapy followed by temozolomide
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	Watch-and-wait or radiotherapy followed by PCV	Temozolomide or bevacizumab [§]	Extrapolation from WHO grade III tumours ^{22,23} and RTOG 9802 trial ¹⁵
Oligodendroglioma, not otherwise specified	Watch-and-wait or radiotherapy followed by PCV	Temozolomide or bevacizumab [§]	Extrapolation from WHO grade III tumours ^{22,23} and RTOG 9802 trial ¹⁵
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	Radiotherapy followed by PCV	Temozolomide or bevacizumab [§]	22,23
Anaplastic oligodendroglioma, not otherwise specified	Radiotherapy followed by PCV	Temozolomide or bevacizumab [§]	22,23
Oligoastrocytoma, not otherwise specified	Watch-and-wait or radiotherapy followed by PCV	Temozolomide or bevacizumab [§]	Extrapolation from WHO grade III tumours ^{22,23} and RTOG 9802 trial ¹⁵
Anaplastic oligoastrocytoma, not otherwise specified	Radiotherapy followed by PCV	Temozolomide or bevacizumab [§]	22,23
Other astrocytic tumours			
Pilocytic astrocytoma Pilomyxoid astrocytoma	Surgery only	Surgery followed by radiotherapy	..
Subependymal giant cell astrocytoma	Surgery only	Surgery	..
Pleomorphic xanthoastrocytoma	Surgery only	Surgery	..
Anaplastic pleomorphic xanthoastrocytoma	Radiotherapy	Surgery followed by chemotherapy with temozolomide	..

IDH=isocitrate dehydrogenase. PCV=procarbazine, lomustine, and vincristine. RTOG=Radiation Therapy Oncology Group. *MGMT*=O⁶-methylguanine DNA methyltransferase. H3=histone 3.

* Maximum safe resection is recommended whenever feasible in all patients with newly diagnosed gliomas.

† Second surgery should always be considered, but clinical benefit may be limited to patients where a gross total resection can be achieved.

‡ Re-exposure to temozolomide and less so nitrosourea treatment has little activity in tumours without *MGMT* promoter methylation.

§ Depending on local availability.

Four molecular biomarkers are central to diagnosing and treating gliomas: IDH mutation, 1p/19q codeletion, histone H3-K27M mutation, and O⁶-methylguanine DNA methyltransferase (*MGMT*) promoter methylation. IDH mutation, 1p/19q codeletion, and histone H3-K27M mutation have been incorporated into the revised WHO tumour classification (table 1), whereas *MGMT* promoter methylation status guides treatment decisions about chemotherapy use.²⁶ *MGMT* promoter methylation status should be tested by the use of molecular genetic tests, such as methylation-specific PCR or pyrosequencing of bisulphite-modified tumour DNA, whereas immunocytochemistry is not an adequate method to establish the *MGMT* status. Immunohistochemical detection of loss of nuclear ATRX expression in IDH-mutant gliomas is characteristic of astrocytic gliomas without 1p/19q codeletion. Thus, additional testing for 1p/19q codeletion might not be required in such cases, unless doubts exist regarding astrocytic differentiation or the validity of ATRX immunohistochemistry. By contrast, retention of nuclear ATRX expression in an IDH-mutant glioma should prompt testing for the 1p/19q codeletion to differentiate an IDH-mutant astrocytic glioma from an IDH-mutant and 1p/19q-codeleted oligodendroglial tumour. Thus, ATRX immunohistochemistry might facilitate diagnostic categorisation of IDH-mutant gliomas but is not a substitute for 1p/19q codeletion testing. Similarly, detection of mutations in the telomerase reverse transcriptase (*TERT*) promoter cannot substitute for 1p/19q codeletion testing because *TERT* promoter mutations are not restricted to IDH-mutant and 1p/19q-codeleted oligodendroglial tumours, but also occur in a minor subset of IDH-mutant astrocytic gliomas and most IDH-wild-type glioblastomas. High-throughput assays based on next generation sequencing or microarray techniques might soon replace single marker assessments. Diagnostic algorithms for patients with glioma should be standardised and should not delay radiotherapy or tumour-specific pharmacotherapy.

Figure 1 shows a commonly used approach for differential diagnostic work-up after histological analysis: the tumours are assessed by immunohistochemistry for the IDH1-R132H mutation and loss of nuclear ATRX protein expression. In the case of diffuse gliomas located in midline structures (thalamus, brain stem, and spinal cord), immunostaining for the histone H3-K27M mutation characterises diffuse midline glioma, histone H3-K27M-mutant. After immunohistochemistry, molecular analyses for less common *IDH1* codon 132 mutations (other than R132H), or *IDH2* codon 172 mutations (eg, by DNA sequencing), and for codeletion of chromosomal arms 1p and 19q (eg, by fluorescent in-situ hybridisation or microsatellite PCR-based loss of heterozygosity analyses) are done according to the individual immunohistochemistry results. IDH mutation and loss of nuclear ATRX expression classify IDH-mutant astrocytic gliomas (figure 1). Additional molecular testing for 1p/19q codeletion is not routinely required but might be performed to further substantiate the diagnosis (eg, in cases with ambiguous histology). In patients older than 55 years at diagnosis, with a histologically typical glioblastoma, without a pre-existing lower grade glioma and with non-midline tumour location, immunohistochemical negativity for IDH1-R132H expression is sufficient for classification as glioblastoma, IDH-wild-type (figure 1). In all other diffuse gliomas, absence of IDH1-R132H immunopositivity should be followed by *IDH1* and *IDH2* sequencing to detect or exclude other, less common IDH mutations.

IDH-wild-type diffuse astrocytic gliomas with loss of nuclear ATRX expression may be additionally tested for histone H3 mutations (figure 1).

General recommendations for therapy

Prognostic factors

Younger age and better performance status are important positive, therapy-independent prognostic factors across glioma entities, and extent of resection is an important therapy-dependent prognostic factor (figure 2). Molecular markers that favour longer survival, such as IDH mutation and 1p/19q codeletion, are now at the core of the WHO classification and define more homogeneous diagnostic and prognostic entities.^{1,26}

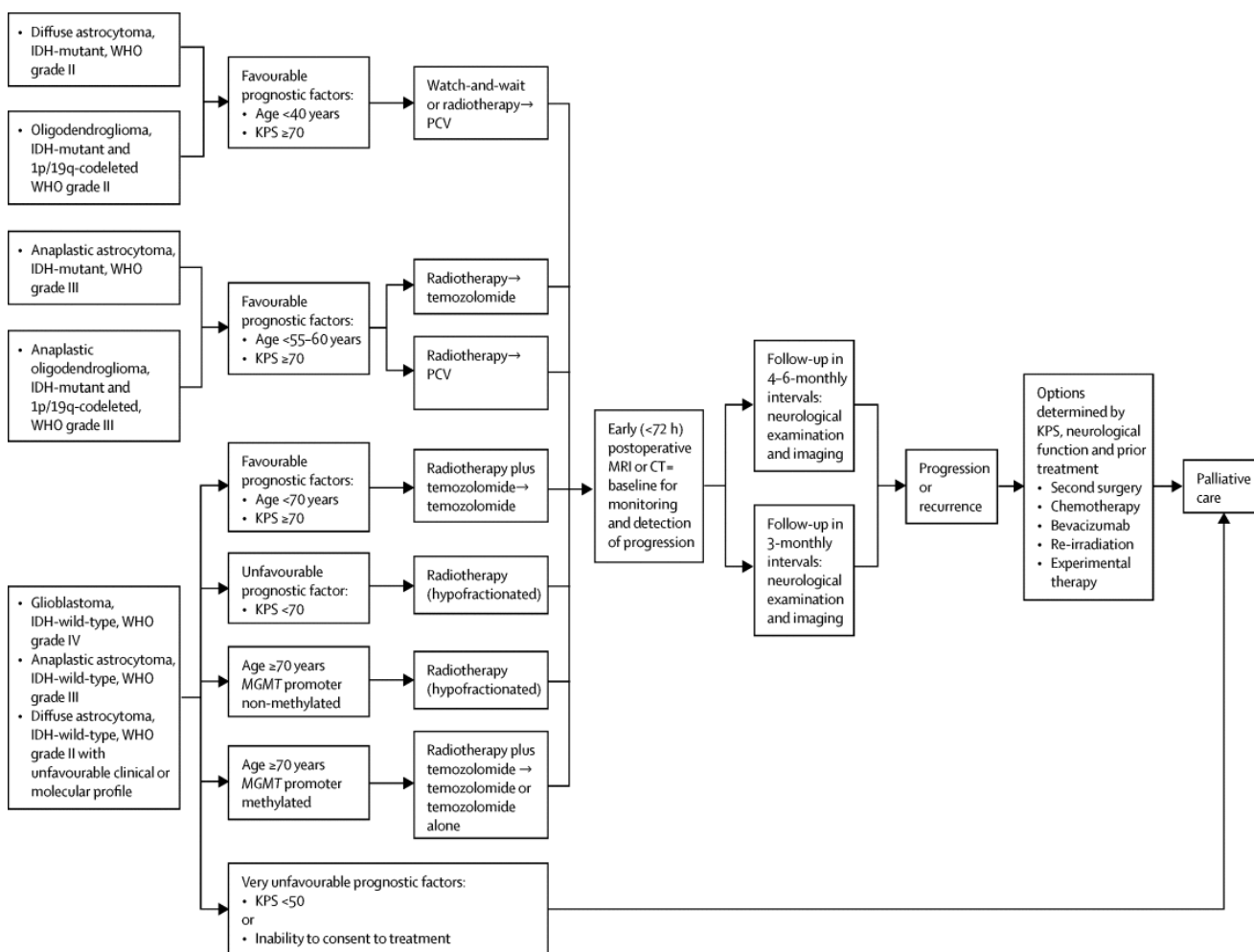


Figure 2. Clinical pathway for glioma

Maximum safe resection is recommended whenever feasible in all patients with newly diagnosed gliomas. IDH=isocitrate dehydrogenase. KPS=Karnofsky performance score. MGMT=O⁶-methylguanine DNA methyltransferase. PCV=procarbazine, lomustine, and vincristine.

Surgical therapy

Beyond a histological diagnosis, the goal of surgery is to remove as much of the tumour as safely possible to improve neurological function. Microsurgical techniques are standard. The use of several tools, including surgical navigation systems with functional MRI datasets, intraoperative MRI, ultrasound, intraoperative functional monitoring and the fluorescent dye 5-aminolevulinic acid to visualise tumour tissue,²⁷ is becoming more frequent in order to increase the extent of resection, while minimising the risk of new neurological deficits.²⁸ The use of evoked potentials (electrical activity in the brain following an external stimulus), electromyography, or mapping in conscious patients under local anaesthesia to monitor and preserve language and cognition, should support resections in eloquent areas (ie, areas of the brain that cannot be removed without causing permanent neurological deficits, such as the cortex and subcortical white matter). The prevention of new, permanent neurological deficits is more important than extent of resection as gliomas are not cured by surgery, because tumour cells infiltrate far beyond the lesion and demonstrate network-like growth, both of which are hallmarks of diffuse gliomas.²⁹ Postoperative deficits due to emerging complications are a negative prognostic factor. Furthermore, quality of life is a high priority to patients and carers. The result of surgery is assessed by early MRI—or CT if MRI is not possible—with and without contrast and diffusion imaging within 24–72 h of surgery, which is part of the standard of care.³⁰ A large residual tumour volume after surgery is a negative prognostic factor, but it remains uncertain whether extent of resection truly matters, or whether resectable tumours have a different biology associated with a less aggressive course of disease.

Radiotherapy

The goal of radiotherapy for patients with gliomas is to improve local control at a reasonable risk benefit ratio. Radiotherapy helps to preserve function and increases survival. Indications for timing, dosing, and scheduling of radiotherapy are determined by diagnosis and prognostic factors, including age, Karnofsky performance score, and extent of resection.³¹ Focal radiotherapy is administered at 50–60 Gy in 1.8–2.0 Gy fractions, depending on prognosis defined by tumour type and grade. Hypofractionated radiotherapy with higher fractions and a lower total dose (eg, 15 × 2.67 Gy) is appropriate in older patients and individuals with poor prognostic factors. The area of residual enhancement on T1 MRI imaging plus the surgical bed is defined as the gross tumour volume. A margin, typically 1.0–1.5 to 2.5 cm including the hyperintensity on T2 or fluid-attenuated inversion recovery imaging, is added to the gross tumour volume to define the clinical target volume. This clinical target volume is then modified to take into account areas in which microscopic spread is unlikely, or to reduce the radiotherapy dose to vital structures. Another margin, usually 0.3–0.5 cm, is added to the clinical target volume to allow for error setup and movement during treatment, to generate the planning target volume.³² PET is being studied for improving target delineation in clinical trials.¹⁰

Organs at high risk of radiotherapy-associated toxicity, including optic nerves, optic chiasm, retinas, lenses, brainstem, pituitary, cochleas, and the hippocampus should be determined. Modern techniques of focused radiotherapy—eg, intensity-modulated or image-guided radiotherapy in patients with newly diagnosed

glioma, and stereotactic radiotherapy in the recurrent setting—might improve the targeted delivery of radiotherapy to better protect surrounding tissue. In children especially, but also in adults with deeply localised tumours, interstitial brachytherapy and proton or heavy ion radiotherapy might be alternatives. Randomised data comparing novel approaches with standard techniques are not available.

Pharmacotherapy

Cytotoxic chemotherapy is part of the standard of care for most patients with glioma (panel; figure 3). This treatment requires regular haematological, hepatic, and renal laboratory tests and exclusion of major lung disease or heart disease and infection. Additionally, blood counts need to be monitored during therapy. Temozolomide, an oral DNA alkylating agent with good blood–brain barrier penetration, is widely used in glioma treatment and has a favourable safety profile, with myelosuppression, notably thrombocytopenia, as the main and dose-limiting toxicity of the drug. Hepatic function should also be assessed regularly. By contrast with temozolomide, nitrosoureas, such as lomustine, carmustine, nimustine, and fotemustine, cause prolonged leukopenia and thrombocytopenia. These toxic effects might necessitate delays to further treatment at reduced dose or even discontinuation and consideration of alternative treatments. Pulmonary fibrosis is probably most often seen with carmustine when compared with other nitrosoureas.³³ Nitrosoureas have become a second choice after temozolomide for glioma treatment in most European countries, although no data from large comparative trials are available and retrospective or subgroup analyses suggest a higher efficacy of procarbazine, lomustine, and vincristine over temozolomide in patients with anaplastic glioma with a good prognosis.^{34,35} Locally delivered carmustine wafers that are implanted into the surgical cavity have provided a modest survival advantage to patients with newly diagnosed WHO grade III or IV gliomas, or recurrent glioblastoma,³⁶ but are now a rarely considered option because of poor efficacy and concerns about safety when combined with newer treatments such as temozolomide, and are used mostly in patients without systemic treatment options. Application of carmustine wafers requires careful patient selection and a gross total resection. Of the various candidate anti-angiogenic drugs investigated in clinical trials in glioma patients, only bevacizumab, an antibody to vascular endothelial growth factor, is approved for recurrent glioblastoma in the USA, Canada, Switzerland, and several other countries outside the European Union. Despite extensive efforts, no single biomarker in tumour tissue or plasma has been shown to predict benefit from or resistance to bevacizumab in independent datasets. Patients with glioma undergoing systemic therapy should have their treatment documented in print or electronically, including laboratory results and information on complications and contraindications. Clinical centres that manage patients with glioma should generate standard operating procedures and instructions for handling side-effects and complications from treatment.

Panel: Dose and mode of administration of chemotherapy protocols in malignant glioma

Temozolomide

- 75 mg/m² orally, daily including weekends during radiotherapy
- 150–200 mg/m² orally, days 1–5, fasting in the morning every 4 weeks for six cycles of maintenance treatment

Nimustine, carmustine, lomustine, and fotemustine

- Different regimens, most commonly lomustine 110 mg/m² orally every 6 weeks

Procarbazine, lomustine, and vincristine

- Procarbazine 60 mg/m² orally, days 8–21
- Lomustine 110 mg/m² orally, day 1
- Vincristine 1.4 mg/m² intravenously (maximum 2 mg), days 8 and 29 for 6–8 weeks

Bevacizumab

- 10 mg/m² once every 2 weeks

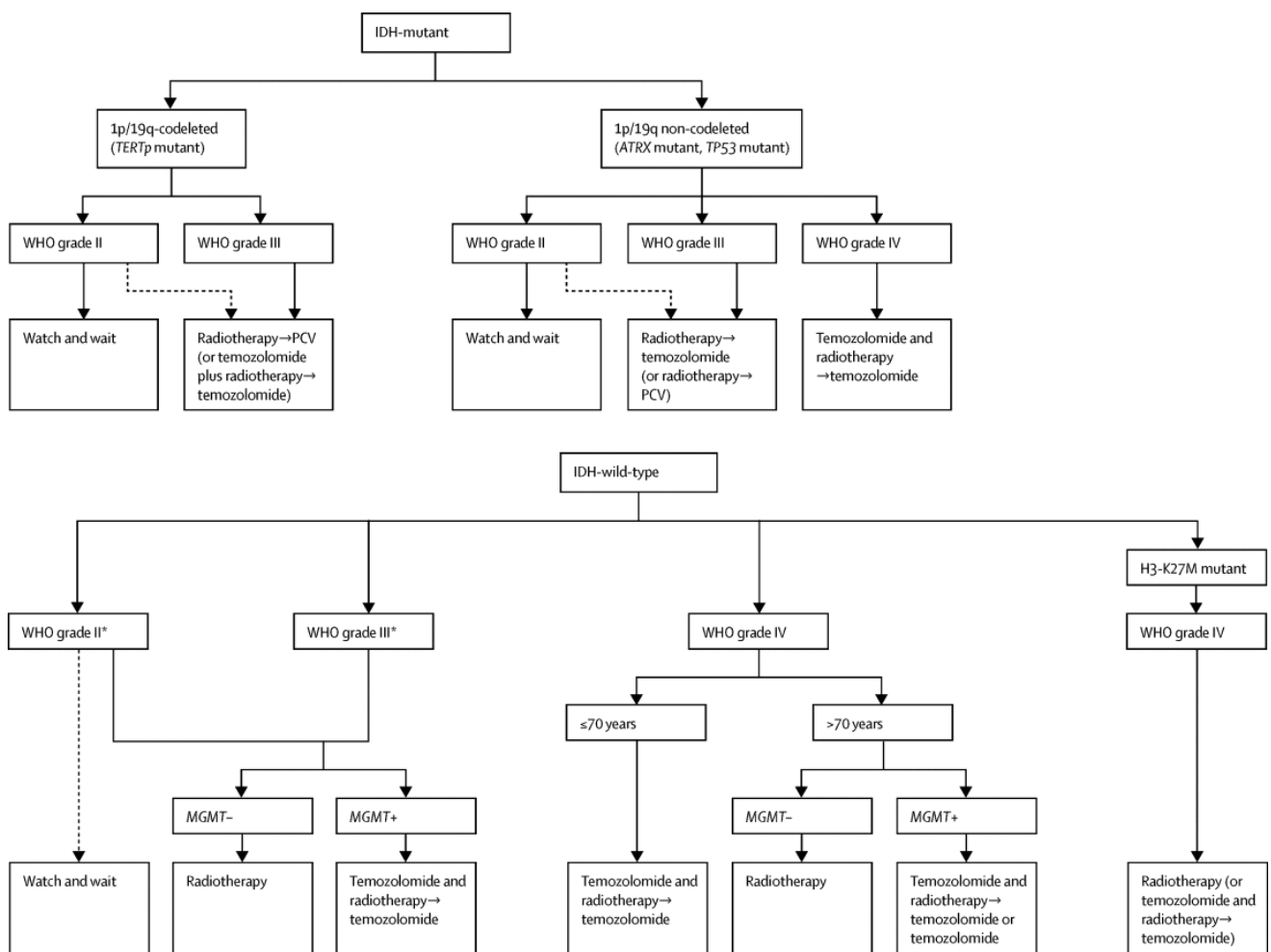


Figure 3. Therapeutic approaches to diffuse astrocytic or oligodendroglial gliomas in adulthood. Supportive care is an option across the entities, but has been omitted for clarity. IDH=isocitrate dehydrogenase. PCV=procarbazine, lomustine, and vincristine.

Other therapeutic approaches

Other approaches to glioma therapy, including various targeted and immunological therapies, notably immune checkpoint inhibitors and vaccines, are of unknown efficacy and should be explored within clinical trials.

Monitoring and follow-up

In addition to clinical examination, MRI is the standard diagnostic measure for the evaluation of disease status or treatment response. 3-month intervals for MRI and follow-up visits are common practice initially in most patients, but longer intervals are appropriate in cases of durable disease control and less aggressive tumours (figure 2). In cases of suspected disease progression, an earlier MRI after 4–6 weeks might be reasonable to confirm progression. Pseudoprogression and pseudoresponse are most likely to occur during the first 3 months of treatment. Particular attention is needed when interpreting scans during this period, and rescanning after shorter intervals is a pragmatic approach in case of doubt. Perfusion MRI and aminoacid PET can help to distinguish pseudoprogression from progression. Biopsies are not uniformly informative because viable tumour cells are regularly detected even in patients with pseudoprogression. To address the risk of pseudoresponse, the Response Assessment in Neuro-Oncology working group has recommended that assessment of non-contrast-enhancing tumour components should be an additional key constituent of response criteria.¹¹ Preliminary evidence shows that lower grade gliomas might exhibit accelerated growth during pregnancy.³⁷ MRI without gadolinium should be used as a safe approach to assess disease activity during pregnancy if considered necessary.

Table 2 shows the key recommendations of the EANO task force³⁹

	Class of evidence	Level of recommendation
General		
Karnofsky performance score, neurological function, age, and individual risks and benefits should be considered for clinical decision making.	I	A
Screening and prevention have no major role for patients with gliomas.	IV	..
Patients with germ line variants or suspected hereditary cancer syndromes should receive genetic counselling and subsequently might be referred for molecular genetic testing.	IV	..
First choice diagnostic imaging approach is MRI with and without contrast enhancement.	IV	..
Pseudoprogression should be considered in patients with an increase in tumour volume on neuroimaging in the first months after local therapeutic interventions, including radiotherapy and experimental local treatments.	II	B
Clinical decision making without obtaining a definitive WHO diagnosis at least by biopsy should occur only in exceptional situations.	IV	..
Glioma classification should follow the new WHO classification of tumours of the central nervous system 2016.	IV	..
Immunohistochemistry for mutant IDH1-R132H protein and nuclear expression of ATRX should be performed routinely in the diagnostic assessment of gliomas.	IV	..
IDH mutation status should be assessed by immunohistochemistry for IDH1-R132H. If negative, immunohistochemistry should be followed by sequencing of <i>IDH1</i> codon 132 and <i>IDH2</i> codon 172 in all WHO grade II and III astrocytic and oligodendroglial gliomas and in all glioblastomas of patients younger than 55 years to allow for integrated diagnoses according to the WHO classification and to guide treatment decisions.	IV	..

	Class of evidence	Level of recommendation
1p/19q codeletion status should be determined in all IDH-mutant gliomas with retained nuclear expression of ATRX.	II	B
<i>MGMT</i> promoter methylation status should be determined in elderly patients with glioblastoma and in IDH-wild-type WHO grade II and III gliomas to guide decision for the use of temozolomide instead of or in addition to radiotherapy.	I	B
Residual tumour volume after surgery is a prognostic factor, therefore efforts to obtain complete resections are justified across all glioma entities.	IV	..
Prevention of new permanent neurological deficits has higher priority than extent of resection in the current surgical approach to gliomas.	IV	..
IDH-mutant gliomas (WHO grade II or III)		
Standard of care for WHO grade II astrocytomas (1p/19q-non-codeleted) that require further treatment includes resection, as feasible, or biopsy followed by involved field radiotherapy and maintenance procarbazine, lomustine, and vincristine chemotherapy (RTOG 9802 trial). ¹⁵	II	B
Standard of care for 1p/19q-non-codeleted anaplastic astrocytoma includes resection, as feasible, or biopsy followed by involved field radiotherapy and maintenance temozolomide. ¹⁶	II	B
Patients with 1p/19q-codeleted WHO grade II oligodendroglial tumours requiring further treatment should be treated with radiotherapy plus procarbazine, lomustine, and vincristine chemotherapy.	III	B
Patients with 1p/19q-codeleted anaplastic oligodendroglial tumours should be treated with radiotherapy plus procarbazine, lomustine, and vincristine chemotherapy (EORTC 26951 and RTOG 9402 trials). ^{22,23}	II	B
Temozolomide chemotherapy is standard treatment at progression after surgery and radiotherapy for most patients with WHO grade II and III gliomas.	II	B
Glioblastoma, IDH-wild-type (WHO grade IV)		
Standard of care for glioblastoma, IDH-wild-type (age <70 years, Karnofsky performance score ≥70) includes resection as feasible or biopsy followed by involved-field radiotherapy and 6 cycles of concomitant and maintenance temozolomide chemotherapy (EORTC 26981 NCIC CE.3 trial). ¹⁷	I	A
Temozolomide is particularly active in patients with <i>MGMT</i> promoter methylation whereas its activity in patients with <i>MGMT</i> promoter-unmethylated tumours is marginal. ³⁸	II	B
Elderly patients not considered candidates for concomitant or maintenance temozolomide plus radiotherapy should be treated based on <i>MGMT</i> promoter methylation status (Nordic, ¹⁹ NOA-08, ²⁰ and NCIC CE.6 EORTC 6062 ²¹ trials) with radiotherapy (eg, 15 × 2.66 Gy) or temozolomide (5 out of 28 days).	II	B
Standards of care are not well defined at recurrence. Nitrosourea regimens, temozolomide rechallenge and, with consideration of the country-specific label, bevacizumab are pharmacological options, but an effect on overall survival remains unproven. When available, recruitment into appropriate clinical trials should be considered.	II	B
IDH=isocitrate dehydrogenase. <i>MGMT</i> =O ⁶ -methylguanine DNA methyltransferase. RTOG=Radiation Therapy Oncology Group. EORTC=European Organisation for Research and Treatment of Cancer. NCIC=National Cancer Institute of Canada.		

Diffuse astrocytoma

Diffuse astrocytomas, IDH-mutant, are the most common WHO grade II astrocytomas. Gemistocytic astrocytomas are a variant of IDH-mutant diffuse astrocytoma characterised by the presence of gemistocytic

neoplastic astrocytes, which should account for at least 20% of all tumour cells.¹ Maximum surgical resection, as feasible, is increasingly considered the best initial therapeutic measure. Watch-and-wait strategies without establishment of a histology-based diagnosis are less commonly pursued, even for patients with incidentally discovered lesions. Younger patients (pragmatic cutoff 40–45 years) with seizures only should be managed by observation alone only after gross total resection. Involved field radiotherapy (50 Gy), which prolongs progression-free survival, but not overall survival, should be considered for patients with incomplete resection or patients older than 40 years.⁴⁰ Chemotherapy alone as initial treatment should be considered investigational, but might be an option in patients with extensive tumours, although progression-free survival is probably shorter with temozolomide than with radiotherapy.⁴¹ The Radiation Therapy Oncology Group 9802 trial¹⁵ in patients with high-risk WHO grade II gliomas who were 18–39 years of age and had undergone a subtotal resection or biopsy, or who were aged 40 years or older compared chemoradiotherapy to radiotherapy alone. The trial reported that the addition of procarbazine, lomustine, and vincristine chemotherapy to radiotherapy (54 Gy) resulted in an overall survival of 13.3 years compared with 7.8 years in patients who received radiotherapy alone. Radiotherapy followed by procarbazine, lomustine, and vincristine constitutes a new standard of care, in view of the absence of other upcoming clinical trial results that are likely to challenge these data. The Radiation Therapy Oncology Group 9802 trial reported that longer overall survival in patients treated with chemoradiotherapy was noted across histological subgroups and, although data are scarce, there was no association between benefit from chemotherapy and any biomarker, however the study was not powered to evaluate these differences.¹⁵ Treatment at progression depends on neurological status, patterns of progression, and first-line therapy. Second surgery should always be considered, usually followed by radiotherapy in previously non-irradiated patients or chemotherapy with alkylating drugs. Temozolomide is often preferred over procarbazine, lomustine, and vincristine chemotherapy because of its favourable safety profile and ease of administration. IDH-wild-type diffuse astrocytomas can have an aggressive course, resembling glioblastoma, especially in elderly patients, but there are less aggressive variants.⁴²

Anaplastic astrocytoma

Anaplastic astrocytomas, IDH-mutant, are the most common WHO grade III astrocytomas. Standard treatment includes maximal surgical removal or biopsy followed by radiotherapy at 60 Gy in 1.8–2.0 Gy fractions (table 1), with doses based on trials in which these tumours were pooled with glioblastomas. The NOA-04 trial^{35,43} showed that procarbazine, lomustine, and vincristine chemotherapy or temozolomide alone were as effective as radiotherapy alone for progression-free survival and overall survival. The European Organisation for Research and Treatment of Cancer (EORTC) 26053 trial (CATNON)¹⁶ explored whether the addition of concomitant temozolomide or maintenance temozolomide to radiotherapy improved outcome compared with radiotherapy alone in patients with newly diagnosed 1p/19q-non-codeleted anaplastic gliomas in a 2 × 2 factorial trial design. An interim analysis suggested that patients treated with 12 cycles of maintenance temozolomide had longer overall survival than patients not treated with maintenance

temozolomide. Maintenance temozolomide has since been introduced as the standard of care, whereas the value of concomitant temozolomide remains unclear.¹⁶ Molecular marker studies in the CATNON trial are pending. A retrospective study¹⁸ of pooled datasets indicated that patients with IDH-wild-type tumours and *MGMT* promoter methylation benefit specifically from chemotherapy with alkylating drugs.

First-line therapy informs treatment choices in patients with recurrent disease. An indication for second surgery should be explored. In patients who relapse after radiotherapy, re-irradiation is an option, with a minimum interval of 12 months from first radiotherapy course. However, the extent and patterns of recurrence restrict the options of radiotherapy in second line treatment, and the overall efficacy remains uncertain because data from randomised trials are scarce. Chemotherapy with alkylating drugs should be considered for chemo-naïve patients who progress after radiotherapy, with temozolomide and nitrosoureas considered to be equally effective in second line treatment.^{44,45} Bevacizumab is also an option used after relapse following radiotherapy and chemotherapy, with progression-free survival at 6 months reported to be between 20–60%.^{46,47} However, controlled data, including those for combined treatment with bevacizumab and chemotherapy, are scarce.

Glioblastoma

Most histological glioblastomas are IDH-wild-type, including the morphological variants of giant cell glioblastoma, gliosarcoma, and epithelioid glioblastoma. To date, no specific treatment recommendations for glioblastoma variants exist. About 50% of the rare epithelioid glioblastomas have a targetable *BRAF*^{V600E} mutation, but the promising activity of BRAF inhibitors in this setting remains to be evaluated systematically. IDH-mutant glioblastomas are increasingly treated in the same way as IDH-mutant anaplastic astrocytoma.

Surgery for IDH-wild-type glioblastoma should be gross total resection when feasible. A small randomised trial⁴⁸ in patients older than 65 years at diagnosis with WHO grade III or IV glioma reported longer overall survival in patients treated with resection compared with those who had a biopsy, but the results remain controversial because of the small sample size and Karnofsky performance score imbalances between groups. Although some studies^{49,50} reported gradual improvement in outcome with increasing extent of resection, only gross total resection might be associated with improved outcome.

Radiotherapy has been the standard of care for glioblastoma since the 1980s, roughly doubling survival.^{31,51} The standard dose is 60 Gy in 1.8–2.0 Gy fractions; 50 Gy in 1.8 Gy fractions improved survival relative to best supportive care in patients 70 years or older with good Karnofsky performance scores.⁵² Patients with unfavourable prognostic factors, defined by age or Karnofsky performance score, are treated with hypofractionated radiotherapy (eg, 40 Gy in 15 fractions), which had similar efficacy to 60 Gy in 30 fractions in a randomised phase II trial.⁵³ In elderly patients (aged >70 years), hypofractionated

radiotherapy is the standard treatment for those with tumours without *MGMT* promoter methylation.^{19,20} Further hypofractionation to 5 fractions of 5 Gy might be feasible without compromising survival,⁵⁴ but is unlikely to be well-tolerated in terms of neurocognitive side-effects, which could become especially important once other treatment options allow long-term survival in elderly glioblastoma patients. Accelerated hyperfractionated regimens, accelerated hypofractionated regimens, brachytherapy, radiosurgery, and stereotactic radiotherapy boosts confer no survival advantage compared with standard regimens.³²

Concomitant and maintenance temozolomide chemotherapy plus radiotherapy is the standard of care for newly diagnosed adult patients in good general and neurological condition, aged up to 70 years.^{17,55,56} A National Cancer Institute of Canada CE.6 EORTC 26062 trial²¹ enrolled patients with newly diagnosed glioblastoma (aged ≥ 65 years) to examine the addition of concomitant and maintenance temozolomide to radiotherapy (40 Gy in 15 fractions) and reported longer overall survival in patients treated with concomitant and maintenance temozolomide and radiotherapy compared with patients treated with radiotherapy alone. Thus, no indication exists that the benefit from temozolomide is reduced with increasing age.²¹

The benefit of temozolomide is most obvious in patients with *MGMT* promoter-methylated glioblastoma.^{21,38} The Nordic trial¹⁹ and NOA-08²⁰ trial resulted in the introduction of *MGMT* promoter methylation testing as standard practice in many European countries in elderly patients not eligible for combined modality treatment: patients with tumours without *MGMT* promoter methylation should be treated with hypofractionated radiotherapy alone. Hypofractionated radiotherapy is also the treatment of choice for elderly patients when the *MGMT* status is unknown. Patients with tumours with *MGMT* promoter methylation should receive temozolomide alone (5 of 28 days) until progression or for 12 months.

Trials⁵⁷⁻⁵⁹ in patients without *MGMT* promoter methylation showed that the omission of temozolomide from first-line standard of care treatment was of no detriment to patients, challenging the view that temozolomide should be used in every patient despite the absence of *MGMT* promoter methylation. This concept is particularly relevant for elderly or frail patients who might be less tolerant of combined modality treatment.

An increased dose of temozolomide is of no benefit in newly diagnosed patients⁶⁰ and the extension of chemotherapy duration beyond six cycles is probably also of no benefit.^{61,62}

Supportive and palliative care are appropriate for patients with large or multifocal lesions with a low Karnofsky performance score, especially if patients are unable to consent to further therapy after biopsy. Local carmustine wafer chemotherapy combined with radiotherapy conferred longer survival from first-line treatment compared with patients treated with radiotherapy alone (13.9 vs 11.6 months) for an intention-to-treat population of patients with high-grade glioma, but clinical outcomes did not differ significantly when

only patients with glioblastoma were considered.^{36,56,63} However, clinical outcomes differed significantly in patients with glioblastoma who underwent a larger than 90% resection.⁶⁴

Two randomised trials^{65,66} done in adult patients with glioblastoma noted that progression-free survival was longer by 3–4 months in patients treated with bevacizumab in addition to concomitant and maintenance temozolomide chemotherapy and radiotherapy compared with patients treated with concomitant and maintenance temozolomide chemotherapy and radiotherapy alone. However, the addition of bevacizumab to this regimen did not affect overall survival compared with concomitant and maintenance temozolomide chemotherapy and radiotherapy alone. However, the clinical significance of increased progression-free survival reported in these trials^{65,66} has been disputed because the reliability of neuroimaging for the assessment of progression is unclear and the RTOG 0825 trial⁶⁵ raised concerns of early cognitive decline in patients treated with bevacizumab. On the basis of these data, bevacizumab has not been approved for newly diagnosed glioblastoma. However, the drug could be useful in individual patients with large tumours who are highly symptomatic and resistant to steroids, who might otherwise not tolerate radiotherapy.

Tumour-treating fields represent a novel treatment modality designed to deliver alternating electrical fields to the brain. An open-label randomised phase III trial⁶⁷ of tumour-treating fields added to standard maintenance temozolomide chemotherapy in newly diagnosed patients with glioblastoma was terminated early when an interim analysis of the first cohort of 315 randomised patients was analysed and longer overall survival was reported in patients treated with tumour-treating fields added to standard maintenance temozolomide chemotherapy compared with patients treated with standard maintenance temozolomide chemotherapy alone (hazard ratio 0.74, 95% CI 0.56–0.98, log-rank $p=0.03$). Analysis⁶⁸ of the full cohort of 695 patients showed that both progression free survival and overall survival were longer in patients treated with tumour-treating fields added to standard maintenance temozolomide chemotherapy compared with patients treated with standard maintenance temozolomide chemotherapy alone.⁶⁸

Questions about the mode of action, interpretation of data, and effect on quality of life have been raised,⁶⁹ and the role and cost-effectiveness of tumour-treating fields in the treatment of newly diagnosed glioblastoma remain to be defined.⁷⁰

Standards of care for patients with recurrent glioblastoma are not well defined. Clinical decision making is influenced by previous treatment, age, Karnofsky performance score, and patterns of progression. Second surgery is considered for 20–30% of patients in clinical practice, commonly for symptomatic but circumscribed lesions and when the interval since the preceding surgery exceeds 6 months. Second surgery might also be considered in the case of early progression in symptomatic patients in whom initial surgery was not adequate. The effect of second surgery on survival might be limited to patients who are candidates for gross total resection of enhancing tumour,⁷¹ but prospective data from randomised trials are not available to confirm a role for second surgery. The efficacy of re-irradiation and the value of aminoacid PET for target delineation

remain debated. Fractionation depends on tumour size. Doses of conventional or near conventional fractionation have been tested, but also higher doses per fraction of 5–6 Gy using stereotactic hypofractionated radiotherapy to a total dose of 30–36 Gy, or even radiosurgery with a single dose of 15–20 Gy, have acceptable toxicity.⁷² Yet, no relevant monotherapy efficacy (progression-free survival rate of 3·8% at 6 months) was demonstrated in a larger randomised trial at 18 fractions of 2 Gy.⁷³

The main systemic treatment options at progression after concomitant and maintenance temozolomide chemotherapy and radiotherapy in Europe are nitrosoureas, temozolomide rechallenge, and bevacizumab. Lomustine is increasingly considered standard treatment because no other treatment has yielded better results in a controlled clinical trial, but progression-free survival rates at 6 months are only in the range of 15–25% with lomustine therapy.^{74,75} Similar results have been reported with alternative dosing regimens of temozolomide,⁷⁶ but activity is probably limited to patients with tumours with *MGMT* promoter methylation.^{77,78} The BR12 trial⁴⁴ showed no benefit of dose-intensified temozolomide over standard-dose temozolomide in temozolomide-naïve patients with malignant glioma, but does not provide information about the value of temozolomide rechallenge for patients pre-treated with temozolomide. Therefore, no reason exists to administer dose-intensified temozolomide to patients who are temozolomide-naïve. Whether dose-intensified regimens are superior to standard-dosed temozolomide in recurrent glioblastoma after a temozolomide-free interval, remains undetermined.

Bevacizumab is approved for recurrent glioblastoma in various countries, but not in the European Union, on the basis of two phase 2 studies^{79,80} which noted that the proportion of patients with a response is around 30% and the length of progression-free survival and overall survival compare favourably with historical controls. The value of bevacizumab in clinical practice is widely accepted because of transient symptom control and the option for steroid sparing in a subset of patients.^{79,80} The BELOB trial⁷⁷ showed that overall survival at 9 months might be longer in patients treated with bevacizumab and lomustine than that in patients treated with either drug alone, but the EORTC 26101 phase III trial⁷⁸ did not confirm that the combination of bevacizumab and lomustine increased overall survival compared with lomustine alone. No other active combination partner for bevacizumab has been identified. Tumour-treating fields were not superior to best physician's choice in a randomised phase III trial.⁸¹

Diffuse midline glioma

Diffuse midline glioma, histone H3-K27M mutant, is a new tumour entity that has been classified as WHO grade IV. The tumour includes most brainstem, thalamic, and spinal diffuse gliomas in children and adults. Surgical options are limited, treatment beyond radiotherapy is not established, and the prognosis is poor. Traditionally, treatment has followed the standards of care for gliomas of the same WHO grade in other anatomical locations.

Oligodendroglioma

Oligodendrogliomas are defined as IDH-mutant and 1p/19q-codeleted grade II tumours by the 2016 WHO classification.¹ In rare cases, without conclusive data on IDH mutation and 1p/19q codeletion status, tumours are classified as oligodendroglioma, not otherwise specified. The diagnosis of oligoastrocytoma is discouraged in the new WHO classification, which states that only exceptional cases that cannot be conclusively tested for IDH mutation and 1p/19q codeletion that show a mixed oligoastrocytic histology can still be classified as oligoastrocytoma, not otherwise specified.¹ Surgery is the primary treatment for IDH-mutant and 1p/19q-codeleted oligodendroglioma. Although contemporary trials addressing this issue are not available, watch-and-wait strategies are justified in patients with macroscopically complete resection, and also in younger patients (aged <40 years) with incomplete resection if the tumour has not already caused neurological deficits beyond symptomatic epilepsy. The standard treatment for oligodendrogliomas is radiotherapy followed by procarbazine, lomustine, and vincristine chemotherapy if further treatment beyond surgery is considered necessary.¹⁵

Anaplastic oligodendroglioma

Anaplastic oligodendrogliomas are defined as IDH-mutant and 1p/19q-codeleted grade III tumours by the 2016 WHO classification;¹ not otherwise specified is only assigned if conclusive molecular information is absent. The diagnosis of anaplastic oligoastrocytoma is discouraged and no longer applicable when tumours are successfully tested for IDH mutation and 1p/19q codeletion. Extent of resection is a prognostic factor.^{43,82} The role of grading (II versus III) in IDH-mutant, 1p/19q-codeleted gliomas remains controversial. Accordingly, watch-and-wait strategies after complete resection might be considered even with WHO grade III tumours in younger patients, notably after gross total resection and in the absence of neurological deficits. Two large randomised clinical trials—EORTC 26951²² and RTOG 9402²³—showed that in a subset of patients with 1p/19q-codeleted oligodendroglial tumours, patients treated with procarbazine, lomustine, and vincristine chemotherapy, either before or after radiotherapy, in first-line treatment had longer overall survival compared with patients treated with radiotherapy alone. Although these results stem from analyses of small patient cohorts, both studies show similar results, validating each other and defining the current standard of care. Important questions remain: whether long-term survivors treated with radiotherapy plus procarbazine, lomustine, and vincristine experience preserved cognitive function and quality of life,⁸³ and whether the longer overall survival could be achieved with concomitant and maintenance temozolomide plus radiotherapy compared with radiotherapy alone. Long-term results from the NOA-04 trial^{35,43} show that chemotherapy alone is not superior to radiotherapy alone in IDH-mutant and 1p/19q-codeleted anaplastic oligodendroglioma or IDH-mutant anaplastic astrocytoma, indicating that chemotherapy with alkylating drugs alone is unlikely to achieve the same outcome as radiotherapy combined with procarbazine, lomustine, and vincristine. Whether the efficacy of concomitant and maintenance temozolomide plus radiotherapy treatment is similar to radiotherapy followed by procarbazine, lomustine, and vincristine is explored in the modified CODEL trial (NCT00887146).

Treatment at progression is influenced by response to first-line treatment. In cases in which radiotherapy and alkylating drugs are not treatment options because patients have not responded, or because of intolerance, bevacizumab has been used,^{84,85} but the drug is of unknown efficacy as controlled studies are lacking.^{84,85} No evidence exists for the use of combined treatment with bevacizumab and cytotoxic drugs in this setting.

Other astrocytic tumours

Pilocytic astrocytoma and its variant, pilomyxoid astrocytoma, are rare tumours in adults and are commonly cured by surgery alone. Radiotherapy is only indicated at progression when surgical options no longer exist. Pilocytic astrocytoma of the optic nerve can be associated with neurofibromatosis type I and cannot be resected unless visual function has already been lost. These lesions often do not require treatment.

Subependymal giant cell astrocytomas are WHO grade I lesions associated with tuberous sclerosis and might respond to mTOR inhibition if treatment after surgery is required.⁸⁶

Pleomorphic xanthoastrocytoma (WHO grade II) occurs predominantly in children and young adults and about 70% of tumours have the *BRAF*^{V600E} mutation.¹ This tumour should be resected and patients may be followed up by the use of a watch-and-wait strategy after gross total resection. Anaplastic pleomorphic xanthoastrocytoma (WHO grade III) should probably be managed with postoperative radiotherapy and not with a watch-and-wait strategy. In recurrent anaplastic pleomorphic astrocytoma, BRAF inhibitors, such as vemurafenib, seem to have limited activity.⁸⁷

Coordination of care and outlook

Diagnosis and management plans for patients with glioma should follow multidisciplinary tumour board recommendations throughout the disease course. Tumour boards composed of experts from different specialties are a forum in which to discuss which procedures can be done locally, which are better done at a specialised centre, which are appropriate for inpatient versus outpatient settings, and which neurorehabilitation measures are useful. Local and national guidelines and upcoming EANO guidelines provide further guidance. Guidelines reflect knowledge and consensus at a specific timepoint. The EANO website will report future updates on this guideline.

Search strategy and selection criteria

This guideline was prepared by a task force nominated by the Executive Board of the European Association for Neuro-Oncology (EANO) in cooperation with the Brain Tumor Group of the European Organisation for Research and Treatment of Cancer in 2016. The task force represents the disciplines involved in the diagnosis and care of patients with glioma and reflects the multinational character of EANO. We used PubMed and the search terms “glioma”, “anaplastic”, “astrocytoma”, “oligodendroglioma”, “glioblastoma”, “trial”, “clinical”, “radiotherapy” and “chemotherapy” to retrieve references for articles published in English between Jan 1,

2001, and July 31, 2016. We also identified publications through searches of the authors' own files. Data available only in Abstract form were only included if we felt they had the potential to change practice. The definitive reference list included articles deemed relevant to the broad scope of this guideline.

Contributors

MiW wrote the first draft of the manuscript. All other authors reviewed the draft and approved the final version of the manuscript.

Declaration of interests

MiW received grants from Acceleron, Actelion, Bayer, Merck, Novocure, Piquor, Isarna, EMD Merck Serono, and Roche; and received personal fees from BMS, Celldex, Immunocellular Therapeutics, Isarna, Magforce, Merck, Northwest Biotherapeutics, Novocure, Pfizer, Roche, Teva, and Tocagen, outside of the submitted work. MvdB received grants and personal fees from Abbvie; and personal fees from Roche, Celldex, Novartis, BMS, and MSD, outside of the submitted work. JCT received grants from BrainLab, outside the submitted work. RoS received non-financial support from Novocure; and honoraria from Roche, Merck KGaA, MSD, Merck, and Novartis, outside of the submitted work. MP received grants from Böehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dome; and received personal fees from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, and Roche, outside of the submitted work. OC received grants, personal fees, and non-financial support from Roche; received personal fees from Ipsen, AstraZeneca, and Celldex; and received personal fees and non-financial support from Servier, during the conduct of the study; and has a patent licensed (Aix Marseille University, 13725437 9 1405). MB received grants and personal fees from Guerbet, Novartis, and Codman; received personal fees from Roche, Teva, Bayer, and Vascular Dynamics; and received grants from Siemens, DFG, Hopp Foundation, and Stryker, outside of the submitted work. JCR received non-financial support from Roche Nederland BV, outside of the submitted work. BGB received personal fees from Merck, and received personal fees and non-financial support from Noxxon Pharma AG, outside of the submitted work. MJBT received personal fees from Roche, outside of the submitted work. MH received non-financial support from MDxHealth; her institution received service fees from Novocure; and received consulting fees from Roche/Genentech, MSD, and BMS, outside of the submitted work. MaW received personal fees from Bristol-Myers-Squibb; and received personal fees from Novocure, and Roche, outside of the submitted work. GR received grants from Roche, and Merck; and received personal fees from Amgen, and Celldex, outside of the submitted work. WW received grants and personal fees from MSD and Genentech/Roche; received grants from Apogenix, Boehringer Ingelheim, and Pfizer; and received personal fees from BMS and Celldex, outside of the submitted work. All other authors declare no competing interests.

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