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

Weller, Michael ; van den Bent, Martin ; Tonn, Jörg C ; Stupp, Roger ; Preusser, Matthias ; Cohen-Jonathan-Moyal, Elizabeth ; Henriksson, Roger ; Le Rhun, Emilie ; Balana, Carmen ; Chinot, Olivier ; Bendszus, Martin ; Reijneveld, Jaap C ; Dhermain, Frederick ; French, Pim ; Marosi, Christine ; Watts, Colin ; Oberg, Ingela ; Pilkington, Geoffrey ; Baumert, Brigitta G ; Taphoorn, Martin J B ; Hegi, Monika ; Westphal, Manfred ; Reifenberger, Guido ; Soffietti, Riccardo ; Wick, Wolfgang ; European Association for Neuro-Oncology (EANO)

DOI: https://doi.org/10.1016/S1470-2045(17)30194-8

Originally published at:
Weller, Michael; van den Bent, Martin; Tonn, Jörg C; Stupp, Roger; Preusser, Matthias; Cohen-Jonathan-Moyal, Elizabeth; Henriksson, Roger; Le Rhun, Emilie; Balana, Carmen; Chinot, Olivier; Bendszus, Martin; Reijneveld, Jaap C; Dhermain, Frederick; French, Pim; Marosi, Christine; Watts, Colin; Oberg, Ingela; Pilkington, Geoffrey; Baumert, Brigitta G; Taphoorn, Martin J B; Hegi, Monika; Westphal, Manfred; Reifenberger, Guido; Soffietti, Riccardo; Wick, Wolfgang; European Association for Neuro-Oncology (EANO) (2017). European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncology, 18(6):e315-e329.
DOI: https://doi.org/10.1016/S1470-2045(17)30194-8

EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas

Prof Michael Weller MD[1], Prof Martin van den Bent MD[2], Prof Jörg C. Tonn MD[3], Prof Roger Stupp MD[4], Matthias Preusser MD[5], Prof Elizabeth Cohen-Jonathan-Moyal MD[6], Prof Roger Henriksson MD[7], Emilie Le Rhun MD[8], Carmen Balana MD[9], Prof Olivier Chinot MD[10], Prof Martin Bendszus MD[11], Jacob C. Reijneveld MD[12], Frederick Dhermain MD[13], Pim French PhD[14], Christine Marosi MD[5], Colin Watts MD[15], Ingela Oberg[16], Geoffrey Pilkington PhD[17], Brigitta G. Baumert MD[18], Prof Martin J.B. Taphoorn MD[19], Monika Hegi PhD[20], Prof Manfred Westphal MD[21], Prof Guido Reifenberger MD[22], Prof Riccardo Soffietti MD[23], Prof Wolfgang Wick MD[24], for the European Association for Neuro-Oncology (EANO) Task Force on Gliomas

[1]Department of Neurology & Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland

[2]Neurooncology Unit, ErasmusMC Cancer Institute, Rotterdam, the Netherlands

[3]Department of Neurosurgery, University of Munich LMU, Munich, Germany

[4]Department of Oncology & Brain Tumor Center, University Hospital and University of Zurich, Zurich, Switzerland

[5]Department of Medicine I and Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria

[6]Département de Radiotherapie, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France

[7]Regional Cancer Center Stockholm Gotland and Department of Radiation Sciences & Oncology, Umeå University Hospital, Sweden

[8]Neuro-oncology, Department of Neurosurgery, University Hospital, Lille, France

[9]Catalan Institute of Oncology (ICO), Hospital Germans Trias i Pujol, Carretera Canyet sn, 08916 Badalona/Barcelona, Spain
[10]Aix-Marseille Université, APHM, CHU Timone, Department of Neuro-Oncology, Marseilles, France
[11]Department of Neuroradiology, University Hospital Heidelberg, Germany
[12]Department of Neurology and Brain Tumor Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[13] Department of Radiotherapy, Gustave Roussy University Hospital, Villejuif, France
[14] Department of Neurology, Erasmus MC, Rotterdam, The Netherlands
[15] Department of Clinical Neurosciences, Division of Neurosurgery, University of Cambridge, UK
[16]Division D – Neurosurgery, Addenbrooke's Hospital CUHFT, Cambridge Biomedical Campus, Hills Road, CB2 0QQ, United Kingdom
[17]Brain Tumor Research Centre, University of Portsmouth, Portsmouth, United Kingdom
[18]Department of Radiation Oncology, MediClin Robert Janker Clinic & Clinical Cooperation Unit Neurooncology, University of Bonn Medical Center, Bonn, Germany
[19] Departments of Neurology, Leiden University Medical Center, and Medical Center Haaglanden, The Hague, The Netherlands
[20]Department of Clinical Neurosciences, University Hospital Lausanne, Lausanne, Switzerland
[21]Department of Neurosurgery, University Hospital Hamburg, Hamburg, Germany
[22]Department of Neuropathology, Heinrich Heine University Düsseldorf, and German Cancer Consortium (DKTK), partner site Essen/Düsseldorf, Düsseldorf, Germany
[23]Department of Neuro-Oncology, University Hospital, Turin, Italy
[24]Neurology Clinic & National Center for Tumor Diseases, University Hospital

Heidelberg, Germany and German Consortium of Translational Cancer Research (DKTK), Clinical Cooperation Unit Neurooncology, German Cancer Research Center, Heidelberg, Germany

Correspondence

Prof. Dr. Michael Weller, Department of Neurology & Brain Tumor Center, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zurich, Switzerland, Tel. +41 44 255 5500, E-Mail: michael.weller@usz.ch

Funding

The preparation of this guideline was not funded. The members of the task force did not receive compensation for their participation.

Summary

This guideline provides recommendations for the clinical care of patients with astrocytic and oligodendroglial gliomas of adulthood. It is based on the 2016 WHO classification of tumors of the nervous system and on scientific developments since the 2014 version of the guideline. The recommendations focus on pathological and radiological diagnostics as well as the major treatment modalities of surgery, radiotherapy and pharmacotherapy. The results from contemporary practice-changing clinical trials have been integrated. The guideline aims to provide guidance for diagnostic and management decisions while limiting unnecessary treatment and cost. It is a source of knowledge for professionals involved in the management of glioma patients, for patients and caregivers, and for health care providers in Europe. Implementing this guideline requires multidisciplinary and multiprofessional structures of care and defined processes of diagnosis and treatment.

Key words

Astrocytoma, oligodendroglioma, glioblastoma, surgery, radiotherapy, temozolomide

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 Organization for Research and Treatment of Cancer (EORTC) in 2016. The task force represents the disciplines involved in the diagnosis and care of glioma patients and reflects the multinational character of EANO. References were retrieved onPubMed with the search terms “glioma”, “anaplastic”, “astrocytoma”, “oligodendroglioma”, “glioblastoma”, “trial”, “clinical”, “radiotherapy” and “chemotherapy” from January 2001 to July 2016. Publications were identified through searches of the authors` own files, too. Only papers in English were reviewed. Data available only in Abstract form were only exceptionally included. The definitive reference list was generated based on relevance to the broad scope of this guideline.

Introduction

This guideline follows the revision of the fourth edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System[1] and builds on previous guidelines.[2,3] It addresses astrocytic and oligodendroglial gliomas of WHO grades II-IV of adulthood and their variants and covers prevention, early diagnosis and screening, therapy, and follow-up. It does not address differential diagnosis, adverse effects of treatment, or supportive or palliative care.

Diagnostics

Early diagnosis and screening

The annual incidence of gliomas is in the range of 6/100,000. Serum markers for early detection have not been identified. Instead, brain magnetic resonance imaging (MRI) has the highest sensitivity to detect small tumors. Gliomas can evolve rapidly over several weeks or months, emphasizing the challenges for population-based prevention or early intervention. Screening is therefore limited to persons at genetic risk, for example, patients with neurofibromatosis type I, or Turcot and Li Fraumeni syndromes. No repeat scanning is indicated in such individuals unless clinically justified. A particular challenge is counseling and screening of relatives of patients whose tumors carry germline mutations associated with gliomagenesis.[4] Prevention strategies are not available.

History and clinical examination

The evolution of neurological symptoms and signs allows to estimate the growth dynamics of gliomas and may reveal familial risk or exogenous risk factors including exposure to irradiation or other conditions associated with brain tumors. Relatives may be required to obtain a reliable history. Characteristic modes of presentation are new onset epilepsy, focal deficits including neurocognitive impairment, and indicators of intracranial mass effect. The physical examination focuses on the detection of systemic cancer and contraindications for neurosurgical procedures. Neurocognitive assessment beyond documenting the Karnofsky performance score (KPS) or the WHO performance status and performing a Mini Mental State Examination (MMSE) or a Montreal Cognitive Assessment has become increasingly common.[5,6]

Ancillary studies

MRI before and after application of gadolinium is the standard method to detect a glioma.[7] In addition, cranial computed tomography (CT) demonstrates calcifications, intra-arterial angiography may aid the surgical strategy, and amino acid positron emission tomography (PET) helps define metabolic hotspots for biopsy.[8] Standardized MRI sequences are also recommended to assess the efficacy of therapeutic interventions.[9] Cerebrospinal fluid studies play 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 tumors. Electroencephalography helps for monitoring tumor-associated epilepsy and in determining causes of altered consciousness.

Preoperative management

Management should follow written local standard operating procedures and multidisciplinary discussion preferentially including dedicated neuroradiologists and neuropathologists as well as neurosurgeons, radiation oncologists and neurooncologists in a brain tumor board. Prior to surgery, unless there are contraindications or the suspicion of primary cerebral lymphoma or inflammatory lesions, corticosteroids may be administered to decrease tumor-associated edema. Additional pharmacological measures such as osmotic agents are rarely necessary. Glioma patients who have suffered epileptic seizures should receive anticonvulsant drugs preoperatively. Primary prophylaxis is not indicated in patients without seizures.[10]

Biopsy or resection

Treatment decisions in glioma patients are based on a tissue diagnosis and the assessment of selected molecular markers. Surgery is thus commonly performed with diagnostic and therapeutic objectives. The surgical management of glioma patients should take place in high-volume specialist centers. A decision for palliative care without histological diagnosis should be avoided unless the risk of the biopsy procedure is considered too high or if the prognosis is likely to be very unfavourable, e.g., in old patients with large tumors and rapid clinical decline. Stereotactic serial biopsies along the trajectory under local anesthesia are associated with low morbidity and a firm diagnosis aids counselling patients and relatives also when tumor-specific therapy is not recommended. Serial sampling allows to avoid undergrading, the procedure requires close cooperation between neuropathologist, neuroradiologist and neurosurgeon.

Histological classification and molecular diagnostics

Intraoperative assessment of cytological specimens or frozen sections before the surgical procedure is terminated assure that sufficient tissue is obtained to establish a diagnosis. Tumor tissue is formalin-fixed and embedded in paraffin for conventional histological staining, including routine hematoxylin-eosin staining and additional immunohistochemical and molecular analyses. If possible, a part of the tissue should be cryopreserved for future scientific molecular marker studies. The diagnostic process follows the WHO classification and consists of histological tumor typing as well as tumor grading using the four-tiered WHO grading scheme from WHO grade I to IV, designed to provide clinicians with information on the tumor's biological behavior and consequently the patient's prognosis and outcome (Fig. 1). The 2016 WHO classification recognizes the major diagnostic role of *isocitrate dehydrogenase* (*IDH*) 1 codon 132 or *IDH2* codon 172 missense mutations ("IDH mutation") and defines diffuse and anaplastic astrocytic and oligodendroglial gliomas essentially as IDH-mutant tumors.[1] Oligodendroglial tumors additionally carry 1p/19q co-deletions. IDH-wildtype diffuse and anaplastic astrocytomas are considered provisional entities. “Not otherwise specified” (NOS) categories have been introduced for those gliomas that cannot be tested for the diagnostically relevant markers or for which testing remains inconclusive. Management recommendations for these NOS categories are included in Table 1, but evidence is low. Oligoastrocytomas and gliomatosis cerebri both lack distinctive genetic and epigenetic profiles[11,12] and are thus no longer considered as distinct glioma entities.[1] Diffuse midline glioma, H3-K27M-mutant, has been introduced as a novel entity characterized by midline tumor location and presence of lysine to methionine mutation at codon 27 of histones 3.3 or 3.1.[1] Altogether, four molecular markers are central to diagnosing and treating gliomas:

IDH mutation, 1p/19q co-deletion, H3-K27M mutation and O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation. IDH mutation, 1p/19q co-deletion and H3-K27M mutation are assigned a role in the revised WHO classification (Table 1) whereas *MGMT* promoter methylation status guides treatment decisions regarding the use of chemotherapy.[13] Immunohistochemical detection of loss of nuclear ATRX expression is helpful to substantiate the diagnoses of IDH-mutant diffuse and anaplastic astrocytomas, and if retained should prompt testing for 1p/19q co-deletion in IDH-mutant gliomas, however, ATRX immunohistochemistry shall not substitute for 1p/19q codeletion testing. High-throughput assays will probably soon be introduced instead of single marker assessments.

Therapy - General recommendations

Prognostic factors

Younger age and better performance status are important positive, therapy-independent prognostic factors across glioma entities. Extent of resection is an important therapy-dependent prognostic factor. Prognostically favorable molecular markers such as IDH mutation and 1p/19q co-deletion are now at the core of the WHO classification and define more homogeneous diagnostic and prognostic entities.[1,13]

Surgical therapy

Beyond establishing a histological diagnosis, the goal of surgery is to remove as much of the tumor as is safely possible with the goal of improving neurological function. Microsurgical techniques are standard. Several tools including surgical navigation systems housing functional MRI datasets, intraoperative MRI, ultrasound, intraoperative functional monitoring and the fluorescent dye, 5-aminolevulinic acid (ALA), to visualize tumor tissue[14] help increase the extent of resection while keeping the risk of new neurological deficits low. The use of evoked potentials, electromyography or mapping in awake patients under local anesthesia to monitor and preserve language and cognition should support resections in eloquent areas. Preventing new permanent neurological deficits is more important than extent of resection because gliomas are not cured by surgery: this is precluded by tumor cell infiltration far beyond the lesion as delineated by neuroimaging and network-like growth, hallmarks of diffuse gliomas.[15] 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 - without and with contrast and diffusion imaging within 24-72 h of surgery.[16]

Radiotherapy (RT)

The goal of RT for patients with gliomas is to improve local control at a reasonable risk benefit ratio. RT helps to preserve function and increases survival. Indications for, timing, dosing and scheduling of RT are determined by diagnosis and prognostic factors, including age, KPS and extent of resection.[17] Focal RT is administered at 50-60 Gy in 1.8-2 Gy fractions, depending on prognosis defined by tumor type and grade. Hypofractionated RT with higher fraction sizes and lower total dose e.g., to 15 x 2.67 Gy, is appropriate in older patients and those with poor prognostic factors, and considered biologically equivalent to 30 x 2 Gy. The area of residual enhancement on T1 imaging plus the surgical bed is defined as the gross tumor volume. A margin, typically 1.0-1.5 to 2.5 cm including the hyperintensity on T_2 / FLAIR imaging is added to define the clinical target volume which is then modified in areas where microscopic spread is unlikely, or to reduce the dose to critical structures. Finally another margin, usually 0.3 to 0.5 cm, is added to allow for error setup and movement during treatment, generating the planning target volume.[18] PET is studied for improving target delineation in clinical trials.[8]

The organs at higher risk of radiotherapy-associated toxicity including optic nerves, optic chiasm, retinae, lenses, brainstem, pituitary, cochleas and hippocampus should be delineated. Modern techniques of focused RT, e.g. stereotactic, intensity-modulated or image-guided RT may improve the targeted delivery of RT to better protect surrounding tissue. In children especially, but also in adults with deeply localized tumors, interstitial brachytherapy and proton/heavy ions radiotherapy may be alternatives. Randomized data comparing such novel approaches with standard techniques are not available.

Pharmacotherapy

Cytotoxic chemotherapy is standard of care for most glioma patients (Table 2). It requires regular hematology, hepatic and renal laboratory and exclusion of major lung or heart disease and infection. Blood counts need to be monitored during therapy. Temozolomide (TMZ), 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 its main and dose-limiting toxicity. Hepatic function should also be assessed regularly. In contrast to TMZ, nitrosoureas such as lomustine (CCNU), carmustine (BCNU), nimustine (ACNU) or fotemustine cause prolonged leukopenia and thrombocytopenia. This may necessitate delays of further treatment at reduced dose or even discontinuation and consideration of alternative treatments. Pulmonary fibrosis is probably most often seen with carmustine. Nitrosoureas have become a second choice after TMZ for glioma treatment in most European countries, although data from larger comparative trials are missing and retrospective or subgroup analyses suggest a higher efficacy of procarbazine, lomustine (CCNU) and vincristine (PCV) over TMZ in good prognosis patients with anaplastic glioma.[19,20] Locally delivered carmustine wafers (Gliadel®) implanted into the surgical cavity have provided a moderate survival advantage to patients with newly diagnosed grade WHO III or IV gliomas, or recurrent glioblastoma,[21] but are now a rarely considered option, and mostly in patients without systemic treatment options. Their application requires careful patient selection and a gross total resection. Among various candidate anti-angiogenic agents explored 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. Glioma patients undergoing systemic therapy should carry a documentation of treatment including laboratory results and information on complications and contraindications. Clinical centers managing glioma patients should generate standard operating procedures and instructions for handling side effects and complications from treatment.

Other therapeutic approaches

Other approaches to glioma therapy including various targeted and immunological therapies, notably immune checkpoint inhibitors, are of unknown activity 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. Three months intervals are common practice initially for most patients, but longer intervals are appropriate in case of durable disease control and less aggressive tumors. *Vice versa*, in case of suspected disease progression short term control MRI may be reasonable to confirm progression. Pseudoprogression and pseudoresponse are most likely to occur during the first three months of treatment. Particular attention is needed when interpreting scans during this period. The Response Assessment in Neuro-Oncology (RANO) working group has recommended that assessment of non-contrast-enhancing tumor components should be an additional key component of response criteria.[9]

Specific recommendations

Figures 2 and 3 and Table 1 provide an overview of therapeutic approaches. Table 3 provides the key recommendations.

Diffuse astrocytoma, IDH-mutant – WHO grade II

These are the most common WHO grade II astrocytomas. Gemistocytic astrocytomas are a subtype of IDH-mutant diffuse astrocytoma.[1] Maximum surgical resection as feasible is increasingly considered the best initial therapeutic measure. Watch-and-wait strategies without establishment of a diagnosis are less commonly pursued. Asymptomatic younger patients with seizures only can be managed by observation alone after gross total resection. Involved field RT (50 Gy) should be considered for patients with incomplete resection and patients older than 40 years. It prolongs progression-free survival (PFS), but not overall survival (OS).[22] Chemotherapy alone as initial treatment should be considered investigational, but may be an option in patients with extensive tumors although PFS is shorter with TMZ than with RT.[23] The RTOG 9802 trial reported a major prolongation of survival by adding PCV polychemotherapy to RT (54 Gy) compared with RT alone from 7.8 to 13.3 years in patients with high-risk WHO grade II gliomas who were 18 to 39 years of age and had undergone a subtotal resection or biopsy, or who were 40 years of age or older. RT followed by PCV constitutes a new standard of care, given the lack of other up-coming clinical trial results likely to challenge these data. Benefit was reported across histological subgroups and, although data are limited, there was no overt link between benefit from PCV and a particular molecular marker profile, potentially due to limited power.[24] Treatment at progression depends on first-line therapy and may involve second surgery, radiotherapy in previously un-irradiated patients or alkylating agent chemotherapy. TMZ is often preferred over PCV polychemotherapy because of its favorable safety profile and ease of administration. IDH-wildtype diffuse astrocytomas can take a rather aggressive course, resembling glioblastoma, in particular in the elderly, but there are also less aggressive variants.[25]

Anaplastic astrocytoma, IDH-mutant – WHO grade III

These are the most common WHO grade III astrocytomas. Standard of care includes maximal surgical removal or biopsy followed by RT at 60 Gy in 1.8–2 Gy fractions (Table 1), largely based on trials where these tumors were pooled with glioblastomas. The NOA-04 trial showed that PCV or TMZ alone were as active as RT alone for PFS and OS.[20,26] The EORTC 26053 trial (CATNON) explored whether the addition to RT of concomitant or maintenance TMZ or both improved outcome over RT alone in patients with newly diagnosed 1p/19q-non-codeleted anaplastic gliomas in a 2 by 2 design. A first interim analysis showed that 12 cycles of maintenance TMZ prolonged OS which should now be considered standard of care whereas no statement on the value of concomitant TMZ can be made at present.[27]

Molecular marker studies in the CATNON trial are pending. A retrospective study of pooled datasets indicated that specifically patients with IDH-wildtype tumors with *MGMT* promoter methylation benefit from alkylating agent chemotherapy.[28]
First-line therapy informs on the choices of treatment in the recurrent setting. An indication for second surgery should be explored. For patients relapsing after radiotherapy re-irradiation is an option with a minimum in the range of 12 months interval since the end of the first RT course. However, size and patterns of recurrence limit the options of re-RT, and the overall efficacy remains uncertain; randomized data are lacking. Alkylating agent chemotherapy should be considered for chemo-naive patients who progress after RT, TMZ and nitrosoureas probably being equally effective.[29],[30] Bevacizumab is used after failure of RT and chemotherapy, with PFS rates at 6 months of 20-60%.[31,32] Controlled data are lacking, including for combining bevacizumab with chemotherapy.

Glioblastoma, IDH-wildtype - WHO grade IV

The majority of histological glioblastomas are IDH-wildtype, including the morphological variants of giant cell glioblastoma, gliosarcoma and epitheloid glioblastoma. There are to date no specific treatment recommendations for glioblastoma variants. About 50% of the rare epitheloid glioblastomas carry a druggable BRAF-V600E mutation, but the promising efficacy of BRAF inhibitors remains to be evaluated systematically. The following applies to IDH-wildtype glioblastoma; IDH-mutant glioblastomas are increasingly treated like IDH-mutant anaplastic astrocytoma.
Surgery for glioblastoma should be gross total resection whenever feasible. A small randomized trial in patients WHO grade III and IV tumors aged > 65 reported improved survival with resection versus biopsy,[33] but remains debated for limited

sample size and KPS imbalances between groups. While some studies reported gradually improved outcome with increasing extent of resection, only gross total resection may be associated with improved outcome.[34,35]

RT has been standard of care for glioblastoma for decades, roughly doubling survival.[17,36] Standard dose is 60 Gy in 1.8-2 Gy fractions; 50 Gy in 1.8 Gy fractions improved survival relative to best supportive care in patients 70 years or older with good KPS.[37] Patients with unfavorable prognostic factors defined by age or KPS are treated with hypofractionated RT, e.g., 40 Gy in 15 fractions.[38] In the elderly, this is the standard of care for patients with tumors without *MGMT* promoter methylation.[39,40] Further hypofractionation to 5 x 5 Gy may be feasible without compromising survival,[41] but is unlikely to be well tolerated in terms of neurocognitive side effects which will assume more relevance once other treatment options allow long-term survival in elderly glioblastoma patients, too. Neither accelerated hyper- or hypofractionated regimens nor brachytherapy, radiosurgery or a stereotactic RT boost are superior to standard regimens for survival.

Concomitant and maintenance TMZ chemotherapy plus RT (TMZ/RT→TMZ) is the standard of care for newly diagnosed adult patients in good general and neurological condition and aged up to 70 years.[42-44] The benefit from TMZ is most prominent in patients with *MGMT* promoter-methylated glioblastoma.[45] Recent trials in *MGMT* promoter unmethylated patients showing no detriment from omitting TMZ have raised doubts whether TMZ should be used in every patient despite lack of *MGMT* promoter methylation.[46-48] There is no benefit from increasing the dose of TMZ in the newly diagnosed setting[49] and probably also not from extending the duration of chemotherapy beyond 6 cycles.[50,51]

The NOA-08 and Nordic trials[39,40] made *MGMT* promoter methylation testing standard practice in many European countries in the elderly: patients with tumors lacking *MGMT* promoter methylation should be treated with hypofractionated RT alone. This is also the treatment of choice for elderly patients when the *MGMT* status is unknown. Elderly patients with tumors with *MGMT* promoter methylation should receive TMZ alone (5/28 until progression or for 12 months) or TMZ/RT→TMZ. In the NCIC CE.6/EORTC 26062 trial enrolling patients ≥ 65 years with newly diagnosed glioblastoma, the addition of concomitant and maintenance TMZ to 40 Gy/15 fractions radiotherapy significantly improved survival. *MGMT* promoter methylation was not prognostic, but highly predictive for benefit from TMZ. Interpretation of the benefit from TMZ in patients with *MGMT*-unmethylated tumors remains controversial. There was overall no indication that the benefit from TMZ was reduced with increasing age.[52] In the absence of comparative data between TMZ alone and chemoradiation, elderly patients with *MGMT* promoter methylation considered eligible for combined modality treatment should be offered TMZ/RT→TMZ. Supportive and palliative care are appropriate for patients with large or multifocal lesions with low KPS, notably if they are unable to consent for further therapy after biopsy.

Local BCNU wafer chemotherapy added to RT conferred a survival benefit of 13.9 over 11.6 months with RT alone for the intention-to-treat population of high-grade gliomas, but the difference was no longer significant when only glioblastoma patients were considered[21,44,53] unless extent of resection was included in the analysis where the effect was again significant in glioblastoma patients with larger than 90% resection.[54]

Two randomized trials conducted in the adult glioblastoma patient population have demonstrated a gain in PFS of 3-4 months, but not OS, when bevacizumab was added to TMZ/RT→TMZ.[55,56] The clinical significance of the PFS gain has been disputed because the reliability of assessing progression by neuroimaging has been questioned and because the RTOG 0825 report raised concerns of early cognitive decline in bevacizumab-treated patients. Bevacizumab was thus not approved for newly diagnosed glioblastoma. It may, however, be useful in individual patients with large tumors highly symptomatic and resistant to steroids who may otherwise not tolerate RT.

Tumor-treating fields (TTFields) represent a novel treatment modality designed to deliver alternating electrical fields to the brain. In an open-label randomized phase III trial improved PFS and OS were demonstrated when TTFields were added to standard maintenance TMZ in newly diagnosed glioblastoma patients.[57] The trial was terminated early when the first cohort of 315 randomized patients was analysed and a survival benefit was reported (hazard ratio 0.74 (95% CI, 0.56-0.98); log-rank p=0.03). Questions regarding mode of action, interpretation of data and impact on quality of life have been raised,[58] and the place and cost-effectiveness of TTFields in the standard of care for newly diagnosed glioblastoma remain to be defined.[59]

Standards of care for patients with recurrent glioblastoma are not well defined. Clinical decision-making is influenced by prior treatment, age, KPS, and patterns of progression. Second surgery is appropriate for 20-30% of patients and is considered for symptomatic, but circumscribed lesions and when the interval since the preceding surgery exceeds 6 months. Surgery may also be considered earlier in symptomatic patients after suboptimal initial surgery. An impact on survival may be limited to patients who are candidates for gross total resection of enhancing tumor.[60] The efficacy of re-irradiation and the value of amino acid PET for target delineation remain debated. Fractionation depends on tumor size. Doses of conventional or near conventional fractionation using 3-3.5 Gy /fraction to a total dose of 30-35 Gy have been tested and several studies using a dose 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 been performed with acceptable toxicity.[61] Yet, no relevant monotherapy efficacy was demonstrated in a larger randomized trial at 18 x 2 Gy.[62]

The main systemic treatment options at progression after TMZ/RT→TMZ in Europe are nitrosoureas, TMZ rechallenge, and bevacizumab. CCNU is increasingly considered standard of care, based on its activity as the control arm of several randomized trials,[46,63] with PFS rates at 6 months of 20%. Similar results have been reported with alternative dosing regimens of TMZ,[64] but activity is probably limited to patients with tumors with *MGMT* promoter methylation.[65,66] The BR12 trial showed no benefit from dose-intensified TMZ over standard-dose TMZ in TMZ-naïve malignant glioma patients,[29] but does not inform on the value of TMZ re-challenge for patients pre-treated with TMZ. There is thus, however, no reason to administer dose-intensified TMZ to TMZ-naïve patients. Whether dose-intensified regimens are superior to standard-dosed TMZ in recurrent glioblastoma after a TMZ-free interval, remains undetermined.

Bevacizumab is approved for recurrent glioblastoma in various countries throughout the world, but not in the European Union, based on response rates in the range of 30% and PFS and OS times comparing favourably with historical controls in two uncontrolled phase II trials.[67,68] Its value in clinical practice is widely accepted because of transient symptom control and the option for steroid sparing in a subset of patients. An effect on OS has not been demonstrated. The superiority of combining bevacizumab with CCNU over either agent alone for OS at 9 months[65] was not confirmed in the EORTC trial 26101.[69] No other active combination partner for bevacizumab has been identified. TTF were not superior to best physician`s choice in a randomized phase III trial.[70]

Diffuse midline glioma, H3-K27M-mutant

This new tumor entity has been assigned the WHO grade IV. It includes the majority of brainstem, thalamic and spinal gliomas in children and adults. Surgical options are limited and treatment beyond RT is not established. The prognosis is poor. Traditionally, treatment has followed the standards for histologically similar gliomas in other locations.

Oligodendroglioma, IDH-mutant and 1p/19q-codeleted - WHO grade II

The new WHO classification defines this tumor as IDH-mutant and 1p/19q-codeleted.[1] In rare instances with lacking or inclusive data on IDH and 1p/19q co-deletion, tumors are classified as oligodendroglioma, NOS. The diagnosis of *oligoastrocytoma* is discouraged in the new WHO classification. Only exceptional cases that cannot be conclusively tested for IDH mutation and 1p/19q co-deletion and show a mixed oligoastrocytic histology may still be classified as oligoastrocytoma, NOS.[1] Surgery is the primary treatment of IDH-mutant and 1p/19q-codeleted oligodendroglioma. The standard of care is RT followed by PCV if further treatment beyond surgery is considered necessary.[24]

Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted - WHO grade III

The new WHO classification defines this tumor as IDH-mutant and 1p/19q-codeleted, NOS is only assigned if conclusive molecular information is lacking. The diagnosis of *anaplastic oligoastrocytoma* is discouraged and no longer applicable when tumors are successfully tested for IDH mutation and 1p/19q co-deletion. Extent of resection is a prognostic factor.[26,71] Two large randomized clinical trials – EORTC 26951 and RTOG 9402 - showed that the addition of PCV chemotherapy, either prior to or after RT, in the first-line treatment prolonged OS by several years in the subset of patients with 1p/19q-codeleted oligodendroglial tumors.[72,73] 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 RT plus PCV experience preserved cognitive function and quality of life[74] and whether the same improvement in OS could be achieved with TMZ/RT→TMZ. Long-term results from the NOA-04 show that chemotherapy alone is not superior to RT alone in either IDH-mutant and 1p/19q-codeleted anaplastic oligodendroglioma or IDH-mutant anaplastic astrocytoma, indicating that alkylating agent chemotherapy alone is unlikely to achieve the same outcome as RT combined with PCV. Whether TMZ/RT →TMZ is similarly effective as RT followed by PCV is explored in the modified CODEL trial (NCT00887146).

Treatment at progression is influenced by type of and response to first-line treatment. If neither RT nor alkylating agents are options because they failed or because of intolerance, bevacizumab has been used,[75,76] but is of unknown efficacy as controlled studies are lacking. There is no evidence to combine bevacizumab with cytotoxic agents in this setting.

Other astrocytic tumors

Pilocytic astrocytoma and its variant, pilomyxoid astrocytoma, are rare tumors in adults and commonly cured by surgery alone. Radiotherapy is only indicated at progression when surgical options no longer exist. Pilocytic astrocytoma of the optic nerve may be associated with neurofibromatosis type I and cannot be resected unless useful 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 may respond to mTOR inhibition if treatment beyond surgery is required.[77]

Pleomorphic xanthoastrocytoma (WHO grade II) occurs predominantly in children and young adults and has a high rate (approximately 70%) of BRAF-V600E mutation. It should be resected and patients may be observed after gross total resection. Anaplastic pleomorphic xanthoastrocytoma (WHO grade III) should probably be managed with postoperative RT and not with a watch-and-wait strategy. In recurrent anaplastic pleomorphic astrocytoma, BRAF inhibitors such as vemurafenib appear to have limited activity.[78]

Coordination of care and outlook

Diagnosis and management plans for glioma patients should follow multidisciplinary tumor board recommendations throughout the disease course. Boards are an forum to discuss which measures can take place locally, which are better done at a specialized center, which are appropriate for in-patient versus out-patient settings, and which neurorehabilitation measures are useful. Local and national guidelines as well as upcoming EANO guidelines provide further guidance. Guidelines reflect knowledge and consensus at a given timepoint. Table 3 summarizes the key recommendations of the EANO task force in 2016. The EANO website (www.eano.eu) will inform of future updates on this guideline.

Declaration of interests

Dr. Weller reports grants from Acceleron, grants from Actelion, grants from Bayer, grants from Merck & Co, grants from Novocure, grants from Piqur, grants from Roche, personal fees from BMS, personal fees from Celldex, personal fees from Immunocellular Therapeutics, grants from Isarna, personal fees from Isarna, personal

fees from Magforce, personal fees from Merck & Co, personal fees from Northwest Biotherapeutics, personal fees from Novocure, personal fees from Pfizer, personal fees from Roche, personal fees from Teva, personal fees from Tocagen, grants from EMD Merck Serono, outside the submitted work.

Dr. van den Bent reports personal fees from Roche, personal fees from Celldex, personal fees from Novartis, personal fees from BMS, personal fees from MSD, grants and personal fees from Abbvie, outside the submitted work.

Dr. Tonn reports grants from BrainLab, outside the submitted work.

Dr. Stupp reports non-financial support from Novocure Ltd, other from Roche, other from Merck KGaA, other from MSD/Merck & Co, other from Novartis, outside the submitted work.

Dr. Preusser reports grants from Böhringer-Ingelheim, from GlaxoSmithKline, from Merck Sharp & Dome, personal fees from Bristol-Myers Squibb, personal fees from Novartis, personal fees from Gerson Lehrman Group, personal fees from CMC Contrast, personal fees from GlaxoSmithKline, personal fees from Mundipharma, personal fees from Roche, outside the submitted work.

Dr. Cohen-Jonathan Moyal has nothing to disclose.

Dr. Henriksson has nothing to disclose.

Dr. Le Rhun has nothing to disclose.

Dr. Balana has nothing to disclose.

Dr. Chinot reports grants, personal fees and non-financial support from Roche, personal fees from Ipsen, personal fees from Astra-Zeneca, personal fees and non-financial support from Servier, personal fees from Celldex, from null, during the conduct of the study; in addition, Dr. Chinot has a patent Aix Marseille Univ

13725437 9 1405 licensed.

Dr. Bendszus reports grants and personal fees from Guerbet, grants and personal fees from Novartis, personal fees from Roche, grants from Siemens, personal fees from Teva, personal fees from Bayer, personal fees from Vascular Dynamics, grants from DFG, from Hopp Foundation, grants and personal fees from Codman, grants from Stryker, outside the submitted work.

Dr. Reijneveld reports non-financial support from Roche Nederland BV, outside the submitted work.

Dr Dhermain has nothing to disclose.

Dr. French has nothing to disclose.

Dr. Marosi has nothing to disclose.

Dr. Watts has nothing to disclose.

Dr. Oberg has nothing to disclose.

Dr. Pilkington has nothing to disclose.

Dr. Baumert reports personal fees from Merck & Co (MSD), personal fees and non-financial support from Noxxon Pharma AG, outside the submitted work.

Dr. Taphoorn reports personal fees from Roche, outside the submitted work.

Dr. Hegi reports non-financial support from MDxHeatlth, other from Roche/Genentech, other from Novocure, other from MSD, other from BMS, outside the submitted work.

Dr. Westphal reports personal fees from Bristol-Myers-Squibb, personal fees from Novocure, personal fees from Roche, outside the submitted work.

Dr. Reifenberger reports grants from Roche, grants from Merck, personal fees from

Amgen and Celldex, outside the submitted work.

Dr. Soffietti has nothing to disclose.

Dr. Wick reports grants and personal fees from MSD, grants from Apogenix, grants from Boehringer Ingelheim, grants and personal fees from Genentech/Roche, grants from Pfizer, personal fees from BMS, personal fees from Celldex, outside the submitted work.

Author contributions

M. Weller wrote the first draft of the manuscript. All other authors reviewed the draft, provided input, and approved the final version of the manuscript.

References

1. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; **131**(6): 803-20.

2. Weller M, van den Bent M, Hopkins K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. *The Lancet Oncology* 2014; **15**(9): e395-403.

3. Soffietti R, Baumert BG, Bello L, et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. *Eur J Neurol* 2010; **17**(9): 1124-33.

4. Rice T, Lachance DH, Molinaro AM, et al. Understanding inherited genetic risk of adult glioma - a review. *Neurooncol Pract* 2016; **3**(1): 10-6.

5. Douw L, Klein M, Fagel SS, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. *Lancet Neurol* 2009; **8**(9): 810-8.

6. Taphoorn MJ, Henriksson R, Bottomley A, et al. Health-related quality of life in

a randomized phase III study of bevacizumab, temozolomide, and radiotherapy in newly diagnosed glioblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(19): 2166-75.

7. Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. *Neuro Oncol* 2015; **17**(9): 1188-98.

8. Albert NL, Weller M, Suchorska B, et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. *Neuro Oncol* 2016.

9. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010; **28**(11): 1963-72.

10. Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why, and what to do about it? *The Lancet Oncology* 2012; **13**(9): e375-82.

11. Sahm F, Reuss D, Koelsche C, et al. Farewell to oligoastrocytoma: in situ molecular genetics favor classification as either oligodendroglioma or astrocytoma.

Acta Neuropathol 2014; **128**(4): 551-9.

12. Herrlinger U, Jones DT, Glas M, et al. Gliomatosis cerebri: no evidence for a separate brain tumor entity. *Acta Neuropathol* 2016; **131**(2): 309-19.

13. Weller M, Pfister SM, Wick W, Hegi ME, Reifenberger G, Stupp R. Molecular neuro-oncology in clinical practice: a new horizon. *The Lancet Oncology* 2013; **14**(9): e370-9.

14. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *The Lancet Oncology* 2006; **7**(5): 392-401.

15. Osswald M, Jung E, Sahm F, et al. Brain tumour cells interconnect to a functional and resistant network. *Nature* 2015; **528**(7580): 93-8.

16. Vogelbaum MA, Jost S, Aghi MK, et al. Application of novel response/progression measures for surgically delivered therapies for gliomas: Response Assessment in Neuro-Oncology (RANO) Working Group. *Neurosurgery* 2012; **70**(1): 234-43; discussion 43-4.

17. Laperriere N, Zuraw L, Cairncross G, Cancer Care Ontario Practice Guidelines Initiative Neuro-Oncology Disease Site G. Radiotherapy for newly diagnosed

malignant glioma in adults: a systematic review. *Radiother Oncol* 2002; **64**(3): 259-73.

18. Niyazi M, Brada M, Chalmers AJ, et al. ESTRO-ACROP guideline "target delineation of glioblastomas". *Radiother Oncol* 2016; **118**(1): 35-42.

19. Lassman AB, Iwamoto FM, Cloughesy TF, et al. International retrospective study of over 1000 adults with anaplastic oligodendroglial tumors. *Neuro Oncol* 2011; **13**(6): 649-59.

20. Wick W, Roth P, Hartmann C, et al. Long-term analysis of the NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with PCV or temozolomide. *Neuro Oncol* 2016.

21. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 2003; **5**(2): 79-88.

22. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. *Lancet* 2005; **366**(9490): 985-90.

23. Baumert BG, Hegi ME, Van den Bent MJ, et al. Temozolomide chemotherapy

versus radiotherapy in high-risk low-grade glioma. A randomized phase III Intergroup study by EORTC/NCIC-CTG/TROG/MRC-CTU (EORTC 22033-26033). *The Lancet Oncology* 2016; **in press**.

24. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. *N Engl J Med* 2016; **374**(14): 1344-55.

25. Reuss DE, Kratz A, Sahm F, et al. Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. *Acta Neuropathol* 2015; **130**(3): 407-17.

26. Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(35): 5874-80.

27. Van den Bent MJ, Erridge S, Vogelbaum MA, et al. Results of the interim analysis of the EORTC randomized phase III CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q co-deletion, an intergroup trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016; **34**: suppl; abstr LBA2000.

28. Wick W, Meisner C, Hentschel B, et al. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. *Neurology* 2013; **81**(17): 1515-22.

29. Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010; **28**(30): 4601-8.

30. Yung WK, Prados MD, Yaya-Tur R, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 1999; **17**(9): 2762-71.

31. Desjardins A, Reardon DA, Herndon JE, 2nd, et al. Bevacizumab plus irinotecan in recurrent WHO grade 3 malignant gliomas. *Clin Cancer Res* 2008; **14**(21): 7068-73.

32. Chamberlain MC, Johnston S. Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma. *J Neurooncol* 2009; **91**(3): 359-67.

33. Vuorinen V, Hinkka S, Farkkila M, Jaaskelainen J. Debulking or biopsy of malignant glioma in elderly people - a randomised study. *Acta Neurochir (Wien)* 2003; **145**(1): 5-10.

34. Kreth FW, Thon N, Simon M, et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. *Ann Oncol* 2013; **24**(12): 3117-23.

35. Asklund T, Malmstrom A, Bergqvist M, Bjor O, Henriksson R. Brain tumors in Sweden: data from a population-based registry 1999-2012. *Acta Oncol* 2015; **54**(3): 377-84.

36. Walker MD, Alexander E, Jr., Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *J Neurosurg* 1978; **49**(3): 333-43.

37. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 2007; **356**(15): 1527-35.

38. Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *Journal of clinical oncology : official journal of the American Society of Clinical*

Oncology 2004; **22**(9): 1583-8.

39. Malmstrom A, Gronberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *The Lancet Oncology* 2012; **13**(9): 916-26.

40. Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *The Lancet Oncology* 2012; **13**(7): 707-15.

41. Roa W, Kepka L, Kumar N, et al. International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2015; **33**(35): 4145-50.

42. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352**(10): 987-96.

43. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *The Lancet*

Oncology 2009; **10**(5): 459-66.

44. Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database Syst Rev* 2013; (4): CD007415.

45. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005; **352**(10): 997-1003.

46. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? *Nature reviews Neurology* 2010; **6**(1): 39-51.

47. Wick W, Weller M, van den Bent M, et al. MGMT testing--the challenges for biomarker-based glioma treatment. *Nature reviews Neurology* 2014; **10**(7): 372-85.

48. Hegi ME, Stupp R. Withholding temozolomide in glioblastoma patients with unmethylated MGMT promoter--still a dilemma? *Neuro Oncol* 2015; **17**(11): 1425-7.

49. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(32): 4085-91.

50. Blumenthal D, Stupp R, Zhang P, et al. The impact of extended adjuvant

temozolomide in newly-diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG. *Neuro Oncol* 2015; **17**(Suppl 5): v2.

51. Gramatzki D, Kickingereder P, Hentschel B, et al. Extended temozolomide for newly diagnosed glioblastoma: an analysis of the German Glioma Network. *Neuro Oncol* 2016; **18**: in press.

52. Perry JR, Laperriere N, O'Callaghan CJ, et al. A phase III randomized controlled trial of short-course radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma (CCTG CE.6, EORTC 26062-22061, TROG 08.02, NCT00482677). J Clin Oncol 34, 2016. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2016; **34**: suppl; abstr LBA2.

53. Westphal M, Ram Z, Riddle V, Hilt D, Bortey E, Executive Committee of the Gliadel Study G. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148**(3): 269-75; discussion 75.

54. Stummer W, van den Bent MJ, Westphal M. Cytoreductive surgery of glioblastoma as the key to successful adjuvant therapies: new arguments in an old

discussion. *Acta Neurochir (Wien)* 2011; **153**(6): 1211-8.

55. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370**(8): 699-708.

56. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370**(8): 709-22.

57. Stupp R, Taillibert S, Kanner AA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. *JAMA* 2015; **314**(23): 2535-43.

58. Wick W. TTFields: where does all the skepticism come from? *Neuro Oncol* 2016; **18**(3): 303-5.

59. Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. *Neuro Oncol* 2016; **18**(8): 1129-36.

60. Suchorska B, Weller M, Tabatabai G, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. *Neuro Oncol* 2016; **18**(4): 549-56.

61. Ryu S, Buatti JM, Morris A, et al. The role of radiotherapy in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2014; **118**(3): 489-99.

62. Wick W, Fricke H, Junge K, et al. A phase II, randomized, study of weekly APG101+reirradiation versus reirradiation in progressive glioblastoma. *Clin Cancer Res* 2014; **20**(24): 6304-13.

63. Batchelor TT, Mulholland P, Neyns B, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(26): 3212-8.

64. Perry JR, Belanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: RESCUE study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2010; **28**(12): 2051-7.

65. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with

recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. *The Lancet Oncology* 2014; **15**(9): 943-53.

66. Weller M, Tabatabai G, Kastner B, et al. MGMT promoter methylation is a strong prognostic biomarker for benefit from dose-intensified temozolomide rechallenge in progressive glioblastoma: the DIRECTOR trial. *Clin Cancer Res* 2015; **21**(9): 2057-64.

67. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(28): 4733-40.

68. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2009; **27**(5): 740-5.

69. Wick W, Brandes A, Gorlia T, et al. Phase III trial exploring the combination of bevacizumab and lomustine in patients with first recurrence of a glioblastoma: the EORTC 26101 trial. *Neuro Oncol* 2015; **17**: suppl 5(LB05).

70. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's

choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *European journal of cancer* 2012; **48**(14): 2192-202.

71. Gorlia T, Delattre JY, Brandes AA, et al. New clinical, pathological and molecular prognostic models and calculators in patients with locally diagnosed anaplastic oligodendroglioma or oligoastrocytoma. A prognostic factor analysis of European Organisation for Research and Treatment of Cancer Brain Tumour Group Study 26951. *European journal of cancer* 2013; **49**(16): 3477-85.

72. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(3): 344-50.

73. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2013; **31**(3): 337-43.

74. Habets EJ, Taphoorn MJ, Nederend S, et al. Health-related quality of life and

cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors. *J Neurooncol* 2014; **116**(1): 161-8.

75. Chamberlain MC, Johnston S. Bevacizumab for recurrent alkylator-refractory anaplastic oligodendroglioma. *Cancer* 2009; **115**(8): 1734-43.

76. Taillibert S, Vincent LA, Granger B, et al. Bevacizumab and irinotecan for recurrent oligodendroglial tumors. *Neurology* 2009; **72**(18): 1601-6.

77. Franz DN, Agricola K, Mays M, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. *Ann Neurol* 2015; **78**(6): 929-38.

78. Chamberlain MC. Salvage therapy with BRAF inhibitors for recurrent pleomorphic xanthoastrocytoma: a retrospective case series. *J Neurooncol* 2013; **114**(2): 237-40.

79. Brainin M, Barnes M, Baron JC, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces--revised recommendations 2004. *Eur J Neurol* 2004; **11**(9): 577-81.

Table 1 – Key treatment recommendations for patients with diffuse astrocytic and oligodendroglial tumors according to the new WHO classification

	Tumor type	First-line treatment[1]	Salvage therapies[2,3]	Comments / References
	Diffuse astrocytic and oligodendroglial tumors			
	Diffuse astrocytoma, IDH-mutant	Wait-and-see or RT→PCV (or TMZ/RT→TMZ)	Nitrosourea (or TMZ rechallenge or bevacizumab[4])	RTOG 9802[24] and per extrapolation from WHO grade III tumors[27]
	Gemistocytic astrocytoma, IDH-mutant	Wait-and-see or RT→PCV (or TMZ/RT→TMZ)	Nitrosourea (or TMZ rechallenge or bevacizumab[4])	
	Diffuse astrocytoma, IDH-wildtype	Wait-and-see (?), RT, RT→PCV or TMZ/RT→TMZ, (by *MGMT* status ?)	TMZ, or Nitrosourea (or TMZ rechallenge) or bevacizumab[4]	Per extrapolation from IDH-wildtype glioblastoma[42]
	Diffuse astrocytoma, NOS	see above, per extrapolation	Nitrosourea (or TMZ rechallenge or bevacizumab[4])	
	Anaplastic astrocytoma, IDH-mutant	(TMZ)/RT→TMZ	Nitrosourea or TMZ rechallenge or bevacizumab[4]	[27]
	Anaplastic astrocytoma, IDH-wildtype	RT or TMZ/RT→TMZ, by *MGMT* status (?)	TMZ, or Nitrosourea (or TMZ rechallenge) or bevacizumab[4]	Per extrapolation from IDH-wildtype glioblastoma [28,42]
	Anaplastic astrocytoma, NOS	see above, per extrapolation	Nitrosourea or TMZ rechallenge or bevacizumab[4]	
	Glioblastoma, IDH-wildtype Giant cell glioblastoma Gliosarcoma *Epithelioid glioblastoma*	TMZ/RT→TMZ, > 65-70 years RT (MGMT unmethylated), or TMZ/RT→TMZ or TMZ (MGMT methylated)	Nitrosourea or TMZ rechallenge or bevacizumab[4], RT for RT-naïve patients	[39,40,42,52]
	Glioblastoma, IDH-mutant	(TMZ)/RT→TMZ	Nitrosourea or TMZ	Per extrapolation from IDH-

			rechallenge or bevacizumab[4]	mutant anaplastic astrocytoma[27]
	Glioblastoma, NOS	TMZ/RT→TMZ, > 65-70 years RT (MGMT unmethylated), or TMZ or TMZ/RT→TMZ (MGMT methylated)	Nitrosourea or TMZ rechallenge or bevacizumab[4], RT for RT-naïve patients	[42]
	Diffuse midline glioma, H3-K27M mutant	RT or TMZ/RT→TMZ		
	Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	Wait-and-see or RT→PCV (or PCV→RT)	TMZ or bevacizumab[4]	Per extrapolation from WHO grade III tumors[72,73] and RTOG 9802[24]
	Oligodendroglioma, NOS	Wait-and-see or RT→PCV (or PCV→RT)	TMZ or bevacizumab[4]	Per extrapolation from WHO grade III tumors[72,73] and RTOG 9802[24]
	Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	RT→PCV (or PCV→RT)	TMZ or bevacizumab[4]	[72,73]
	Anaplastic oligodendroglioma, NOS	RT→PCV (or PCV→RT)	TMZ or bevacizumab[4]	[72,73]
	Oligoastrocytoma, NOS	Wait-and-see or RT→PCV (or PCV→RT)	TMZ or bevacizumab[4]	Per extrapolation from WHO grade III tumors[72,73] and RTOG 9802[24]
	Anaplastic oligoastrocytoma, NOS	RT→PCV (or PCV→RT)	TMZ or bevacizumab[4]	[72,73]
	Other astrocytic tumors			
	Pilocytic astrocytoma *Pilomyxoid astrocytoma*	Surgery only	Surgery → RT	
	Subependymal giant cell astrocytoma	Surgery only	Surgery	
	Pleomorphic xanthoastrocytoma	Surgery only	Surgery	
	Anaplastic pleomorphic	RT	Surgery → ChT (TMZ)	

	xanthoastrocytoma			

[1]maximum safe resection is recommended whenever feasible in all patients with newly diagnosed gliomas
[2]second surgery should always be considered, but clinical benefit may be limited to patients where a gross total resection can be achieved
[3]reexposure to TMZ and less so nitrosourea treatment has little activity in tumors lacking MGMT promoter methylation
[4]depending on local availability

Table 2 - Chemotherapy protocols in malignant gliomas

Protocol	Dose and mode of administration
TMZ	75 mg/m^2 daily p.o. including weekends during RT 150–200 mg/m^2 D1- D5 p.o. fasting in the morning every 4 weeks for 6 cycles of maintenance treatment
ACNU (nimustine), BCNU (carmustine), CCNU (lomustine), fotemustine	Different regimens, most commonly CCNU p.o. 110 mg/m^2 every 6 weeks
PCV	Procarbazine 60 mg/m^2 p.o. D8–D21 CCNU 110 mg/m^2 p.o. D1 Vincristine 1.4 mg/m^2 i. v. (maximum 2 mg) D8 +D29 x (6-)8 weeks
Bevacizumab	10 mg/m^2 x 2 weeks

Table 3 - Key recommendations*

General	**C**	**L**
Karnofsky performance score (KPS), 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 relevant germ line variants or suspected hereditary cancer syndromes should receive genetic counselling and based on that might be referred for molecular genetic testing.	IV	-
The diagnostic imaging approach of first choice is magnetic resonance imaging (MRI) without and with contrast enhancement.	IV	-
Peudoprogression should be considered in patients with an increase of tumor 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 very exceptional situations.	IV	-
Glioma classification should follow the new WHO classification of tumors 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	IV	-

assessment of gliomas.		
IDH mutation status should be assessed by immunohistochemistry for IDH1-R132H. If negative, immunohistochemistry should be followed by sequencing of *IDH1* codon 132 and *IDH*2 codon 172 in all WHO grade II and III astrocytic and oligodendroglial gliomas and in all glioblastomas of patients younger than 55 years of age to allow for integrated diagnoses according to the WHO classification and to guide treatment decisions.	IV	-
1p19q co-deletion status should be determined in all IDH-mutant gliomas with retained nuclear expression of ATRX.	II	B
MGMT promoter methylation status should be determined in elderly patients with glioblastoma and in IDH-wildtype WHO grade II/III gliomas to guide decision for the use of TMZ instead of or in addition to RT.	I	B
Since extent of resection is a prognostic factor, efforts at obtaining complete resections are justified across all glioma entities.	IV	-
The prevention of new permanent neurological deficits has higher priority than extent of resection in the current surgical approach to gliomas.	IV	-
IDH-mutant WHO grade II/III gliomas		
Standard of care for (1p/19q-non-codeleted) WHO grade II diffuse astrocytoma requiring further treatment includes resection as feasible or biopsy followed by involved field RT and maintenance PCV (RTOG 9802).[24]	II	B

Standard of care for 1p/19q-non-codeleted anaplastic astrocytoma includes resection as feasible or biopsy followed by involved field RT and maintenance TMZ (CATNON).[27]	II	B
Patients with 1p/19q-codeleted WHO grade II oligodendroglial tumors requiring further treatment should be treated with radiotherapy plus PCV chemotherapy.	III	B
Patients with 1p/19q-codeleted anaplastic oligodendroglial tumors should be treated with radiotherapy plus PCV chemotherapy (EORTC 26951, RTOG 9402).[72,73]	II	B
Temozolomide chemotherapy is standard treatment at progression after surgery and radiotherapy for most patients with WHO grade II/III gliomas.	II	B
Glioblastoma, IDH-wildtype (WHO grade IV)		
Standard of care for glioblastoma, IDH-wildtype (age < 70 years, KPS ≥ 70) includes resection as feasible or biopsy followed by involved-field radiotherapy and concomitant and maintenance (6 cycles) TMZ chemotherapy (TMZ/RT→TMZ) (EORTC 26981 NCIC CE.3).[42]	I	A
TMZ is particularly active in patients with *MGMT* promoter methylation whereas its activity in patients with *MGMT* promoter-unmethylated tumors is marginal.[45]	II	B
Elderly patients not considered candidates for TMZ/RT→TMZ should be treated based on *MGMT* promoter methylation status (NOA-08, Nordic Trial, NCIC CE.6/EORTC 6062) with radiotherapy (e.g., 15 x 2.66 Gy) or	II	B

TMZ (5/28).[39,40,52]		
At recurrence, standards of care are less well defined. Nitrosourea regimens, TMZ re-challenge and, with consideration of the country-specific label, bevacizumab are options of pharmacotherapy, but an impact on OS remains unproven. When available, recruitment into appropriate clinical trials should be considered.	II	B

*C class of evidence, *level of recommendation[79]

Figure Legends

Figure 1. Graphic illustration of a commonly used diagnostic algorithm for integrated classification of diffuse astrocytic and oligodendroglial gliomas according to the WHO classification 2016 (Louis et al. 2016). Following histological analysis, diffuse gliomas of WHO grade II, III or IV are assessed by immunohistochemistry for IDH1-R132H mutation and loss of nuclear expression of ATRX protein. In case of diffuse gliomas located in midline structures (thalamus, brain stem and spinal cord), immunostaining for histone 3 K27M (H3-K27M) mutation characterizes diffuse midline gliomas, H3-K27M-mutant. Following immunohistochemistry, molecular analyses for less common *IDH1* codon 132 mutations (other than R132H) or *IDH2* codon 172 mutations (e.g. by DNA sequencing) as well as for codeletion of chromosomal arms 1p and 19q (e.g. by fluorescent *in situ* hybridization or microsatellite PCR-based loss of heterozygosity analyses) are carried out according to the individual immunhistochemical results. *IDH-mutation and loss of nuclear ATRX expression suffice for classification as IDH-

mutant astrocytic gliomas. Additional molecular testing for 1p/19q codeletion is not routinely required but may be performed to further substantiate the diagnosis, e.g. in cases with ambigous histology. **In patients older than 55 years of age at diagnosis with a histologically typical glioblastoma, without a pre-existing lower grade glioma and with non-midline tumor location, immunohistochemical negativity for IDH1-R132H suffices for classification as glioblastoma, IDH-wildtype. In all other instances of diffuse gliomas, lack of IDH1-R132H immunopositivy should be followed by *IDH1* and *IDH2* sequencing to detect or exclude other, less common IDH mutations. ***IDH-wildtype diffuse astrocytic gliomas with loss of nuclear ATRX expression may be additionally tested histone 3 mutations. Abbreviations: A II, diffuse astrocytoma WHO grade II; AA III, anaplastic astrocytoma WHO grade III; GB IV, glioblastoma WHO grade IV; O II, oligodendroglioma WHO grade II; AO III, anaplastic oligodendroglioma WHO grade III. The provisional WHO entities of diffuse astrocytoma, IDH-wildtype, and anaplastic astrocytoma, IDH-wildtype, are indicated in italics.

Figure 2. Clinical Pathway “Glioma”.

Figure 3. Diagnostic and therapeutic approach to gliomas in adulthood. Note that the option of supportive care exists across the entities, but is not included for clarity.