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EANO Guideline on the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma

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Conflicts of interest

MW has received research grants from Antisense Pharma, Bayer, Merck Serono, MSD and Roche and honoraria for lectures or advisory boards from Antisense Pharma, Magforce, Merck Serono, MSD and Roche. He was the principal investigator of phase II or phase III trials investigating temozolomide (MSD) in newly diagnosed anaplastic glioma and glioblastoma as well as recurrent glioblastoma and bevacizumab in glioblastoma.

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JCT has received honoraria for lectures or advisory boards from Merck Serono, Medac, BrainLab and Roche.

RoSt served on advisory boards of Merck KGaA, MSD, and Roche/Genentech. He is a principal investigator on trials evaluating temozolomide in low-grade glioma, and NovoTTF or cilengitide in newly diagnosed glioblastoma.

ECJM has received honoraria for advisory boards from Merck Serono.

RH is member of the Steering Committee of the AVAGlio study (Roche).

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OC is consultant for Roche and has received honoraria for advisory boards from Astra-Zeneca and MSD. He serve as the PI of the AVAGlio trial.

ZR is a consultant to Novocure.

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WW reports on having received consulting and lecture fees from MSD, Roche and Magforce. WW has received research support from Apogenix, Boehringer Ingelheim, Eli Lilly, MSD, and Roche. He serves on the Steering Committee of the AVAglio trial involving bevacizumab in glioblastoma and has been lead investigator in glioma trials involving temozolomide, bevacizumab, enzastaurin and APG101.

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Summary

This guideline provides recommendations for the diagnostic and therapeutic procedures for patients with malignant gliomas. It differentiates evidence-based standards from reasonable options or non-evidence-based measures that should no longer be considered. The recommendations herein shall provide a framework and assurance for the choice of diagnostic procedures and therapeutic measures and aim to reduce complications from unnecessary treatment and cost. The guideline will contribute to a critical appreciation of concurrent medications with a focus on the controlled use of anticonvulsants and steroids. It shall serve as a guideline for all professionals involved in the diagnostics and care of glioma patients and also as a source of knowledge for insurance companies and other institutions involved in the cost regulation of cancer care in Europe. Implementation of the recommendations summarized here will require interdisciplinary structures of care for brain tumor patients and structured processes of diagnostic and therapeutic procedures.

Key words

Anaplastic, glioma, glioblastoma, surgery, radiotherapy, temozolomide, bevacizumab

Search strategy and selection criteria

This guideline was prepared by a task force assembled by the Executive Committee of the European Association for Neuro-Oncology (EANO) in 2013. The task force was designed to represent the different disciplines involved in the diagnosis and care of malignant glioma patients as well as to reflect the multinational composition of EANO. References for this review were identified through searches of PubMed with the search terms “glioma”, “anaplastic”, “glioblastoma”, “trial”, “clinical”, “radiotherapy”

and “chemotherapy” from January 2005 to January 2013. Articles were also identified through searches of the authors` own files. Only papers in English were reviewed. Data available only in Abstract form were not included with one exception. The final reference list was generated on the basis of originality and relevance to the broad scope of this review.

Introduction

The current guideline on the diagnosis and treatment of gliomas follows the Third Revision of the World Health Organization (WHO) Histological Classification of Tumors of the Central Nervous System.[1] It covers WHO grade III anaplastic astrocytomas, oligodendrogliomas and oligoastrocytomas, WHO grade IV glioblastomas including its variants, gliomatosis cerebri, and WHO grade III and IV gliomas of brainstem and spinal cord. The guideline covers prevention, early diagnosis and screening, therapy, follow-up and rehabilitation of patients with malignant gliomas. It does not cover differential diagnoses of gliomas and adverse effects of therapeutic measures in depth. The structure of the guideline was based on the national guideline on gliomas of the German Society of Neurology and the German Cancer Society (www.dgn.org).

A Webappendix summarizes EANO`s recommendations for the general approach to patients with malignant gliomas with coverage of diagnostic aspects – early diagnosis and prevention, history, clinical examination, neuroimaging, cerebrospinal fluid analyses, electroencephalography, preoperative management, biopsy and resection, histological classification and grading, molecular diagnostics – as well as general recommendations for therapy - surgical therapy, radiotherapy (RT), pharmacotherapy and other therapeutic approaches.

The guideline aims at serving medical professionals of all disciplines involved in the

diagnosis and care of glioma patients, in particular neurologists, neurosurgeons, radiation oncologists, neuropathologists, neuroradiologists, oncologists, pediatric oncologists, epileptologists, psycho-oncologists, rehabilitation specialists, palliative care and neurooncology nursing specialists. Further, the recommendations may serve as a valuable source of information for patients, relatives, other health professionals and health insurances.

Specific recommendations

Anaplastic astrocytoma – WHO grade III

Anaplastic astrocytomas exhibit inhomogeneous density on CT and appear as hyperintense, space-occupying lesions on T_2-weighted/fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). They tend to show patchy enhancement upon contrast administration and commonly exhibit peritumoral edema. However, a significant proportion of up to 30% of these tumors may show no enhancement on CT or MRI. Abnormal vessels may be visualized by MRI angiography. Favorable prognostic factors include young age, high Karnofsky performance score (KPS), isocitrate dehydrogenase (*IDH)*-1/2 mutation, and O^6-methylguanine DNA methyltransferase (*MGMT)* promoter methylation.[2] Further, loss of alpha-thalassemia/mental retardation syndrome X-linked (ATRX) expression defines a subgroup of anaplastic astrocytic tumors with a more favorable prognosis.[3] The traditional standard of care for anaplastic astrocytoma includes maximal resection as feasible or biopsy followed by involved-field RT to 60 Gy administered in 1.8–2 Gy fractions (Table 1).[4] Historical randomized clinical trials using this treatment

modality have confirmed a doubling of median survival time compared with surgery alone. An efficacy of adjuvant chemotherapy using nitrosourea compounds as a part of first-line treatment was suggested by meta-analysis, e.g., the 1-year survival rate was reported to be increased from 58% to 63%, and the 2-year survival rate from 31% to 37% in a meta-analysis of published trials.[5] However, such meta-analyses are potentially biased by a greater likelihood of negative trials not to be published. No survival benefit for the addition of procarbacine, 1-(2-chlorethyl)-3-cyclohexyl-1-nitrosourea (CCNU) and vincristine (PCV) chemotherapy to RT was demonstrated in the subgroup of anaplastic glioma patients in a large Medical Research Council (MRC) trial.[6] Conversely, the German Neuro-Oncology Group (NOA)-04 trial indicated that alkylating agent chemotherapy alone using PCV or temozolomide (TMZ) was similarly effective as RT alone regarding progression-free survival, with overall survival data being similar, but not mature especially for the patients with good prognosis when first published.[7] The CATNON trial (European Organization for Research and Treatment of Cancer (EORTC) 26053) was based on the assumption that adjuvant chemotherapy is not standard of care in *1p/19q*-non-co-deleted tumors, the majority of which are anaplastic astrocytomas, and explores the added value of concomitant or adjuvant TMZ or both added to first-line RT. A retrospective analysis from NOA-04, NOA-08 and the German Glioma Network suggested that the *IDH*-1/2 status might serve as a predictive biomarker for benefit from the addition of TMZ to RT: patients with *IDH*-1/2-wildtype tumors with a methylated *MGMT* promoter might benefit from the inclusion of alkylating agent chemotherapy in the first-line treatment.[8] The present standard of care outside clinical trials, based on NOA-04,[7] remains RT alone or alkylating agent chemotherapy alone for patients with anaplastic astrocytoma (which typically lacks *1p/19q* co-deletion) until long-term results from NOA-04 and data from

CATNON become available. TMZ is commonly preferred over PCV because of favorable safety and tolerability profile.

At progression the option of second surgery should be explored. Initial therapy determines the options at recurrence. For pre-irradiated patients, hypofractionated RT using, e.g., 6-7 × 5 Gy or 10-13 × 3 Gy may be feasible if recurrences are circumscribed and chemotherapy is contraindicated. Re-irradiation should be given as fractionated stereotactic RT, conformal RT with tight margins or image-guided radiotherapy (IGRT). However, the size and patterns of recurrent tumor often preclude re-irradiation, and the overall efficacy is disputed. Alkylating agent chemotherapy is the treatment of choice for most chemo-naive patients who progress after RT. TMZ and nitrosoureas are probably equally effective. A median progression-free survival of 23 weeks and a progression-free survival rate at 6 months of 46% in a phase II setting led to the approval of TMZ in this indication;[9] 14 of 111 patients in this study had anaplastic oligoastrocytoma. The comparative study of TMZ and a variant of the standard European PCV regimen (Table 2) confirmed similar efficacy.[10] Bevacizumab is commonly used after failure of RT and alkylating agent chemotherapy, depending on local availability, with progression-free survival rates at 6 months of 20-60%.[11-13] Controlled trials are missing, however, and there is no evidence to combine bevacizumab with cytotoxic agents in this setting.

Anaplastic oligodendroglioma and oligoastrocytoma - WHO grade III

The entity of anaplastic oligoastrocytoma remains a matter of debate for years and has been challenged because of poor interobserver agreement and incomplete molecular definition. In the NOA-04 trial which had central neuropathology review at

study entry,[7] anaplastic oligodendroglioma and mixed anaplastic oligoastrocytoma shared the same, more favorable course than anaplastic astrocytoma. In the coming revision of the WHO classification, molecular markers should be integrated to refine the current morphology-based classification of anaplastic gliomas.[2,3] Among anaplastic gliomas, there is high correlation between oligodendroglial morphology and the *1p/19q* co-deletion. Tumors with *1p/19q* co-deletion probably invariably carry *IDH*-1/2 mutations and frequently demonstrate *MGMT* promoter methylation as well as telomerase reverse transcriptase *(TERT)* promoter mutations.[14] In contrast, *TP53* mutation and loss of *ATRX* expression are rare in *1p/19q*-co-deleted gliomas, but common in diffuse and anaplastic astrocytomas. This may help to dissect the controversial entity of anaplastic oligoastrocytoma.[3]

Extent of resection is a prognostic factor in these tumors, too.[7,15] Although RT (54-60 Gy, 1.8-2 Gy-fractions) has been considered standard of care for anaplastic oligodendroglial tumors, their chemosensitivity to nitrosoureas and TMZ has long been recognized, and ongoing controversies do not focus on whether to give RT or alkylating chemotherapy at all, but rather when and in what sequence. Long-term results of the two early large independent randomized clinical trials – EORTC 26951 and Radiation Therapy Oncology Group (RTOG) 9402 – that explored the value of PCV polychemotherapy, either prior to or immediately after RT, indicate that the inclusion of chemotherapy in the first-line treatment confers a survival advantage which becomes evident only after follow-up of more than six years and only in the subgroup of patients with *1p/19q*-co-deleted tumours.[16-19] Thus, *1p/19q* co-deletions have also predictive value for benefit from chemotherapy, in addition to the characterization of a prognostically more favorable subgroup of patients with anaplastic oligodendroglial tumors. Although these results mostly stem from retrospective analyses of small patient cohorts and are thus explorative, both studies

show very similar results in the patients with *1p/19q*-co-deleted tumors and thus validate each other. Important questions remain, however, including: how many of the long-term survivors treated with RT plus PCV experienced preserved cognitive function and quality of life? Could the same improvement in overall survival have been achieved with the combination of RT and TMZ or even with alkylating agent chemotherapy alone? Long-term results from the NOA-04[7] trial which compared RT versus TMZ versus PCV alone might shed light on some of these questions. At present, phase III clinical trials in patients with *1p/19q*-co-deleted oligodendroglial tumors should include RT plus PCV as a standard arm. In clinical practice, many sites have reverted to classical RT plus PCV as a standard of care, others prefer TMZ/RT→TMZ or even TMZ alone in particular in young patients (Table 2, Supplementary Figure). Accordingly, the amended 3-group CODEL trial shall now compare RT→PCV with TMZ/RT →TMZ) and TMZ alone.

Treatment at progression is influenced by type of and response to first-line treatment as outlined for anaplastic astrocytoma. If neither RT nor alkylating agents are options because they failed or because of intolerance, bevacizumab can be considered as a salvage strategy, depending on local availability.[11,13,20,21] Proper controlled studies are lacking here, however, and there is also no evidence to combine bevacizumab with cytotoxic agents in this setting.

Glioblastoma (WHO grade IV)

Glioblastomas are space-occupying lesions on MRI or CT which exhibit irregular boundaries and commonly enhance after administration of contrast agents. Central necrosis and perilesional edema are common. Angiography shows highly abnormal

vasculature with arteriovenous shunting and early venous drainage. Interestingly, in the growing population of elderly patients with malignant gliomas, there is no major difference in prognosis between anaplastic astrocytoma and glioblastoma.[22-24]

The therapeutic role of surgery is no longer disputed. A small randomized trial from Finland in glioblastoma or anaplastic astrocytoma patients aged > 65 showed a median survival of 171 days after resection *versus* 85 days after biopsy (p=0.035).[25] This study has been criticized because of small patient numbers (n=30 enrolled, 13 versus 10 patients per arm evaluable) and major KPS imbalances between arms. While some recent clinical series have reported gradually extended survival associated with extent of resection, other studies proposed that only a gross total resection is associated with better outcome.[26] Meanwhile many tools are available to increase the extent of resection while keeping the risk of new neurological deficits low. These include the routine use of surgical navigation systems housing functional MRI datasets when available, intraoperative MRI and intraoperative functional monitoring. The fluorescent dye, 5-aminolevulinic acid (ALA) helps to visualize glioblastoma tissue during microsurgical tumor resection. Its use was associated with an increased rate of gross total resections and an increased progression-free survival rate at 6 months.[27] Whether its use prolongs survival remains unknown,[28] moreover, the pivotal study was performed before TMZ/RT→TMZ became standard of care.

RT has been standard of care for glioblastoma for decades, with an undisputed major survival benefit.[4] The RT volume commonly includes the T_1-enhanced region plus a 2-3 cm safety margin on the T_2 or FLAIR abnormality planned as described above. The standard dose is 54-60 Gy administered in 1.8-2 Gy fractions. A regimen of 50 Gy in 1.8 Gy fractions was superior to best supportive care in patients 70 years or older.[29] Patients with adverse prognostic factors defined by age or performance status or both are now commonly treated with hypofractionated RT, e.g., 40 Gy in 15

fractions.[30] In the elderly, this is now the preferred regimen for patients with tumors lacking *MGMT* promoter methylation.[23,31] Neither accelerated hyper- nor hypofractionated regimens nor brachytherapy nor radiosurgery or a stereotactic RT boost have been shown to be superior to standard fractionation in terms of survival. The combination of nitrosourea-based chemotherapy with RT in newly diagnosed glioblastoma increased the 1-year survival rate from 31% to 37% and the 2-year survival rate from 9% to 13% in a meta-analysis.[5] No differences between single nitrosourea compounds or between monotherapy and nitrosourea-based combination therapies were identified. The British study comparing RT alone with RT plus PCV showed no increase of survival with the addition of chemotherapy.[6] Local 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU) wafer chemotherapy added to RT conferred a survival benefit of 13.9 over 11.6 months over RT alone for the intention-to-treat population, but the difference was no longer significant when patients with anaplastic gliomas were removed from the cohorts.[32-34] Its efficacy and safety in combination with TMZ/RT→TMZ have not been adequately explored. Concomitant and adjuvant TMZ chemotherapy plus RT (TMZ/RT→TMZ) is the standard of care for adult patients with newly diagnosed glioblastoma aged up to 70 and in good general and neurological condition.[35,36] The benefit from TMZ is most prominent in patients with glioblastoma with *MGMT* promoter methylation.[37,38] TMZ is given at 75 mg/m^2 during RT and for six maintenance cycles on 5 out of 28 days at 150-200 mg/m^2 thereafter. There is no benefit from increasing the dose of TMZ in the setting of newly diagnosed disease[39] and extending the duration of chemotherapy beyond 6 cycles is also not supported by clinical trial data. For individual patients, increasing the number of adjuvant TMZ cycles may be considered, e.g., for individual patients with stable or incompletely regressing, residual, contrast-enhancing tumors at completion of 6 cycles of TMZ.

Two randomized trials conducted in the adult glioblastoma patient population have demonstrated a gain in progression-free survival of 3-4 months, but not overall survival, when patients with newly diagnosed glioblastoma received bevacizumab in addition to TMZ/RT→TMZ.[40,41] Interpretation of the data from these trials remains controversial,[42] and a decision on approval in newly diagnosed glioblastoma in Europe is pending.

For the increasing population of elderly patients with glioblastoma, new standards of care were defined in 2012. Based on the NOA-08 and Nordic trials,[23,31] *MGMT* testing should be considered standard practice.[43] Patients with tumors lacking *MGMT* promoter methylation should receive hypofractionated RT alone. This is also the preferred treatment for patients with tumors with unknown *MGMT* status. Those with tumors with *MGMT* promoter methylation should be treated with TMZ alone (5/28 until progression or for 12 months) or with TMZ/RT→TMZ. The role of early RT in addition to TMZ in these patients will be better understood when data from the ongoing EORTC National Cancer Institute of Canada (NCIC) Clinical Trial Group elderly trial can be compared with those of the NOA-08 and Nordic trials.

Best supportive care may the preferred option in patients with large or multifocal lesions with KPS below 50, notably in patients who cannot provide informed consent for further therapy beyond biopsy.

Standards of care for patients with recurrent glioblastoma are not well defined and clinical decision making is commonly based on prior treatment, age, KPS, prior therapy, and patterns of relapse. Second surgery should typically be considered with large, but circumscribed lesions causing neurological deficits and when the interval from last surgery is more than 6 months. However, surgery for progressive glioblastoma may also be considered earlier in symptomatic patients, especially in patients with suboptimal initial surgery. Approximately 20-30% of patients with

recurrent glioblastoma are candidates for second surgery. The role of re-irradiation is uncertain, including the role of amino acid positron emission tomography (PET) for target delineation, and multiple fractionation regimens have been proposed, e.g., from 6 x 5 Gy to 18 x 2 Gy.[44,45] The three strategies of medical treatment for glioblastoma recurring after TMZ/RT→TMZ most commonly used across Europe include nitrosourea-based regimens, alternative dosing regimens of TMZ, and bevacizumab. The activity of CCNU has been confirmed in the standard arms of randomized trials exploring the activity of the protein kinase C-β inhibitor, enzastaurin,[46] or the vascular endothelial growth factor (VEGF) receptor inhibitor, cediranib,[47] with progression-free survival rates at 6 months of 20%. Somewhat better control rates at 6 months have been reported with a continuous dosing regimen of TMZ,[48] but not in recent phase II trial exploring a 21 out of 28 days schedule.[49] The BR12 trial which enrolled recurrent, TMZ-naïve malignant glioma patients provided no evidence for superiority of dose-intensified TMZ over standard-dosed TMZ,[50] but these data are of limited value in assessing the role of TMZ rechallenge for patients pre-exposed to TMZ. They do, however, suggest that there is no rationale for using dose-intensified TMZ in recurrent glioma patients who are TMZ-naive.

Bevacizumab has been approved for the treatment of recurrent glioblastoma in various countries throughout the world, but not in the European Union, based on two prospective, but uncontrolled phase II trials that reported radiological response rates of 30% or more and progression-free and overall survival times interpreted to be superior to historical controls.[51,52] A value of bevacizumab in the management of progressive malignant gliomas in clinical practice is almost universally accepted because of evident, albeit transient, symptom relief and steroid-sparing effects. However, timing and dosing schedules remain controversial, and an effect on overall

survival remains to be demonstrated. No active combination partner for bevacizumab has been identified in the setting of progressive disease, albeit in uncontrolled or non-comparative trials, suggesting that bevacizumab monotherapy should be administered outside clinical trials. Preliminary data indicate that the combination of bevacizumab and CCNU may be superior to either agent alone,[53] suggesting that this combination warrants further exploration as planned in a phase III trial by the EORTC.

Gliomatosis cerebri

The diagnosis of gliomatosis cerebri is based on the histological verification of a glioma and requires the radiological demonstration of diffuse signal alteration suggestive of tumor affecting at least three cerebral lobes. The diagnosis is thus not based on histology alone and hence rather operational. Typically, the tumor involves both cerebral hemispheres and may extend into the basal ganglia and brain stem. Gliomatosis cerebri may correspond to WHO grades II, III or IV, based on the histological findings in the respective biopsy specimens. The diagnostic concept of gliomatosis cerebri has proven difficult to operationalize in clinical practice and trials and is likely to be revised with support of molecular markers and advanced imaging technology. The imaging features are quite characteristic and include a diffuse hyperintense tumor on T_2 / FLAIR images involving both the white and gray matter, non-enhancing or with small patchy areas of contrast enhancement. Perfusion MRI and MR spectroscopy can be useful to differentiate rare non-neoplastic lesions. Gliomatosis cerebri imaging resembles diffuse (WHO grade II) astrocytomas in most patients, but the median survival is in the range of only 30 months for patients eligible

for a clinical trial.[54] In selected patients where intracranial pressure is markedly elevated, decompressive craniectomy may rarely be considered at the time of biopsy to prevent rapid neurological deterioration. The course is highly variable, but occasionally younger patients can be followed for years without specific therapy. *IDH*-1/2 mutations are associated with a better outcome. Surgery is commonly limited to a diagnostic biopsy. RT and alkylating chemotherapy are active treatments. The role of RT as initial treatment is limited because of the high dose required for the control of glioma growth and the large target volumes required in gliomatosis cerebri. Both PCV and TMZ are commonly used as alternatives to RT.[55,56] The NOA-05 trial explored the efficacy of primary PC chemotherapy, omitting vincristine because of poor blood brain barrier penetration, and observed treatment failure at 8 months in less than half of the patients, and a median overall survival of 30 months.[54]

Brain stem gliomas and spinal gliomas

Diffuse intrinsic pontine gliomas are a major challenge in pediatric neuro-oncology. While children are often treated based on neuroimaging alone, histological verification of the diagnosis is considered mandatory in adults, especially in case of enhancing lesions, because of a higher error rate by imaging alone and a broader range of differential diagnoses.[57] Magnetic resonance spectroscopy can aid differential diagnosis if biopsy is not considered feasible or declined. Anaplastic gliomas and glioblastomas of brain stem and spinal cord are rare and no data from clinical studies are available. Resection is limited to exophytic tumors because of the expected neurological deficits with surgery in the brainstem and spinal cord. RT is the standard of care, and TMZ or nitrosoureas or bevacizumab may be employed in the course of disease following the considerations outlined above for supratentorial

tumors of the same WHO grades.[58]

Monitoring and follow-up

Whenever feasible, MRI should be used to monitor the efficacy of pharmacotherapy or as surveillance imaging after completion of treatment.[59] Intervals of 3 months are recommended for most patients with malignant gliomas, although longer intervals may be considered for patients with prolonged disease control, notably young patients with *1p/19q*-co-deleted oligodendroglial tumors.

Supportive care and patient management

Raised intracranial pressure

Raised intracranial pressure due to growth of a glioma is an emergency situation that requires immediate intervention, commonly using high doses of steroids and less commonly osmotic agents. Acute surgical decompression is rarely required. Whether decompressive surgical interventions make sense in the further course of disease once the diagnosis has already been established and primary therapy administered, requires consideration of the options for further treatment after the surgical intervention.

Thromboembolic events

Glioma patients are at increased risk of thromboembolic events throughout the

course of disease for many reasons, including: motor deficits, steroid medication, RT, chemotherapy, immobility, and release of vasoactive molecules from glioma cells. The significance of this comorbidity increases with the use of antiangiogenic agents as therapeutics against gliomas because these agents are also associated with the risk of ischemic and hemorrhagic vascular events. Although anticoagulation using coumadin derivatives is feasible in glioma patients, low molecular weight heparins are often preferred for a favorable safety profile.[60] A single study on primary prophylaxis using such agents was prematurely stopped, but provided no evidence for a decreased incidence of first thromboembolic events.[61] Vena cava filters may be an option for patients who cannot be anticoagulated.

Epilepsy

Glioma patients who never suffered symptomatic seizures should not receive primary prophylaxis with anticonvulsant drugs.[62] A single seizure usually necessitates the institution of drug treatment until the underlying tumor growth is controlled by tumor-specific therapy.[63] If no further seizure occurs after surgery and the tumor appears to be controlled by treatment, tapering of anticonvulsants should be attempted within the first weeks or months after surgery and further tumor-specific therapy. Recurrent seizures after surgery usually indicate life-long need for anticonvulsants. The choice of drug for patients requiring secondary prophylaxis is guided by various considerations.[64,65] The classical drugs include carbamazepine, valproic acid and phenytoin and are of similar efficacy. All anticonvulsants are associated with relevant toxicities in brain tumor patients. Phenytoin and carbamazepine share an unfavorable side effect profile, including drug interactions, and are therefore not suited for long-term therapy of brain tumor patients. Moreover,

carbamazepine is not available i.v. and commonly induces vertigo and nausea upon initial dosing, notably in elderly patients. Long-term administration impairs cognitive function. The enzyme-inducing properties of phenytoin, carbamazepine and barbiturates may decrease the activity of many chemotherapeutic agents whereas enzyme-inhibitory properties of valproic acid may accentuate toxicity from, and possibly activity of, chemotherapy, e.g., valproic acid-treated patients had superior outcome, but also experienced increased hematological toxicity, in the experimental arm of the EORTC NCIC TMZ trial.[66] Agents such as levetiracetam, gabapentin, lamotrigin or topiramate offer advantages compared with the classical agents, mainly because of lack of drug interactions. In particular levetiracetam is often preferred because of good tolerability, rapid dosing, and intravenous availability. Lamotrigine is an attractive alternative if slow dosing is an option. Lacosamide and perampanel are new drugs that reqire investigation in brain tumors. Clonazepam and other benzodiazepines should only be used transiently, e.g., during dosing of lamotrigine. This document does not address the competence to drive with a brain tumor because this is subject to country-specific regulations which are beyond the scope of this guideline.

Steroids

The need to continue steroid treatment in brain tumor patients should be critically reviewed at each visit because of the major burden of side effects with an impact on quality of life and the potential interference with tumor-specific therapies. Drug interactions, increased risk of infection and thrombosis, myopathy, and depression are only a few of the frequently observed side effects. The option to taper steroids rapidly after tumor debulking should not be missed. Patients who have undergone

significant resection often tolerate RT with no steroids, or else a modest dose in the first week. Patients who have undergone biopsy only may require steroids at the start of RT, but moderate doses (4-8mg daily) will suffice, and can often be tailed off during or soon after treatment. Bevacizumab is a powerful steroid-sparing agent, but should not be used solely for this purpose. Other approaches to replace steroids as anti-edema agents in neuro-oncology are being explored.

Psychological and social support

Psychological stress and the social impact of the disease affecting patients and their families and caregivers must not be underestimated. Psychiatric comorbidity should be actively explored and treated accordingly, employing both psychotherapy and pharmacotherapy.[67] Recognition of the social impact of having a brain tumor and adequate counseling in such circumstances are an integral aspect of care for brain tumor patients. The impact of therapy in this patient population with limited life span must also be considered.[68] Diverse support may be beneficial from individuals such as neuro-oncology nurse specialists, social workers, counselors, clinical psychologists, palliative medicine professionals, and patient focus groups.

Rehabilitation

The need for rehabilitative measures should be explored during and after tumor-specific therapy. Type and intensity of these measures depend not only on cognitive and neurological function, but also on age and expected course of disease. In-patient and out-patient rehabilitation are options. Amelioration of neurological and neuropsychological deficits are the main goals of neurological rehabilitation in brain

tumor patients. Coping strategies for living with a malignancy is the main goal for rehabilitation with a psychological focus.

Palliative care

The appropriate timepoint and setting for communicating the foreseeable restrictions and limitations of tumor-specific measures needs to be carefully assessed and not taken too late in the course of the disease. During advanced stages of disease specific anti-neoplastic treatments may no longer be warranted and palliative care concepts acquire major significance. This calls for a stronger involvement of specialized nurses, social workers and a coordination of care at home or in another adequate setting.[69] Important pharmacological measures include the use of antiemetics, analgesics, corticosteroids and anticonvulsants. If swallowing difficulties are expected, patients and caregivers should be instructed on how to administer medication, notably sublingual or rectal anticonvulsants. Fluid replacement may become necessary. In the terminal stage, analgesics and sedatives should be provided in sufficient doses. Support to find the best individual setting of dying should be offered and a strategy for the last phase of the illness discussed together with patients and caregivers at an appropriate stage.

Coordination of care

Clinical decision making for patients with malignant gliomas should ideally be based on interdisciplinary tumor board recommendations from the first diagnostic and therapeutic decisions onwards. Such boards may also be the ideal forum to discuss which parts of the treatment plan can be realized locally, which parts require a

specialized center, which measures require in-patient versus out-patient settings, and what intensity of neurorehabilitative measures is in the patient`s interest. Local and national guidelines may serve for orientation beyond this guideline.

Outlook

Guidelines reflect the state of knowledge at a given timepoint. Table 3 summarizes the key recommendations of the EANO task force in 2013. The EANO website (www.eano.eu) will inform of future updates on this guideline.

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Table 1 - **Management options for newly diagnosed and progressive malignant gliomas**

Tumor	Newly diagnosed	Progression
Anaplastic astrocytoma WHO grade III	Resection or biopsy *and* radiotherapy *or* chemotherapy (or combined modality treatment)	Resection and chemotherapy or radiotherapy or bevacizumab
Anaplastic oligodendroglioma or oligoastrocytoma WHO grade III with *1p/19q* co-deletion	Resection or biopsy and chemotherapy with (or without) radiotherapy	Resection and chemotherapy or radiotherapy or bevacizumab
Anaplastic oligodendroglioma and oligoastrocytoma WHO grade III without *1p/19q* co-deletion	Resection or biopsy and radiotherapy or chemotherapy (or combined modality treatment)	Resection and chemotherapy or radiotherapy or bevacizumab
Glioblastoma WHO grade IV (< 65-70 years)	Resection or biopsy and radiotherapy plus TMZ (TMZ/RT→TMZ)	Re-resection, re-irradiation, chemotherapy

Tumor	Newly diagnosed	Progression
		(rechallenge), bevacizumab
Glioblastoma WHO grade IV (> 65-70 years)	Resection or biopsy and radiotherapy or TMZ (± radiotherapy) based on *MGMT* and performance status	Resection and chemotherapy or radiotherapy

Table 2 - Chemotherapy protocols in malignant gliomas

Protocol	Dose and mode of administration
TMZ	150–200 mg/m^2 D1- D5 p.o. x 4 weeks
ACNU, BCNU, CCNU*	Different regimens,e.g., 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 or 15 mg/m^2 x 3 weeks

*ACNU, 1-[(4-Amino-2-methylpyrimidin-5-yl) methyl]-3-(2-chlorethyl)-3-nitrosourea

Table 3 - Key recommendations*

General	**C**	**L**
Karnofsky performance score (KPS), neurological function, age, and individual risks and benefits need to be considered for clinical decision making in Neuro-Oncology.	I	A
Screening and prevention have no major role in malignant gliomas.	IV	-
Patients with 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	-
An apparent increase of tumor volume on neuroimaging in the first months after local therapeutic interventions including radiotherapy and experimental local treatments may reflect pseudoprogression.	II	B
Clinical decision making without obtaining a definitive histological diagnosis at least by biopsy should occur only in very exceptional situations.	IV	-
Histological diagnoses should follow the current WHO classification of tumors of the central nervous system.	IV	-
Three molecular markers (1p19q co-deletion, *MGMT* promoter methylation, *IDH*-1/2 mutation) are valuable prognostic markers. A role	II	A

for clinical decision making is currently largely limited to *MGMT* promoter methylation in elderly glioblastoma patients and 1p19q co-deletion in patients with anaplastic oligodendroglial tumors.		
The prevention of new permanent neurological deficits has higher priority than extent of resection in the current surgical approach to gliomas.	IV	-
Anaplastic gliomas (WHO grade III)		
Standard of care for anaplastic astrocytoma includes resection as feasible or biopsy followed by involved field radiotherapy.	I	A
Based on the NOA-04 trial, chemotherapy using TMZ or the PCV regimen are as effective as radiotherapy in the treatment of anaplastic gliomas including anaplastic astrocytomas.	II	B
Based on the EORTC 26951 and RTOG 9402 trials, patients with 1p/19q-co-deleted anaplastic oligodendroglial tumors should not be treated with radiotherapy alone, but alkylating agent chemotherapy with (or without) radiotherapy.	II	B
Temozolomide chemotherapy is standard treatment at progression after surgery and radiotherapy.	I	A
Based on the NOA-04 trial, anaplastic oligoastrocytomas of WHO grade III are treated as anaplastic oligodendrogliomas.	II	B

Glioblastoma (WHO grade IV)		
Standard of care for glioblastoma (age < 65-70 years) 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).	I	A
Elderly patients not considered candidates for TMZ/RT→TMZ should be treated with radiotherapy (e.g., 15 x 2.66 Gy) or TMZ (5/28) based on *MGMT* promoter methylation status (NOA-08, Nordic Trial).	I	A
At recurrence, standards of care are less well defined. Nitrosourea regimens, TMZ rechallenge and, with consideration of the country-specific label, bevacizumab are options of pharmacotherapy. When available, recruitment into appropriate clinical trials should be considered.	II	B

*C class of evidence, *level of recommendation[70]

WEBAPPENDIX

This webappendix summarizes EANO`s recommendations for the general approach to patients with malignant gliomas with coverage of diagnostic aspects – early diagnosis and prevention, history, clinical examination, neuroimaging, cerebrospinal fluid analyses, electroencephalography, preoperative management, biopsy and resection, histological classification and grading, molecular diagnostics – as well as general recommendations for therapy - surgical therapy, radiotherapy, pharmacotherapy and other therapeutic approaches.

Diagnostics

Early diagnosis and prevention
The annual incidence of malignant gliomas is approximately 4-5/100,000. Simple serum tests as a screening tool for early diagnosis are not available, instead, neuroimaging, preferably magnetic resonance imaging (MRI), is necessary to detect even early lesions. Anecdotal clinical evidence indicates that glioblastomas may evolve within few months, further supporting that early diagnosis and screening are not feasible at a population level and should therefore be restricted, if recommended at all, to individuals at genetic risk, e.g., patients with neurofibromatosis types I and II or Li Fraumeni syndrome. Whether such patients should undergo repeated neuroimaging in the absence of new neurological symptoms or signs, remains uncertain.

History
History taking will determine the first symptoms and signs attributable to the tumor and their evolution. It may disclose risk factors such as evidence for hereditary cancer predisposition, history of previous irradiation to the nervous system, immune deficiency, alcohol or other drug abuse, or other conditions associated with brain tumors or their differential diagnoses. Depending on neurocognitive function at presentation, history taking from relatives may provide valuable information. Clinical features suggestive of a brain tumor include manifestation of a seizure disorder, focal neurological signs, personality changes and ultimately symptoms and signs of increased intracranial pressure.

Clinical examination
The physical examination is done with specific consideration of the differential diagnosis of a metastatic tumor with a primary site outside the CNS and possible risks for neurosurgical intervention. The neurological examination documents neurological deficits caused by the tumor at presentation and is important as a baseline for monitoring the future course of disease and complications from treatment. A formal neuropsychological assessment in addition to Karnofsky performance score (KPS) and Minimental State Examination (MMSE) is recommended. As a minimum requirement, KPS and MMSE should be documented.

Neuroimaging
Whenever feasible, MRI without and with contrast enhancement is the investigation of choice when an intracranial tumor is suspected. In specific situations, additional diagnostic measures may be requested, e.g., cranial computed tomography (CT) to better delineate calcifications, angiography for surgical planning, or aminoacid positron emission tomography (PET) to select the most active tumor region for biopsy. The aminoacid tracers ^{18}F-fluoroethyltyrosine (FET) and ^{11}C-methionine (MET) provide a better signal-to-noise ratio in the brain than fluorodeoxyglucose (FDG).[1] Neuroimaging, preferentially MRI, is also the most important measure to monitor response to therapy and course of disease, preferably based on standardized criteria which are under continuous development.[2] Ideally patients should be on stable steroid doses for at least 5 days prior to imaging. When tumors are located within, or adjacent to eloquent brain regions and functional tracts, functional MRI (fMRI) and white matter tractography may help to assess the feasibility of surgery and serve as a guide to planning the operation. The role of further imaging techniques including perfusion MRI, single photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) in routine clinical care still needs to be defined. MRS measures the concentration and spatial distribution of metabolites like choline or N-acetylaspartate. A choline/ N-acetylaspartate ratio $\geq$2 indicates increased cellular proliferation and reduced neuron density and highlights metabolically active part of the tumor in high-grade gliomas.[3] This metabolic ratio has been shown to predict survival[4] and relapse location in glioblastoma.[5]
Pseudoprogression, an apparent increase of the tumor volume on contrast-enhanced neuroimaging, in the absence of new lesions and often without clinical deterioration, may represent a major diagnostic challenge notably within the first months after the completion of radiotherapy or after experimental local surgical interventions.[6] In cases of possible pseudoprogression, current treatment (if any) should not be stopped and earlier follow-up imaging at 4-8 week interval should be considered, taking into consideration the clinical condition. Failure to recognize pseudoprogression carries the risk of stopping a potentially effective treatment regimen, and instituting a salvage treatment that is not needed and the efficacy of which will be overestimated, given the spontaneous resolution of pseudoprogression. Conversely, the introduction of antiangiogenic agents

has also led to the recognition of pseudoresponses if response assessment is solely based on contrast-enhanced scans, a phenomenon also addressed by the Response Assessment in Neuro-Oncology (RANO) group.[2] A pseudoresponse typically is characterized by decreased contrast enhancement, but stable or increased T2 or FLAIR abnormality frequently associated with restriction of diffusion on diffusion-weighted imaging (DWI).

Cerebrospinal fluid (CSF) analyses
CSF analyses are of limited overall value in the differential diagnosis of brain tumours in adults, and lumbar puncture is contra-indicated in patients with raised intracranial pressure, notably with posterior fossa lesions. Glioma cells are rarely detected in the CSF, even when using sensitive techniques in patients with MRI-documented leptomeningeal seeding, but occasionally CSF analysis may help to distinguish gliomas from other brain tumors, e.g., primary cerebral lymphomas, germ cell tumors or metastatic brain tumors, or inflammatory conditions.

Electroencephalography (EEG)
EEG may serve as an indicator of seizure risk and may be useful in monitoring pharmacotherapy in patients with tumor-associated symptomatic epilepsy or for the differential diagnosis of rapid decline or changes in neurocognitive function or vigilance.

Preoperative management
Prior to brain tumor surgery, unless there are contraindications or the suspicion of primary cerebral lymphoma or inflammatory lesions such as vasculitis or sarcoidosis, corticosteroids are commonly administered to decrease tumor-associated edema. The pre-operative use of steroids should be guided by the patients' symptoms. Many patients will require a very low dose of steroids, if any, prior to surgery. Additional pharmacological measures such as osmotic agents, e.g., mannitol, are rarely necessary unless the patient presents with an acute deterioration due to increased intracranial pressure or mass effect. Dexamethasone is the most widely used steroid, has a long half-live and can be given as an intravenous bolus of up to 40 mg in patients with severely elevated intracranial pressure and then orally at up to 16 mg daily pre and during surgery. A single administration in the morning suffices, given the long half-life, and steroids should be tapered after surgery as feasible. The shorter the patients have received steroids and the lower the doses were, the quicker can they be withdrawn.
Glioma patients who have suffered epileptic seizures at presentation should receive anticonvulsant drugs preoperatively. Agents available as intravenous preparations such as levetiracetam, valproic acid, phenytoin or benzodiazepines are often preferred in the acute phase. There is no evidence for a higher rate of perisurgical bleeding complications with valproic acid prophylaxis,[7] but valproic acid is nevertheless avoided for that fear by many neurosurgeons. Phenytoin is no longer recommended because of its side effect profile and drug interactions. Given the trend towards earlier postoperative extubation, the advantage of intravenous availability is currently loosing significance, and other, solely oral agents may also be considered as agents of first choice.[8]

Biopsy/resection
The establishment of a specific neuro-oncological management concept requires a microscopic morphological diagnosis of the tumor tissue complemented by an increasing panel of molecular genetic markers. Surgical interventions in glioma patients are thus commonly both diagnostic and therapeutic measures. Because of the relevant, although rare differential diagnoses and the psychological burden of a mere imaging-guided tumor diagnosis, watch-and-scan strategies or palliative care only strategies without histological verification of the diagnoses should be exceptional. They are justified only if the risk of the biopsy procedure is thought to outweigh the gain of information gathered by the intervention or if the prognosis of the patient is too poor, i.e., elderly patients with extensive disease burden and deteriorating performance status. A stereotactic biopsy with local anesthesia can be safely performed even in frail patients to obtain a definitive diagnosis which is commonly helpful in guiding patients and relatives in situations where no further tumor-specific therapy will be instituted. To be fully informative, serial samples along the trajectory should be acquired during stereotactic biopsy, necessitating an experienced team of surgeons and neuropathologists. This is because tumors may be heterogeneous histologically, with astrocytic and oligodendrocytic features in different regions and different grades of malignancy in distinct areas. Definitive diagnoses should be obtained accordingly in more than 90% of the patients, with morbidity of 3-4% and mortality below 1%. Molecular analyses are possible even in these small specimens. Since markers like isocitrate dehydrogenase (*IDH*)-1/2 mutation, loss of heterozygosity (LOH) *1p/19q* and methylation of the *MGMT* promoter are homogeneously distributed within the solid tumor tissue, the risk of a sampling error is low as long as vital tumor tissue samples are available for molecular analysis.[9,10] Undergrading because of sampling error should be considered if neuroimaging suggests a higher grade of malignancy than the histological findings.
Type and extent of neurological deficits and the likelihood of their improvement are important considerations when planning a surgical procedure for glioma patients. Although extent of resection is considered a prognostic factor for all malignant gliomas, this has been most convincingly demonstrated for complete resections of contrast-enhancing tumor verified by early postoperative imaging.[11,12] The risk of complications from surgery is

likely to vary with the caseload of the institution and the individual experience of the surgeon. There is consensus that new neurological deficits should be avoided and are not justified to achieve a greater extent of resection. The general condition including age, comorbidity and co-medication contributes to the overall surgical risk.

Histological classification and grading

During a surgical procedure it needs to be ascertained that adequate tissue has been obtained. This can be accomplished either by intraoperative cytological assessment when a neuropathologist is present in the operating theatre or by rapid section assessment before the surgical procedure is terminated. The tissue is assessed macroscopically to identify and label central tumor parts and infiltration zones. Part of the sample is formalin-fixed and embedded in paraffin for conventional histological stainings, including a routine hematoxylin-eosin staining as well as additional histochemical and immunohistochemical analyses. Ideally, part of the tissue is also cryopreserved either for immediate or delayed molecular marker studies.

The diagnostic process follows the WHO classification and consists in histological tumor typing as well as tumor grading using the four-tiered WHO grading scheme from WHO grade I to WHO grade IV which was designed to provide clinicians with information on the tumor's biological behavior and consequently the patient's prognosis and outcome. Cellular and nuclear atypia, high cellularity, increased mitotic activity, pathological mitoses, microvascular proliferation and necrotic areas serve as important features to assign a higher grade of malignancy in gliomas.[13] Special neurohistological stains as well as immunohistochemical studies supplement the diagnostic process. These include connective tissue stains, e.g., Elastica-van-Gieson and trichrome staining of Masson, for the differentiation of mesodermal and glial tumors, as well as silver stain for the same purpose and for the differentiation of cerebral lymphomas. Common immunohistochemical markers for gliomas include glial fibrillary acidic protein (GFAP) and protein S100. In contrast, gliomas are negative for epithelial markers (cytokeratins) and lymphocytic markers (CD20, CD45) which differentiates metastatic carcinomas and lymphomas. Further, melanomas, meningiomas, sarcomatous tumors and germ cell tumors can be distinguished from gliomas based on specific marker profiles. In contrast, among the gliomas, there are no specific immunohistochemical markers to differentiate between astrocytic, oligodendroglial and oligoastrocytic tumors. GFAP expression is usually more prominent in astrocytic gliomas than in oligodendrogliomas. Immunohistochemical detection of mutant IDH-1^{R132H} protein aids in the identification of diffuse astrocytic and oligodendroglial gliomas and their separation from other tumors and from reactive gliosis. Quantification of the proliferation-associated nuclear antigen Ki-67 using the MIB1 antibody is commonly used to characterize proliferative activity as a surrogate marker of growth and may aid tumor grading.

Molecular diagnostics

The molecular profiling of gliomas is currently based mainly on three markers which are highly relevant for diagnostic purposes and clinical decision making: *1p/19q* co-deletion, O^6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation and *IDH*-1/2 mutation.[14] Deletion of the entire chromosomal arms *1p* and *19q* (*1p/19q* co-deletion) detected by fluorescence *in situ* hybridisation (FISH) or microsatellite-based PCR for LOH or multiplex ligation-dependent probe amplification (MLPA) is a typical molecular lesion of oligodendroglial tumors. It is associated with improved prognosis, a less aggressive course of disease and favorable responses to radiotherapy and alkylating agent chemotherapy, or both.[15-19] The demonstration of promoter methylation of the *MGMT* gene assessed by methylation-specific PCR or pyrosequencing of bisulfite-modified DNA is associated with superior outcome in anaplastic glioma patients treated with radiotherapy or alkylating agent chemotherapy[19,20] and with specific benefit from temozolomide (TMZ) in glioblastoma patients.[21-24] Retesting the *MGMT* status at recurrence is not necessary since the methylation status remains stable, at least in glioblastoma,[25,26] moreover, a prognostic or predictive value of the *MGMT* status at recurrence is less well defined.

Mutations of the *IDH*-1 or -2 genes are found in up to 80% of patients with diffuse gliomas of WHO grades II and III as well as in secondary glioblastomas (WHO grade IV), defined as glioblastomas derived from progression of a lower grade glioma. In contrast, *IDH*-1/2 mutations are only detected in 5-10% of tumors from patients with primary glioblastoma and never in pilocytic astrocytomas or ependymomas. Thus the assessment of the *IDH*-1/2 mutation status provides primarily diagnostic information. Within each tumor category, *IDH*-1/2-mutant tumors have a better prognosis. The *IDH*-1/2 status can be assessed by PCR and (pyro)sequencing; moreover, the most common mutant variant, IDH-1^{R132H}, can be detected by immunohistochemistry. While a firm role for the *IDH*-1/2 status in clinical decision making remains to be established, it may in the future provide a biological basis for molecularly based separation of diffuse grade II/III gliomas and primary glioblastomas.

IDH-1/2 mutations are associated with the *glioma CpG island methylator phenotype* (G-CIMP), a molecular phenotype associated with a favourable outcome, too. We expect that high-throughput analyses may sequentially supplement and gradually replace single marker assessment.

Therapy - General recommendations

Surgical therapy

While stereotactic surgical interventional strategies commonly serve diagnostic purposes, open neurosurgical operations are performed with therapeutic intention, depending on patient age, suspected diagnosis and tumor localization. Stereotactic biopsies are preferred for difficult tumor locations, multiple lesions, and frail patients in poor general condition where the risk of surgery-associated morbidity is high. The primary therapeutic goals of surgery for high-grade supratentorial gliomas are to remove the solid tumor mass as feasible, to relieve intracranial pressure and to restore or maintain neurological function. Microsurgical techniques are now standard of care. Neuronavigation, ultrasound, MRI and fluorescent agents have been employed to localize tumor tissue intraoperatively. The role of fluorescence-guided resection using 5-aminolevulinic acid (ALA) in achieving a higher rate of gross total resections translating into improved progression-free survival at 6 months was demonstrated in a prospective randomized clinical trial,[11] resulting in approval of 5-ALA in the European Union. Efforts at resections in eloquent areas should be supported by monitoring brain function using, e.g., motor evoked potentials, somatosensory evoked potentials, electromyography or mapping and monitoring in awake patients using local anesthesia to assess and preserve language and cognitive functions. The avoidance of new neurological deficits should take higher priority than the extent of resection because malignant gliomas cannot be cured by surgery, and quality of life is emerging as a significant prognostic factor and is of major importance for patients. The overall therapeutic impact of surgical treatment of gliomas is limited by tumor cell infiltration beyond the macroscopically visible lesion, a biological hallmark of these tumors. This limits the extent and efficacy of all current surgical approaches. To determine and to document the outcome of surgical resections for gliomas and to recognize early postoperative complications, it is recommended to obtain an early postoperative MRI without and with contrast enhancement within 48-72 hours of surgery.[27] If MRI is not available or in case of contraindications, a CT without and with contrast agent should be performed.

Radiotherapy

Despite the diffusely infiltrating nature, most gliomas grow macroscopically as a unifocal lesion and recur at the same site. Local control of tumor growth is therefore highly relevant. Radiotherapy has been demonstrated to prolong life while maintaining quality of life, specifically in patients with low residual tumor burden. Indication for, and dosing and scheduling of radiotherapy, depend on the histological grading according to the WHO classification and prognostic factors such as age, Karnofsky performance score (KPS) and extent of resection. Radiotherapy for malignant gliomas is commonly given to a total dose of 60 Gy in 1.8-2 Gy fractions, critical brain areas may be protected by limiting the dose there to 54 Gy. Modern techniques of focused radiotherapy, e.g. stereotactic radiotherapy, radiosurgery, intensity-modulated radiotherapy (IMRT) or image-guided radiotherapy improve the accuracy and localization of radiotherapy delivery. They may allow higher doses to be delivered safely, or standard doses to be prescribed with reduced irradiation of healthy areas of brain in comparison with conventional radiotherapy. However, randomized trials to confirm the superiority of these novel techniques over standard treatment have not been performed. The same is true for differential types of radiation. Previous trials on dose intensification beyond 60 Gy or the combination with stereotactic radiosurgery or brachytherapy were negative in glioblastoma.

Whole brain radiotherapy of circumscribed gliomas increases morbidity, but does not improve control over local conformal radiotherapy of the involved tumor region and is therefore contraindicated. Targeted radiotherapy focused on the tumor region reduces morbidity, and may permit higher (and repeated) irradiation doses.

When planning treatment, the area of residual enhancement on T1 imaging plus the surgical bed is first delineated as the gross tumor volume (GTV). A margin, typically 1.5 to 2.5 cm including the hyperintensity on T_2 / FLAIR imaging is added to define the clinical target volume (CTV), which is then modified in areas where microscopic spread is unlikely, e.g. across the intact falx or into bone, or to reduce the dose to a critical structure, e.g. optic chiasm or brainstem. Finally a further margin, usually 0.5 cm, is added to allow for any movement during treatment, which generates the planning target volume (PTV).

After microsurgical resection of a malignant glioma, the normal surrounding tissue may exhibit contrast enhancement caused by the surgical procedures which cannot be distinguished from residual or recurrent tumor on CT or MRI. The identification of tumor tissue for radiation planning is challenging in such situations. Early postoperative DWI MRI may identify ischemic lesions around the surgical cavity. Novel approaches try to base the determination of the target volume on PET using amino acid tracers such as ^{11}C-MET or ^{18}F-FET[28,29] or MRI spectroscopy using choline/N-acetylaspartate metabolite cartography.[5,30]

Several studies have shown that PET plus MRI will identify a different target volume compared to MRI alone. Whether radiation planning based on PET plus MRI compared with MRI alone results in superior outcome for the patients remains to be demonstrated in a randomized fashion.

Exact and reproducible positioning of the patients during planning and conduct of radiotherapy using an immobilisation device, mask or frame, is essential. Planning requires the acquisition of a dedicated MRI or CT in irradiation position, the image-guided adaptation of isodose distribution to the target volume and transfer via a therapy simulator. A three-dimensional dose adaptation is highly recommended. The dose specification follows

the *International Commission on Radiological Units* (ICRU) 50/62 with reference to the isodose surrounding the target volume and maximum dose. Minimal documentation requirements consist of dose distribution in the three planes, digital or simulation imaging, and portal imaging to confirm the reproducibility of the therapy fields of irradiation.
The irradiation tolerance of normal brain depends, amongst others, on the fractionation. The TD 5/5 (Tolerance dose 5/5, adverse effect risk of 5% within 5 years) with conventional fractionation in single doses of 1.8–2 Gy is estimated to be 60 Gy administered over 6 weeks. The tolerated dose of radiosensitive structures such as optic nerve, chiasm, eye, brain stem or inner ears needs to be considered, and doses to these structures should be calculated and documented. Shorter courses of radiotherapy with higher fraction sizes are appropriate in older patients and those with poor prognostic factors, but necessitate reduction of the total dose, e.g., to 15 x 2.66 Gy, which is biologically equivalent.

Pharmacotherapy
Classical cytotoxic chemotherapy is an established treatment modality for patients with malignant gliomas. Normal blood cell counts, adequate liver and renal function and the absence of severe pulmonary or cardiac disease or active infection are required prior to therapy. Regular monitoring of blood counts is required during chemotherapy. The most commonly used agent, TMZ, is usually well tolerated.[31-33] TMZ does not have cumulative myelotoxicity, but seldom causes early grade 4 myelotoxicity necessitating dose reduction or even definitive discontinuation. Since TMZ may rarely induce severe liver damage, regular monitoring of liver enzymes is recommended. In cases of suspected TMZ-induced alveolitis, chemotherapy should be stopped, and should not be resumed if the diagnosis has been confirmed. Nitrosoureas such as lomustine (CCNU) can induce prolonged leukopenia and thrombopenia, requiring dose reductions for the subsequent cycles, or a change of regimen. The risk of pulmonary fibrosis may be higher with carmustine (BCNU). Nitrosoureas are now agents of second choice relative to TMZ for glioma treatment in most countries in Europe. Several experimental pharmacological agents are currently being explored for efficacy in malignant gliomas, in particular in the field of angiogenesis inhibition. At present only bevacizumab, an antibody to vascular endothelial growth factor (VEGF), is approved for the treatment of patients with recurrent glioblastoma in the USA, Canada, Switzerland and various other countries, although not in the European Union. To monitor chemotherapy it is advisable to provide the patients with an adequate document sometimes referred to as a chemotherapy pass where the results of laboratory controls and unusual observations of the patients or other comments can be documented. Institutions involved in the care of malignant glioma patients should have written guidelines and standard operating procedures how to deal with the most severe complications listed above.
The standard duration of TMZ chemotherapy is 6 cycles for newly diagnosed glioblastoma in combination with radiotherapy. In case of efficacy defined as complete or partial response or stable disease, alkylating agent chemotherapy administered as a single treatment either for newly diagnosed or recurrent disease is commonly stopped after 8-12 cycles of TMZ or 4-6 cycles of nitrosourea-based chemotherapy, however, the optimal treatment duration has never been formally evaluated in patients with recurrent gliomas. Bevacizumab for recurrent gliomas is commonly given until progression.

Other therapeutic approaches
New approaches of glioma therapy including suicide gene therapy, various approaches of immunotherapy, or device-based therapies such as tumor-treating fields (TTF)[34] or electromagnetic nanotherapy should only be administered in the context of clinical trials. The approval of the latter in the EU concerns their status as devices and is based on safety, but not efficacy.

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Supplementary Figure: Clinical Pathway – Malignant Glioma

<table>
<tr>
<td rowspan="4">❍ Anaplastic astrocytoma WHO grade III
❍ Anaplastic oligodendroglioma/oligoastrocytoma WHO grade III

❍ Prognostic factors:
o Age
o KPS
o Contrast enhancement
o Histological diagnosis</td>
<td rowspan="2">❍ Astrocytoma</td>
<td>❍ Favorable prognostic factors:
o Age < 55-60
o KPS ≥ 70</td>
<td>▶ Surgery
▶ Radiotherapy (54-60 Gy) or chemotherapy (or combination)</td>
<td rowspan="4">▶ Early (< 72 h) post-operative MRI or CT = baseline for monitoring and detection of progression</td>
<td rowspan="4">▶ Follow-up in 3-4-monthly intervals: neurological examination and imaging</td>
<td rowspan="8">❍ Progression or recurrence</td>
<td rowspan="8">Options
▶ Second surgery
▶ Chemotherapy
▶ Re-irradiation
▶ Experimental therapy</td>
<td rowspan="8">▶ Palliative care</td>
</tr>
<tr>
<td>❍ Unfavorable prognostic factors:
o Age > 60
o Karnofsky-Index < 70</td>
<td>▶ Surgery
▶ Radiotherapy or chemotherapy</td>
</tr>
<tr>
<td rowspan="2">❍ Oligodendroglioma or oligoastrocytoma</td>
<td>❍ without 1p/19q codeletion</td>
<td>▶ Surgery
▶ Radiotherapy or chemotherapy</td>
</tr>
<tr>
<td>❍ with 1p/19q codeletion</td>
<td>▶ Surgery
▶ Chemotherapy plus radiotherapy (or chemotherapy)</td>
</tr>
<tr>
<td colspan="2" rowspan="5">❍ Glioblastoma WHO grade IV</td>
<td>❍ Favorable prognostic factors:
o Age < 65-70
o KPS ≥ 70</td>
<td>▶ Surgery
▶ Radiotherapy (54-60 Gy) plus chemotherapy (temozolomide)</td>
<td rowspan="4">▶ Early (< 72 h) post-operative MRI or CT = baseline for monitoring and detection of progression</td>
<td rowspan="4">▶ Follow-up in 3-monthly intervals: neurological examination and imaging</td>
</tr>
<tr>
<td>❍ Unfavorable prognostic factors:
o KPS < 70</td>
<td>▶ Surgery
▶ Radiotherapy (hypofractionated)</td>
</tr>
<tr>
<td>❍ Age > 65-70
MGMT promoter non-methylated</td>
<td>▶ Surgery
▶ Radiotherapy (hypofractionated)</td>
</tr>
<tr>
<td>❍ Age > 65-70
MGMT promoter methylated</td>
<td>▶ Surgery
▶ Chemotherapy (±Radiotherapy)</td>
</tr>
<tr>
<td colspan="6">❍ Very unfavorable prognostic factors:
o KPS < 50
or
❍ Inability to consent</td>
</tr>
</table>