



EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma

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This guideline provides recommendations for diagnostic and therapeutic procedures for patients with malignant gliomas. We differentiate evidence-based standards from reasonable options or non-evidence-based measures that should no longer be considered. The recommendations herein should 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 contributes to a critical appreciation of concurrent drugs with a focus on the controlled use of anticonvulsants and steroids. It should 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 summarised here will need interdisciplinary structures of care for patients with brain tumours and structured processes of diagnostic and therapeutic procedures.

Introduction

This guideline for the diagnosis and treatment of gliomas follows the Third Revision of the *WHO Classification of Tumours of the Central Nervous System*.¹ It covers WHO grade III anaplastic astrocytomas, oligodendrogliomas, and oligoastrocytomas; WHO grade IV glioblastomas (including its variants) and 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 for 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.

The guideline aims to serve medical professionals of all disciplines involved in the diagnosis and care of patients with glioma, particularly neurologists, neurosurgeons, radiation oncologists, neuropathologists, neuroradiologists, oncologists, paediatric oncologists, epileptologists, psycho-oncologists, rehabilitation specialists, palliative care nursing specialists, and neuro-oncology nursing specialists. Furthermore, the recommendations could serve as a valuable source of information for patients, relatives, other health professionals, and health insurance companies.

General recommendations

Recommendations for the general approach to patients with malignant gliomas, including diagnostic aspects—ie, early diagnosis and prevention, history, clinical examination, neuroimaging, cerebrospinal-fluid analyses, electroencephalography, preoperative management, biopsy and resection, histological classification and grading, molecular diagnostics—and general recommendations for therapy (eg, surgical therapy, radiotherapy, pharmacotherapy, and other therapeutic approaches) are summarised in the appendix.

Specific recommendations

Anaplastic astrocytoma—WHO grade III

Anaplastic astrocytomas have inhomogeneous density on CT scans and appear as hyperintense, space-occupying lesions on T₂-weighted fluid-attenuated inversion recovery (FLAIR) MRI. They tend to show patchy enhancement after contrast administration and often have peritumoural oedema. However, a substantial proportion (up to 30%) of these tumours can show no enhancement on CT or MRI. Abnormal vessels can be visualised by MRI angiography. Favourable prognostic factors include young age, high Karnofsky performance score, *IDH1/2* mutation, and *MGMT* promoter methylation.² Furthermore, loss of *ATRX* expression may define a subgroup of anaplastic astrocytic tumours with a more favourable prognosis.³

The traditional standard of care for anaplastic astrocytoma includes maximum resection as feasible or biopsy, followed by involved-field radiotherapy to 60 Gy given in 1.8–2 Gy fractions (table 1).⁴ Findings from randomised trials^{5,6} using radiotherapy after resection or biopsy showed a doubling of median survival time compared with surgery alone. Findings from a meta-analysis⁷ suggested efficacy for adjuvant chemotherapy using nitrosourea compounds as a part of first-line treatment; the proportion of patients who survived for 1 year increased from 58% to 63%, and for 2 years increased from 31% to 37%. However, meta-analyses are potentially biased because trials with negative findings are less likely to be published than trials with positive findings. The addition of PCV (procarbazine, lomustine, and vincristine) chemotherapy to radiotherapy had no survival benefit for the subgroup of patients with anaplastic glioma in a large Medical Research Council (MRC) trial.⁸ Conversely, findings from the German Neuro-Oncology Group (NOA)-04 trial⁹ showed that alkylating chemotherapy alone (eg, PCV or temozolomide) was as effective as was radiotherapy alone in terms of progression-free survival, with similar overall

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	Newly diagnosed	Progression
Anaplastic astrocytoma, WHO grade III	Resection or biopsy followed by radiotherapy or chemotherapy (or combined modality treatment)	Resection and chemotherapy, radiotherapy, or bevacizumab
Anaplastic oligodendroglioma or oligoastrocytoma, WHO grade III, with 1p/19q co-deletion	Resection or biopsy, followed by chemotherapy, with or without radiotherapy	Resection and chemotherapy, radiotherapy, or bevacizumab
Anaplastic oligodendroglioma and oligoastrocytoma, WHO grade III, without 1p/19q co-deletion	Resection or biopsy, followed by radiotherapy or chemotherapy (or combined modality treatment)	Resection and chemotherapy, radiotherapy, or bevacizumab
Glioblastoma, WHO grade IV, (age <65–70 years)	Resection or biopsy, followed by radiotherapy plus concurrent temozolomide, followed by adjuvant temozolomide	Re-resection, reirradiation, rechallenge chemotherapy, or bevacizumab
Glioblastoma, WHO grade IV (age >65–70 years)	Resection or biopsy, followed by radiotherapy, or temozolomide with or without radiotherapy based on MGMT and performance status	Resection and chemotherapy or radiotherapy

Table 1: Management options for newly diagnosed and progressive malignant gliomas

	Dose and mode of administration
Temozolomide	150–200 mg/m ² , days 1–5, orally, for 4 weeks
Nimustine, carmustine, and lomustine	Different regimens (eg, lomustine 110 mg/m ² , orally, every 6 weeks)
PCV	Procarbazine 60 mg/m ² , orally, days 8–21; lomustine 110 mg/m ² , orally, day 1; vincristine 1.4 mg/m ² , intravenously to a maximum of 2 mg, days 8 and 29, for 6–8 weeks
Bevacizumab	10 mg/kg for 2 weeks, or 15 mg/kg for 3 weeks

PCV=procarbazine, lomustine, and vincristine.

Table 2: Chemotherapy protocols in malignant gliomas

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See Online for appendix

survival in both groups, but at the time of publication, there was insufficient follow-up to draw meaningful conclusions for the overall survival data, particularly for the patients with good prognosis.

A retrospective analysis¹⁰ of the NOA-04, NOA-08, and German Glioma Network studies suggested that *IDH1/2* mutation status could serve as a predictive biomarker of benefit from the addition of temozolomide to radiotherapy; patients with *IDH1/2* wildtype tumours with a methylated *MGMT* promoter might benefit from the inclusion of alkylating chemotherapy in first-line treatment.

The present standard of care outside clinical trials, based on NOA-04,⁹ remains radiotherapy or alkylating chemotherapy alone for patients with anaplastic astrocytoma (which typically lacks 1p/19q co-deletion). Temozolomide is often preferred to PCV because of its favourable safety and tolerability profile. The CATNON trial (European Organisation for Research and Treatment of Cancer [EORTC] 26053, NCT00626990) is examining the addition of temozolomide to first-line radiotherapy, as concomitant or adjuvant temozolomide, or both, for patients with tumours without the 1p/19q co-deletion, most of which are anaplastic astrocytomas. Long-term results from NOA-04 and data from CATNON should

direct whether the standard of care for these patients should be modified.

At progression, the option of second surgery should be explored. Initial therapy generally establishes the therapeutic options at recurrence. Alkylating chemotherapy is the treatment of choice for most patients previously untreated with chemotherapy who progress after radiotherapy. Temozolomide and nitrosoureas are probably equally effective. A median progression-free survival of 23 weeks and 46% of patients remaining progression-free at 6 months in a phase 2 trial led to the approval of temozolomide in this indication;¹¹ 14 of 111 patients in the study had anaplastic oligoastrocytoma. A similar study of temozolomide and a variant of the standard PCV regimen used widely in Europe (table 2) showed similar efficacy.¹² Bevacizumab is often used after failure of radiotherapy and alkylating chemotherapy, dependent on local availability, with 20–60% of patients remaining progression free at 6 months.^{13–15} However, controlled trials have not been done, and no evidence supports the combination of bevacizumab with cytotoxic drugs for these patients.

For recurrent patients who have already had radiation, hypofractionated radiotherapy (eg, with 25–30 Gy in five fractions of 5 or 6 Gy, or with 35 Gy in ten 3.5 Gy fractions) is feasible if recurrences are circumscribed and chemotherapy is contraindicated. Further irradiation should be given as fractionated stereotactic radiotherapy, conformal radiotherapy with tight margins, or image guided radiotherapy. However, the size and patterns of recurrent tumours often preclude reirradiation, and the overall efficacy is disputed.

Anaplastic oligodendroglioma and oligoastrocytoma—WHO grade III

The definition of anaplastic oligoastrocytoma remains a matter of debate and has been challenged because of poor inter-observer agreement and incomplete molecular definition. Extent of resection is a prognostic factor in these tumours, too.^{9,16} In the NOA-04 trial,⁹ in which histological diagnoses were verified by central neuropathology review at study entry, anaplastic oligodendroglioma and mixed anaplastic oligoastrocytoma had similar clinical courses, which were more favourable than that of anaplastic astrocytoma. In the next revision of the WHO classification, molecular markers should be integrated to refine the present morphology based classification for anaplastic gliomas.^{2,3} Among anaplastic gliomas, there is high correlation between oligodendroglial morphology and 1p/19q co-deletion. Tumours with 1p/19q co-deletion almost always have *IDH1/2* mutations, and often have *MGMT* promoter methylation and *TERT* promoter mutations.¹⁷ By contrast, *TP53* mutation and loss of *ATRX* expression are rare in 1p/19q-co-deleted gliomas, but common in diffuse and anaplastic astrocytomas. This finding could help to better dissect the controversial entity of anaplastic oligoastrocytoma.³

Although radiotherapy (54–60 Gy, 1.8–2 Gy fractions) has been considered standard of care for anaplastic oligodendroglial tumours, their sensitivity to nitrosoureas and temozolomide has long been recognised, and ongoing controversies do not focus on whether to give radiotherapy or alkylating chemotherapy at all, but rather when and in what sequence. Long-term results of the two early, large, independent randomised clinical trials—Radiation Therapy Oncology Group (RTOG) 9402^{18,19} and EORTC 26951^{20,21}—that explored the value of PCV polychemotherapy, either before or immediately after radiotherapy, suggest that the inclusion of chemotherapy in first-line treatment confers a survival advantage which becomes evident only after follow-up of more than 6 years and only in the subgroup of patients with 1p/19q-co-deleted tumours. Thus, 1p/19q co-deletions have also predictive value for benefit from chemotherapy, in addition to the characterisation of a prognostically more favourable subgroup of patients with anaplastic oligodendroglial tumours. 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 tumours. Important questions remain, however; for example, how many of the long-term survivors treated with radiotherapy plus PCV experienced preserved cognitive function and quality of life? Could the same improvement in overall survival have been achieved with the combination of radiotherapy and temozolomide or even with alkylating chemotherapy alone? Long-term results from the NOA-04 trial,⁹ which compared radiotherapy versus temozolomide versus PCV alone, might shed light on some of these questions. At present, phase 3 clinical trials in patients with 1p/19q-co-deleted oligodendroglial tumours should include radiotherapy plus PCV as a standard group. In clinical practice, many sites have reverted to classic radiotherapy plus PCV as a standard of care, whereas other clinicians prefer temozolomide concurrent with radiotherapy, followed by adjuvant temozolomide or even temozolomide alone, particularly in young patients (table 2, appendix). Accordingly, the amended three-group CODEL trial (NCT00887146) will compare radiotherapy followed by PCV with temozolomide concurrent with radiotherapy followed by adjuvant temozolomide with temozolomide alone.

Treatment following progression is affected by type of and response to first-line treatment as outlined for anaplastic astrocytoma. If neither radiotherapy nor alkylating chemotherapy are options because they failed or because of intolerance, bevacizumab can be considered as a salvage strategy, depending on local availability.^{13,15,22,23} Proper controlled studies are lacking here, however, and there is also no evidence to combine bevacizumab with cytotoxic drugs for these patients.

Glioblastoma—WHO grade IV

Glioblastomas appear as space-occupying lesions on MRI or CT with irregular boundaries and often enhance after administration of contrast agents. Central necrosis

and perilesional oedema 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.^{24–26}

Surgery is a key element within the management, either as diagnostic biopsy or as a microsurgical resection. However, class I evidence for the value of microsurgical resection is still lacking. In a small randomised trial²⁷ in Finland, patients with glioblastoma or anaplastic astrocytoma older than 65 years had a median survival of 171 days after resection compared with 85 days after biopsy ($p=0.035$).²⁷ This study has been criticised because of small patient numbers (30 enrolled, 13 patients biopsied vs 10 patients resected) and major imbalances in Karnofsky performance scores between groups. Although some recent clinical series have reported gradually extended survival associated with extent of resection, investigators of other studies proposed that only a gross total resection is associated with better outcome.²⁸ 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 visualise glioblastoma tissue during microsurgical tumour resection. Its use was associated with an increased rate of gross total resections and an increased progression-free survival rate at 6 months.²⁹ Whether its use prolongs survival remains unknown;³⁰ moreover, the pivotal study was performed before temozolomide concurrent with radiotherapy followed by adjuvant temozolomide became standard of care.

Radiotherapy has been standard of care for glioblastoma for decades, with an undisputed major survival benefit.⁴ The radiotherapy volume often includes the T₁-enhanced region plus a 2–3 cm safety margin on the T₂ or FLAIR abnormality.⁴ The standard dose is 54–60 Gy given in 1.8–2 Gy fractions. A regimen of 50 Gy in 1.8 Gy fractions was better than best supportive care in patients aged 70 years or older.³¹ Patients with adverse prognostic factors defined by age or performance status or both are now often treated with hypofractionated radiotherapy (eg, 40 Gy in 15 fractions).³² In elderly patients, this regimen is now preferred for patients with tumours lacking *MGMT* promoter methylation.^{26,33} Neither accelerated hyperfractionated nor hypofractionated regimens nor brachytherapy nor radiosurgery or a stereotactic radiotherapy boost have been shown to be superior to standard fractionation in terms of survival.⁴

A meta-analysis found the combination of nitrosourea-based chemotherapy with radiotherapy in newly diagnosed glioblastoma increased the proportion of

patients achieving 1-year survival from 31% to 37% and 2-year survival from 9% to 13%.⁷ No differences between single nitrosourea compounds or between monotherapy and nitrosourea-based combination therapies were identified. The MRC trial comparing radiotherapy alone with radiotherapy plus PCV showed no increase of survival with the addition of chemotherapy.⁸ Local 1,3-bis(2-chlorethyl)-1-nitrosourea (BCNU) wafer chemotherapy added to radiotherapy conferred survival of 13·9 months compared with 11·6 months for radiotherapy alone for the intention-to-treat population, but the difference was no longer significant when patients with anaplastic gliomas were removed from the cohorts.^{34–36} Its efficacy and safety in combination with temozolomide concurrent with radiotherapy followed by adjuvant temozolomide have not been adequately explored.

Concomitant and adjuvant temozolomide chemotherapy plus radiotherapy is now the standard of care for adult patients with newly diagnosed glioblastoma aged up to 70 years and in good general and neurological condition.^{37,38} The benefit from temozolomide is most prominent in patients with glioblastoma with *MGMT* promoter methylation.^{39,40} Temozolomide is given at 75 mg/m² during radiotherapy and for six maintenance cycles on 5 out of 28 days at 150–200 mg/m² thereafter. There is no benefit from increasing the dose of temozolomide in the setting of newly diagnosed disease⁴¹ and extending the duration of chemotherapy beyond six cycles is also not supported by clinical trial data. For individual patients, increasing the number of adjuvant temozolomide cycles may be considered—eg, for patients with stable or incompletely regressing, residual, contrast-enhancing tumours at completion of six cycles of temozolomide.

Findings from two randomised trials in adults with glioblastoma have shown 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 temozolomide and radiotherapy followed by temozolomide.^{42,43} Interpretation of the data from these trials remains controversial.⁴⁴

For the increasing population of elderly patients with glioblastoma, new standards of care were defined in 2012. On the basis of findings from the NOA-08 and Nordic trials,^{26,33} *MGMT* testing should be standard practice.⁴⁵ Patients with tumours lacking *MGMT* promoter methylation should receive hypofractionated radiotherapy alone, which is also the preferred treatment for patients with tumours with unknown *MGMT* status. Those with tumours with *MGMT*-promoter methylation should be treated with temozolomide alone (treatment for 5 of every 28 days until progression or for 12 months) or with temozolomide and radiotherapy followed by temozolomide. The role of early radiotherapy in addition to temozolomide in these patients will be better understood when data from the ongoing EORTC and National Cancer Institute of Canada (NCIC) Clinical Trial

Group elderly trial (NCT00482677) can be compared with those of the NOA-08 and Nordic trials.

Best supportive care can be the preferred option in patients with large or multifocal lesions with Karnofsky performance scores of less than 50, particularly 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 often based on previous treatment, age, Karnofsky performance score, and patterns of relapse. About 20–30% of patients with recurrent glioblastoma are candidates for second surgery, which should typically be considered when patients have large but circumscribed lesions causing neurological deficits and when the interval between surgeries is more than 6 months. However, surgery for progressive glioblastoma can also be considered earlier in symptomatic patients, especially in patients with suboptimum initial surgery. The role of reirradiation is uncertain, including the role of aminoacid PET for target delineation, and multiple fractionation regimens have been proposed—eg, from six doses of 5 Gy to 18 doses of 2 Gy.^{46,47} The three strategies of medical treatment for glioblastoma recurring after temozolomide with concurrent radiotherapy followed by temozolomide most often used across Europe include nitrosourea-based regimens, alternative dosing regimens of temozolomide, and bevacizumab. The activity of lomustine has been confirmed in the standard groups of randomised trials exploring the activity of the protein kinase C-β inhibitor, enzastaurin,⁴⁸ or the VEGF receptor inhibitor, cediranib,⁴⁹ with progression-free survival at 6 months of 20%. Somewhat better control at 6 months has been reported with a continuous dosing regimen of temozolomide,⁵⁰ but not in a recent phase 2 trial exploring a 21 out of 28 days schedule.⁵¹ The BR12 trial,¹² which enrolled recurrent, temozolomide-naive patients with malignant glioma provided no evidence for superiority of dose-intensified temozolomide over standard-dosed temozolomide, but these data are of limited value in assessment of the role of temozolomide rechallenge for patients pre-exposed to temozolomide. They do, however, suggest that there is no rationale for use of dose-intensified temozolomide in patients with recurrent glioma who are temozolomide-naive.

Although bevacizumab has been approved for the treatment of recurrent glioblastoma in several countries, it has not been approved in the European Union on the basis of findings from two prospective (but uncontrolled) phase 2 trials that showed radiological response rates of 30% or more and progression-free and overall survival times interpreted to be better than those of historical controls.^{52,53} The 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 has not been shown. 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 given outside clinical trials. Preliminary data indicate that the combination of bevacizumab and lomustine might be better than either drug alone,⁵⁴ suggesting that this combination warrants further exploration as planned in a phase 3 trial by the EORTC.

Gliomatosis cerebri

The diagnosis of gliomatosis cerebri is based on the histological verification of a glioma and needs radiological demonstration of diffuse signal changes suggestive of a tumour affecting at least three cerebral lobes. The diagnosis is thus not based on histology alone. Typically, the tumour affects both cerebral hemispheres and can extend into the basal ganglia and brainstem. Gliomatosis cerebri can correspond to WHO grades II, III, or IV, based on histological findings in the respective biopsy specimens, but resembles diffuse (WHO grade II) astrocytomas in most patients. The diagnostic concept of gliomatosis cerebri has proven difficult to use in clinical practice and trials, and will probably be revised with support of molecular markers and advanced imaging technology. The imaging features are quite characteristic and include a diffuse hyperintense tumour on T₂/FLAIR images involving both the white and grey matter, non-enhancing or with small patchy areas of contrast enhancement. Perfusion MRI and magnetic resonance spectroscopy can be useful to differentiate rare non-neoplastic lesions. In selected patients in whom intracranial pressure is substantially high, decompressive craniectomy can ultimately be considered at the time of biopsy to prevent rapid neurological deterioration. The clinical course of gliomatosis cerebri is highly variable, but occasionally younger patients can be followed up for years without specific therapy. *IDH1/2* mutations are associated with improved outcomes. Surgery is often restricted to a diagnostic biopsy. Radiotherapy and alkylating chemotherapy are active treatments. The role of radiotherapy as initial treatment is limited because of the high dose needed for control of glioma growth and the large target volumes needed in gliomatosis cerebri. Both PCV and temozolomide are often used as alternatives to radiotherapy.^{55,56} The NOA-05 trial⁵⁷ explored the efficacy of primary chemotherapy with procarbazine and lomustine, omitting vincristine because of poor penetration of the blood–brain barrier; investigators reported treatment failure at 8 months in fewer than half of patients, and a median overall survival of 30 months.

Brainstem gliomas and spinal gliomas

Diffuse intrinsic pontine gliomas are a major challenge in paediatric neuro-oncology. Although children are

often treated on the basis of neuroimaging alone, histological verification of the diagnosis is usually mandatory in adults, especially in cases of enhancing lesions, because of a higher error rate by imaging alone and a broader range of differential diagnoses.⁵⁸ Magnetic resonance spectroscopy can aid differential diagnosis if biopsy is not feasible or refused by the patient. Anaplastic gliomas and glioblastomas of brainstem and spinal cord are rare and no data from clinical studies are available. Resection is restricted to exophytic tumours because of the expected neurological deficits with surgery in the brainstem and spinal cord. Radiotherapy is the standard of care, and temozolomide or nitrosoureas or bevacizumab can be used in the course of disease following the considerations for supratentorial tumours of the same WHO grades.⁵⁹

Monitoring and follow-up

Whenever feasible, MRI should be used to monitor the efficacy of pharmacotherapy or as surveillance imaging after completion of treatment.⁶⁰ Intervals of 3 months are recommended for most patients with malignant gliomas, although longer intervals might be considered for patients with lengthy disease control, notably young patients with 1p/19q-co-deleted oligodendroglial tumours.

Supportive care and patient management

Raised intracranial pressure

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

Thromboembolic events

Patients with glioma are at increased risk of thromboembolic events throughout the course of disease for many reasons, including motor deficits, steroid drugs, radiotherapy, chemotherapy, immobility, and release of vasoactive molecules from glioma cells.⁶¹ The importance of this comorbidity increases with the use of antiangiogenic drugs as therapeutics against gliomas because these drugs are also associated with the risk of ischaemic and haemorrhagic vascular events. Although anticoagulation using coumadin derivatives is feasible in patients with glioma, low-molecular-weight heparins are often preferred due to a favourable safety profile.⁶¹ A single study⁶² about primary prophylaxis using such drugs was prematurely stopped, but provided no evidence for a decreased incidence of first thromboembolic events. Vena cava filters might be an option for patients who cannot be anticoagulated.

Epilepsy

Patients with glioma who never suffered symptomatic seizures should not receive primary prophylaxis with anticonvulsant drugs.⁶³ A single seizure usually necessitates anticonvulsant drug treatment until the underlying tumour growth is controlled by tumour-specific therapy.⁶⁴ If no further seizure occurs after surgery and the tumour seems to be controlled by treatment, tapering of anticonvulsants should be attempted within the first weeks or months after surgery and further tumour-specific therapy. Recurrent seizures after surgery usually indicate lifelong need for anticonvulsants. The choice of drug for patients requiring secondary prophylaxis is guided by various considerations.^{65,66} The classic drugs include carbamazepine, valproic acid, and phenytoin and are of similar efficacy. All anticonvulsants are associated with relevant toxicities in brain tumour patients. Phenytoin and carbamazepine share an unfavourable side-effect profile, including drug interactions, and are therefore not suited for long-term therapy of patients with brain tumours. Moreover, carbamazepine is not available intravenously and often induces vertigo and nausea after initial dosing, particularly in elderly patients. Long-term use impairs cognitive function. The enzyme-inducing properties of phenytoin, carbamazepine, and barbiturates can decrease the activity of many chemotherapeutic drugs, whereas the enzyme-inhibitory properties of valproic acid might accentuate toxic effects from, and possibly activity of, chemotherapy; for example, patients given valproic acid had improved outcomes, but also increased haematological toxic effects, in the experimental group of the EORTC NCIC temozolomide trial.⁶⁷ Drugs such as levetiracetam, gabapentin, lamotrigine, or topiramate offer advantages compared with the classic drugs, 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 need investigation in patients with brain tumours. Clonazepam and other benzodiazepines should only be used transiently (eg, during dosing of lamotrigine). This guideline does not address the competence to drive with a brain tumour, because driving capabilities are subject to country-specific regulations which are beyond the scope of this guideline.

Steroids

Steroids are often prescribed to patients for control of tumour-associated oedema. The need to continue steroid treatment in patients with brain tumours should be reviewed at each visit because of the major burden of side-effects, with effects on quality of life and the potential interference with tumour-specific therapies. Drug interactions, increased risk of infection and thrombosis, myopathy, and depression are only a few of

the frequently reported side-effects. The option to taper steroids rapidly after tumour debulking should not be missed. Patients who have undergone substantial resection often tolerate radiotherapy with no steroids, or a small dose in the first week. Patients who have undergone biopsy might only need steroids at the start of radiotherapy, but moderate doses (4–8 mg daily) will suffice, and can often be tailed off during or soon after treatment. Bevacizumab is a powerful steroid-sparing drug, but should not be used solely for this purpose. Other approaches to replace steroids as anti-oedema drugs in neuro-oncology are being explored.

Psychological and social support

Psychological stress and the social effects of the disease on patients and their families and caregivers should not be underestimated. Psychiatric comorbidity should be actively explored and treated accordingly, with both psychotherapy and pharmacotherapy.⁶⁸ Recognition of the social effects of having a brain tumour and adequate counselling in such circumstances are an integral aspect of care for patients. The effects of therapy in this patient population with reduced life span also need to be considered.⁶⁹ Diverse support can be beneficial from individuals such as nurse specialists in neuro-oncology, social workers, counsellors, clinical psychologists, palliative-medicine professionals, and patient focus groups.

Rehabilitation

The need for rehabilitative measures should be explored during and after tumour-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. Inpatient and outpatient rehabilitation are options. Amelioration of neurological and neuropsychological deficits are the main goals of neurological rehabilitation in brain tumour patients. Coping strategies for living with a malignancy are the main goal for rehabilitation with a psychological focus.⁷⁰

Palliative care

The appropriate timepoint and setting for communication with patients about the foreseeable restrictions and limitations of tumour-specific measures needs to be carefully assessed, and not done too late in the course of the disease. During advanced stages of disease, specific antineoplastic treatments might not be warranted, and palliative care becomes very important. Patients need specialised nurses, social workers, and coordinated care at home or in another adequate setting.⁷¹ Important pharmacological measures include the use of antiemetics, analgesics, corticosteroids, and anticonvulsants. If swallowing difficulties are expected, patients and caregivers should be instructed about how to give drugs (particularly sublingual or rectal anticonvulsants). Fluid replacement

	Class of evidence ²⁷	Level of recommendation ²⁷
General recommendations		
Karnofsky performance score, neurological function, age, and individual risks and benefits need to be considered in 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 on this basis might be referred for molecular genetic testing	IV	..
The diagnostic imaging approach of first choice is MRI without and with contrast enhancement	IV	..
An apparent increase of tumour 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 a definitive histological diagnosis at least by biopsy should occur only in very exceptional situations	IV	..
Histological diagnoses should follow the present WHO classification of tumours of the CNS	IV	..
Three molecular markers (1p/19q co-deletion, MGMT promoter methylation, IDH1/2 mutation) are valuable prognostic markers; the role of clinical decision making at present is mostly restricted to MGMT promoter methylation in elderly patients with glioblastoma, and 1p/19q co-deletion in patients with anaplastic oligodendroglial tumours	II	A
The prevention of new permanent neurological deficits has higher priority than does extent of resection in the present 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
On the basis of the NOA-04 trial findings, ⁹ chemotherapy with temozolomide or PCV is as effective as radiotherapy in the treatment of anaplastic gliomas, including anaplastic astrocytomas	II	B
On the basis of the EORTC 26951 and RTOG 9402 trial findings, ^{18–21} patients with 1p/19q co-deleted anaplastic oligodendroglial tumours should not be treated with radiotherapy alone, but should receive chemotherapy with alkylating agents with or without radiotherapy	II	B
Temozolomide chemotherapy is standard treatment at progression after surgery and radiotherapy	I	A
On the basis of the NOA-04 trial findings, ⁹ anaplastic oligoastrocytomas (WHO grade III) are treated as anaplastic oligodendroglomas	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 adjuvant (six cycles) temozolomide chemotherapy ²⁷	I	A
Elderly patients who are not candidates for temozolomide concurrent with radiotherapy followed by adjuvant temozolomide should be treated with radiotherapy (eg, 15 doses of 2–66 Gy) alone or temozolomide (5/28) based on MGMT promoter methylation status, on the basis of the findings of the NOA-08 and Nordic trials ^{26,33}	I	A
At recurrence, standards of care are less well defined; nitrosourea regimens, temozolomide rechallenge, and (with consideration of the country-specific label) bevacizumab are options for pharmacotherapy; when available, recruitment into appropriate clinical trials should be considered	II	B
PCV=procarbazine, lomustine, and vincristine.		

Table 3: Key recommendations

can 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 recommendations from interdisciplinary tumour boards from the first diagnostic and therapeutic decisions onwards. Such boards could also be the ideal forum for discussion of which parts of the treatment plan can be achieved locally, which parts need a specialised centre, which measures need inpatient or outpatient settings, and what intensity

of neurorehabilitative measures is in the patient's interest. Local and national guidelines could serve for orientation beyond this guideline.

Conclusions

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

Contributors

MW prepared the first draft of the paper. All authors reviewed and revised the paper twice. All authors approved the final version of the paper.

Declaration of interests

MW has received research grants from Antisense Pharma, Bayer, Merck Serono, and Roche and honoraria for lectures or advisory boards from Antisense Pharma, Magforce, Merck Serono, MSD, and Roche.

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He was the principal investigator of phase 2 or phase 3 trials investigating temozolomide (MSD) in newly diagnosed anaplastic glioma and glioblastoma as well as recurrent glioblastoma and bevacizumab in glioblastoma. MvdB has received honoraria from Roche, MSD, to-BBB, MerckAg, and Abbvie, and research support from Roche and Abbvie. KH has received honoraria from Roche. JCT has received honoraria for lectures or advisory boards from Merck Serono, Medac, BrainLab, and Roche. RSt 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. EC-J-M has received honoraria for advisory boards from Merck Serono. RH is member of the steering committee of the AVAGlio study (Roche). CB has received honoraria from Roche, Merck Serono, and Novartis for lectures and advisory boards. OC is consultant for Roche and has received honoraria for advisory boards from AstraZeneca and MSD. He served as the principal investigator of the AVAGlio trial. ZR is a consultant to Novocure. GR has received a research grant from Roche and honoraria for advisory boards from Merck Serono and Roche. RSo has received grants and honoraria for lectures and advisory boards from MSD, Roche, Merck Serono, and Mundipharma. 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. AF and DF declare no competing interests.

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References

- Louis DN, Ohgaki H, Wiestler OD, et al. WHO classification of tumours of the central nervous system. Lyon: IARC, 2007.
- Weller M, Pfister SM, Wick W, Hegi ME, Reifenberger G, Stupp R. Molecular neuro-oncology in clinical practice: a new horizon. *Lancet Oncol* 2013; **14**: e370–79.
- Wiestler B, Capper D, Holland-Letz T, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. *Acta Neuropathol* 2013; **126**: 443–51.
- Laperriere N, Zuraw L, Cairncross G, and the Cancer Care Ontario Practice Guidelines Initiative Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. *Radiother Oncol* 2002; **64**: 259–73.
- 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**: 333–43.
- Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med* 1980; **303**: 1323–29.
- Stewart LA, and the Glioma Meta-analysis Trialists (GMT) Group. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002; **359**: 1011–18.
- Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. *J Clin Oncol* 2001; **19**: 509–18.
- 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. *J Clin Oncol* 2009; **27**: 5874–80.
- 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**: 1515–22.
- Yung WKA, Prados MD, Yaya-Tur R, et al, and the Temodal Brain Tumor Group. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. *J Clin Oncol* 1999; **17**: 2762–71.
- Brada M, Stenning S, Gabe R, et al. Temozolomide versus procarbazine, lomustine, and vincristine in recurrent high-grade glioma. *J Clin Oncol* 2010; **28**: 4601–08.
- Desjardins A, Reardon DA, Herndon JE 2nd, et al. Bevacizumab plus irinotecan in recurrent WHO grade 3 malignant gliomas. *Clin Cancer Res* 2008; **14**: 7068–73.
- Chamberlain MC, Johnston S. Salvage chemotherapy with bevacizumab for recurrent alkylator-refractory anaplastic astrocytoma. *J Neurooncol* 2009; **91**: 359–67.
- Seystahl K, Wiestler B, Hundsberger T, et al. Bevacizumab alone or in combination with irinotecan in recurrent WHO grade II and grade III gliomas. *Eur Neurol* 2013; **69**: 95–101.
- 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. *Eur J Cancer* 2013; **49**: 3477–85.
- Arita H, Narita Y, Fukushima S, et al. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. *Acta Neuropathol* 2013; **126**: 267–76.
- Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. *J Clin Oncol* 2013; **31**: 337–43.
- Cairncross G, Berkey B, Shaw E, et al, and the Intergroup Radiation Therapy Oncology Group Trial 9402. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006; **24**: 2707–14.
- van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol* 2006; **24**: 2715–22.
- 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. *J Clin Oncol* 2013; **31**: 344–50.
- Chamberlain MC, Johnston S. Bevacizumab for recurrent alkylator-refractory anaplastic oligodendroglioma. *Cancer* 2009; **115**: 1734–43.
- Taillibert S, Vincent LA, Granger B, et al. Bevacizumab and irinotecan for recurrent oligodendroglial tumors. *Neurology* 2009; **72**: 1601–06.
- Barnholtz-Sloan JS, Williams VL, Maldonado JL, et al. Patterns of care and outcomes among elderly individuals with primary malignant astrocytoma. *J Neurosurg* 2008; **108**: 642–48.
- Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol* 2010; **120**: 707–18.
- Wick W, Platten M, Meisner C, et al, and the NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol* 2012; **13**: 707–15.
- Vuorinen V, Hinkka S, Färkkilä M, Jääskeläinen J. Debulking or biopsy of malignant glioma in elderly people—a randomised study. *Acta Neurochir (Wien)* 2003; **145**: 5–10.
- Kreth FW, Thon N, Simon M, et al. Gross total but not incomplete resection of GBM prolongs survival in the era of radiochemotherapy. *Ann Oncol* 2013; **24**: 3117–23.
- Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, and the ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2006; **7**: 392–401.
- Stummer W, Reulen HJ, Meinel T, et al, and the ALA-Glioma Study Group. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery* 2008; **62**: 564–76.
- Keime-Guibert F, Chinot O, Taillandier L, et al, and the Association of French-Speaking Neuro-Oncologists. Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 2007; **356**: 1527–35.

- 32 Roa W, Brasher PM, Bauman G, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol* 2004; **22**: 1583–88.
- 33 Malmström A, Grønberg BH, Marosi C, et al, and the Nordic Clinical Brain Tumour Study Group (NCBTSG). Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *Lancet Oncol* 2012; **13**: 916–26.
- 34 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**: 79–88.
- 35 Westphal M, Ram Z, Riddle V, Hilt D, Bortey E, and the Executive Committee of the Gliadel Study Group. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148**: 269–75.
- 36 Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K. Chemotherapeutic wafers for high grade glioma. *Cochrane Database Syst Rev* 2008; **3**: CD007294.
- 37 Stupp R, Mason WP, van den Bent MJ, et al, and the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352**: 987–96.
- 38 Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database Syst Rev* 2013; **4**: CD007415.
- 39 Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 2005; **352**: 997–1003.
- 40 Stupp R, Hegi ME, Mason WP, et al, and the European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups, and the National Cancer Institute of Canada Clinical Trials Group. 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. *Lancet Oncol* 2009; **10**: 459–66.
- 41 Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol* 2013; **31**: 4085–91.
- 42 Chinot O, Wick W, Mason W, et al. Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370**: 709–22.
- 43 Gilbert MR, Dignam J, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370**: 699–708.
- 44 Weller M, Yung WK. Angiogenesis inhibition for glioblastoma at the edge: beyond AVAGlio and RTOG 0825. *Neuro Oncol* 2013; **15**: 971.
- 45 Weller M, Stupp R, Hegi ME, et al. Personalized care in neuro-oncology coming of age: why we need MGMT and 1p/19q testing for malignant glioma patients in clinical practice. *Neuro Oncol* 2012; **14** (suppl 4): iv100–08.
- 46 Grosu AL, Weber WA, Franz M, et al. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005; **63**: 511–19.
- 47 Fogh SE, Andrews DW, Glass J, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. *J Clin Oncol* 2010; **28**: 3048–53.
- 48 Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 2010; **28**: 1168–74.
- 49 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. *J Clin Oncol* 2013; **31**: 3212–18.
- 50 Perry JR, Bélanger K, Mason WP, et al. Phase II trial of continuous dose-intensive temozolomide in recurrent malignant glioma: RESCUE study. *J Clin Oncol* 2010; **28**: 2051–57.
- 51 Norden AD, Lesser GJ, Drappatz J, et al. Phase 2 study of dose-intensive temozolomide in recurrent glioblastoma. *Neuro Oncol* 2013; **15**: 930–35.
- 52 Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009; **27**: 4733–40.
- 53 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. *J Clin Oncol* 2009; **27**: 740–45.
- 54 Taal W, Oosterkamp HM, Walenkamp AME, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB study): a randomised controlled phase 2 trial. *Lancet Oncol* 2014; **15**: 943–53.
- 55 Herrlinger U, Felsberg J, Küker W, et al. Gliomatosis cerebri: molecular pathology and clinical course. *Ann Neurol* 2002; **52**: 390–99.
- 56 Sanson M, Cartalat-Carel S, Taillibert S, et al, and the ANOCEF group. Initial chemotherapy in gliomatosis cerebri. *Neurology* 2004; **63**: 270–75.
- 57 Glas M, Bähr O, Felsberg J, et al, and the Neuro-Oncology Group of the German Cancer Society. NOA-05 phase 2 trial of procarbazine and lomustine therapy in gliomatosis cerebri. *Ann Neurol* 2011; **70**: 445–53.
- 58 Rachinger W, Grau S, Holtmannspötter M, Herms J, Tonn JC, Kreth FW. Serial stereotactic biopsy of brainstem lesions in adults improves diagnostic accuracy compared with MRI only. *J Neurol Neurosurg Psychiatry* 2009; **80**: 1134–39.
- 59 Laigle-Donadey F, Doz F, Delattre JY. Brainstem tumors. *Handb Clin Neurol* 2012; **105**: 585–605.
- 60 Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; **28**: 1963–72.
- 61 Perry JR. Thromboembolic disease in patients with high-grade glioma. *Neuro Oncol* 2012; **14** (suppl 4): iv73–80.
- 62 Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost* 2010; **8**: 1959–65.
- 63 Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. *Cochrane Database Syst Rev* 2008; **2**: CD004424.
- 64 Kerrigan S, Grant R. Antiepileptic drugs for treating seizures in adults with brain tumours. *Cochrane Database Syst Rev* 2011; **8**: CD008586.
- 65 Rudà R, Trevisan E, Soffietti R. Epilepsy and brain tumors. *Curr Opin Oncol* 2010; **22**: 611–20.
- 66 Weller M, Stupp R, Wick W. Epilepsy meets cancer: when, why, and what to do about it? *Lancet Oncol* 2012; **13**: e375–82.
- 67 Weller M, Gorlia T, Cairncross JG, et al. Prolonged survival with valproic acid use in the EORTC/NCIC temozolomide trial for glioblastoma. *Neurology* 2011; **77**: 1156–64.
- 68 Rooney A, Grant R. Pharmacological treatment of depression in patients with a primary brain tumour. *Cochrane Database Syst Rev* 2010; **3**: CD006932.
- 69 Henriksson R, Asklund T, Poulsen HS. Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: a review. *J Neurooncol* 2011; **104**: 639–46.
- 70 Piil K, Juhler M, Jakobsen J, et al. Controlled rehabilitative and supportive care intervention trials in patients with high-grade gliomas and their caregivers: a systematic review. *BMJ Support Palliat Care* 2014; published online June 2. DOI:10.1136/bmjspcare-2013-000593.
- 71 Heese O, Vogeler E, Martens T, et al, and the German Glioma Network. End-of-life caregivers' perception of medical and psychological support during the final weeks of glioma patients: a questionnaire-based survey. *Neuro Oncol* 2013; **15**: 1251–56.
- 72 Brainin M, Barnes M, Baron JC, et al, and the Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces—revised recommendations 2004. *Eur J Neurol* 2004; **11**: 577–81.