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EFNS GUIDELINES/CME ARTICLE

Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force

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Background: Diffuse infiltrative low-grade gliomas of the cerebral hemispheres in the adult are a group of tumors with distinct clinical, histological and molecular characteristics, and there are still controversies in management.

Methods: The scientific evidence of papers collected from the literature was evaluated and graded according to EFNS guidelines, and recommendations were given accordingly.

Results and conclusions: WHO classification recognizes grade II astrocytomas, oligodendrogliomas and oligoastrocytomas. Conventional MRI is used for differential diagnosis, guiding surgery, planning radiotherapy and monitoring treatment response. Advanced imaging techniques can increase the diagnostic accuracy. Younger age, normal neurological examination, oligodendroglial histology and 1p loss are favorable prognostic factors. Prophylactic antiepileptic drugs are not useful, whilst there is no evidence that one drug is better than the others. Total/near total resection can improve seizure control, progression-free and overall survival, whilst reducing the risk of malignant transformation. Early post-operative radiotherapy improves progression-free but not overall survival. Low doses of radiation are as effective as high doses and better tolerated. Modern radiotherapy techniques reduce the risk of late cognitive deficits. Chemotherapy can be useful both at recurrence after radiotherapy and as initial treatment after surgery to delay the risk of late neurotoxicity from large-field radiotherapy. Neurocognitive deficits are frequent and can be caused by the tumor itself, tumor-related epilepsy, treatments and psychological distress.

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Background

Low-grade gliomas (LGGs) are a group of tumors with distinct clinical, histological and molecular characteristics. These guidelines will focus on the diffuse infiltrative WHO grade II tumors of the cerebral hemispheres in the adult. Brain stem or cerebellar tumors, which are rare and present specific problems of management, will not be discussed.

LGGs represent up to 30% of gliomas and affect patients at a younger age than high-grade gliomas. LGGs are commonly located in or close to eloquent areas, i.e. those areas of the brain involved in motor, language, visuospatial and memory function [1].

The 5-year overall (OS) and progression-free survival (PFS) rates in randomized studies range from 58% to 72% and 37% to 55%, respectively.

Patients with LGGs may survive for up to 20 years [2], but these tumors grow continuously [3,4] and tend to progress to a higher grade, leading to neurological disability and ultimately to death.

The optimal treatment of patients with LGG is still controversial [5].

Search strategy

We searched the following databases: the Cochrane Library to date; Medline–Ovid (January 1966 to date); Medline–ProQuest; Medline-EIFL; Embase–Ovid (January 1990 to date); CancerNet; Science Citation Index. We used specific and sensitive keywords, as well as combinations of keywords, and publications in any language of countries represented in the Task Force. The search was completed in June 2009.

Methods for reaching consensus

The Panel covered all fields of expertise in neuro-oncology, i.e. neurosurgeons, neurologists, neuropathologists, radiation and medical oncologists and a clinical trial expert.

The scientific evidence of papers collected from the literature was evaluated and graded according to EFNS guidelines, and recommendations were given accordingly [6]. Class I evidence was derived from prospective, randomized, well-controlled clinical trials; class II evidence was derived from prospective studies, including observational studies, cohort studies and case–control studies; class III evidence was derived from retrospective studies; class IV evidence was derived from uncontrolled case series, case reports and expert opinion. As for recommendations, level A required at least one class I study or two consistent class II studies, level B at least one class II study or overwhelming class III evidence and level C at least two consistent class III studies. Regarding Pathology and Genetics, the classification of evidence was limited to the aspects that are mostly strong in terms of prognosis, whilst clinical features and conventional MRI were simply reviewed but not graded. When sufficient evidence for recommendations A–C was not available, we gave a recommendation as a 'Good Practice Point' if agreed by all members of the Task Force. When analyzing results and drawing recommendations, at any stage, the differences were resolved by discussions.

Review of the evidence

Pathology and genetics

World Health Organization (WHO) classification [7] recognizes grade II astrocytomas, oligodendrogliomas and oligoastrocytomas (Class I). Morphological features distinguish astrocytoma from oligodendroglioma. However, application of the same diagnostic criteria poses difficulties for the separation of oligoastrocytoma from both astrocytoma and oligodendroglioma as the diagnostic features present as a continuum from one to the other end of the histological spectrum and modern surgical approach and scientific interest in fresh tumor tissue reduce the amount of material seen by the neuropathologists. This aggravates the inherent sampling problem and prevents WHO to provide a recommendation on the proportion of tissues with astrocytic or oligodendroglial differentiation required for the diagnosis of oligoastrocytoma.

Diffuse astrocytomas include fibrillary, gemistocytic and protoplasmic variants. The most common is the fibrillary astrocytoma. It is important to separate gemistocytic astrocytoma, because it is more prone to malignant progression. Fibrillary astrocytoma is composed of a uniform cell population with only moderate nuclear atypia in a fine fibrillary tumor matrix. The hallmark of the gemistocytic variant are cells with ballooned eosinophilic cytoplasm and eccentric nuclei making up more than 20% of the tumor cells. The mitotic activity in astrocytomas WHO grade II is very low; single mitosis should not result in the diagnosis of anaplastic astrocytoma, whilst single mitosis in stereotactic biopsy should raise the suspicion of anaplasia. The Ki-67/MIB-1 labelling index in diffuse astrocytoma usually is $<4\%$. Tumor necrosis, vascular proliferation, vascular thrombosis and high mitotic activity are not compatible with diffuse astrocytoma WHO grade II. The best immunohistochemical marker is glial fibrillary acidic protein, which is expressed in both tumor cells and the astrocytic processes. Molecular findings typical for diffuse astrocytoma are *TP53* mutations in 50% of cases; gemistocytic astrocytoma carries *TP53* mutations in more than 80% whilst combined 1p/19q deletion is rare [8]. Somatic mutations in the *IDH1* gene have been reported in 75% of astrocytomas [9].

Oligodendrogliomas are moderately cellular and typically exhibit perinuclear halos termed 'fried egg' or 'honey comb' pattern. Occasionally, tumor cells with a

small strongly eosinophilic cytoplasm are encountered and termed 'mini-gemistocytes'. Oligodendrogliomas have a dense network of capillaries and frequently contain calcifications. Occasional mitoses and a Ki-67/MIB-1 labelling index up to 5% are compatible with oligodendroglioma WHO grade II. There is no immunohistochemical marker specific for oligodendroglioma. The molecular hallmark of oligodendrogliomas is combined loss of 1p/19q occurring in 80% of these tumors [10] (Class II), whilst TP53 mutations are encountered in only 5%. Somatic *IDH1* mutations are present in 80% of oligodendroglioma [9].

Oligoastrocytomas should be diagnosed upon detection of convincing astrocytic and oligodendroglial components, but the interobserver difference for the diagnosis of oligoastrocytoma remains high [11]. Most oligoastrocytomas carry either 1p/19 loss or *TP53* mutations, and there is a tendency for these aberrations to be present in both tumor compartments [12]. Up to 80% of oligoastrocytomas carry somatic mutations in *IDH1*.

Both genetic (i.e. 1p/19q deletion) and epigenetic (MGMT and RASSF1A promoter methylation) changes seem to be important for gliomagenesis and response/resistance to radiotherapy (RT) and chemotherapy [13].

Clinical features

Seizures are the commonest presentation and may be partial or generalized. They occur in over 90% of patients and are intractable in 50%. Seizures are more frequently associated with cortically based tumors, particularly in frontal, temporal and insular/parainsular location and with oligodendroglial tumors [14]. There is no clear association between severity of epilepsy and behavior of the tumor.

Focal neurological deficits are unusual, developing over many years.

Raised intracranial pressure is rare in patients with supratentorial tumors and is typically seen in posterior fossa and intraventricular tumors. Intratumoral hemorrhage can occur.

Conventional and advanced neuroimaging

Conventional MRI is useful for differential diagnosis, guiding biopsy or resection, planning RT and monitoring treatment response [15]. LGGs appear as low-signal mass lesions on T1-weighted MRI and high signal on T2-weighted and FLAIR sequences. Contrast enhancement is usually absent; when present, it may indicate a focal area of high-grade transformation, although some tumors, particularly oligodendrogliomas, have patchy enhancement, which remains stable over time.

The use of advanced imaging techniques can increase the diagnostic accuracy [16,17] (Class II–III).

Proton Magnetic Resonance Spectroscopy (MRS) measures major metabolites in tumor tissue. The typical spectrum of a LGG shows elevated choline, reflecting increased membrane turnover and decreased N-acetyl-aspartate, reflecting neuronal loss, but similar abnormal spectra may be seen in non-neoplastic lesions. Grading of gliomas is not possible by spectroscopy alone, as there is considerable overlap between low-grade and high-grade lesions. The presence of lactate and lipids is associated with higher proliferative activity and more aggressive behavior [18]. MRS is helpful in guiding a biopsy to an area of high-grade activity, but not in longitudinal monitoring [19].

Dynamic susceptibility contrast MRI (DSC-MRI) allows measurement of relative cerebral blood volume (rCBV) that correlates with vascularity at the histological level. Increase in rCBV in LGGs predicts high-grade transformation before gadolinium enhancement occurs [20]; however, these observations are limited to astrocytomas, as oligodendrogliomas have significantly higher rCBV [21].

Dynamic contrast-enhanced imaging (DCE-MRI) measures the permeability of the blood-brain barrier by means of the transfer coefficient, K^{trans}, which is related to tumor grade, although the correlation is not as strong as for rCBV [22].

Regarding diffusion-weighted imaging, apparent diffusion coefficient (ADC) values are lower and more variable in oligodendrogliomas compared with astrocytomas [23]. There is no correlation between ADC and choline [24].

Quantitative MRI in oligodendrogliomas with loss of heterozygosity of chromosome 1p/19q shows more heterogeneous T1- and T2-dependent signal, less distinct margins and higher rCBV than tumors with intact chromosomes [25,26].

Pet imaging

PET with [18F]-fluorodeoxyglucose (FDG) is of limited value, as LGGs show a low FDG uptake compared to the normal cortex. The usefulness of FDG-PET is limited to the detection of malignant transformation in astrocytomas [27] (Class III) and to the differentiation of radiation necrosis from tumor recurrence [28] (Class II).

PET with 11C-methionine (MET) is most frequently used, and the uptake of MET correlates with the proliferative activity of tumor cells. The background uptake with MET-PET in normal brain tissue is lower than with FDG-PET, providing good contrast with tumor uptake and delineation of LGG [29]. LGGs with

an oligodendroglial component show a higher MET uptake.

PET with MET is useful in differentiating LGGs from non-tumoral lesions [30] (Class II), guiding stereotactic biopsies [31] (Class II), defining pre-operative tumor volume [29] (Class II) and monitoring response to treatment [32] (Class III).

As for novel tracers, 18F-fluoro-L-thymidine is a proliferation marker but does not enter the brain unless there is a blood–brain barrier defect, and therefore the usefulness seems limited [33].

Prognostic factors

Age over 40 years and presence of pre-operative neurological deficits are adverse prognostic factors [34,35] (Class I).

Regarding neuroimaging findings, larger tumors and tumors crossing the midline correlate with a short OS and PFS [34] (Class II). Growth rates are inversely correlated with survival [4] (Class III). There are conflicting reports as to whether contrast enhancement is associated with a worse prognosis [36,37].

A low CBV [38] and a low uptake of ^{11}C-MET [39] correlate with longer PFS and OS (Class III).

Oligodendrogliomas have a better prognosis than astrocytomas, whereas oligoastrocytomas have an intermediate outcome (Class I).

1p loss (with or without 19q loss) is a favorable prognostic factor [40–42] (Class II). MGMT promoter methylation could predict a shorter time to progression in untreated patients [43], whilst predicting longer PFS and OS in patients receiving chemotherapy with temozolomide (TMZ) [44] (Class III).

IDH1 codon 132 mutation has been recently suggested as an independent favorable prognostic factor [45].

Antiepileptic treatment

There are no trials dealing with antiepileptic drugs (AEDs) in patients with LGG and seizures. The level of evidence is strong for treatment of seizures in general.

In patients with single seizures, immediate treatment with antiepileptic drugs increases time to recurrent seizures compared to delayed treatment, without differences with respect to quality of life or serious complications [46] (Class 1).

Patients with no history of seizures have no benefit from prophylactic treatment [47–49] (Class I).

Carbamazepine, phenytoin and valproate have Class 1 evidence of efficacy [50]. Lamotrigine, gabapentin, oxcarbazepine and topiramate have shown equivalence to carabamazepine, phenytoin and valproate [51]. In the SANAD study, lamotrigine was superior to carbamazepine, gabapentin and topiramate [52]. Valproate may potentiate the hematotoxicity from chemotherapy.

Enzyme-inducing antiepileptic drugs (EIAEDs) interact with some chemotherapy agents (nitrosoureas, paclitaxel, cyclophosphamide, topotecan, irinotecan, thiotepa and molecular agents), being associated with lower plasma levels and lower bone marrow toxicity [47] (Class II).

Surgery

Surgery is necessary to provide tissue for distinguishing between the histologic types, grading the malignancy and assessing the molecular status of tumors. Moreover, there are scenarios that pose problems of differential diagnosis between LGGs and non-neoplastic lesions (demyelination, inflammation or infection), and thus histological verification is mandatory.

Total resection improves seizure control, particularly in patients with a long epileptic history and insular tumors [14] (Class II).

The use of brain mapping techniques increases the percentage of patients in which a total and subtotal resection is achieved and has decreased the percentage of post-operative permanent deficits [53–55] (Class II).

Awake surgery is a well-tolerated procedure, which could enable (i) to increase the indications of resection in eloquent areas, (ii) to identify the structures crucial for brain functions, especially language, both at cortical and subcortical level, (iii) to optimize the extent of resection, the glioma removal being performed according to functional boundaries [55] (Class III). Awake surgery has increased the safety of re-operation owing to mechanisms of brain plasticity.

The effect of the extent of surgery on OS and PFS is still uncertain. There are no randomized trials that have specifically addressed this question. There is a general trend for most of the recently published articles [56,57] to support extensive resections based on the surgeon's intraoperative impression (Class II). A critical point is a precise definition of total resection that for LGGs that do not enhance implies removal of all the hyperintense regions on T2 or FLAIR images and thus can only be determined by comparing pre-operative and post-operative tumor volumes on MRI. This has been performed by few studies only, and all have shown that total/near total resection decreases the incidence of recurrence and the risk of malignant transformation and improves PFS and OS [54,58] (Class III).

Nonetheless, even with intraoperative MRI-guided surgery, total resection is achieved in no more than 36% of patients [59].

The initial report of RTOG 9802 [60], which performed observation after surgery in patients with age ≤ 40 years and complete resection, reported a 5-year survival rate of 93%, but 52% of patients progressed within 5 years and received salvage RT (Class II).

The timing of surgery is controversial in patients who are young, present with an isolated seizure (medically well controlled) and with small tumors. Potential surgical morbidity may compromise the otherwise intact functional status, and some authors have advocated deferring surgery in lieu of radiographic control ('watch and wait policy') [61,62], especially in oligodendroglial tumors [63]. The risk of deferring surgery includes managing at a later timepoint a larger tumor, which may have undergone anaplastic transformation.

Radiotherapy

Four phase III randomized trials have been performed so far (Table 1).

EORTC 22845 [57,64] investigated the role of RT timing. Although improved PFS was demonstrated for patients treated with immediate RT, this did not translate into improved OS (Class I). Besides prolonging the time to tumor progression, RT has several other potential benefits, such as symptom control, particularly epileptic seizures [65].

Two randomized trials investigated different radiation doses. The EORTC 22844 and NCCTG studies showed no advantage for higher versus lower doses [66,67] (Class I). If higher doses are used, an increased toxicity is observed, with a 2-year incidence of radiation necrosis of 2.5% [66] or lower levels of functioning, concerning quality of life, especially for fatigue, insomnia and emotional functioning [68].

RTOG 9802 has compared RT alone vs RT plus PCV [69]. As two-thirds of patients in the RT arm who progressed received chemotherapy at progression, this trial might be considered a trial of early chemotherapy vs chemotherapy at progression. PFS but not OS were improved (Class I). However, beyond 2 years, the addition of PCV to RT conferred a significant OS and PFS advantage and reduced the risk of death by 48% and progression by 55%, suggesting a delayed benefit for chemotherapy. Grade 3–4 toxicity was higher amongst patients receiving RT + PCV (67% vs 9%) (Class I).

Patients treated with whole-brain RT have a higher incidence of leucoencephalopathy and cognitive deficits in comparison with patients treated with focal RT [70] (Class II). In studies using modern standards of RT, less negative impact on cognition are observed [71–73] (Class II), although recent data related to patients who had a neuropsychological follow-up at a mean of 12 years and were free of tumor progression suggest that those without RT maintain their cognitive status whereas patients receiving RT do worse on attentional and executive functioning as well as information processing speed [74].

Chemotherapy

The usefulness of chemotherapy for patients progressing after surgery and RT is well established (Class II), with more data available for oligodendroglial tumors. PCV (Procarbazine, CCNU and Vincristine) and TMZ yield similar objective response rates on CT/MRI (45–62%) and duration of response (10–24 months), with a toxicity profile favoring TMZ in terms of better tolerability (reduced myelotoxicity) and higher dose intensity [75–79]. The response rate of enhancing tumors, possibly reflecting high-grade pathology, is higher than that of non-enhancing tumors. A clinical benefit (i.e. reduction of seizure frequency and improvement of neurological deficits) is commonly seen in patients responding radiologically and in some patients with stable disease.

Chemotherapy (PCV or TMZ), as initial treatment after surgery, has been investigated in 'high-risk patents'

Table 1 Phase III trials on radiotherapy and chemotherapy for low-grade gliomas

Study	Treatment Arms/no of patients	5-year PFS, % (*P* value)		5-year OS, % (*P* value)	
EORTC 22845	S (157)	37	$P = 0.02$	66	NS
	S + RT (154)	44		63	
EORTC 22844	S + RT 45 Gy (171)	47	NS	58	NS
	S + RT 59.4 Gy (172)	50		59	
NCCTG	S + RT 50.4 Gy	55	NS	72	NS
	S + RT 64.8 Gy	52		64	
RTOG 94.02	S + RT (125)	46	$P = 0.005$	63	NS
	S + RT + PCV (126)	63		72	

PFS, progression-free survival; OS, overall survival.

(i.e. those with incomplete resection, persisting seizures and progression on CT/MRI).

All studies have level of evidence of Class II [80–83]. Complete responses are generally lacking, with a prevalence of minor over partial responses (overall, 53%), and maximum tumor shrinkage can be delayed as long as 24–30 months. Patients more likely to respond have symptomatic/enlarging oligodendroglial tumors, but mixed tumors or astrocytic tumors may respond as well. Most patients with seizures have a clinical benefit, even in the absence of a radiological change. Evaluation of response on conventional MRI (T2-weighted and/or FLAIR images) is difficult in non-enhancing tumors.

Chemotherapy with nitrosureas can be an effective initial treatment for unresectable astrocytomas [84] (Class IV).

Response rate after chemotherapy is higher, and duration of response is longer in patient with 1p/19q loss than in those with 1p/19q intact [83] (class III).

Protracted low doses of TMZ could offer potential advantages over standard doses, especially in unmethylated tumors [85] (Class III), but the toxicity could be increased [86]. Pre-operative chemotherapy could reduce tumor infiltration/extension and thus improve the surgical resectability [87] (Class IV).

Neurocognitive deficits

Neurocognitive deficits in LGGs can be caused by tumor itself, tumor-related epilepsy, treatments and psychological distress. The cognitive decline that might ultimately lead to dementia negatively affects the patient's quality of life and well-being. Consequently, neurocognitive function is increasingly incorporated as secondary outcome measure in clinical trials in patients with LGG.

In the literature, neurocognitive outcome has been assessed systematically in a limited number of studies, with a relatively small number of patients (Class II).

Regarding the effects of the tumor, Tucha *et al.* (2000) [88] found neurocognitive deficits such as impairment of executive functions and memory attention in 91% of patients before surgery. Patients with glioma are prone to have more global neurocognitive deficits, unlike patients with stroke who tend to have site-specific deficits. Patients with tumor in the dominant hemisphere have more memory problems and poorer attention, verbal fluency and verbal learning than those with non-dominant tumors [89] and have less chance to normalize following surgery [90].

Because of the reduction of tumor mass, surgery is more beneficial or at least does not further deteriorate the neurocognitive functioning (Class II). However, surgery can give rise to transient focal neurocognitive deficits [55].

The severity of neurocognitive deficits after RT ranges from mild attention or memory disturbances to dementia (Class II). A follow-up of the Klein *et al.*, 2003 study [74] has demonstrated that there is a relation between neurocognitive status and cerebral atrophy and leukoencephalopathy, and radiological abnormalities increases only in the irradiated group.

Neurocognitive side effects of AEDs can add to previous damage by surgery or RT (Class II). The older AEDs (phenobarbitone, phenytoin, carbamazepine and valproic acid) can decrease neurocognitive functioning by impairing attention and memory [91]. Amongst newer AEDs, gabapentin, lamotrigine and levetiracetam have fewer adverse neurocognitive effects, whilst topiramate is associated with the greatest risk of neurocognitive impairment [92].

A randomized trial has shown that cognitive rehabilitation has a salutary effect on both short- and long-term cognitive complaints and mental fatigue [93] (Class II).

Recommendations

- Astrocytomas, oligodendrogliomas and oligoastrocytomas are diagnosed using morphological criteria according to WHO classification (Level A).
- Combined loss of 1p/19q is a marker in favor of the diagnosis of oligodendroglioma or oligoastrocytoma (Level B).
- MRI with contrast enhancement is the gold standard to monitor LGG after surgery: an MRI examination every 6 months might be enough, unless the physicians think otherwise (good practice point).
- MRS is useful for the differentiation of LGG from non-tumoral lesions, pre-operative definition of extent and guiding stereotactic biopsies (Level C).
- DSC-MRI can be employed in the follow-up to predict malignant transformation (Level C).
- PET with FDG is useful for detecting malignant transformation in astrocytomas (Level C) and for differentiation between radiation necrosis and tumor recurrence (Level B)
- PET with MET is useful for differentiation of LGG from non-tumoral lesions (Level B), guiding stereotactic biopsies (Level B), pre-treatment evaluation (Level B) and monitoring treatment (Level C).
- Prophylactic AEDs must not be used before any epileptic seizures have occurred (Level A).
- AEDs should be started after the first seizure (Level A).

- AEDs should be individualized according to seizure type, comedication, comorbidity and patient preferences (good practice point).
- In patients who need a treatment with chemotherapeutics, non-EIAEDs are to be preferred (Level B).
- Surgical resection represents the first treatment option, with the goal to maximally resect the tumor mass whenever possible, whilst minimizing the postoperative morbidity (Level B).
- The identification of the eloquent cerebral areas, which have to be preserved during surgery, is performed through pre-operative neuroimaging modalities (functional MRI, fiber tracking) and intraoperative brain mapping techniques (Level B), and awake surgery could improve the results (Level C).
- When surgery is not feasible (because of tumor location, extension or comorbidities), a biopsy (either stereotactic or open) should be performed to obtain a histological diagnosis (good practice point).
- For patients with unfavorable prognostic factors (older age, incomplete or no resection, existing neurological symptoms), an adjuvant treatment is indicated at any time (Level B), and this is more commonly RT (good practice point).
- A total RT dose of 50.4–54 Gy in fractions of 1.8 Gy represents the current standard of care (Level A). Modern RT techniques (conformal dose delivery or intensity modulated techniques) should preferably be used (Level B).
- Younger patients (<40 years of age) with (nearly) complete resection and tumors with an oligodendroglial component have a more favorable prognosis and can be observed after surgery (Level B), but close follow-up is needed (good practice point).
- Chemotherapy is an option for patients with recurrence after surgery and radiation therapy (Level B).
- Chemotherapy is an option as initial treatment for patients with large residual tumors after surgery or unresectable tumors to delay the risk of late neurotoxicity from large-field RT, especially when 1p/19q loss is present (Level B).
- Neuropsychological tests, at diagnosis and during the follow-up, can be useful, being selected according to the needs of the clinical setting (good practice point). The neuropsychological tests must have standardized materials and administration procedures, published normative data, moderate to high test–retest reliability, brief administration time (30–40 min) and be suitable to monitor changes over time (good practice point).
- Cognitive rehabilitation can be helpful (Level B).

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