

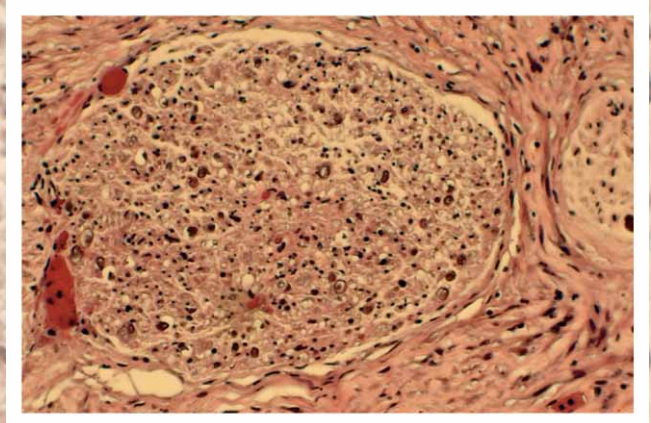
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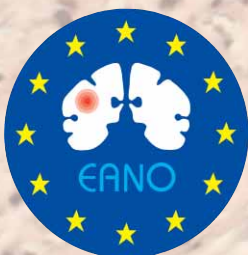
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Guidelines on the Management of Low-grade Gliomas: EANO Task Force Report

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Abstract: In adults, diffuse infiltrative low-grade gliomas of the cerebral hemispheres are a group of tumours with distinct clinical, histological, and molecular characteristics whose management is still controversial. Scientific evidence from the literature was evaluated and graded according to the EFNS guidelines and recommendations were given accordingly. The WHO classification recognizes grade-II astrocytomas, oligodendrogliomas, and oligoastrocytomas. MRI is used for differential diagnosis, guiding surgery, planning radiotherapy, and monitoring treatment response. Advanced imaging tech-

niques can increase the diagnostic accuracy. Younger age, normal neurological examination, oligodendroglial histology, and 1p loss are favourable prognostic factors. Prophylactic administration of antiepileptic drugs is not useful whilst there is no evidence that one drug is superior to others. Total/near total resection can improve seizure control as well as progression-free and overall survivals while 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 an initial treatment after surgery to delay the risk of late neurotoxicity from large-field radiotherapy and improve seizure control. Neurocognitive deficits are frequent and can be caused by the tumour itself, tumour-related epilepsy, treatments, and psychological distress. **Eur Assoc Neurooncol Mag 2011; 1 (1): 37–44.**

Key words: low-grade glioma, guideline, diagnosis, treatment

■ Introduction

Low-grade gliomas (LGGs) are a group of tumours with distinct clinical, histological, and molecular characteristics. These guidelines will focus on diffuse infiltrative WHO grade-II tumours of the cerebral hemispheres in adults. Brain stem or cerebellar tumours, 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, ie, 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 58–72 % and 37–55 %, respectively. Patients with LGGs may survive for up to 20 years [2], but these tumours 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].

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■ 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), Cancer Net, and Science Citation Index. We used specific and sensitive key words as well as combinations of key words, and publications in any language from countries represented in the Task Force. The search was completed in June 2011.

■ Methods for Reaching Consensus

The panel covered all fields of expertise in neuro-oncology, ie, neurosurgeons, neurologists, neuropathologists, radiation and medical oncologists, and a clinical trials expert.

The scientific evidence of papers collected from the literature was evaluated and graded according to the 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 2 consistent class-II studies, level B at least one class-II study or overwhelming class-III evidence and level C at least 2 consistent class-III studies. Regarding pathology and genetics, the classification of evidence was limited to the strongest aspects 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 all Task Force members agreed. When analyzing results and drawing recommendations, at any stage, the differences were resolved by discussion.

■ Review of the Evidence

Pathology and Genetics

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

Diffuse astrocytomas include fibrillary, gemistocytic, and protoplasmic variants. The most common is the fibrillary astrocytoma. It is important to separate gemistocytic astrocytomas because they are more prone to malignant progression. The fibrillary astrocytoma is composed of a uniform cell population with only moderate nuclear atypia in a fine fibrillary tumour matrix. The hallmark of the gemistocytic variant are cells with ballooned eosinophilic cytoplasm and eccentric nuclei making up > 20 % of the tumour cells. The mitotic activity in astrocytomas WHO grade II is very low; single mitosis should not result in the diagnosis of an anaplastic astrocytoma, while single mitosis in stereotactic biopsy should raise the suspicion of anaplasia.

The single most frequent molecular alteration in astrocytomas is the IDH1 mutation reported in 75 % of astrocytomas [8]. However, this alteration is seen with comparable frequency in oligodendroglial tumours and thus represents a marker unifying astrocytomas, oligoastrocytomas, and oligodendrogliomas of WHO grades II and III.

Development of an IDH1-R132H mutation-specific antibody (H09) greatly assists in the diagnosis of astrocytomas as well as oligodendrogliomas and oligoastrocytomas [8]. H09 covers > 90 % of all IDH1 mutations in diffuse gliomas and separates these tumours from other lower-grade gliomas [9]. The Ki-67/MIB-1 labelling index in diffuse astrocytomas usually is < 4 %. Tumour necrosis, vascular proliferation, vascular thrombosis, and high mitotic activity are not compatible with diffuse astrocytomas WHO grade II. The best immunohistochemical marker is glial fibrillary acidic protein, which is expressed in both tumour cells and astrocytic processes. Molecular findings typical for diffuse astrocytoma are TP53 mutations in 50 % of cases; gemistocytic astrocytomas carry TP53 mutations in > 80 % whilst combined 1p/19q deletion is rare [10]. Oligodendrogliomas are moderately cellular and typically exhibit perinuclear halos termed “fried egg” or “honey comb pattern”. Occasionally, tumour 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 oligodendrogliomas WHO grade II. There is no immunohistochemical marker specific for oligodendrogliomas.

The molecular hallmark of oligodendrogliomas is combined loss of 1p/19q occurring in 80 % of these tumours [11] (class II), whilst TP53 mutations are encountered in only 5 %. Somatic IDH1 mutations are present in 80 % of oligodendrogliomas [12, 13]. Oligoastrocytomas should be diagnosed upon detection of convincing astrocytic and oligodendroglial components, but the interobserver difference for the diagnosis of oligoastrocytomas remains high [14]. Most oligoastrocytomas carry either 1p/19q loss or TP53 mutations and there is a tendency for these aberrations to be present in both tumour compartments [15]. Up to 80 % of oligoastrocytomas carry somatic mutations in IDH1 [12, 13].

Clinical Features

Seizures are the most common presentation and may be partial or generalized. They occur in > 90 % of patients and are intractable in 50 %. Seizures are more frequently associated with cortically based tumours, particularly in frontal, temporal, and insular/parainsular location and with oligodendroglial tumours [16].

There is no clear association between severity of epilepsy and behaviour of the tumour. Focal neurological deficits are unusual, developing over many years. Raised intracranial pressure is rare in patients with supratentorial tumours and is typically seen in posterior fossa and intraventricular tumours. Intratumoural haemorrhage can occur.

Conventional and Advanced Neuroimaging

Standard MRI sequences are useful for differential diagnosis, guiding biopsy or resection, planning radiotherapy (RT), and monitoring treatment response [17]. 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 tumours, particularly oligodendrogliomas, have patchy enhancement, which remains stable over time.

The use of advanced imaging techniques can increase diagnostic accuracy [18, 19] (class II–III). Proton Magnetic Resonance Spectroscopy (MRS) measures major metabolites in tumour tissue. The typical spectrum of an 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 a considerable overlap between low- and high-grade lesions. The presence of lactate and lipids is associated with higher proliferative activity and more aggressive behaviour [20]. MRS is helpful in guiding a biopsy to an area of high-grade activity but not in longitudinal monitoring [21]. Dynamic susceptibility contrast MRI (DSC-MRI) allows for the 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 [22]; however, these

observations are limited to astrocytomas since oligodendrogliomas have significantly higher rCBV [23]. 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 the tumour grade although the correlation is not as strong as for rCBV [24]. Regarding diffusion-weighted imaging, apparent diffusion coefficient (ADC) values are lower and more variable in oligodendrogliomas compared with astrocytomas [25]. There is no correlation between ADC and choline [26]. Quantitative MRI in oligodendrogliomas with loss of heterozygosity of chromosome 1p/19q shows more heterogeneous T1- and T2-dependent signals, less distinct margins, and higher rCBV than in tumours with intact chromosomes [27, 28].

PET Imaging

PET with [18F]-fluorodeoxyglucose (FDG) is of limited value since LGGs show a low FDG uptake compared to the normal cortex. The usefulness of FDG-PET is limited to the detection of anaplastic transformation in astrocytomas [29] (class III) and to the differentiation of radiation necrosis from tumour recurrence [30] (class II). PET with 11C-methionine (MET) is most frequently used and the uptake of MET correlates with the proliferative activity of tumour cells. The background uptake with MET-PET in normal brain tissue is lower than with FDG-PET, providing good contrast with tumour uptake and delineation of LGG [31].

LGGs with an oligodendroglial component show a higher MET uptake. PET with MET is useful in differentiating LGGs from non-tumoural lesions [32] (class II), guiding stereotactic biopsies [33] (class II), defining pre-operative tumour volume [31] (class II), and monitoring response to treatment [34] (class III).

18F-fluoro-L-thymidine is a proliferation marker but does not enter the brain unless there is a blood-brain-barrier defect, therefore its usefulness seems limited [35].

More recently, the amino acid tracer 18F-fluoro-ethyl-L-tyrosine (FET) has been used for biopsy guidance and treatment planning in gliomas [36]. FET has the advantage of a longer half-life than MET, enabling tracer production in a central cyclotron and transport to other units. The experience of FET-PET is somewhat limited compared to MET-PET, but the tracer shows a very similar uptake intensity and distribution in brain tumours.

Prognostic Factors

Age > 40 years and presence of pre-operative neurological deficits are adverse prognostic factors [37–39] (class I).

Regarding conventional neuroimaging, larger tumours and tumours crossing the midline correlate with a short OS and PFS [37] (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 [40, 41]. A low CBV [42] and low uptake of 11C-MET [43] correlate with longer PFS and OS (class III). Overall, measurement of rCBV correlates with time to pro-

gression or death and can be replicated across different institutions [44].

Oligodendrogliomas have a better prognosis than astrocytomas, whereas oligoastrocytomas have an intermediate outcome (class I). 1p loss (with or without 19q loss) is a favourable prognostic factor [45–47] (class II). MGMT promoter methylation could predict a shorter time to progression in untreated patients [48], while predicting longer PFS and OS in patients receiving chemotherapy with temozolomide (TMZ) [49] (class III).

IDH1 codon 132 mutations are of major prognostic importance for glioblastomas and anaplastic gliomas (WHO grade III) [50, 51], and are also prognostic for overall survival in diffuse gliomas of WHO grade II (class III) [52].

Antiepileptic Treatment

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

Patients with no history of seizures have no benefit from prophylactic treatment [53–55] (class I).

In patients with single seizures, immediate treatment with antiepileptic drugs increases time to second seizure and first tonic-clonic seizure compared to delayed treatment, without differences with respect to quality of life or serious complications [56] (class I).

Older anticonvulsant agents, eg, carbamazepine, phenytoin, and valproate, have class-I evidence for efficacy and effectiveness in placebo-controlled trials in adults [57]. Regulatory requirements to demonstrate efficacy of newer AEDs as monotherapy differ between Europe and the United States. European regulators require a comparison with an established, optimally dosed AED, typically using a non-inferiority design, whereas in the US superiority is required to be demonstrated versus a comparator. Superiority monotherapy trials in the US have traditionally relied on inclusion of controls with a suboptimal (low-dose) comparator [58]. Newer anticonvulsants, including lamotrigine, gabapentin, oxcarbazepine, and topiramate, have shown equivalence but generally not superiority to carbamazepine, phenytoin, and valproate [59, 60]. A randomised controlled trial (RCT) of carbamazepine versus newer anticonvulsants (gabapentin, lamotrigine, oxcarbazepine, or topiramate) demonstrated longer time to treatment failure with lamotrigine [61]. Comparator studies of lamotrigine versus slow-release carbamazepine also show a slightly better cognitive profile for lamotrigine. Levetiracetam has a license for monotherapy usage in partial symptomatic epilepsy and has also demonstrated equivalence to carbamazepine in a short-duration 28-week RCT [62]. Levetiracetam can be introduced and built up quickly which may be seen as an advantage in comparison to other drugs, such as lamotrigine. Levetiracetam is also available for intravenous use, as is valproate. Studies suggest that newer anticonvulsants are as effective as the older ones and may have a better side effect profile in some areas (rash), but evidence is lacking; moreover, drug withdrawals in comparison studies are generally similar [60].

Valproate may potentiate the haematotoxicity of chemotherapy. Enzyme-inducing antiepileptic drugs (EIAED) 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 [53] (class II).

The decision to withdraw treatment should be individualised, taking into account lifestyle issues and withdrawal should be gradual and take place over approximately 6 months [63].

Status epilepticus is a medical emergency and 2–5 % of all cases of status epilepticus in most studies and 12 % in one study were due to an underlying tumour [64]. The mortality from a tumour-associated status epilepticus is up to 20 %. In patients without a tumour, a recent meta-analysis of 11 RCTs of > 2000 people demonstrated that intravenous lorazepam was superior to diazepam [65]. For benzodiazepine-refractory status epilepticus, phenytoin infusion is standard practice. For a tonic-clonic status resistant to lorazepam and phenytoin, anaesthetic doses of propofol, midazolam, or barbiturates are employed. In partial status epilepticus, the European Federation of Neurological Sciences guidelines in adults support the role of intravenous levetiracetam or intravenous valproate prior to using anaesthetics [66].

Surgery

Surgery is necessary to provide tissue for distinguishing between the histologic types, grading the malignancy, and assessing the molecular status of tumours. Moreover, there are scenarios that pose problems of differential diagnosis between LGGs and non-neoplastic lesions (demyelination, inflammation, or infection), thus histological verification is mandatory. Total resection improves seizure control, particularly in patients with a long epileptic history and insular tumours [16] (class II). The use of brain mapping techniques increases the percentage of patients in whom a total and subtotal resection is achieved and has decreased the percentage of post-operative permanent deficits [67–69] (class II). Awake surgery is a well-tolerated procedure which could enable us (1) to increase the indications of resection in eloquent areas, (2) to identify the structures crucial for brain functions, especially language, both at the cortical and subcortical levels, and (3) to optimize the extent of resection with glioma removal being performed according to functional boundaries [69] (class III). Awake surgery has increased the safety of reoperation 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 specifically addressing this question. There is a general trend for most of the recently published articles [70, 71] 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 non-enhancing LGGs implies removal of all the hyperintense regions on T2 or FLAIR images and thus can only be determined by comparing pre- and post-operative tumour volumes on MRI. This has been performed in a 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 [68, 72] (class III).

Recent studies demonstrated that delineation of truly functional areas by intraoperative mapping in high-risk patients to maximize tumour resection can dramatically improve long-term OS [73] and that awake mapping in non-eloquent areas can allow to achieve “supratotal” resection (ie, to take a margin around the tumour visible on MRI) with a significant impact on anaplastic transformation [74] (class III).

Nonetheless, even with intraoperative MRI-guided surgery, total resection is achieved in no more than 36 % of patients [75].

When complete resection is not possible for functional reasons, reoperation(s) can be considered, with an impact on OS while preserving brain functions [76, 77] (class III).

The initial report of RTOG 9802 [78], which performed observation after surgery in patients aged ≤ 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 young patients who present with an isolated seizure (medically well-controlled) and with small tumours. 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”) [79, 80], especially in oligodendrogial tumours [81]. The risk of deferring surgery includes managing a larger tumour at a later point in time which may have undergone anaplastic transformation.

Radiotherapy

Four phase-III randomized trials have been performed so far (Table 1). EORTC 22845 [71, 82] 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 tumour progression, RT has several other potential benefits, such as symptom control, particularly of epileptic seizures [83]. Two randomized trials investigated different radiation doses: the EORTC 22844 and NCCTG studies showed no advantage for higher versus lower doses [84, 85] (class I). If higher doses are used, increased toxicity is observed with a 2-year incidence of radiation necrosis of 2.5 % [84] or lower levels of functioning concerning quality of life, especially for fatigue,

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

Study	Treatment arms	n	5-year PFS		5-year OS	
			%	p	%	p
EORTC 22845	S	157	37	= 0.02	66	ns
	S + RT	154	44	= 0.02	63	ns
EORTC 22844	S + RT 45 Gy	171	47	ns	58	ns
	S + RT 59.4 Gy	172	50	ns	59	ns
NCCTG	S + RT 50.4 Gy	na	55	ns	72	ns
	S + RT 64.8 Gy	na	52	ns	64	ns
RTOG 94.02	S + RT	125	46	= 0.005	63	ns
	S + RT + PCV	126	63	= 0.005	72	ns

PFS: progression-free survival; OS: overall survival; S: surgery; RT: radiotherapy; PCV: chemotherapy (procarbazine, ccv + vincristine); na: not available; ns: not significant

insomnia, and emotional functioning [86]. RTOG 9802 compared RT alone vs RT plus PCV [87]. As $\frac{2}{3}$ 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 was 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 among patients receiving RT + PCV (67 % vs 9 %; class I). Patients treated with whole-brain RT had a higher incidence of leucoencephalopathy and cognitive deficits in comparison with patients treated with focal RT [88] (class II). In studies using modern standards of RT, less negative impact on cognition is observed [89–91] (class II), although recent data related to patients who had a neuropsychological follow-up at a mean of 12 years and were free of tumour progression suggest that those without RT maintain their cognitive status whereas patients receiving RT do worsen with regard to their attentional and executive functionings as well as information processing speed [92].

Chemotherapy

The usefulness of chemotherapy for patients progressing after surgery and RT is well-established (class II), with more data available for oligodendroglial tumours. 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 favouring TMZ in terms of better tolerability (reduced myelotoxicity) [93–97]. The response rate of enhancing tumours, possibly reflecting high-grade pathology, is higher than that of non-enhancing tumours. A clinical benefit (ie, 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 patients (ie, those with incomplete resection, persisting seizures, and progression on CT/MRI). All studies have a level-of-evidence class II [98–101]. Complete responses are generally lacking with a prevalence of minor over partial responses (overall, 53 %), and tumour volume decrease can be delayed as long as 24–30 months and persist once chemotherapy is terminated [102]. Patients more likely to respond have symptomatic/enlarging oligodendroglial tumours but mixed or astrocytic tumours may respond as well. Most patients with seizures have a clinical benefit, even in the absence of a radiological change [103, 104]. Evaluation of response on conventional MRI (T2-weighted and/or FLAIR images) is difficult in non-enhancing tumours: new criteria, proposed by the RANO International Group, have been recently proposed (June 2011) [105], and require validation in future studies. Chemotherapy with nitrosoureas can be an effective initial treatment for unresectable astrocytomas [106] (class IV). The response rate after chemotherapy is higher and duration of response is longer in patients with 1p/19q loss than in those with 1p/19q intact [101] (class III). Protracted low doses of TMZ could offer potential advantages over standard doses, especially in unmethylated tumours [107] (class III), but toxicity could be increased [108]. Pre-

operative chemotherapy could reduce tumour infiltration/extension and thus improve surgical resectability [109] (class IV).

Overall, quality of life does not seem to change over time while patients are receiving temozolomide [110] (class II).

Neurocognitive Deficits

Neurocognitive deficits in LGGs can be caused by the tumour itself, tumour-related epilepsy, treatments, and psychological distress. The cognitive decline that might ultimately lead to dementia negatively affects 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 tumour, Tucha et al [111] found neurocognitive deficits, such as impairment of executive functions and memory attention, in 91 % of patients before surgery. Similar findings corroborate the notion that neurocognitive impairments in these patients mainly originate from the tumour itself and/or confrontation with the diagnosis [112].

Patients with gliomas are prone to have more global neurocognitive deficits, unlike patients with stroke who tend to have site-specific deficits. Patients with a tumour in the dominant hemisphere have more memory problems and poorer attention, verbal fluency, and verbal learning than those with non-dominant tumours [113] and have a smaller chance to normalize following surgery [114]. Due to the reduction of tumour mass, surgery is beneficial for neurocognitive functioning (class II). Long-term improvement of verbal memory compared to preoperative assessment has been reported after low-grade glioma resections in frontal premotor and anterior temporal areas [115], usually after transient focal neurocognitive deficits [116].

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 [92] demonstrated that there is a relation between neurocognitive status and cerebral atrophy and leucoencephalopathy, and radiological abnormalities increase only in the irradiated group. Neurocognitive side effects of AEDs can add to previous damage by surgery or RT (class II). Older AEDs (phenobarbitone, phenytoin, carbamazepine, and valproic acid) can decrease neurocognitive functioning by impairing attention and memory [117]. Among newer AEDs, gabapentin, lamotrigine, and levetiracetam have fewer adverse neurocognitive effects while topiramate is associated with the greatest risk for neurocognitive impairment [118]. A randomized trial showed that cognitive rehabilitation has a salutary effect on both short- and long-term cognitive complaints and mental fatigue [119] (class II).

Recommendations

- Astrocytomas, oligodendrogliomas, and oligoastrocytomas are diagnosed using morphological criteria according to the WHO classification (level A).

- Immunohistochemical analysis with IDH1-R132H mutation-specific antibody H09 distinctly separates the vast majority of astrocytomas, oligodendrogliomas, and oligoastrocytomas from other lower-grade glioma variants and greatly assists in the diagnosis of these tumours in samples deriving from the tumour periphery.
- Combined loss of 1p/19q is a marker in favour of the diagnosis of oligodendrogliomas or oligoastrocytomas (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 physicians decide differently (good practice point).
- MRS is useful for the differentiation of LGG from non-tumoural lesions, pre-operative definition of extent, and guiding stereotactic biopsies (level C).
- DSC-MRI can be employed during 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 tumour recurrence (level B).
- PET with MET is useful for the differentiation of LGG from non-tumoural 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, co-medication, comorbidity, and patient preferences (good practice point).
- In patients requiring 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 tumour mass whenever possible while minimizing post-operative morbidity (level B).
- Identification of the eloquent cerebral areas, which have to be preserved during surgery, is performed by means of pre-operative neuroimaging modalities (functional MRI, fibre tracking), and intraoperative brain mapping techniques (level B).
- Awake surgery could improve the results by delaying the risk of anaplastic transformation and by increasing long-term survival (level C).
- Reoperation could improve survival while preserving brain function and might be more frequently considered (level C).
- When surgery is not feasible (because of tumour location, extension, or comorbidities), a biopsy (either stereotactic or open) should be performed to obtain a histological diagnosis (good practice point).
- For patients with unfavourable 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 be preferred (level B).
- Younger patients (< 40 years of age) with (nearly) complete resection and tumours with an oligodendroglial component

have a more favourable prognosis and can be observed after surgery (level B), but close follow-up is mandatory (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 tumours after surgery or unresectable tumours to delay the risk of late neurotoxicity from large-field RT (especially when 1p/19q loss is present) and to improve seizure control (level B).
- Neuropsychological tests at diagnosis and during follow-up can be useful, being selected according to the needs of the clinical setting (good practice point). They 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).

■ Conflict of Interest

RS, BGB, LB, HD, MF, WG, RG, FG, KHX, MK, BM, JR, TS, AS, and WW have no conflict of interest to declare.

AvD: Under a licensing agreement between DIANOVA GmbH, Hamburg, Germany, and the German Cancer Research Center, Andreas von Deimling is entitled to a share of royalties received by the German Cancer Research Center on the sales of H09 antibody. The terms of this arrangement are being managed by the German Cancer Research Center in accordance with its conflict of interest policies.

RS: Scientific advisory boards for Roche, MSD/Merck & Co, Merck KGaA, MDxHealth; principle investigator for research including Merck Serono and MSD/Merck & Co.

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