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# Neurocognitive functioning in adult WHO grade II gliomas: impact of old and new treatment modalities

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**In the treatment of patients with low-grade glioma, there still is controversy on how surgical intervention, radiation therapy, and chemotherapy contribute to an ameliorated progression-free survival, overall survival, and treatment-related neurotoxicity. With the ongoing changes in treatment options for these patients, neurocognitive functioning is an increasingly important outcome measure, because neurocognitive impairments can have a large impact on self-care, social and professional functioning, and consequently, health-related quality of life. Many factors contribute to neurocognitive outcome, such as direct and indirect tumor effects, seizures, medication, and oncological treatment. Although the role of radiotherapy has been studied extensively, the adverse effects on neurocognitive function of other treatment-related factors remain elusive. This holds for both resective surgery, in which the use of intraoperative stimulation mapping has a high potential benefit concerning survival and patient functioning, and the use of chemotherapy that might have some interesting new applications, such as the facilitation of total resection for initially primary or recurrent diffuse low-grade glioma tumors. This article will discuss these treatment options in patients with low-grade glioma and their potential effects on neurocognitive functioning.**

**Keywords:** chemotherapy, cognition, low-grade gliomas, radiotherapy, surgery.

World Health Organization (WHO) grade II diffuse gliomas, commonly referred as low-grade gliomas (LGGs), are generally slowly growing, locally infiltrative tumors in young or middle-aged adults.[1,2] Although some patients survive for decades,[3] these tumors invariably progress to the more aggressive, anaplastic gliomas or secondary glioblastomas,[4] especially in older patients.[5] The prognosis of a primary or secondary glioblastomas is equally poor, when corrected for age at diagnosis.[4]

With regard to treatment options for these tumors, relatively little has changed since the position article by Cairncross and Laperriere in 1989.[6] They state that:

"*We believe there is insufficient evidence to justify the aggressive treatment (ie, surgery, radiotherapy, and chemotherapy) of all low-grade gliomas of the cerebral hemispheres. The indolent nature of these tumors makes it difficult, in the absence of a properly controlled clinical trial, to evaluate the true effectiveness of intervention. Conclusions and recommendations based solely on the analysis of retrospective data are suspect. Further, the indolent course of these neoplasms raises the possibility that the potential benefits of treatment will, in the long run, be offset by treatment-related toxic effects.*"

Although a recent article, for instance, suggests that a nihilistic approach to surgical treatment of gliomas might be based on overgeneralizations of data from older studies,[7] management of LGG is still controversial. This controversy mainly concerns the question of whether in young patients with limited disease and symptoms an aggressive treatment approach including immediate surgical intervention should be pursued or that a delayed intervention is expected to significantly contribute to an ameliorated progression-free survival, overall survival, and treatment-related neurotoxicity. The same holds for the timing of radiation therapy, either as adjuvant treatment immediately following surgery or as delayed treatment until there is clinical or radiological evidence of recurrent or progressive disease. The decision as to whether a patient with LGG should receive resection, radiotherapy, or chemotherapy is also based on a number of other factors, including age, performance status, location of tumor, and evidently, patient preference. Because LGGs are such a heterogeneous group of tumors with variable

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natural histories, the risks and benefits of each of the 3 therapies must be carefully balanced with the data available from limited prospective studies. With 5-year and 10-year progression-free rates of 50% and 12%, respectively, for supratentorial low-grade astrocytomas, low-grade oligodendrogliomas, and mixed gliomas,[8] and a median better survival of 16.7 years for the latter 2 groups,[9] patients with LGG can survive in a stable state for several years after diagnosis. The long-term effects of the disease and its treatment on neurocognitive functioning and, thus, on health-related quality of life in these long-term survivors are especially salient.

After discussing the rationale for the assessment of neurocognitive functioning in patients with brain tumor, we will discuss treatment options in patients with LGG (surgery, radiotherapy, chemotherapy, antiepileptics, and corticosteroids) and their potential effects on neurocognitive functioning.

## Rationale for the Assessment of Cognitive Functioning

In addition to seizures, patients with LGG may, to a lesser extent, present with headaches, focal neurologic signs, and neurocognitive impairment. Cognitive deficits associated with brain tumors can be induced by compression of normal brain, either directly or indirectly, by reactive edema. In addition to compression, the invasion of parenchymal glial tumors directly into functional brain regions or indirectly by disconnection of structures can further contribute to neurocognitive deficits.[10–12] Although an increasing number of studies indicate that primary brain tumors and their treatment are often associated with neurocognitive deficits, there is still limited knowledge about its incidence, nature, severity, and causes.

Because most patients with glioma cannot be cured, palliation of symptoms and maintenance or improvement of physical functioning and health-related quality of life are important goals of treatment. Evaluation of treatment in these patients should thus not only focus on progression-free or overall survival, but should also aim at functional outcome and at adverse treatment effects on the normal brain. Functional outcome refers to neurological, cognitive, professional, and social performance of an individual, usually abstracted as health-related quality of life. With regard to the effects of tumor and treatment on the normal brain, neurocognitive functioning is a useful outcome measure for patients with brain tumor, because neurocognitive deficits, even mild, may negatively affect health-related quality of life,[13] professional reintegration, interpersonal relationships, and leisure activities.

## Factors Affecting Neurocognitive Functioning

Many potential factors contribute to neurocognitive functioning, including the tumor, distant mechanical effects on the normal brain by the tumor, tumor-related epilepsy, and its treatment, and psychological distress and the premorbid level of neurocognitive functioning. In attempting to determine the isolated effect of any treatment on cognition, the multifactorial processes involved should be recognized.

### *Surgery*

After radiological diagnosis, resective surgery that aims at prolonging survival by maximization of tumor removal while minimizing morbidity is usually the first of several treatment options for patients with LGG. Mainly because of the lack of randomized trials comparing surgery with a conservative approach that delays surgery until tumor progression, there remains controversy about the role of surgery in the initial treatment of patients with LGG. On the basis of reviews of the literature that have found an impressive trend toward improved survival,[14–16] many neurosurgeons favor a maximal safe resection at the time of diagnosis. However, there is a bias in these observations, because the surgical results are compared with those in patients in whom it was not possible to do a maximal resection. Considering the extent of surgery, retrospective evidence supports a more extensive resection rather than simple debulking in patients undergoing resection.[16–18] In a recent meta-analysis on the usefulness of intraoperative stimulation mapping the outcomes of 90 reports published from 1990 through 2010, 8091 adult patients who had undergone resective surgery for supratentorial infiltrative glioma, with or without intraoperative stimulation mapping, were analyzed.[19] The authors found intraoperative stimulation mapping in infiltrative glioma resections to be associated with fewer late severe neurologic deficits and more extensive resection and to involve eloquent locations more frequently. From these findings, they conclude that intraoperative stimulation mapping should be universally implemented as standard of care for glioma surgery that aims at achieving a maximal extent of tumor resection. In patients with small, minimally symptomatic LGGs, a more conservative approach is usually considered.[9,20,21] However, this approach in which aggressive surgery and radiotherapy are delayed until there is radiological evidence of tumor growth, intractable seizures, progressive neurologic impairment, or transformation to a high-grade glioma (HGG) is based on older studies not including intraoperative stimulation mapping as a standard element adjunct to surgical procedures.

Because of the limited number of studies including pre- and postoperative neurocognitive evaluations, the true incidence and extent of neurocognitive dysfunction related to resective brain tumor surgery is unknown. However, several interesting observations have been made in smaller observational cohort studies. Although reductions in neurocognitive functioning may originate from the tumor and/or potentially from confrontation with the diagnosis,[22] surgery may also affect functional outcome in several unpredictable directions.

Improvement in neurocognitive functioning has been observed in several studies after brain tumor resection. Long-term improvement of verbal memory, compared with preoperative assessment, has been reported after LGG resections in frontal premotor and anterior temporal areas,[23–25] usually after a transient immediate postoperative worsening. Stable neurocognitive performance was observed after brain tumor resection in some studies. For instance, patients with tumors of the third ventricle demonstrated neurocognitive impairment in memory, executive functioning, and fine manual speed prior to surgery, without worsening of cognition after surgical removal.[26,27] Of several executive tasks, only letter fluency performance was impaired in patients after glioma surgery in left frontal locations, compared with right frontal and posterior lesions.[28] Visuospatial processing in patients after resective glioma surgery in left and right, frontal and parietal locations was comparable to that of normal subjects, according to one study,[29] and impaired spatial and positional memory processing was demonstrated in patients with tumors in the right posterior parietal cortex or in the frontal cortex in other studies.[30,31] Deterioration in neurocognitive functioning after resection of parenchymal frontal or precentral tumors[24,32] was mostly associated with minor attentional deficits. Resection of the right prefrontal cortex rather than the left was associated with a selective attentional impairment, as evidenced by the Stroop test performance.[33] After resection of the supplementary motor area, patients exhibited impaired procedural learning and agraphia.[34,35] Subsets of patients with resections involving the frontal lobe demonstrated a variety of deficits. For instance, impaired sequence ordering of novel material was observed particularly in right-sided lesions, whereas recognition memory was unaffected,[36] and planning and executive impairment, irrespective of side, site, and size.[37,38] Furthermore, severe executive deficits in a reward learning task were observed in patients after bilateral fronto-orbital resections for various tumor types[39] and impaired virtual planning of real life activities after resections in the left and right prefrontal cortex, which could not be explained by memory deficits.[40,41] Increases in T2-weighted hyperintensities during the early period following surgery are consistent with these postsurgical neurocognitive defects.[42]

Deterioration of neurocognitive functioning or lack of improvement following surgery of LGG in or near eloquent brain areas might theoretically be adverted by performing awake craniotomies with intraoperative electrical mapping.[43–45] Theoretically, because sound data on neurocognitive outcome associated with this procedure are lacking, delineation of true functional and nonfunctional areas by intraoperative mapping in high-risk patients to maximize tumor resection can dramatically improve long-term survival[46] A review that questioned whether it is actually necessary to leave a security margin around eloquent structures found that a no-margin technique and the repetition of both cortical and subcortical stimulation to preserve eloquent cortex and the white matter tracts optimize the extent of resection.[47] Some authors even demonstrate that favorable outcome of LGG in noneloquent areas in the left dominant hemisphere can be further enhanced by a supratotal resection (ie, with a resection margin beyond radiological abnormalities).[48] Evidently, sufficiently powered follow-up studies are needed to demonstrate that these relatively new principles of tumor surgery also benefit patients in terms of neurocognitive functioning and health-related quality of life.

### *Radiotherapy*

Radiotherapy can be used after surgery to treat residual tumor mass. Controversies in the use of radiotherapy for LGGs concern the optimal timing and radiation dose. EORTC trial 22845 randomized 311 patients with WHO grade II astrocytoma or oligodendroglioma to receive immediate or delayed radiotherapy and found that, although immediate postoperative radiotherapy significantly prolonged progression-free survival, it did not enhance overall survival.[49] Of interest, better seizure control was observed in patients receiving postoperative radiotherapy. Patients with greater risk of rapid tumor progression may receive radiotherapy immediately following surgery.[5,14,15] The lack of survival benefit with immediate adjuvant radiotherapy has been used as a justification to postpone radiation until disease progression, thereby postponing or avoiding potential radiation-induced encephalopathy.

Cognitive deficits are the hallmark of late-delayed encephalopathy,[50] which is an irreversible and progressive complication that may follow radiotherapy by several months to many years through vascular injury, causing ischemia of surrounding tissue and demyelination, local radionecrosis, and cerebral atrophy. The severity of neurocognitive deficits ranges from mild or moderate to dementia with progressive mental slowing and deficits in attention and memory, occuring in at least 12% of patients who receive radiotherapy.[51] In these cases, MRI shows diffuse atrophy with ventricular enlargement and severe confluent white matter abnormalities.[52] Nonspecific diffuse white matter changes, demyelination, and cerebral atrophy can be found in nearly all patients receiving high-dose volumes[53] and may be related to neurocognitive status.[54,55] It should be noted, however, that increases in MRI hyperintensities during the early period following adjuvant radiotherapy for LGG are likely not related to radiation effects, but rather to surgical procedures.[42] These hyperintensities are consistent with postsurgical neurocognitive defects.

Although short-term follow-up studies show limited or transient effects of radiotherapy,[11] a number of studies in long-term survivors of LGG (ie, $>5$ years following radiotherapy) concluded that radiotherapy in these patients poses a significant risk of long-term leukoencephalopathy and neurocognitive impairment. Surma-Aho et al.[56] reported that patients with LGG with a follow-up of 7 years had more neurocognitive deficits after early radiotherapy than did control subjects without radiotherapy. Moreover, leukoencephalopathy

was more severe in the group with postoperative irradiation. A study among LGG survivors 6 years after diagnosis and initial treatment showed that the use of radiotherapy was associated with poor neurocognitive function on only a few tests and not restricted to one specific neurocognitive domain.[57] This finding suggests that neurocognitive deficits in these patients should not be attributed to radiotherapy, but rather to the tumor or other treatment factors, including epilepsy.[58] Serious memory deficits, however, are still to be expected when fraction doses exceed 2 Gy.[57] A follow-up of the Klein et al. 2002 study[57] demonstrated that, regardless of fraction dose, all tumor progression-free patients with LGG who had irradiation had neurocognitive deterioration 13 years after radiotherapy, whereas all patients without irradiation remained stable.[54] Taken together, early neurocognitive dysfunction in patients with LGG is most likely the result of the tumor. However, in long-term LGG survivors, radiation may cause some impairment, even when the radiotherapy is given focally and fraction size is limited.

### *Chemotherapy*

The results from recent studies on the effects of tumor resection in eloquent areas using intraoperative stimulation mapping are promising. Unfortunately, a large number of LGGs with a diffuse growth pattern still cannot be removed without substantial compromise of healthy brain tissue, thus preventing satisfactory oncological control. In this group of patients, the use of chemotherapy can be considered. Results from observational studies indicate that chemotherapy may be effective in patients with oligodendroglial tumors, but the role of chemotherapy in diffuse low-grade astrocytomas is less clear.[59] Chemotherapy can reduce volume and infiltration of LGG[60–67] and can further facilitate total resection for initially primary or recurrent diffuse tumors,[68,69] with preservation of quality of life and probably also of neurocognitive functioning.[70]

Chemotherapy-related neurotoxicity to the central nervous system may be increased by intra-arterial administration, especially in combination with osmotic blood-brain barrier disruption, meant to increase the local concentration of chemotherapy in the brain.[71,72] Modern delivery techniques might prevent some of the neurotoxicity, however.[73] Neurotoxicity may also be increased by chemotherapy given after, or even during, radiotherapy.[74,75] In these cases, the chemotherapeutic drugs also reach higher concentrations in normal brain tissue because of leakage of the blood-brain barrier caused by radiotherapy. In this way, radiation may potentiate the toxic effects of chemotherapy.[76] Finally, intrathecal chemotherapy, compared with systemically applied chemotherapy, has a higher likelihood of causing central nervous system toxicity.[74] The increasd risk of cognitive deficits after chemotherapy in combination with the apolipoprotein E4 alleles also suggests a genetic role in chemotherapy-induced cognitive decline.[77]

Neurocognitive functioning in patients with LGG was studied as secondary outcome measure in EORTC phase III study 22033–26033, in which after stratification for genetic 1p loss, primary temozolomide therapy was compared with radiotherapy.[78] Although this study is closed for recruitment, data are not yet available. Because, apart from EORTC study 22033–26033, none of the aforementioned clinical trials involving patients with LGG assessed neurocognitive functioning as secondary outcome measure, potential effects of chemotherapy on neurocognitive functioning should be deduced with great caution from the few studies involving patients with HGG. Although phase II clinical trials using bevacizumab therapy in both newly diagnosed and recurrent HGG yield promising results, bevacizumab only shows some effectiveness in the pediatric LGG population.[79,80] In a recent phase II study that evaluated neurocognitive changes over time in 167 patients with recurrent glioblastoma treated with bevacizumab, most patients with an objective response or progression-free survival $>6$ months had poorer neurocognitive functioning, compared with the general population at baseline, and had improved or stable neurocognitive functioning at the time of response or at the 6-month assessment.[81] With regard to the use of temozolomide therapy, a small study showed that, before treatment, the majority of patients with glioblastoma show clear-cut deficits in neurocognitive functioning. During the first 6 months of their disease, however, patients with progression-free glioblastoma who undergo radiotherapy plus concomitant and adjuvant temozolomide treatment do not deteriorate in neurocognitive functioning.[82] A phase II one-arm study in patients with previously untreated anaplastic astrocytoma, oligoastrocytoma, or oligodendroglioma evaluated the long-term efficacy and safety of accelerated fractionated radiotherapy combined with intravenous carboplatin.[83] After radiotherapy, patients received procarbazine, lomustine (CCNU), and vincristine (PCV) for 1 year or until tumor progression. Serious clinical neurologic deterioration and/or dementia requiring full-time caregiver attention was observed in 10% of patients.

### *Antiepileptics*

Seizures occur as a presenting symptom in approximately 50% of LGG cases and have a prevalence $>80\%$.[84] The seizures originate not from the tumor but from adjacent brain tissue.[85,86] Nevertheless, both radiation therapy[49,87] and lesionectomy[88,89] may significantly reduce or even eliminate medically refractory seizures in patients with LGG. Furthermore, patients with WHO grade II diffuse astrocytomas often experience neuropsychological and psychological problems that are aggravated by epilepsy and its treatment.[57,58,90,91]

Cognitive adverse effects of antiepileptic drugs can add to neurocognitive decline because of tumor effects, previous surgery, or radiotherapy, and therefore appropriate choice and dose of antiepileptic drug is crucial. The classical antiepileptic drugs (phenytoin,

carbamazepine, and valproic acid) are known to decrease neurocognitive functioning.[92,93] Of importance, these drugs may also have pharmacological interactions with chemotherapy[94,95] and, thus, potentially affect survival. These drugs may result in impaired attention and neurocognitive slowing, which can subsequently have effects on memory by reducing the efficiency of encoding and retrieval.[93] The importance of the classical antiepileptic drugs as a risk factor for neurocognitive deficits has been reported in a study on stable disease in long-term LGG survivors[58] in which neurocognitive deficits were significantly related to the use of antiepileptic drugs. Because patients in this study who took antiepileptic drugs had neurocognitive impairment even in the absence of seizures, the use of drugs primarily affects neurocognitive function. Moreover, AED use in patients with LGG may be associated with highly elevated levels of fatigue,[96] which is also associated with poorer neurocognitive outcome. Several new generation AEDs, such as oxcarbazepine[97] and levetiracetam as add-on therapy,[98] appear to have fewer adverse neurocognitive effects than the classical agents. Of the newer agents, topiramate is associated with the greatest risk of neurocognitive impairment, although this risk is decreased with slow titration and low target doses.[99,100] It appears to be safe to switch patients from phenytoin to levetiracetam monotherapy after craniotomy for supratentorial glioma.[101]

*Corticosteroids*

The potentially neurotoxic effects of corticosteroids are often misdiagnosed and underestimated,[102] and corticosteroids may induce behavioral, psychic, and neurocognitive disturbances because of functional and, over time, structural alterations in specific brain target areas. Corticosteroids may cause mood disturbances, psychosis, and neurocognitive deficits, particularly in declarative memory performance. Steroid dementia is a reversible cause of neurocognitive deficits even in the absence of psychosis. Cognitive deficits may originate from neurotoxic effects on both the hippocampal and the prefrontal areas[103] and have been shown to be reversible with dose reduction or discontinuation of treatment.[104]

## Assessment of Neurocognitive Functioning

Formal neurocognitive examination is time consuming and may fatigue patients with brain tumors, thereby biasing results. Less time-consuming alternatives, such as the Mini Mental State Examination (MMSE), may underestimate the proportion of patients with actual cognitive decline, and important but small changes in cognition can be missed. However, the MMSE appears to be sensitive enough to detect cognitive deficits associated with tumor progression.[105]

Because a combination of cortical and subcortical lesions, epilepsy, surgery, radiotherapy, AEDs, corticosteroids, and psychological distress contributes to neurocognitive dysfunctioning in an individually unpredictable way, it is most pragmatic to choose a core testing battery that gauges a broad range of neurocognitive functions. The test battery that meets important psychometric criteria (i.e. standardized materials and administration procedures, published normative data, moderate to high test-retest reliability, a relatively brief administration time [30–40 min], suitable to monitor changes over time) has successfully been used and is still being used in a number of EORTC, NCCTG, NCI-C, RTOG, MRC, and HUB multisite clinical trials, and it has been shown that neurocognitive functioning has independent prognostic significance in patients with LGG.[106] Moreover, neurocognitive deterioration indicates tumor progression before signs of disease recurrence are evident on CT or MRI.[107–109] The tests were as follows: memory, Hopkins Verbal Learning Test;[110] verbal fluency, Controlled Oral Word Association;[111] visual-motor scanning speed, Trail Making Test Part A;[112] and executive function, Trail Making Test Part B.[112]

Those interested in a more extensive discussion on bedside neurocognitive testing in patients with brain tumor and indications for neuropsychological consultation are referred to the online ECCO-initiated library of ACOE CME accredited oncology instruction videos by accessing http://www.ecco-org.eu/oncovideos/Neuro-Oncology.aspx.[113].

## Conclusion

With the development in treatment options for patients with LGG, neurocognitive functioning is an increasingly important outcome measure, because neurocognitive impairments can have a large impact on self-care, social and professional functioning, and consequently, on health-related quality of life. Many factors contribute to neurocognitive outcome, such as direct and indirect tumor effects, seizures, medication, and oncological treatment. Although the role of radiotherapy has been studied extensively, the adverse effects on neurocognitive function of other tumor and treatment-related factors remain elusive. This not only holds for resective surgery, in which the use of intraoperative stimulation mapping has a high potential benefit concerning survival and patient functioning, but also for the use of chemotherapy. Although chemotherapy might have some interesting new applications, such as the facilitation of total resection for initially primary or recurrent diffuse LGG tumors, systematic studies are needed to fully understand the effects of chemotherapy on neurocognitive function. Likewise, concerted action into studying the costs and benefits of presurgical, intrasurgical, and postsurgical neurocognitive assessments related to outcome in these patients is warranted.

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