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REVIEW ARTICLE

Diffuse low-grade glioma: a review on the new molecular classification, natural history and current management strategies

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Abstract The management of diffuse supratentorial WHO grade II glioma remains a challenge because of the infiltrative nature of the tumor, which precludes curative therapy after total or even supratotal resection. When possible, functional-guided resection is the preferred initial treatment. Total and subtotal resections correlate with increased overall survival. *High-risk* patients (age >40, partial resection), especially IDH-mutated and 1p19q-codeleted oligodendroglial lesions, benefit from surgery plus adjuvant chemoradiation. Under the new 2016 WHO brain tumor classification, which now incorporates molecular parameters, all diffusely infiltrating gliomas are grouped together since they share specific genetic mutations and prognostic factors. Although low-grade gliomas cannot be regarded as *benign* tumors, large observational studies have shown that median survival can actually be doubled if an early, aggressive, multi-stage and personalized therapy is applied, as compared to prior *wait-and-see* policy series. Patients need an honest long-term therapeutic strategy that should ideally anticipate neurological, cognitive and histopathologic worsening.

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Introduction

Low-grade glioma (LGG) is a group of heterogeneous neuroepithelial tumors arising from supporting glial cells of the central nervous system. The World Health Organization (WHO) has traditionally classified gliomas in four grades, according to histopathologic features like atypia, anaplasia, mitotic activity, microvascular proliferation and the presence of necrosis [1]. Classically, LGGs consisted of WHO grade I tumors, lacking all theses features, and WHO grade II tumors, presenting only atypia [2]. However, these two sub-categories have been shown to be clinically and molecularly very different [3]. WHO grade I LGGs are truly *benign* tumors that can be cured with surgical removal. Instead, WHO grade II LGGs are diffuse and infiltrative intracerebral lesions rarely curable [4]. WHO grade II gliomas include astrocytoma, oligodendroglioma and mixed oligoastrocytoma [1]. They are slowly progressing conditions that carry the potential for malignant transformation and almost invariably progress to a high-grade glioma [4, 5].

In 2014, the *International Society of Neuropathology* gathered in the Netherlands and established guidelines for incorporating molecular parameters into the classification of brain tumor entities [6]. This combined histopathologic and genotypic diagnostic classification is the greatest change introduced between the 2007 and the 2016 WHO classification updates. In the new classification, all diffusely infiltrating gliomas are grouped together regardless

of the cell of origin, astrocytes or oligodendrocytes, since they all share specific genetic mutations and prognostic factors [7].

In this review we will focus on supratentorial WHO grade II gliomas of the adult, which account for 15% of all gliomas [1, 4]. These tumors are also known as *diffuse* LGGs because of their infiltrative and invasive nature. LGG has been defined by Duffau as "*…a progressive, invasive and chronic disease of the central nervous system*" [4]. These tumors seem to grow slow but continuously over time, usually along the white matter fibers of the hemispheres [4, 5]. Once malignant differentiation occurs, they behave as WHO grade III or IV tumors and a rapid neurological deterioration is expected before death [5]. Currently, the mean survival of LGGs is generally less than 10 years from diagnosis [3–5].

The impact on progression-free survival (PFS), overall survival (OS) and quality of life (QOL) of the various treatment options for LGGs is controversial and under research. This condition has been traditionally considered a chronic and somehow *benign* disease, with no or little impact on the QOL of patients, other than the need for seizure control. A *wait-and-see* policy has been classically advocated, largely because LGGs usually affect young adults without major neurological defects, presenting with tumors that tend to grow in eloquent areas of the brain where even biopsy was considered dangerous [4]. The classical order of therapies included complete or partial resection, or just biopsy, followed by radiation therapy in cases of incomplete resection, and finally followed by chemotherapy at the time of recurrence or progression.

This treatment paradigm is currently being abandoned towards a more aggressive and individualized approach applicable from the very initial stages [3, 4]. The ultimate goal of therapy is to avoid malignant transformation of the tumor, which is the event that limits survival [8]. This modern approach promotes early surgical removal, maximize tumor tissue resection, repeat operations as needed, delay radiation therapy as much as possible and prescribe chemotherapy according to specific molecular markers of the tumor. Adjuncts to surgery like preoperative fiber-tract image-based planning, intraoperative electro stimulation brain mapping or performing craniotomy with the patient awake, help to improve the rate of complete resection, which in turn minimizes the possibility of malignant transformation and seems to improve OS [4, 8, 9].

In the last decade, some new concepts have arisen relating the management of LGGs. These include molecular and genotypic diagnosis [7], neuroplasticity [10], functional-guided resection [8, 11] and the notion of *supratotal* resection [12, 13]. It is known that glial tumor cells extend even 20 mm beyond the actual limits of the tumor visible in T2/FLAIR MR images. Complete tumor resection including these margins and beyond (that is, supratotal) minimizes residual tumor load. Although not curative, supratotal resection performed in non-eloquent areas prevents or delays malignant transformation. The clinical implications of these new issues have contributed to a better understanding of the biological behavior of LGGs. When confronting a patient with a LGG, it is crucial to balance the natural history of the disease against the actual risks and the impact on survival and QOL of the various treatment modalities applicable in every particular case.

This paper reviews the implications of the new WHO classification of LGGs, the natural history of supratentorial diffuse LGGs of the adult and the impact of therapies on survival and QOL under the current philosophy of earlier, multi-stage, comprehensive and personalized treatment.

New classification of LGGs

The 2016 WHO Classification of Tumors of the Central Nervous System [7] is an update of the previous classification from 2007 that includes, for the first time, molecular and genetic parameters, in addition to the previous well-known histopathologic features, to define and sub-categorize brain tumor entities. This is a major breakthrough in pathological diagnosis that specifically restructures the diagnosis of diffuse gliomas. Historically, it was not uncommon that *mixed* oligoastrocytic tumors were frequently diagnosed at some centers while they were rarely encountered at some others [14]. The combination of histologic and genotypic parameters adds objectivity and inter-observer concordance, which results in improved diagnostic accuracy [15]. In fact, the limiting factor for this new classification method is the actual availability and choice of genotyping or surrogate genotyping assays. Tumors that do not fit into the newly defined categories or those not being tested for molecular parameters are now classified under a *NOS* (*Not Otherwise Specified*) designation [7].

Under the 2016 WHO classification, *diffuse gliomas* are now grouped together instead of being subcategorized according to the cell type of origin. The reason is that they share growth pattern, clinical behavior, genetic mutations and prognostic markers. Therefore, diffuse gliomas now include WHO grade II and III astrocytomas and oligodendrogliomas, grade IV glioblastomas, midline gliomas and diffuse gliomas of the childhood [7]. *Gliomatosis cerebri* is no longer a distinct subcategory and it is now considered just a pattern of growth found in many glial tumors [16].

The WHO grade II diffuse astrocytomas and grade III anaplastic astrocytomas are now divided into three

categories each: *IDH-mutant* (the great majority), *IDH-wildtype* (very rare) and NOS. Some studies suggest that the prognostic differences between IDH-mutant WHO grade II diffuse astrocytomas and IDH-mutant WHO grade III anaplastic astrocytomas are not as marked as previously believed [17, 18]. Nevertheless, the prognosis of IDH-mutant cases seems to be more favorable than IDH-wild-type for both grade II and grade III astrocytomas [7]. Additional changes of the 2016 WHO classification include the deletion of two diffuse astrocytoma variants: *protoplasmic* astrocytoma and *fibrillary* astrocytoma (which largely overlaps with the standard diffuse astrocytoma). However, the *gemistocytic* astrocytoma remains as an IDH-mutant distinct variant [7]. The diagnosis of diffuse astrocytoma is based on the confirmation of the mutant IDH status plus ATRX loss and TP53 mutation, both characteristic although not required for diagnosis.

WHO grade II oligodendrogliomas and grade III anaplastic oligodendrogliomas both exhibit IDH gene family mutations and 1p/19p codeletion, but no ATRX and TP53 mutations [7]. This fact permits an easy differentiation from astrocytomas. However, the diagnosis of *oligoastrocytoma* (mixed tumor) is strongly discouraged by the 2016 WHO classification, and it is actually assigned to a NOS designation, since almost every mixed phenotypic tumor can be classified either as astrocytic or oligodendrocytic using genetic testing [19]. It must be noted that, under this new classification, grade II oligodendroglioma may progress to grade III oligodendroglioma but does not lead to grade IV glioblastoma, which always seems to derive from an astrocytic precursor [7].

In summary, WHO grade II diffuse astrocytomas and oligodendrogliomas are now considered nosologically more similar between them than are diffuse astrocytomas and pilocytic (WHO grade I) astrocytomas; both IDH-mutant grade II and grade III astrocytomas may not have very distinct prognosis (the so-called *intermediate diffuse glioma* proposed by Rigau [20], a continuum between grade II and grade III glioma); diffuse astrocytomas can be easily distinguished from oligodendrogliomas according to their ATRX and TP53 mutation status and the presence of 1p/19q codeletion; and mixed oligoastrocytomas is a *NOS category* since genetic testing is usually capable of differentiating both lineages. Table 1 provides a summary of the 2016 WHO classification of grade II tumors and some comments on their relevant biological markers.

Natural history of diffuse LGGs

Low-grade glioma patients typically exhibit three clinical stages [3–5]: *pre-symptomatic*, a period of unknown duration in which the tumor slowly infiltrates the brain but the patient remains largely asymptomatic; *symptomatic*, a period of 7 years on average in which the patient usually presents epilepsy and perhaps subtle cognitive disorders, generally compatible with a nearly normal social and occupational life; and finally *malignant transformation*, a period of about 2–3 years in which the tumor accelerates its growth and dedifferentiates to a WHO grade III or IV glioma. In this phase, patients deteriorate their neurological functions (epilepsy usually worsens and new neurological defects ensue) until death occurs, despite of treatment. Although survival is affected by some prognostic factors (see Table 2), average OS from diagnosis is 5–6 years, ranging from 3 to 10 years [4]. According to these figures, this condition may not be regarded as a *benign* lesion.

Historically, patients harboring LGGs were commonly offered observation of the lesion (the *wait-and-see* policy), or just a biopsy to rule out a malignant tumor, as well as medication for epilepsy, which is present in at least 90% of the cases [4, 21]. The majority of LGGs occur in young adults without major neurological defects who enjoy near normal life for some years [3]. However, some cognitive disorders can be ascertained in up to 90% of the patients if specific neurocognitive tests are applied [22, 23]. These defects in executive functions, memory, emotion or concentration can be attributed to the tumor infiltration of subcortical white matter tracts and connections [22], to epilepsy, to antiepileptic medication [24], to radiation therapy [25] or to psychological factors [26]. However, marked neurological defects are not expected in LGG patients even though they frequently grow in eloquent areas of the brain [4].

According to some studies, LGGs grow continuously over time at a steady rate of about 4–5 mm per year [27]. There is an inverse correlation between growth rate and survival: tumors growing >8 mm/year exhibit an overall survival of about 5 years from diagnosis [28]. Some authors advocate for repeating neuroimaging 3 months after the initial diagnostic MRI in order to measure the growth rate of the tumor, before any treatment option is offered [4, 28]. This baseline measure can also be useful for evaluating the response to therapies. Since LGGs are very irregular in shape, the ideal method to estimate the tumor size and growth is a computerized 3D segmentation measurement based on the addition of *FLAIR*-affected areas in axial cuts of the MRI [4]. Other less accurate methods like a visual estimation or the *axbxc/2* rule (using the largest diameters) are subjective, less accurate and not advisable [3]. As tumor cells migrate along the white matter tracts of the brain and invade important subcortical connecting structures, a certain degree of cognitive dysfunction is expected due to a disconnecting syndrome. Finally, malignant transformation is always expected leading to death.

Table 1 New 2016 WHO classification of WHO *grade II* glial tumors and their relevant biological markers [7]

Diffuse astrocytic and oligodendroglial tumors	Characteristics
Diffuse astrocytoma, IDH-mutant	The *Fibrillary* variant is assumed to be the actual diffuse astrocytoma. *Gemistocytic* is the only variant of astrocytomas currently recognized. ATRX loss and TP53 mutation are characteristic but not required for the diagnosis of diffuse astrocytoma
Gemistocytic astrocytoma, IDH-mutant	
Diffuse astrocytoma, IDH-*wildtype*	If sequencing for IDH1 codon 132 and IDH2 codon 172 gene mutations alone or both are negative, it can be diagnosed as *wildtype*
Diffuse astrocytoma, NOS	Astrocytic tumors that do not fit in the previous categories or genetic testing not performed
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	Both mutations are needed for oligodendroglioma diagnosis
Oligodendroglioma, NOS	Phenotypical oligodendroglial tumors that do not fit in the previous category or genetic testing not performed
Oligoastrocytoma, NOS	Mixed astrocytic and oligodendroglial tumors are currently subcategorized under the NOS designation. Although this diagnosis is discouraged, *true* cases of mixed tumors are reported
Other glial or mixed *grade II* tumors	*Pleomorphic xantoastrocytoma*
	Atypical choroid plexus pailloma
	Central anad extraventricular neurocytoma
	Cerebellar liponeurocytoma

ATRX Alfa-Talasemia X-linked Mental Retardation gene, *IDH-mutant:* harbors mutations in Isocitrate Dehydrogenase 1 or 2 genes, *NOS* not otherwise specified

Table 2 Prognostic factors negatively affecting outcome in LGGs [69]

Age >40 years
Neurological defects at presentation
Absence of seizures as presentation
Karnofsky performance status <70
Tumors larger in size (>6 cm in diameter)
Tumors crossing midline
Rapid growth rate (over 8 mm/year)
MR spectroscopy: presence of lactates and lipids
Histology: astrocytoma worse than oligoastrocytoma, and the latter worse than oligodendroglioma
Pignatti score [87] is a compound of factors: age >40, largest diameter >6 cm, tumor crossing midline, astrocytic histology and neurologic defect
Molecular markers: 80% of diffuse LGGs exhibit the IDH1/2 mutation and frequently the TP53 mutation (present in 80% of gemistocytic variant, constituting a factor of worse prognosis). 70–80% of oligodendrogliomas present the 1p/19q codeletion (but only 5% the TP53 mutation), which implies longer survival

Seizures occur in more than 90% of LGG patients at some stage of the disease. They are more commonly found in oligodendrogliomas affecting the cortical areas of the frontal, temporal or insular lobes [21]. There is level I evidence that in LGG patients with a history of epilepsy treated with immediate antiepileptic medication, there is a reduction in the occurrence of seizures in the following 1–2 years, which does not affect QOL nor results in severe complications, as compared to deferred treatment [29, 30]. Antiepileptic medication associates short and long-term toxicity, interacts with steroid therapy and chemotherapy and up to 49% of patients are initially considered resistant [21, 31]. The antiepileptic agents of choice are Levetiracetam and Valproic acid because of their effectiveness and pharmacologic profile [32, 33]. Surgery [21], chemotherapy [34] and radiotherapy [35] also seem to improve the control of seizures. Reappearance of seizures after an initial successful control usually indicates tumor progression [5].

Regarding diagnosis, both preoperative MR images and biopsy samples have been shown to be insufficient for establishing the diagnosis of LGG because of their false positive and negative rates. Up to 30% of non-contrast enhancing glial masses may ultimately be glioblastoma [36, 37]. Contrarily, at least 15% of LGG are progressively contrast-enhancing lesions, a sign of worse prognosis [38]. Additionally, brain biopsy in LGGs commonly underestimates the histologic grade in a relevant percentage of patients [39].

Some important facts about the natural history and impact of treatment options for LGGs are resumed in Table 3. Some novel concepts in the management of LGGs are discussed below and summarized in Table 4.

Role of surgical resection in diffuse LGGs

The eventual multicenter randomized controlled clinical trial aimed to demonstrate whether extensive surgical resection of LGGs compared to observation prevents malignant transformation and improves survival is unlikely to be conducted for ethical reasons. However, large observational studies and literature reviews have shown that the *extent of resection* (leaving a minimal residual disease) has a positive impact on the natural history of the disease and it is an independent predictor of survival regardless of age, preoperative tumor volume and functional status [40–52].

According to a growing body of evidence, the extent of resection seems to correlate with a more favorable life

Table 3 Important facts about the natural history and management of LGG

LGGs	Facts
Definition and epidemiology	Infiltrative chronic glial disease. New 2016 WHO grade II diffuse tumor categorization according to phenotypic and genotypic markers [7]
	LGG account for 5% of all primary brain tumors and 15% of all gliomas. Average age at diagnosis between 30 and 40. No gender preponderance
Diagnosis	T2/FLAIR-weighted MRI. Baseline neuropsychological tests. Functional and DTI MRI for surgery planning. Contrast enhancement and brain biopsy are not reliable enough to establish diagnosis.
	Definite diagnosis: histopathologic features plus genotypic markers
Natural history	Pre-symptomatic period (unknown duration); symptomatic period (7 years); progression and malignization (2–3 years). Subtle neurocognitive affectation usually present from diagnosis. Focal defects rare
Epilepsy	Present in at least 90% of patients. Improved seizure control rate by surgical resection and adjuvant therapies. Initially intractable in 30–40%. Levetiracetam and Valproic Acid are the agents of choice
General treatment protocol	*Low-risk* patients (age under 40, complete resection) are generally observed after total or subtotal resection
	High-risk patients (age over 40, partially resected) are generally operated on and given adjuvant therapy (radiotherapy plus PCV or temozolomide chemotherapy)
Surgical removal	*Maximum safe resection* is the treatment of choice. Positive impact on PFS, OS and QOL when complete or sub-total resections are performed. Intraoperative electro stimulation mapping during *awake* craniotomy provides higher extent of resection and less permanent postoperative deficits
	Residual tumor volume (over 5–10 cc) correlates with malignant transformation. Multiple reoperations are feasible. *Neuroplasticity* (relocation of specific local brain functions) allows multiple and sequential resections in previously unresectable eloquent areas
	Possible and promising indication for *preventive* surgery in incidentally found LGG
Chemotherapy	Established efficacy in WHO grade III tumors
	In *high-risk* WHO grade II patients, PCV plus radiation therapy doubles PFS and OS. Oligodendroglial, IDH mutated and codeleted patients benefit most. Temozolomide is likely to be as effective as PCV regimens and less toxic. Neoadjuvant temozolomide needs further research
Radiotherapy	Prolongs PFS and OS when administered with adjuvant chemotherapy. May induce long-term cognitive affectation. Also recommended for inoperable tumors and for chemotherapy resistant patients
Global personalized approach	According to tumor and patient characteristics, a personalized multi-stage approach is warranted aiming to leave as minimal tumor residual volume as possible and keeping acceptable quality of life at all times
Survival	Influenced by prognostic factors. The extent of resection and residual volume are determinants of anaplastic transformation
	Average survival in series advocating for wait-and-see policy: 6–7 years
	Average survival in series performing aggressive initial resections: 10 years from diagnosis; may be extended to up to 15 years (personalized multi-stage therapies including functional-guided repeated operations)

Table 4 Novel concepts in the management of LGGs

Concept	Comments
Molecular classification	Allows differentiation of LGG variants with prognostic implication. The new 2016 WHO brain tumor classification introduces genetic alterations for subdividing tumor entities
Individualized multistage strategy	Patients harbor different tumors in terms of growth rate, brain location, tumor size and response to adjuvant therapies. Clinical, radiological, genetic and therapeutic factors need to be considered in order to recommend a personalized treatment strategy that anticipates malignant transformation and neurological deterioration, and privileges the maintenance of the QOL as much as possible
Functional-guided surgery	Since preoperative MR imaging (even DTI and functional MRI) and tumor biopsy are not reliable enough for therapy planning, a strategy of functional-guided (intraoperative cortical and subcortical electro stimulation, ideally with the patient awake) surgery is warranted. Total resection and subtotal resection (leaving a residual mass of less than 5–10 cc) correlates with increased PFS and OS. Functional-guided resection reduces the rate of postoperative neurological defects
Supratotal resection	Since glial tumor cells extends up to 20-mm beyond the actual limits of the tumor visible in MRI, resection beyond MRI margins aims to minimize tumor residual load. Although it is not curative, supratotal resection performed in non-eloquent areas prevents or delays malignant transformation
Neuroplasticity	Eloquent brain areas adjacent to tumor mass tend to *move away* from the disease induced by tumor growth and therapies applied. This brain functional characteristic allows sequential operations in previously unresectable areas
Preventive surgery	Smaller and asymptomatic LGGs can be detected in an eventual screening program. These incidental lesions may benefit from earlier aggressive resection

expectancy meaning a significant increase in OS [40, 41, 43, 45–51]. Adequate postoperative radiological assessment is crucial in evaluating response to treatment. When T2/FLAIR-weighted postoperative images are not specifically revised, the residual tumor volume is commonly underestimated [4]. The absence of signal abnormality in this MR sequence means complete resection, which correlates with OS. Moreover, incomplete tumor removal also seems to provide significantly longer OS, since residual volume (of less than 5–10 cc) acts as a predictor of malignant transformation [40, 42]. It has been reported that patients with an extent of resection greater than 90% have an estimated 5-year OS of 93%, and those between 70 and 90% and less than 70% have an estimated 5-year OS of 84 and 41%, respectively [43]. *Early* surgical removal seems to provide better tumor control and OS compared to biopsy and watchful waiting [4]. The largest patient series published provided by the *French Glioma Network* (a multicenter study on 1097 LGG patients) has demonstrated that the extent of resection and the residual volume are independent prognostic factors of survival, and OS can be increased up to 15 years, which doubles the traditional life expectancy reported in studies where complete resection was not attempted [51]. Currently, some European Guidelines also recommend early and maximum tumor resection as the initial therapeutic option in LGG [26]. Furthermore, when resection is extended beyond the margins of the tumor (the so-called *supratotal* resection) in non-eloquent areas, malignant transformation seems to be avoided (at least temporarily) and adjuvant treatment can be delayed [12]. This is a new concept in the surgical management of LGG and its impact on OS and QOL is currently under research.

Biopsy carries the risk of under (in up to 30% of the cases) or over-grading the tumor due to sampling error because of the small amount of tissue obtained and the heterogeneity of the tissue within the tumor [39]. Besides, the risk of serious complication of tumor biopsy seems to be similar to that of surgical removal itself, about 2% according to modern large series [51, 53]. Therefore, the only indication of biopsy would be for patients unwilling to be operated, for those inoperable because of concomitant severe medical conditions and in very diffuse and extensive lesions where not even subtotal resection is likely to be achieved.

Some *adjuncts to surgery* like preoperative functional and diffuse tensor image (DTI) MRI studies [54, 55], awake craniotomy [56] and intraoperative cortical and subcortical brain mapping [53] have shown to provide more extensive and safer surgical resections in LGGs. In *non-eloquent* areas, image-guided resection (that is, resection of the T2/FLAIR signal altered tissue) may be inferior to *functional-guided* resection (based on intraoperative electrical stimulation mapping), in terms of complete resection rates [4, 13]. This is paramount because tumors cells in LGGs usually infiltrate the surrounding normal brain parenchyma up to 20 mm beyond the actual limits visible in the MR images [12]. The objective of functional-guided resection is to perform complete tumor tissue resection until an eloquent area is reached. Because of inter-individual functional differences, anatomical landmarks are not enough to warrant safe resections, even

by using functional and DTI MR imaging [4]. *Eloquent* regions are better identified with electro stimulation of the cortical and subcortical structures in a patient undergoing awake surgery [26, 52, 53]. The advantages of this technique include an improved extent of resection, allows extensive tumor removal in previously considered inoperable regions like the insula, the language-related areas or the central regions, and minimizes the chances of permanent postoperative deficits (currently under 2%), as confirmed in a recent meta-analysis by De Witt Hamer et al. [57]. However, transient postoperative deficits may be expected in certain areas, like resections within the supplementary motor cortex. There seems to be an improvement in QOL due to better seizure control and neuropsychological stabilization after a personalized functional-guided complete resection [45, 53]. Currently, intraoperative electro stimulation mapping can be regarded as a standard of care in LGG surgery [57]. Furthermore, early and radical surgery has been performed even for *incidental* LGG (usually smaller in size) with minimum morbidity, as proposed by Duffau [58]. This is an interesting issue since this experience opens the door to a screening policy and an eventual *preventive* surgery for LGG [59]. Figure 1 shows preoperative and postoperative MR images as well as intraoperative views of a right temporal-insular LGG subtotal resection guided by cortical and subcortical electro-stimulation.

Patients harboring LGGs need honest *information* on the nature and likely course of their disease. They need to know that surgery (even supratotal resection) and adjuvant therapies are currently unable to cure the disease. These patients undergo regular clinical and radiological assessment by clinicians for years until deterioration occurs. Therefore, an empathic and trusty relation needs to be built between the clinician and the patient in order to discuss the risks and benefits of the various treatments offered throughout the remaining life of the patient. Since the rate of growth of the tumor and the residual volume can be reliably calculated, a second or third preventive therapy can be recommended before the threshold risk of malignant transformation is reached [8]. In general, before surgery is indicated, three preoperative steps are recommended [4]: to define the tumor location and extension, both cortical and subcortically; to calculate tumor volume and growth rate (in two consecutive MRI separated by 2–3 months); and to perform specific neuropsychological assessment. These baseline studies provide key information for developing an *individualized* strategy.

Reoperation after a few years of the initial complete resection (usually after 4–5 years on average) is feasible largely because of brain *plasticity* [60]. This concept means that specific brain functions can be remapped, literally *pushed away* from the tumor area, induced by the resection, the postoperative rehabilitation process and the re-growth of the tumor itself [61]. Reoperation should be indicated before malignization is judged to occur, but not too early, in order to minimize the risk of QOL deterioration [8]. However, reoperation in patients in which less than subtotal resection is expected should not be attempted because of the uncertain oncologic benefit. Exceptions to this policy would be patients with intractable epilepsy or those presenting with intracranial hypertension [4].

After complete or supratotal resection, watchful waiting is largely advocated. However, patients considered for early adjuvant therapy are those undergoing partial resection in which the tumor grows rapidly or for patients exhibiting intractable seizures. At present, adjuvant therapy comprises radiation therapy and chemotherapy.

Role of adjuvant therapy in diffuse LGGs

Radiotherapy

Radiation has been classically considered the standard adjuvant therapy in the management of LGGs. However, the indication and timing of radiotherapy remains controversial because of the mid and long-term potential cognitive toxicity [62] and its unproven effectiveness regarding OS [63]. In the past, two prospective randomized studies failed to establish a dose–response benefit in the management of LGGs. The EORTC 22844 randomized trial [64] on 313 patients could not provide significant differences between two radiation schedules (45 Gy in 5 weeks against 59.4 Gy in 6 weeks) regarding OS and PFS. Another phase III randomized trial [65] on 203 patients compared low versus high dose (50.4 Gy in 28 fractions against 64.8 Gy in 36 fractions). In this study, the authors found a slightly lower survival rate and higher incidence of radiation necrosis in the high dose group.

Regarding the timing of radiotherapy, the EORTC 22845 randomized trial [66] on 311 LGG patients showed an improved PFS (5.4 vs. 3.7 years), after a median of 6 years of follow up, in the group receiving immediate postoperative radiotherapy (54 Gy in 6 weeks) compared to those receiving radiotherapy at the time of progression. However, OS was not improved (7.4 vs. 7.2 years) and QOL was not assessed.

Interestingly, the results from the RTOG 9802 randomized trial [67] showed that *low-risk* LGG patients (complete resection and age <40) exhibited a 93% 5-year survival rate and a 5-year PFS of 48% *without* any adjuvant therapy, results very similar to those obtained by postoperative radiotherapy alone (44% 5-year PFS in the study EORTC 22845, as shown in Table 5).

Long-term cognitive sequels associated to radiation therapy are a matter of concern in the management of

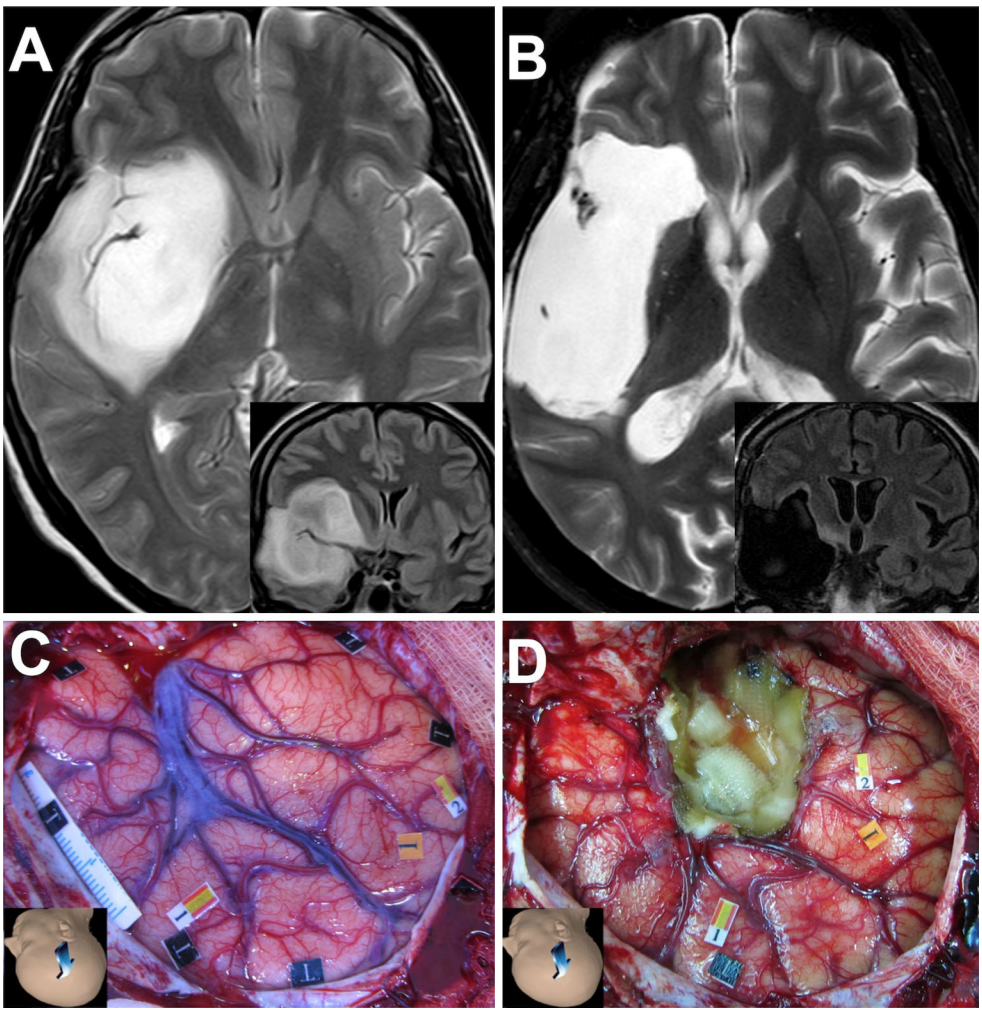

Fig. 1 A 39 year-old woman with a right temporal-insular low-grade glioma was operated on with intraoperative electrical stimulation mapping at the Hospital Universitario Marqués de Valdecilla in Santander (Spain). **a** Preoperative axial T2- and coronal FLAIR-weighted magnetic resonance images. The preoperative tumor volume was 83.2 ml. **b** Postoperative axial T2- and coronal FLAIR-weighted magnetic resonance images. The resection was extended until eloquent structures were encountered. The postoperative tumor volume was 4.1 ml, with a small residue at the anterior perforating substance. **c** Intraoperative photograph taken before tumor resection, where the frontal and temporal lobes and the sylvian fissure are exposed. Intraoperative electrical stimulation of the cortex elicited the following responses: flag with number *1* speech arrest at the ventral premotor cortex, flag with number *2* anomia at the posterior part of the middle temporal gyrus, and orange label with number *1* verbal working memory deficit. **d** Intraoperative photograph taken after tumor resection. The patient was neurologically intact after surgery

LGGs. Brain radiotherapy has been related to cognitive disorders ranging from mild memory or attention impairment to dementia. These long-term effects are relevant because LGGs usually affect young adults with good previous QOL and long survival expectancy, in which large volumes of the brain may need to be irradiated. The study by Douw et al. [62] evaluated the long-term cognitive sequels in 65 LGG patients, after a median follow up of 12 years. Cognitive worsening occurred in 53% of irradiated patients as compared to 27% in non-irradiated. The main sequels were attentional and executive function defects, as well as, impairment of information processing speed. Likewise, the study by Surma-aho et al. [68], on 160 LGG patients, showed that radiotherapy associated an increased rate of cognitive impairment and leukoencephalopathy. However, it is likely that new conformational radiotherapy schemes and proton therapy may result in less cognitive affectation, although sound evidence supporting their use is still lacking.

In summary, patients with the highest probability of progression (age over 40 years, preoperative tumor size over 5 cm, partial resection, astrocytic histology, lack of codeletion and lack of IDH mutation) seem to benefit most from radiation therapy [69], but its effect on OS and PFS seems to be only marginal compared to no adjuvant therapy in low-risk patients [67]. Radiotherapy is currently offered

Table 5 Relevant randomized trials regarding adjuvant therapy in LGG

Trial	Study protocol	Results and comments
Radiotherapy		
NCCTG/RTOG/ECOG	Phase III trial ($N = 337$)	No differences in 5-year PFS and OS between low dose (50.4 Gy) and high dose (64.8 Gy)
(Shaw et al. [65])	Surgery + RT low dose versus surgery + RT high dose	
EORTC 22844	Phase III trial ($N = 343$)	No differences in 5-year PFS and OS between low dose (45 Gy) and high dose (59.4 Gy)
(Karim et al. [64])	Surgery + RT low dose versus surgery + RT high dose	
EORTC 22845	Phase III trial ($N = 311$)	Improved PFS (5.4 vs. 3.7 years) and 5-year PFS (37 vs. 44%) in the group receiving immediate postoperative radiotherapy. No QOL assessment
(van den Bent [66])	Surgery + RT at progression versus surgery + early RT	
Chemotherapy		
EORTC 22033–26033	Phase III trial ($N = 477$)	No differences in PFS. Immature data on OS
(Baumert et al. [70])	*High-risk* group: age >40, symptomatic, radiologic evidence of progression after surgery	Better PFS in IDH-mutant, non-codeleted patients treated with radiotherapy
	Surgery + TMZ versus Surgery + RT	
Radiotherapy + chemotherapy		
RTOG 9802	Phase III trial ($N = 251$)	Improved median PFS (10.4 vs. 4 years) and median OS (13.3 vs. 7.8 years) in the PCV group
(Buckner et al. [67])	*High-risk* group: age >40, incomplete resection regardless of age	
	Surgery + RT versus Surgery + RT + PCV	Improved 5-year PFS (44 vs. 61%) and 5-year OS (63 vs. 72%)
		Better if treated with PCV, oligodendroglial histology and female gender
RTOG 0424	Phase II trial ($N = 129$)	3-year PFS: 73.1% (vs. 54% of historic cohorts)
(Fisher et al. [80])	*High-risk* group: age >40, astrocytic, midline involvement, size >6 cm, focal defect	3-year OS: 59.2%
	RT + TMZ followed by TMZ	

TMZ temozolomide, *RT* radiotherapy, *PCV* Procarbazine, CCNU and Vincristine, *PFS* progression-free survival, *OS* overall survival

to this high-risk subset of patients and for patients progressing after chemotherapy [4].

Chemotherapy

The concern about the long-term cognitive effects of radiotherapy in LGG patients led to the conduction of the EORTC 22033–26033 study [70] on 477 patients in which radiotherapy (54 Gy) was compared to temozolomide in dense scheme. The preliminary results showed no statistically significant differences in PFS between the two arms. The QOL reported by the patient and the global cognitive function, measured with the Mini-Mental State Examination (MMSE), were similar in both arms [71]. After a median of 4 years follow up, median PFS was comparable in both groups (46 months, 95% CI 40–56 vs. 39 months, 95% CI 35–44, HR 1.16, 95% CI 0.9–1.5). According to the molecular categorization obtained in 80% of the patients, outcome was similar for chemo and radiotherapy in IDH-mutant and codeleted patients, although benefit seemed greater in the radiated group with IDH-mutant but non-codeleted. However, it must be noted that the results of temozolomide alone are still inferior to those of radiotherapy followed by PCV according to the results from the RTOG 9802 study. In the near future we will be able to assess the impact of salvage radiotherapy on OS in a temozolomide-alone cohort. At this moment, deferring radiotherapy in high-risk WHO grade II patients would be considered in very high volume IDH-mutant and codeleted tumors needing wide radiation fields.

Whether temozolomide and PCV are equivalent in terms of efficacy is still under research. Similar response rates and survival has been reported for both chemotherapies, about 25–80% objective responses and median time to maximum tumor size reduction of 9–40 months [72]. The recently redesigned randomized phase III CODEL trial (that includes WHO grade II and III gliomas) will help to elucidate whether temozolomide and PCV are equivalent or not [72, 73].

Temozolomide has been studied as initial treatment in 1p deleted oligodendroglial tumors with a 31% objective response and a median time to maximum tumor response of 12 months [74]. However, no specific recommendation is yet available for the use of *neoadjuvant* temozolomide chemotherapy as first-line treatment in LGG.

Combined radiation therapy and chemotherapy

Several studies confirmed the clinical benefit of chemotherapy in diffuse WHO grade III gliomas [75–77]. The RTOG-94027 [7] and EORTC-26951 [77] trials clearly established the prognostic and predictive value of 1p/19p codeletion in WHO grade III oligodendrogliomas. Radiotherapy followed by 6 cycles of PCV versus radiotherapy alone provided better median PFS (157 vs. 50 months) in codeleted patients, also with a tendency to improve OS (HR 0.56, 95% CI 0.31–1.03) [77]. Given the toxicity of PCV and the improved prognosis of codeleted oligodendroglial tumors, the impact of concomitant and adjuvant temozolomide to radiotherapy against radiotherapy plus adjuvant PCV needs further investigation. As resumed by Le Rhun et al. [78], in a recent review, maturation of the NOA-04 study [75] and the results of the currently accruing studies, CODEL (for codeleted anaplastic gliomas) and the recently completed CATNON trial (for uni or non-codeleted), will likely refine current up-front treatment recommendations for anaplastic gliomas [79].

The *RTOG 9802 study* [67] confirmed the benefit of adding PCV chemotherapy to radiotherapy in WHO grade II high-risk patients in terms of median OS (13.3 vs. 7.8 years, HR 0.59, 95% CI 0.42–0.83, $p = 0.003$) and median PFS (10.4 years vs. 4 years, HR 0.5, 95% CI 0.36–0.68, $p < 0.001$), after a median follow up of 12 years. Moreover, cognitive function assessed with the MMSE, was not affected by the adjuvant PCV scheme. The retrospective molecular analysis (IDH categorization) obtained in 45% of the cohort confirmed the prognostic and positive predictive value of the IDH mutation in the oligodendroglial subgroup. However, since the impact of PCV added to radiotherapy on OS was not statistically significant in the astrocytoma subgroup, it remains unclear whether adding chemotherapy to IDH-wildtype tumors provides any benefit. Nevertheless, the results from this randomized phase III trial have set a new standard in high-risk LGG management relating adjuvant therapy.

The previous phase II RTOG-0424 trial [80] in which temozolomide was administered concomitant and adjuvant to radiotherapy, showed results similar to that of RTOG 9802 in terms of 3-year OS (73.1%, 95% CI 65.3–80.8). However, a phase III trial is still needed to recommend the substitution of the more toxic PCV regimen by temozolomide.

In summary, there is a well-established role of chemotherapy for WHO grade III tumors, especially those expressing 1p/19q codeletion, in terms of PFS although not so clear on OS. In WHO grade II high-risk patients, the addition of PCV to radiation therapy markedly improves PFS, doubles OS and seems to preserve cognitive function. The substitution of the PCV regimen by the less toxic temozolomide scheme (alone or concomitant) is still under research but it seems at least comparable, in terms of QOL and survival.

Areas of controversy

Currently, we lack a well-established definition of *high-risk* LGG patients. The criteria used to define this subset of patients differ among studies [4, 72, 81] (see Table 5).

According to the RTOG 9802, patients older than 40 or incompletely resected regardless of age are considered as high-risk. However, a 50 year-old patient harboring an IDH-mutated and 1p19q-codeleted tumor that has been completely resected, should receive radiotherapy and concomitant PCV? Moreover, this trial did not find significant improvement of OS in non-mutated IDH and non-codeleted astrocytic tumors. Thus, should we consider radiotherapy + PCV treatment in a 45-year-old patient with a non-codeleted non-mutated tumor? Do the benefits and risks of PCV chemotherapy overcome those of temozolomide alone?

Adjuvant therapy is usually recommended in patients presenting with bad prognostic factors. Many of these factors are also predictive of bad response to treatment. LGG patients usually present with a combination of good and bad prognostic and predictive factors. Theoretically, it would be reasonable to indicate adjuvant therapy only in patients with bad prognostic factors *but* presenting with factors predictive of good response to treatment. For example, in a patient older than 40, with a codeleted oligodendroglial large tumor but only partially resected. However, this differential treatment recommendation needs to be tested.

Very few studies evaluate the long-term toxicity of therapies applied. In the RTOG 9802 trial, the MMSE test was used to determine cognitive decline in patients undergoing chemoradiation. However, MMSE was designed for dementia and it is a relatively insensitive tool for assessing cognitive state in LGG patients [72]. Currently, we lack prospective long-term studies in which detailed pre-treatment neuropsychological testing is used to evaluate cognitive function over time. We also do not know whether adjuvant therapy provides an overall adequate balance between a certain gain in OS and the QOL enjoyed throughout those years.

Finally, the management of recurrent disease is not standardized and salvage therapies are generally performed according to prior treatments. Low-risk patients initially observed are usually operated on and then irradiated. High-risk patients initially treated with radiotherapy and PCV chemotherapy are ultimately rescued with temozolomide [72]. Nevertheless, the response rate after progression or failure of previous treatment is discouraging [81].

Emerging therapies in LGG

Since LGGs are typically slow growing tumors, some interest has arisen in emerging or alternative therapies aimed to prevent or slow their development into high-grade neoplasms. However, a recent systematic review has failed to provide level I–II evidence addressing this issue [82]. Currently, there are no published objective data assessing the efficacy of immunotherapy or tumor vaccines for clinical use in LGG. However, Okada et al. [83] have conducted a phase I study to evaluate the safety and immunogenicity of subcutaneous vaccinations with synthetic peptides for glioma-associated antigen (GAA) epitopes in adults with high-risk LGGs, obtaining robust GAA-specific responses, whose impact on survival should ideally be confirmed in future clinical trials.

The effect of dietary supplements with some antioxidants on survival is inconsistent according to the study by DeLorenze et al. [84]. These authors found that moderate lycopene intake was detrimental on survival while moderate folate was beneficial, although actual plasma concentrations were not measured. The retrospective review of 182 LGG patients published by Chaichana et al. [85] in 2010 indentified persistent hyperglycemia (defined as glucose >180 mg/dl three or more times between 1 and 3 months postoperatively) as a statistically significant factor for decreased survival, increased recurrence and increased malignant transformation. A questionnaire-based review of 621 patients from six German neuro-oncological centers showed that at least 40% of patients harboring gliomas of all grades admitted to use unproved *complimentary or alternative therapies*, without their physicians' knowledge, motivated not by dissatisfaction with the standard treatment but in a desire *to do more* [86]. Other emerging therapies, like electric field therapy, nanoparticles or other dietary schemes, currently under investigation in high-grade gliomas, may provide clinical benefit in future LGG studies. However, the long natural history of LGGs, their relative infrequency and the need for multicenter collaboration complicate the conduction of research studies, mainly because patients need to be followed more than 5 years, which has implications in long-term funding [82].

Conclusions

The management of diffuse supratentorial WHO grade II gliomas remains a challenge because of the infiltrative nature of the tumor which precludes curative therapy after total or even supratotal resection. Currently, the aim of therapy is focused on delaying the malignant transformation of the tumor. Surgical resection of all the T2/FLAIR-weighted MR affected tissue provides the best chance for stabilizing the disease. Intraoperative cortical and subcortical electro stimulation is a surgical adjunct that helps to identify eloquent areas of the brain and facilitates a more complete and safer resection, which correlates with an increased PFS and OS.

Low-risk patients (complete resection and age under 40) should undergo maximal safe resection followed by close observation. According to the results from the RTOG 9802 randomized trial, a new standard of treatment has been established for *high-risk* patients. These patients (especially IDH-mutated and 1p19q-codeleted oligodendroglial lesions) benefit from surgery plus adjuvant chemoradiation. The effects of radiation and chemotherapy seem to be synergic in prolonging PFS and OS. However, the definition of low and high-risk cohorts is still unclear. Acknowledging molecular parameters may help in selecting good responders to therapies.

The natural history and treatment of LGGs allow patients to live a near normal life for some years before progression to a higher grade occurs. Although epilepsy is almost always present at some time of the disease, antiepileptic medication, surgery and adjuvant therapy seem to have a positive impact on seizure control. Additionally, subtle cognitive alterations can be ascertained from the beginning of the disease. The risk of neurocognitive function decline is a matter of concern when confronting treatment options, especially early radiation therapy.

Although LGGs cannot be regarded as *benign* tumors, large observational studies have shown that median survival can actually be doubled if early, aggressive, multistage and personalized therapy is applied, as compared to series in which the *wait-and-see* policy was advocated. Thus, patients need an honest long-term therapeutic strategy that should ideally anticipate neurological, cognitive and histopathologic worsening. The maintenance of QOL should be the primary goal when advising adjuvant therapy or repeated operations. The impact of these therapies on incidentally found LGGs, contextualized in an eventual screening program, is an interesting and attractive idea that deserves specific research in future prospective studies.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest regarding this manuscript.

Informed consent Not needed for a literature review. No humans or animals participated in this study.

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