Diffuse low-grade glioma, oncological outcome and quality of life: a surgical perspective

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Purpose of review
Because diffuse low-grade glioma (DLGG) is constantly migrating in the brain until malignant transformation, the historic wait-and-watch attitude was replaced by an early therapeutic management. Moreover, advances in cognitive neurosciences allowed an improved understanding of neuroplasticity reactional to DLGG growth. Here, the aim is to reevaluate the role of surgery regarding both oncological and functional outcomes.

Recent findings
Recent data evidenced the significant benefit of maximal well tolerated resection on survival and quality of life (QoL). By removing a diffuse neoplastic disease up to eloquent neural networks identified by intraoperative awake mapping and cognitive monitoring, overall survival is about the double compared with biopsy, whereas the rate of severe persistent deficits was significantly reduced. Postoperative QoL may even be improved owing to functional rehabilitation and epilepsy control.

Summary
Early and functional mapping-guided surgery is currently the first treatment in DLGG. Surgical resection(s) should be integrated in a global personalized management that must be tailored to the brain connectome of each patient. To optimize the oncofunctional balance, the next step is a screening, to detect and to treat DLGG patients earlier, and to increase the rate of 'supramarginal excision' in the setting of a 'prophylactic connectomal neurooncological surgery'.

Keywords
awake surgery, brain plasticity, functional brain mapping, low-grade glioma, quality of life

INTRODUCTION

Supratentorial diffuse low-grade glioma (DLGG, WHO grade II glioma [1]) in adults is a primary brain neoplasm that evolves with a growth rate about 4 mm/year, migrates along the white matter tracts and ineluctably progresses to a high-grade glioma, resulting in cognitive and neurological disorders, and ultimately to death [2▪▪]. Epilepsy is the first symptom in most of DLGG patients, who are generally young (20–40 years) and who lead a normal life. The rate of incidental discovery is increasing thanks to a facilitated access to MRI [3]. The overall survival (OS) is only around 6 years when a simple biopsy, possibly followed by chemotherapy and/or radiotherapy, is achieved [4,5▪▪], from 7.7 years in DLGG with favourable prognostic scores to only 3.2 years in patients with negative factors (as age $\geq$ 40 years, neurological deficit, large glioma volume or astrocytoma subtype) [6].

Based upon a standard neurological examination, it was thought that DLGG patients did not exhibit functional deterioration. However, when an objective neuropsychological evaluation is performed, a high rate of cognitive disabilities is actually observed, particularly concerning executive functions such as attention or working memory, speed processing, verbal and nonverbal semantics, decision making, emotion or behavior [7], including in patients with incidental DLGG, wrongly considered as 'asymptomatic' [8]. These disturbances are explained by the limitations of neuroplastic potential related to the progressive invasion of the

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KEY POINTS

- Early functional-guided surgery has a significant benefit on both oncological and functional outcomes of DLGG patients.
- Thanks to maximal well tolerated resection performed using intraoperative awake mapping and cognitive monitoring, overall survival is about the double compared with biopsy, while the rate of severe persistent deficits is less than 2%.
- Postoperative quality of life may even be improved in DLGG patients owing to functional rehabilitation and epilepsy control.
- Surgical resection(s) must be incorporated in a global individualized management that should be tailored to the brain connectome of each patient.
- With the goal to optimize the oncofunctional balance, screening can be considered in order to detect and to treat DLGG patients earlier, while increasing the rate of suprototal excision in the setting of a 'prophylactic connectomal neurooncological surgery'.

cerebral connectome by tumoral cells [9]. Intractable seizures are also frequent and disabling.

Due to this better understanding of adverse consequences of DLGG on both QoL and OS, the conservative watch-and-wait policy, that prevailed for many decades, has been replaced by a more active therapeutic strategy starting by early and maximal well tolerated surgical resection, and then by tailoring the sequence of treatments over years for each patient with the ultimate aim of improving not only the quantity of life but also the quantity of time with an optimal QoL [10]. The goal of a multistage and personalized therapeutic approach is to transform a neoplasm preprogrammed to become malignant in a chronic tumoral disease under control in patients enjoying an active life. Here, the purpose is to review the recent literature, increasingly supporting the benefit of precocious and radical surgery in DLGG patients on both oncological and functional outcomes.

EARLY MAXIMAL SURGICAL RESECTION IMPROVES SURVIVAL IN DIFFUSE LOW-GRADE GLIOMA PATIENTS

As long as there was no objective assessment of the extent of resection (EOR) on postoperative MRI, the impact of surgery on OS in DLGG varied across series, due to an undervaluation of the residue in this poorly demarcated tumor. Regrettably, even in recent trials, the EOR was only based on the subjectivity of neurosurgeons [11]. The sole option to calculate rigorously the EOR is to measure the possible residual volume on postsurgical T2/fluid-attenuated inversion recovery (FLAIR)-weighted MRI. Experiences in which the EOR was calculated on pre and postsurgical MRI evidenced that OS was significantly improved with maximal resection in comparison to a simple biopsy or debulking (see [12] for a recent review). In two pseudo-randomized surveys that investigated OS in parallel populations of DLGG patients managed in departments with different strategies, early surgery was correlated with a significantly greater OS around 14 years, whereas survival was only about 6 years with a biopsy followed by watchful attitude [4,5▪▪]. Importantly, this survival benefit was found only if the residual volume was less than 15 ml [4]. A recent series confirmed that postoperative volume was associated with OS, with a hazard ratio of 1.01 [95% confidence interval (95% CI): 1.002–1.02; $P = 0.016$] per cm^3 increase in volume [13]. A threshold of around 90% of EOR has also been reported, as patients with at least 90% of EOR had 5 and 8-year OS rates of 97 and 91%, respectively, while patients with less than 90% of EOR had 5 and 8-year OS rates of only 76 and 60%, respectively [14]. The wide surgical cohort described by the French Glioma Consortium, with over one thousand DLGG, confirmed that both EOR and postsurgical residual volume represented independent prognostic factors significantly associated with a prolonged OS [15,16]. OS was around 13 years since the first therapy and 15 years since the initial symptom [15,16], namely, about the double compared with the OS in series with no attempt to achieve early radical excision [8,17] or with simple biopsy [4,5▪▪]. In addition, maximal removal is correlated with a longer malignant progression-free survival, supporting that the surgical benefit on OS is because resection can postpone DLGG degeneration by decreasing the tumoral volume [18]. Thus, the concept of 'supracomplete' resection has been suggested [19], with the aim of removing a margin beyond MRI-defined abnormalities, as even FLAIR-weighted MRI underestimates the spatial extent of DLGG [20]. Supramarginal excision significantly delays malignant transformation while defering adjuvant oncological treatment compared with DLGG patients who benefited from 'only' complete resection [19], even with a long-term follow-up of 132 months (range, 97–198 months) [21▪].

Remarkably, greater EOR and OS are not correlated to the molecular profile. Although one could argue that prolonged OS after resection might be because DLGG amenable to radical excision have more favourable genetic markers, for example isocitrate dehydrogenase (IDH)-mutation or 1p19q codeletion, a cohort with 200 consecutive DLGG evidenced that a better surgical resectability was independent of molecular pattern: these data support the positive role of surgery *per se* [22]. A recent series with IDH wild-type low-grade astrocytomas surgically resected found that only 16% of patients died at a median time from radiological diagnosis of 3.5 years (range, 2.6–4.5 years), while survival from diagnosis was 77.27% at 5 years (no patients with a follow-up over 5 years died) [23▪▪]. Similarly, Jakola *et al.* [5▪▪] showed that the surgical benefit on OS remained after adjustment for genetic markers. If only a partial excision is performed due to the tumoral involvement of critical neural networks, neoadjuvant chemotherapy may be considered, in order to elicite a glioma shrinkage and to make possible a subsequent surgery with a greater EOR [24]. Such a shrinkage is not dependent on the molecular profile [24]. Consequently, the therapeutic management of DLGG must not rely solely on routine genetic markers but must also take account of patient-specific clinical and radiological criteria [25].

In summary, early and maximal resection is currently the gold standard in DLGG [2▪▪,12]. Therefore, biopsy should no longer be proposed in suspected DLGG, except if at least a subtotal removal is not possible, as in gliomatosis-like. As recurrence is common, reoperation must be considered as an independent prognostic factor significantly associated with a longer OS [15]. EOR in eloquent areas may be improved during subsequent surgeries thanks to mechanisms of neuroplasticity, opening the window to a multistage therapeutic strategy [26].

FUNCTIONAL MAPPING-BASED SURGICAL EXCISION IMPROVES QUALITY OF LIFE IN DIFFUSE LOW-GRADE GLIOMA PATIENTS

DLGG surgical removal has a dual goal, that is a benefit on OS and a functional gain. Considerable variations in the anatomofunctional organization of the brain represent a major issue [27], a fortiori in DLGG that elicites cerebral reorganization, allowing a functional compensation, at least to some extent [9,28▪▪]. The use of awake mapping by means of intraoperative cortical and axonal electrostimulation combined with real-time neurocognitive monitoring throughout the surgical removal resulted in a preservation and even in an improvement of QoL [29]. The principle is to pursue the resection up to eloquent networks – and not to stop it according to radiological limits, which in essence do not reflect the real extent of the glioma due to its diffuse feature – in order to optimize the oncofunctional balance by increasing the EOR (notably by achieving a supramarginal resection if safely possible) while sparing the critical neural structures [30▪▪]. Thus, awake mapping with direct electrostimulation should be used more systematically, including for DLGG located in regions classically but wrongly regarded as 'noneloquent', as the right 'nondominant' hemisphere [31]. Surgical advances have made possible to map and to monitor not only basic motor and language functions into the operating theater but also higher order cognitive and emotional functions, such as complex movement (e.g. bimanual coordination), visuospatial cognition and attention processing, calculation and reading, verbal and nonverbal semantics, working memory, judgement and even mentalizing (theory of mind) or metacognition [32]. A specific pannel of tasks can be selected for the intraoperative monitoring according to the needs of the patient, detailed during the presurgical phase based upon his/her job, hobbies, lifestyle and the results of the neuropsychological examination [33]. The decision cannot be longer made on the glioma location solely, but by taking account of the QoL defined by each patient.

This paradigmatic shift from image-guided glioma removal to functional-based resection has permitted a dramatic improvement of the functional outcomes. Comparison between DLGG patients who underwent surgery with or without intraoperative mapping demonstrated a significant decrease of the rate of persistent deteriorations in the cohorts with electrostimulation [34,35]; moreover, patients were discharged home earlier [35]. In DLGG patients who underwent two consecutive surgeries, without and then with awake mapping during the first and the second intervention, respectively, 33% of impairments occurred following surgery under general anaesthesia, whereas no permanent worsening was observed after awake resection [36]. A meta-analysis that reviewed 8091 adult patients operated on for a supratentorial glioma, with or without intrasurgical electrical mapping, releaved that tumour removal using mapping was correlated to significantly fewer permanent severe neurological deteriorations (3.4% with mapping versus 8.2% without mapping), while the glioma involved eloquent sites more frequently [37]. Similarly, the development of intrasurgical mapping in the same institute enabled a significant increase of resections in critical structures (35% without mapping versus 62% with mapping) [34]. This is important, as DLGG commonly involves eloquent areas: awake mapping optimizes the percentage of well tolerated surgical excisions for gliomas within regions classically deemed as inoperable (e.g. Broca's area, Wernicke's area, Rolandic area or the insula) [38] (Fig. 1). Therefore, the risk of permanent disabling deficits is nowadays less than 3%, and even nil in a recent prospective cohort of 374 awake craniotomies [39]. Regarding higher-order functions, longitudinal

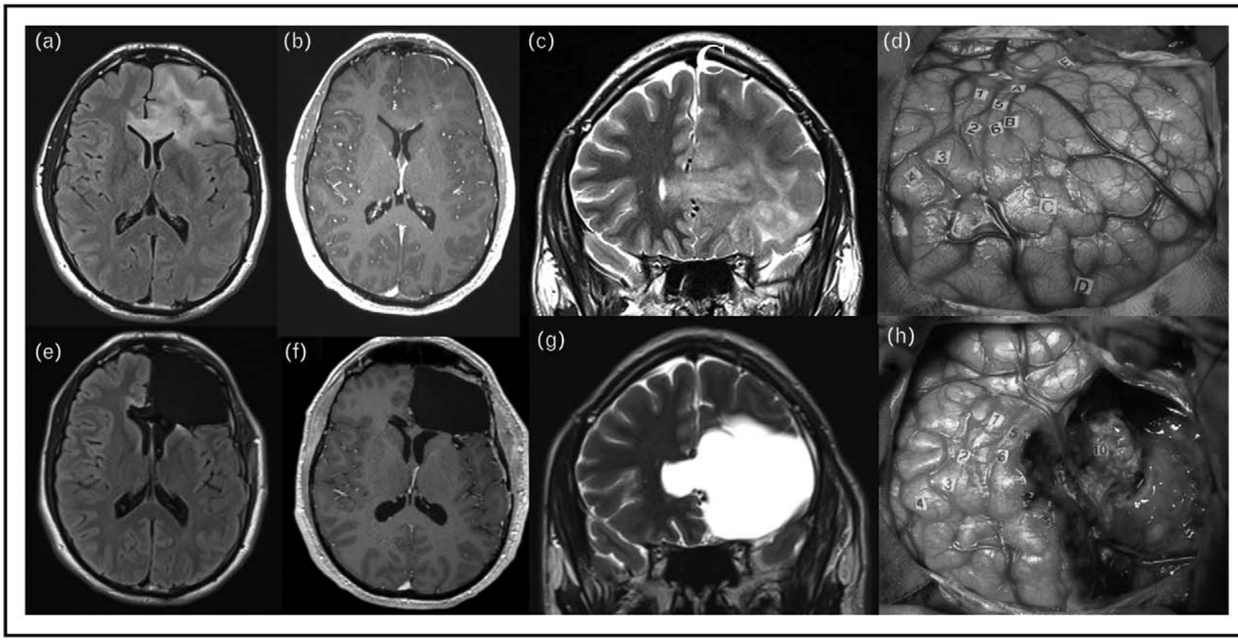

FIGURE 1. (a–c) Preoperative axial FLAIR (a), axial enhanced T1 (b) and coronal T2-weighted MRI (c) achieved in a 35-year-old right-handed man who experienced migraines for several years, which allowed the incidental discovery of a voluminous left frontal diffuse low-grade glioma with a small nodular enhancement. The neurological examination was normal. Nonetheless, the preoperative neuropsychological evaluation revealed a slight deficit of verbal working memory. (d) Intraoperative view before resection in awake patient. The anterior part of the right hemisphere is on the left and its posterior part is on the right. Letter tags correspond to the projection on the cortical surface of the tumor boundaries identified using ultrasonography. Number tags show zones of positive direct electrostimulation mapping as follows: 1 and 2: ventral premotor cortex (inducing anarthria during stimulation); 3 and 4: primary motor cortex of the face; 5 and 6: sites of anomia during stimulation. (e–g) Postoperative axial FLAIR (a), axial enhanced T1 (b) and coronal T2-weighted MRI (c) demonstrating a complete resection. The patient resumed a normal familial, social and professional life within 3 months following surgery, with an improvement of the neuropsychological examination thanks to a postsurgical cognitive rehabilitation. Despite the existence of a focus of malignization (with endothelocapillar proliferation) in the middle of a diffuse WHO grade II astrocytoma (IDH1 mutated, non codeleted), no adjuvant treatment was administrated. The imaging is stable with 7 years of follow-up, and the patient continues to enjoy an active life, with no symptoms. (h) Intraoperative view after resection, achieved up to eloquent structures, both at cortical and subcortical levels. Indeed, direct electrostimulation of white matter tracts enabled the identification of the following functional neural netwoks: the anterior part of the superior longitudinal fasciculus (lateral portion) running to the ventral premotor cortex, and generating articulatory disturbances (tag 11): this bundle represented the posterior and deep limit of the resection; the frontal part of the inferior fronto-occipital fasciculus, with a branch running to the dorsolateral prefrontal cortex, and eliciting semantic paraphasia (tag 10) during stimulation: this bundle represented the posterolateral limit of the resection; the frontostriatal tract, inducing arrest of movement of the left upper limb and slowness of initiation for language (tag 12) suring stimulation: this bundle represented the posteromesial and deep limit of the resection. FLAIR, fluid-attenuated inversion recovery.

follow-up studies demonstrated that surgery is possible without eliciting long-term neuropsychological decline [40,41], especially thanks to early postoperative cognitive rehabilitation [42▪].

Functional-based resection can also improve the QoL. In 45 patients with gliomas within functional regions, the same battery of neurocognitive tests was administrated before and 1 year after surgery: an improvement in two areas of verbal fluency was observed at the 1-year evaluation. This supports the likely existence of latent neural networks subserving cognition, able to be activated over time [43]. Another longitudinal investigation studied verbal working memory before and after awake resection for eight DLGGs in eloquent zones [44]. Although 91% of patients experienced verbal working memory disorders before surgery, at 3 months after resection, five patients recovered their preoperative score and three significantly improved it following adapted cognitive rehabilitation [45]. Interestingly, a greater EOR is not an additional risk factor for neurocognitive outcome [43,45]. Furthermore, maximal resection is a predictor of seizure control. In a large cohort with 1509 DLGGs, epilepsy relief was correlated to the EOR, as subtotal ($P = 0.007$) and total ($P < 0.001$) removals were independent predictors of complete seizure control [16]. Especially, in paralimbic DLGG that frequently generates intractable epilepsy, intraoperative mapping led to a greater EOR with resection of mesiotemporal structures, even if not invaded on the preoperative MRI [46]. Hippocampal excision allowed seizure control in all cases, with an improvement of the Karnofsky Performance Scale score because all patients resumed their professional activities after surgery, although they were not able to work before operation [46]. In a recent DLGG series, among 61.8% of the employed patients not capable to work before resection, 82.4% of them resumed their employment following surgery [47].

THE CONCEPT OF PROPHYLACTIC CONNECTOMAL NEUROONCOLOGICAL SURGERY

Despite the huge potential of neuroplasticity that allows surgery in 'eloquent regions' without permanent worsening, brain reshaping has nonetheless limitations, especially concerning the white matter tracts (cortical areas have a higher potential of reorganization) [9,28▪▪]. Therefore, it might not be possible to achieve (sub)total resection when DLGG has already invaded structures still functionally critical. The goal, then, is to induce remapping thanks to postoperative functional rehabilitation and to reoperate later, by taking advantage of this neural remodeling to optimize the EOR during the second surgery while preserving QoL [26]. When the subcortical connectivity is too infiltrated by the neoplasm, as mentioned, a neoadjuvant chemotherapy can be considered, to open the door to a (re)operation if the glioma has shrunk: this strategy also prevents cognitive deficits [48].

However, to increase the likelihood of (supra)-complete resection, the best way is to diagnose these tumours earlier, when they are smaller, not too diffuse and when they have not yet generated neurological symptoms. In surgical series for incidental DLGG (iDLGG), because gliomas were less voluminous than in symptomatic DLGG, the rate of (supra)total excision was much higher [49,50]. In addition, all iDLGGs patients, operated on with awake mapping, resumed their professional life, with no persistent functional worsening, and with no long-lasting epilepsy [51]. Consequently, because a high rate of iDLGG patients suffer from slight neurocognitive disability before surgery [8], and because they will experience seizures several months/years after diagnosis if left untreated, early surgical removal may avoid these symptoms by preventing glioma migration in neural circuits still functional [3]. Thus, prophylactic surgery in iDLGG favourably impacts both OS and QoL.

TOWARDS A SCREENING FOR DIFFUSE LOW-GRADE GLIOMA?

In this setting, our team has suggested a screening in the general population [52,53]. Indeed, the risk of overtreatment in iDLGG is low, because after an initial period of 4 years, the risk of dying from another cause is lower than the risk of dying from the silent iDLGG [52,53]. Moreover, a survey showed that 67% of healthy individuals were in favour of a screening MRI [54▪▪], a percentage in agreement with the rate of individuals that effectively completed MRI in the context of a screening in a cohort with 2176 participants [55]. Of course, surgery for iDLGG must avoid not only motor or language disabilities but also any deterioration of cognitive, emotional or social abilities, in young patients who enjoy a normal life. In our experience based upon a prospective series with 21 patients who underwent early surgery for iDLGG, no patients had permanent neurological deficits, total/supratotal resection was achieved in 67% of cases, all patients are still alive and have an active familial, social and professional life, with 49 months of follow-up (range 20–181 months) [51]. Nonetheless, because these results are preliminary, they should be validated in a pilot multicentric study, initially with selected patients, especially with a family history of glioma and with a higher genetic susceptibility to develop glioma [56]. Therefore, these patients should be referred to ultra-specialized centers, with experts in neurosurgery, neuropsychology, neuroradiology, neuropathology and neuro-oncology, which can obtain optimal results with a high level of reliability [30▪▪,54▪▪].

CONCLUSION

Precocious and radical well tolerated functional mapping-based surgery is today the first therapy in DLGG because it enables an improvement of both OS and QoL. In practice, an objective measurement of the EOR on T2/FLAIR MRI and a neuropsychological assessment must be systematically achieved before and after each resection. Early postsurgical cognitive rehabilitation is also recommended, whenever needed. Surgical excision(s) should be integrated in a global individualized management, which must be adapted to the cerebral connectome of each patient, by dealing with the dynamic relationships between the DLGG behaviour and the reactional brain reshaping over time [10,30▪▪]. Such a personalized multistep management breaks with the rigid guidelines issued from randomized trials [57▪▪]. To optimize the oncofunctional balance, the next step is a screening, to detect and to treat DLGG patients earlier, and to increase the rate of supramarginal removal in the setting of a 'prophylactic connectomal neurooncological surgery'.

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