Update

A new philosophy in surgery for diffuse low-grade glioma (DLGG): Oncological and functional outcomes

Une nouvelle philosophie dans la chirurgie des gliomes diffus de bas grade : résultats oncologiques et fonctionnels

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A B S T R A C T

Background and purpose. – Surgery for diffuse low-grade glioma (DLGG) was debated for a long time. Discrepancies in the classical literature are mainly due to the lack of objective radiological assessment of the extent of resection (EOR). Here, the goal is to review the recent data on oncological and functional outcomes.

Methods. – Surgical series with calculation of EOR on postoperative MRI were reviewed.

Results. – In all modern series, a more aggressive resection predicted significant improvement in overall survival (OS) compared with a simple debulking. Especially, an extended removal of a margin beyond the MRI-defined abnormalities (“supra-total” resection) significantly increased OS by delaying malignant transformation. Furthermore, advances in intraoperative brain mapping techniques resulted in a minimization of neurological deficits.

Discussion/Conclusion. – These recent data strongly argue in favor of achieving a maximal resection of DLGG as the first therapeutic option. Biopsy should be considered only in very diffuse lesions (gliomatosis) or when a subtotal resection is not a priori possible. Thus, neurosurgeons should change their mind, by operating the brain involved by a chronic tumoral disease rather than by trying to remove a “tumor mass”. The aim is not to achieve a simple “tumorectomy”, but the most extensive resection of the brain invaded by DLGG, on the condition that this part of the brain is not crucial for cerebral functions. This new philosophy suggests to perform early and maximal resection according to functional (and not purely oncological or anatomical) boundaries in awake patients. This perspective is the best way to build a personalized “functional surgical neuro-oncology”.

R É S U M É

Objectif. – La chirurgie des gliomes diffus de bas grade (GDBG) a longtemps été controversée. Les contradictions dans la littérature classique sont essentiellement dues au manque d’évaluation radiologique objective de l’étendue de la résection (ER). Le but est ici de passer en revue les données récentes concernant les résultats fonctionnels et oncologiques.

Méthode. – Les séries chirurgicales avec calcul objectif de l’ER sur une IRM postopératoire ont été analysées.

Résultats. – Dans toutes les séries récentes, une résection plus extensive était associée à une majoration de la survie globale en comparaison par rapport à une simple biopsie élargie. En particulier, l’ablation d’une marge au-delà des anomalies IRM (résection « supra-totale ») a significativement augmenté la survie en retardant la transformation maligne. De plus, l’avancée des techniques de cartographie fonctionnelle peropératoire a permis une minimisation des déficits neurologiques.
1. Introduction

Surgery for diffuse low-grade glioma (DLGG) was debated for a long time. This controversy was underlain by two main questions: what is the actual impact of resection on the natural history of DLGG?; what is the functional risk?

Here, the goal is to review the large amount of recent evidences supporting a significant role of surgery on overall survival (OS), by delaying anaplastic transformation (AT) in DLGG patients, while preserving or even improving the quality of life (QoL). Thanks to conceptual advances in the understanding of dynamic relationships between DLGG progression and cerebral networks reorganization, as well as thanks to methodological development in brain mapping techniques, the benefit-risk ratio of surgery dramatically increased in the past decade [1]. Such an improvement of the onco-functional balance of surgical resection should result in a paradigmatic shift in DLGG, by switching from a traditional “wait and see” attitude towards an early and maximal surgery based on functional-mapped guided resection. Moreover, a multistage surgical approach integrated in a personalized multimodal therapeutic strategy should be more systematically considered [2].

2. New insights into the natural course of diffuse low-grade glioma (DLGG): tumor growth and brain plasticity

2.1. Tumor growth

Contrary to what was claimed in the classical literature, there is no stable DLGG. Objective calculation of growth rate (based on at least two magnetic resonance imaging [MRI] spaced by 3 months before any treatment) showed that all DLGG had a constant growth during their pre-malignant phase, with a linear increase of the mean diameter (computed from the volume) around 4 mm a year [3]. This growth was observed not only in symptomatic patients, but also in incidentally discovered DLGG [4,5]. Thus, the concept of “progression-free survival” does mean nothing—at least before chemotherapy or radiotherapy—because the growth rate is similar before and after surgery in cases of incomplete resection [6]. Furthermore, there is an inverse correlation between growth rates and survival in DLGG, showing that the mean velocity of diameter expansion is a better prognostic factor than the neuropathological examination performed according to the current World Health Organization (WHO) classification [7].

These tumors are migrating along the white matter tracts (U fibers, association, projection and commissural pathways) [8]. Thus, DLGG is not a “tumor mass”, but is, in fact, an infiltrating chronic disease progressively invading the central nervous system, especially the subcortical connectivity. Such a diffusion of glioma cells may induce cognitive disorders, probably due (at least partly) to a “disconnection syndrome” [9].

Finally, DLGG will ineluctably become malignant. Such AT will lead to functional deficit with a worsening of QoL and ultimately to death. In two European Organization for Research and Treatment of Cancer (EORTC) randomized multicenter trials with more than 600 patients, in the subgroup of patients with a favorable prognostic score, the OS was 7.7 years—whereas the in the subgroup of patients with a poor prognostic score, the OS was only 3.2 years [10,11]. Clinical (age, neurologic and cognitive status, Karnovsky Performance Status [KPS] score), radiological (tumor volume, location and kinetics, metabolic parameters), pathological and molecular factors are correlated with the risk of AT and OS [12–15].

These data show that DLGG cannot be considered any more as a “benign” tumor, but as a precancerous disease.

2.2. Functional considerations in diffuse low-grade glioma (DLGG) patients

DLGG usually involves young adults who enjoy a normal life. Yet, neurological deficits are rare in patients with DLGG (usually diagnosed after inaugural seizures), even if these tumors are frequently located within “eloquent areas” [16]. This is due to mechanisms of cerebral plasticity, explained by the fact that DLGG is a slow-growing tumor, giving many years to the brain for functional remapping—with a recruitment of perilesional or remote areas within the ipsilesional hemisphere and/or of contra-hemispheric homologous areas [17–19]. The recent integration of these concepts into the therapeutic strategy resulted in dramatic changes in the management of DLGG patients, with an increase of surgical indications in functional areas classically considered as “unresectable” [20,21].

Nonetheless, cognitive deficits are often observed when objective cognitive assessments are performed at time of diagnosis, despite a normal social and professional life, challenging the traditional view of “DLGG patients with a normal examination” [22]. Indeed, many DLGG patients experienced disorders of executive functions, attention, concentration, working memory or emotion [23,24]. Therefore, an extensive neuropsychological evaluation should be performed in all cases.

In summary, although it was traditionally claimed that DLGG was a “benign tumor involving patients with a normal life”, it is now clearly demonstrated that tumor induces functional disturbances and will progress to a higher grade of malignancy—thus leading to severe deficit and ultimately to death. Thus, one should definitely move towards an early therapeutic management, to delay cognitive decline as well as AT.

3. The impact of surgical resection in diffuse low-grade glioma (DLGG)

A phase III randomized trial comparing early versus later irradiation demonstrated that early radiotherapy had no significant impact on OS [25]. Rather, irradiation may generate delayed cognitive disorders [26]. Therefore, because radiotherapy is not the first therapeutic option to consider in DLGG, the impact of surgery has been more rigorously studied in the recent literature.
Comprehensive reviews suggested that a more extensive resection of DLGG was correlated with a more favorable OS [27,28]. In an analysis of 10 studies since 1990, Sanai and Berger showed that the OS changed from 61.1 to 90.5 months with a greater extent of resection (EOR) — i.e. gross–total versus subtotal resection, respectively [29]. However, the main problem explaining discrepancies in the classical literature is related to the fact that, in the vast majority of series, EOR was not objectively assessed on postoperative MRI, but was based on the sole subjectivity of the surgeons or on a single computed tomography scan, with no volume measurement of the residue. Due to the invasive feature of DLGG, the residual tumor was doubtlessly underestimated in numerous studies, resulting in erroneous conclusions about the benefit of surgery. In fact, T2/FLAIR-MRI is the only way to actually calculate the postsurgical volume of (possible) residual tumor (Fig. 1).

3.1. The modern literature

In all the recent series since 2005 based on an objective postoperative evaluation of EOR on T2/FLAIR-MRI, a more aggressive resection predicted a significant improvement in OS compared with a simple debulking. These studies agreed with the fact that when no signal abnormality was visible on control MRI (“complete resection”), patients had a significantly longer OS compared with patients having any residual abnormality. In the series by Smith et al. including 216 DLGG, after adjusting for the effects of age, KPS, tumor location and tumor subtype, EOR remained a significant predictor of OS (hazard ratio [HR] = 0.972; 95% confidence interval [CI], 0.960 to 0.983; P < 0.001), with 8-year OS of 98% of patients with complete resection [30]. In 156 DLGG, Claus et al. reported that patients who underwent incomplete resection were at 4.9 times the risk of death relative to patients with total resection [31]. In 222 DLGG, Duffau et al. found a significant correlation between complete resection and OS [32]. Yeh et al. also demonstrated that, in multivariate analysis performed in a consecutive series with 93 DLGG, EOR and postoperative KPS showed independent prognostic significance for OS rates [33]. McGirt et al. observed that gross–total resection versus subtotal resection was independently associated with increased OS (HR: 0.36; 95% CI: 0.16–0.84; P = 0.017) [34]. In 130 DLGG studied by Ahmadi et al., extended surgery was shown to significantly prolong OS [35]. Schomas et al. also reported that, in an experience with 314 DLGG patients, adverse prognostic factors for OS identified by multivariate analysis were tumor size 5 cm or larger, presentation with sensory motor symptoms, pure astrocytoma histology, Kernohan grade 2, and patients undergoing less than subtotal resection [36]. In 190 DLGG, Ius et al. demonstrated that patients with an EOR of 90% or greater had an estimated 5-year OS rate of 93%, those with EOR between 70% and 85% had a 5-year OS rate of 84%, and those with EOR less than 70% had a 5-year OS rate of 41% (P < 0.001) [37]. Finally, the French Glioma Network published the largest surgical series of DLGG even reported, showing with an experience of 1097 patients that EOR as well as the post-surgical residual volume were independent prognostic factors significantly associated with a longer OS [38].

Even in incomplete tumor removal, patients with a greater percentage of resection had a significantly longer OS. The survival was significantly better with at least 90% EOR compared with less than 90% EOR, whereas EOR of at least 80% remained a significant predictor of OS [30]. The postoperative tumor volume is also a predictor of survival, with a significantly longer OS when the residue is less than 10 cm³ (“subtotal resection”) compared with more than 10 cm³ (“partial resection”). In a subgroup of 122 DLGG patients who underwent surgery with intraoperative functional mapping, Duf fau et al. showed that, with a median follow-up of 4 years, 20.6% of patients with more than 10 cm³ of residue died, while only 8% of patients with less than 10 cm³ of residue died — and that no patients with complete resection died (P = 0.02) [32].

Such an impact on OS is due to the fact that surgery delayed histological upgrading, because the volume of residual tumor serves as a predictor of AT. In the series Smith et al., after adjusting for the effects of age, KPS, tumor location and tumor subtype, EOR remained a significant predictor of malignant progression-free survival (HR = 0.983; 95% CI: 0.972 to 0.985; P = 0.005) [30]. In 191 consecutive DLGG patients, Chaichana et al. also showed that gross-total resection was an independent factor associated with AT (RR: 0.526, 95% CI: 0.221–1.007; P = 0.05) [39].

3.2. Towards a supra-total resection of diffuse low-grade glioma (DLGG)

Biopsy samples within and beyond MRI-defined abnormalities showed that conventional MRI underestimated the actual spatial extent of DLGG, since tumor cells were present around the area of MRI abnormality without reaching it. However, a recent series reported that a “supra-total” resection — that is, resection extending beyond the area of MR imaging signal abnormalities — performed in 15 patients with a DLGG within “noneloquent” brain regions avoided AT with a mean follow-up of 35.7 months (range 6–135) [40]. This series was compared with a control group of 29 patients who had “only” complete resection for a DLGG: AT was observed in seven cases in the control group but in no cases in the series of patients who underwent supra-total resection (P = 0.037). Furthermore, adjuvant treatment was administered in 10 patients in the control group while only one patient who underwent supracomplete resection had adjuvant treatment (P = 0.043). However, four of 15 patients with supracomplete resection experienced recurrence, probably due to the fact that it was not possible to take at least 20 mm of margin all around the tumor in all patients due to functional limitations. It means that the goal of supra-total resection is to delay AT and the administration of adjuvant therapy, without claiming to cure DLGG patients [40].

3.3. The value of re-operation(s)

Because relapse is possible after total or even supra-total resection, and because continuous growth of the residual tumor is ineluctable after incomplete resection, the impact of a second surgery was investigated. In 40 patients re-operated for recurrent DLGG without other intervening therapy between surgeries, Schmidt et al. showed that a gross-total resection was associated with an increased time to repeated surgery [41]. In 130 DLGG, Ahmadi et al. observed that extended resection for non-malignant relapse (a total resection could be achieved in 53.1% of recurrent tumors) prolonged the OS significantly [35]. In the French Glioma Network series, subsequent surgical resection was an independent prognostic factor significantly associated with a longer OS [38]. Martino et al. also reported a consecutive series of 19 patients who underwent a second surgery for recurrent DLGG in eloquent areas [42]. A total or subtotal resection was achieved in 73.7% of patients during the re-operation, despite an involvement of functional areas. Such “multistage surgical approach”, with an initial maximal function-guided resection, followed by a period of several years, and then a second surgery with optimization of EOR while preserving QoL, is possible thanks to mechanisms of brain plasticity induced both by the tumor (re)growth as well as by the first resection itself [43,44]. The median time between surgeries was 4.1 years and the median follow-up from initial diagnosis was 6.6 years with no death during this period. Thus, the authors suggested to consider re-operation(s) in all recurrent DLGG. Nonetheless, due to a high rate of AT histologically proven of 57.9% at re-operation,
it was proposed to "over-indicate" an early re-intervention rather than to perform a late surgery when AT already occurred [42].

3.4. The limited role of biopsy in diffuse low-grade glioma (DLGG)

Currently, the indications of biopsy are very limited in DLGG. Indeed, by combining clinical and radiological data, the diagnosis of glioma is typical in the vast majority of cases. Thus, the main goal of neuropathological examination is to give the actual grade of the glioma. However, there is a high risk of sampling error. Muragaki demonstrated that overgrading of WHO grade I gliomas occurred in 11% of cases and undergrading of WHO grade III gliomas in 28% [45]. Conversely, maximal DLGG resection provides a more extensive amount of tumoral tissue, and thus increases the reliability of the histological diagnosis and grading [28].

Fig. 1. A. Preoperative axial FLAIR-weighted MRI showing a left frontal diffuse low-grade glioma (DLGG) incidentally discovered (headaches) in a young right-handed adult with a normal neurological examination and enjoying a normal life. The preoperative neuropsychological examination demonstrated slight attentional disorders. B. Intraoperative photograph. Left: view before resection showing the tumor limits (letter tags) identified by ultrasonography as well as the eloquent cortical structures (number tags) detected by direct electrostimulation (DES). Right: view after glioma removal, performed according to functional boundaries — detected by DES both at cortical and subcortical levels throughout the resection (no neuronavigation, no intraoperative MRI). In other words, a functional-mapped guided resection was achieved, and not an image-guided resection. C. Postoperative axial FLAIR-weighted MRI, demonstrating a resection of the DLGG (histologically confirmed), including its part involving the so-called "Broca's area" as well as within the corpus callosum. Despite an extensive left frontal lobectomy, the patient recovered, and returned to normal social and professional lives (full-working) 3 months after surgery, with no symptoms. Interestingly, there was an improvement of the objective cognitive assessment performed 3 months following the resection in comparison with the pre-surgical evaluation, thanks to a specific cognitive rehabilitation. No antiepileptic drugs and no adjuvant oncological treatments were given.

A. IRM préopératoire, coupe axiale, pondération FLAIR, qui montre un gliome de bas grade, diffuse, frontal gauche, de découverte fortuite (céphalées), chez un jeune adulte droitier présentant un examen neurologique normal et menant une vie normale. Le bilan neuropsychologique préopératoire a objectivé quelques troubles modérés de l’attention. B. Photographies peropératoires. À gauche : vue avant la résection, montrant les limites de la tumeur (étiquettes avec lettres) identifiées par échographie, de même que les structures corticales fonctionnelles (étiquettes avec chiffres) détectées par stimulations électriques directes. À droite : vue après la résection du gliome, effectuée selon des limites fonctionnelles — détectées par stimulations électriques peropératoires à la fois en cortical et sous-cortical tout au long de l’exérèse (pas de neuronavigation, pas d’IRM peropératoire). En d’autres termes, il s’agit d’une résection guidée par la cartographie fonctionnelle et non par l’image. C. IRM postopératoire, coupe axiale, pondération FLAIR, qui montre la résection d’un gliome de bas grade diffus (confirmé par l’histologie) incluant une partie impliquant la région dite « de Broca », de même que le corps calleux. En dépit d’une lobectomie frontale gauche étendue, le patient a récupéré et a repris une vie sociale et professionnelle normale (travaille à plein temps), trois mois après l’intervention, sans symptôme résiduel. Il est intéressant de noter qu’une amélioration cognitive a été mise en évidence sur un bilan objectif effectué trois mois après l’exérèse, en comparaison par rapport à l’évaluation préopératoire, et ceci, grâce à une rééducation spécifique. Aucun traitement n’a été donné, ni antiepileptique, ni oncologique adjuvant.
Furthermore, biopsy has no therapeutic impact. Therefore, because the risk of MR-guided stereotactic biopsies is still around 2% of permanent deficits [46], their indications for presumed DLGG are essentially contraindications of surgery. Beyond patients who don’t want or who are not able to undergo surgical resection for medical reasons, biopsy can be mainly considered in diffuse lesions, such as gliomatosis, or when a subtotal resection is not a priori possible. Such a pre-surgical prediction can be optimized by the use of a probabilistic map of postoperative residue, based on the computation of residual gliomas resected according to functional boundaries: this atlas allows a preoperative estimation of the expected EOR with a success rate of 82% [47].

4. Functional considerations: awake surgery for maximal resection of diffuse low-grade glioma (DLGG)

4.1. The conceptual shift from an image-guided surgery towards a functional mapping-guided resection

Based on these strong oncological results, brain surgeons should change their mind, by operating the nervous system involved by a chronic tumor disease — and no more by operating a “tumor mass” [21]. The goal is not to content with a single “tumorectomy”, i.e. removal of the part of the tumor visible on imaging, but to perform the most extensive resection of the brain invaded by DLGG, on the condition that this part of the brain is not crucial for cerebral functions. Thus, neurosurgeon should adapt his surgical procedure to the individual cerebral anatomo-functional organization. The technique within the central nervous system has to be different from the surgical technique outside the brain. Indeed, the first principle in glioma surgery should be to tailor the resection according to functional boundaries, with no margin, to maximize the tumor removal while preserving eloquent structures [44].

The methods of intrasurgical imaging (neuro-navigation, intraoperative MRI) suffer from serious limitations. First, from an oncological point of view, conventional T2/FLAIR-MRI does not show the whole tumoral disease but only the top of the iceberg. Indeed, tumors appear on MRI only for cell densities above 500 cells/mm³ [48]. Therefore, when DLGG is distant from eloquent structures, image-guided resection is by definition a non-sense. Indeed, it is possible in these specific cases to remove more tumoral cells while preserving the function, i.e. to perform a “super-total” resection, with the impact on AT detailed above, on the condition nevertheless not to constraint the resection according to the MRI [40]. The use of neuro-navigation or intraoperative MRI is based on a reductionist concept, that is, the exclusive removal of the signal abnormality, with no attempt to increase the resection beyond these landmarks — even if they do not reflect the whole glioma disease. Consequently, image-guided resection may represent a loss of chance for patients with a DLGG outside critical regions [9].

From a functional point of view, due to a great interindividual anatomo-functional variability, even though anatomical landmarks remain essential during cerebral surgery, they are definitely not enough. The aim is to continue the removal of the brain invaded by DLGG until crucial eloquent structures have been encountered, both at cortical and subcortical levels, with no margin around these functional boundaries [49]. Neurosurgeons have tendency to believe that the data provided by functional MRI and diffusion tensor imaging are the “absolute truth”. Yet, functional neuroimaging is based on biomathetical reconstruction, with results which may change according to the model, explaining its lack of reliability at the individual level, especially regarding cognitive functions such as language [50,51]. Furthermore, neuroimaging is not able to differentiate areas crucial for brain functions from regions which could be functionally compensated. Thus, there is a double risk: to not select a patient for DLGG surgery because fMRI activations are visible very near or within the tumor, while it was in fact possible to remove it with no permanent deficit (thus with a loose of chance from an oncological point of view); or to induce a permanent deficit due to a false negative.

4.2. Cortico-subcortical mapping using direct electrostimulation (DES): a major role to improve the onco-functional balance of surgery

Intraoperative electrostimulation mapping in awake patient is actually the more reliable method to identify eloquent regions. The goal here is not to detail the methodology of direct electrostimulation (DES), which was extensively described in previous reports [52,53]. This is an easy, safe, non-expensive, reliable and reproducible technique allowing the identification of crucial (non-functionally compensable) structures at the level of the cortex, white matter pathways and deep gray nuclei— and thus to perform real-time anatomo-functional correlations throughout the resection [54].

In the past decade, brain mapping has led to an impressive improvement of both functional and oncological outcomes in DLGG surgery. First, patients who were classically not selected for surgery, on the basis of pure anatomical criteria (e.g. gliomas involving the “Broca’s area”), can now benefit from resection with no dogmatic a priori against the surgical feasibility due to tumor location. The use of intrasurgical DES allowed a significant increase of the surgical indications for DLGG involving so-called “eloquent areas”, when compared with a control group of patients who underwent resection under general anesthesia with no mapping [32]. For example, surgical resection is possible with no permanent neurological worsening for DLGG within Broca’s area, Wernicke’s area, insula, left dominant inferior parietal lobule, retrocentral area and even the precentral region [20,44,52].

Furthermore, the rate of permanent neurological deficits was shown to be significantly lesser thanks to awake mapping, i.e. less than 2% in the recent series using DES [54,55]. This rate is very reproducible among the teams using awake mapping worldwide. Indeed, a recent meta-analysis studying more than 8000 patients who underwent surgical resection for a brain glioma demonstrated that the use of intrasurgical mapping allowed a statistically significant reduction of permanent deficit, despite an increased rate of resection within eloquent areas [56].

This meta-analysis also showed that EOR was increased [56]. This is in line with a recent series in which 9 patients underwent two consecutive surgeries for a DLGG: the first resection was performed in a traditional way, that is, under general anesthesia and without mapping, whereas the subsequent surgery was done in a maximal way, in awake patients using DES. Following the re-operation, postoperative MRI showed that the resection was improved in all cases compared with the first surgery (P = 0.04), with no permanent neurological worsening [57]. Finally, a series of 281 patients demonstrated that the use of functional mapping-guided resection of DLGG in presumed eloquent areas, thanks to a reliable delineation of true functional and nonfunctional regions, allowed not only a maximization of EOR but also a significant improvement of OS [58].

5. Conclusion

Currently, as stated by the European guidelines, surgery is the first therapeutic option in DLGG patients [59]. Because DLGG is a diffuse brain disease, which frequently invades eloquent regions, neurosurgeons should take the habit to see the brain first, and not the tumor, by performing early and maximal resection according
to functional (and not purely oncological or anatomical) boundaries in awake patients. This perspective seems to represent the best way to build a modern and personalized "functional surgical neuro-oncology". The next step will be to evolve towards "preventive neurosurgery" by achieving removal of incidentally discovered DLG in asymptomatic patients [60].

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

References


