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ABSTRACT

Low-grade glioma is characterized by slow growth, infiltrative pattern through white matter tracts and progression to a malignant tumour type. The traditional classification is newly replaced by molecular stratification. This reorganisation gathers glioma with similar prognosis and treatment protocols. The preferential location of that tumour in eloquent areas constituted, over time, a real challenge regarding the best surgical approach. Because of the high risk of postoperative neurological deficits initially a more conservative management was adopted. Once with the development of preoperative and intraoperative functional assessment techniques, a higher degree of resection was possible in the limits of cortico-subcortical eloquence, being well known that this is a statistically significant factor for survival. We present in this paper the natural evolution of low-grade glioma, their new molecular classification, prognostic factors and the various approach proposed for eloquent ones.

NATURAL HISTORY AND THE NEW MOLECULAR CLASSIFICATION

Diffuse low-grade gliomas or World Health Organisation grade II gliomas (LGG) represents a group of tumours developed from oligodendrocyte and astrocytic precursors, with a slow and continuously growth pattern, infiltrative character, usually along white matter tracts and progression towards a malignant histological type. Traditionally this includes diffuse astrocytoma, oligodendroglioma and oligoastrocytoma [35,66].

Keywords

low-grade glioma,
LGG,
molecular markers,
functional area tumour,
intraoperative
neuropsychological
monitoring



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In the new classification of central nervous system tumours from 2016, the phenotypical and genotypical manifestation are in the foreground. The molecular markers like isocitrate dehydrogenase (IDH) mutant / wild type, codeletion of chromosome 1p and 19q, α thalassemia mental retardation X-linked (ATRX) and tumour protein p53 (TP53) genes stratify patients in groups with the same prognostic and guides the cases to a specific therapeutic protocol [36,43]. According to those markers, nowadays, LGG grade II includes: oligodendroglioma IDH mutant and 1p / 19q codeleted, diffuse astrocytoma IDH mutant and diffuse astrocytoma IDH wild type. In patients to which these molecular markers cannot be evaluated the histological diagnosis will be oligodendroglioma not otherwise specified (NOS) or diffuse astrocytoma, NOS [16,35].

LGG occurs usually in young adult, 30-35 years old being the incidence peak [61]. Regarding the natural history of these lesions, it may be summarized in four steps. The first one consists in biological glioma tumoral cells transformation with no clinical manifestation and no routine head MRI detection [34]. The chronological order, from a molecular point of view is represented by IDH mutation, which is thought to be the first, next codeletion of chromosome 1 and 19 (1p/19q) occur and after telomerase reverse transcriptase (TERT) promotor mutation is produced. Some germ lines are associated with tumour grade, the former being found in low-grade glioma and the latter in high-grade glioma [3].

In the second step, the silent stage, the patient is asymptomatic but with imagistic alterations. In this period glioma may be incidentally diagnosed. In the literature, the percentage of incidental LGG (iLGG), from all LGGs, is approximatively similar between studies: 3-10% (Smits et al., 2019) – 3,8%-9,6% (Ius et al., 2020) [27,62]. They have a smaller volume and usually are within non-eloquent brain areas. Even though the diagnostic is obtained after imagistic head investigation for other reasons than a tumour, 36% of all the patient with LGG had the workload decreased for at list one year before lesion discovery [62]. In a study from 2013, Pallud et al., evaluated 148 iLGG cases and observed that the mean time duration until the next phase was $14 \pm 7,8$ years [46]. Concerning the growth rate of iLGG which was obtained after at list two MRI investigation evaluation at 3 months interval was found to be ranging from

2,93 mm/year (Opoku – Darko et al., 2019) to approximately 4mm/year (Pallud et al., 2013) [43,46].

In the third step, the symptomatic stage, the lesion generates clinical manifestation, most frequently epileptic seizures, which are a proof of somatotopic organization of the cortex where the tumor locates. For example, pericentral region induce Jacksonian motor or somatosensory seizures; temporal lobe – déjà vu phenomena, memory dysfunctions, auditory hallucinations; Wernicke area – sensitive aphasia; Broca area – speech arrest, mutism; insula – paraesthesia, dysarthria, abdominal and thoracic discomfort [47,62]. The average period of this stage is about 7 years and sometimes subtle cognitive impairment may be associated. In general, the cognitive performance is similar to that of healthy population, but specific neurophysiological assessment protocols may highlight memory, attention and executive function disturbance [14,15,49].

The fourth step, the malignant stage consists in tumor malignant progression to a higher histological grade. This happens over a period of 2-3 years and the clinical manifestations are more complex, with neurological degradation and in the final stage death occurs [16,19,34].

SURVIVAL AND PROGNOSTIC FACTORS

The survival rate of LGG grade II it is variable, ranging from a few months to over 15 years. The possible factors which may influence the overall survival (OS) are represented by the neurosurgical and oncological management, the histological type or more precise by molecular markers and by clinical parameters [2,22]. Some of them are independent and cannot be changed, but on others we may act. Taking this into account, Zhao et al., proposed in 2019 a nomogram to predict individual 5- and 9-years OS, using 7 clinical and paraclinical parameters [67].

A meta-analysis published in 2019 by Brown et al., confirms that extent of resection has a statistically significant impact over survival rate and progression free survival at 2, 5, 10 years. This parameter constitutes an independent predictor, not being influenced by age or preoperative tumor volume [8,16]. The same results are confirmed and by Choi et al., in a paper from 2020 where he showed that for patients in whom gross total resection (GTR) could not be performed presented recurrence more

frequently after radiotherapy (IDH wild type: 57,9% and IDH mutant: 47,6%) [12].

Regarding the precise value of the extent of resection, there are no exact values, positive effects were observed even from a debulking of 40 % of the tumor and a residual volume <15cm³ (Roelz et al., 2016), but is well known the statistical significance of a higher resection [2,52]. This is confirmed in a paper of Lus et al., in which 190 cases of LGG located in functional areas were included. A resection less than 70% compared with one of more than 90% had a risk of death 19,7 times higher, tumour progression was found to be 13,6 times higher and malignant transformation 9,7 times higher [28].

The best prognostic is carried by oligodendroglioma IDH mutant and 1p/19q codeleted and the worse by astrocytoma IDH wild

type [8,35]. The negative prognostic was associated with a tumor volume > 5 cm (Nitta et al., 2015), functional area location (Gousias et al., 2014), Karnofsky performance scale ≤ 80% (Gousias et al., 2014), age ≥ 40 years (Franceschi et al., 2018) and IDH wild-type genetics (Lombardi et al., 2020) [22,25,35,42].

Clinical manifestation with neurological deficits, the absence of seizures, tumour crossing the midline, short time of symptoms before diagnosis, rapid growth rate and the astrocytic type carry an unfavourable impact [16,19,24,30,44]. In **Table I** we have a schematic representation of the new classification of LGG grade II with their specific molecular markers, the impact over survival rate and some specific characteristics.

Table 1. Low grade glioma, the molecular diagnosis markers, and survival impact [1, 16,19, 32,36, 38, 40].

Tumor nomenclature	Molecular markers and prognosis	Notes
Oligodendroglioma, IDH mutant and 1p/19q codeleted	IDH mutant (70-80% of the tumors) – longer OS 1p/19q codeleted Tp53 (5% of the tumors)	-the best prognosis. -more sensitive to chemotherapy.
Oligodendroglioma, NOS	No molecular marker evaluated	
Diffuse astrocytoma, IDH mutant	IDH mutant – mandatory. Tp53 mutation –may be found, shorter OS. ATRX loss – may be found.	-the classical variants protoplasmic and fibrillary astrocytoma were deleted. - small difference in OS compared to anaplastic astrocytoma IDH mutant*.
Gemistocytic astrocytoma, IDH mutant	Tp53 mutation in >80% of cases	-the only type of astrocytoma recognized
Diffuse astrocytoma, IDH wild type	No mutation present of IDH1 codon 123 and or IDH2 codon 172	- usually, uncommon. - not all have poor prognosis. - some have similar manifestation as glioblastoma.
Diffuse astrocytoma, NOS	No molecular marker evaluated	
Oligoastrocytoma, NOS	Oligodendroglioma and astrocytic elements Only in the absence of molecular assessment Under previous entities	- “true” lesion with spatial distinct of both elements in the same tumor are reported.

* OS for diffuse astrocytoma IDH mutant was 10,9 years and for anaplastic astrocytoma IDH mutant 9,3 years in a large series similar regarding the age distribution (Reuss et al., 2015) [51].

SURGICAL APPROACH

The infiltrative feature of these lesions determined Duffau to describe them as “an infiltrating chronic disease that progressively invades the central nervous system”, usually the subcortical pathways are affected, and so different neurological functions

may be altered [19]. Regarding their location, usually are found in eloquent areas, especially in supplementary motor area and insula, followed by language centres. The preferential development may be explained by cytoarchitectonic (agranular – dysgranular – granular cortex) and functional

similarities between these brain regions [17]. As far their position, the surgical management remain a challenge for every neurosurgeon. Over time, the strategies changed aiming a higher degree of resection with minimal neurologic postsurgical deficits [6].

Because of the increased risk of postoperative neurologic dysfunction for gliomas located in eloquent areas, functional preoperative and intraoperative techniques use is mandatory. The evolution of surgical strategies for these lesions was correlated with the rapid and continuous development of imagistic diagnosis modalities and intraoperative functional assessment techniques. Even though the extent of resection is correlated with survival, nowadays the quality of patient's life is one of the main goals [21, 50, 53].

The surgical management of eloquent LGG suffered many changes over the time. Initially, the approach "wait and see" was applied, but nowadays we can talk even about supratotal resection. The conservative treatment was indicated for incidental glioma and for young patients with minor symptoms [9,21,54].

After a period, when "wait and see" policy was the only measure taken, biopsy become a part of the surgical management, especially for young patients with no neurological deficits, no mass effect and with minor symptoms. This type of treatment has one drawback: because of the tumors heterogeneity, even image-guided stereotactic samples may impair the histological diagnoses, undergrading the lesion. Muragaki et al., highlighted in an article from 2008 that tumors with low proliferative activity, MIB-1 less than 3% and mixt gliomas are more susceptible to this error. This situation may induce a wrong inclusion of the case in a protocol treatment and a misinterpretation of the prognosis. On the one hand, a way to lower this possibility is to perform multiple sampling from various parts of the tumor. On the other hand, for neoplasms located in functional areas this action may be associated with postoperative neurological dysfunctions [41].

Nowadays the bias, in histological interpretation induced by stereotactic biopsy sampling compared with the specimens obtained from a classical intervention is reduced because of molecular analysis and new classification of the gliomas [29].

Clinical studies concluded that early surgery may delay malignant transformation and increases

overall survival in low grade glioma patients. Maximal resection in functional limits is indicated and for tumours located in functional areas of the brain. The development of intraoperative neurological functions assessment technologies e.g., neurophysiological monitoring (Magil et al., 2018; Bander et al., 2020), 3D tractography integrated in neuro-navigation system (Romero-Garcia et al., 2020), awake craniotomy (Saito et al., 2018; Wang et al., 2019), fluorescein-based surgery (Coburger et al., 2019), intraoperative MRI (Caras et al., 2020; Scherer et al., 2020) help in obtaining a maximal resection with minimal postoperative dysfunction [6, 10, 13, 31, 37, 53, 56, 59, 63].

Jackola et al., highlighted the important survival advantage when comparing wait and see approach with early tumor resection. For the first group the median of OS was 5,8 years and 14,4 years for the second group [29].

In a metaanalysis performed by Yang et al., in 2018 a comparison was made between biopsy and surgical resection (GTR and subtotal resection – STR). OS was found to be 3,7 years in biopsy patients' group, 6,6 years for STR cases and 10,6 years for GTR cases. Statistical significance was obtained comparing biopsy with any degree of resection, in favour of surgical debulking [65]. Considering the ones above, only biopsy is performed in patients who have contraindication for an open surgery because of severe medical pathologies or when even subtotal resection is not feasible [19].

As mentioned before, the study of LGG literature considers eloquence as a negative prognostic factor. Chang et al., showed that this parameter induced over the 281 functional located diffuse glioma cases an increased hazard ratio with shorter OS and PFF [11]. A shift from image – guided surgery to functional – guided resection made possible to perform a higher degree of resection by delineating the preoperative presumed eloquent situated lesion from the ones truly eloquent. When cortical mapping was negative and the functional area was actually relocated and not in contact with the tumour, the survival of those cases was longer and similar to those in non-eloquent areas [4,11].

Even if the glioma is developing in eloquent area, the slow growth pattern, is considered as an advantage which allows the neuroplasticity process to act. This concept was at the base of the proposal of individualized multistage surgery. A better

understanding of brain plasticity, development of neurocognitive protocol assessment for cerebral tumours and personalized postsurgical cognitive and functional rehabilitation increased the chance for a better outcome. Duffau presented the steps of this approach. After the first operation, where a subtotal resection was performed, limited by the functional borders, the patient was evaluated periodically clinically and radiologically and a second surgery was scheduled, if needed, considering the tumor regrowth and cortical remapping. This allows to increase the extent of resection and to maintain the neurological integrity [18,19,21].

One of the first presentation of this technique performed over 19 cases of eloquent LGG was from 2009. The results of Martino et al. showed the safety of this strategy. The patients were operated two times with a median time of 4,1 years between intervention and intraoperative neurophysiological monitoring was used. The functional guided surgery resulted in allowing 94,7% of the cases to have a normal socio-professional life [39].

Another strategy proposed for eloquent LGGs was the safe margin technique resection. This policy was based on the development of perioperative assessment methods, especially functional magnetic resonance imaging (fMRI) and brain mapping. In the early 90s, using intraoperative neurophysiological monitoring, Ojemann recommended a 7-10 mm secure margin preservation around positive sites, after observing that this is associated with fewer postoperative neurological deficits. The results were based on the fact that for cortical mapping the electrodes from the subdural grid were placed at one-centimetre distance from each other [26, 57].

In the same surgical direction are presented the results of 54 motor area tumour resection using the fusion of preoperative fMRI with neuro-navigation, in an article of Krishnan et al. published in 2004. In 83,33% of the cases gross total resection was achieved and subtotal (80-95% of the tumour volume) was performed to the rest of the patients, the postoperative new deficits were recorded in 16,7% of the cases. The author observed and concluded that a distance less than 5 mm from the tumour to the active functional site is associated with high risk of motor dysfunction and a greater distance than 10 mm is safe for gross total resection [33].

New fMRI studies confirmed the relationship between the tumour borders and the location of the

eloquent sites, regarding the postoperative new neurologic deficits. In 2011 Wood et al. observed some difference between the behaviour of the motor and primary language areas regarding the distance to the lesion. For motor strip when the distance was 1 - 2 cm compared to greater than 2 cm, the incidence of neurological dysfunction was 39%, a 34% increase was observed when less than 1cm was met. As for language area a nonlinear manifestation was found. The prevalence of aphasia increased significantly when the distance was less than 1 cm. The difference of the functional and structural organization of the motor area and language areas may explain these results, beside the high grade of individual variability of the latter [64].

It is well known that not only the cortical functional sites are important and need to be preserved but also the subcortical motor and language pathways. In 2015 Bailey et al. evaluated if the lesion to distance activation (LAD) is a predictor factor for the perioperative language and motor deficits. He used fMRI and assessed the superior longitudinal fasciculus (SLF) and corticospinal tract (CST) with diffusion tensor imaging (DTI) on 76 cases of functional located tumours. Postoperative, the only significant difference was noted for motor LAD with a trend level effect. The involvement of CST was significantly statistically for pre and postoperative motor deficit, in comparison SLF involvement had a significance only between asymptomatic and symptomatic preoperative cases [5].

Sollman et al. presented in 2020 the results of evaluating the impact of the distance from the lesion to CST or arcuate fascicle (AF) of 250 functional located tumours which were assessed using navigated transcranial magnetic stimulation and DTI fibre tracking. The most statistically significant postoperative neurological impact observed for CST was for a distance less than 12mm, for AF less than 16mm and the value of 25 mm for any other language tract [61]. In an previews study from 2019, Sollman et al. found that a distance greater than 8 mm from the tumour to the AF and one greater than 11mm for the other fascicle involved in the language pathways were associated with permanent aphasia. These differences may be explained by the difference between the two studies regarding the cases numbers and the fact that the permanent deficit was not so high, hindering the statistical evaluation [60].

White matter dissection, development of 3D tractography helped in discovering and understanding the subcortical pathways anatomy. A functional atlas of white matter fibres was proposed after evaluating 130 eloquent tumours operated awake and with intraoperative neurophysiological monitoring [58]. The anatomo-functional structure of the brain is the bases of the next type of approach used for functional located gliomas: cortical subpial dissection. Duffau and Gil-Robles compared the results regarding the postoperative deficits of the patient with eloquent glioma operated with and no safe margins around the functional area. They did not find a significative difference between the two techniques when the permanent deficit was evaluated (1-2,5% vs. 1,7%), even though the transient deficit was higher for the latter technique, this suggesting that subpial dissection and intraoperative mapping is a safe strategy for eloquent LGG. The assessment of cortical areas along with the projection tracts, long distance association fibres and short association fibres (U-fibre) increase the degree of resection while preserving and minimizing the postoperative deficits [23]. A tailored intraoperative monitoring may improve the neurological outcome, but the survival rate was found to be the same (Pan et al., 2020) [48].

Even though it seems utopian, the question about the feasibility of supramarginal resection for presumed eloquent glioma was asked. This concept has at the basis the observation made after biopsy tissue, from beyond the abnormal FLAIR-MRI signal, was evaluated and tumor cells were found, even at a distance of 20 mm from the preoperative images lesion demarcation. The first study with a long follow-up period (132 months) showed no case of malignant transformation and no relapse at half of patients, highlighting the impact of supramarginal resection over tumor progression [7, 20, 45].

An extensive analyse was performed by Rossi et al., in an article from 2020 regarding this supposition. The study group included 449 glioma cases, 413 of them imagistic located in functional areas. The results showed that the most important and statistically significant factor associated with achieving this degree of resection was the duration of the symptoms longer than 6 months and was independent of age, sex and tumor volume. The safety of this procedure for lesion preoperatively presumed to be in eloquent area and a good

neurological outcome is explained by the activation of neuroplasticity processes with a high reorganisation of the cortico-subcortical pathways and intraoperative identification of the functional sites outside the tumors margins. Smaller odd of obtaining this result was for parietal lesions compared with temporal and frontal location. From all four hundred forty-nine patient supratotal resection was obtained in 32,2% and total resection in 40,8% of the cases. Regarding the postoperative new deficits, the transient type remitted in 1-2 week and the permanent one was lower in comparison with those from the patient's group where subtotal or partial removal was performed (6,6% vs 0,55%; 6,6% vs 0.68%, $p < .001$) [55].

CONCLUSION

Considering the natural history, the continuous, slow growth and histological progression make the surgical treatment of low-grade gliomas to be the first choice in their management. The development of preoperative radiologic evaluation and intraoperative function assessment techniques, especially cortical and subcortical mapping helps in performing a higher degree of resection with minimal neurological dysfunction and for eloquent located LGG. We witness the evolution and the advance made regarding the surgical approach of these tumours from wait and see policy to even evaluation the feasibility of supramarginal resection.

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