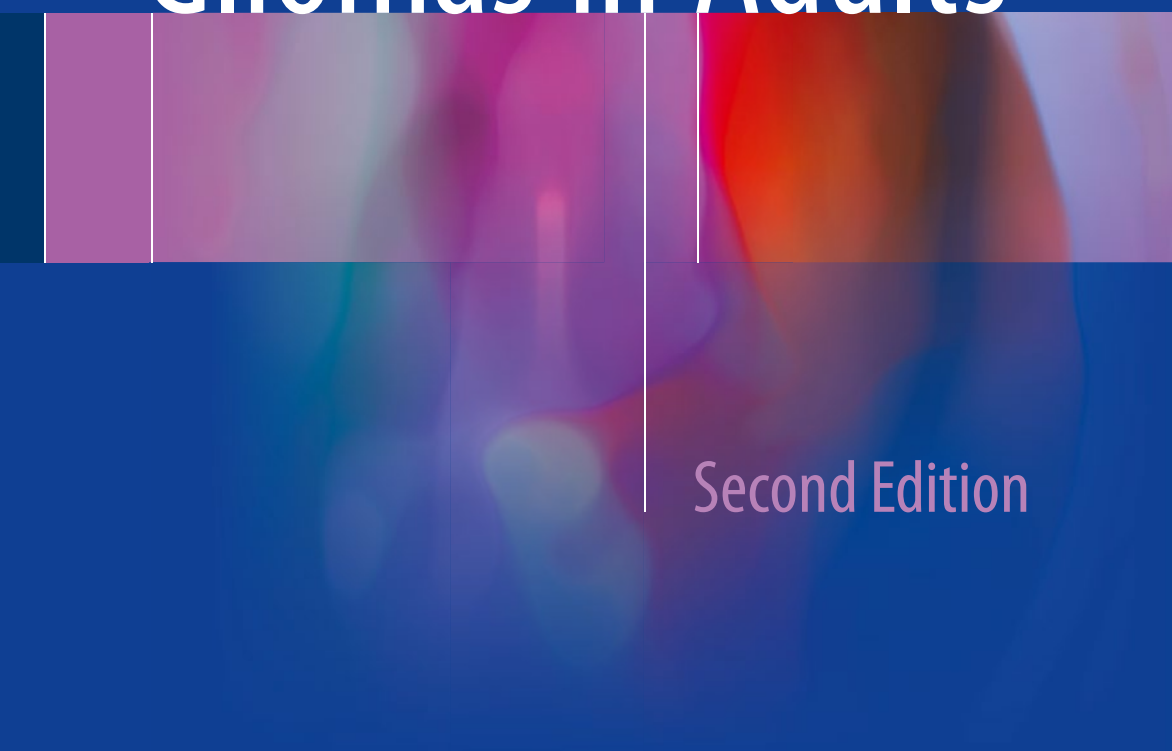
Hugues Duffau
*Editor*

# Diffuse Low-Grade Gliomas in Adults



Second Edition

Springer

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# Foreword

It is a pleasure for me to write the foreword to the second edition of this textbook entitled *Diffuse Low-Grade Gliomas in Adults*. The first edition was a resounding success establishing this as the definitive source on the subject. This collective body of work was desperately needed when it came on the scene several years ago. Led by the editor, Hugues Duffau, it comprehensively covered every topic in great detail by a cast of experts in the field. In this sense, the second edition is a continuation of the depth and breadth of the knowledge necessary to fully appreciate and understand this extraordinarily complex subject.

The book starts off with critically important chapters covering the evolving area of population science and molecular classification. It is quite timely since the World Health Organization has issued its latest phenotype-genotype categories of low-grade gliomas based on up-to-date genomic information which is now used to distinguish these tumors. The section on fundamental sciences documents the biology of these tumor types and nicely characterizes them and why they behave as they do clinically. I particularly like the way in which the clinical and diagnostic features of these tumors are depicted in a series of detailed chapters on these subjects. Certainly, the most important aspect of this disease is to aggressively and safely resect the tumor. The extent of tumor resection remains at the forefront as the most powerful predictor of patient outcome, yet achieving this goal is often difficult and requires a significant attention to functional patterns of connectivity either within or adjacent to the tumor. To this end, Dr. Duffau is a master at explaining and detailing these intricate functional considerations that are so important in achieving a safe maximal resection. This includes a fundamental understanding of neuroplasticity which is covered quite nicely by Dr. Duffau. Subsequent chapters thoroughly cover the therapeutic strategies and options for managing this tumor following surgery. Finally, this text ends with several interesting and informative chapters that are germane to this topic such as how to model and predict patterns of growth and behavior as well as the origin of this tumor and the potential role of population-based screening for incidental lesions.

In essence, this text remains the definitive source on this complicated subject. It has been kept up nicely with the evolving science and clinical practice of how best

to approach and manage diffuse low-grade gliomas in adults. I applaud Dr. Duffau and his colleagues for once again bringing everything known about this tumor within the confines of one textbook. This is a must read for anyone in the field!

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# Contents

# Chapter 1
# Introduction: From the Inhibition of Dogmas to the Concept of Personalized Management in Patients with Diffuse Low-Grade Gliomas

**Hugues Duffau**

**Abstract** Recent technical and conceptual advances in genetics, cognitive neurosciences, imaging, and treatments have revolutionized our understanding of diffuse low-grade glioma, leading to challenge dogmas and to the fundamental concept of *personalized management*. Moreover, a better knowledge of the brain connectome and neuroplasticity enables us to take into consideration interactions between the disease (the glioma) and the host (the brain), and thus to elaborate dynamic and multimodal therapeutic strategies with the goal *to increase the median survival as well as to improve the quality of life* - that is, to move toward a "functional neurooncology". In the era of "evidence-based medicine", it is crucial not to forget "individual-based medicine".

**Keywords** Diffuse low-grade glioma • personalized management • individual-based medicine • functional neurooncology • brain plasticity

"opheléein ê mê blaptein" (first be useful, then do not be harmful)
Hippocrate

Supratentorial diffuse low-grade glioma (DLGG) is a rare and complex entity in adults, which has been matter of debate for many decades. This controversy was due to several factors. First, for a long time, the natural course of this disease has been poorly investigated and thus it was poorly understood. In the classical literature,

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most of authors considered DLGG as a "stable" and even as a "benign" brain tumor. As a consequence, the "wait and see" policy was traditionally advocated, due to the theoretical risk of treatment(s) in young adults usually enjoying a "normal life". In other words, from a functional point of view, the dogma was to claim that these patients "are doing well", because they have generally no deficit on a standard neurological examination (even if they are in rule under anti-epileptic drug(s) due to inaugural seizures in 80–90% of cases). Furthermore, medical and surgical neurooncologists also believed that it was almost impossible to remove this kind of tumors without generating functional deficits—especially when located within the so-called "eloquent areas", as frequently observed. Above all, it was argued that surgical removal, mainly based on the subjective estimation of the extent of resection by neurosurgeons, had no impact on the natural history of DLGG, and that the most appropriate management was therefore to achieve only a biopsy with the aim of obtaining neuropathological examination—in order to decide whether a simple follow-up could be considered or whether radiotherapy should be performed. This means that the treatment was selected almost exclusively on the basis of the morphological criteria according to the previous WHO classification (astrocytoma versus oligodendroglioma versus mixed glioma; grade II versus III). Finally, the clinical results were evaluated in the vast majority of series on only few parameters, that is, the progression free survival (PFS), overall survival (OS), and, optionally, Karnofsky Performance Scale.

In this book, breaking with the traditional conservative attitude, the aim is to comprehensively review recent technical and conceptual advances in genetics, cognitive neurosciences, imaging and treatments that have revolutionized our understanding of DLGG, leading to the fundamental principle of *personalized active and dynamic therapeutic strategies*. In addition, beyond the pure oncological considerations, a better knowledge of brain processing enables now to take into consideration interaction between the disease (the glioma) and the host (the brain), and thus to modulate the therapeutic strategies with the goal *to increase the median survival as well as to improve the quality of life*—i.e. to solve the classical dilemma opposing the increase of OS versus the preservation of cerebral functions [1]. In this setting, the purpose of this 2nd Edition is to revisit the biology, behavior and management of DLGG, in order to open new avenues to the origins of this tumor, its natural history, as well as the present and future regarding individualized therapeutic attitudes.

In fact, based on a large amount of original data published in the last decade, it is time to inhibit the traditional dogmas and to evolve towards a paradigmatic shift in the comprehension and the treatment of this disease. First, in this textbook, it will be demonstrated that this tumor is not stable but that it has a constant growth and migration along the subcortical pathways, with, ultimately, a malignant transformation leading to neurological deficits and death—with a median survival about 6–7 years [1]. Therefore, it is crucial to better investigate the natural course of the glioma at the individual level by calculating the velocity diameter expansion before any treatment, because this is a major prognostic factor, i.e. one of the best predictor of OS [2, 3]. In a series of 34 patients, it was observed that tumor growth within

6 months was better than baseline volumes, relative cerebral blood volume, or apparent diffusion coefficient in predicting time to malignant transformation in untreated DLGGs and was independent of other parameters [4]. Furthermore, the spontaneous velocity of diametric expansion is also a predictor independent of molecular marker, as IDH1 mutation status [5]. As a practical consequence, the spontaneous growth rate should be measured systematically at the beginning of the management of a DLGG without delaying treatment and should be added to the other known risk parameters to adapt treatment and follow-up on an individual basis.

Moreover, neurooncologists have to understand that this glioma is not a "tumor mass" compressing the parenchyma, but that this diffuse lesion is in fact an infiltrative disease of the brain, extending far away beyond the abnormalities visible on neuroimaging [6]. It was previously thought that the abnormalities visible on neuroimaging (as hypersignal on FLAIR-weighted MRI) corresponded to the whole disease (associated with oedema), leading to speak about "normal brain" around these signal abnormalities—which is totally wrong. This issue is crucial for the therapeutic (as surgical and radiation) management: indeed, a resection cannot be achieved according to "oncological" limits issued from radiological examination (as preoperative MRI, intrasurgical neuronavigation or intraoperative neuroimaging) because this information is not the reflect of the entire glioma, but only the tip of iceberg [7]. In the same spirit, with respect to tumor monitoring, new endpoints will be proposed, due to the fact that PFS is thus meaningless in DLGG before any treatment or after an incomplete surgical resection, since in essence all DLGGs are continuously growing (whereas this endpoint would be unambiguous after a "total resection" or could be also more or less properly defined under adjuvant treatment such as chemotherapy/radiotherapy). In this context, the classical radiological criteria, as initially proposed by Mac Donald [8] or more recently by the RANO group [9], are not appropriate to monitor DLGG kinetics. It will be demonstrated that an objective and accurate 3D volumetric assessment should be performed for each examination on FLAIR-weighted MRI, with computation of a individual growth rate before and after each therapy [10, 11]. New metabolic criteria will also be helpful to increase the sensitivity of this radiological monitoring.

From a functional point of view, it will be shown in this textbook that, contrary to conventional wisdom, these patients have generally neurocognitive and/or mood disorders at the time of diagnosis, including in cases of incidental DLGG [12]. These deficits are mainly related to the migration of the tumoral cells along the white matter tracts, thus limiting the potential of neuroplasticity due to the invasion of the brain connectome [13, 14]. Longitudinal neuropsychological assessments have shown a worsening in high cognitive functions, as non verbal delay recall scores, after a one year « wait and see » follow-up [15]. These results plead against a conservative attitude in DLGG patients, not only for oncological purpose but also with regard to the health related quality of life (QoL). Thus, neuropsychological examination should be systematically performed before and after each treatment—the classical neurological examination being not sensitive enough to objectively evaluate DLGG patients [16]. Indeed, the presence of an abnormal baseline cogni-

tive score is a strong predictor of poorer OS in DLGG patients [17]. This issue is very important to tailor the management with the aim not only of increasing OS but also of optimizing the duration with a normal QoL: for example, by minimizing the rate of postoperative deficit by means of intrasurgical electrical mapping in order to preserve the neural networks essential for brain functions [18]; or by preventing the long-term negative consequences of radiotherapy on high cognitive functions by avoiding early irradiation [19].

On the lights of this better knowledge of natural history, original individualized and multimodal therapeutic attitudes will be proposed in this book. Regarding surgery, its first aim is to allow an extensive histomolecular examination in DLGG, knowing that this is a heterogeneous tumor: many gliomas may exhibit "more aggressive" micro-foci in the core of a "low-grade" glioma [20]. In practice, this is the reason why, each time surgical resection is feasible, biopsy should be avoided, due to its high risk of under-quotation. Furthermore, in the past decade, numerous evidences have supported the significant impact of maximal resection on the course of DLGG, by delaying malignant transformation and therefore by increasing median survival [21–23]. Interestingly, although OS was around 6–7 years in series with a simple biopsy [24, 25], OS was significantly increased to 14–15 years in surgical series based upon early and maximal resection, as reported by the French Glioma Consortium about over one thousand DLGG [26]. In other words, radical resection is able to approximately double the survival—thanks to an impact of surgery *per se*, independently of the molecular profile of the DLGG [27]. Interestingly, longitudinal non-invasive neuroimaging and intraoperative electrophysiological mapping (direct electrical stimulation of cortex as well as subcortical white matter pathways) methods have enabled a better comprehension of the dynamic functional anatomy in each patient [28], leading to maximize the surgical indications in traditional "eloquent areas", while preserving or even improving the QoL [29]—thanks to epilepsy control as well as optimization of cognition after a specific functional rehabilitation [30, 31]. In parallel, this new philosophy based upon functional mapping-guided resection and not anymore on (anatomical/oncological) image-guided resection has also allowed a significant increase of the extent of resection—and thus of OS, as previously mentioned [32]. Especially, when a supratotal resection (beyond signal abnormalities on FLAIR-weighted MRI) can be achieved, the rate of death and even the rate of malignant transformation is nil with a median follow-up of 11 years [33]. In other words, stronger links between cognitive neurosciences and neurooncology have (at least partly) solved the classical dilemma in DLGG which so far opposed OS versus QoL, by maximizing both oncological as well as functional outcomes, owing to new surgical concepts which take into account cerebral plasticity and connectomics—i.e. the view of a brain organized in parallel distributed and interactive cortico-subcortical sub-networks [34]. In particular, it was demonstrated that a reoperation allowing a more extensive resection could be considered following a partial removal (for functional reasons) performed some years before, thanks to mechanisms of remapping that occurred in the meantime [35]. Moreover, new drugs of chemotherapy have increasingly been used in DLGG, since their tolerance was dramatically improved (e.g. Temozolomide with oral administration) and their

impact have begun to be shown, both from an oncological point of view (possible tumor stabilization or even shrinkage) and from a functional point of view (e.g. possible control of intractable epilepsy). This is the reason why original therapeutic strategies have recently been proposed, such as neoadjuvant chemotherapy in cases of inoperable DLGG (for example due to a bilateral invasion of the brain) allowing a shrinkage of the tumor and then opening the door to a subsequent surgery [36]. In the same state of mind, the actual benefit-to-risk ratio of radiotherapy was also re-examined, leading to delay irradiation [1].

Recent molecular data enabled a better understanding of the biology of DLGG, starting to explain the heterogeneity in their behavior and prognosis, despite a possible common clinical, radiological and even neuropathogical presentation. Based upon the recent histo-molecular WHO classification [37], new insights into genomics will be exposed in this book, with a discussion about their possible prognostic (or even predictive?) value. However, despite advances in genetics, it seems questionable to apply a similar therapeutic protocol to all patients belonging to a same "subgroup" defined only on the basis of the molecular pattern, without seeing the full picture at the individual level. Indeed, as mentioned by Boggs and Mehta (see the chapter on Radiotherapy in the treatment of DLGG): "It is important to understand that treatment stratification based on molecular profiling has not yet been reported prospectively. Examinations of predictive and prognostic capabilities of *IDH, TERT,* and *TP53* have only been examined retrospectively or as an unplanned subgroup analysis of prospective studies. Thus, outside the auspices of a clinical trial, genomic classification should not be used to guide clinical decision-making".

Finally, a better knowledge of the origin of DLGG may lead to identify new therapeutic targets as well as to develop new anti-cancer drugs, for instance in order to induce differentiation of stem cells [38]. In addition, the use of biomathematical modelling could also enable a better approximation of the glioma "date of birth" [39]. This might lead to propose a screening of a subpopulation in which early detection of DLGG could be performed by MRI [40], with the goal to diagnose incidental DLGG and to switch towards an earlier and more efficient treatment in asymptomatic patients [41].

In summary, the current philosophy in DLGG patients is to anticipate (before neurological or even cognitive worsening) a personalized, multimodal and long-term management strategy from the diagnosis (both in symptomatic as well as in incidental discovered DLGG) to the malignant stage of the disease, with on-line therapies adjusted over time on the basis of regular functional feedback and radiological monitoring. Indeed, *due to the better understanding of the poor spontaneous prognosis of DLGG, the "wait and see" policy is not acceptable anymore*. Although clinicians have to remember the classical "primum non nocere" principle, they also have to be aware about the fact that they can be harmful by inaction, i.e. by observing the tumor evolution while doing nothing: their role is first of all to be useful by treating the disease. For instance, although a complete surgical resection was not achievable during a first surgery due to the invasion of structures still critical for brain functions, such a total resection can become possible later owing to mechanisms of cerebral reshaping and/or following a shrinkage induced by adjuvant che-

motherapy. In other words, this book proposes new individualized strategies dealing with the interactions between the natural course of DLGG, reaction neuroplasticity, and onco-functional modulation induced by serial treatments [1, 42]. This recursive therapeutic philosophy breaks with the traditional attitude, by proposing a holistic and dynamic tailored strategy rather than by deciding dogmatically to administrate a protocol on the basis of few selected criteria statistically validated but with no value at the individual level (e.g. the arbitrary definition of "high risk DLGG patient" partly based upon an age over 40 years [43]). Thus, the risk of guidelines based on the new histomolecular WHO classification is in fine to evolve against the deep concept of precision medicine [44], because one cannot define a patient solely in terms of tumoral molecular profile. Furthermore, because this therapeutic strategy can only be recursive in essence, this school of care is at the opposite from the current guidelines resulting from randomized studies. According to the « evidence-based medicine », only the histomolecular initial diagnosis prescribes the treatment. This rigid view, which is an oversimplification reducing a multiparametric dynamic disease to a single attribute, can lead to overtreatment (e.g. brain irradiation with adverse effects on cognition), and does not take into account the most important criterion: the patient him(her)self. In this state of mind, it is worth noting that randomized controlled trials (RCT) are not adapted to this disease, due to the long OS—thus with difficulties in the practical organization and above all leading to the fact that the final results are often disputable given the advances in diagnostic and therapeutic techniques made in the meantime. In addition, problems related to design, analysis, and reporting limit many RCTs and how they can be applied to manage patients in routine practice [45]. Especially, surrogate end points are used widely in RCTs despite lack of validation that they predict improvement in duration or quality of survival—e.g., an increased PFS when early radiotherapy is administrated is not predictive of an improved OS [46]. Moreover, regarding ethical considerations, one should remind that that there is a paradox to claim that the service must be patient centered while proposing that patients can be recruited into RCTs that will generate evidences to move the discipline forward. Can the neurooncologist certify that there is no potential antagonism between the benefit for the patient now versus the benefit for the discipline later? This issue likely explains, at least in part, why no surgical trials have ever been built in DLGG. As a consequence, prospective collection of data should be more systematically achieved to implement large national and international databases [47]. In fact, in DLGG patients, in whom the survival is today significantly longer (with OS between one to two decades) thanks to an earlier and serial therapeutic management allowing to delay/prevent malignant transformation, *QoL should become the first endpoint*. Indeed, the goal is to transform a pre-malignant glioma with unpredictable evolution to a chronic tumoral disease under control in patients enjoying an active familial, social and professional life. In this spirit, opening new avenues to individualized, preventive and "functional neurooncology" [48], the ultimate aim is to give to human beings bearing DLGG a real life that includes planning for their long-term future—such as deciding whether to get a loan to buy a house or to have a baby. To this end, a honest, strong and unique relationship between the medical and/or surgical oncologist and

the patient as well as his/her family is essential, based on a clear and complete information which should be given *since the beginning of the management* as well as during the follow-up over years. In other words, in the era of "evidence-based medicine", it is crucial not to forget "individual-based medicine".

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# Part I
# Epidemiology and Classification

# Chapter 2
# Epidemiology of Diffuse Low Grade Gliomas

**Luc Bauchet**

**Abstract** Diffuse low grade gliomas (DLGGs) belong to primary central nervous system tumors (PCNSTs) and include diffuse astrocytomas (fibrillary/gemistocytic/protoplasmic astrocytomas), oligodendroglioma and oligoastrocytoma, according to the previous WHO classification. Here, we present the 2016 WHO Classification, but epidemiological data are available only for the previous one. Although specific epidemiological publications focusing on DLGG are very rare, it is nonetheless possible to collect information concerning DLGG by selecting data from the whole epidemiological literature on gliomas. The present work summarizes definitions and descriptive epidemiological data for DLGG and PCNST. DLGGs account for approximately 15% of all gliomas, and incidence rate is about 1/100,000 person-years. Main prognostic factors (e.g., age, performance status, location, volume and growth rate of the tumor, extent of surgical resection, histology, biology, etc.) are discussed and it is shown how they influence survival. Recent literature proposes a lot of spontaneous prognostic factors, but until now, just a few are validated. On the other hand, little data are available to define best combinations of the different therapeutic strategies at the individual level (successive surgeries, chemotherapy, radiotherapy and new treatments). This chapter proposes new efficient methodology to evaluate medical care and quality of life taking into account the specific property of the brain, i.e. neuroplasticity. The developments of modern informatics technology will revolutionize our methods of recording data. Collaboration between all medical specialties (including epidemiology and biostatistics) and development of large databases are the key of efficiency for the future. This chapter also summarizes the knowledge about DLGG risk factors and proposes new directions for searching etiologies of these tumors.

**Keywords** Brain tumor • Database • Epidemiology • Glioma • Low grade glioma • Neuro-epidemiology • Neuro-oncology • Neuropathology • Neurosurgery

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## 2.1 Introduction

Referring to the previous (2007) World Health Organization (WHO) Classification of central nervous system (CNS) tumors [1], diffuse low grade gliomas (DLGGs) included diffuse astrocytomas (fibrillary astrocytoma, gemistocytic astrocytoma, protoplasmic astrocytoma), oligodendroglioma and oligoastrocytoma with the corresponding ICD-O codes: 9420/3, 9411/3, 9410/3, 9450/3 and 9382/3, respectively. Recently, the WHO classification of CNS tumors used molecular parameters in addition to histology to define many tumor entities, thus formulating a concept explaining how CNS tumor diagnoses should be structured in the molecular era. The 2016 CNS WHO Classification officially represents an update of the 2007 4th Edition rather than a formal 5th Edition, but many changes appear in the classification of diffuse gliomas (e.g., isocitrate dehydrogenase (IDH) gene mutations, and 1p/19q codeletion status) (Tables 2.1 and 2.2). Moreover, when any access to molecular diagnostic testing is lacking, a diagnostic designation of NOS (i.e., not otherwise specified) is permissible for some tumor types. These have been added into the classification in those places where such diagnoses are possible. A NOS designation implies that there is insufficient information to assign a more specific code. In this context, in most instances, NOS refers to tumors that have not been fully tested for the relevant genetic parameter(s), but in rare instances, it may also include tumors that have been tested but that do not show the diagnostic genetic alterations. In other words, NOS does not define a specific entity, rather it designates a group of lesions that cannot be classified into any of the more narrowly defined groups. A NOS designation thus represents those cases about which we do not know enough pathologically, genetically and clinically and which should, therefore, be subject to future study before further refinements in the classification can be made [2].

In this new classification, the diffuse gliomas include the WHO grade II and grade III astrocytic tumors, the grade II and III oligodendrogliomas, the grade IV glioblastomas, as well as the related diffuse gliomas of childhood. This approach leaves those astrocytomas that have a more circumscribed growth pattern, lack IDH gene family alterations and frequently have *BRAF* alterations (pilocytic astrocytoma, pleomorphic xanthastrocytoma) or *TSC1*/*TSC2* mutations (subependymal giant cell astrocytoma), distinct from the diffuse gliomas. In other words, diffuse astrocytoma and oligodendrogliomas are now nosologically more similar than diffuse astrocytoma and pilocytic astrocytoma are [2].

Furthermore, two diffuse astrocytoma variants have been deleted from the 2007 WHO Classification: protoplasmic astrocytoma, and fibrillary astrocytoma, since this diagnosis overlaps nearly entirely with the standard diffuse astrocytoma. As a result, only gemistocytic astrocytoma remains as a distinct variant of diffuse astrocytoma, IDH-mutant.

The diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires the demonstration of both an IDH gene family mutation and combined whole-arm losses of 1p and 19q (1p/19q codeletion). In the absence of positive mutant R132H IDH1 immunohistochemistry, sequencing of *IDH1* codon 132 and *IDH2* codon 172 is recommended.

**Table 2.1** 2016 WHO Classification of the diffuse astrocytic and oligodendroglial tumors, adapted from Louis et al. 2016 [2]

| Diffuse astrocytic and oligodendroglial tumors | ICD-O codes |
|---|---|
| Diffuse astrocytoma, IDH-mutant | 9400/3 |
| Gemistocytic astrocytoma, IDH-mutant | 9411/3 |
| *Diffuse astrocytoma, IDH-wildtype* | *9400/3* |
| Diffuse astrocytoma, NOS | 9400/3 |
| Anaplastic astrocytoma, IDH-mutant | 9401/3 |
| *Anaplastic astrocytoma, IDH-wildtype* | *9401/3* |
| Anaplastic astrocytoma, NOS | 9401/3 |
| Glioblastoma, IDH-wildtype | 9440/3 |
| Giant cell glioblastoma | 9441/3 |
| Gliosarcoma | 9442/3 |
| *Epithelioid glioblastoma* | *9440/3* |
| Glioblastoma, IDH-mutant | 9445/3[a] |
| Glioblastoma, NOS | 9440/3 |
| Diffuse midline glioma, H3 K27M-mutant | 9385/3[a] |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted | 9450/3 |
| Oligodendroglioma, NOS | 9450/3 |
| Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted | 9451/3 |
| *Anaplastic oligodendroglioma, NOS* | *9451/3* |
| *Oligoastrocytoma, NOS* | 9382/3 |
| *Anaplastic oligoastrocytoma, NOS* | 9382/3 |

The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) {742A}. Behavior is coded/0 for benign tumors; /1 for unspecified, borderline, or uncertain behavior; and/3 for malignant tumors
The classification is modified from the previous WHO classification, taking into account changes in our understanding of these lesions
*Italics*: Provisional tumor entities. *NOS* not otherwise specified
Notes:
- *Oligoastrocytoma, NOS* and *Anaplastic oligoastrocytoma, NOS* share the same code (9382/3)
- The diagnoses of WHO grade II oligoastrocytoma and WHO grade III anaplastic oligoastrocytoma are, therefore, assigned NOS designations, indicating that they can only be made in the absence of appropriate diagnostic molecular testing. In the 2016 WHO Classification, the diagnosis of oligoastrocytoma/anaplastic oligoastrocytoma is strongly discouraged
[a]These new codes were approved by the IARC/WHO committee for ICD-O

**Table 2.2** Grading of selected diffuse astrocytic and oligodendroglial tumors according to the 2016 WHO Classification, adapted from Louis et al. 2016 [2]

| Selected diffuse astrocytic and oligodendroglial tumors | Grade |
|---|---|
| Diffuse astrocytoma, IDH-mutant | II |
| Anaplastic astrocytoma, IDH-mutant | III |
| Glioblastoma, IDH-wildtype | IV |
| Glioblastoma, IDH-mutant | IV |
| Diffuse midline glioma, H3 K27M-mutant | IV |
| Oligodendroglioma, IDH-mutant and 1p/19q-codeleted | II |
| Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted | III |

In the absence of testing capabilities or in the setting of inconclusive genetic results, a histologically typical oligodendroglioma should be diagnosed as NOS.

In the 2016 CNS WHO Classification, the diagnosis of oligoastrocytoma is strongly discouraged. Nearly all tumors with histological features suggesting both an astrocytic and an oligodendroglial component can be classified as either astrocytoma or oligodendroglioma using genetic testing. The diagnoses of WHO grade II oligoastrocytoma and WHO grade III anaplastic oligoastrocytoma are, therefore, assigned NOS designations, indicating that they can only be made in the absence of appropriate diagnostic molecular testing [2].

Thus in 2016, strictly speaking, DLGGs include (with the corresponding ICD-O codes):

1) Diffuse astrocytoma, IDH-mutant (9400/3),
2) Gemistocytic astrocytoma, IDH-mutant—which is a variant of the first one (9411/3)
3) Diffuse astrocytoma, IDH-wildtype (*9400/3*),
4) Diffuse astrocytoma, NOS (9400/3),
5) Oligodendroglioma, IDH-mutant and 1p/19q-codeleted (9450/3),
6) Oligodendroglioma, NOS (9450/3),
7) Oligoastrocytoma, NOS (9382/3).

From an epidemiological point of view, three important issues should be noted regarding this new classification:

– First, this new classification underscores the link between DLGG, diffuse anaplastic glioma (DAG), and even glioblastoma IDH mutant. The question of the spontaneous occurrence of DAG or the constant occurrence of DAG from initially DLGG is currently not resolved, but many factors are in favor of the transformation of DLGG. This point is important in epidemiology, because it may change the values of incidence and prevalence of these tumors.
– Secondly, as it was in the previous classification, ICD-O codes are not enough specific to describe all DLGG subtypes (because some DLGG subtypes have the same code). That is why some brain tumor databases (as the French Brain Tumor DataBase) suggest recording both the ICD-O code and the histological type and subtyping for each entity.
– Thirdly, because the 2016 WHO Classification is new, no data are yet available in brain tumor registries or in population studies. Only specific studies that include molecular parameters are available (see the chapter by Jacobs et al. on "Molecular Epidemiology of DLGG").

So, in the present chapter, we will only describe epidemiology for DLGG defined by the previous WHO classification.

Moreover, specific epidemiological publications for DLGG are rare. However, it is possible to obtain epidemiological data concerning DLGG by selecting some articles referring to all primary central nervous system tumors (PCNSTs), neuroepithelial tumors, gliomas, or even to low grade gliomas (LGGs). These publications

can come from registry works, or from consortium studies. The main difficulties are that definitions, referring histology or topography coding could vary with time, countries, and people involved in.

In the first part of this chapter, we will focus on PCNST generalities and definitions, then we will discuss the proportion of DLGG among PCNST, sex ratio and median ages at diagnosis for DLGG, and we will show few surgical data for gliomas in France. We will finish the first part by explaining why the term of DLGG is more appropriate than the term of LGG.

The second part will present data concerning incidence, survival and prevalence for DLGG.

The third part will summarize prognostic factors for DLGG, knowing that they will be detailed in other chapters of this book.

The last part will introduce new methodologies: (1) for improving clinical epidemiology (to benefit from a best evaluation of oncological care on survival and on quality of life for DLGG patients), (2) for looking for etiologies for these tumors, because until now, except in very few cases, the causes of DLGG are not known, and (3) for early detection of DLGGs.

## 2.2 PCNST and DLGG: Generalities

### *2.2.1 PCNST Generalities and Definitions*

PCNSTs represent a complex heterogeneous group of pathological entities that may be benign, malignant or of unpredictable evolution [1–10]. These tumors represent a major public health problem [11]. The term "primary brain tumor" has been defined in numerous ways in the literature. The primary difficulty in building a tumor registry and/or a data base is to define the type of tumor to be recorded.

Recent publications [12–20], the classification system of the World Health Organization [1, 2, 6], and the European recommendations for coding tumors of the brain and CNS [21] include all primary benign and malignant tumors located in the CNS, including its envelopes and the beginning of the nerves localized in the skull and spine. PCNSTs include tumors of neuroepithelial tissue (gliomas and all other neuroepithelial tumors), tumors of the meninges (meningiomas, mesenchymal tumors and other tumors of the meninges), tumors of the cranial and paraspinal nerves, lymphomas and hematopoietic neoplasms, and others.

By definition, this excludes metastatic tumors. But even now, there are still discrepancies concerning the inclusion of lymphoma, pituitary and pineal glands, and olfactory tumors of the nasal cavity, in the different databases and registries. It is important to note that some institutions account for primary malignant tumors, only.

Coding systems have been introduced as an indispensable interface between pathologists and cancer registries. The *international classification of diseases for oncology (ICD-O)* was established more than 30 years ago. It assures that histopathologically stratified population-based incidence and mortality data become available for epidemiological and oncological studies. The histology (morphology) code is increasingly complemented by genetic characterization of human neoplasms. The ICD-O histology codes have been adopted by the systematized nomenclature of medicine (SNOMED), issued by the College of American Pathologists. ICD-0-3 and SNOMED codes are available in Louis et al. [1, 2] and in Rigau et al. [19]. All glioma morphology codes are shown here (see Table 2.3) [23].

The ICD-O topography codes largely correspond to those of the tenth edition of the *International statistical classification of diseases, injuries and causes of death (ICD-10)* of the WHO. ICD-O-3 topography codes include: brain (C71.0–C71.9), meninges (C70.0–C70.9), spinal cord, cauda equina, cranial nerves, and other parts of the central nervous system (C72.0–C72.9) [24]. Now, many registries use these codes, but some registries still record malignant tumors only [25]. Some registries (e.g., Central Brain Tumor Registry of the United States –CBTRUS-) include more topography codes as pituitary and pineal glands (C75.1–C75.3), and olfactory tumors of the nasal cavity [C30.0 (9522–9523)].

Another challenge for registries and databases is to record and to detail all cases of defined tumors (i.e., all histological types and all histological subtypes, when it is possible).

### 2.2.2 Proportion of DLGGs Among PCNSTs and Gliomas

We present the proportion of each major type of PCNST and the distribution of DLGG in the French Brain Tumor DataBase (FBTDB) for the 2006–2011 period (Fig. 2.1a–c). We point out (1) FBTDB records cases with histological confirmation only, knowing that usually, registries record the cases with and without histological confirmation, and (2) the distribution of the different subtypes of PCNST is similar in France and in the USA, except for oligodendroglial tumors (see [19]). Recently, most studies (e.g., [26, 27]) have reported a recent increase of oligodendroglial tumors in comparison to astrocytic tumors; however, French neuropathologists are more influenced by the classification proposed by Daumas-Duport et al. [28] than American neuropathologists.

We could see here the difficulties to compare data from different institutions when histological diagnosis is not completely reproducible [29].

An additional difficulty to know the overall proportion of DLGG is that (1) some institutions use terminology such as “low grade gliomas” (LGG, see below) and (2) when some information are not detailed enough, registries include some cases in astrocytoma not otherwise specified (NOS) or in glioma NOS, even in unspecified neoplasm.

However, we can consider that the overall DLGG represents about 13–16% of all gliomas.

**Table 2.3** Histological repartition of the 18,627 glioma cases with clinical and surgical data from French Brain Tumor Database, period 2004–2009, adapted from Zouaoui et al. [22]

| | ICD-O | ADICAP | N | M | F | m | Med | CRYO | REPORTED SURGERY | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | T | R % | B% |
| **TUMORS OF NEUROEPITHELIAL TISSUE** | | | | | | | | | | | |
| Glioma NOS | 9380/3 | N7R0 | 358 | 218 | 140 | 48,83 | 55,0 | 41 | 312 | *31,4%* | *68,6%* |
| **ASTROCYTIC TUMOURS** | | | | | | | | | | | |
| Astrocytoma NOS | 9400/3 | N7S0 | 251 | 146 | 105 | 42,95 | 45,0 | 39 | 211 | *40,8%* | *59,2%* |
| Pilocytic Astrocytoma | 9421/1 | N0S8 | 938 | 486 | 452 | 16,64 | 13,0 | 263 | 688 | *86,6%* | *13,4%* |
| Pilomyxoïd Astrocytoma | *9425/3* | *(0001)* | 5 | 1 | 4 | 8,80 | 7,0 | 1 | 3 | *33,3%* | *66,7%* |
| Subependymal Giant cell astrocytoma | 9384/1 | N0T2/3 | 73 | 35 | 38 | 18,12 | 17,0 | 18 | 51 | *94,2%* | *5,8%* |
| Pleomorphic xantho-astrocytoma | 9424/3 | N7S9 | 72 | 38 | 34 | 34,11 | 31,0 | 19 | 43 | *86,0%* | *14,0%* |
| Fibrillary astrocytoma | 9420/3 | N7S2 | 147 | 88 | 59 | 40,19 | 45,0 | 50 | 113 | *34,5%* | *65,5%* |
| Gemistocytic astrocytoma | 9411/3 | N7S4 | 82 | 53 | 29 | 48,42 | 49,0 | 25 | 67 | *53,7%* | *46,3%* |
| Protoplasmic astrocytoma | 9410/3 | N7S6 | 18 | 8 | 10 | 46,05 | 43,5 | 2 | 15 | *46,7%* | *53,3%* |
| Anaplastic astrocytoma | 9401/3 | N7T6 | 516 | 289 | 227 | 55,94 | 59,0 | 145 | 439 | *31,7%* | *68,3%* |
| Glioblastoma | 9440/3 | N7X0 | 9652 | 5712 | 3940 | 61,90 | 63,0 | 2695 | 6751 | *63,2%* | *36,8%* |
| Giant cell glioblastoma | 9441/3 | N7X2 | 172 | 98 | 74 | 55,33 | 58,5 | 58 | 132 | *70,5%* | *29,5%* |
| Gliosarcoma | 9442/3 | N7X4 | 112 | 73 | 39 | 58,29 | 59,0 | 34 | 78 | *93,6%* | *6,4%* |
| Gliomatosis cerebri | 9381/3 | N7R9 | 62 | 37 | 25 | 47,80 | 50,0 | 14 | 35 | *20,0%* | *80,0%* |
| | | | 12100 | 7064 | 5036 | 56,49 | 61,0 | 3363 | 8626 | | |
| | | | | *58,5%* | *41,5%* | | | *27,3%* | | *61,8%* | *38,2%* |
| **OLIGODENDROGLIAL TUMOURS** | | | | | | | | | | | |
| Oligodendroglioma | 9450/3 | N7V0 | 1781 | 1014 | 767 | 43,96 | 43,0 | 487 | 1547 | *56,9%* | *43,1%* |
| Anaplastic oligodendroglioma | 9451/3 | N7V4 | 1621 | 911 | 710 | 53,18 | 55,0 | 514 | 1455 | *62,4%* | *37,6%* |
| | | | 3402 | 1925 | 1477 | 48,35 | 49,0 | 1001 | 3002 | | |
| | | | | *56,6%* | *43,4%* | | | *29,4%* | | *59,6%* | *40,4%* |
| **OLIGOASTROCYTIC TUMOURS** | | | | | | | | | | | |
| Oligoastrocytic tumours NOS | 9382/3 | N7R4 | 49 | 24 | 25 | 41,08 | 44,0 | 9 | 30 | *63,3%* | *36,7%* |
| Oligoastrocytoma | 9382/3 | N7V2 | 558 | 309 | 249 | 44,00 | 42,0 | 148 | 460 | *51,5%* | *48,5%* |
| Anaplastic Oligoastrocytoma | 9382/3 | N7V3 | 1055 | 601 | 454 | 53,63 | 56,0 | 276 | 907 | *54,6%* | *45,4%* |
| | | | 1662 | 934 | 728 | 50,02 | 52,0 | 433 | 1397 | | |
| | | | | *56,2%* | *43,8%* | | | *26,1%* | | *53,8%* | *46,2%* |
| **EPENDYMAL TUMOURS** | | | | | | | | | | | |
| Subependymoma | 9383/1 | N0W6 | 94 | 69 | 25 | 51,49 | 52,5 | 26 | 67 | *91,0%* | *9,0%* |
| Myxopapillary ependymoma | 9394/1 | N7W2 | 157 | 98 | 59 | 39,57 | 38,0 | 32 | 101 | *97,0%* | *3,0%* |
| Ependymoma, NOS | 9391/3 | N7W0 | 601 | 328 | 273 | 42,13 | 44,0 | 137 | 397 | *93,7%* | *6,3%* |
| Cellular ependymoma | 9391/3 | N7W1 | 33 | 19 | 14 | 34,91 | 37,0 | 11 | 17 | *94,1%* | *5,9%* |
| Papillary ependymoma | 9393/3 | N7W4 | 23 | 14 | 9 | 40,69 | 36,0 | 6 | 13 | *100,0%* | *0,0%* |
| Clear cell ependymoma | 9391/3 | N7W5 | 34 | 20 | 14 | 30,11 | 21,5 | 4 | 28 | *89,3%* | *10,7%* |
| Ependymoma, anaplastic | 9392/3 | N7W8 | 149 | 86 | 63 | 25,90 | 13,0 | 61 | 113 | *91,2%* | *8,8%* |
| Tanicytic ependymoma | *9391/3* | *(0002)* | 14 | 10 | 4 | 40,28 | 43,5 | 3 | 10 | *60,0%* | *40,0%* |
| | | | 1105 | 644 | 461 | 39,74 | 41,0 | 280 | 746 | | |
| | | | | *56,6%* | *43,4%* | | | *25,2%* | | *91,4%* | *8,6%* |
| **TOTAL GLIOMES** | | | 18627 | 10785 | 7842 | 53,43 | 57,0 | 5118 | 14083 | | |
| | | | | *57,9%* | *42,1%* | | | *27,5%* | | *62,2%* | *37,8%* |

**Nomenclature: ICD-O: see Louis et al. 2007 [1], ADICAP: French nomenclature, available at: http://medphar.univ-poitiers.fr/registre-cancers-poitou-charentes/documents_registre/adicap_version5_4_1_2009.pdf**

Abbreviations: *T* total, *B* biopsy, *R* resection, *M* male, *F* female, *N* number, *Med* median age at diagnosis, *m* mean age at diagnosis, *CRYO* cryopreservation

The italicized ICD-O numbers are provisional codes proposed for the 4th edition of ICD-O

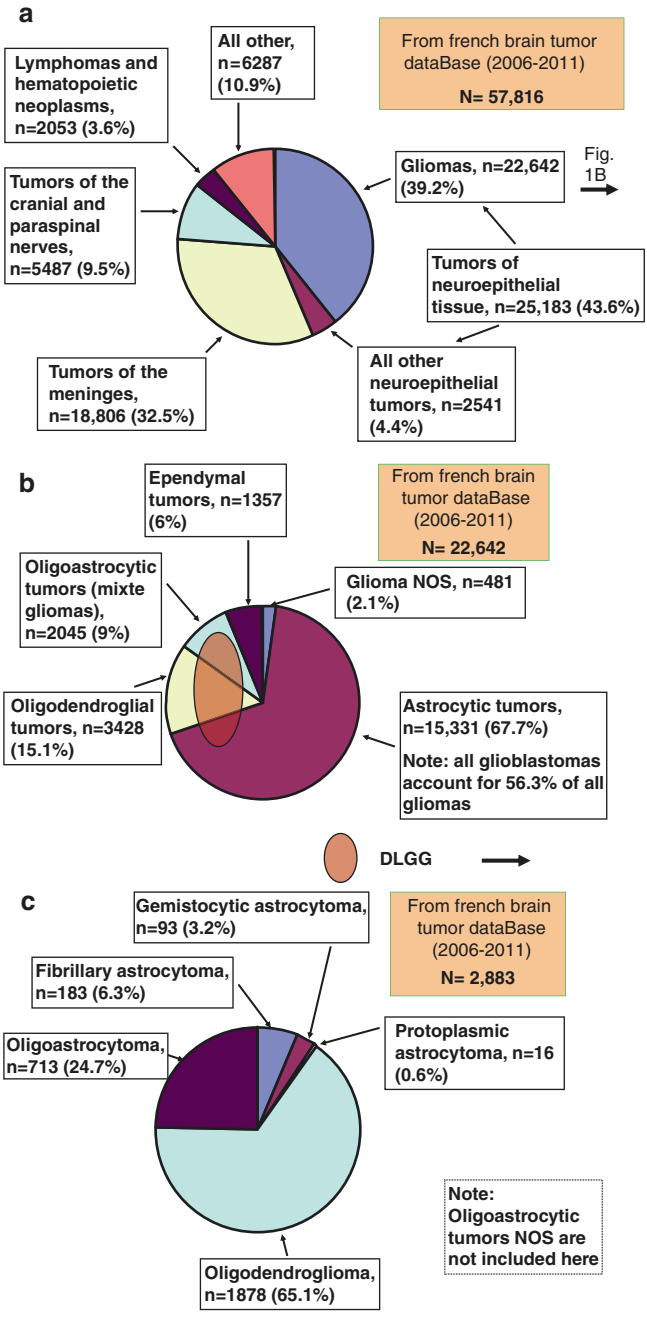


**Fig. 2.1** (**a**–**c**) Data from French Brain Tumor DataBase (2006–2011). (**a**) Distribution of all primary central nervous system tumors by main histological types. (**b**) Distribution of all gliomas (all sites: included supratentorial, infratentorial and spinal cord) by main histological subtypes. (**c**) Distribution of all diffuse low grade gliomas (all sites: included supratentorial, infratentorial and spinal cord) by all histological subtypes, excepted oligoastrocytic tumors NOS. Abbreviations: *DLGG* diffuse low grade glioma, *NOS* not otherwise specified

### 2.2.3 *Sex Ratio, Median Age at Diagnosis and Few Surgical Data for DLGG*

The number of males and females and the median age at diagnosis (MAD) for DLGG in FBTDB (period: 2004–2009) [23] are shown in Table 2.3. Sex ratios, MAD in CBTRUS [15, 17] and in FBTDB are shown in Table 2.4. Sex ratio (male/female) for all DLGG is very similar in CBTRUS **(1.33)** and in FBTDB **(1.32)**. It is the same for MAD for each sub type of DLGG. One can hypothesis that these similarities across the Atlantic could argue for genetic components of these tumors. To be rigorous about classification system, we can notice (1) gemistocytic astrocytoma were not included in DLGG in 2009 and 2012 CBTRUS reports (probably, because gemistocytic astrocytomas are more aggressive tumors, CBTRUS counted gemistocytic astrocytomas with anaplastic astrocytomas [note: 2015 CBTRUS report includes gemistocytic astrocytomas in diffuse astrocytomas, as in the 2007 WHO Classification] (2) CBTRUS does not separate oligoastrocytomas from anaplastic oligoastrocytomas, because these tumors have the same SNOMED code (9382/3) (see Tables 2.1 and 2.3).

Another important thing to notice when one speaks of MAD is how diagnosis is defined. When surgery is performed, registries and the large majority of databases use usually the date of the histological diagnosis. If we refer to clinical studies, some of them specify the age of radiological diagnosis, or sometimes, the age at first symptom. For example, the "Reseau d'étude des gliomes" (REG, a French consortium that studies DLGG) considered several starting points for their analyses: the date of available radiological diagnosis (which did not differ significantly from the date of clinical onset) and the date of first treatment. Among 1091 patients (collected at adult age), it was noted that median age (MA) at discovery was 37 years old (rage: 4–75) and the **MA at first treatment was 44 years old** (range: 18–76) [30]. Probably, this discrepancy would be decreased in the future, because clinicians seem to treat DLGG earlier than in the past.

**Table 2.4** Sex ratio and median age at diagnosis in CBTRUS [15, 17] and FBTDB [23]

| | Sex ratio (Male/Female) | | Median age at diagnosis | |
|---|---|---|---|---|
| | CBTRUS 2012 | FBTDB 2012 | CBTRUS 2009 | FBTDB 2012 |
| Protoplasmic & fibrillary astrocytoma | 1.4 | 1.4 | 47 | 45 |
| Oligodendroglioma | 1.2 | 1.3 | 41 | 43 |
| Mixed glioma | 1.3[a] | 1.3[b] | 42[a] | 42[b] |

[a]CBTRUS does not differentiate oligoastrocytoma and anaplastic oligoastrocytoma (same SNOMED code)

[b]Here, FBTDB specifies oligoastrocytoma only

Surgical data concerning DLGG are rare in population studies. Table 2.3 shows the percentages of resection versus biopsy for 14,083 gliomas and all subtypes (included DLGG) (FBTDB, collected data from 2004 to 2009). Of the 54 institutions that participated, the proportion of resection versus biopsy varied considerably from one institution to another (data not shown). We can also note that at least 27% of all glial tumors were cryopreserved (see [19, 23]). This is very important for future biological studies.

### *2.2.4 The Term of DLGG Is More Appropriate Than the Term of LGG*

For many years, epidemiological studies have investigated all gliomas or even all PCNST. More recently, the term "low grade glioma (LGG)" has been introduced. LGG is probably used as a practical definition being quite simply in opposition to the term "high grade glioma (HGG)". LGGs are slow growing, intrinsic lesions that contain glioma cells. Referring to the WHO classification of tumors of the CNS by Louis et al. [1], LGG may be defined by grade I (GI) and grade II (GII) gliomas and includes subependymal giant cell astrocytoma (GI), pilocytic astrocytoma (GI), pilomyxoid astrocytoma (GII), diffuse astrocytoma (GII), pleomorphic xanthoastrocytoma (GII), oligodendroglioma (GII), oligoastrocytoma (GII), subependymoma (GI), mixopapillary ependymoma (GI) and ependymoma (GII). Some authors include gangliomas, desmoplastic gangliomas [31], and even dysembryoplastic neuroepithelial tumors (DNETs) [32]. However, many studies on LGG exclude ependymomas and refer to astrocytic and/or oligodendrocytic tumors only. Furthermore, some pediatric studies mainly focus on pilocytic astrocytic tumors, and some adult studies often focus on GII astrocytic and/or oligodendrocytic tumors only.

Here, the term "diffuse low grade gliomas (DLGG)" includes grade II gliomas for diffuse astrocytomas, oligodendrogliomas and oligoastocytomas (mixed gliomas). This term is much more precise—because in essence it excludes well delineated grade I and II gliomas, and ependymomas with a different natural history. One benefit of this term is also to ignore the difficulties to differentiate an oligoastrocytoma from an astrocytoma or an oligodendroglioma. Moreover, even if heterogeneities are present in the GII glioma group of diffuse astrocytomas, oligodendrogliomas and oligoastocytomas, these tumors are often studied together. Usually they concern middle-aged adults with professional activities. The main clinical presentation is epilepsy with or without mild cognitive disorders. Focal deficit and/or raised intracranial pressure are possible but very infrequent. And the majority of these tumors have typical imaging characteristics on MRI as non-enhancing infiltrative lesions involving the white matter and frequently extending to the cortical surface [33]. Moreover, now the new WHO CNS Classification specifies the group of diffuse astrocytic and oligodendroglial tumors [2], Tables 2.1 and 2.2.

## 2.3 Incidence, Survival and Prevalence for DLGG

Epidemiological data for DLGG are patchy. In 2016, we can consider that we have (1) good incidence data in some countries, (2) some interesting elements regarding survival, (3) little items on the prevalence.

### *2.3.1 Incidence*

As mentioned previously, incidence data could vary from countries because the coding rules are not exactly the same all over the world. For example, referring to the 2007 WHO Classification, diffuse astrocytoma include fibrillary astrocytoma, gemistocytic astrocytoma, and protoplasmic astrocytoma, but some registries include astrocytoma NOS also. Classically, registries record cases with and without histological confirmation. It means that a number of cases of tumor are diagnosed by radiology, or even by clinical data only, or even by death certificate only. This is why the author decides to show data from (1) registries (e.g., Central Brain Tumor Registry of the United States—CBTRUS, and Austrian Brain Tumor Registry—ABTR) and (2) from histological population-based study (e.g., French Brain Tumor DataBase—FBTDB) that include all cases with histological validation only (Table 2.5). Histological population-based studies are more accurate but underestimate the true incidence [34–36]. Some other publications (e, g., [20, 37, 38]) present incidence data on DLGG, and one recent publication summarizes incidence data of glioma and some sub-types in different countries [39].

When we want to compare the incidence of one specific tumor from one country to another, another issue to consider is the differences in the two populations. Crude rates, whether they represent incidence, mortality, morbidity or other health events, are summary measures of the experience of populations that facilitate this comparative analysis. However, the comparison of crude rates can sometimes be inadequate, particularly when the population structures are not comparable for factors such as age, sex or socioeconomic level. For example, median age at diagnosis of glioblastoma is 64 years; because the age distribution is different in occidental word than in developing countries, we can not compare the crude rate of glioblastoma in US to the crude rate of glioblastoma in India. To enable international comparison, age-standardized rates from the FBTDB data were calculated with the USA, Worldwide, and Europe populations as references (Table 2.5).

Moreover, from epidemiological point of view, the difficulty in grading the diffuse gliomas in grade II vs. III by pathologists in some cases could modify the incidence of DLGG vs. DAG (e.g., microfoci in DLGG [40]). In the past, neurosurgeons

**Table 2.5** Comparison of the incidence rates (IR) of DLGGs and some PCNSTs (per 100,000) from USA registry (CBTRUS), Austrian registry (ABTR), and FBTDB

| Registry or population-based study | IR adjusted on the USA population | IR adjusted on the worldwide population | IR adjusted on the Europe population | IR adjusted on the French population |
|---|---|---|---|---|
| CBTRUS[a] 2008–2012 [18] | | | | |
| Tumors of neuroepithelial tissue | 6.62 | | | |
| Diffuse astrocytoma[b] | 0.53 | | | |
| Oligodendroglioma | 0.25 | | | |
| Oligoastrocytic tumors[c] | 0.20 | | | |
| Total[b,c] | 0.98 | | | |
| FBTDB[d] 2006–2011 | | | | |
| Tumors of neuroepithelial tissue | 6.160 | 5.507 | 6.343 | 6.771 |
| Gliomas | 5.418 | 4.623 | 5.587 | 6.088 |
| Fibrillary astrocytoma | 0.048 | 0.050 | 0.051 | 0.049 |
| Gemistocytic astrocytoma | 0.024 | 0.021 | 0.025 | 0.025 |
| Protoplasmic astrocytoma | 0.004 | 0.004 | 0.004 | 0.004 |
| Oligodendroglioma | 0.501 | 0.437 | 0.502 | 0.505 |
| Oligoastrocytoma | 0.191 | 0.171 | 0.192 | 0.192 |
| Total[e] | 0.768 | 0.683 | 0.774 | 0.775 |
| FBTDB[d] 2006–2009 [33] | | | | |
| All diffuse grade II gliomas[f] | 0.83 | 0.76 | 0.86 | 0.85 |
| ABTR[a] 2005 [14] | | | | |
| Tumors of neuroepithelial tissue | 7.26 | | | |
| Gliomas | 6.6 | | | |
| Diffuse astrocytoma[b] | 0.75 | | | |
| Oligodendroglioma | 0.20 | | | |
| Oligoastrocytoma | 0.27 | | | |
| Total[b] | 1.22 | | | |

Abbreviations: *DLGG* diffuse low grade glioma, *NOS* not otherwise specified, *PCNST* primary central nervous system tumor

[a]Central Brain Tumor Registry of the United States (CBTRUS) and Austrian Brain Tumor Registry (ABTR) are registries, including cases with and without histological validation

[b]Astrocytomas NOS are included

[c]Anaplastic oligoastrocytomas are included

[d]French Brain Tumor DataBase (FBTDB) is histological population-based study, including cases with histological validation only. Since 2006, FBTDB has been collected all histological case in France except in over sea departments [36]. To enable international comparisons, standardized rates for all tumors were also calculated with USA, worldwide and Europe, populations as references

[e]Without any NOS categories

[f]NOS WHO grade II glioma are included

gave only small samples to pathologists; now bigger samples of the tumor are analyzed by the pathologist, and pathologists have more sophisticated techniques. So we could imagine that incidence of DLGG would decrease slightly while incidence of DAG would increase slightly.

The 2016 WHO Classification integrates biology but the difficulties still persist in differentiating GII and GIII in some cases.

In occidental world, the incidence rate for all DLGG is between 0.6 and 1.3/100,000 person-years. So, we can hypothesize that the value of 1/100,000 person-years, or a little bit less, could be considered as a good approximation.

So, this first conclusion about incidence of about 1/100,000 person-years for DLGG in occidental world implies few comments and questions:

The variation of incidence between each subtype of DLGG seems more important than the variation of the overall incidence. It means that histological criteria between astrocytoma, oligodendroglioma and oligoastrocytoma are probably variable from one country (or one center) to another. Does the new WHO Classification will do better? We cannot answer yet.

What can explain the (relatively small) discrepancies between the overall incidence of DLGG from one country (or one area) to another, in the occidental world? Only methodology? Or real difference? We cannot answer yet. But we can notice that incidence of overall DLGG is higher (1) in men than in women (see sex ratio of M/F of about 1.3), and (2) in White than in Black in USA. CBTRUS data [15] give incidence rates (per 100,000 person-years, age-adjusted to the 2000 U.S. standard population): protoplasmic and fibrillary astrocytoma: 0.10, oligodendroglioma: 0.31, mixed glioma: 0.19; Male/Female: 0.13/0.08, 0.34/0.27, 0.24/0.16; White/Black: 0.12/0.04, 0.34/0.13, 0.21/0.08 for the same histology respectively. Furthermore, the FBTDB showed that the geographical distribution by region of the DLGG had significant differences, with higher incidence rates in Northeast and central parts of France [34].

From epidemiological point of view, two additional points need to be mentioned. First, the incidental findings on MRI are increasing with the use of MRI for many other clinical situations (brain traumas, headaches, neurologic disorders, etc.) and even for research purposes [41–43]. Secondly, DLGG patients have a long silent stage before to be symptomatic, and some teams discuss screening and preventive therapeutic management [44–46]. So, we can imagine that the incidence of DLGG could rise in the future.

### *2.3.2 Survival*

In 2016, many interesting publications are available in the literature about gliomas survival. But unfortunately, most of them include a lot of different subtypes. Many publications analyze only clinical, or therapeutic, or biologic prognostic factors. So,

it is very difficult to conclude precisely. Of course survival of DLGG is better than diffuse high grade gliomas, but DLGG is still an ultimately fatal disease.

US survival rates for DLGG [diffuse astrocytoma (including fibrillary, gemistocytic, protoplasmic, and NOS astrocytomas), oligodendroglioma, and mixed glioma (including oligoastrocytoma grade II and III because they have the same SNOMED code) and selected glioma subtypes [i.e., anaplastic oligodendroglioma, anaplastic astrocytoma, glioblastoma, and glioma malignant NOS] for comparison, are presented in Table 2.6 (adapted from 2015 CBTRUS report [18], period 1995–2012). The estimated 5-/10-year relative survival rates for diffuse astrocytomas and oligodendrogliomas are 47.9/37.6 and 79.8/64.0%, respectively. Three points could be noted: (1) the estimated 5- and 10-year relative survival rates for mixed gliomas (included oligostrocytomas and anaplastic oligoastrocytomas) are 62.0/47.8%, respectively; (2) the number of glioma NOS is particularly high and (3) survival of glioma NOS is not so poor as glioblastoma survival.

In the population-based study of the Canton of Zurich, Switzerland (N = 122 DLGG, period 1980–1994), the survival rate (mean follow-up 7.5 ± 4.8 years) was highest for patients with oligodendroglioma (78% at 5 years, 51% at 10 years), followed by those with oligoastrocytoma (70% at 5 years, 49% at 10 years) and fibril-

**Table 2.6** One-, Two-, Three-, Four-, Five-, and Ten-year relative survival rates[a,b] for diffuse low grade gliomas, anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, and glioma malignant NOS, SEER 18 registries, 1995–2012[c], from 2015 CBTRUS report [18]

| Histology | N[d] | 1-Yr | 2-Yr | 3-Yr | 4-Yr | 5-Yr | 10-Yr |
|---|---|---|---|---|---|---|---|
| Diffuse astrocytoma[e] | 6635 | 72.2% | 61.5% | 55.4% | 51.2% | 47.9% | 37.6% |
| Oligodendroglioma | 3602 | 93.9% | 89.5% | 86.2% | 82.9% | 79.8% | 64.0% |
| Mixed glioma[f] | 2130 | 87.6% | 77.9% | 71.4% | 66.1% | 62.0% | 47.8% |
| Anaplastic astrocytoma | 4101 | 62.1% | 44.0% | 35.70% | 31.2% | 27.9% | 19.8% |
| Anaplastic oligodendroglioma | 1441 | 81.5% | 68.9% | 62.4% | 57.0% | 52.5% | 38.9% |
| Glioblastoma | 33,204 | 37.2% | 15.2% | 8.8% | 6.3% | 5.1% | 2.6% |
| Glioma malignant, NOS | 4717 | 63.2% | 52.7% | 49.3% | 47.6% | 46.1% | 41.3% |

*NOS* not otherwise specified

[a]The cohort analysis of survival rates was utilized for calculating the survival estimates presented in this table. Long-term cohort-based survival estimates reflect the survival experience of individuals diagnosed over the time period, and they may not necessarily reflect the long-term survival outlook of newly diagnosed cases

[b]Rates are an estimate of the percentage of patients alive at 1, 2, 3, 4, 5, and 10 year, respectively

[c]Estimated by CBTRUS using Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov) SEER*Stat database: Incidence—SEER 18 Registries research Data + Hurricane Katrina impacted Louisiana cases, Nov 2014 Sub (1973–2012 varying) —Linked to county attributes—Total U.S., 1969–2013 counties, National Cancer Institute, DCCPS, surveillance research program, cancer statistics branch, released April 2015, based on the November 2014 submission

[d]Total number of case that occurred within the SEER registries between 1995 and 2012

[e]Diffuse astrocytoma includes fibrillary, gemistocytic, protoplasmic, and NOS astrocytomas

[f]Mixed glioma includes oligoastrocytoma and anaplastic oligoastrocytoma

lary astrocytoma (65% at 5 years, 31% at 10 years). Survival of patients with gemistocytic astrocytoma was poor, with survival rates of 16% at 5 years and 0% at 10 years [38].

Elsewhere in Europe, data from cancer registries are not specific for DLGG and vary with periods of time and regions. For example, the Danish registry, one of the oldest registries, compared the overall survival of patients with oligodendroglial tumors (oligodendrogliomas and anaplastic oligodendrogliomas) during the periods 1943–1977 and 1978–2002. The median survival increased from 1.4 years (95% confidence interval [CI], 1.0–1.6) to 3.4 years (95% CI, 2.6–4.2) during the period of study [47]. More recently, EUROCARE group (included data from 39 cancer registries located in different regions of Europe) showed that estimates of 5-year relative survival rates (95% CI) for patients with oligodendrogliomas/anaplastic oligodendrogliomas, alive in 2000–2002, were 74.1 (64.4–81.8)/35.1 (21.2–49.5) in Northern Europe, 65.8 (57.5–73.0)/35.5 (24.4–46.9) in UK and Ireland, 75.5 (61.8–85.2)/29.7 (13.4–48.3) in Central Europe, 47.8 (32.4–62.0)/6.1 (1.3–16.6) in Eastern Europe, 63.8 (51.4–74.1)/33.3 (14.7–53.6) in Southern Europe, and 67.2 (62.5–71.6)/31.5 (25.0–38.3) in all cases [48]. The last data of primary malignant brain tumors from EURCARE (including 58 cancer registries, period 2000–2007) have grouped many glioma types, and it is not possible to separate DLGG. But for the group of "oligodendroglioma, anaplastic oligodendroglioma, oligoastrocytoma and anaplastic oligoastrocytoma", the 5-years relative survival for the subgroup of 45–54 years old patients and the subgroup of 55–64 years old patients were 51.4 and 31.0% in the period 1999–2001, versus 60.4 and 38.5% in the period 2005–2007 with $p = 0.005$ and $p = 0.02$, respectively [49]. In the work by Crocetti et al. [50], data from 76 cancer registries out of the 89 that accepted to participate in the RARECARE project were considered. The estimated 5-year relative survival was 14.5% for astrocytic tumors (42.6% for low grade astrocytomas, 4.9% for high grade astrocytomas, and 17.5% for gliomas NOS), and 54.5% for oligodendroglial tumors (64.9% for low grade and 29.6% high grade). Survival data for gliomas including data for some subtypes of DLGG are available in few other countries (e.g., England, Korea, Netherland, and Sweden [51–54]). Ostrom et al. [39] compared some of them.

US population data show that all DLGGs have survival averaging approximately 6 [54]–7 years [55], although variation in survival is quite large with at least 20% of patients surviving for two decades [55]. The median survival for patients with astrocytoma, mixed glioma, and oligodendroglioma is 5.2, 5.6, and 7.2 years, respectively.

One important question is to know if survival of DLGG is improved with the new medical technology. The answer of this question is not so easy.

Data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute suggest that for the majority of low grade glioma patients, overall survival has not significantly improved over the past three decades [56]. Data from other, but smaller works showed a modest improvement at least for

tumors with oligodendroglial component [47, 49, 53], and some important clinical studies showed a median survival longer than 10 years (e.g., [30]).

Generally speaking, the length of the mean survival of DLGG, the heterogeneous medico-surgical care, the choice of the best personalized therapeutic, the acquisition of experience of new technologies (awake surgery, second or third surgery eventually, chemotherapies, new modalities of radiotherapy, etc.), needs a follow-up of at least 10–20 years to demonstrate an improvement at population level. Moreover, very few registries collect many prognostic factors as functional status, biology, quality of resection, all therapeutic lines, etc. to compare survival.

### *2.3.3 Prevalence*

Prevalence rates are ideally suited to provide an overall estimate of cancer survivorship and direction for health planning as they reflect the complex relationships between incidence, survival, and population demographics—and hence to provide valuable information to the research and medical community. But prevalence data for PCNSTs are limited and very difficult to obtain. In theory, this would imply that the registration of cases is (and has been) exhaustive for many years (to account for long survivors), and that the histological classification systems have not changed over this long period. In 2001, Davis et al. showed that the prevalence rate for all PCNST was 130.8 per 100,000 with approximately 350,000 individuals estimated to be living with this diagnosis in the United States in 2000. The prevalence rate for primary malignant tumors was 29.5 per 100,000, the prevalence rate for primary benign tumors was 97.5 per 100,000, and 3.8 per 100,000 for primary borderline tumors [57]. The same group published new prevalence data in 2010. On the basis of the sum of non-malignant and averaged malignant estimates, the overall prevalence rate of individuals with a PCNST (as defined by CBTRUS) was estimated to be 209.0 per 100,000 in 2004 and 221.8 per 100,000 in 2010. The female prevalence rate (264.8 per 100,000) was higher than in males (158.7 per 100,000). The average prevalence rate for malignant tumors (42.5 per 100,000) was lower than for non-malignant tumors (166.5 per 100,000) [58]. In Europe, Crocetti et al. [50] published that the estimated prevalence rate for all astrocytic tumors of CNS was 20.4/100,000, and the estimated prevalence rate for oligodendroglial tumors of CNS was 2.7/100,000, with an incidence rate (per 100,000 person-years, age standardized on European population) of 4.4 and 0.4, respectively.

If until now, no specific prevalence data for DLGG are available in large population, we could use a crude approximation. If the average duration of disease and the population of patients are stationary, the prevalence can be estimated by the incidence (I) and the mean duration of disease (D) with the following equation: $P \approx I \times D$. Given the survival data (see previous and following paragraphs and without taking into account that survival could be improved), a crude approximation of

the DLGG mean duration could be about 7–12 years. An estimation of the incidence rate for DLGG was ≈1/100,000 person-years (see above). So according to this crude approximation (and with I ≈ 1/100,000 person-years), the approximate value of the prevalence rate for DLGG would be about 10/100,000, or even more if we consider that the mean survival is longer. It is important to notice that the prevalence rate for DLGG is higher than the prevalence rate for glioblastoma.

On the other hand, as it has been noted by Mandonnet et al. [59], DLGG is a progressive primary brain tumor for which several stages can be discerned (i.e., one of them is a long clinical silent stage). Now, it is possible to have an estimation of the prevalence of silent DLGG by MRI performed in healthy subjects. In the conditions of the experiments, the prevalence of DLGG was between 0.1 and 0.2% of the studied population [41–43].

## 2.4 Prognostic Factors for DLGG

Due to the lack of class I evidence concerning the impact of available treatments for DLGG, and the difficulties to make large clinical trials on DLGG (limited number of patients and long survival), the knowledge of spontaneous prognostic factors is crucial for analyzing the effects of the different therapeutic strategies performed on different populations. Except for age, sex and race, little is known for these factors in population based-studies: so most of prognostic factors come from clinical studies.

### *2.4.1 Age, Sex and Race*

Age is one of the most important spontaneous prognostic factors for DLGG. Survival of diffuse astrocytomas and oligodendroglioma by age groups (CBTRUS 2015 data, period 1995–2012, [18]) are shown in Table 2.7. In the study by Claus and Black [55] entitled "survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas (*Data from the SEER Program, 1973–2001)*", improved survival was significantly associated with female gender (hazard ratio [HR], 0.84; 95% CI, 0.74–0.95), younger age, white race (HR, 0.70; 95% CI, 0.54–0.93), histology, and later year of diagnosis. In Europe, Crocetti et al. [50] noted that for glial tumors, the 5-year survival was slightly higher for women (20.7%; 95% CI 19.6–21.9) than for men (18.7%; 95% CI 17.8–19.7). Sant et al. [48] found also slightly better survival for women than men only for malignant PCNSTs. For many cancers, women survive longer than men, and this has been attributed to lower prevalence of comorbidities in women, a better performance status (allowing full application of effective surgical and adjuvant treatments) as well as a better "resistance" to disease [60].

**Table 2.7** One-, Two-, Five-, and Ten-year relative survival rates[a,b] for diffuse astrocytoma and oligodendroglioma by age groups, SEER 18 registries, 1995–2012[c], from 2015 CBTRUS report [18]

| Age group | N[d] | 1-Yr | 2-Yr | 5-Yr | 10-Yr |
|---|---|---|---|---|---|
| Diffuse astrocytoma[e] | | | | | |
| 0–19 | 992 | 92.7% | 87.0% | 82.7% | 80.3% |
| 20–44 | 2349 | 92.4% | 85.2% | 65.9% | 47.2% |
| 45–54 | 1046 | 74.6% | 60.2% | 42.9% | 31.2% |
| 55–64 | 933 | 54.7% | 34.4% | 21.0% | 12.8% |
| 65–74 | 712 | 37.6% | 24.3% | 13.4% | 9.3% |
| 75+ | 603 | 21.3% | 10.8% | 5.4% | 2.0% |
| Oligodendroglioma | | | | | |
| 0–19 | 273 | 96.7% | 94.7% | 91.9% | 89.3% |
| 20–44 | 1832 | 98.0% | 95.4% | 86.0% | 68.6% |
| 45–54 | 792 | 94.2% | 89.1% | 79.1% | 61.8% |
| 55–64 | 431 | 87.8% | 78.2% | 65.4% | 48.3% |
| 65–74 | 176 | 77.3% | 68.4% | 50.6% | 34.4% |
| 75+ | 98 | 61.0% | 50.6% | 38.4% | 18.4% |

[a]The cohort analysis of survival rates was utilized for calculating the survival estimates presented in this table. Long-term cohort-based survival estimates reflect the survival experience of individuals diagnosed over the time period, and they may not necessarily reflect the long-term survival outlook of newly diagnosed cases

[b]Rates are an estimate of the percentage of patients alive at 1, 2, 5, and 10 year, respectively

[c]Estimated by CBTRUS using Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov) SEER*Stat database: incidence—SEER 18 registries research data + Hurricane Katrina impacted Louisiana cases, Nov 2013 Sub (1973–2012 varying) —Linked to county attributes—Total U.S., 1969–2013 counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer statistics branch, released April 2015, based on the November 2014 submission

[d]Total number of case that occurred within the SEER registries between 1995 and 2012

[e]Diffuse astrocytoma includes fibrillary, gemistocytic, protoplasmic, and NOS astrocytomas

### *2.4.2 Clinical Status*

The clinical and neurological status, before and/or after an oncological treatment, classically influences survival [61, 62]. The presence of a neurological deficit increases with age, tumor extension and mass effect [63]. At time of diagnosis, the existence of epilepsy is inversely linked to the presence of a deficit, and consequently carries a favorable prognostic value when isolated [64–66].

### *2.4.3 Tumor Location, Size and Growth Rates*

DLGGs are commonly located in or close to eloquent areas, i.e. those areas of the brain involved in motor, language, visuospatial and cognitive functions [30, 62, 67–69]. Larger tumors and tumors crossing the midline correlate with a shorter

survival [64]. Growth rates are inversely correlated with survival [70–72]. It is important to note that DLGGs show a constant linear growth before malignant transformation. Very slow progression is possible, but these tumors always grow. The average slope is about 4 mm of mean diameter per year before and/or after surgical resection (without adjuvant therapy) [73–75].

### *2.4.4 Prognostic Scores*

In a recursive partitioning analysis, Bauman et al. [76] identified four prognostic groups of patients with statistically different median survivals (MS): (1) [KPS <70 and age >40y, MS: 12 m], (2) [KPS ≥70, age >40y, and enhancement present, MS: 46 m], (3) [KPS <70 and age: 18–40y, or KPS ≥70 and age >40y, no enhancement, MS: 87 m], and (4) [KPS ≥70 and age: 18–40y, MS: 128 m], with the following abbreviations: *KPS* Karnofsky performance Status, *y* years, *m* months.

In 22844 and 22845 EORTC trials, Pignatti et al. [64] showed that age >40 years, astrocytoma histology subtype, largest diameter of the tumor >6 cm, tumor crossing the midline, and presence of neurologic deficit before surgery were unfavorable prognostic factors for survival. The total number of unfavorable factors can be used to determine the prognostic score.

In the University of California at San Francisco LGG prognostic scoring system, patients were assigned a prognostic score based upon the sum of points assigned to the presence of each of the four following factors: (1) location of tumor in presumed eloquent cortex, (2) KPS Score ≤80, (3) age >50 years, and (4) maximum diameter >4 cm [77, 78]. Survival estimates according to this DLGG score were applied in 537 patients and are exposed in Tables 2.8 and 2.9.

**Table 2.8** Hemispheric diffuse low grade glioma scoring system (UCSF), adapted from Chang et al. [77, 78]

| | Yes/No |
|---|---|
| Age >50 years | 1/0 |
| KPS ≤80 | 1/0 |
| Eloquent cortex location (presumed) | 1/0 |
| Maximum diameter >4 cm | 1/0 |
| Score | 0–4 |

Note: gemistocytic astrocytomas were excluded
Abbreviation: *KPS* Karnofsky performance status

**Table 2.9** Survival estimates (cumulative overall survival probabilities) according to the UCSF hemispheric diffuse low grade glioma score in the combined construction and validation sets (N = 537), adapted from Chang et al. [78]

| | 0 year | | 2.5 years | | 5 years | | 10 years | | 12.5 years | |
|---|---|---|---|---|---|---|---|---|---|---|
| DLGG score | P | NR | P | NR | P | NR | P | NR | P | NR |
| All patients | 1 | 537 | 0.92 | 423 | 0.80 | 250 | 0.62 | 74 | 0.44 | 25 |
| Score 0 | 1 | 81 | 1.0 | 72 | 0.98 | 56 | 0.97 | 30 | 0.85 | 15 |
| Score 1 | 1 | 139 | 0.98 | 119 | 0.90 | 72 | 0.77 | 19 | 0.40 | 3 |
| Score 2 | 1 | 204 | 0.95 | 164 | 0.81 | 96 | 0.52 | 21 | 0.35 | 7 |
| Score 3 | 1 | 93 | 0.76 | 56 | 0.53 | 21 | 0.29 | 4 | NA | NA |
| Score 4 | 1 | 20 | 0.68 | 12 | 0.46 | 5 | NA | NA | NA | NA |

Note: gemistocytic astrocytomas were excluded
Abbreviations: *NA* not applicable, *NR* Number of patients at risk, *P* probability

### *2.4.5 Imaging and Biological Prognostic Factors*

Beside these clinical prognostic factors, imaging prognostic factors (conventional, diffusion, perfusion, spectroscopy MRI and PET imaging), as well as molecular and genetic prognostic factors (i.e., 1p/19q codeletion, IDH1/2, TERT, ATRX, p53, PDGF, methylation, etc.) are being identified. They will be presented elsewhere in this book, but it is important to mention that they have to be validated in large population studies.

### *2.4.6 Therapeutic Prognostic Factors*

Among available treatments for DLGG, only large resection seems to show improving survival and delaying tumor progression, in population-based parallel cohorts [79] and in many different clinical studies [e.g., 61, 65, 79–82]. Moreover, "supratotal resection" (when it is feasible) delays the time to malignant transformation and increases the overall survival [84]. The EORTC study 22,845 revealed an advantage for immediate postoperative radiotherapy in terms of progression-free survival (5.3 vs. 3.4 years), but not for overall survival [85]. One recent publication describes some clinical situations where radiotherapy can be discussed and/or proposed [86] (this point will be discussed in the following paragraph). The role of chemotherapy for DLGG remains to be defined. But some interesting results have been published with chemotherapy using either PCV (Procarbazine, CCNU, and Vincristine) or Temozolomide [87–92]. Chemotherapy could be used for unresectable DLGG, at progression, or now as neoadjuvant chemotherapy followed by surgical resection [93, 94]. In a recent clinical trial, for specific clinical conditions (cohort of patients with grade II glioma who were younger than 40 years of age and had undergone subtotal tumor resection or who were 40 years of age or older), progression free survival and overall survival were longer among those who received combination

chemotherapy (PCV) in addition to radiation therapy than among those who received radiation therapy alone [94]. On the other hand, some studies showed that re-operation in DLGG patients at progression, after a period with a strict clinical and MRI follow up, gave a good quality of life and good overall survival [29, 89, 94–96], particularly when the residual volume was <10 cc [97].

About clinical epidemiology for DLGG, some points need to be underlined:

- First, **endpoints in DLGG** studies remain to be better defined [99, 100]. Given the continuous linear growth of DLGG on MRI [73, 74], progression-free survival is poorly defined. Time to malignant transformation would be better, but this criteria is not often used in the literature [101, 102].
- Second, given the long time survival of DLGG patients, it is very important to **evaluate the quality of life** after any treatment [103–105], as well as cumulative time with a good quality of life [102].
- Third, **biology and genetics** for gliomas are undergoing a revolution [105–111]. But until now, only statistical results have been repored, sometime using different techniques, often based on retrospective studies, and very few publications take into account clinical and therapeutic prognostic factors. So, we must be very careful to propose or not propose a specific treatment for a given individual.
- Fourth, DLGGs are slow growing tumors, and they develop in a specific organ: the brain. And the brain has abilities to reorganize itself by forming new neural connections throughout life and different pathologies. This is **the brain plasticity**. In case of DLGG, compensatory reactions begin before the operation, in response to the tumoral growth, they remain active during and after the surgery. This compensation can involve the perilesional adjacent areas, the distant ipsilateral cerebral structures and the homologous contra-lateral regions [112]. Slow growing tumor and brain plasticity are two main points that differentiate DLGGs from other malignant tumors. So, oncological reasoning must be weighted by these two points.
- Fifth, until now, **no study evaluated the impact of multi step treatments in a large population**. The past can explain that. Indeed, 40 years ago, biology and MRI were not available, it was impossible to evaluate DLGG. Because they are slow growing tumors, many teams practiced the "wait and see" attitude. Otherwise, the first treatment known to have efficacy in the brain malignancies (i.e., glioblastoma) was radiotherapy. So, the question for DLGG was to perform radiotherapy early or delayed after biopsy (or partial resection). Then, with the development of MRI and neurosurgical methods (intraoperative ultrasound, neuronavigation, intraoperative MRI, and cortical as well as subcortical stimulations in awake patients) it was possible to perform resections based on anatomical and functional landmarks. No registry data took into account the subpial dissection with the repetition of both cortical and subcortical stimulation to preserve eloquent cortex as well as the white matter tracts, but one meta-analysis showed that the intraoperative stimulation mapping is significantly associated with fewer late severe neurologic deficits and more extensive resection [113].

So the next step for clinical epidemiology in total or subtotal resection of DLGG is to evaluate surgery alone, with treatment at progression only (surgery again if possible, or chemotherapy), as long as the tumor seems not to be transformed, in a population based-study. Of course, main spontaneous prognostic factors (histology, biology, **velocity** of tumor expansion, multimodal MRI characteristics, as well as performance status, age, etc.) should be collected. One of the present difficulties is that prospective population based study collecting all main prognostic factors does not exist. Even if clinical trial is very difficult to conduct, it is easier to collect money to perform a clinical trial than to build an exhaustive prospective database. Recently, a clinical trial showed that PCV + radiotherapy is better than radiotherapy alone in grade II glioma patients who were younger than 40 years of age and had undergone subtotal tumor resection, or who were 40 years of age or older [95]. Nonetheless, even if this clinical trial is well performed, it does not answer the main clinical question in the every day practice. Moreover, if this paper is misinterpreted, someone could propose PCV + radiotherapy, directly after surgery, for all DLGG patients older than 40 years, or for subtotal resection patient younger than 40 years.

Recently, a proposal of dynamic multi steps therapeutic strategy in DLGG before malignant transformation has been proposed [98], it remains to be evaluated in a large population based-study.

### *2.4.7 Prognostic Factors: Conclusion*

Now we have a lot of candidates for spontaneous (clinical, radiological and biological) prognostic factors, but we have validated only a few in population studies. On the other hand, we have just few suspected therapeutic prognostic factors. So, future studies will include a lot of works to validate these spontaneous prognostic factors and to determine efficient prognostic therapeutic factors. New strategies and new systems for evaluating medical care of patients are needed.

## 2.5 New Methodologies for Clinical and Analytical Epidemiology for DLGG and PCNST

### *2.5.1 New Methodology for Clinical Epidemiology for PCNST*

As mentioned, the number of candidates as prognostic factors is very important. On the other hand, surgery, radiotherapy, chemotherapy have prognostic impact, but the application criteria remain also to be actually determined. Moreover, given the long survival of DLGG patients, treatments are now applied to different stages of the disease (slow progression without transformation, phase with microfoci of malignization, and phase with fast malignant evolution). Again, there is no therapeutic

approach formally evaluated to preset the order and duration of treatments. Finally, the study of the quality of life after each treatment is a major factor.

The methodology currently used in present tumors registries does not consider all these factors. The works performed in single institutions often involve selected patients with an insufficient number of patients to validate the various prognostic factors and the different therapeutic approaches.

One solution could be to build large clinical, biological and therapeutic databases, with an attempt to complete registration for all patients. Regional or national databases involving all participating medical teams, epidemiologists and biostatisticians are now possible [19, 22, 35, 113–115]. This supposes to note and register main clinical (i.e., symptoms, KPS, MMSE –mini mental status exam-, and/or other neuro cognitive evaluation), radiological (i.e., tumor location, enhancement, tumor volume, tumor growth rate, multimodal imaging data when available), surgical (i.e., extent of resection, residual volume of the tumor), histological and biological (i.e., 1p-19q codeletion, IDH 1/2 mutation, and others when available) factors, treatments performed, quality of life, and dates of malignant transformation and death. Of course, all of these factors are not always noted in medical notes, but it is in progress. Of note, as brain tumors (i.e., DLGG) are more frequently seen in specialized and/or academic institutions, most of these factors are collected now. Some strategies have already been proposed for DLGG [61, 118], but need to be evaluated at population level.

To date, the registration of all these items across a region or country could seem unrealistic, but the development of computing systems (see the complexity and efficiency of informatics systems of banks or plane companies) as well as cooperation between different medical specialties and biostatisticians can open the door to such strategies.

Often, the main limitation to the current registration of these data is the lack of time for clinicians to capture these elements in a computer database. The use of clinical research technicians to enter data into a computer system is a solution used by some major centers, and this allows the construction of local databases. However, current economic conditions do not facilitate an employment of clinical research technician in all departments.

Now, healthcare information systems are growing up rapidly. One old method, but still in application, is the “passive” computer archiving (only storage of medical notes, medical exams and imaging without any computer requests available). More recently, computer requests are developed, mainly for economic purposes, but medical applications become a large avenue for future healthcare information systems. The computer interface systems have also made great progress, and advances in health information technology also include mobile computing systems (i.e., tablet-PC and smartphone applications). The goal of future applications is that data from medical notes (operative report, pathology report, biology report, multidisciplinary meeting report, radiotherapy report, chemotherapy report, quality of life evaluation, etc.) and imaging are directly exported towards specific data base without having to re-enter data.

The difficulties in implementing such a system are not technical, but involve confidentiality rules and sharing (or pooling) medical data between different actors of the healthcare system. The rules of confidentiality vary from countries to others. But many secured systems are now available. Second, many patients are now accustomed to sign consent forms for medical studies. Third, when we explain to brain tumors patients the interest to participate in medical research, very few patients refused to be involved. Fourth, in many countries now, patients own their medical data and it is possible to send medical data of patients to any doctor (or medical institution) chosen by the patient himself. So if patients sign a form allowing sending their medical data to a secure medical institution (data base with all required authorizations), hospital administrative authorities can not refuse.

Until now, the sharing of medical data between different institutions is often difficult because of competition regarding scientific publications. But the system proposed here is not the discovery of a new potential prognostic factor or of a new technique: it is a validation across a population of items already published in clinical series (i.e., original research or clinical trials).

Moreover, the evaluation of medical practices and the definition of quality criteria are increasingly required by government authorities. The new methodology presented here is designed both for validation of prognostic factors and/or therapeutic strategies as well as for evaluation of quality of care. But for efficiency, this has to be managed by group of specialists (neurosurgeons, neuro-oncologists, neuropathologists, etc., with the help of epidemiologists and biostatisticians), and not by technicians disconnected of neuro-oncology.

This proposed strategy was recently supported by the notion of precision medicine.

### *2.5.2 Precision Medicine*

The concept of precision medicine, i.e. prevention and treatment strategies that take individual variability into account, is not new [119–121]. Precision medicine is an emerging approach for disease treatment and prevention that incorporates individual variability in genes, environment, and lifestyle for each person. While some advances in precision medicine have been made, the practice is not currently in use for most diseases [122].

Brain tumors and DLGG particularly, are good candidates for developing precision medicine. A lot of works in genomic, transcriptomic, proteomic, genetics, epigenetic, imagery, etc., are in progress but their significances are still unknown at population level. Targeted therapies [123, 124] and specific immunotherapies [125, 126] begin to develop. Etiologies for most all PCNST are not known [4, 39]. Prevention does not yet exist for them. And so forth.

But we have to keep in mind that we need systems of big data analysis not for biology only, but also including imagery, all clinical parameters as quality of life and treatment data, in order to share data at population level. We have to take into

account the cerebral plasticity, to keep the best quality of life as long as possible, and adapt therapies to the activities and wishes of the patients.

Of note, the Brain Tumor Epidemiology Consortium (BTEC) starts to investigate brain tumor epidemiology in the era of precision medicine [127].

### *2.5.3 Risk Factors and Methods to Investigate Causes of DLGG*

Because DLGG tumors are rare, it is difficult for any single clinical series to assemble a large number of cases, enough to explore etiological risk factors. These tumors are often combined with other glial tumors in analyses for epidemiological studies, which makes it difficult to disentangle the association between the risk factors under study and the association with glioma (as DLGG). However, DLGGs patients have age at diagnosis, biology, clinical and imaging characteristics different from patients with other glial tumors, suggesting potentially different risk factors (see the chapter by Darlix et al. on the "Origins of DLGG").

The identification of 1p/19q loss in ≈70% of oligodendrogliomas [128, 129] and its correlation with improved survival, and the fact that specific genes are involved in the biology of oligodendroglial tumors [130] suggest that the etiology of oligodendroglioma may differ from the etiology of other gliomas. On the other hand, IDH1/2 mutations are the only known genetic alteration with a high prevalence (80% of cases) in all WHO grade II diffuse gliomas, and their frequency does not change during the progression from diffuse astrocytoma (WHO grade II) to anaplastic astrocytoma (WHO grade III) and secondary glioblastoma (WHO grade IV). Similarly, oligodendroglioma (WHO grade II) shows a frequency of IDH1 mutation similar to that in anaplastic oligodendroglioma (WHO grade III) [131].

The high frequency of IDH1/2 mutations in oligodendrogliomas, astrocytomas, and secondary glioblastomas derived thereof suggests these tumors share a common progenitor cell population, and the absence of this molecular marker in primary glioblastomas suggests a different cell of origin [132] (see the next chapter by Jacobs et al. on "Molecular Epidemiology of DLGG").

Known risk factors for glioma include inherited genetic syndromes [39, 133, 134] and exposure to high-dose ionizing radiation [39, 135, 136]. A family history of brain tumors (about 5% [39, 137]) and mutagen sensitivity have previously been associated with an increased risk of glioma, while allergies/asthma and chicken pox have been associated with a decreased risk of glioma [4, 39, 138, 139].

A summary of possible risk factors that have been investigated for glioma is available in the review by Bondy et al. and Ostrom et al. [4, 39]. Smoking, alcohol consumption, dental X-rays, and head injury are not believed to be associated with the risk of glioma. Other nongenetic risk factors that have been investigated include cellular telephone use [140–146] (note: the results of the international project "Mobi-Kids"—the main objective is to assess the potential link between the risk of

brain tumors and environmental risk factors, including the use of communication devices—are expected soon), diet [147–150], anti-inflammatory drug use [151, 152], pesticides [153–155] (note: assessment of the exposition is difficult and specific methodology is needed [156]), exogenous hormones [157–159] and other lifestyle factors [160], air pollution [161, 162], virus [127, 163–165], and so on. All these factors are still debated as possible risk factors (or not) for gliomas and do not give enough information and/or inconclusive results for DLGG. Only very few works studied environmental risk factors for DLGG (i.e., [166]), and data were mainly inconclusive. McCarthy et al. [128] investigated risk factors for oligodendroglial tumors (329 Oligodendrogliomas, 146 anaplastic oligodendroglioma and 142 mixed gliomas). Data came from seven case–control studies (five US and two Scandinavian) and were pooled. Results for oligodendrogliomas and anaplastic oligodendrogliomas (for comparison) are shown in Table 2.10.

Asthma was associated with a decreased risk of oligodendroglioma (OR = 0.5; 95% CI: 0.3–0.9). Significant heterogeneity between Scandinavian sites and US sites was found for family history of other cancers, while the Scandinavian sites found a significantly increased risk in those with oligodendroglioma (OR = 4.0; 95% CI: 1.7–9.6) compared with the US sites for which no association was found (OR = 1.0; 95% CI: 0.7–1.3). For variables that were reported by only US study sites (Table 2.11), having had chickenpox was associated with a decreased risk of oligodendroglioma (OR = 0.6; 95% CI: 0.4–0.9); and compared with the use of a public water source, use of bottled water was inversely associated with oligodendroglioma (OR = 0.4; 95% CI: 0.2–0.9). Finally in this study, no significant associations were noted for ever regular alcohol drinking, diabetes, antidepressant use, anti-inflammatory use, solvent exposure, paint exposure, pesticide exposure, or farm exposures. Only history of seizures was associated with oligodendroglioma and anaplastic oligodendroglioma, but as seizures are symptoms, it is difficult to conclude at a risk factor. One surprising result is that Medical X-rays to the head and neck was associated with a decreased risk of these tumors. No explanation is available.

With respect to environmental exposures, future studies should pay greater attention to whether or not suspect agents can cross the blood brain barrier or whether they can reach the brain by other routes [4].

Studies of syndromes, familial aggregation and mutagen sensitivity, and genome-wide association studies are detailed in the next chapter by Jacobs et al.

In summary, a lot of works has still to be done for understanding glioma causes and for evaluating all therapeutic strategies. As PCNSTs includes more than 140 histological types and subtypes, with probably (1) different biological mechanisms involved in tumorogenesis and (2) different risk factors, the French neuro-oncology community decided to record and analyze each histological type and subtype specifically. French Brain Tumor DataBase (FBTDB) was born in 2004 [12]. This work aims of prospectively recording all PCNST cases in France, for which histological diagnosis is available. The objectives are (1) to create a national database and network to perform epidemiological studies, (2) to implement clinical and basic

**Table 2.10** Adjusted odds ratios (ORs) for data on selected exposures collected at 5 US and 2 Scandinavian (Sweden and Denmark) sites for oligodendroglioma (OGD) and anaplastic oligodendroglioma (AO) compared with frequency-matched controls, adapted from McCarthy et al. [128]

| Exposure | Oligodendroglioma, adj. OR[a] (95% CI) | Anaplastic oligodendroglioma, adj. OR[a] (95% CI) | Number OGD/AO | Number controls | Study sites excluded[b] |
|---|---|---|---|---|---|
| Ever smoker | 0.9[c] (0.7, 1.2) | 0.9 (0.7, 1.4) | 328/146 | 1255 | None |
| Family history of brain tumor | 1.6 (0.9, 3.1) | **2.2**[d] **(1.1, 4.5)** | 271/122 | 995 | 2, 6 |
| Family history of cancer | 1.1[e] (0.8, 1.4) | 1.1 (0.7, 1.5) | 324/144 | 1230 | None |
| Asthma | **0.5**[d] **(0.3, 0.9)** | **0.3**[d] **(0.1, 0.9)** | 174/92 | 674 | 1, 3, 4.1 |
| Allergies[f] | 1.1[e] (0.8, 1.6) | 0.6 (0.4, 1.1) | 245/97 | 880 | 1, 4.1 |
| Asthma and/or allergies[f] | 0.9 (0.6, 1.2) | **0.6**[d] **(0.4, 0.9)** | 222/122 | 869 | 3, 4.1 |
| Eczema | 0.6 (0.3, 1.3) | 0.4 (0.1, 1.3) | 136/72 | 541 | 1, 3, 4.1, 4.2 |
| History of seizures | **6.7**[c,d] **(4.3, 10.6)** | **8.7**[d] **(5.0, 15.2)** | 248/130 | 1036 | 3 |
| Antihistamine use | 1.0 (0.6, 1.4) | 1.2 (0.7, 1.9) | 229/123 | 866 | 2, 4.1, 7 |
| Dominant hand | | | | | |
| -Left vs right | 1.2 (0.6, 2.3) | 1.1 (0.4, 2.8) | 122/64 | 494 | 1, 3, 4.1, 4.2 |
| -Both vs right | 1.1 (0.3, 3.4) | 0.9 (0.1, 7.5) | | | |
| Radiation treatment | 1.1 (0.5, 2.6) | 1.3 (0.5, 3.4) | 327/146 | 1247 | None |
| Dental X-rays | 0.8 (0.5, 1.2) | 1.3 (0.5, 2.9) | 212/86 | 772 | 1, 4.1, 4.3 |
| Medical X-rays to the head and neck | **0.7**[d] **(0.5, 1.0)** | **0.6**[d] **(0.4, 1.0)** | 179/80 | 731 | 1, 3, 4.3 |
| Any trauma to the head | 1.3 (1.0, 1.8) | 1.0 (0.6, 1.5) | 267/110 | 1037 | 5, 7 |

95% CI: 95% confidence intervals

[a]Unconditional logistic regression, adjusting for age group, gender, and site

[b]1 = MD Anderson, 2 = NCI, 3 = NIOSH, 4.1 = UCSF series 1, 4.2 = UCSF series 2, 4.3 = UCSF series 3, 5 = UIC/Duke, 6 = Sweden, 7 = Denmark

[c]P value for interaction term with site was <0.05 among US sites with available data. For oligodendroglioma, site-specific adj. OR (95% CI) for smoking ranged from MD Anderson: 0.4 (0.2, 0.9) to Duke/UIC: 2.3 (1.0, 5.3); for history of seizures ranged from NIH: 1.2 (0.4, 3.9) to Duke/UIC: 35.2 (4.0, 311.2); For anaplastic oligodendroglioma, site-specific adj OR (95% CI) for medical X-rays ranged from UCSF: 0.4 (0.1, 0.9) to NIH: 2.6 (0.7, 10.4)

[d]$P < 0.05$

[e]P value for test for heterogeneity was <0.05 between US and Scandinavian sites. For oligodendroglioma, site-specific adj. OR (95% CI) for family history of other cancers for Scandinavian and US sites, respectively, was 4.0 (1.7, 9.6) and 1.0 (0.7, 1.3); for allergies for Scandinavian and US sites, respectively, was 4.6 (1.3, 15.5) and 0.9 (0.6, 1.3)

[f]Allergies for the Denmark and Sweden data only includes hay fever

**Table 2.11** Adjusted odds ratios (ORs) for data on select exposures collected only at 5 US sites for oligodendroglioma (OGD) and anaplastic oligodendroglioma (AO) compared with frequency-matched controls, adapted from McCarthy et al. [128]

| Exposure | Oligodendroglioma, adj. OR[a] (95% CI) | Anaplastic oligodendroglioma, adj. OR[a] (95% CI) | Number OGD/AO | Number controls | Study sites excluded[b] |
|---|---|---|---|---|---|
| Ever regular alcohol drinker | 0.8 (0.6, 1.2) | 0.7 (0.5, 1.2) | 287/120 | 1092 | None |
| Diabetes I or II | 0.8 (0.4, 1.9) | 0.7 (0.2, 2.0) | 192/108 | 754 | 3, 4.1 |
| Chicken pox | **0.6**[c] **(0.4, 0.9)** | **0.5**[c] **(0.3, 0.9)** | 172/100 | 731 | 2, 3 |
| Antidepressant use | 0.9 (0.6, 1.3) | 0.8 (0.5, 1.4) | 177/104 | 745 | 2, 3 |
| Anti-inflammatory use | 0.9 (0.6, 1.4) | 0.9 (0.5, 1.4) | 148/98 | 586 | 2, 3, 4.1 |
| Solvent exposure | 0.9 (0.7, 1.3) | 1.2 (0.7, 2.0) | 203/83 | 733 | 4.1, 4.2, 4.3 |
| Paint exposure | 1.4 (1.0, 2.0) | 1.4 (0.8, 2.4) | 225/100 | 834 | 4.1, 4.2 |
| Pesticide exposure | 1.1 (0.7, 1.6) | 1.6 (0.8, 3.2) | 223/99 | 826 | 4.1, 4.2 |
| Farm exposures | 0.7 (0.5, 1.1) | 0.8 (0.5, 1.4) | 200/81 | 760 | 1, 2 |
| Water source | | | | | |
| - Private vs public | 1.0 (0.7, 1.6) | 1.6 (0.8, 3.1) | 199/83 | 727 | 4.1, 4.2, 4.3 |
| - Bottled vs public | **0.4**[c] **(0.2, 0.9)** | 0.5 (0.2, 1.3) | | | |

95% CI: 95% confidence intervals

[a]Unconditional logistic regression, adjusting for age group, gender, race, site, and interview year

[b]1 = MD Anderson, 2 = NCI, 3 = NIOSH, 4.1 = UCSF series 1, 4.2 = UCSF series 2, 4.3 = UCSF series 3, 5 = UIC/Duke

[c]P value <0.05

research protocols, and (3) to harmonize the health care of patients affected by PCNST.

Since 2006, more than 9500 new cases of PCNST per year are recorded by FBTDB (French metropolitan population in 2008 ≈ 62,000,000 inhabitants, crude rate of newly diagnosed and histologically confirmed PCNST = 15.55/100,000 person years, period 2006–2011, N = 57,816) [36]. This is very close to the estimated incidence of newly diagnosed and histologically confirmed PCNST in France by the "Registre des tumeurs de la Gironde" (15.27/100,000 person years, with overall crude rate of 20.17/100,000, unchanged when standardizing on the French population [20], and 75.7% of overall tumors were histologically confirmed, last data from Tumor Registry of Gironde—http://etudes.isped.u-bordeaux2.fr/REGISTRES-CANCERS-AQUITAINE/Snc/S_Resultats.aspx).

A recent specific work of FBTDB was to study the geographical distribution of DLGG and the geographical distribution of diffuse grade III gliomas (DGIIIG) on the metropolitan French territory (years 2006–2009) [34] (note: metropolitan France

territory includes mainland France and nearby islands in the Atlantic Ocean and Mediterranean Sea and excludes all overseas territories).

Even if in this study the authors were mainly interested by the distribution of DLGG, they decided to study also the distribution of DGIIIG because histological grading of gliomas could be sometimes debated by some pathologists [29]. Results showed heterogeneity in the distribution of DLGG and the distribution of DGIIIG among the French territory, with a higher number of cases in the northern, eastern and some central areas of France for both glioma groups. Even if small discrepancies exist between the two distributions (DLGG/DGIIIG), they are globally comparable [34]. The next step of this work will be to compare environmental, genetic and functional factors, between areas with high incidence and areas with low incidence. This could be another way to look for risk factors of DLGGs.

Once again, for rare tumors, we see the difficulties to gather enough patients to study etiologies and clinical management. Unfortunately, registries do not directly collect enough data to analyze etiologies and clinical management for DLGG patients. So, big clinical and biological database are needed to do it. We just mentioned the French initiative of the FBTDB above, but other ways are also possible. In Europe, it could be possible to build such database with grants from EU funding program (e.g., "Horizon 2020"). Another possibility to studies etiologies of rare tumors is to build a cohort of million healthy people in collecting biological, genetics and environmental data, as it was proposed in the US Precision Medicine Initiative (http://www.sciencemag.org/news/2016/02/nih-s-1-million-volunteer--precision-medicine-study-announces-first-pilot-projects). Concerning DLGG, it would probably be necessary to collect several million people and to collect data since early childhood until adult age. So, it is an expensive but interesting way also. Another recent proposition to study etiologies and clinical management of DLGG patients was proposed by Elizabeth Claus and first published in the International Brain Tumor Alliance (IBTA) magazine (http://theibta.org/our-publications/#our-pub-title). As mentioned above, the development of secure web and smartphone-based research tools along with collaboration with patient organizations (such as the IBTA) allows scientists to identify, enroll, collect data from, and share results and information with patients with greater ease. Researchers benefit from direct contact with a highly engaged group of potential study subjects, while patients and caregivers benefit from access to scientific and clinical expertise and from the opportunity to voice their interest and concerns regarding research undertakings. The proposed "International Low Grade Glioma Registry" represents one such web-based research effort. The overall goal for this "registry" is to gather data for the study of adult patients with low grade glioma as well as to provide an international forum for dissemination of information on the topic.

Whatever the future techniques that will be used to collect big data in order to explore the etiologies of DLGG, different kinds of etiology have to be considered. We have seen that those genetic, environmental factors, and interaction between genetic and environment could explain (at least in part) etiologies of DLGGs [167], but, in addition, we propose to study two other ways:

– First, it can be hypothesized that the biological pathways involved in the genesis of DLGG may differ according to the tumor location, as DLGGs are located in (or near) functional areas of the brain [68], and as anatomo-molecular studies showed significant correlations between the DLGG locations and tumor genetics, with a higher rate of IDH mutation and 1p19 codeletion in frontal tumors (specific work in progress in our institution). This hypothesis is also supported by the fact that the physiology of glial cells can be determined (or modified) by neurons located around of glial cells [168], and/or by the microenvironment [169, 170]. This hypothesis is called "the molecular theory" (see the chapter by Darlix et al. on "The origins of DLGG").
– Secondly, arguments for the influence of functional parameters and of the subject's activities on the glial cells can be found in the literature on training-induced macroscopic structural changes (of both white and grey matter) in human and animals. A number of neuroimaging studies in healthy volunteers showed that learning could generate a significant increase of gray matter volume in areas specifically involved in tasks extensively repeated [171]. Interestingly, an implication of the glial cells, either direct (i.e., proliferation of the glial cells [172, 173]) of indirect (i.e., synaptogenesis [174, 175] or myelination [176, 177]) has been suggested. Thus, we might suggest that such modifications in the local glial properties may favor or prevent DLGG, or at least interfere in the development of DLGG in some specific brain locations. This hypothesis is called "the functional theory".

Finally, we do not know whether the initial event of the occurrence of the DLGG is before the conception, in utero, during the childhood, or at the beginning of adult age. So whatever the technique, and whatever the way that we are looking for the etiology(ies) of DLGG, we have to take into account all these periods. Moreover, it is speculated that some cancers may be initiated somewhere in the human body, and often, the immune system destroys it, before the cancer is developing. Does this phenomenon exist into the brain? Currently, this is unknown.

This leads to another question: does the initial cell abnormality (presumably carried by DNA) have the same mechanism as the further development of the glioma itself?

### *2.5.4 Early Detection of DLGGs*

The impact and the ways for considering the early detection (or screening) of these specific tumors can be discussed (see the chapter by Mandonnet et al. "From management of incidental DLGG to screening of silent DLGG"). DLGGs usually affect young adult and have major adverse economic and social impacts. Prevalence of DLGG is probably underestimated as patients have a long history of illness after the occurrence of symptoms. As mentioned, treatment, especially surgical

resection, may significantly increase the overall survival in DLGG by delaying malignant transformation, and may also improve the quality of life. Many recent reports have indeed demonstrated the actual impact of surgery on the natural history of DLGG [62, 66, 80, 84, 178]. Such demonstration has been possible by performing an objective evaluation of the extent of resection (EOR) on postoperative MRI: all recent studies with postsurgical MRI observed a significant relationship between the EOR and overall survival (for a review, see [178]). This is the reason why it was recently propose to operate asymptomatic patient with a DLGG [45, 179]. Indeed, all incidental DLGGs are progressive tumor, with a constant radiological growth (median velocity of diametric expansion around 3.5 mm/year, i.e. very close to the growth rate of symptomatic DLGG) [180]. Moreover, incidental DLGGs differ significantly from symptomatic DLGGs: they have smaller initial tumor volumes ($p < 0.001$), lower incidence of contrast enhancement ($p = 0.009$), and are more likely to undergo gross total surgical removal ($p < 0.001$). Patients with incidental DLGG frequently suffer from neuropsychological disturbances [181], and the risk of inducing seizures by surgery in incidental DLGG is very low (much lower than the risk of epilepsy during symptomatic phase of DLGG): it does not represent an argument against early surgery [182]. The majority of incidental DLGGs are IDH1 mutated and are predominantly oligodendroglial tumors. The favorable prognosis of incidental DLGGs may be accounted by the higher practicability of extensive resection, non-eloquent tumor location, smaller tumor volume, and perhaps the biology [183]. So if this strategy and this result are confirmed in larger study, we could argue that effective treatment does exist at the early phase of the illness.

In future, early detection of DLGG could be performed by three different ways, at least. First, MRI is considered without risk: abnormality of signal on FLAIR or T2-weighted images is easy to detect in fast exams. Combining screening of some neurological illness and/or neurovascular illness by MRI could be a realistic first approach. Then, multimodal MRI and consecutive MRIs have good diagnostic power and may result in specific treatments and/or follow-up. Secondly, if progress in knowledge of risk factors of DLGG occur (be they environmental, and/or genetic, and/or functional), it will be possible to define groups of patients with increase of risk of DLGG. And it could be proposed to these patients to have MRI. We can notice that Gerin et al. [183] recently proposed a model for estimating date of birth of DLGG. Within the assumptions of this model, the authors have identified two types of tumor: the first corresponds to very slowly growing DLGG that appears during adolescence, and the second type corresponds to slowly growing DLGG that appears later, during early adulthood. All these tumors become detectable around a mean patient age of 30 year-old. So, this represents the first step for defining one subgroup of the population, in which the DLGG screening could be done. Thirdly, many researches on biological markers (in blood, urine, saliva, etc.) for gliomas are on going now. For example, we can expect that progress in nanotechnology will help to detect very small level of such biological markers.

## 2.6 Conclusion

In large clinical series or in databases in which cases are histologically confirmed, DLGGs account for approximately 15% of all gliomas. In occidental population, incidence rate for DLGG can be estimated about 1/100,000 person-years, if we consider that some astrocytomas and gliomas NOS (high number in registries) are probably DLGG. Prevalence rate for DLGG is probably higher than prevalence rate for glioblastoma, but remains to be defined more precisely. Until now, causes of DLGG are mainly unknown. Some spontaneous prognostic factors have been identified (i.e., age, KPS, tumor growth rate, volume and location of the tumor, biology, genetic). Extent of resection has been increasingly shown to correlate with improved outcome, as well as with better seizure control and reduced histological upgrading rates. Many biological and radiological factors are candidates to be prognostic factors now, but evaluations on large population studies are required. Therapeutic strategies using several successive surgeries (spread over time), chemotherapy, radiotherapy, and combination of different treatments are not currently codified. Therefore many evaluations are also required, by taking into account of brain plasticity and quality of life.

To move forward quickly and effectively in the knowledge of biological processes, identifying the causes, assessment of oncological care and quality of life after any treatment, the medical and scientific community must significantly changes its current practice of recording data. The creation or development of large database (including clinical, radiological, biological, genetic, and functional data) involving most major medical centers and different specialties (neurosurgery, neurology, neuro-oncology, neuropathology, neuroradiology, biology, epidemiology and biostatistics): the use of modern informatics technology will yield major results in the relatively near future.

Knowledge of molecular biology and genetics will develop. The functional theory, as possible etiology for DLGG, has to be investigated. That will make possible to better understand the genesis of DLGG and other PCNST. But the observation remains a simple and effective method for searching causes of DLGG and other PCNST. The study of the spatial and temporal distribution of DLGG (and other TPSNC) cases on large area will allow for searching environmental, genetic, and functional differences in populations with high and low incidence. By this easy way, it could be possible to discover factors and/or their interactions responsible for the initiation and development of DLGG and/or others PCNST.

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# Chapter 3
# Molecular Epidemiology of Diffuse Low-Grade Glioma

**Daniel I. Jacobs, Elizabeth B. Claus, and Margaret R. Wrensch**

**Abstract** Molecular epidemiologic studies of diffuse WHO grade II glioma (diffuse low-grade glioma, DLGG) have contributed greatly to our knowledge of these slow-growing but highly infiltrative tumors. Such studies have yielded valuable insights into factors that modify risk of disease development including several germline genetic variants, exposure to ionizing radiation, and history of allergy. Furthermore, new frameworks for molecular classification of low-grade gliomas have emerged that delineate tumor subtypes with distinct etiologies and outcomes; therapeutic strategies may ultimately be tailored accordingly. In this chapter, we summarize these and other recent insights into the molecular epidemiology of DLGG in adults.

**Keywords** Diffuse low-grade glioma • Glioma • DLGG • Molecular epidemiology • Genetic susceptibility • Risk factors

## 3.1 Introduction

Diffuse low-grade gliomas (DLGG; World Health Organization [WHO] grade II) are infiltrative tumors arising from glial cells of the brain that account for approximately 15% of all gliomas [1, 2]. DLGGs are more common among Caucasians and males, and peak in incidence between 35 and 44 years of age.

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Although grade II gliomas are considered to be slow-growing and survival is superior than that for high grade gliomas (WHO grades III and IV), the tumors are not benign and almost inevitably recur and/or progress to higher grade lesions even following the most aggressive treatment modalities. Median survival is approximately 7–12 years and has not appreciably improved over the past three decades [3, 4].

While the exact causes of DLGG are unknown, recent epidemiological studies have enhanced our understanding of potential risk factors, including rare familial and common inherited genetic variants that predispose to low-grade glioma. Novel classification schemes based on objectively measured tumor markers have emerged that delineate molecular subgroups with distinctive clinical behavior, patient characteristics, associated germline variants, and overall survival. Finally, associations between low grade glioma and environmental and developmental factors, such as history of allergy or atopic disease, have been discovered that inform disease pathogenesis. The purpose of this chapter is to provide a summary of these and other recent insights into the molecular epidemiology of DLGG in adults and to highlight important unresolved questions in this field.

## 3.2 Molecular Classification

Gliomas are traditionally classified according to cell morphology and WHO grade, whereby a grade II designation describes neoplasms with atypical, diffusely infiltrative cells without anaplasia or mitotic activity [5]. The tumors are further classified by the cell type of closest resemblance and include astrocytomas, oligodendrogliomas, and oligoastrocytomas (mixed gliomas), which are comprised of astrocytes, oligodendrocytes, and a combination of both cell types, respectively. However, traditional grading and histological classification is subjective, poorly reproducible, and limited in its prediction of clinical outcomes [6–8]. The WHO has recently released new classification guidelines that address this deficiency by incorporating both histological and molecular criteria, and other clinically informative classification schemes based on objectively measured tumor markers are gaining favor as complementary or alternate means of tumor characterization.

### *3.2.1 Updated WHO Guidelines*

In a significant departure from previous WHO classification guidelines, the 2016 edition incorporates both genotypic and phenotypic features for glioma classification [1]. In this scheme, the determination of tumor grade continues to be made according to the aforementioned criteria, and tumors are still evaluated for their histologic appearance (i.e., astrocytic and/or oligodendroglial cell populations).

However, grade II glioma definitions are refined by the inclusion of IDH mutation and 1p/19q codeletion status. Mutations in *IDH1 or IDH2* (together, IDH) are the most commonly seen molecular alteration in low-grade gliomas, occurring in more than 80% of cases [9, 10] and occur in tumors more likely to be located in the frontal lobe [11–13]. Co-deletion of chromosome arms 1p and 19q is commonly seen in oligodendrogliomas [14]. Grade II gliomas can thus be classified as: Diffuse astrocytoma, IDH-mutant, *Diffuse astrocytoma, IDH-wildtype*, or Diffuse astrocytoma, NOS (ICD-O 9400/3); Oligodendroglioma, IDH-mutant and 1p/19q codeleted or Oligodendroglioma, NOS (ICD-O 9450/3); or Oligoastrocytoma, NOS (ICD-O 9382/3).

Several interesting changes in tumor classification arise as a result of this new scheme. For one, the authors state that in the event of a discrepancy between histology and molecular features, "genotype trumps the histological phenotype" (e.g., an astrocytic tumor with IDH mutation and 1p/19q codeletion would be classified as *oligodendroglioma, IDH-mutant and 1p/19q co-deleted*). Additionally, the authors note that genotype-centric classification is likely to diminish the diagnosis of oligoastrocytoma (for which diagnosis has particularly high interobserver variability), instead typically categorizing such tumors into astrocytomas or oligodendrogliomas on the basis of their molecular features despite the observed histology. Furthermore, in the absence of definitive molecular profiling, the not-otherwise-specified (NOS) designation is used along with the histologic appearance. One consequence of the new classification system is that the proportion of tumors classified as NOS will likely increase, as this designation will also be used for tumors that are conclusively genotyped but do not fall into the new, more strictly defined categories. A flowchart outlining the algorithm for low-grade glioma classification is presented in Fig. 3.1. While the revised classification guidelines represent an important step towards the objective classification of low-grade gliomas, the new guidelines are likely to present challenges for clinicians and researchers in adopting the new structure and reconciling the old and new tumor groups.

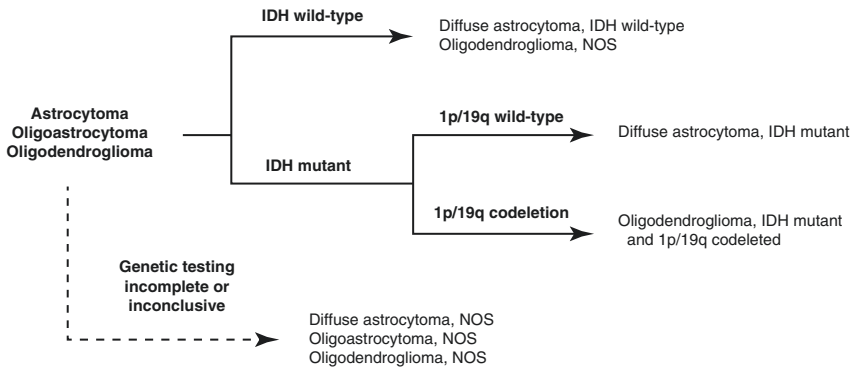


**Fig. 3.1** Low-grade glioma classification algorithm according to new WHO guidelines [1]

### 3.2.2 *Integrative Molecular Classification*

In additional efforts to construct clinically-relevant and objective tumor subclasses, two recent landmark studies have proposed classification schemes defining subgroups of lower-grade glioma (grades II and III) with distinct patterns of molecular and clinical features. Using unsupervised clustering of genomic, transcriptomic, epigenomic, and proteomic data from 293 lower-grade gliomas, an analysis from the TCGA network defined three disease subgroups according to IDH, *TP53*, and 1p/19q status [15]. Two groups were defined by those with IDH mutation with or without 1p/19q codeletion; the first included patients who also tended to have *CIC*, *FUBP1*, *NOTCH1*, PI3 kinase pathway, and *TERT* promoter alterations, while the second group was characterized by patients who also tended to have *TP53* and *ATRX* mutations. The authors suggested that development of these two types of lower-grade gliomas is initiated by IDH mutation and G-CIMP establishment, then driven forward by either *TP53* mutation or 1p/19q codeletion. Tumors without an IDH mutation marked a third group that was molecularly and clinically comparable to that seen in primary grade IV glioma (glioblastoma), displaying frequent *PTEN*, *EGFR*, *NF1*, *TP53*, or *PIK3CA* alterations.

In a second, larger study by Eckel-Passow et al. including TCGA cases as well as cases from two independent sets from the UCSF Adult Glioma Study and the Mayo Clinic, 615 lower-grade gliomas were classified into five groups according to IDH mutation, 1p/19q codeletion, and *TERT* promoter mutation status [16]. The classification scheme proposed by Eckel-Passow et al. is similar to that proposed by the TCGA study but incorporates *TERT* promoter rather than *TP53* mutation status to further refine three groups into five, generating a comprehensive classification system that also incorporates higher glioma grades; a comparison of the molecular alterations that define the two classification schemes is illustrated in Fig. 3.2. The lower-grade glioma groups included tumors without any of the three alterations (7%, "triple-negative"), with IDH mutation only (45%), *TERT* mutation only (10%), *TERT* and IDH mutations (5%), and with all three alterations (29%, "triple-positive"). As in the TCGA study, subgroups were associated with characteristic acquired alterations: *CIC*, *FUBP1*, and *NOTCH1* mutations were seen in triple-positive tumors,

| TCGA | 1 | 2 | | 3 | |
|---|---|---|---|---|---|
| Eckel-Passow et al. | 1 | 2 | 3 | 4 | 5 |
| IDH | + | + | + | – | – |
| TERT | + | + | – | + | – |
| 1p/19q/CIC/FUBP1/NOTCH | + | – | – | – | – |
| TP53/ATRX | – | + | + | – | – |
| PI3 pathway | + | – | – | + | – |
| PTEN/EGFR/NF1 | – | – | – | + | + |

**Fig. 3.2** Comparison of molecular alterations characterizing lower-grade glioma subtypes by TCGA and Eckel-Passow et al. [15, 16]. Symbols '+' and '–' denote presence or absence of corresponding gene/chromosomal alterations, respectively

PI3 kinase pathway mutations in triple-positive and *TERT* mutation only tumors, *TP53* and *ATRX* mutations in tumors with IDH mutation with and without *TERT* promoter mutation, and *EGFR*, *PTEN*, and *NF1* mutations in triple-negative and *TERT* mutation only tumors. Subgroups also had characteristic patterns of copy-number changes and TCGA expression subtypes [17]; interestingly, tumors harboring IDH mutations with or without *TERT* and 1p/19q alterations were most closely related to the proneural expression pattern, while triple-negative or *TERT* mutation only tumors were more likely to display classical or mesenchymal expression patterns, indicating greater molecular similarity to primary glioblastoma.

Additionally, the five subgroups had notable differences in the distribution of histologic subtypes. These data, along with population-level incidence data, can be used to construct population-based estimates of the proportion of grade II astrocytomas and oligodendrogliomas by histology and molecular subtype [16, 18] (Fig. 3.3).

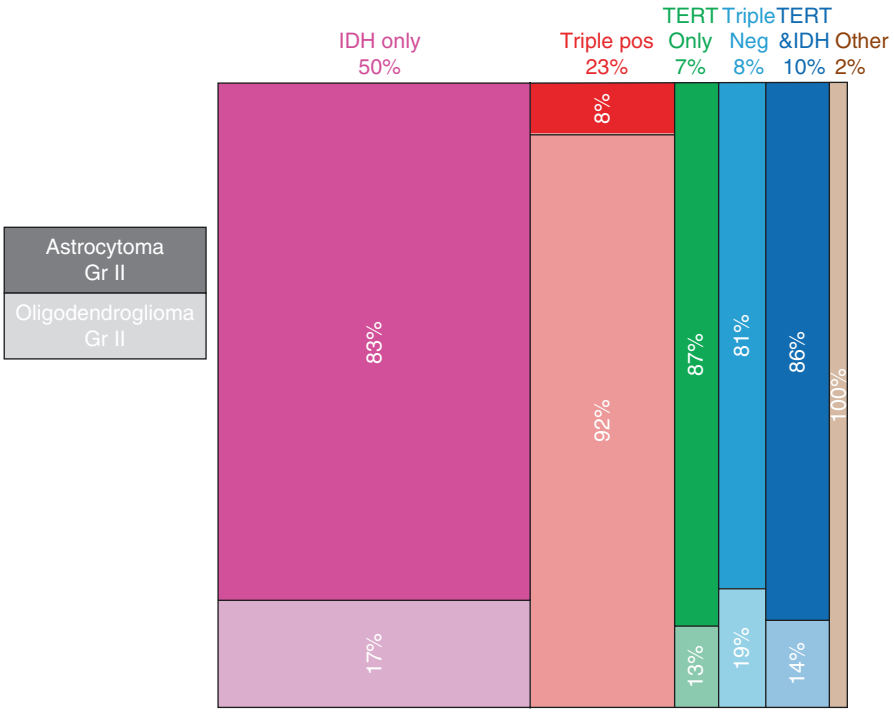


**Fig. 3.3** Estimated population proportions of grade II astrocytomas and oligodendrogliomas by histology and molecular subtype. Percentages along top row denote the estimated proportions of each molecular subtype (IDH mutation only, Triple positive (IDH mutation, TERT mutation, and 1p-19q codeletion), TERT mutation only, Triple Negative (neither IDH or TERT mutation and 1p-19q not co-deleted), TERT mutation and IDH mutation, or Other) among grade II astrocytomas and oligodendrogliomas combined, and percentages within boxes denote the estimated proportions of each histological subtype within a given molecular subtype. Dark and light shading correspond to astrocytoma and oligodendroglioma, respectively. (Proportions were estimated based on data from Eckel-Passow et al. [16] and the Central Brain Tumor Registry of the United States (CBTRUS) [2] and calculated according to the method described by Rice et al. [18])

According to these estimates, nearly three-quarters of grade II astrocytomas and oligodendrogliomas combined are triple-positive or have IDH mutation only. Interestingly, among grade II astrocytomas and oligodendrogliomas, triple-positive tumors tend to be predominantly oligodendrogliomas, while all other subtypes tend to be astrocytomas. It is important to note that these estimates do not include oligoastrocytomas due to the lack of available population data by grade for this histologic type, and that histological subtypes are based on traditional definitions before the 2016 updated WHO guidelines.

## 3.3 Heritable Genetic Influences

While DLGGs are most often sporadic, ~5% of glioma cases are familial in nature, and the risk of glioma development is approximately twice that in first-degree relatives of glioma patients than for the general population [19–23]. Although such familial aggregation can be a reflection of shared environmental exposures, a growing number of constitutive genetic risk factors have been identified that cause glioma or contribute to glioma susceptibility.

### *3.3.1 Familial Susceptibility*

Rarely, gliomas are caused by single-gene hereditary cancer syndromes; for example, Li-Fraumeni syndrome can cause astrocytomas or other malignancies as a result of an inherited *TP53* mutation [24]. Other glioma-causing syndromes include neurofibromatosis, Lynch syndrome, melanoma-neural system tumor syndrome, and Ollier disease [25, 26] (Table 3.1).

In non-syndromic families, linkage studies have been used in an effort to identify glioma-associated risk loci. An early linkage analysis of a small number of individuals with varying glioma grades detected a potential familial glioma locus at 15q23-q26 [27]. A larger nonparametric linkage analysis conducted by the Gliogene Consortium in families segregating glioma of all grades found a significant linkage peak at 17q12-21.32 and suggestive peaks at 6p22.3, 12p13.33-p12.1, and 18q23 [28]; a subsequent parametric analysis supported the prior finding of a risk locus on chromosome 17q [29]. Follow-up targeted sequencing of the 17q region identified candidate missense variants implicating four genes (*MYO19*, *KIF18B*, *SPAG9*, and *RUNDC1*) of potential importance to gliomagenesis [30]. It should be noted that since the distribution of glioma grades in the Gliogene Consortium is comparable to that of non-familial cases, the majority of cases included in the aforementioned analyses had higher grade tumors [31], so whether the identified loci are specifically associated with low-grade glioma risk is unknown.

**Table 3.1** Familial syndromes associated with increased risk of low-grade glioma[a]

| Syndrome | Gene(s) | Mode of inheritance | Other features/ predispositions | Associated glioma subtypes |
|---|---|---|---|---|
| Li-Fraumeni syndrome | *TP53* | Dominant | Breast, brain cancer, soft-tissue sarcoma, other cancers | All types |
| Lynch syndrome | *MSH2, MLH1, MSH6, PMS2* | Dominant | Gastrointestinal, endometrial, other cancers | All types |
| Melanoma-neural system tumor syndrome | *CDKN2A* | Dominant | Malignant melanoma | All types |
| Melanoma-oligodendroglioma susceptibility syndrome | *POT1* | Dominant with reduced penetrance | Malignant melanoma | Oligodendroglioma and oligoastrocytoma |
| Neurofibromatosis 1 | *NF1* | Dominant | Neurofibromas, schwannomas, café-au-lait macules | Astrocytoma |
| Ollier disease/ Maffucci syndrome | *IDH1/ IDH2* | Dominant with reduced penetrance | Intraosseous benign cartilaginous tumors, other cancers | All types |

[a]Table adapted from references [25] and [90]

In a further effort to identify glioma-driving germline mutations, whole exome sequencing was performed in 90 members of 55 families with aggregation of glioma. The analysis identified three families, each with at least one low-grade oligodendroglioma, harboring three different mutations in *protection of telomeres protein 1* (*POT1*) [32]. POT1 is a component of the telomere shelterin complex involved in telomere maintenance and DNA damage response, and loss of *POT1* expression has been shown to cause telomere lengthening [33–35]. This study represents the first characterization of *POT1* mutation as a potential glioma (particularly low-grade oligodendroglioma) predisposition syndrome, and adds to a growing literature indicating that the lengthening of telomeres is a hallmark of gliomagenesis [36].

### *3.3.2 Common Inherited Susceptibility Variants*

A series of genome-wide association studies (GWAS) conducted since 2009 has identified common genetic variants at six genetic loci that are related specifically to the inherited risk of low-grade glioma development, and another four that appear to affect risk of all glioma grades (Table 3.2). Single nucleotide polymorphisms (SNPs)

**Table 3.2** Inherited variants associated with risk of low-grade glioma and all grades of glioma

| Chromosome location | Candidate gene | rsID | Odds ratio | Associated tumor subtype(s) |
|---|---|---|---|---|
| 5p15.33 | *TERT* | rs2736100 | 1.35 | All glioma subtypes |
| 8q24.21 | *CCDC26* | rs55705857 | 5.00 | Oligodendroglial, IDH-mutant astrocytic tumors |
| 9p21.3 | *CDKN2B* | rs1412829 | 1.35 | Astrocytomas grade II-IV |
| 10q25.2 | *VTI1A* | rs111696067 | 1.19 | Low-grade glioma |
| 11q23.2 | *ZBTB16* | rs648044 | 1.25 | Low-grade glioma |
| 11q23.3 | *PHLDB1* | rs498872 | 1.50 | IDH-mutant glioma |
| 12q21.2 | (Intergenic) | rs12230172 | 1.23 | Low-grade glioma |
| 15q24.2 | ETFA | rs1801591 | 1.36 | Low-grade glioma |
| 17p13.1 | TP53 | rs78378222 | 2.70 | All glioma subtypes |
| 20q13.33 | RTEL1 | rs6010620 | 1.40 | All glioma subtypes |

in the 8q24.21 region near long-intergenic noncoding RNA *CCDC26* display the strongest associations with low-grade glioma, specifically with oligodendroglial tumor development [37–40]. Fine-mapping of the 8q24.21 region pinpointed rs55705857 as the strongest risk allele in the region, yielding strikingly large odds ratios for risk of oligodendroglial tumors as well as IDH-mutant astrocytomas (~5-fold increased risk) [41, 42]. rs55705857 maps to a highly conserved DNase hypersensitive region of *CCDC26* that may be related to *CCDC26* expression via transcription factor or polycomb complex binding. Interestingly, it was observed in the study by Eckel-Passow et al. that subjects carrying the risk allele at rs55705857 were at increased risk of developing gliomas in all three subgroups characterized by IDH mutation [16].

SNPs near *PHLDB1* at chromosome 11q23.3 have also been associated with the risk of low-grade glioma, and specifically with the risk of IDH-mutated gliomas [39, 40, 43]. An association has been observed between inheriting a risk allele at 11q23.3 and developing gliomas in the IDH-mutation-only subclass [16]. A follow-up functional study implicated either *PHLDB1* or nearby *DDX6* as target genes in the locus and identified a candidate functional SNP in an enhancer element regulating *DDX6* [44]. Most recently, in the largest GWAS of glioma to date, Kinnersley et al. reported the identification of four new lower-grade glioma risk loci at 10q25.2 near *VTI1A*, 11q23.2 near *ZBTB16*, 12q21.2, and 15q24.2 near *ETFA* [45].

Variants in four other gene regions appear to be related to the development of all grades of glioma (although some grade-specific associations have varied across studies). These include polymorphisms at 5p15.33 in *TERT*, 9p21.3 near *CDKN2A*/*CDKN2B* (which appear to affect risk of astrocytic tumors in particular), 17p13.1 in *TP53*, and at 20q13.33 near RTEL1 [16, 25, 40, 46–49]. Variants in three additional regions (3q26.2 near *TERC*, 7p11.2 near *EGFR*, and 12q23.33 near *POLR3B*) appear to be predominantly associated with high-grade glioma, although again reports have varied [40, 45, 46, 50, 51].

## 3.4 Environmental and Developmental Risk Factors for DLGG

Epidemiological studies have explored many exposures for association with glioma risk with inconsistent results, particularly for low-grade glioma development [25, 52]. Due to the rare nature of these tumors and frequent pooling of glioma grades in many previous epidemiologic studies, the evidence for associations with many factors (e.g., occupational exposures, dietary factors, anti-inflammatory agents) is limited and inconclusive, and will require larger studies with detailed exposure histories and well-annotated biospecimens for increased study validity. A summary of the established, probable, and unlikely risk factors for low-grade glioma is presented in Table 3.3. The risk factors with the best evidence for contributing to low-grade glioma risk, namely exposure to ionizing radiation and history of allergies or atopic disease, are discussed here.

### *3.4.1 Radiation Exposure*

Therapeutic or high-dose ionizing radiation is a long-established cause of brain tumors in adults [53]. Although subtype- or grade-specific data are limited in published studies [25], cases of grade II glioma, specifically, among individuals previously exposed to radiation therapy have been reported [54, 55]. With regard to medical diagnostic radiation exposure, a suggestive association for an increase in low-grade glioma risk has been reported [56], but studies are limited and results inconsistent for this exposure. The impact of nonionizing radiation from cell phone

**Table 3.3** Non-genetic risk factors for low-grade glioma

| Exposure | Direction of association |
|---|---|
| Established risk factors | |
| High-dose ionizing radiation | Increased risk |
| Male vs. female gender | Increased risk |
| White vs. African American ethnicity | Increased risk |
| Probable risk factors | |
| History of allergies/asthma | Decreased risk |
| Probably not risk factors | |
| Alcohol consumption | |
| Antihistamine use | |
| Cellular phone use | |
| Diagnostic radiation | |
| Head injury | |
| Low-frequency magnetic fields | |
| Smoking | |

use has been the subject of much research and speculation. In 2011, radiofrequency fields were classified by the International Agency for Research on Cancer (IARC) as a possible carcinogen due to the observation of increased glioma risk among heavy cell phone users [57]. Subsequent epidemiologic studies have not supported an association between cell phone use and glioma development overall [25], and studies that have stratified by glioma grade have not identified associations between cell phone use and low-grade glioma risk [58].

### *3.4.2 History of Allergy and Atopy*

Epidemiologic studies have revealed an inverse association between allergic conditions and glioma development that is robust to an array of study designs (i.e., single site, multisite, nested case control; prospective cohort; meta-analysis) and exposure metrics [59–62]. Several recent studies have specifically assessed the association of allergy, asthma, and antihistamine use with low-grade glioma risk. Two independent studies published in 2011 found associations between allergy or asthma history and significantly reduced risks (~30–50%) of low-grade glioma development that were comparable in magnitude to associations for higher grade gliomas [63, 64]. Self-reported history of antihistamine use was not associated with low-grade glioma risk in either of these studies. In a study specific to oligodendroglial tumors, history of asthma was associated with a 50% reduction in grade II oligodendroglioma risk [65]. Other studies have reported weaker protective effects of allergy history against low-grade glioma than for high-grade glioma [66, 67].

Most recently, an analysis in the Glioma International Case-Control Study (GICC) population of the role of allergies or other atopic conditions on glioma susceptibility demonstrated a borderline significant ~20% reduction in risk in glioma associated with history of any allergy (OR = 0.79, 95% CI: 0.61–1.02). When stratified by tumor grade, the association was significant for high-grade (OR = 0.75, 95% CI: 0.58–0.98) but not low-grade (OR = 0.84, 95% CI: 0.63–1.11) glioma [62]. With regard to respiratory allergies in particular, the study demonstrated a statistically significant ~30% reduction in glioma risk (OR = 0.72, 95% CI: 0.58–0.90); stratified by tumor grade, the association was comparable for high-grade glioma (OR = 0.70, 95% CI: 0.57–0.85) but was attenuated for low-grade glioma (OR = 0.80, 95% CI: 0.62–1.03). Thus, the protective effect of allergies appears to be less pronounced for low-grade than for high-grade glioma, although it should be noted that a smaller sample was analyzed for low-grade glioma, and there is the potential for recall bias that may be differentially poor among cases, particularly among high-grade subjects. Finally, both asthma status and a history of eczema were associated with statistically significant decreased risks of glioma overall and of low-grade glioma in particular (all ~20–30% reductions), and no significant association was detected for long-term antihistamine use.

## 3.5 Survival

While survival after diagnosis with DLGG is better than that for high-grade glioma patients, it has not improved over the last several decades and DLGG is still ultimately a fatal disease with median survival between 7 and 12 years [3, 4]. Tumor histology and certain clinical factors have been linked to DLGG survival; however, these features are limited in their clinical value and ability to predict tumor progression and/or survival. In recent years, novel molecular biomarkers and tumor classifications have emerged that are remarkably informative for outcome prediction.

### *3.5.1 Histological and Clinical Prognostic Factors*

Tumor histology and several clinical variables have been shown to affect the prognosis of patients diagnosed with DLGG. Median survival is longest for patients diagnosed with oligodendroglial tumors (~12.5 years) and shortest for patients with astrocytic tumors (~7 years), with intermediate survival for oligoastrocytomas (~11 years) [3, 4]. Relative survival rates (1-, 2-, 5-, and 10-year) for diffuse astrocytoma and oligodendroglioma by age are presented in Fig. 3.4**,** and clearly illustrate the poorer overall survival for astrocytoma relative to oligodendroglioma, and the worse survival among older age groups for both histological subtypes**.** Other prognostic variables include functional level as measured by Karnofsky performance status and tumor size and location [52]. While there is considerable observational evidence that the extent of surgical resection is associated with better survival [68], it has been noted that this may be related to differential tumor aggressiveness according to operable vs. inoperable brain locations or clinical judgment [3].

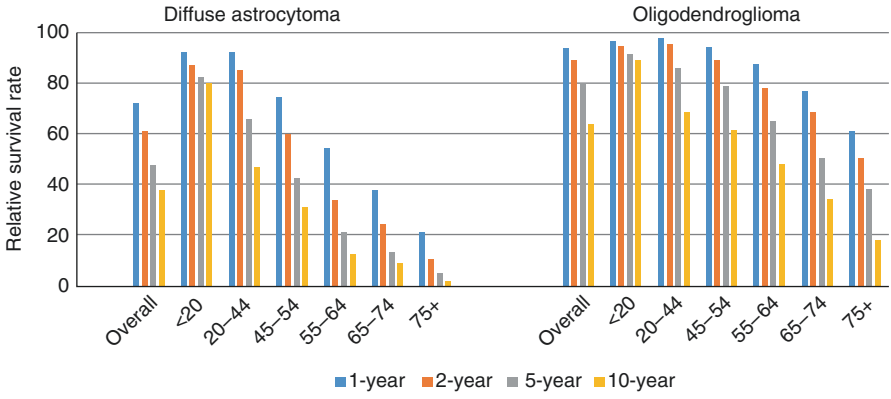


**Fig. 3.4** Relative survival rates (1-, 2-, 5-, and 10-year) for diffuse astrocytoma and oligodendroglioma by age group. (Data from Ostrom et al. [2])

Evidence is more conclusive that early surgical resection improves survival relative to a watchful waiting approach [69, 70]. Radiation therapy has been shown to delay time to recurrence, but does not improve and may worsen overall survival [3, 71]. Data on the impact of chemotherapy with temozolomide (TMZ) on DLGG survival are limited [72–75].

### *3.5.2 Molecular Biomarkers and Survival*

Studies have shown that the common acquired alterations driving DLGG development also have distinct prognostic implications. IDH mutations, which are seen in the majority of low-grade gliomas, are associated with improved overall survival and may also predict improved response to TMZ, although results are inconsistent [25, 76–79]. Codeletion of chromosomes 1p and 19q is another key prognostic factor in DLGG that is predictive of significantly improved survival, particularly for patients with oligodendroglial tumors, and may also improve TMZ response [76, 79–82]. Conversely, *TP53* mutations are associated with significantly poorer survival among DLGG patients, which is consistent with the observation of frequent *TP53* mutations in secondary GBM [14, 83, 84].

Additionally, promoter methylation of DNA repair gene *MGMT* is an important marker of TMZ response and overall survival in GBM [85]. While *MGMT* methylation is commonly seen in DLGG, results have been inconsistent regarding the predictive/prognostic value of the marker for low-grade glioma and further research is needed [73, 76, 77, 86, 87]. With respect to germline markers of survival, carriage of the glioma risk allele at rs55705857 on chromosome 8q24.21 has been associated with improved progression-free survival for patients treated with procarbazine, lomustine, and vincristine [88].

The previously discussed molecular subclasses of low-grade glioma as defined in two recent reports are also highly predictive of clinical outcomes [15, 16], and are generally consistent with one another and with what is known regarding the prognostic value of individual markers. Among the three classes of low-grade glioma defined by the TCGA network report (IDH-mutant ± 1p/19q codeletion; IDH wild-type), patients with both IDH mutation and 1p/19q codeletion had the most favorable outcomes, followed by patients with IDH mutation only. Patients without IDH mutation had the poorest overall survival, and outcomes that were much more similar to those experienced by patients with primary GBM [15].

Among the classes of lower-grade glioma defined by 1p/19q codeletion, *TERT* mutation, and IDH mutation in the report by Eckel-Passow et al., patients with triple-positive or *TERT* + IDH-mutated tumors had the most favorable clinical outcomes. Improved survival for these subtypes, which tend to correspond with the inherited risk allele at 8q24 and the proneural gene expression pattern, is consistent with previous knowledge [17, 88, 89]. Patients with only *TERT* mutations had far worse survival than any other subgroup, and patients with triple-negative or IDH-mutation only tumors had intermediate outcomes [16].

## 3.6 Conclusion

During the past decade, the careful application of high-throughput genomic technology in increasingly large population-based studies has yielded enormous gains for our understanding of low-grade glioma, from the identification of predisposing genetic events to the molecular characterization of clinically meaningful tumor subclasses. Genome-wide association studies have revealed inherited genetic variants that are associated with the development of all subtypes of glioma as well as several that appear to be specifically related to grade II glioma development, most notably at 8q24.21. According to a recent estimate, approximately 40% of the familial risk of lower-grade glioma development can be explained by known risk loci [45]; additional risk variants are sure to emerge with the analysis of larger numbers of subjects with more homogenous tumor subtypes. Recent landmark studies, building on many years of prior work, have helped define such subtypes of DLGG that are far more biologically and clinically uniform than are traditional histological tumor types. This knowledge will help inform customized therapeutic strategies driven by both germline and tumor biomarkers.

Epidemiologic studies have also identified factors that impact risk of low-grade glioma development including exposure to ionizing radiation and allergy history, however many exposures have not been adequately studied. Future research will require large sets of well-annotated biospecimens and detailed exposure histories to investigate potential risk factors with increased validity, and to assess differential impacts by genetic makeup and on the development of different tumor subtypes. Taken together, a deeper understanding of the genetic and environmental etiology of this complex disease, with increasingly detailed characterization of individual tumors and patterns of clinical behavior by tumor sub-classes, will facilitate the development of personalized adaptive treatment strategies to improve survival and quality of life for patients.

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# Chapter 4
# Molecular-Genetic Classification of Gliomas and Its Practical Application to Diagnostic Neuropathology

**José E. Velázquez Vega and Daniel J. Brat**

**Abstract** Gliomas represent a broad category of tumors affecting the central nervous system of patients of all ages. Those that are diffusely infiltrative, such as the diffuse astrocytomas and oligodendrogliomas, occur most frequently in the cerebral hemispheres of adults and have a strong tendency toward clinical progression. The highest grade form, glioblastoma (GBM), WHO grade IV, has a dismal prognosis and can present either de novo or evolve from a lower grade precursor. The classification and grading of diffuse gliomas has historically been based primarily on histopathologic features, yet molecular biomarkers have now become an established component of the neuropathologic diagnosis, since molecular alterations are more reproducible classifiers and provide additional value in prognostication and prediction of therapeutic response. *Isocitrate dehydrogenase (IDH)* mutations are frequent in grade II and III diffuse gliomas of adults, as well as secondary GBMs, and are a major discriminate of biologic class. *IDH*-mutant diffusely infiltrative astrocytomas (grades II and III), as well as secondary GBMs, are characterized by *TP53* and *ATRX* mutations. Oligodendrogliomas are also *IDH*-mutant, but instead are characterized by 1p/19q co-deletion and mutations of *CIC, FUBP1*, *Notch1* and the *TERT* promoter. Primary GBMs typically lack *IDH* mutations and demonstrate *EGFR, PTEN, TP53, PDGFRA, NF1* and *CDKN2A/B* alterations and *TERT* promoter mutations. Pediatric gliomas differ in their spectrum of disease from those in adults; high grade gliomas occurring in children frequently have mutations in *H3F3A*, *ATRX* and *DAXX*, but not *IDH*. Low grade neuroepithelial tumors of childhood, such as pilocytic astrocytoma, pleomorphic xanthoastrocytoma, ganglioglioma, dysembryoplastic neuroepithelial tumor and angiocentric glioma have molecular pathogenesis and clinical behavior distinct from adult gliomas often harbor mutations or activating gene rearrangements in *BRAF, FGFR1 and MYB*.

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## 4.1 Introduction

The molecular genetic understanding of diffuse gliomas has improved dramatically in the past decade, and with it, the neuropathologic classification has also evolved in parallel. Not too long ago, diffuse gliomas were subdivided into oligodendrogliomas, astrocytomas and oligoastrocytomas based entirely on their histologic appearance under the microscope and graded from II to IV using morphologic criteria included within the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) [1]. An abundance of evidence that emerged in the past 10 years now clearly indicates that molecular genetic subdivisions of diffuse gliomas are more reflective of their biologic properties and can be relied upon to reproducibly establish clinically meaningful diagnoses [2–4]. The revised 4th edition of the WHO Classification emphasizes the importance of molecular-genetics and establishes a new era in diagnostic neuropathology, in which genotype is incorporated into an integrated diagnosis rather than reported as an ancillary test result. While these changes remain a work in progress, a solid diagnostic platform is firmly in place [4, 5].

Bailey and Cushing's original classification of brain tumors in the early twentieth century was based on their presumed histogenesis and it introduced many of the diagnostic categories that we still recognize today [6, 7]. In their diagnostic schema and those that followed for the next 90 years, the prototypic diffuse astrocytomas exhibited irregular, hyperchromatic nuclei embedded within a fibrillary background while oligodendrogliomas were characterized by round, uniform nuclei, perinuclear halos ('fried-egg appearance') and a delicate network of branching fine capillaries ('chicken-wire' vasculature). Although the term "oligoastrocytoma" did not appear in the original classification, it did not take long for this diagnosis to gain popularity, since it was difficult to clearly place all diffuse gliomas into either the astrocytoma or oligodendroglioma category based on morphology, and some tumors appeared to contain both histologies under the microscope. The proper classification of these entities impacted tumor grading as well, since criteria for grading differed among histologic classes. For example, among astrocytomas, presence of mitoses (often just one) distinguished a diffuse astrocytoma (WHO grade II) from an anaplastic astrocytoma (WHO grade III) while necrosis and/or microvascular proliferation were required for a diagnosis of GBM (WHO grade IV) [1, 7]. For oligodendroglioma, on the other hand, the presence of florid microvascular proliferation and necrosis does not have the same grading implications, since a WHO grade IV does not exist. The distinction between a low grade oligodendroglioma (WHO grade II) and an anaplastic oligodendroglioma (WHO grade III) relied on identifying many mitoses (>6 six per ten high power fields), florid microvascular proliferation or areas of necrosis [8, 9]. The designation of oligoastrocytomas introduced additional diagnostic confusion in the past, since criteria for their classification and grading were

not agreed upon and the lack of reproducibility was considerable. Altogether, the classification of tumor lineage and grade based on morphologic criteria alone led to unacceptable levels of diagnostic discordance and caused confusion in patient care.

Molecular diagnostics, in conjunction with histopathologic and clinico-radiologic findings, are now an integral component of diagnostic surgical neuropathology and are routinely used to subdivide gliomas into diagnostic categories of clinical significance [10, 11]. In this chapter we focus on relevant emerging molecular pathways in gliomagenesis, the molecular classification of infiltrating gliomas and the diagnostic, prognostic and predictive implications of molecular biomarkers.

## 4.2 Isocitrate Dehydrogenase (IDH) 1/2 Mutations Divide Adult Infiltrating Gliomas Into Clinically Relevant Subsets

Isocitrate dehydrogenase genes are central to the molecular understanding and diagnosis of diffuse gliomas. The five genes encoding isocitrate dehydrogenases (*IDH1, IDH2, IDH3α, IDH3β,* and *IDH3γ*) can be further subdivided into two subclasses: (1) three are NAD(+)-dependent and localize to the mitochondrial matrix; (2) two are NADP(+)-dependent, with one localized to the mitochondria and the other to the cytoplasm. All catalyze the oxidative decarboxylation of isocitrate, producing α-ketoglutarate and carbon dioxide. The IDH3 isoform exists as a heterotetramer consisting of two alpha, one beta and one gamma subunit and is the NAD(+)-dependent isocitrate dehydrogenase that catalyzes the rate-limiting step of the tricarboxylic acid cycle (Krebs cycle) within the mitochondria. IDH1 and IDH2 are homodimers catalyzing the same reaction outside the context of the Krebs cycle and, in contrast to IDH3, use NADP+. IDH1 is the only isoform localized to the cytoplasm [12, 13].

Somatic heterozygous mutations in the *IDH1* and *IDH2* genes (chromosomes 2q33.3 and 15q26.1, respectively) are now thought to represent initiating pathogenic events in a subset of diffuse gliomas and divide them into biologically distinct subsets [14–18]. Initial studies showed that *IDH1* mutations resulted in a loss of the enzyme's role in catalyzing the conversion of isocitrate to α-ketoglutarate, yet subsequent studies demonstrated a gain-of-function that led to accumulation of the oncometabolite 2-hydroxyglutarate (2-HG) [19]. Only mutations within the enzymatic active sites of IDH1/2 confer the ability to convert α-ketoglutarate to 2-HG. Elevated levels of 2-HG inhibit enzymes that regulate cellular epigenetic status, including α-ketoglutarate-dependent histone demethylases, the TET family of 5-methylcytosine (5mC) hydroxylases and DNA demethylases, resulting in genome-wide epigenetic alterations [13, 20, 21]. Among the diffuse gliomas, the subset with the highest level of DNA methylation is referred to as CpG island methylator phenotype (G-CIMP) and these are directly related to the presence of *IDH* mutations [20–25]. Epigenetic changes set in motion by *IDH* mutations result in global changes in gene transcription that promote gliomagenesis [22].

*IDH* mutations are now recognized as a defining molecular event in the large majority of lower grade infiltrating gliomas and secondary GBMs. More than 80%

of WHO grades II and III astrocytomas and secondary GBMs are *IDH*-mutated, while only about 5% of primary GBMs are [14, 15, 17, 26–29]. By current definitions, all oligodendrogliomas are *IDH*-mutated and show the additional finding of chromosome 1p and 19q co-deletion. *IDH1* and *IDH2* mutations are centered at the enzyme's active site and result in a substitution for a key arginine at codons R132 and R172, respectively [15, 30, 31]. The most frequent *IDH* mutation, representing 92.7% of all mutations, occurs at codon 132 of the *IDH1* gene, and results in the substitution of arginine for histidine (R132H) [30]. *IDH1* mutations are followed in frequency by R132C (4.1%), R132S (1.5%), R132G (1.4%), and R132L (0.2%) [30]. Residue R172 in exon 4 of the *IDH2* gene is homologous to R132 in the *IDH1* gene, with R172K representing 65% of all *IDH2* mutations followed by R172M (19%), and R172W (16%) [30]. *IDH2* mutations occur at much lower frequencies (approximately 3%) than *IDH1* mutations among the diffuse gliomas, but are more frequent in oligodendrogliomas than astrocytomas [30]. Other uncommon *IDH* mutations occurring at much lower frequencies have also been reported [15, 18, 30].

Adult patients with infiltrating gliomas harboring *IDH* mutations are significantly younger than those without these mutations; however *IDH* mutations are uncommon in patients younger than 18-years-old and very rare in tumors of childhood [15, 30–35]. The median age of patients with *IDH*-mutant low grade gliomas was 36-years compared to 44-years for those harboring 'wild-type' (wt) tumors [27]. In contrast to *IDH*-wt diffuse gliomas, those that carry IDH mutations exhibit a slower rate of progression and improved clinical outcomes, grade for grade [15, 34]. The finding of an *IDH* mutation in a glioma strongly supports the diagnosis of a diffusely infiltrative glioma since they are rarely, if ever, found in other CNS neoplasms. *IDH* mutations are thought to be stable through the course of disease, but further study is needed [13]. Following an initiating *IDH* mutation, the differentiation of a diffuse glioma into the astrocytoma phenotype involves the acquisition *TP53* mutations (chromosome 17p13.1) and alterations (mutation or deletion) of *α-Thalassemia/Mental Retardation Syndrome X-linked* (*ATRX*; chromosome Xq21.1). In contrast, an oligodendroglioma phenotype is accompanied by whole arm losses of chromosomes 1p/19q, and mutations of *CIC, FUBP1* and *telomerase reverse transcriptase promoter (TERT-p)* [15–17, 26, 35–38].

## 4.3 The Molecular Signature of IDH-Mutant Astrocytomas

The Cancer Genome Atlas Research Network (TCGA) investigation of WHO grades II and III diffuse gliomas (morphologically diagnosed as oligodendrogliomas, astrocytomas and oligoastrocytomas) used an integrated, multiplatform whole genome approach and found that these tumors could be divided into three molecular subgroups that were best represented using two biomarkers: *IDH* mutations and co-deletion of 1p/19q. Two of the subgroups were *IDH*-mutated but separated on the basis of whole arm losses of chromosomes 1p/19q. The third subgroup harbored neither *IDH* mutations nor 1p/19q co-deletion and was referred to as *IDH*-wt.

Approximately two-thirds of the *IDH*-mutant WHO grade II and III diffuse gliomas had intact 1p/19q; of these 94% had mutations in *TP53* and 86% had inactivation of *ATRX,* a gene involved in chromatin remodeling pathways and DNA methylation [16]. Thus, the molecular signature of *IDH*-mutant astrocytoma includes *IDH* mutation, *TP53* mutation and functional loss of *ATRX* [14, 15, 28, 34, 36, 39].

The tight coupling of *IDH* and *TP53* mutations with inactivating alterations of *ATRX* has now been firmly established. Among *IDH*-mutant tumors, inactivating mutations of *ATRX* appear to be restricted to those carrying *TP53* mutations and this combination is almost mutually exclusive with co-deletion of 1p/19q [16, 38–43]. The neuropathologic diagnosis of an *IDH*-mutant diffuse astrocytoma of grade II, III or IV can be established by documenting *IDH* mutations, ATRX loss and *TP53* mutations. There are a number of ways to achieve this, including focused or whole genome sequence analysis. Immunohistochemistry for IDH-1 R132H, ATRX and p53 is also reliable and cost-effective in the routine workup of infiltrating gliomas. The finding of immunoreactivity for IDH-1 R132H, p53 (strong in over 10% of cells) together with the loss of nuclear ATRX staining is diagnostic of an *IDH*-mutant diffuse astrocytoma and grading criteria can then be applied (Fig. 4.1).

Together with *Death-domain associated protein* (*DAXX;* chromosome 6p21.3), ATRX is a core mediator of a chromatin remodeling complex necessary for the incorporation of histone variant H3.3 into the telomeres of chromosomes. Telomere maintenance is required for chromosomal integrity in the setting of numerous cell divisions associated with long-term tumor growth. ATRX/DAXX complex-mediated

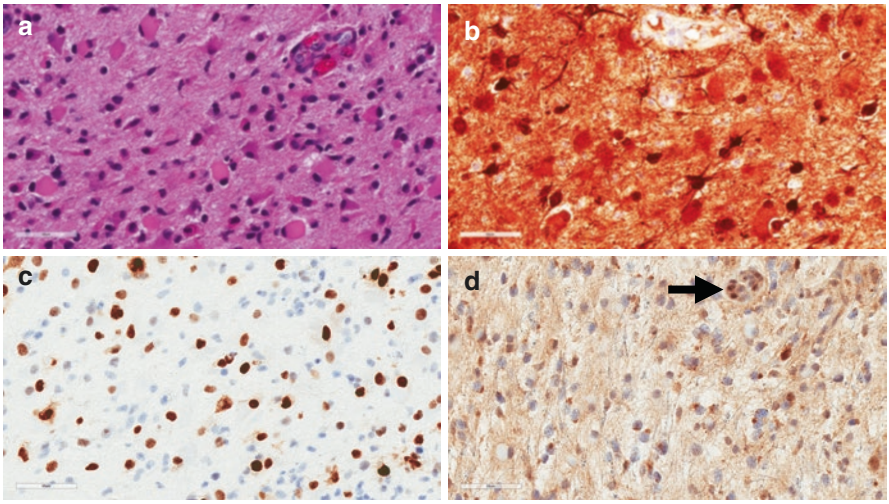


**Fig. 4.1** (**a**) This infiltrating astrocytoma has hyperchromatic elongated astrocytic nuclei as often seen in the prototypic infiltrating astrocytomas but a significant proportion of tumor cells exhibit abundant globose eosinophilic cytoplasm ('gemistocytic morphology'). (**b**) The IDH-1 R132H-specific immunostain is strongly positive with diffuse cytoplasmic immunoreactivity. (**c**) A significant proportion of tumor nuclei are positive for p53 immunostain. (**d**) Loss of nuclear immunoreactivity is observed with ATRX immunostain (*arrow* shows internal positive control in endothelial cells)

chromosomal maintenance has been implicated in telomere stability and its alteration results in alternative lengthening of telomeres (ALT), a telomerase-independent pathway for telomere maintenance that has been recognized in a significant subgroup of malignancies. Mutations in *DAXX* or *ATRX* impair the heterochromatic state of the telomeres, probably because of reduced incorporation of chromatin onto H3.3 histones. *TP53* mutations play a complimentary role with genomic instability and ALT, since tumor cells presumably then have the capacity to evade apoptosis and become immortalized [38, 41, 44–49]. Nearly all *ATRX*-mutated cases of diffuse glioma also harbor *TP53* mutations and it is thought that *TP53* mutations occur first and predispose toward the acquisition of *ATRX* alterations [38]. Others have shown that the ALT phenotype in astrocytomas is correlated with a younger patient age; loss of ATRX expression by immunohistochemistry; p53 immunoreactivity; *IDH* mutations; and absence of epidermal growth factor receptor (*EGFR*) amplifications [50].

Prognostic markers for *IDH*-mutant astrocytomas will need to be better defined in order to stratify risk for this population and there is potential that additional genetic events may provide additional value. ATRX may be one such marker, since *IDH*-mutant, 1p/19q-intact WHO grade II gliomas with ATRX loss have been shown to have a longer median progression free survival (PFS; 4.4 years), and median overall survival (OS; 12.7 years) compared to *IDH*-mutant, 1p/19q-intact, *ATRX*-wt subgroup (PFS, 2.2 years and OS, 6.9 years), consistent with previous survival analyses [27, 51, 52]. A subset of *IDH*-mutant, 1p/19q-intact infiltrating gliomas have focal gains of 4q12 (*platelet-derived growth factor receptor alpha; PDGFRA*), 12q14 (*CDK4*), or 8q24 (*MYC*), providing additional markers for future investigation [16, 53].

## 4.4 The Molecular Signature of Oligodendrogliomas

Oligodendroglioma is the archetypal brain tumor with a molecular signature. While past studies primarily based on histomorphologic classifications emphasized the correlation of 1p/19q co-deletion with the oligodendroglioma phenotype and its chemosensitivity, more recent studies have stressed that the combination of *IDH* mutation and 1p/19q co-deletion is definitional rather than just an association [9, 16, 27, 42]. Thus, while *TP53* mutations and *ATRX* alterations characterize *IDH*-mutant astrocytomas, oligodendrogliomas are defined by *IDH* mutations and 1p/19q co-deletions, but not *ATRX* and *TP53* alterations, highlighting the relatively strict molecular dichotomy of *IDH*-mutant diffuse gliomas [16, 27, 42]. Therefore, assessment of the chromosomal arms 1p and 19q, in conjunction with *TP53, ATRX* and *IDH* mutations is essential in the diagnostic algorithm that effectively stratifies diffuse gliomas [27, 42, 51] (Figs. 4.2 and 4.3). Among the diffuse gliomas, *IDH*-mutant, 1p/19q co-deleted oligodendrogliomas have the longest median PFS (5.6 years) and OS (15.3 years), a finding supported by many [24, 27, 52, 54].

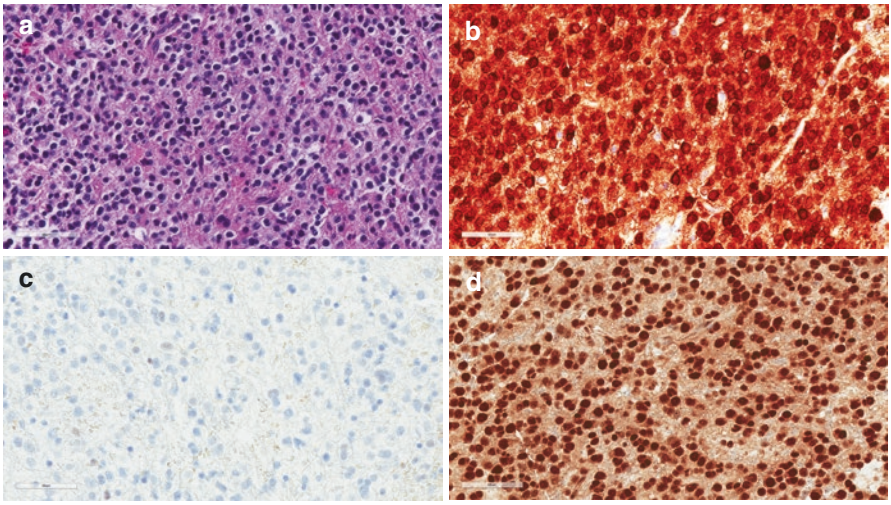


**Fig. 4.2** (**a**) This low grade oligodendroglioma is comprised of tumor cells with round monomorphous nuclei and perinuclear cytoplasmic clearing ('halos'). (**b**) The IDH-1 R132H-specific immunostain is strongly positive with diffuse cytoplasmic immunoreactivity. (**c**) The p53 immunostain is negative. (**d**) ATRX immunostain highlights intact nuclear expression

Reifenberger et al. first reported that oligodendrogliomas showed a high frequency of loss of heterozygosity on the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) [55]. Subsequent studies demonstrated that the signature 1p/19q co-deletion is mediated through an unbalanced translocation t(1:19)(q10:p10) followed by the loss of the derivative chromosome, resulting in whole arm deletions of 1p and 19q [9, 56, 57]. Fluorescent in situ hybridization (FISH) for 1p/19q became a popular method for assessing co-deletions and is still widely used. However, it is important to realize that FISH only recognizes focal losses specific to the probes [42, 58]. Since focal losses can occur on 1p and 19q without whole arm losses, particularly in the setting of genomic instability in high grade gliomas, tests that assess only focal losses will occasionally lead to false positive results, potentially leading to the inappropriate diagnosis of oligodendroglioma [59]. Clinical tests that evaluate the entire arms, such as cytogenomic microarrays, reduce this possibility [42].

Although the R132H IDH1 mutation is the most frequent *IDH* mutation in oligodendrogliomas, there is a slightly higher frequency of *IDH2* mutations than in *IDH*-mutant astrocytomas. Other molecular-genetic alterations that occur in *IDH* -mutant, 1p/19q co-deleted oligodendrogliomas are inactivating mutations of the tumor suppressor genes *far-upstream binding protein 1* (*FUBP1*) gene and in the human homolog of the *Drosophila* capicua (*CIC*), on chromosomes 1p31.1 and 19q13.2, respectively. *FUBP1* encodes a DNA binding protein involved in c-Myc regulation and *CIC* is a downstream component of the receptor tyrosine (RTK) pathway. Mutations in *FUBP1* and *CIC* occur secondary to the unbalanced translocation with

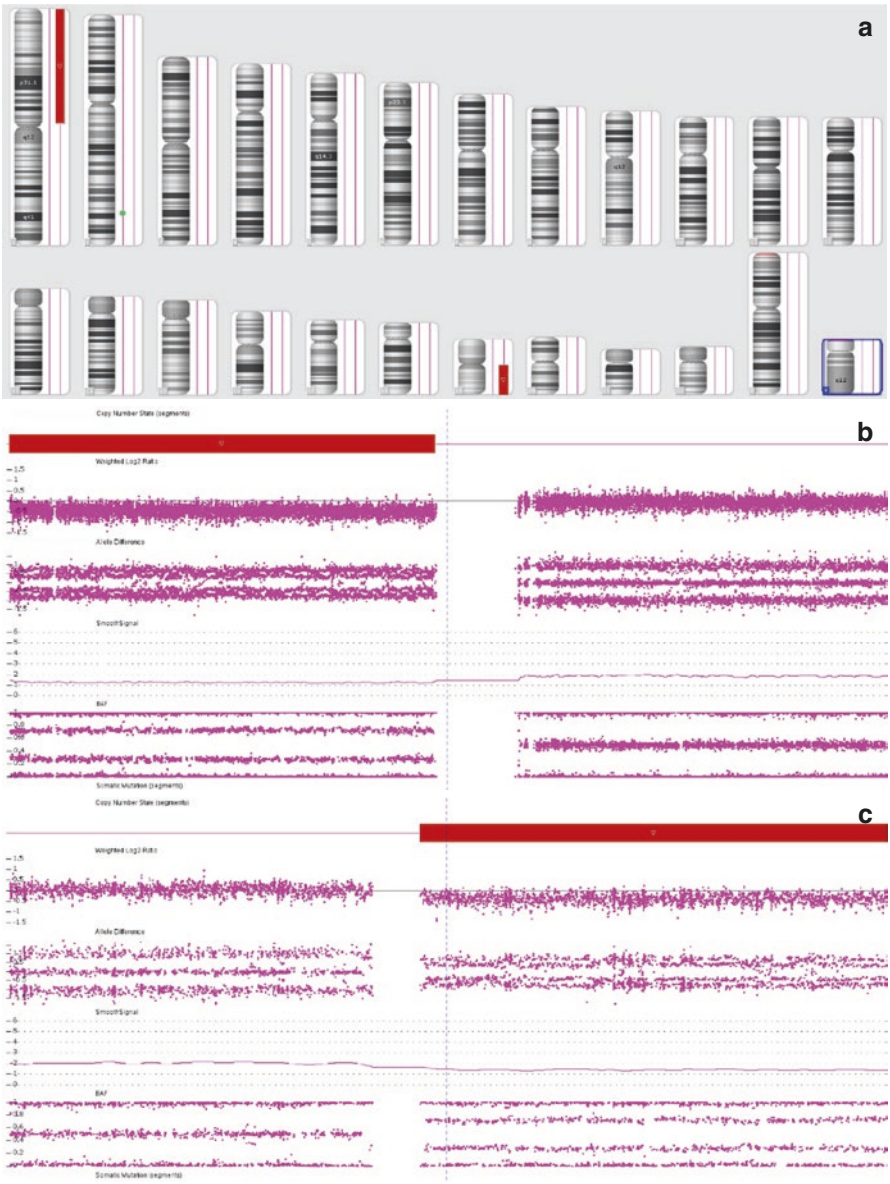


**Fig. 4.3** (**a**) General view (Karyoview) of an *IDH*-mutant infiltrating glioma arising in the left frontal lobe of middle age male showing whole arm losses of 1p and 19q, and consistent with Oligodendroglioma, WHO grade II. This array detected the *IDH1* R132H mutation (*green* dot in chromosome 2). (**b** and **c**) show the detailed view of chromosomes 1 and 19, respectively, and their corresponding whole-arm losses of 1p and 19q

a frequency of 20–30% and 46–83%, respectively. These mutations are exceedingly rare in astrocytomas and are mutually exclusive with *TP53* and *ATRX* mutations [9, 16, 49, 60–63]. At present, the prognostic or predictive significance of *FUBP1* and *CIC* mutations in oligodendrogliomas remains unclear although a recent study found that outcomes of 1p/19q co-deleted gliomas were not altered by these mutations [62].

A well-known histopathologic mimic of anaplastic oligodendroglioma is the small cell variant of GBM, which needs to be distinguished since they have such differing clinical features. Small cell GBMs harbor *EGFR* (chromosome 7q12) amplifications in about 70% of the cases [9, 58, 64–66], whereas these amplifications are not seen in oligodendrogliomas and are mutually exclusive with *IDH* mutations and co-deletions of 1p/19q [59, 62]. Furthermore, imbalances of chromosome 7 and losses of chromosome 10q23 (*phosphatase and tensing homolog; PTEN*) in the context of a high grade glioma supports the diagnosis of GBM.

Nearly all *IDH*-mutated, 1p/19q co-deleted tumors also carry highly specific mutations in the *TERT* gene promoter (C228T or C250T), upstream of the *TERT* ATG start site [67–74]. *TERT-p* mutations are rare in diffuse gliomas with *ATRX* and *TP53* mutations [37, 62, 67, 74]. In distinction to ALT, activating mutations in the *TERT-p* result in enhanced telomerase activity and lengthening of telomeres. While several reports describe concordance as high as 100%, in the TCGA study of lower grade gliomas, 96% of *IDH*-mutant, 1p/19q co-deleted tumors carried *TERT-p* mutations, while only 4% of *IDH*-mutant, 1p/19q intact tumors showed this mutation [16]. However, *TERT-p* mutations are also common in up to nearly 90% *IDH*-wt GBMs [67–73]. Nearly all *IDH*-wt infiltrating gliomas with chromosome 7 gain and chromosome 10 loss harbor *TERT-p* mutations or exhibit upregulated *TERT* expression [37]. *TERT-p* mutations carry an unfavorable prognosis in the absence of *IDH* mutations (*IDH*-wt GBMs) and a favorable prognosis in the presence of *IDH* mutation and 1p/19q co-deletion (oligodendrogliomas). Although *ATRX* and *TERT-p* mutations are nearly mutually exclusive, rare cases have been reported with both or neither [67]. Among *TERT-p* mutated gliomas, there is no difference in telomere length between *IDH*-mutant and *IDH*-wt cases. However, telomeres are longer in *ATRX* altered gliomas than those with *TERT-p* mutations [37].

Thus, the molecular landscape of oligodendroglioma includes mutations in *IDH* and *TERT-p* in conjunction with whole arm losses of chromosomes 1p and 19q. Gliomas harboring these three mutations have classic oligodendroglioma phenotype and have prolonged OS [67, 75]. Other genes mutated in this subset include *NOTCH1, PIK3CA, PIK3R1, ZBTB20,* and *ARID1A*. Inactivating mutations in *NOTCH1* are only rarely identified in *IDH*-mutant, 1p/19q intact or *IDH*-wt infiltrating astrocytomas [16, 38, 61]. Other than a 1p/19q co-deletion, very few recurring whole arm copy number alterations (CNA) have been identified in oligodendrogliomas [16].

## 4.5 Molecular Signatures Argue Against Mixed Lineage Gliomas

The "mixed gliomas", including oligoastrocytoma and GBM with oligodendroglioma component (GBM-O), have historically suffered from considerable interobserver variability in classification and grading. The 2007 WHO Classification recognized mixed gliomas as oligoastrocytomas grades II-III, as well as GBM-O, WHO grade IV, and defined them as diffusely infiltrating gliomas composed of two distinct neoplastic cells [1]. Nevertheless, in recent years numerous investigations have concluded that mixed gliomas can be usually classified as either astrocytomas or oligodendrogliomas at the molecular-genetic level and have questioned the need for the diagnosis of oligoastrocytoma [2, 16, 26, 27, 30, 35–42, 51, 58, 60, 61, 65, 67–71, 75–78]. While *IDH*-mutant gliomas are characterized by co-deletions of 1p/19q and *TERT-p* mutations or by *TP53* and *ATRX* mutations, there is no current molecular signature for oligoastrocytoma [2, 27, 38, 42]. In the TCGA analysis, the majority of tumors diagnosed as oligoastrocytomas were *IDH*-mutant and had *TP53* mutations (*IDH*-mutant astrocytomas); the remainders were found to be *IDH*-mutant and 1p/19q co-deleted (oligodendroglioma) or *IDH*-wt [16]. Others have found that most oligoastrocytomas had molecular features of oligodendrogliomas [42]. Similarly, genomic and transcriptomic studies of GBM-O have concluded that they represent either anaplastic oligodendrogliomas, *IDH*-mutant GBMs or *IDH*-wt GBMs at the molecular level, casting doubt on the need for a GBM-O designation [3]. Only rarely are cases encountered that exhibit a genuine composite of distinct tumor types, made of discrete areas of oligodendroglioma and astrocytoma, each harboring their hallmark genetic makeup [79]. It is fully expected that the application of molecular tests will result in decreased interobserver and interinstitutional variability in the diagnosis of diffuse gliomas, as well as reduced confusion related to the clinical management that has been associated with a diagnosis of mixed gliomas. At present, oligoastrocytomas are still recognized as a histological diagnosis in the revised 4th edition of the WHO Classification but its use is discouraged and, if used, should be followed by a not otherwise specified category (NOS) classifier to highlight that molecular testing was not performed or its results were inconclusive [4].

## 4.6 Molecular Signatures Identify Clinically Aggressive IDH-wt Infiltrating Gliomas

The presence or absence of *IDH* mutations stratifies adult infiltrating gliomas into two distinct subsets characterized by dissimilar genetic alterations and clinical behaviors, suggesting biologically distinct diseases despite histomorphologic similarities. The majority of primary (or *de novo*) GBMs are *IDH*-wt infiltrating gliomas (95%). This is in stark contrast to the grade II and III infiltrating gliomas,

which are *IDH*-wt in only 20–25% of cases [14–16, 42]. By the currently employed histomorphologic criteria for grading infiltrating gliomas, *IDH*-wt grade II and III gliomas lack necrosis and microvascular proliferation, and therefore fall short of the histologic definition of GBM, yet their molecular-genetic profiles are strikingly similar to those of *IDH*-wt GBMs and they also display aggressive clinical behavior [16, 25]. In the TCGA analysis, grade II–III IDH-wt infiltrating gliomas had a genetic profile similar to primary (*IDH*-wt) GBM and exhibited a median OS of 1.7 years [16].

Given the clinical and genomic similarities, these lower grade *IDH*-wt astrocytomas could represent undersampled or incipient GBMs that have not yet developed the microvascular proliferation or necrosis required to be histologically diagnosed as a WHO Grade IV tumor [16, 38, 42, 80, 81]. In a recent study of 160 *IDH*-wt grade II and III astrocytomas, Reuss et al. found that 78% were molecular equivalents to conventional *IDH*-wt GBM, with similar frequencies in *TERT-p* mutations, 7p gain/10q loss, amplifications of *EGFR* or combined 10q/13q/14q co-deletion. A median survival of 19.4 months was noted, consistent with the TCGA analysis. Furthermore, if those grade II and III astrocytomas with H3 mutations were included, then 87% of these *IDH*-wt astrocytomas were molecularly and clinically indistinguishable from GBM [80]. Lower grade *IDH*-wt infiltrating gliomas have a much lower frequency of *TP53* mutations than *IDH*-mutant astrocytomas. While 94% of *IDH*-mutant, 1p/19q intact infiltrating gliomas harbored *TP53* mutations, only 25% of *IDH*-wt infiltrating grade II-III gliomas are *TP53* mutated, similar to the frequency observed in *IDH*-wt GBMs [15, 34].

Other genetic alterations frequently associated with *IDH*-wt GBMs and lower grade gliomas include those involving *PTEN, EGFR, MDM4, CDK4, NF1, PIK3CA, RB1, PTPN11, PIK3R1,* and *CDKN2A* [16]. More recently, Di Stefano et al. reported *FGFR-TACC* fusions in approximately 3% of lower grade *IDH*-wt infiltrating astrocytomas, a frequency similar to that seen in primary GBMs, providing additional evidence of the similarity of clinical behaviors between these entities. *FGFR-TACC* fusions were not present in *IDH*-mutant gliomas and were mutually exclusive with *EGFR* amplifications, but often co-occurred with *CDK4* amplifications [82]. Overall, as compared to the *IDH*-mutant counterparts, *IDH*-wt gliomas have greater activation of signaling through *EGFR, MET,* and *BRAF*; upregulated cell cycle activators; and reduced cell cycle inhibitors [81]. *IDH*-wt gliomas also have upregulation of transcription factors known as master regulators, as well as their target genes [37].

A small subset (currently estimated a less than 1%) of adult low grade infiltrating *IDH*-wt gliomas harbor *BRAF* V600E somatic mutations on chromosome 7q34 resulting from a substitution of valine by glutamic acid at codon 600 (V600E) and are thought to represent a distinct clinicopathologic entity with an improved prognosis [83–85]. *BRAF* V600E mutations, which constitutively activate the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway, are far more frequent in grade I, non-infiltrative gliomas, pediatric diffuse gliomas and epithelioid GBMs and may have therapeutic implications [32, 83, 84]. Lastly, Ceccarelli et al. described a novel subgroup of *IDH*-wt infiltrat-

ing gliomas that genetically and epigenetically resemble pediatric pilocytic astrocytomas and carry a favorable outcome [37]. Additional studies of IDH-wt infiltrating gliomas are necessary to address the implications of subgroups that exhibit less aggressive clinical behavior.

## 4.7 Primary and Secondary Glioblastomas Have Distinct Genetic Signatures

GBM is histologically defined as a high grade infiltrative astrocytoma with microvascular proliferation, necrosis or both, that has a short survival, generally less than 2 years [29, 86]. The revised 4th edition of the WHO Classification reflects the primary molecular subsets of adult GBMs by dividing them into (1) GBM, *IDH*-wt, (2) GBM, *IDH*-mutant and (3) GBM, NOS. (4). The last category is reserved for cases in which *IDH* assessment could not be performed or was not available. GBMs are often referred to as "primary" (or *de novo*) when they present to medical attention as grade IV disease as the first manifestation, and as "secondary" when they have evolved over time from a grade II or III infiltrating astrocytoma. Primary and secondary GBMs are histologically indistinguishable except for larger extents of necrosis more frequently found in the former [28]. Despite their morphologic overlap, primary and secondary GBMs differ in their genetic and epigenetic landscape, with *IDH* mutations being much more frequent in secondary GBMs. Secondary GBMs arise in younger patients (usually less than 45 years) and are associated with longer survivals [14, 28, 29]. Primary GBMs represent the vast majority of cases (over 90%), are nearly all *IDH*-wt, and are characterized by a rapid clinical onset of symptoms, most often in an elderly patient.

The genetic hallmark alterations of primary, *IDH*-wt GBMs include mutations of *PTEN* and *TERT-p*, gain of chromosome 7/loss of chromosome 10, deletions of *CDKN2A,* and amplifications of proto-oncogenes, most notably, *EGFR, PDGFRA* or *c-MET*. Although the sequence of oncogenic events in *IDH*-wt primary GBMs has not been determined, it has been suggested that *TERT-p* mutations, present in up to 90% of adult GBMs, may precede the characteristic combined gain of chromosome 7/loss of chromosome 10, seen in 60% of primary *IDH*-wt GBM, followed by additional oncogenic events [37, 87]. Three core signaling pathways are nearly always altered in primary, *IDH*-wt GBM and include (1) the receptor tyrosine kinase pathway [RTK/RAS/phosphoinositide 3-kinase (PI3K)], (2) the P53 pathway and (3) the Retinoblastoma (Rb) pathway, which are altered in 88%, 87% and 78% of GBMs, respectively [86, 88]. The most frequently altered genes in the RTK/RAS/PI3K pathway include *PTEN, neurofibromin-1 (NF1), EGFR, PIK3R1, PIK3CA,* and *PDGFRA*. Alterations in the Rb pathway include *CDK4, CDK6, CCND2, CDKN2A/B* and *RB1*. The genes frequently altered in the p53 pathway include *MDM2, MDM4* and *TP53* [14, 28, 29, 54, 78, 86, 88, 89]. More recently, Morris et al. reported recurrent somatic mutations in the *FAT* tumor suppressor (*Drosophila*)

homolog 1 (*FAT1;* chromosome 4q35.2) in 20.5% of GBMs, resulting in its inactivation and leading to aberrant Wnt activation and tumorigenesis [90].

Brennan et al. has shown that 57% of GBM had evidence of mutation, rearrangement, altered splicing and/or focal amplification of *EGFR,* reflecting its status as a key oncogenic event in this disease [89]. Furthermore, approximately 50% of *EGFR* amplified tumors also harbor the variant III (EGFRvIII) deletion that leads to constitutive tyrosine kinase activation [4, 78, 91]. Approximately15–18% of primary, *IDH*-wt GBMs carry *PDGFRA* amplifications while *MDM2* and *CDK4* amplifications are present in 5–15% and 14–18% of the cases [4, 14, 29, 78, 89].

Deletions of the *CDKN2A* gene (chromosome 9p21), encoding the tumor suppressor proteins p16 (INK4a) and p14 (ARF) (activators of Rb and p53, respectively) are seen in up to 50% of GBMs [4, 14, 76–78]. *TP53* and *RB1* mutations and deletions are seen in 28–35% and 8–12% of primary GBMs, correspondingly [4, 14, 78, 89]. Activating mutations of *PI3K* are present in 12–25% of primary GBMs, with mutations in either *PIK3CA* or *PIK3R1* driving increased enzymatic activity. Deletions or mutations in *PTEN*, the primary negative regulator of the PI3K/AKT signaling pathway, occur in approximately 25–35% of GBMs. Mutations or deletions of *NF1*, a Ras antagonist, have been identified in up to 10–18% of primary GBMs [4, 14, 29, 78, 86, 88, 89].

*BRAF* V600E mutations are present in less than 5% of all GBMs, but are overrepresented in epithelioid GBM with approximately 50% harboring the mutation [29]. Approximately, 5% of adult primary GBMs carry *H3F3A* mutations. While the frequency of *BRAF* and *H3F3A* mutations is much lower in adult gliomas than those of children, it is important to remember that both *H3F3A* mutations and BRAF mutations will be present in tumors that do not have *IDH* mutations (i.e., *IDH* testing will reveal an "*IDH*-wt" status) and testing for these mutations will need to be performed in the relevant clinical setting in order to document these distinct diseases [29, 42]. Mutation specific immunostains against the *BRAF* V600E (VE1) and the H3 (H3K27M) mutations are readily available and clinically useful for practical diagnostic neuropathology (Fig. 4.4).

*IDH* mutations occur at a very low frequency in clinically diagnosed primary GBM (less than 5%) [4, 28, 92]. It is likely that *IDH*-mutant primary GBMs progressed from a non-symptomatic lower grade glioma that evaded diagnosis [28, 92]. As a corollary, secondary GBMs can occasionally be *IDH*-wt when they arise following the diagnosis of lower grade glioma; not surprisingly, secondary GBMs that lack *IDH* mutations usually have a poor prognosis [92]. Regardless, the *IDH* mutation status is more relevant to the clinical behavior of the GBM than the primary or secondary designation. Similar to the molecular-genetic makeup of their precursor lesions, *IDH*-mutant, secondary GBM frequently harbor *TP53* and *ATRX* alteration: 85% of secondary GBMs are *IDH*-mutated and *TP53* and *ATRX* mutations are seen in 81% and 71%, respectively [4, 40, 92]. Since these mutations occur early in gliomagenesis, additional alterations identified within *IDH*-mutant, secondary GBMs are likely acquired during biological progression and can serve as prognostic markers [93]. Secondary *IDH*-mutant GBMs contain the highest number of alternating,

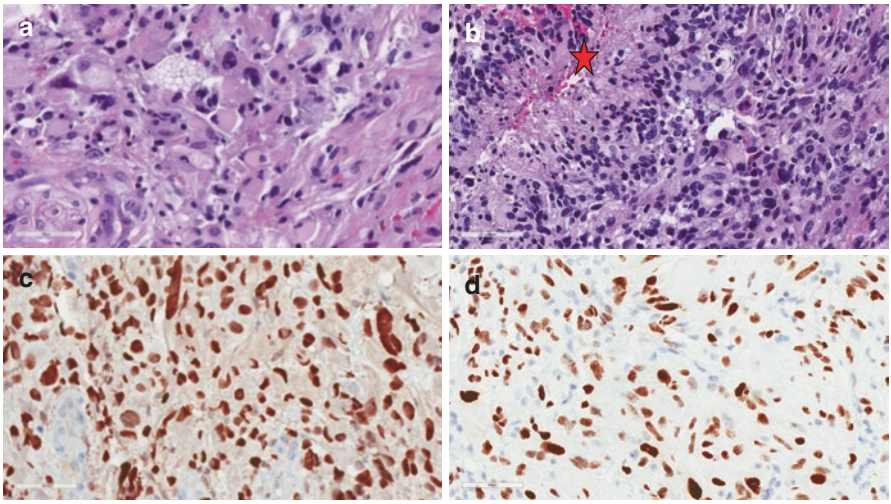


**Fig. 4.4** (**a** and **b**) This GBM arose in the thalamus of a middle-aged man and was morphologically heterogeneous. The tumor was highly cellular with abundant pleomorphic cells. Pseudopalisading necrosis is evident (star in **b**). (**c**) The K27M immunostain shows strong diffuse nuclear positivity. Therefore this is best classified as a K27M-Midline GBM, WHO grade IV. (**d**) p53 immunostain is strongly positive as well. This GBM was *IDH*-wt and ATRX immunostain showed nuclear retention (not shown). *TP53* and *ATRX* mutations often co-occur with H3K27M mutations but have the highest correlation in G34R/V-mutated GBMs

intrachromosomal breakpoints, consistent with chromothripsis [81]. Thus, the GBM genotypes account for biologic differences in histologically indistinguishable tumors and improves the ability to predict patient outcomes [86].

## 4.8 Pediatric Gliomas Are Genetically and Biologically Distinct from Their Adult Counterparts

Pediatric gliomas are most frequently either low grade and circumscribed, or high grade and diffusely infiltrative. The low grade, well circumscribed astrocytomas (most often pilocytic astrocytomas) frequently arise in the cerebellum, followed by the cerebral hemispheres, deep midline structures, optic pathway, brainstem and spinal cord [94]. Non-infiltrative or poorly infiltrative gliomas with an affinity for the temporal lobe, are also more frequent in children and include pilocytic astrocytomas (PA, WHO grade I), gangliogliomas (WHO grade I), dysembryoplastic neuroepithelial tumor (DNET, WHO grade I) and pleomorphic xanthoastrocytomas (PXA, WHO grade II or III) [4]. The histologic findings of Rosenthal fibers, eosinophilic granular bodies (EGB's) and a low grade glioma with a biphasic appearance usually points to a diagnosis of PA and the finding of a *KIAA1549:BRAF* fusion is typical. This fusion event results from tandem duplications in the chromosome 7q34

region and is observed in more than 70% of PA's, predominantly in those arising within the cerebellum, but also in other locations [95]. A temporal lobe-predominant glioma with a relatively solid growth pattern exhibiting a combination of spindle-shaped and xanthomatous cells and pleomorphic, multinucleated astrocytes in association with EGBs points to a diagnosis of PXA and the presence of a *BRAF* V600E mutation is supportive [96]. *BRAF* V600E mutations are frequent events in pediatric CNS neoplasia including gangliogliomas (20–40%), PXA's (60–70%), DNET (30%), diffuse astrocytomas (23%) and PA's (5–10%) [32, 97].

Most low grade neuroepithelial tumors of children have only one dominant somatic genetic event that affects protein coding. In the majority, such solitary alterations are mutually exclusive and include *NF1, RAF* or *RAS*, the receptor tyrosine kinases *fibroblast growth factor receptor 1* (*FGFR1*; chromosome 8p11.23), and *V-Myb avian myeloblastosis viral oncogene homologue* (*MYB;* chromosome 6q23.3) or in its homologue, *MYBL1* (chromosome 8q13.1) [32]. In a study of 249 pediatric low grade gliomas, which included multiple histologic entities, 90% showed recurrent somatic alterations and 83% showed rearrangements or structural alterations [98]. The most frequent genetic alterations were found in genes encoding *FGFR1,* the *neurotrophic tyrosine receptor kinase 2* (*NTRK2;* chromosome 9q21.33), *KRAS* (chromosome 12p12.1), the *receptor tyrosine kinase adaptor tyrosine-protein phosphatase non-receptor type 11* (*PTPN11;* chromosome 12q24), *NF1* (chromosome 17q11.2), and *BRAF* (chromosome 7q34) [97]. Alterations of *BRAF, FGFR1, PTPN11,* and *NTRK2* all lead to the activation of the MAPK/ERK signaling pathway, making it a primary driver of pediatric low grade gliomas [32, 99]. The most specific genotype-phenotype association was the tight linkage between angiocentric glioma and the *MYB-QKI* translocation [98].

Others studies have also emphasized the significance of alterations in *MYB/MYBL1, FGFR1* and *BRAF* V600E in pediatric low grade gliomas and suggest a relationship between tumor histology and genetic alterations [32, 43, 84, 100, 101]. Qaddoumi et al. reported a high frequency of *FGFR1* alterations those tumors dominated by round, regular bland "oligodendroglial-like" tumor cells, including 82% of DNETs and 40% of diffuse oligodendroglial tumors. Tumors with astrocytic differentiation and "diffuse" patterns were more frequently characterized by *MYB* alterations, with 41% of pediatric diffuse astrocytomas showing structural rearrangements and 87% of angiocentric gliomas showing the specific *MYB-QKI* fusion [100]. These findings clearly demonstrate that low grade infiltrating gliomas arising in the pediatric population are distinct from those in adults, since the *IDH* mutations of adult diffuse gliomas are rare in the pediatric diseases and the mutations in the pediatric diseases are not present in those of adults [43]. However, the *IDH*-wt status of pediatric infiltrating low grade gliomas does not imply a more biologically aggressive behavior; the rate of progression of lower grade gliomas in the pediatric population is significantly lower than their histologically comparable adult counterparts [43, 100, 102].

Among the pediatric low grade gliomas, oligodendrogliomas represent a diagnostic challenge, since they are histologically similar to adult tumors, yet do not often harbor their defining genetic alterations of *IDH* mutations and 1p/19q

co-deletion. Only 18% of pediatric oligodendrogliomas harbor an *IDH* R132H mutation and only 25% exhibit 1p/19q co-deletion. Those that were *IDH*-mutant and 1p/19q co-deleted ('adult-type') occurred in older children and adolescents [102]. As described above, *FGFR* alterations are more frequent in pediatric oligodendrogliomas, but occur in less than half [32, 102]. *BRAF* alterations are absent in pediatric oligodendrogliomas, but the diffuse leptomeningeal glioneuronal tumor (known also as disseminated oligodendroglial-like leptomeningeal tumor), which was recently codified in the revised WHO Classification, are reported to harbor concurrent *KIAA1549:BRAF* gene fusions and 1p deletions [4, 9, 103, 104]. The precise relationship of this entity to other pediatric brain tumors, such as pilocytic astrocytoma or oligodendroglioma will require further investigation.

The high grade gliomas of childhood are also clinically and genetically distinct from those of adults. Pediatric high grade gliomas nearly always arise *de novo* and very rarely are the result of progression from a lower grade glioma. Although they differ from their adult counterparts in terms of location, clinical behavior, mutational landscape and gene expression profiles, they can similarly be separated into molecular subclasses [78]. Mutations targeting RTK/RAS/PI3K pathway, histone modification or chromatin remodeling and cell cycle regulation have been respectively found in 68%, 73% and 59% of these tumors, including diffuse intrinsic pontine gliomas (DIPG) and non-brainstem gliomas [105]. One of these classifications that included both adult and pediatric GBMs and used DNA methylation profiles identified six molecular classes: IDH, K27, G34, RTK I (PDGFRA), Mesenchymal and RTK II (Classic) [78, 106]. Two of these classes —the K27 and G34— were dominated by pediatric cases that harbored the respective *H3F3A* mutations. Korshunov et al. recently performed a large scale genomic and epigenetic integrated analysis of 202 pediatric GBMs which unexpectedly showed that 20% displayed methylation profiles similar to either low grade gliomas or PXA's, had a better OS and were also enriched for PXA-associated molecular alterations including *BRAF* V600E mutations and homozygous deletions of 9p21 (*CDKN2A*). The remaining 162 pediatric GBMs stratified into the following four subgroups: *IDH1*-mutant (6%), H3.3 G34-mutant (15%), H3.3/H3.1 K27-mutant (43%), and those GBMs that were wild type for H3 and *IDH* (36%) [107].

A genetic signature of pediatric high grade gliomas (and a smaller subset that occur in adults) includes mutations that arise in the histone variant H3.3 encoded by the genes *H3F3A* (chromosome 1q42.12) and *H3F3B* (chromosome 17q25.1), or H3.1 genes (*HIST1H3B* and *HIST1H3C,* both located on chromosome 6p22.2) [107, 108]. Two specific histone mutations in H3.3 in pediatric GBMs are mutually exclusive with *IDH* mutations; one is present at amino acid 27 resulting a substitution of lysine for methionine (K27M) and the second at position 34 resulting in a substitution of glycine for either arginine or valine (G34R/V) [109, 110]. *H3F3A* K27M is strongly aligned with high grade gliomas of the midline of younger children, with the classic presentation in the pons or thalamus. The G34R/V variant is more typical of supratentorial high grade astrocytomas and is observed in older children and young adults. The presence of an H3K27M mutation correlates with malignant behavior and shorter survival regardless of its histologic features [43,

106, 109–111]. *TP53* and *ATRX* mutations co-occur with H3.3 mutations, with the highest correlation in G34R/V GBMs and with lower, yet significant, overlap with K27M mutations [29, 110]. *H3F3A* K27M mutations have been described in high grade astrocytomas of the spinal cord in the pediatric and young adult population, further supporting the associations with younger age, aggressiveness and midline location [112].

DIPG represents a specific form of pediatric high grade glioma that typically presents between 6 and 7 years of age and has a dismal median survival of 10 months [111]. *H3F3A* mutations are present in over 70% of these tumors and *PDGFRA* amplifications are present in 28–36% [111]. Other alterations that may prove to be clinically significant include missense mutations in *ACVR1* (also known as *ALK2*; chromosome 2q23-q24) in up to 32% [105]. To date, IDH mutations have not been identified in DIPG's [111, 113]. In comparison to the pediatric counterparts, adult brainstem infiltrating gliomas occur less frequently and have a better outcome, most likely because they represent a distinct disease process or include a combination of dissimilar diseases [113].

## 4.9 Ancillary Testing for Biomarker-Driven Diagnosis of Infiltrating Gliomas

Distinguishing glioma lineage based on histomorphologic criteria alone can be challenging, since tumors frequently exhibit overlapping features and numerous studies have documented substantial intra- and interobserver discordance. As noted above, molecular biomarkers are objective and reproducible classifiers that can be used to complement and improve morphology-based diagnoses. Many of the biomarkers discussed above have been developed for routine use in diagnostic neuropathology and are included in immunohistochemical, molecular-genetic and cytogenomic testing platforms [114].

One of the most important prognostic and predictive biomarker used in the clinical management of patients with high grade gliomas is the methylation status of the promoter for *O6-methylguanine-DNA methyltransferase (MGMT)*. MGMT is a DNA repair enzyme with the ability to restore guanine from O6-methylguaninie induced by alkylating agents such as temozolomide (TMZ) [29, 87]. Hence, low levels of MGMT would be expected to correlate with an improved response to alkylating agents. *MGMT* promoter methylation, which occurs in about 40% of GBMs and correlates with low protein expression levels of MGMT, is consistent with enhanced response to therapy and improved overall survival. Promoter methylation is typically assessed by methylation-specific PCR [78, 115, 116]. MGMT immunohistochemistry is currently not recommended for clinical practice [108].

Gene sequencing is becoming more widely available and can be accomplished in a focused, single gene approach, a targeted gene panel, or whole exome or whole genome approach. As noted above, many genetic alterations are specific to the development and progression of glial neoplasms. From a diagnostic perspective,

genes of interest include, but are not limited to, *IDH1, IDH2, TP53, ATRX, CIC, FUBP1, TERT, NOTCH1, DAXX, EGFR, PTEN, NF1, RB1, BRAF, MYB, MYBL1, MYC, FAT, FGFR1, NTRK, ACVR1, H3F3A, HIST1H3B, PDGFRA,* and *SETD2*. Depending on the gene and its specific type of alteration, it can be assessed by immunohistochemistry, FISH or cytogenomic microarray, focused or high-throughput sequencing technologies, or multiplexed platforms.

Many gliomas are characterized by highly recurrent genomic alterations that are best assessed by a focused analysis. For example, cerebellar pilocytic astrocytomas are enriched by *KIAA1549:BRAF* gene fusions and angiocentric gliomas exhibit *MYB* alterations, most notably *MYB-QKI* rearrangements [95, 98]. While FISH probes can be used to test for some gene rearrangements, sequencing may be required in others. However, given the growing number of driver genes involved in gliomagenesis and the genomic variability of CNS tumors, next-generation sequencing (NGS) platforms are gaining application in diagnostic neuropathology [97]. NGS panels have been developed that include genes relevant to CNS neoplasms for the detection of single nucleotide variations, fusions and CNAs and have shown high sensitivity and specificity with concordance as high as 98% when compared to well-established single biomarker methods [117, 118].

Assessment of CNAs has great diagnostic utility in surgical neuropathology and both single-nucleotide polymorphism array and array comparative genomic hybridization technologies have been employed. The quality and quantity of CNAs among gliomas tend to correlate with classification, grade, progression, and prognosis [119]. FISH is a commonly employed technique to assess for CNAs at single locus including, for example, amplifications of *EGFR* and *PDGFRA*, as well as deletions of *PTEN* and *CDKN2A* in high grade astrocytomas [78]. Similarly, FISH for 1p/19q co-deletion has been used as a diagnostic marker of oligodendroglioma.

Whole genome methods (cytogenomic microarray) for assessing CNAs are increasingly being employed due to the abundance of diagnostically relevant information that is obtained. The assessment of whole arm losses of 1p and 19q is becoming critical for *IDH*-mutant glioma, since the event is definitional for oligodendroglioma (Fig. 4.3). Since the detection of 1p and 19q losses by FISH documents only focal deletions on these chromosome arms rather than the whole chromosomal arm losses associated with the unbalanced translocation that is the signature of oligodendroglioma, it is expected that false positives may result, especially in genomically unstable high grade gliomas [42, 87]. For example, Clark et al. showed that 5.7% of GBMs showed 1p/19q co-deletion by either FISH and/or PCR-based LOH but that the vast majority of these (over 90%) also had 10q LOH and/or *EGFR* amplifications, which virtually never occur in the setting of *IDH* mutations and whole arm losses of 1p/19q [59]. Thus, a false positive detection rate of approximately 6% would be expected using FISH as a marker for whole arm losses of 1p and 19q in the setting of high grade gliomas. Whole genome assessment of CNA also reliably detects gain of chromosome 7 and loss of chromosome 10, which are typical of *IDH*-wt GBMs and have been shown to correlate with a tendency of shorter survival when occurring in conjunction with 9p losses [119].

Among *IDH*-mutated gliomas, CNAs have diagnostic and potentially prognostic value. Gains of 7q are an early event in a subset of *IDH*-mutant astrocytomas and are mutually exclusive with loss of 1p/19q [119]. *IDH*-mutant gliomas with *TP53* mutations typically have at least one of the following CNAs: +7q, +8q, −9p, −11p and +12p. These CNAs are associated with a poor prognosis and/or progression and may be related to the gains or losses of *MET, MYC, CDKN2A, CDKN1C,* and *KRAS*, respectively [120]. Other losses potentially related to astrocytoma progression include 17p, the site of *TP53* and 10q, the site of *PTEN* [93]. *IDH*-mutant GBMs have been shown to harbor higher levels of CNAs and increased incidence of chromothripsis in comparison to their precursor lesions and to *IDH*-wt tumors of all grades [81].

Amplification events are often prognostically significant and are viewed as potential targets of therapy in both pediatric and adult glioma [107]. Common amplification events in primary, *IDH*-wt GBMs include several regions of interest (ROI) that contain oncogenes on the following chromosomes: 7p11.2, 7q21.2, 7q31.2 for *EGFR/CDK6/MET*, respectively; 12q14 and 12q15 for *CDK4*/*MDM2*, correspondingly; and 4q12 (*PDGFRA*). Among IDH-mutant high grade gliomas, *PDGFRA* amplifications are noted with increased frequency with higher grade and also are an independent prognostic factor in de novo *IDH*-mutant GBMs [121]. Homozygous and hemizygous deletion events that commonly occur in *IDH*-wt GBMs include the following ROI's: 17q11.2, 10q23, 9p21.3 and 13q14, corresponding to *NF1, PTEN, CDKN2A/CDKN2B*, and *RB1* genes, respectively [4, 29, 54, 87, 89, 91]. *BRAF* alterations at 7q34 can also be detected using cytogenomic microarrays.

Immunohistochemistry (IHC) is a cost-efficient method that is widely available and can be used for determining the protein expression patterns that correlates with genetic alterations. Commonly used IHC stains used to classify gliomas include IDH1 R132H, p53, ATRX, H3K27M, BRAF, CIC, and FUBP1 [42, 80, 108]. *IDH* mutations are critical for distinguishing between subtypes of gliomas and can also be used to distinguish between glioma and reactive gliosis. *IDH1* R132H mutation accounts for more than 90% of all *IDH* mutations and a monoclonal mutant-specific antibody recognizes the mutant protein with cytoplasmic immunoreactivity with high sensitivity and specificity [87, 122]. Since other rare non-R132H *IDH1/2* mutations will not be recognized with this immunostain and as the designation of a diffuse glioma in adults as *IDH*-wt has gained important clinical and therapeutic significance, gene sequencing analysis of *IDH1* codon 132 and *IDH2* codon 172 is recommended in the event of a negative or indeterminate result with *IDH1* R132H immunostain [78, 108]. It has recently been suggested that sequencing may not be warranted in the setting of a negative R132H immunostain in GBMs arising in patients older than 55 years due to the rarity of non-R132H IDH1 mutations [4, 5].

*TP53* mutations are frequent in lower grade, *IDH*-mutant infiltrating astrocytomas and are almost mutually exclusive with 1p/19q co-deletions. The detection of p53 by IHC can be used as a surrogate for *TP53* mutations and in support of an astrocytic lineage, but only with some significant caveats. The p53 immunostain recognizes the normal protein and is not specific for mutations. *TP53* mutations

leads to reduced degradation of the protein and nuclear accumulation of both mutant and wild-type gene products [78]. Strong nuclear p53 positivity in >10% tumor nuclei is a predictor of *TP53* mutations, but should be evaluated in the context of morphology and other test results [108]. Inactivating mutations in *ATRX* commonly co-occur with *TP53* mutations in the setting of *IDH*-mutant lower grade infiltrating astrocytomas [16]. In combination with 1p/19q and *IDH1/2* mutational status, *ATRX* alterations have become part of the molecular diagnostic algorithm for the refinement of diffuse glioma lineage. *ATRX* mutation results in a truncated protein and in abrogated protein expression, which correlates very well with loss of nuclear immunoreactivity of ATRX [42, 78]. Of note, it is important to evaluate the immunoreactivity of non-neoplastic nuclei, such as those of endothelial cells, as an internal positive control in order to correctly assess ATRX status [108]. Several studies have highlighted its prognostic value since better clinical outcomes have been noted in *IDH*-mutant astrocytomas with ATRX loss as compared to *ATRX*-wt subsets [27, 123].

The revised 4th edition of the WHO Classification recognizes the entity of diffuse midline glioma, H3 K27M-mutant, highlighting the tight coupling of this mutation to a specific form of high grade glioma [4]. K27M mutations involving either the H3.3 or H3.1 histones can be detected by nuclear staining using H3K27M immunohistochemistry with a sensitivity and specificity of 100% [124] (Fig. 4.4). Another clinically useful immunostain is the mutation specific *BRAF* V600E (VE1) which has a sensitivity of 100% and a specificity of 98% for the mutation, but only if strong cytoplasmic positivity is considered as positive [108].

Both *CIC* and *FUBP1* mutations are specific to oligodendrogliomas and are found only in the setting of *IDH* mutations and 1p/19q co-deletion. Loss of nuclear CIC expression by IHC suggests a loss-of-function mutation but the sensitivity and specificity is relatively low (69% and 87%, respectively) [108]. Loss of nuclear FUBP1 by IHC correlates with inactivating mutations with a sensitivity of 100% and specificity of 90% in oligodendrogliomas. However, there is currently no consensus for evaluating these immunostains and their prognostic values have not been completely elucidated [87, 108].

## 4.10 Conclusion

Gliomas are common brain tumors that are highly variable with respect to location, histomorphology, molecular-genetic signatures, clinical behavior and treatment responses. The diagnosis of gliomas in the past has suffered from low reproducibility due to intraobserver, interobserver and interinstitutional variability [125]. Specific molecular alterations, or their combinations, are now known to carry diagnostic, prognostic and/or predictive value. Molecularly defined subsets of gliomas are more cohesive and reproducible, capturing the biologic features better than histopathology alone. We are in transition from a histology-based practice to an integrative, biomarker-driven diagnosis that will optimize patient stratification and

treatment and enhance research efforts. With the revised 4th edition of the WHO Classification, molecular parameters have been added to histologic class to define many entities [4]. Other entities have been dropped or discouraged, such as gliomatosis cerebri and oligoastrocytomas, which can both be unequivocally assigned to other molecularly defined subgroups [2, 126].

Important progress has been made by integrating molecular-genetic alterations with tumor classification, but new questions that have arisen require further attention. In particular, risk stratification within genetic subsets of disease will need to be re-evaluated and optimized, a subject of ongoing investigations. Recent studies suggest that histologic grade (II vs III) and mitotic activity are not highly informative among *IDH*-mutant infiltrating gliomas for predicting outcome [52]. It has also been demonstrated that there are little differences in age at presentation and survival between grade II and III *IDH*-mutated astrocytomas [127]. Furthermore, *IDH*-wt anaplastic astrocytomas, which are a WHO grade III neoplasm, have a poorer outcome than *IDH*-mutant GBMs, a WHO grade IV neoplasm [128]. As molecular platforms evolve and become more sophisticated, the field of diagnostic neuropathology will undergo further maturation and the need for comprehensive molecular analysis of CNS tumors will increase with the identification of clinically significant genetic biomarkers.

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# Chapter 5
# Towards an Intermediate Grade in Glioma Classification

**Valérie Rigau**

**Abstract** Glial tumors are known to be difficult to classifify. Due to insights in genetic alterations of gliomas the 2016 WHO classification of tumors in CNS presents a new diagnostic approach introducing integrated histological and molecular diagnosis in the classification of diffuse gliomas. This approach will probably lead to better reproducibility between pathologists than histopathological criteria alone. However, the classification still defines histological grades of malignancy, and histologic grade is still an important factor in deciding treatment. For diffuse infiltrating gliomas the grades are GII (LGG), GIII and GIV (HGG). GII gliomas, despite their low grade, are infiltrative and will progress to higher grades of malignancy. The duration of transition from GII to GIII is highly variable. Identification of predictive markers of malignant progression could help identify patients who could benefit from early adjuvant treatments. We have studied the heterogeneity within GII gliomas, and find that some tumors harbor foci with histopathological and molecular features similar to higher grade. We suggest that these foci may represent initiation of malignant transformation. The term GII+ could be applied to these tumors indicating an intermediate grade, and the identification of these tumors can be valuable in order to optimize individual treatment.

**Keywords** Diffuse low-grade glioma • Heterogeneity • Neuropathology • Intermediate grade

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## 5.1 Introduction

Gliomas account for 70% of primary brain tumors and constitute a heterogeneous group of tumor entities. Traditionally, these tumors have been classified into subtype and grade based on their morphological characteristics alone. The insights in the genetic alterations found in these tumors have led to consensus for an integrated diagnostic approach, defined in the latest World Health Organization (WHO) classification [1]. Well-established molecular parameters (i.e IDH status, and 1p/19q codeletion) are now incorporated into the classification of diffuse infiltrating gliomas, now consisting essentially of two main subtypes, i.e. astrocytomas, and oligodendrogliomas. The former diagnosis of oligoastrocytoma should be avoided, and tumors with a mixed morphology are recommended classified as either astrocytoma or oligodendroglioma based on molecular findings. According to studies, the use of integrated phenotypic and genotypic parameters will provide an increased level of objectivity in the histo-pathological evaluation and classification of these tumors.

However, the classification still defines four histological grades of malignancy, where the diffuse gliomas are graded II-IV. Grade II (GII) is considered low-grade tumors (LGG), whereas grades III (GIII) and IV (glioblastomas) are high-grade tumors (HGG). GII defines tumors with slightly increased cellularity and some cytological atypia, GIII are tumors with poor prognosis that show histological features of malignancy, such as nuclear atypia and mitotic activity. Grade IV have additionally micro vascular proliferation and/or necrosis. Microvascular proliferation and necrosis can also be present in GIII oligodendrogliomas. GII gliomas, despite their low proliferation rate, are infiltrative and inescapably progress to higher grades of malignancy. The duration of transition from GII towards GIII is highly variable. Early maximal surgical resection is the optimal therapeutic option for GII as it is expected to delay the malignant transformation [2]. The best schedule for chemotherapy and radiotherapy is still under debate. Though it would be useful to identify patients who could benefit from early adjuvant treatment, no reliable histological or molecular criterion is currently available for predicting the duration of transition from a low-grade glioma into a tumor of aggressive phenotype. Therefore, the identification of predictive markers of malignant progression would be a major step to improve personalized therapeutic strategies in patients with LGG.

Although a single biopsy has long been recommended, surgical resection is now considered as the optimal treatment for GII [2]. Advances in neurosurgical procedures, such as awake brain surgery, give the opportunity to perform wider resections than those done by classical surgery. Availability of such large surgical specimens allows a complete histological evaluation and a comprehensive overview of tumor samples. This is crucial as GII tumors may exhibit intratumoral heterogeneity.

## 5.2 Toward an Intermediate Grade

Among the large number of GII operated in our institution (approximately 145/year), we have noticed in a subset of tumors the presence of foci with higher cellularity, florid vascularization or very early features of endothelial proliferation. Because these tumors did not show mitotic activity they did not fulfill the criteria of GIII, and they were classified as GII according to the current recommendations of the WHO classification. However, we hypothesized that these foci could represent early sites of malignant progression although the current classification did not take these intermediate features into consideration [3].

In about 30% of cases we found heterogeneous foci in a background of diffuse low-grade glioma (Fig. 5.1). The foci measuring less than 10 mm were termed micro foci, whereas the ones near the size of 10 mm were called macro foci. Their presence varied from a single focus to multiple foci, and they were often located in the center of the resected specimen. In all cases, these heterogeneous foci harbored increased cell density, which appears to be an early event. In these cellular micro

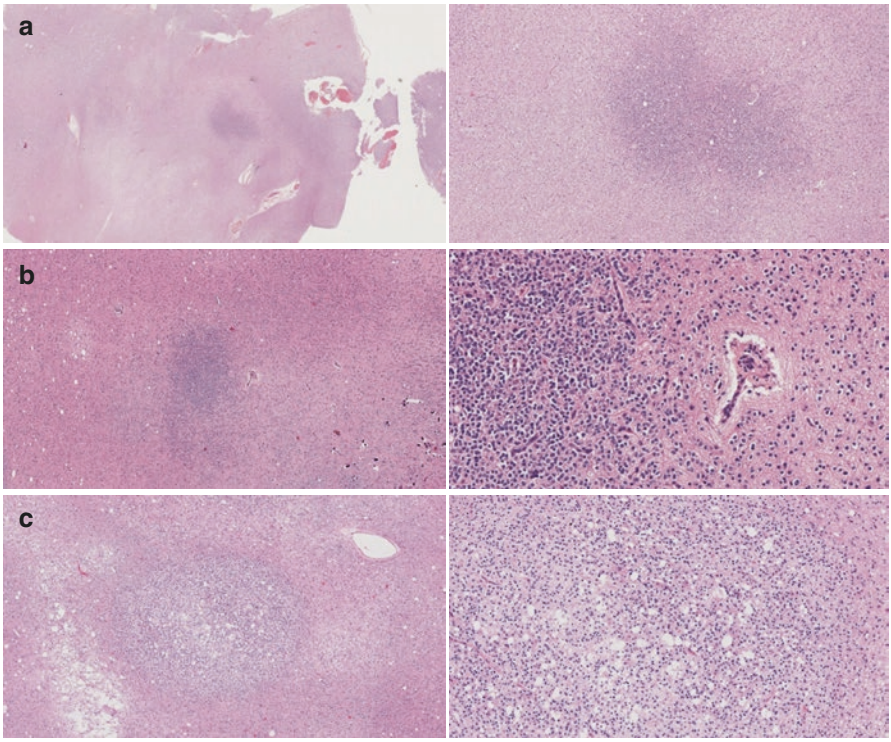


**Fig. 5.1** Three examples (a = case 1; b = case 2; c = case 3) of microfoci of "intermediate grade" at low magnification (*left*) and at high magnification (*right*) with the low grade glioma in background

foci we could also find more pronounced nuclear atypia than elsewhere in the tumor, although this varied more and was not a constant feature. In the cellular macro foci we found vascular hyperplasia with endothelocapillar hyperplasia. Since all the histological criteria for WHO grade III were not present the diagnosis of diffuse low-grade glioma GII was made. However, the presence of the foci described were stated in the neuropathological report.

In a previous study, we investigated whether these foci displayed histological or immunohistochemical (IHC) similarities to GIII, such as hypoxia, high proliferative activity, increased vascularization, and activation of oncogenic pathways. For this purpose, we compared the histological, immunohistochemical and molecular features of these heterogeneous gliomas (called "GII+" in this study) to those of homogeneous GII and anaplastic GIII [3].

It is now well established that the grade II gliomas are premalignant tumors that will ineluctably evolve towards higher grade of malignancy.

The current WHO classification [1] however describes GII and GIII tumors as clearly distinct entities. This clear-cut distinction overlooks the possibility of a continuum between GII and GIII tumors. Moreover, the morphological border between GII and GIII is not precisely defined in the WHO classification. For instance, the notions of "prominent microvascularisation" or "high cellularity" are subjective and do not give precise parameters of evaluation.

We find the main limitation of the WHO grading of diffuse gliomas to be the lack of an intermediate grade between grade II and grade III as we often see tumors that in fact exhibit features in between the two grades. It seems logical and obvious that there is a biological continuum between the grades, and we purpose the use of an intermediate term in the future. The presence of the described foci of increased cellularity and proliferation of vessels may correspond to grade II in transformation to grade III. It is interesting to note that while some show signs of cellular atypia, others show signs of neoangiogenesis [3].

## 5.3 Discussion

As mentioned, because the cognitive performance of the patient is under control during the procedure, awake neurosurgery allows extensive resection of gliomas. Large and non-damaged samples are therefore available for histopathological evaluation. We noticed the recurrent presence of hyper cellular micro foci in GII specimens obtained by awake neurosurgery. We theorized that those foci might be the early signs of malignant progression to GIII. Aggressiveness in gliomas is probably underestimated in biopsy specimen because of the intra-tumor heterogeneity. Indeed, some GII might contain transformation nests that are not visible by routine imaging techniques but that could be detected by pathological and IHC examination after surgery.

Hyper cellularity was a consistent feature of the foci, suggesting it might be the earliest anaplastic event, contrary as mentioned in the 2016 classification which

describe a predictable sequence: atypia, mitosis, increased cellularity, and micro vascular proliferation and/or necrosis. The results of our IHC and molecular investigations were in favor of the hypothesis of a transition from GII to GIII initiated by the generation of small hypercellular or hypervascularized areas. Indeed, in all the GII+ cases studied, we observed several alterations that were present only in the foci and not in the tumor tissue background. We observed that the proliferation index and the vascularization of GII+ foci -measured objectively using digital calculation- were close to those of GIII whereas they stood out from those of the GII background. In addition, in two cases, we observed cells expressing HIF-1$\alpha$ in the foci but not in the background in two cases of GII+ tumors [3]. It revealed hypoxic conditions specific present in the foci and might be a sign of pejorative evolution since HIF-1$\alpha$ expression has been correlated to higher grade and poor prognosis in astrocytic tumors [4]. In our experience, the increased vascularization and hypoxia were not correlated clinically to the occurrence of MRI enhancement [3]. This might be explained by insufficient sensitivity of MRI in regard to the very small size of these foci. Contrast enhancement may only detect late events whereas histological examination allows the detection of this early subclinical change reflecting neoplastic progression. To note, specific techniques of spectroscopy or perfusion MRI [5, 6] and techniques of nuclear medicine, such as dynamic 18F-fluorethyltyrosine (18FET) positron emission tomography (PET), could also be promising to identify high risk in low-grade gliomas [7].

Moreover, other authors [8] showed that dynamic contrast-enhanced MRI was helpful to predict the presence of areas of increased hypoxia and proliferation in gliomas. Therefore, we assume that microscopic evaluation of the vascularization associated with cell proliferation in GII+ micro foci, combined with nuclear imaging, might become central in managing the care of GII patients.

We have demonstrated that the foci of GII+ cases displayed increased proliferation and cellularity, vascular hyperplasia and signs of hypoxia. In addition, we identified oncogenic alterations in the foci [3]. Alterations of EGFR-activated pathways are known to be involved in gliomas tumor genesis. Amplification of *EGFR* has been described in 45% of glioblastomas and in 10% of GIII whereas it is not reported in GII [9, 10]. EGFR overexpression is commonly found in low-grade astrocytomas and oligodendrogliomas [9]. While we did not observe amplification of *EGFR,* we observed overexpression of EGFR. It has been reported that EGFR expression increases with the grade of malignancy [11, 12]. Overexpression in the absence of amplification can be explained by point mutations or by non-genomic deregulation, such as transcriptional, translational or post-translational changes. However, it might also be caused by differences in the sensitivity or specificity of IHC and FISH methods [13]. AKT is a downstream effector of the tyrosine kinase receptors EGFR and PDGFRA. Its activation plays a role in glioma progression and is the most frequent alteration in glioblastomas (cancer genome atlas). The expression of P-AKT has been shown to correlate to the grade of the gliomas [14]. It has also been correlated to angiogenesis [15]. We detected an expression of EGFR and P-AKT significantly higher in the foci than in the background in eight and five cases of GII+, respectively. All the five foci that showed a positive expression of P-AKT

displayed an overexpression of CD31, a marker of angiogenesis, while four of them overexpressed EGFR (Hirsch's score > 200) [3]. This suggests a synergy of these different alterations. Altogether, the foci showed activation of the EGFR-PI3K pathway at various levels. The activating mechanisms other than EGFR amplification, such as inactivation of *PTEN*, activating mutation *PI3KCA* or amplification of *AKT* need to be further investigated in order to understand the causes of EGFR pathway activation [16, 17].

*TP53* mutations have been described as major events in the process of tumor initiation. They are predominantly observed in secondary glioblastomas [18]. They are considered as an early alteration in glioma genesis. The intensity of anti-P53 immunostaining, which detects abnormal forms of the protein accumulated in the nucleus, has been correlated to the astrocytoma type and to tumor grade [19]. We have shown the intensity of the P53 staining in the foci to be higher than in the background in two GII+ cases [3]. This suggests that clonal mutations of *TP53* might have arisen in the foci. TP53 positive tumor cells of the foci could therefore harbor genetic instability leading to anaplasia.

We also detected quantitative chromosomal abnormalities only in the foci of some tumors, such as polysomies for chromosomes 7 and 12 [3]. Polysomy 7 has frequently been described in glioblastoma [13]. Our results indicate that the foci had not only different morphological features and expression pattern from the tumor background, but that they also presented different genomic profiles, suggesting the presence of several tumor clones in these heterogeneous gliomas.

Furthermore, in our experience, survival curves depend on the tumor grade. We observed significantly shorter mean overall survival in patients with GII+ tumors compared to GII, and longer survival compared to GIII tumors [3].

We failed to find any similar study concerning morphological or histological features of heterogeneity of LGG in the literature.

However, numerous studies enhance biological heterogeneity and mechanistic insights into the genetic and epigenetic mechanisms driving glioma progression. In their study, Bai et al. [20] compare the genomic landscapes of high-grade glioma to their low-grade counterparts. They identified several convergent alterations, notably activation of the MYC and RTK-RAS-PI3K signaling pathways, alterations in cell cycle regulators, up regulation of the FOXM1- and E2F2-mediated cell cycle transitions and epigenetic silencing of developmental factors. All these pathways converge in a synergistic stimulation of cellular proliferation.

Others, as Van Thuijl et al. [21] studied clinical relevant copy number aberrations (CNAs) indicative of aggressive tumor behavior. These CNAs display extensive intra tumoral heterogeneity in LGG.

A very interesting review about glioma neovascularization is presented by Hardee and Zagzag [22]. They emphasize five mechanisms by which gliomas achieve neovascularization: vascular co-option, angiogenesis, vasculogenesis, vascular mimicry and glioblastoma-endothelial cell trans differentiation. They highlight that hypoxia and the hypoxia-inducible factors (HIFs) play a crucial role in creating a microenvironment that helps preserve the stem-like fraction in gliomas.

Also contributing are hypoxia-independent mechanisms like P53 and vascular growth factor (VEGF). Vascular co-option seems to be the initial step in the cascade of vascular events leading to angiogenesis. Co-opted vessels express angiopoietin-2 (ANG-2) [23]. HIF-1 dependent mechanisms play a role in the up-regulation of ANG-2, and in the presence of ANG-2, VEGF enables migration and proliferation of endothelial cells and stimulates sprouting of new blood vessels. So, when we highlight the presence of HIF-1 positive cells in G2+ foci, we imply that mechanisms of co-option are engaged.

## 5.4 Conclusions

To sum up, we have found that some grade II gliomas are heterogeneous and harbor foci with distinct morphological and molecular features. These features are similar to those of GIII and are not found in homogeneous GII tumors. Our findings suggest that these foci play a role in the initiation of transformation to anaplastic gliomas, and support the idea of a biological continuum between GII and GIII. It also advocates the importance of multidisciplinary meetings with case-by-case discussion. Identification of tumors with these histopathological distinctions as an intermediate grade (GII+) can provide important information for optimizing individual LGG therapeutic strategy.

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# Part II
# Fundamental Science

# Chapter 6
# Pathogenesis of Diffuse Low-Grade Gliomas

**Courtney Pendleton, Kazuya Motomura, and Atsushi Natsume**

**Abstract** Accurate classification of low grade gliomas remains a challenge for clinicians and pathologists alike. The World Health Organization (WHO) histology-based classification scheme presents a unique dilemma in the description of low grade gliomas. Low grade gliomas demonstrate a highly variable clinical course, and while lacking the proliferative markers and necrosis that are hallmarks of high grade gliomas, they may demonstrate extremely aggressive growth and progression. Recent studies have helped delineate genetic markers that correlate with low grade glioma clinical behavior. These markers, both alone and in combination, offer the possibility of more accurate prognostication than histopathologic features alone. However, the interaction of these genetic mutations, and the pathways by which they may arise sequentially, are incompletely understood. Further research into the genetic mutations found in low grade gliomas may offer the ability to better classify, treat, and predict the outcome of these tumors.

**Keywords** Low grade gliomas • Prognostic genetic markers • Genetic heterogeneity

## 6.1 Genetic Classification of Grade II/III Gliomas

The accurate classification of low grade gliomas has long been a challenging issue for neuropathologists and neurooncologists. The main difficulty arises from the need to improve diagnostic clarity and prognostication of “lower grade” gliomas,

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histologically assigned to grade II and grade III according to the World Health Organization (WHO) grading. There is considerable variability in the clinical behavior of grade II and grade III gliomas, and histological characteristics are not consistently accurate predictors of which tumors will remain low grade, and which will demonstrate an aggressive course progressing towards grade IV (glioblastoma).

The Knudson hypothesis of tumorigenesis, initially defined in retinoblastoma, but subsequently extrapolated to multiple oncologic processes [1], offers a system for understanding the clinical prognosis and risk of progression of these low grade gliomas. Although it is widely understood that multiple "hits" or genetic mutations in oncogenic and oncoprotective genes will predispose cells to malignancy, the molecular basis of low grade glioma pathogenesis and progression remain incompletely defined. Recent molecular studies of these tumors highlight mutations with clinical and pathogenic relevance, which provides the possibility of a new genetic classification of gliomas that more accurately reflects their malignant potential [2, 3].

In the current WHO grading, gliomas are classified into four categories on the basis of histopathological findings. Among these, grade IV gliomas, or glioblastomas (GBMs), account for two-thirds of all gliomas, and are characterized by unique histological features including microvascular proliferation and tumor necrosis. They have a uniformly aggressive clinical course, with a 2-year overall survival of only 26.5% [4]. Conventionally, grade III gliomas are assigned to the high-grade glioma category, although recent papers have considered these tumors, along with grade II gliomas to be "lower grade" gliomas, given that a substantial portion of these tumors demonstrate more indolent behavior, with an overall survival range from 1 year to 15 years. Conversely, some grade II gliomas demonstrate a highly aggressive clinical course indistinguishable from grade IV tumors, despite clear histological features consistent with a low grade glioma. It is these tumors, which demonstrate clinical behavior inconsistent with histologic classification, that raise questions regarding the need for a genetic or molecular classification system. Further complicating the use of the WHO histologic classification system in lower grade gliomas is the role of inter- and intra-observer variability in identifying histopathologic features, particularly in distinguishing between grade II and grade III gliomas [5, 6].

During the past 10 years, substantial progress has been made regarding the molecular pathogenesis of gliomas, in particular the role of *IDH*-mutations (mutations in *IDH1* and *IDH2*) in predicting the clinical behavior and prognosis of low grade gliomas [2, 3]. On the basis of the *IDH*-mutation status, WHO grade II and grade III gliomas can be primarily classified into *IDH*-mutated, true 'low-grade' gliomas and *IDH*-wild type gliomas. The latter recapitulate, in every respect, grade IV gliomas, which generally demonstrate *IDH*-wild type genetics, except for the lack of microvascular proliferation and tumor necrosis [2, 3]. The *IDH*-mutated, the low-grade gliomas are further divided into two discrete subsets according to the presence (Type−1) or absence (Type−2) of 1p/19q co-deletion [2, 3]. The identification of *IDH*-mutation concurrent with 1p/19q codeletion offers important insight to the behavior of lower grade gliomas. Recent integrated molecular studies

demonstrated that gliomas with *IDH*-mutation and 1p/19q co-deletion are more likely to demonstrate oligodendroglioma histopathologic structure. In addition, these tumors were found to have a high rate of concomitant *TERT* promoter mutations, with or without accompanying *CIC, FUBP1,* and *NOTCH1* mutations. These tumors were not found to demonstrate *TP53* mutations, which were considered a hallmark of gliomas with *IDH*-mutation and no 1p/19q codeletion (98.7%). This finding led the authors to conclude that the 1p/19q codeletion was mutually exclusive from the *TP53* mutation, which is consistent with the observation that Type-1 gliomas follow a more indolent course consistent with lower grade gliomas, while Type-2 gliomas demonstrate a clinical course similar to more aggressive high grade gliomas (Table 6.1) [2, 3]. While a large subset of Type-2 gliomas show biallelic *TP53* inactivation, which is very rare in Type-1 tumors, the underlying mechanism of the exclusiveness of 1p/19q co-deletion and biallelic *TP53* mutation is unclear [2]. Many WHO grade II and III gliomas progress to higher-grade gliomas, which is in accordance with the frequency of *IDH*-mutation in secondary GBM. As secondary GBM often demonstrate *IDH*-mutation, *TP53* mutation, and lack 1p/19q codeletion, these Type-2 lower grade gliomas may be predisposed to demonstrate malignant transformation.

**Table 6.1** Clinical and genetic features in genotypes of grade II/III gliomas

| | Type-1 | Type-2 | Type-3a | Type-3b |
|---|---|---|---|---|
| Clinical characteristics | | | | |
| Age, median (IQR), y | 45 (36–54) | 36 (30–44) | 43 (28–49) | 57 (46–64) |
| OS, mean (95% CI), y | 16.38 (14.15–NA) | 7.88 (6.76–9.70) | 9.13 (5.05–NA) | 1.83 (1.53–2.23) |
| Genetic alterations | | | | |
| *IDH1/2* mutations | Mutated | Mutated | Wild type | Wild type |
| 1p/19q co-deletion | Present | Absent | Absent | Absent |
| Common mutations | *TERT* promoter, *CIC*, *FUBP1*, *NOTCH1* | *TP53*, *ATRX* | *BRAF* (Occasionally) | *EGFR*, *NF1*, *TP53*, *PTEN*, *TERT* promoter |
| Common copy number alterations | Loss of chromosome 4 | UPD of 17p<br>Gain of 7q and 10p<br>Loss of 11p | Low frequency | Amplification of *EGFR*<br>HD of *CDKN2A/2B*<br>Gain of 7q and 19p<br>Loss of chromosome |
| Glioma methylation phenotype | Positive | Positive | Negative | Negative |

*IQR* interquartile range, *OS* overall survival, *UPD* uniparental disomy, *HD* homozygous deletion

Several lesions are relatively specific to Type-2 gliomas, most frequently *ATRX* mutation and 17p loss of heterozygosity [2, 3]. ATRX mutation is most often a loss of function mutation, and has been found to be almost mutually exclusive with the 1p/19q codeletion. This mutation was found most frequently in anaplastic astrocytomas, and was associated with a significantly better clinical course than those tumors with wild type-ATRX [7].

*IDH*-mutated gliomas invariably show CpG island methylator phenotype (CIMP). However, there are differences in the CIMP methylation patterns between Type-1 gliomas (CIMP-A) and Type-2 gliomas (CMIP-B), suggesting the 1p/19q co-deletion, *TERT* promoter mutation, and/or biallelic *TP53* mutation affect the pattern of DNA methylation [2, 3]. Other investigators identified a minority of *IDH*-wild type gliomas distinguished by a unique pattern of DNA methylation, although seen almost exclusively in WHO grade III tumors, and not enriched in WHO grade II subtype [3].

## 6.2 Intra-Tumoral Genetic Heterogeneity

Each genetic subtype may demonstrate significant inter-tumor heterogeneity in terms of genetic lesions other than canonical *IDH1/2*, *TP53*, and *TERT* promoter mutations, and 1p/19q co-deletion [2]. Regional heterogeneity may be closely correlated with the history of clonal evolution, illustrating how a tumor expands outward from its origin, intermingling cells with different genetic mutations in the periphery, to increase overall heterogeneity. Despite the presence of parallel mutations involving common targets, prominent regional heterogeneity raises concern that sequencing of bulk tumor may not detect rare but important mutations or tumor cell subpopulations that exist at low levels.

For instance, an oligodendroglioma, IDH1 mut, 1p/19q co-del seems to arise from somewhere with *IDH1, TERT* promoter, and *TCF12* mutations and 1p19q LOH and propagated to a common branch-point by acquiring mutations in *CIC* (p.R202W), *FUBP1* (c.1041+1G>-), and *FUBP1* (c.1706-1G>A). The tumor then further extends to a location with mutations in *MLL3, ARID2*, and *ARID1B*, another location with *CIC* (p.A235T) and *SMARCC2* mutations, and the common branch with *CIC* p.Q172X, *CIC* p.T767fs, or to different directions with *CIC* p.R1515C and *MLL2*, frequently showing confluence in periphery between multiple components from surrounding branches.

This is also true in *IDH*-wild type gliomas; with the lack of common, canonical mutations, *IDH*-wild type gliomas are more heterogeneous than *IDH*-mutated gliomas [2, 3]. *TERT* promoter mutations have been demonstrated in Type-1 and Type-2 lower grade gliomas [8], and have a differential effect on progression free survival dependent on the 1p/19q codeletion status. Specifically, in *IDH*-wild type tumors the presence of a *TERT* promoter mutation correlated with a shorter progression free survival interval, while in *IDH*-mutated tumors, a *TERT* promoter mutation demonstrated an increased progression free survival. The interactions between

1p/19q codeletion, *TERT* promoter mutation, and other concurrent mutations are not yet completely understood, and a better delineation of the interactions of these mutations may help to further classify lower grade gliomas.

Relying on the discrete genotypes, the "molecular" classification better correlates and predicts clinical behavior of gliomas than histopathological grading. A subset of *IDH*-wild type gliomas classified as WHO grade II tumors, which lack typical genetic lesions of GBM, exhibit a younger mean age of onset and a substantially superior survival to *IDH*-wild type WHO grade III gliomas, and may be better classified as a unique subgroup. Since no known genetic markers, including *TERT* promoter mutation, seem to successfully separate this subset (unpublished data), the classification of these lesions still depends on histology. Although *IDH*-wild type lower grade gliomas show slightly better prognosis than glioblastomas, many molecular features of *IDH*-wild type lower grade gliomas are indistinguishable from WHO grade IV gliomas, and include a high frequency of genetic lesions affecting cell cycle regulation (*CDKN2A/B*, *CDK4*, and *RB1*), receptor tyrosine kinase and other cell signaling (*EGFR, PDGFR, PTEN*, and *NF1*), and the TP53-related pathway (GBM-specific lesions) [2, 3].

## 6.3 Prognostic Relevance of Genetic Alterations

Given the inter-tumor heterogeneity created by the presence of additional genetic lesions in each low grade glioma genetic subtype, it is possible that within each overall genetic subtype, additional subgroups may exist with distinct biological behaviors and prognosis. Identifying these more specific subgroups may allow for better risk stratification and prognostication, and inform the development of optimal therapy to improve the overall clinical outcome. Recent studies reported a number of genetic alterations implicated in an adverse effect on survival in a particular genetic subtype, including *CIC* mutation in *IDH*-mutant LGGs with 1p/19q-codeletion [9], loss of chromosome 9p, PI3 kinase (*PIK3CA* and *PIK3R1* mutations), and *CDKN2A* deletion in *IDH*-mutant LGGs without 1p/19q-codeletion [10–12], and mutated *TERT* promoter in *IDH*-wild type LGGs [13]. However, the effects on overall survival have not systemically been confirmed in a large cohort of fully genotyped patients with prolonged follow-up data to evaluate the overall survival of LGGs.

## 6.4 Rapid and Less-Invasive Detection of Mutated Proteins

An "immuno-wall microdevice," is such a device that features a chip with an attached highly-specific antibody that binds to the protein produced by the gene in which the mutation has occurred. When a sample containing the mutated protein is added to the device, the protein binds to the antibody, which is then specifically

detected by a source of fluorescence. In contrast, if the sample is from normal tissue without this mutation, or is from a tumor other than a glioma, no fluorescence occurs.

The immuno-wall determines whether a sample is positive for a specific mutation in *IDH*. The device was proven highly accurate, as confirmed by complete sequencing of the gene in question in each sample [14].

The small sample size required for the device reduces the invasiveness of sample harvesting. In fact the process takes only 15 min, enabling completion during an operation. The immuno-wall could markedly increase success of glioma treatment by rapidly providing data to inform the course of the operation and tissue to remove. The data indicate that a sample with just 500 cells or 500 ng of protein is sufficient to give a positive result. This suggests that the immuno-wall can identify the margins of tumors where only low numbers of cancerous cells are present. Alternatively, sampling could even involve only obtaining blood or cerebrospinal fluid, rather than removing brain tissue, making the procedure even less invasive.

## 6.5 Conclusion

Although recent advances in the understanding of lower grade glioma genetics make it possible to distinguish between multiple subtypes, and better define overall clinical prognosis and risk of malignant transformation, frequent intra-tumor heterogeneity may also complicate the role of non-canonical mutations as prognostic markers, since they are often detected only in a subset of tumor cells [2]. While these new genetic classification models may offer significant benefits over the WHO histopathologic model, these issues need to be addressed in the future for better understanding and management of lower grade gliomas.

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# Chapter 7
# Dissemination of Diffuse Low-Grade Gliomas: Tools and Molecular Insights

**Nicolas Leventoux, Zahra Hassani, and Jean-Philippe Hugnot**

**Abstract** Diffuse low grade diffuse gliomas (DLGGs), which represent approximately 15% of gliomas, are slow-growing tumors (3–4 mm of mean diameter per year) comprising oligodendrogliomas (OG) and astrocytoma (AG). These gliomas are clinically very heterogeneous and their prognosis somewhat unpredictable, making difficult definition of appropriate treatment. Although initially silent, diffuse low-grade gliomas progress into a more aggressive pathology, ultimately causing death of the patient. Their diffusive nature makes them difficult to fully remove by the surgical approach. Understanding the molecular pathways underlying DLGG dissemination would open new lines of treatments aiming at limiting their spread throughout the brain. However, the rare occurrence of these tumors, the difficulties in growing them in culture, and the quasi-absence of DLGG derived cell lines have definitely impeded the progress of knowledge on this topic. This explains the very few data available today on DLGG invasion and calls for more efforts from the scientific community to tackle this complex challenge. Here we present the in vitro/in vivo models and tools for studying DLGG migration and discuss the influence of location, genetics and molecular components driving their dissemination. We also

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consider data obtained on the migration of normal oligodendrocyte precursor cells as a possible source for guiding our understanding of glioma cell dissemination. Finally, we point out important issues to address in order to move forward on this topic.

**Keywords** Oligodendroglioma • Astrocytoma • Oligodendrocyte progenitors • Migration • Diffuse low-grade glioma • Molecular basis

## 7.1 Introduction

As already noted by Virchow in the nineteenth century [1], gliomas do not exhibit an obvious border that separates tumor from healthy brain tissue, making surgical resection difficult and regularly incomplete. Residual tumoral cells will continue to grow and invade the brain while acquiring further mutations. Development of therapies that would reduce the dissemination of these cells and confine them to a limited area would be greatly beneficial, making the surgical approach fully efficient. Therefore, it is important to understand at the anatomical, cellular, and molecular levels how glioma cells disseminate into the brain so as to build an integrated model which could be used to elaborate new therapeutic approaches. Very good reviews on the molecular mechanisms underlying high-grade glioma invasion already exist (see, for instance, [2–15]), so the present chapter does not intend to cover this topic again. In contrast very little is specifically known on how DLGG cells spread into the brain parenchyma. It is not yet established if DLGG invasion is simply a slower but identical version to high-grade glioma dissemination. However, given that glioblastomas (GBMs) and DLGGs differ substantially in their genetic alterations, it is likely that low and high-grade glioma migration relies both on common and different modalities. The rare occurrence of DLGGs, the difficulties in growing them in culture, and the quasi-absence of DLGG derived cell lines have definitely impeded the progress of knowledge on this topic. In this chapter, we will focus on the available tools used to study DLGG dissemination and on the few molecular data obtained so far. We will also consider data obtained on the migration of normal oligodendrocyte precursor cells as a possible source for guiding our understanding of glioma cell dissemination. Finally, we will point out important issues to address in order to move forward on this topic.

## 7.2 1-In Vitro/In Vivo Animal Models and Tools for Studying DLGG Migration

### *7.2.1 Cell Cultures*

So far no cell lines have been successfully derived from bona fide grade II gliomas. By using a specific and defined media our lab has managed to keep DLGG cells with expression of mutated IDH1 (found in 80% of DLGG) for several weeks in vitro (Fig. 7.1, unpublished data).

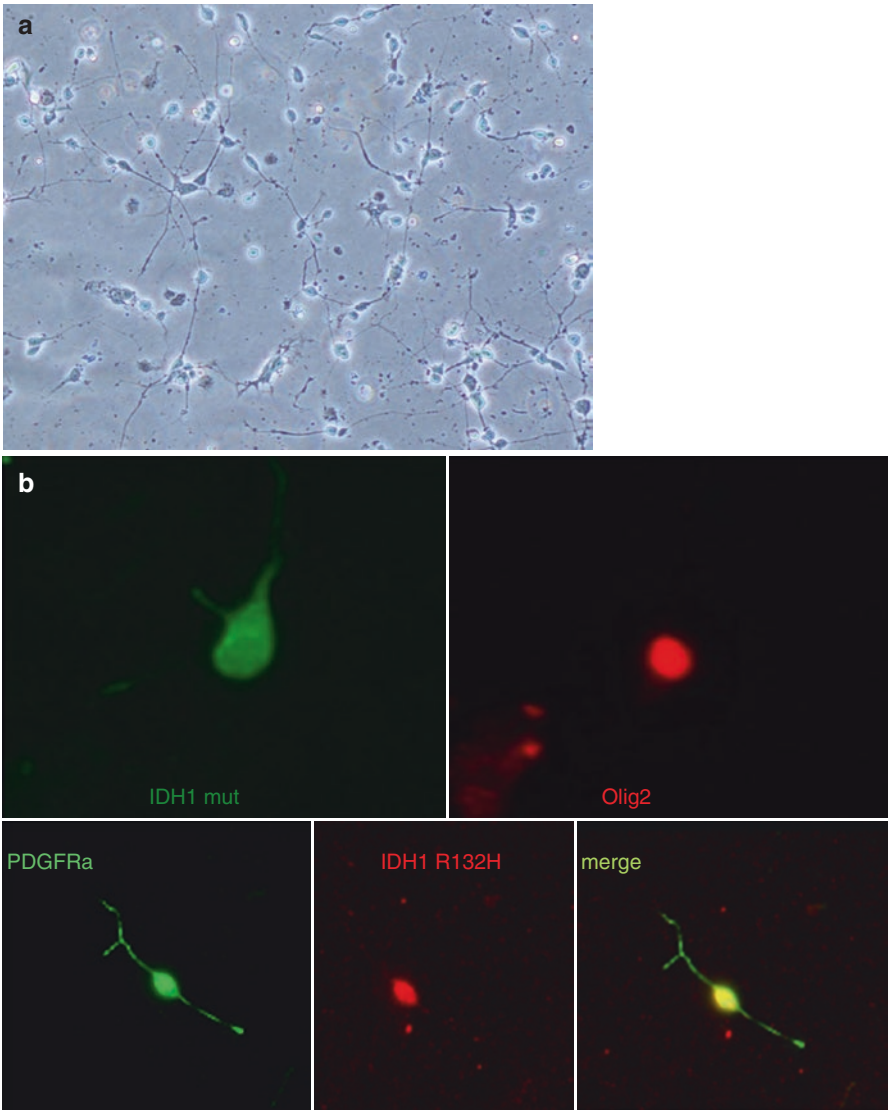


**Fig. 7.1** (**a**) Photograph of a grade II diffuse glioma culture maintained 2 weeks after resection. (**b**) Detection of cells expressing the mutated form of IDH1 with R132H specific antibody. Co labelling with markers of OPC cells (OliG2 and PDGFRa) are presented

However, no or very limited proliferation was observed and cells could not be amplified. This may be due to the propensity of DLGG cells to undergo senescence in vitro [16]. However, interesting cell lines have been isolated from grade III gliomas. In 2010, two cell lines (BT054 and BT088) with IDH1 mutation and 1p19q deletions were isolated from grade III oligodendrogliomas [17] and in 2012, the BT142 cell line was derived from a grade III oligoastrocytoma. BT142 has aggressive tumor-initiating capacity in orthotopic xenografts [18]. Other groups isolated

three cell lines with 1p19q deletions (OligPC40, OligPC49, Hs683) from grade III oligodendrogliomas [19, 20]. Additionally, three less genetically-characterized cells lines were isolated from oligodendrogliomas in 2003 [21].

### *7.2.2 Animal Models*

Although animal models for DLGGs have been developed [22], these models do not include the classical mutations found in these tumors in man (notably IDH1, ATRX mutations and 1p19q codeletions). Therefore, the relevance of these models for studying DLGG dissemination remains to be established. A brain-specific IDH1 R132H conditional knock-in mice using the nestin-Cre promoter was generated in 2012 [23]. However as the nestin promoter is active early during development (E10.5), mice died shortly after birth as the result of massive hemorrhage within the cerebral hemispheres and cerebellum. Analysis confirmed the lack of cerebral development and the presence of large cavities in mutant brains so the relevance of these animals for low grade gliomagenesis was very limited. New transgenic mice enabling cell and time-specific expression of mutated IDH1 are under construction in several labs and these will be very useful tools to model DLGG. In addition to these genetic models, the above-mentioned cell lines grafted intracranially can generate useful models to study OG or AG dissemination even if they are derived from grade III and not grade II tumors. For DLGG tumors which cannot be amplified in vitro, serial grafts in mice could be an alternative to propagate these tumors. This has been demonstrated for a human anaplastic oligodendroglioma carrying mutations for FUBP1, CIC, and IDH1 [24].

### *7.2.3 Tools*

Considering the diversity and the complexity of glioma migration modalities, multiple assays (see, for instance [25–28]) have been used to model high-grade glioma invasion in vitro. In contrast, very few studies aimed at exploring DLGG cell migration in vitro [29–32]. An original model developed by Colin et al. used freshly obtained tumoral explants (500 $mm^3$) which they placed on poly-D-lysine-coated coverslips to analyze glioma cell migration [30]. This study revealed that OG (grade II and III) explants tended to generate few migrating cells. A more sophisticated approach (slice assay) was used by Palfi et al. [32] and de Boüard S [31] who implanted DII-labeled glioma fragments into 400-mm-thick slices of 7 days-old mice brains. In this organotypic assay, invasive glioma cells showed patterns of dissemination and phenotypes similar to those observed in vivo. This assay allowed a quantitative analysis of the invasive potential of gliomas of different types and grades.

As glioma dissemination can occur through migration along nerve fibers, several assays have been designed in vitro to model this phenomenon. One elegant method uses long retinal axons from embryonic chicken which are seeded with glioma cells and which are then visualized by videomicroscopy [27]. Synthetic fibers are also now commonly used. They offer several possibilities of modification regarding their stiffness, their diameter and can be functionalized with extracellular matrix proteins such as laminin [33–36]. The use of such nanofibres has also been considered as a potential therapeutic approach to guide glioma cells toward a cytotoxic hydrogel [36]. Microfluidic chambers and topographic patterns consisting of regular, parallel ridges are also used to study high grade glioma cell migration [37, 38]. Of note, analysis of tumor single-cell migration using high grade glioma patient resections could reveal different cell behavior between patients and predicts outcomes [37]. These different approaches could possibly be used for studying DLGG tumors so as to reveal inter patient heterogeneity. Another technique to be considered as a powerful tool to study DLGG dissemination is intravital imaging. In this approach, fluorescent glioma cells are grafted intracranially and visualized with biphotonic microscopy [39]. Combined with animals expressing fluorescent proteins in specific cell types such as vessels or microglia, this technique can reveal close interactions between glioma cell and other cell types in their environment.

Finally, database and bioinformatics tools are becoming very important and fast growing tools for studying glioma dissemination. For instance, the Ivy Glioblastoma Atlas Project (http://glioblastoma.alleninstitute.org) explored the anatomic and genetic basis of glioblastomas at the cellular and molecular levels. Of special interest, this database contains cellular resolution images of in situ hybridization tissue for several hundred of genes. Gene expression maps within the tumors are provided and this enables identification of genes which are differently expressed at the leading edge or around the vessels. Generalization of such approach in the context of DLGG would certainly provide useful insights on their dissemination.

## 7.3 2-Dissemination of DLGG: Influence of Location and Genetics

Gliomas have a propensity to be diffusely infiltrative, and it is now known that these migratory cells are refractory to conventional therapy, which may contribute to treatment failure [15, 40]. Investigation of growth patterns is therefore fundamental to understand the cellular interactions and tissue organization of these tumors. Glioma cells appear to invade the normal tissue in three main ways: [2, 41]: (1) migration along the nerve fibers which possibly leads to the perineuronal satellitosis (i.e., clustering of neoplastic cells around neurons) frequently observed in OGs, (2) migration along the vessels, and (3) cellular accumulation and spread through meninges. Data suggest important differences in the mode of invasion between AG and OG cells as a result of differences in genetic alterations, cellular phenotypes, or/and brain locations.

Glioma spatial organization could be divided in three patterns: type I (solid bulk tumor), type II (solid tumor with a diffuse halo of infiltrating cells), and type III (diffuse cloud of cells, no solid bulk) [42]. DLGG mainly comprise type II and III structures. Using an assay where tumors fragment are placed in young rodent brain slices, Palfi et al. [32] found was a clear differences between OGs and AG. OGs tended to be less invasive than astrocytomas and grew as circumscribed tumoral masses. In contrast, astrocytomas were more infiltrative. Further investigations on the correlation between molecular alterations and the in vitro growth patterns established that tumors with 1p19q loss were less invasive in this assay, which is very consistent with the prominent association of this genomic alteration with OGs. They also observed that there was no overt difference between grade II and grade III glioma invasion in this assay. OGs with 1p19q codeletion show a proneural phenotype characterized by a high level of expression of genes which are classically expressed during central nervous system development and in neuronal cells such as alpha-internexin [43]. In addition, electrical activity including action potentials has been described in OG cells [44]. Thus, it is possible that somehow this neuronal-like phenotype may endow the cells with a less invasive capacity compared to astrocytomas.

With regard to localization, DLGG showed a constant relationship with the cortex and a larger volume when they came in contact with the ventricles [45]. OG tumors have a propensity to arise in the gray matter or superficial white matter most commonly in the frontal lobe, but oligodendrogliomas may also arise in other regions of the central nervous system. OG imaging often present as an oval or round sharply marginated mass. Persson et al. [46] reported that 1p/19q-deleted OGs preferentially arose in white matter regions, while low-grade astrocytoma tumors were more frequently associated with the lateral ventricles. Chen et al. [47], reported seven cases located in the grey matter without definite involvement of white matter and 13 cases initially located in the junction of grey and white matter. They propose that glioma invasion may be facilitated by white matter fiber tracts and restricted by grey matter. Destruction of the grey matter could favor access to fibers and dissemination of tumoral cells.

Genetic alterations and probably epigenetic modifications impact the mode of DLGG dissemination. For instance, Jenkinson et al. [48] reported that for OG, tumors with infiltrative growth were more likely to have intact 1p/19q, and those with mixed or solid growth patterns were more likely to have 1p/19q loss. However establishing correlations between the magnetic resonance imaging patterns and the genetic alterations found in DLGG turned out to be challenging and conflicting due to the small number of cases examined and the paucity of genetic data. However, over the last 5 years, one major advance in the field has been obtained by high throughput sequencing of DLGG and the constitution of clinically-annotated database such as REMBRANDT and TCGA (http://betastasis.com/glioma/rembrandt/; http://betastasis.com/glioma/tcga_gbm/). These studies have unraveled many genes and pathways which are altered in DLGG [49–54]. These results have also led to a new WHO histomolecular classification of DLGG published in 2016 [55] where molecular alterations prevails over histological characteristics. Gliomas subtypes

such as oligoastrocytomas and GBMO (glioblastoma with oligodendroglioma component) are now mainly defined molecularly [56, 57]. Remarkably, integrated multi-omics analysis of OG revealed previously unrecognized heterogeneity among 1p/19q co-deleted tumors and identified three new subgroups [53]. It is anticipated that such deep characterization of DLGG will lead to new studies correlating MR and genetically-defined DLGG to shed new light on the still-obscure heterogeneous modalities of DLGG dissemination subtypes.

## 7.4 3-Molecular Components Driving DLGG Migration

In DLGG, oligodendroglioma and astrocytoma cells have different morphology, express different genes and have different dysregulated pathways. This probably account for their different mode of dissemination in the brain. Indeed, it has been found that mutations in p53 and ATRX [alpha-thalassemia/mental retardation syndrome X-linked] are mainly found in astrocytomas [58], whereas genome-wide sequencing has recently revealed the frequent alteration of Fubp1, Tert and Cic genes in OGs [59]. How these alterations impact on cellular migration is totally unknown, but this will certainly be a major subject of investigation in the next decade.

Proteins and proteoglycans involved in migration during brain development appear to be differentially expressed between oligodendroglioma and astrocytoma tumors. For examples Vim, Id4, FABP7, Connexin 43, TrkA/B/C brevican, neurocan, tenascin-C, versican, Chi3L1, CD44, Gap43 are preferentially expressed in AG [60–65] whereas the phosphatase receptor rPTPbeta/zeta, Olig2 and PDGFRa are preferentially expressed by OG [64, 66]. It is likely that these different entities could give tumoral cells different ability to migrate along the vascular network, the nerve fibers or the subpial space.

Of special interest is CD44, a receptor for hyaluronic acid (HA, also called hyaluronan). Hyaluronic acid is an anionic, non-sulfated glycosaminoglycan widely distributed in neural tissues. Radotra and collaborators [67, 68] used a Matrigel system to study glioma cell migration and found that adding HA to the Matrigel increased migration in a dose-dependent manner. They further investigated the mechanisms by which glioma cells migrate in HA-enriched Matrigel and found that CD44 was involved in this process, as blocking CD44 with a specific antibody led to a significant reduction in glioma cell migration. This study was done in vitro using an anaplastic astrocytoma-derived cell line. Nevertheless, given the preferential migration of OG cells along HA-rich white matter fibers, it seems likely that CD44s and HA play a role on OG migration in vivo as well. As HA inhibits oligodendrocyte maturation [69], it can be hypothesized that HA participates in the dissemination of OG cells by maintaining them in an undifferentiated precursor-like state which is prone to migration.

In 2006, McDonald et al. used OG tumor sections from 177 patients to identify the genetic consequences of the 1p36 deletion observed in 60–80% of OGs [70].

They identified SHREW1 (also known as AJAP1) as the unique gene present in the deleted region and found that OG cells from 30 patients showed significantly reduced SHREW1 expression as compared to normal tissue. SHREW1 is a membrane protein involved in adherent junctions. The authors demonstrated that overexpression of SHREW1 in a GBM cell line (U251) inhibit cell adhesion and migration, and thus propose that loss of its expression in OD may promote cell dissemination.

Gap junctions and connexin protein are increasingly regarded as important players in high grade glioma dissemination and this probably applies in DLGG [71]. One remarkable discovery is the presence, in low and high grade astrocytomas, of a network of microtubes interconnecting tumoral cells [65]. These microtubes can be as long as 500 μm and in a mice model for astrocytoma can reach the contralateral hemisphere. Cells are interconnected by this microtubule network via gap junctions which express connexin 43. The growth cone associated protein Gap-43 appears to have a central role in the formation of these microtubules. Very interestingly, these protrusions infiltrate the normal brain at the invasive front and are used for movement of cell nuclei. This microtube network has been detected in low grade astrocytomas with an IDH1 R132H mutation whereas no such network was found in 1p19q deleted OG. This highlights the difference in astrocytomas and oligodendrogliomas and their mode of dissemination.

Another class of protein which are gaining interest in DLGG migration are galectins. Galectins is a family of mammalian lectins with specificity to beta-galactosides. They are involved in growth-regulatory mechanisms and cell adhesion of several cancers. In the normal brain, Galectin-3 maintains cell motility of precursor cells from the subventricular zone to the olfactory bulb [72]. Galectin-1 is preferentially expressed at the tumor margin and promotes glioblastoma cell invasion [73]. Very interestingly, Galectin-1 is also involved in glioma immune escape [74] by suppressing NK immune surveillance [75]. Using the Hs683 1p19q deleted oligodendroglioma cell line, Le Mercier et al. [76] demonstrated that loss of Galectin 1 reduce chemoresistance, neoangiogenesis, and migration of these cells suggesting that in addition to GBM, this lectin could also have an important role in DLGG dissemination.

The use of high throughput techniques combined with functional assays will certainly identify new proteins involved in DLGG migration. For instance, based on the observation that OGs with 1p19q are less aggressive than their non-deleted counterparts, Rostomily et al. [77] undertook the comparative proteomics of OGs with or without 1p19q deletion. They found that about 10% of the differentially expressed genes were involved in invasion/migration. The list of genes presented in their Appendix II could be used to decipher the differential migratory properties of OG with or without 1p19q deletion and open new lines of investigations on the invasive properties of OG. In 2015, high throughput sequencing in OG with 1p19q deletion [54], led to the identification of mutations in SASH3 and GDI1 genes. The protein encoded by SASH3 gene contains a Src homology-3 (SH3) domain and a sterile alpha motif (SAM), both of which are found in proteins involved in cell signaling and this protein may function as a signaling adapter protein. GDI1 genes codes for a Rab GDP dissociation inhibitor alpha which is expressed in neural tis-

sues. Paradoxically, overexpression of SASH3 and GDI1 wild-type proteins in oligodendroglioma cell lines enhanced their migration in vitro compared to mutated proteins.

In addition to the endogenous mechanisms pertaining to tumoral cells in DLGG migration, one must also consider the influence of the extracellular matrix [ECM] and the interactions with neighboring tumoral and non tumoral cells. In fact, cells at the invasive edge in high grade and DLGG upregulate metalloproteases (MMP2, MT1-MMP) to degrade or modify their environment [78]. These cells also express proteins such as angiopoietin-2 which can impair formation of the blood-brain barrier [79] and secrete their own extracellular matrix protein such as laminin [78]. The mutated form of IDH1 found in the majority of DLGG may also have a direct impact on the structure of ECM as D-2-hydroxyglutarate produced by the mutant IDH1 leads to reduction of prolyl-hydroxylation of collagen, causing defect in its maturation and basement membrane aberrations [23]. Other component of the ECM such as CSPGs (glycosylated chondroitin sulfate proteoglycans) are also to be considered as central actors regulating dissemination. Silver et al. found that noninvasive lesions are associated with a rich matrix enriched in CSPGs, whereas these are essentially absent from diffusely infiltrating tumors [80]. CSPGs may induce migration of resident reactive astrocytes out of the tumor mass which results in encapsulation of noninvasive lesions, acting as a barrier to directly inhibit tumor dissemination.

With regards to DLGG cell interactions with non-tumor cells, very little is known. In the grey matter, OG cells closely interact with neurons and accumulate to generate the so-called peri-neuronal satellitosis [41, 81]. In high grade gliomas, neuron activity has been shown to release the synaptic protein neuroligin-3 (NLGN3) which acts as a mitogen for glioma cells [82]. If a similar signaling occurs in low grade OG remains to be fully demonstrated. In the white matter, OG are entrapped in a fibrillary background composed of axons and fibrillary reactive gliosis [81] suggesting close interactions between reactive astrocytes and glioma cells. Indeed, in a mouse model for glioma [83], Sin et al., reported that reducing coupling of reactive astrocytes with glioma cells by knocking down the gap junction protein Cx43, resulted in reduction of glioma spreading into the brain parenchyma [83]. Using a vitro model and the C6 glioma mouse cell line, Oliveira et al., also reported that heterocellular glioma cells/astrocytes interactions through gap junctions support tumor cell migration [84]. These results indicated an important role for reactive astrocyte in the formation of an invasive niche which could possibly manipulated to reduce migration.

One last interesting possibility to consider is that DLGG cell could change phenotype depending on their environment and can adopt a new gene expression profile adequate for migration in a given environment. Indeed, activation of BMP signaling induces astrocytic differentiation of clinically-derived oligodendroglioma cells [19]. Conversely, in a mouse model for glioma, PDGF autocrine stimulation could dedifferentiates astrocytes to induce oligodendrogliomas and oligoastrocytomas [85]. In addition, it appears that oncogenic signaling is dominant to cell of origin and can dictate astrocytic or oligodendroglial tumor development from oligoden-

drocyte precursor cells [61]. For instance, activation of K-Ras and Akt in oligodendrocyte progenitor cells led to astrocytic tumors when combined with p19(Arf) loss [61]. This interconversion between astrocytoma and oligodendroglioma might occur as a result of a switch between master transcription factors governing astrocyte or oligodendrocyte fate. Indeed, the mutual antagonism between Sox10 and NFIA transcription factors which regulates the diversification of glial lineages during development, may also control the formation of astrocytoma vs oligodendroglioma subtypes [86]. Further analysis is necessary to ascertain whether this phenotypic interconversion occurs in patient tumors.

## 7.5 4-Insights from Oligodendrocyte Progenitor Migration

Given the suspicion that OG tumors are derived from the tumorigenesis of oligodendrocyte precursor cells (OPCs) [87], it is likely that OGs share some common molecular properties with OPCs. So as to propose new potential targets worthy of investigation as potential OG migration drivers, we will list and review the main pathways known to direct OPC migration and propose how these data could be used and applied to research on OG invasion.

Several categories of molecules are involved in OPC migration: (a) long-distance signaling proteins play a chemoattractive or chemorepelling effect on OPCs, thus controlling their direction; (b) proteins of the extracellular matrix provide a beneficial or repulsive substrate to migrating cells; and (c) structural proteins expressed by the migrating OPC provide a favorable cytoskeleton configuration. A comprehensive review on OPC migration provides substantial information on the signals involved in this process [88, 89]. Of these signals, we present here the ones that are likely to be shared by OGs.

The first obvious signal involved in OPC migration and likely to play a role on DLGG survival is PDGF. In OPCs, PDGF-induced migration is mediated by Cdk5, involving the phosphorylation of the non-receptor tyrosine kinase Fyn [90]. Cdk5 phosphorylates the WAVE2 protein which forms a multiprotein signal transduction complex binding to receptor kinases and actin, with an effect on cell shape and motility [91]. Overexpression of a WAVE2 construct where the site of phosphorylation has been mutated leads to reduction of PDGF mediated migration of OPC. WAVE2 has been shown to be involved in cellular migration [92] and plays a pivotal role in melanoma cell migration [93] and other cancer metastasis [94]. Given the role of WAVE2 on OPC migration [90] and on several types of cancers, WAVE2 is likely to be involved in DLGG invasion. Comparative proteomics between OGs with or without 1p19q deletion identified WAVE3 as a protein significantly more expressed in tumor cells with deletion than in cells without deletion [77]. Proteins of the WAVE (or WASF) family could thus supply informative clues on the migratory properties of DLGG.

The best characterized chemotactic signals driving OPC migration during development are semaphorins (3F and 3A) and netrin-1 [95]. Indeed, semaphorin 3A was

shown to have a repulsive effect on OPCs in explants, whereas semaphorin 3F and netrin-1 attract OPCs. One study investigated the expression of seven class-3 semaphorins, SEMA4D, VEGF, and the NRP1 and NRP2 receptors in 38 adult glial tumors and showed that Sema3A expression was similarly expressed in low-grade and high-grade gliomas [96]. Sem3A has been shown to promote dispersal of GBM cells [97] and it would be interesting to investigate its role on DLGG migration. Interestingly, Nasarre et al. showed that Sem3A can have either a chemorepellent or a chemoattractant effect on GBM cell lines depending on the present partners [98], thus making it a prime target for glioma migration investigations.

One important point to emphasize is the specific pattern of migration adopted by OPCs depending on their localization in the brain. Indeed, using heterotypic quail/chick xenografts, Olivier et al. [99] demonstrated that OPCs transplanted from the rostral to caudal brain domain and vice versa changed their migratory properties. Their neat approach identified several routes of migration followed by OPCs depending on their original location and emphasized the key role of environmental cues upon OPC migration. Based on these data, it is easily predictable that gliomas arising from OPC tumorigenesis might comply with the same rules. This hypothesis is consistent with a recent study on GBM [100] showing that SVZ derived or cortex-derived GBM cells (GBM6 and GBM9, respectively) present different invasive properties. It is thus necessary, when studying DLGG dissemination, to report precisely their site of appearance, so as to be able in the future to predict the more likely pattern of diffusion of a tumor based on its initial localization in the brain.

Finally, in 2016, Tsai et al. [101] demonstrated that during development, OPCs use the vasculature as a physical substrate for migration. They associate with the vascular endothelium surface of nearby blood vessels and can even jump between vessels. The Wnt-Cxcr4 pathways was involved in these OPC-endothelial interactions. Considering that glioma cells often reactivate developmental programs to grow and disseminate, it is likely that a similar process occurs in oligodendrogliomas.

## 7.6 Issues To Be Addressed

There are several issues that would deserve further explorations in order to clarify the means by which DLGG cells disseminate into the brain: (1) Identifying infiltrated tumoral cells in the normal tissue: Diffuse low-grade tumoral cells exhibit only a mild nuclear atypia so they are difficult to distinguishing from normal cells in infiltrated tissues. So until recently it was very difficult to delimit the actual dissemination of tumoral cells which probably extend far beyond MRI-defined abnormalities. Indeed, using serial stereotactic biopsies and MIB1/Olig2 staining, Pallud et al. [102] found that tumoral cells can be observed at sites up to at least 15 mm beyond brain imaging aberrations. A major advance in the field is the development of an antibody recognizing the mutated form of the IDH1 enzyme [R132H] which is commonly found in DLGGs [103]. This antibody allows the precise detection of isolated tumoral cells by immunohistochemistry. Using this tool, Sahm et al. analyzed the

infiltration pattern of three anaplastic OGs and considering the widespread dispersion of tumoral cells concluded that gliomas should be addressed not as a focal but as a systemic disease [104]. Similar analysis performed on DLGGs would reveal the actual extends of the tumor. (2) Distinguishing migratory versus non-migratory glioma cells: The tumoral tissue is composed of cells in different states (for instance, proliferative vs. quiescent cells) and it is likely that in DLGG, only a fraction of the cells are actually invading the normal tissue. It will be very useful to uncover reliable markers to identify and purify these cells in order to analyze precisely the molecular components and active pathways involved in this process. Whereas such markers are starting to be uncovered for high-grade gliomas, thanks to differential microdissection of the tumor core versus invasive margin [105], such tools are not yet available for DLGGs. In addition, it appears that DLGGs exhibit two main patterns of spatial organizations: solid tumor plus a diffuse halo of infiltrating cells or dispersed cloud of cells with no solid bulk [42, 81]. The molecular and cellular mechanisms behind this heterogeneity of patterns are not documented and warrant further exploration. (3) Differential migration in the white and gray matters: Brain white and gray matters differ in many aspects (cellular composition, vascular density, organization, biochemical composition) so it is expected that glioma cells invade these two components in a different way. In particular, the white matter contains myelin which constitutes the insulating sheath for neurons but which is also a non-permissive substrate for neurite growth, attachment, and spreading of a lot of cell types. Interestingly, Amberger et al. [106] found that low-grade astrocytomas appeared to be strongly sensitive to inhibitors present in myelin, whereas OGs were able to spread and migrate on this substrate. Using the C6 glioma line which showed no spreading inhibition on myelin, this group went on to show that these cells expressed the MMP14 metalloprotease (MT1-MMP). This protease degraded the Nogo protein, a major inhibitor present in myelin [107] and allowed glioma cells to spread on this substrate [108]. It is anticipated that such a mechanism might operate for low-grade OG cell dissemination, but this remains to be formerly demonstrated. In the normal brain, oligodendrocytes are closely associated with nerve fibers, whereas astrocytes interact closely with vessels to form the blood–brain barrier. Therefore, spreading of OGs along nerve fibers and of astrocytoma cells along vessels could represent a pathological counterpart of the normal situation.

## 7.7 Future Prospects

Controlling DLGG cell dissemination in the brain would represent a major advance for treating these diseases as the time to tumor progression after surgery is thought to depend on the number of glioma cells infiltrating the resected margin [109, 110]. In addition, in the non-pathological brain, neural precursor cells are produced and migrate in at least two locations: the hippocampus and the subventricular zone. Therefore, any treatment aiming at reducing low-grade glioma cell invasion may potentially interfere with these processes and may have serious side effects. It is

thus central to identify molecular targets and/or signaling pathways specific to tumoral cells so as to spare normal cells. As described before, useful insights could be obtained by exploring both the migration of normal and pathological brain cells to find a potential glioma Achilles' heel to target. Not only migrating cells represent deadly infiltrated snipers sneaking into the brain, but these cells may also be more resistant to treatment, as in high-grade gliomas, they may be less prone to apoptosis apoptotic [40, 111]. Hence, deciphering the molecular and cellular basis for dissemination of diffuse low-grade gliomas represents a major goal to find innovating cures.

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# Chapter 8
# The Genomics of Diffuse Low-Grade Gliomas

**Maleeha Ahmad, Robert J. Weil, and Nicholas F. Marko**

**Abstract** The goal for this chapter is to present a comprehensive discussion on the current literature regarding the genomics of diffuse low-grade gliomas in the light of the recently published 2016 edition of the WHO Classification Tumors of the Central Nervous System with reference to the current literature on molecular genetics of these glioma entities.

**Keywords** Low-grade glioma • Diffuse astrocytoma • Oligodendroglioma • Oligoastrocytoma • IDH-mutant • 1p/19q co-deleted • TP53 • ATRX • TERT promoter

## 8.1 Introduction

This chapter is written in light of the newly published 2016 4th edition of the WHO Classification Tumors of the Central Nervous System [1]. Outdated terminology has been avoided and the authors' emphasis here is to highlight the current increased use of integrated molecular markers as parameters to delineate objective diagnostic entities of diffuse astrocytic and oligodendroglial tumors.

The category of diffuse glioma refers to astrocytic tumors (WHO grade II and III), oligodendrogliomas (grade II and III), oligoastrocytomas (WHO grade II and III), glioblastomas and pediatric diffuse gliomas. Low-grade gliomas have historically and histopathologically referred to WHO grade II tumors. Additionally, the 2016 WHO Classification Tumors of the Central Nervous System has grouped together all diffuse gliomas on the basis of their shared IDH1 and IDH2 genetic status, thereby providing a prognostic grouping of the tumors. Thus, the current WHO classification is based on combined phenotypic (histological) and genotypic classification, yielding integrated diagnoses. We also note the addition of the designated term NOS

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which refers to lesions that cannot be classified into any precisely defined groups and hence do not have a specific code assigned to them.

This chapter is divided into the three adult groups of diffuse astrocytic and oligodendroglial tumors with a consistent sub-grouping of the molecular genomics for each of the tumor types:

1. Diffuse astrocytoma IDH-mutant
2. Oligodendroglioma IDH-mutant and 1p/19q-codeleted
3. Oligoastrocytoma NOS.

## 8.2 Diffuse Astrocytoma IDH-Mutant

This is defined by the 2016 WHO Classification Tumors of the Central Nervous System as "A diffusely infiltrating astroscytoma with a mutation in either IDH1 or IDH2 gene, with the diagnosis supported by presence of ATRX and TP53 mutation" [1]. Diffuse astrocytomas correspond to WHO grade II and have an intrinsic capacity for malignant progression to IDH-mutant anaplastic astrocytoma and eventually to IDH-mutant glioblastoma.

### *8.2.1 Epidemiology of Diffuse Astrocytomas*

Diffuse astrocytomas account for 11–15% of all astrocytic brain tumors with a slight male predominance male: female 1.3:1 [2]. Genetic susceptibility for diffuse astrocytomas is seen in patients with inherited TP53 germline mutations (such as the Li-Fraumeni syndrome and Ollier type multiple enchondromatosis) [2].

### *8.2.2 Prognostic and Predictive Factors for Diffuse Astrocytomas*

The EORTC European Organization for Research and Treatment of Cancer [EORTC] trials [eotrc.org/clinical-trials 22,844 and 22,845] showed the following clinical characteristics were associated with a poor clinical outcome:

- Patient over 40 years of age
- Pre-operatively neurological deficits
- Largest tumor diameter being greater than 6 cm and crossing the midline
- Histology of astrocytoma, with gemistocytic astrocytoma correlating with a poorer prognosis.
  - Gemistocytic astrocytomas are approximately 10% of all WHO grade II diffuse astrocytomas, with a higher male: female ratio of 2:1.

  - This is a variant of the IDH-mutant diffuse astrocytoma with a high frequency of TP53 mutations >80% of cases with progression to anaplastic astrocytoma and IDH-mutant glioblastoma, more commonly than other diffuse astrocytomas [3].

- IDH -1/2 mutations have a favorable course compared to IDH-wildtype tumors, in particular those which have a genotype of 7q gain and 10q loss
  - IDH-wildtype diffuse astrocytoma is rare and should be considered a provisional entity for classification into other tumors with additional genetic analyses.

### *8.2.3 Gain of Function Mutations*

IDH mutations are observed in both solid tumors [gliomas, chondrosarcomas, colorectal cancer and melanoma] and hematopoietic neoplasms [most commonly acute myeloid leukemia] [4]. IDH mutations are consistent and frequent in diffuse astrocytomas (88%), oligodendrogliomas (79%) and oligoastrocytomas (94%), as well as in the secondary glioblastomas arising from them [5].

The IDH1 gene (2q33) and IDH2 gene (15q26) encode the enzyme isocitrate dehydrogenase 1 of the cytosolic citric acid cycle. IDH1 and IDH2 are homodimeric enzymes that catalyze the conversion of isocitrate to α-ketoglutarate and produce nicotinamide adenine dinucleotide phosphate NADPH. Mutations in IDH1 occur at arginine 132, with mutations in IDH2 occurring at arginine 172 or arginine 140 (analogous to R132H in IGH1). While both IDH1 and IDH2 mutations occur in diffuse low-grade gliomas, IDH2 mutations are much less common than IDH-1 [6].

Glioma associated IDH-1 and IDH-2 mutations result in a gain of function to the metabolic isocitrate dehydrogenase enzymes 1 and 2. The mutant protein loses the normal enzymatic activity and starts production of oncometabolite R-2-hydroxyglutarate, which consumes NADPH. R-2-HG also competitively inhibits α-ketoglutarate dependent dioxygenases, with subsequent epigenetic inhibition of histone lysine demethylases and 10–11 transolocation (TET) family of 2 5-methyl cytosine hydroxylase [7, 8]. Thus, mutant IDH changes the inherent redox environment by altering the ratio of NADPH to NADP, with NAD depletion as a metabolic susceptibility characteristic of IDH-1 mutant tumors [9, 10].

IDH mutations are thought to be among the first in genetic alterations in WHO grade II diffuse gliomas. Watanabe et al. analyzed over 300 gliomas and showed that, in 51 cases, IDH1 mutations were early gliomagenesis events. No cases of IDH1 mutation occurred after acquisition of TP53 mutation or loss of 1p/19q [5]. Additionally, IDH1 R132H mutations has been shown to be the only mutation consistently present in both initial and recurrent glioma samples [11, 12].

The presence and identification of the oncometabolite R-2-HG leads us to the current hypothesis of IDH mutations being oncogenic [13]. Restricted cellular differentiation and DNA hypermethylation are hallmarks of mutant IDH-associated

tumors and are thought to occur from the R-2-HG effects on inhibition of histone demethylation and DNA hypermethylation [4, 14]. We await the results of trials of IDH-mutant cells showing increased sensitivity to drugs targeting histone modifications, as shown by progressive accumulation of histone methylation in R-2-HG producing IDH-mutant astrocyte [4].

Gliomas have a CpG island methylator phenotype (G-CIMP) with distinctive and extensive epigenomic aberrations. These have been directly correlated to IDH1 mutations with widespread hypermethylation in gene promoter regions silencing the expression of cellular differentiation factors. The epigenomic alterations resulting from mutant IDH1 activate key gene expression programs in G-CIMP positive proneural glioblastomas and are predictive of improved survival [15, 16]. Accordingly, IDH mutation and G-CIMP maintain the glioma cells of origin in stem cell-like physiological states more likely to tumorigenesis [16].

Gain of function IDH mutations refer to hypermethylation at the cohesin and CTCF binding sites. CTCF (CCCTC-binding factor) is a transcription methylation-sensitive insulator protein and the loss of CTCF at domain boundary results in an aberrant interaction with receptor tyrosine kinase gene PDGRFRA platelet derived growth factor receptor $\alpha$, which is downregulated. In IDH wild-type gliomas the PDGFRA is upregulated and proliferation of tumorigenesis occurs [17].

### *8.2.4 Loss of Function Mutations*

The vast majority of IDH-mutant diffuse astrocytomas (and grade III anaplastic astrocytomas and grade IV glioblastomas) harbor class-defining loss of function mutations in TP53 and ATRX.

Watanabe et al. showed that nearly two-thirds of diffuse astrocytomas that contained a TP53 mutation also harbored an IDH1 mutation [5]. IDH and TP53 mutations are strongly coupled to inactivating alterations in ATRX. Almost all (98%) infiltrating gliomas with an IDH1 mutation and ATRX mutation have an ALT (alternating lengthening of telomeres) phenotype. Diffuse astrocytomas, therefore, have the molecular signature of an IDH 1/2 mutation, with TP53 and ATRX mutations and ALT phenotype [6]. The most frequent type of diffuse astrocytoma is the molecular combination of ATRX loss and IDH mutation [16]. The genomic instability of IDH-mutant diffuse astrocytomas is reflected in characteristic DNA copy number abnormalities, including low-level amplification events involving oncogenes MYC and CCND2 in mutually exclusive subsets [18].

TP53-dependent chromatin remodeling factor ATRX (α thalassemia/mental retardation X-linked) has been linked to the nuclear processes of gene expression, DNA repair, replication and recombination [19]. ATRX encodes an essential chromatin remodeling protein (ATRX), the deficiency of which has been associated with epigenomic dysregulation and telomere dysfunction [18, 19]. The loss of ATRX function has been shown to cause both meiotic and mitotic defects with chromosomal alignment in spindle formation [18, 20].

The association of ATRX and the ALT (alternating lengthening of telomeres) phenotype is important, as telomerase is not detected in 10–15% of cancers, ATRX mutations seem to induce an abnormal telomere maintenance mechanism known as alternative lengthening of telomeres [20]. Distinct telomere maintenance mechanisms appear to be required for the pathogenesis of all diffuse gliomas. These can be mediated by activated telomerase or alternative lengthening of telomeres. ATRX is lost in 90% of in vitro immortalized ALT cell lines and therefore a suppressor of the ALT pathway [19, 21]. Wild-type ATRX expression results in ALT pathway activation in somatic hybrids. ALT is also associated with extensive genomic rearrangements, marked micronucleation, altered double-strand break repair, and defects in the G2/M checkpoint [21].

ATRX deficiency is associated with generalized genomic instability and may induce p53-dependent cell death [18]. TP53 mutations in diffuse astrocytoma enable tumor cell survival in the setting of ATRX loss, as cells lacking ATRX are more sensitive to DNA damaging agents and result in apoptotic mechanisms occurring even during peak proliferation [22, 23].

## 8.3 Diffuse Astrocytoma NOS

The entity "diffuse astrocytoma NOS" refers to a tumor *"with morphological features if diffuse astrocytoma in which the IDH status has not been fully assessed"*. Importantly, this term is used in the WHO Classification of Tumors of the Central Nervous System as a separate histopathological entity from IDH-mutant diffuse astrocytomas.

## 8.4 Pediatric Diffuse Astrocytoma

Adult mutations in IDH1/2, ATRX and TP53 are generally not found in pediatric diffuse astrocytomas [24]. There are distinct genetic profiles of diffuse astrocytomas in children with multiple permutations of alterations in the following genes: MYB, MYBl1, BRAF, RAF1 and FGFR1 [25].

## 8.5 Oligodendroglioma IDH-Mutant and 1p/19q-Codeleted

The 2016 WHO Classification Tumors of the Central Nervous System defines this entity as "*a diffusely infiltrating, slow-growing glioma with IDH-1 or IDH-2 mutation and codeletion of chromosomal arms 1p and 19q"*. IDH-mutant and 1p/19q codeleted oligodendrogliomas characteristically extend into the adjacent brain parenchyma in a diffuse manner and histologically correspond to WHO grade II tumors.

### 8.5.1 Epidemiology of Oligodendrogliomas

Oligodendroglial tumors account for 1.7% of all primary brain tumors and 5.9% of all gliomas, with a male to female ratio of 1.3:1 [2, 26]. Most oligodendrogliomas develop sporadically, in terms of gender distribution, age, morphology and grade [1]. Most familial gliomas appear to comprise clusters of two cases suggesting low penetrance, and that the risk of developing additional gliomas has a low likelihood [27]. Isolated cases of familial oligodendroglioma with 1p/19q codeletion and Ki-67 proliferative index of >3% have been reported and are associated with a poor prognosis [28].

### 8.5.2 The Genetic Mutations of Oligodendrogliomas

Since the turn of the twentieth century, oligodendrogliomas have been identified as "the quintessential molecularly-defined brain tumor" [29]. This glioma sub-category has the characteristic 1p/19q co-deletion, with unbalanced translocation between chromosomes 1 and 19 resulting in the loss of the der[1;19] [p10;q10] chromosome, and causing whole-arm deletions of 1p and 19q, with retention of the der[t(1;19)(q10;p10)] chromosome [1, 30–32]. Additionally, 1p/19q codeleted oligodendrogliomas frequently harbor concurrent genetic mutations in IDH1/2, TERT promoter, CIC and FUBP1, with lack mutations in ATRX and TP53.

Similar to diffuse astrocytomas, IDH mutations occur early in within the evolution of oligodendrogliomas, and all 1p/19q codeleted oligodendrogliomas harbor IDH mutations [29, 32]. A majority of these will exhibit mutations of IDH1, with the remaining minority containing mutations of IDH2. The latter occur predominantly in oligodendroglial tumors but infrequently in diffuse astrocytomas [33]. Combined whole-arm loss of 1p and 19q is invariably associated with IDH mutation, thus detection of 1p/19q codeletion in the absence of IDH mutation should raise algorithmic suspicion of incomplete/partial deletions (e.g. poor-outcome IDH-wildtype anaplastic astrocytomas and glioblastomas) [18].

IDH-mutant and 1p/19q codeleted oligodendrogliomas typically retain nuclear expression of ATRX and usually lack widespread nuclear p53 staining [34]. TP53 is usually absent and mutually exclusive with 1p/19q deletion, with mutual exclusivity noted of TP53 mutation and 1p/19q codeletion seen in IDH-mutant gliomas [35]. 1p/19q codeletion was associated with longer overall survival and TP53 mutation with shorter overall survival [36].

Moreover, as described above for diffuse astrocytomas, IDH mutations result in overproduction of R-2-HG. This promotes tumorigenesis by remodeling chromatin, and widespread changes in DNA methylation lead to concurrent hypermethylation of multiple CpG islands [G-CIMP] [15, 16]. As a consequence of G-CIMP, numerous genes may be epigenetically inactivated in oligodendrogliomas. This includes the common tumor suppressor genes CDKN2-A and -B and RB-1 [29–31]. At present, the G-CIMP phenotype appears to be a positive prognostic factor for outcome

of oligodendroglial tumors with possible predictive response to chemotherapy [31]. At the mRNA level, IDH-mutant and 1p/19q codeleted oligodendrogliomas often show a proneural, glioblastoma-like gene expression signature [37]. Thus, the early genetic changes in oligodendrogliomas are IDH mutation, 1p/19q codeletion, and TERT mutation. CIC mutations are noted to occur later in tumor progression [35].

### *8.5.3 TERT Promoter Role in Oligodendrogliomas*

The mutation in the TERT promoter (TERTp-mut) results in enhanced telomerase activity and lengthened telomeres as seen in gliomagenesis [30]. TERTp-mut has been identified in 60.8% of gliomas and globally associated with a poor outcome [38]. Koelsche et al. showed TERTp-mut to be strongly associated with with 1p/19q loss but inversely proportional to ATRX expression and IDH mutations [39]. Thus, TERT promoter mutations are observed in almost all IDH mutant and 1p/19 codeleted oligodendrogliomas but exceptional in IDH-mutant diffuse astrocytomas [40]. The considerable overlap between TERT promoter mutation and 1p/19q codeletion in IDH-mutant gliomas suggests TERT promoter may be useful as a surrogate marker for 1p/19q codeletion.

### *8.5.4 Mutation of CIC Gene in Oligodendrogliomas*

The CIC gene is the homolog of the Drosophila gene capicua on chromosome 19q13.2 and is somatically mutated as a consequence of tumor progression [35, 41, 42]. CIC mutations are associated with oligodendroglioma histology, 1p/19q codeletion, and IDH1/2 mutation [41, 43]. CIC mutated, 1p/19q codeleted tumors have an unfavorable prognosis [26].

### *8.5.5 Mutation of FUBP1 Gene in Oligodendrogliomas*

A smaller subset of the IDH-mut and 1p/19q codeleted tumors carry mutations in the FUBP1 gene [encoding far-upstream element binding protein] on 1p31.1 [35]. FUBP1 mutations are consistently associated with CIC mutations [43], and CIC mutations are universally present in 1p/19q deleted oligodendrogliomas [44]. Allelic losses in the regions of 19q and 1p that harbor CIC and FUBP1 are a common feature of both oligodendrogliomas and oligoastrocytomas [43]. Overexpression of FUBP1 can stimulate MYC expression, the FUBP1-PUF60 protein complex negatively regulates MYC expression [42, 45]. The inactivating mutations of CIC and FUBP1 in a significant proportion of IDH-mut and 1p/19 codeleted oligodendrogliomas may provide insight into the molecular pathogenesis of these tumors.

### *8.5.6 Other Notable Miscellaneous Genetic Mutations in Oligodendrogliomas*

Other genes on 1p and on 19q that may exhibit aberrant promoter methylation and/or reduced expression in IDH-mutant and 1p/19q codeleted oligodendrogliomas include [18, 30, 41]:

1p: CAMTA1, CHD5, CITED4, DFFD, DIRAS3, PRDX1, ATRX, AJAP, TP73
19q: EMP3, ARHGAP35, PEG3, ZNF296.

Approximately half of all WHO grade II oligodendrogliomas and anaplastic oligodendrogliomas show strong expression of epidermal growth factor receptor (EGFR) mRNA and protein in the absence of EGFR gene amplification [46]. The simultaneous expression of the mRNAs for the pre-and pro- forms of EGFR and transforming growth factor alpha indicates the possibility of autocrine-, juxtacrine, or paracrine growth stimulation via the EGFR system.

Elevated expression of PDGFRA seems to be both rare and also independent of 1p/19q codeletion [18]. Vascular endothelial growth factor (VEGF) and its receptors serve as angiogenic factors in oligodendroglial tumors, particularly in anaplastic oligodendrogliomas [46]. Approximately 15% of all oligodendrogliomas mutations have been noted in NOTCH1 pathway [47]. Other less commonly mutated genes include the epigenetic regulator genes (e.g. SETD2) and other histone methyltransferase genes and genes of the SWI/SNF chromatin remodeling pathway. These mutations will continue to be the focus of ongoing research and trials [35, 48].

## 8.6 Glioma Molecular Grouping and Clinical Significance

Recent studies have suggested prognostic glioma groups based on the presence or absence of the mutation status of IDH, 1p/19q, and TERTp-mut [18, 30, 38]. This framework also provides the ability to incorporate other genetic mutations to further refine the diagnosis of gliomas (e.g. ATRX, TP53, EGFR) [49].

Labussiere et al. prognosticate and stratify four glioma groups based on TERTp-mut and IDH mutation status and provide the overall survival [38]:

1. TERTp-mut and IDH-mut with 1p/19q codeletion gliomas is associated with an overall survival of greater than 17 years. These tumor markers are consistent with oligodendrogliomas.
2. TERTp-wt and IDH-mut with TP53 mut gliomas is associated with an overall survival of 97.5 months, this is consistent with the molecular pathology of diffuse astrocytomas.
3. TERTp-wild type and IDH-wild type is associated with an overall survival of 31.6 months
4. TERTp-mut and IDH-wild type with EGFR amplification is associated with an overall survival of 15.4 months.

Eckel-Passow et al. used three molecular markers to prognosticate five glioma groups based on the prevalence in over a thousand glioma subjects [30], as seen in Table 8.1.

There are five key aspects to glioma molecular stratification and prognostication to be noted here:

1. Triple positive gliomas are most strongly associated with oligodendrogliomas and the minor allele of SNP rs55705857 (G;G)on the gene-poor area of 8q24.21. These are associated with an overall better benefit from adjuvant chemotherapy and radiation [18, 30].
2. Adults with tumors with only IDH-mut nearly always have acquired mutations in TP53 and ATRX; with the average age [37y] of diagnosis [30]. An IDH-only mutation is seen in half of all patients with an oligodendroglial component and two-thirds of astrocytomas (WHO grade II/III) [30].
3. Gliomas with only TERTp mutations are primarily glioblastomas, with triple-negative gliomas comprising 7% of grade II/III gliomas and 17% of grade IV tumors [30].
4. Triple-negative gliomas typically do not acquire ATRX mutations. It is relatively rare to identify gliomas with TERT-p mut and IDH-mut with an intact 1p/19q, however, the essential point here is to note that the presence of an IDH mutation does not always indicate a favorable prognosis [18].
5. Importantly, ATRX and TERTp-mut are not always mutually exclusive [30]. Glioma groups have shown the both the presence and absence of both ATRX and TERT-p mutations in a non-mutually exclusive manner [16, 50].

Table 8.2 provides clarification regarding the molecular markers, prevalence and survival for diffuse astrocytomas and oligodendrogliomas.

**Table 8.1** Showing the prognostication of five glioma groups based on prevalence

| Molecular markers | Prevalence (n > 1000 glioma subjects) (%) |
|---|---|
| IDH mutation only | 45 |
| Triple-positive [TERTp-mut, IDH-mut, 1p/19q codeletion] | 29 |
| TERTp-mutation only | 10 |
| Triple negative [TERTp- wild type, IDH-wild type, 1p/19q intact] | 7 |
| TERTp-mut and IDH-mut | 5 |

**Table 8.2** Prevalence and survival based on molecular markers for diffuse astrocytomas and oligodendrogliomas [30, 51]

| | IDH-mut | 1p/19q-mut | TP53 | TERTp-mut | ATRX loss | Prevalence | Survival |
|---|---|---|---|---|---|---|---|
| Diffuse astrocytoma | + | − | + | − | + | 5% | 97.5 months |
| Oligodendroglioma | + | + | − | + | + | 29% | 17 years |

## 8.7 Pediatric Oligodendrogliomas

Pediatric oligodendrogliomas typically lack combined IDH mutation and 1p/19q codeletion but occasionally demonstrate BRAF fusion genes [1]. High throughput molecular profiling of pediatric low-grade diffuse gliomas reveals duplications of portions of FGFR1 gene or rearrangements of MYB in >50% of tumors with both oligodendroglial and oligoastrocytic histology. This indicates the diffuse gliomas in children are genetically and biologically distinct from their adult counterparts [25, 52].

## 8.8 Oligoastrocytoma NOS

The 2016 WHO Classification Tumors of the Central Nervous System [1] defines oligoastrocytomas NOS as "*a diffusely, slow-growing glioma composed of a conspicuous mixture of two distinct neoplastic cell types morphologically resembling tumor cells with either oligodendroglial or astrocytic features, and in which molecular testing could not be completed or was inconclusive*".

The use of the term oligoastrocytoma or mixed glioma is discouraged in the current WHO classification, with an emphasis on genetic profiling of the oligoastrocytoma to be typical of either diffuse astrocytoma or oligodendroglioma and reserving the NOS diagnosis as an exception. Tumors with combined IDH mutation and 1p/19q co-deletion are thus classified as IDH-mutant 1p/19q co-deleted oligodendroglioma, irrespective of a mixed or ambiguous histology. Tumors with IDH mutation but without 1p/19q codeletion are classified as IDH-mutant diffuse astrocytoma, also irrespective of mixed or ambiguous histology.

Oligodendroglial tumors commonly exhibit joint allelic losses of chromosomal arms 1p and 19q, in both oligodendrogliomas and oligoastrocytomas [43, 53]. CIC mutations were shown in a third of oligoastrocytomas, which increase to a 100% incidence in the presence of 1p/19q codeletion; additionally, 1p/19q codeletions were noted to occur in approximately 60% of oligoastrocytomas, noted to be a lower rate than seen in oligodendrogliomas [43]. FUBP1 mutations were seen in 23% of oligoastrocytomas with CIC mutations and in less than 10% of all oligoastrocytomas [42, 43].

Nuclear ATRX immunoreactivity is strongly associated with 1p/19q codeletion in both oligoastrocytomas and oligodendrogliomas [26]. Thus, it is important to note, that loss of ATRX positivity in the tumor cell nuclei but retained nuclear expression in non-neoplastic cells supports the diagnosis of IDH-mutant diffuse astrocytoma [16, 54]. Strong nuclear immunopositivity for p53, typically as a consequence of TP53 mutation, is often associated with loss of nuclear ATRX expression and virtually exclusive with 1p/19q codeletion [34, 54].

Recent data supports the formation of a diagnostic algorithm for diffuse and anaplastic oligo- and astrocytic gliomas based on stepwise analyses starting with immunohistochemistry for ATRX and R132H-mutant IDH1, followed by testing

for 1p/19q codeletion and then followed by IDH sequencing of the tumors that were negative for R132H-mutant IDH1, this is to ensure "stringent" separation of astrocytoma from oligodendroglioma to minimize the confusing diagnosis and prognostication of "oligoastrocytoma" or previously used term "glioblastoma with oligodendroglial component" [16].

## 8.9 Conclusion

This chapter discusses the new 2016 edition of the WHO Classification of the Tumors of the Central Nervous System in light of recent literature to highlight the standard stratification of tumors, under the guidance of qualified molecular markers in histologically similar gliomas. Additionally, different glioma subsets have been identified by the mutation status of IDH, TP53, TERT-promoter and 1p/19q codeletion, differing on both the diagnostic and prognostic basis. We look forward to the evolution of tumor molecular profiles and incorporating the continual new knowledge into our practice as Neurosurgeons and Neuroscientists.

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# Chapter 9
# Diffuse Low-Grade Glioma Associated Stem Cells

**Federica Caponnetto, Antonio Paolo Beltrami, Tamara Ius, Miran Skrap, and Daniela Cesselli**

**Abstract** Precision medicine is a medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient, taking advantage of a multimodal approach considering not only patient's genetic content but also other molecular and cellular analysis.

Because of their heterogeneous clinical behavior, low-grade glioma (LGG) can benefit from this approach.

At this regard, recent publications took advantage of integrated wide-genome studies to identify genetic signatures endowed with a prognostic potential.

However, there is evidence that cancer progression is driven not only by genetic alterations but also by the tumor microenvironment. To deepen the comprehension of the role played by this latter on LGG heterogeneity, we isolated from glioma a population of stem cells, named Glioma-Associated Stem Cell (GASC), representative of the tumor microenvironment. Importantly, GASC resulted to be the strongest predictors of LGG patients' overall survival and malignant progression free survival, outperforming the state-of-the-art prognostic factors, including IDH1/2 mutation and 1p/19q co-deletion.

In this chapter, we will first briefly review the increasing knowledge on the role played by the tumor microenvironment. Subsequently, we will focus our attention on GASC and their ability to increase the biological aggressiveness of glioma stem cells through the release of extracellular vesicles named exosomes. Finally we will demonstrate how this patient-based approach can provide a groundbreaking method to predict prognosis and to exploit novel strategies aimed at targeting the tumor stroma.

**Keywords** Low-grade glioma • Tumor microenvironment • Mesenchymal stem cells • Glioma associated stem cells • Exosomes • Precision medicine

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## Abbreviations

| | |
|---|---|
| bFGF | Basic fibroblast growth factor |
| CNS | Central nervous system |
| CSC | Cancer stem cells |
| ECM | Extracellular matrix |
| EGF | Epidermal growth factor |
| EGFR | Epidermal growth factor receptor |
| Eph | Ephrin |
| GASC | Glioma associated stem cells |
| GSC | Glioma stem cells |
| HGG | High grade glioma |
| HIF | Hypoxia inducible factors |
| IDH1/2 | Isocitrate dehydrogenases 1/2 |
| IL | Interleukin |
| LGG | Low-grade glioma |
| MASC | Multipotent adult stem cells |
| MGMT | O6-Methylguanine DNA methyltransferase |
| MPFS | Malignant progression free survival |
| MSC | Mesenchymal stem cells |
| NSC | Neural stem cells |
| OS | Overall survival |
| PFS | Progression free survival |
| Shh | Sonic hedgehog |
| SNP | Single nucleotide polymorphism |
| TAM | Tumor-associated macrophage |
| TGFβ | Transforming growth factor beta |
| VEGF | Vascular endothelial growth factor |
| WHO | World Health Organization |

## 9.1 Introduction

Low-grade gliomas (LGG) are characterized by a heterogeneous clinical behavior that can be only partially predicted employing current state-of-the-art markers, hindering the decision-making process [1].

Precision medicine is a medical model that proposes the customization of healthcare, with medical decisions, practices, and/or products being tailored to the individual patient [2]. In this model, diagnostic testing is crucial to select appropriate and optimal therapies and relies on a multimodal approach considering not only patient's genetic content but also other molecular and cellular analysis [2].

At this regard, recent publications taking advantage of integrated wide-genome studies have suggested for LGG novel molecular classifications that, with respect to the histological one, are endowed with a superior prognostic stratification power [3–5].

At the same time, there is evidence that cancer progression is driven not only by genetic alterations but also by the tumor microenvironment [6]. To deepen the comprehension of the role played by this latter on LGG heterogeneity, we isolated from gliomas a population of stem cells, named Glioma-Associated Stem Cells (GASC), representative of the tumor microenvironment. Surprisingly, GASC resulted to be the strongest predictors of LGG patients' overall survival (OS) and malignant progression free survival (MPFS), outperforming the state-of-the-art prognostic factors [7].

In this chapter, we will first briefly review the increasing knowledge on the role played by the tumor microenvironment on glioma biology and clinical behavior and we will describe proposed strategies aimed at targeting the tumor stroma. Subsequently, we will focus our attention on GASC and their ability to increase the biological aggressiveness of glioma-initiating cells (GSC) through the release of extracellular nanovesicles named exosomes. Finally, we will demonstrate how this patient-based approach can provide a groundbreaking method to predict prognosis and to exploit novel strategies aimed at targeting the tumor stroma.

## 9.2 The Tumor Microenvironment

Recently, a great interest has been arisen by the tumor-associated microenvironment (TME) [8, 9]. This latter consists of: the non-cancerous cells present in the tumor (e.g. blood vessels, immune cells and fibroblasts); proteins and extracellular vesicles produced by all of the cells present in the tumor and acting as signaling factors; the extracellular matrix (ECM). In carcinomas, the TME has been increasingly recognized as a key factor in multiple stages of cancer development and progression, particularly local resistance, immune-escaping, and distant metastasis [10].

Intriguingly, some biological characteristics of the stromal elements of tumors have been shown to be of prognostic and predictive value and could offer novel targeting opportunities [11–14].

The study of the glioma microenvironment has now identified some key-players paving the way to innovative therapies aimed at "curing" the microenvironment [15, 16].

### *9.2.1 The Criminal Conspiracy*

Gliomagenesis is a very complex process that not only requires the presence of cancer stem cells, known as glioma stem cells (GSC), but also of a favorable microenvironment that allows the development of the pathology [17–19].

Specifically the TME contributes to gliomagenesis by forming specialized niches (e.g. vascular niche, hypoxic niche and immune niche) that home GSC preserving their self-renewal capacity [20].

Importantly, the relationship between GSC and their niche is anything but passive. It is indeed a dynamic entity characterized by bidirectional feedbacks between cancer cells and TME cells that continuously influence and "remodel" each other. For example, the glioma niche provides trophic factors to cancer stem cells, while GSC, thank to their stemness-related properties, are able to activate the microenvironment inducing a phenotype promoting invasion, resistance and metastasis [21].

In fact, as stated by Hanahan and Weinberg, the hallmarks of cancer, i.e. the biological capabilities acquired during the multistep development of human tumors (e.g. sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, activating invasion, reprogramming of energy metabolism and evading immune destruction), are the result of the interaction of tumor cells with the repertoire of recruited, apparently normal cells that constitutes the TME [8, 9].

This is the case also for the most studied hallmarks of gliomas including: vasculogenesis, angiogenesis, as well as others phenomena such as vascular co-option and vasculogenic mimicry [22–25], and immune-escaping, also through the shifting of immune cells, such as tumor-associated macrophages (TAM) into immunosuppressive M2 cells [26, 27].

Importantly, in the glioma TME, besides tumor cells, tumor-supporting cells, ECM [28] and soluble factors [5, 29–36], a key role is also played by hypoxia and acidic stress [17–19, 21, 37].

In fact, acidic stress plays a fundamental role in sustaining the glioma niche [37, 38]. As oxidative stress settles, the pH of the microenvironment becomes acidic, and this is one of the triggers of the GSC phenotype [37].

Hypoxia is another key factors involved in the maintenance of the neoplastic microenvironment as well as in the regulation and expansion of GSC. Indeed, oxygen ($O_2$) levels are pivotal in driving tumor progression, migration, invasion and chemo-resistance. This phenomenon is achieved by the so-called hypoxia inducible factors (HIFs) which are proteins that regulate and direct the response of cells to oxygen dysregulations, controlling the transcription of genes involved in hypoxia [34, 35, 39].

What is interesting is the fact that, within a tumor, an $O_2$ gradient exists [36]. The level of hypoxia influences the composition of the TME (cells and factors) and concomitantly the GSC features. For this reason, it is possible to recognize, starting from the center of the necrotic area toward the periphery, different kind of niches, that is a quiescent-, a perivascular- and an invasive- one, respectively [34, 36]. Similarly, Pistollato et al., analyzing several human glioblastoma tissues, have shown that an intratumoral hypoxic gradient drives stem cells distribution and MGMT expression [36, 39], thus supporting the notion that heterogeneity in the TME can influence GSC properties, underlying once again the multifaceted origin of tumor heterogeneity.

### 9.2.2 The Therapeutic Opportunity

Therapies targeted against the TME represent a promising approach for treating cancer [16]. Differently from cancer cells, TME cells would be less prone to develop drug-resistance through mutations. Indeed, multiple TME-directed therapies are now under evaluation in clinical trials [40, 41].

However, since TME has the ability to induce both beneficial and adverse consequences for tumorigenesis, disrupting the pro-tumorigenic TME is a challenging task [41]. In fact, since the microenvironment is capable of normalizing tumor cells, "re-education" of stromal cells, rather than targeted ablation per se, may be an effective strategy for treating cancer [41].

Consistently, depletion of stromal cells, for example by various angiogenesis inhibitors, have had limited benefits, possibly because they simply block the pro-tumorigenic effects of the TME [42, 43].

More successful seem to be instead immunotherapies, a paradigmatic reprogramming approach aimed at blocking mechanisms of immune evasion by tumors. At this regard, the use of blockade of CTLA-4 (ipilimumab), PD1 receptor (nivolumab) or PD-L1 (lambrolizumab), extremely effective in metastatic melanoma, has been recently proposed for glioblastoma patients [42, 43].

Another example of repolarization or re-education of cells within the TME, it is represented by the use of a CSF-1R inhibitor to target macrophages and microglia in the TME of gliomas [15]. In a murine model, the Joyce's group showed that CSF-1R inhibition result in a robust decrease in tumor volume concomitant with a significant prolongation in survival [15]. Reprogramming rather than depletion of tumor associated macrophages (TAM) seemed to be the mechanism by which the treatment was effective [15]. Accordingly, several approaches to inhibit CSF-1R are currently being used in clinical trials [15]. However, although TME would be less susceptible to genetic modifications inducing drug-resistance, the Joyce's group wanted to explore the possibility of developing resistance during a prolonged use of anti-TME therapies. Taking advantage of genetic mouse models of glioblastoma, they demonstrated that gliomas, during the course of long-term experiments, acquire resistance to the macrophage-targeted therapy. The resistance resulted to be microenvironment–driven [16] and could be reverted by the concomitant blockade of the Phosphatidylinositol 3-kinase (PI3K) pathway [16]. In fact, in response to long-term CSF-1R inhibition, TAM increase their secretion of IGF-1 into the extracellular environment. This increase results in activation of IGF-1R on tumor cells and downstream PI3K signaling thus supporting tumor growth.

This work clearly demonstrates that although stromal cells are less susceptible to genetic mutation than are cancer cells, a tumor can become resistant to a TME-targeted therapy [16]. Moreover, it underlines the fact that cancer is a dynamic entity characterized by a bidirectional feedback between cancer cells and their microenvironment. Only an integrated analysis of cancer cells with their microenvironment will help in understanding both their parallel evolution during tumor progression and their capacity to develop drug resistance. This requires the development of in vitro model able to capture all these elements.

*In conclusion, many factors are involved in glioma progression. Beside GSC, the TME has been demonstrated to be crucial not only in the initial phase of the neoplasm but also for its maintenance and progression. Therefore, the glioma microenvironment can profoundly influence tumor prognosis and targeting it could turned out to be the new frontier for glioma treatment. However, this requires the optimization of robust, patient-based in vitro models that would allow exploiting all these aspects.*

## 9.3 Glioma Associated Stem Cells

In our laboratory we have optimized a method to isolate from several human tissues (e.g. heart, bone marrow, liver, peripheral blood, skin and adipose tissue), a population of stem cells characterized by a wide differentiation ability, being able, independently from the tissue of origin, to differentiate into derivatives of all the three germ layers [44]. We named these cells Multipotent Adult Stem Cells (MASC), and in these years, we have exploited their role for regenerative purposes and as in vitro model of degenerative diseases [44–53].

The isolation protocol consists first in digesting tumor fragments in a collagenase-II solution and then in culturing the obtained single cell suspension onto fibronectin-coated dishes in a medium selective for the growth of multipotent adult stem cells (i.e. in a medium at low serum concentration and supplemented with epidermal growth factor (EGF) and platelet-derived growth factor-BB (PDGF-BB) [7].

When we applied this culture protocol to neoplastic tissues [7, 54, 55], we realized that isolated cells, although unable to induce a tumor when injected into immunodeficient mice (they were not tumor-initiating cells), were characterized by tumor-supporting ability, thus possibly representing a patient-based model of the tumor microenvironment (Fig. 9.1).

### *9.3.1 GASC Are a Population of Stem Cells with Tumor-Supporting Function*

Since 2006, the above-mentioned protocol has been applied to both high-grade and low-grade gliomas of the supratentorial region. Despite the stringent culture conditions, proliferating cell lines were obtained from about 95% of both LGG and high-grade gliomas (HGG). We named these cells Glioma-Associated Stem Cells or GASC. To date, our cell bank includes more than 250 GASC lines, indicative of the high efficiency of the optimized method.

To demonstrate whether GASC possessed stem cell properties we investigated whether in vitro they display an undifferentiated phenotype as well as clonogenicity and multipotency, two stemness-related properties (Fig. 9.1).

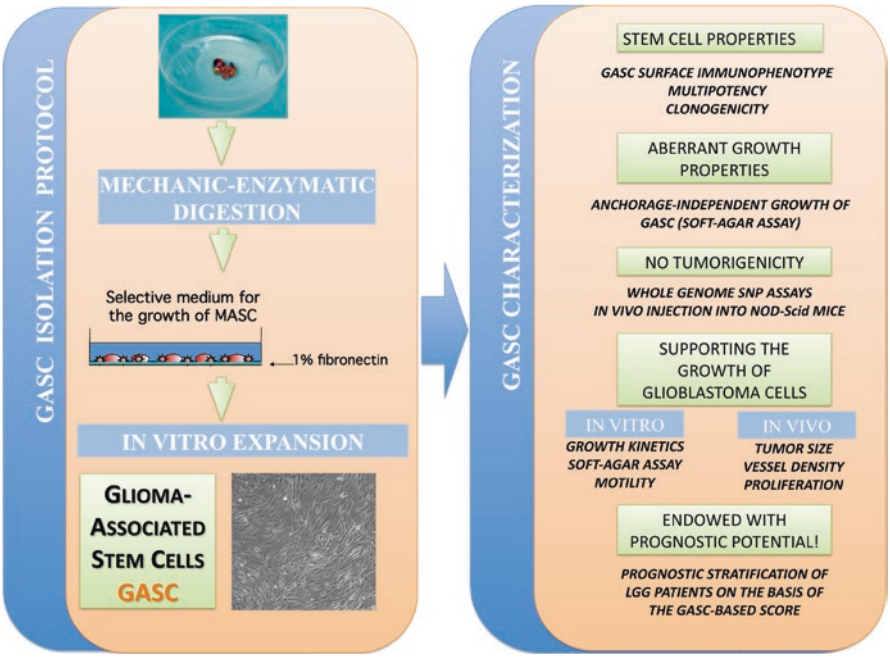


**Fig. 9.1** GASC features. The scheme depicts the protocol used to isolate GASC, the GASC features that have been analyzed and the assays used

Indeed, since one week from seeding, proliferating cells, independently from the grade of the glioma of origin, displayed a fibroblast-like morphology and were highly positive for the expression of intermediate filaments characterizing an undifferentiated state (e.g. vimentin and nestin), while the glial fibrillary acidic protein (GFAP) was expressed only in a minority of the cells. GASC also expressed the pluripotent-state specific transcription factors Oct-4, Nanog and Sox-2. All these features were retained at the third passage in culture. Regarding their surface phenotype, GASC presented a mesenchymal phenotype as assessed by flow-cytometry testing a wide panel of positive/negative markers, according to the International Society for Cellular Therapy [56].

In order to test whether GASC were characterized by stem cell properties, a single-cell cloning assay was performed demonstrating the presence of self-renewing clonal cells that maintained a stable undifferentiated phenotype.

Moreover, when cultured under appropriate differentiation-inducing conditions, clonal GASC acquired lineage-specific features. Specifically, when exposed to a neural differentiation medium, cells displayed morphological changes and differentiated into neuronal-like, glial-like and oligodendrocyte-like cells. Similarly to MASC isolated from normal tissues [44–53], GASC retain also the ability to differentiate along mesodermic (e.g. endothelial-, osteoblast- and myocyte-like cells), and endodermic (e.g. hepatocyte-like cells) derivatives, although with a very low efficiency.

However, despite some similarities, the growth properties of GASC were significantly different from those of MASC obtained from normal tissues [44–53]. Specifically, GASC displayed an anchorage-independent growth, being able to grow as spheroids when seeded into a soft agar. This aberrant growth property is typical of tumor cells but can be also presented by tumor-supporting cells.

To exclude the possible neoplastic nature of GASC, a whole genome Single Nucleotide Polymorphism (SNP) analysis was performed. Indeed comparing the SNP profile of GASC-lines with the ones of the respective tumor of origin, all tested GASC were devoid of the genetic alterations characterizing the matched glioma tissues. Accordingly, when injected into the striatum of NOD-Scid mice, $10^5$ either polyclonal or clonal GASC were unable to give rise, even after 8 months, to tumors, excluding their tumor-initiating capacity.

To test instead the tumor-supporting ability of GASC, two commercially available glioblastoma cells lines (A172 and U87) were grown in the presence of the supernatant of GASC. Both cell lines, when conditioned by GASC, displayed a significantly increased growth kinetic and capacity to grow in soft agar. Interestingly the tumor-supporting ability was increased in GASC isolated from high-grade glioma, with respect to those obtained from LGG.

More recently, unpublished data from our laboratory shows that GASC possess a tumor-supporting function also when injected in vivo into an orthotopic murine model of glioblastoma.

*In conclusions, both LGG and HGG contain a population of cells characterized by stem cell properties and aberrant growth properties. These cells are not tumor-initiating cells but act as tumor-supporting cells.*

### *9.3.2 How GASC Exert Their Tumor-Supporting Function*

Understanding the mechanism through which GASC support the tumor growth can open the way to novel therapeutic strategies aimed at interfering with this harmful cross talk. Up to now, we have determined that GASC can act on tumor cells by releasing exosomes [7] and by modulating GSC adhesive properties [57].

#### 9.3.2.1 GASC Act Through the Release of Exosomes

It has been recently shown that the potent cross talk between cancer cells and tumor-associated stromal cells can be, at least in part, mediated by the release of exosomes [58–61]. These latter are extracellular vesicles, smaller than 150 nm in diameter, that originate in the multivesicular body compartment and are released into the extracellular space and in the body fluids from many cell types [58–62]. Since exosomes can deliver to target cells their content of biologically active molecules (e.g. proteins, mRNAs, miRNAs, lncRNAs), thus modifying their physiological state, they act as a potent intercellular communication system [61, 63–65].

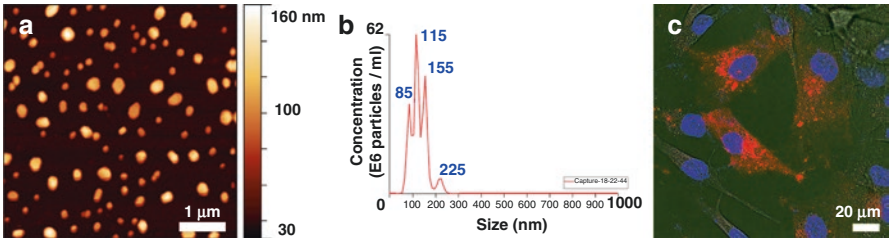


**Fig. 9.2** GASC release exosomes in the supernatant. (**a**) Atomic force microscopy topographic height of GASC-derived exosomes. The exosomes appear as circular structures with diameters ranging from 20 to 120 nm. (**b**) Size distribution (diameter in nm) and concentration of exosomes resulting from the Nanoparticle Tracking Analysis. (**c**) DiD-labeled exosomes (*red* fluorescence) appear to be internalized by glioblastoma cells (overlaid phase-contrast image). Nuclei are depicted by the *blue* fluorescence of DAPI

At this regard, Skog's group showed that glioblastoma tumor cells could release exosomes, containing mRNA, miRNA and angiogenic proteins, able to act on endothelial cells, possibly favoring the development of a tumor-permissive microenvironment [66]. Interestingly, exosomes can be also released into the bloodstream [66] and act on distant sites taking part to the formation of a pre-metastatic niche [59, 67, 68]. Conversely, it has been shown that tumor-associated fibroblasts, through the release of exosomes, could induce, in breast tumor cells, the acquisition of a metastatic phenotype [60].

For this reason, we wondered whether GASC could exert their tumor-supporting action in this way [7]. Exosomes were therefore isolated from GASC culture supernatants and their presence was confirmed by Atomic Force Microscopy and Light Scattering (particles with a diameter ranging from 20 to 110 nm) (Fig. 9.2).

In order to establish whether glioblastoma cells could incorporate GASC-derived exosomes, we labeled these latter with the lipophilic DiD-dye and, as shown in Fig. 9.2, after 4 h of incubation, DiD-labeled exosomes could be identified within the cells [7].

To unequivocally demonstrate that the tumor-supporting fraction of GASC supernatant was indeed due to exosomes and not to other soluble factors, we compared the capacity of: un-fractioned GASC supernatants, exosome-depleted GASC supernatants and GASC-derived exosomes to modify growth kinetic, migration ability and anchorage-independent growth of A172 cells, showing that indeed exosomes were the main responsible for the effects observed. Same effects were observed when we evaluated a clinically more relevant experimental setting, isolating from the same HGG, both GASC and GSC and we verified that GASC-exosomes profoundly modified the growth pattern of GSC as well as their motility and anchorage-independent growth [7]. Exosomes released by non-tumorigenic Wi38 fibroblast did not affect GSC, confirming the specific role of GASC-derived exosomes.

Interestingly, exosomes released both from HGG and LGG were able to increase the in vitro aggressiveness of glioblastoma cells, although those from LGG at a significant lower extent, thus suggesting that the degree of the tumor-supporting ability was proportional to the grade of malignancy of the tumor of origin.

At this regard, unpublished data from our laboratory seem to confirm the existence of differences in the miRNA content of exosomes released by GASC obtained from LGG and HGG, and even from LGG with a different prognosis [7].

*Altogether, these results showed that functional features of tumor-supporting cells characterize GASC and that this effect can be at least in part attributable to the release of exosomes.*

#### 9.3.2.2 GASC Can Modulate the Adhesive Properties of Glioma Stem Cells

Active cell migration and invasion is a peculiar feature of glioma that renders this tumor able to migrate and infiltrate eloquent areas making difficult the achievement of a radical surgery. Migrating cancer cells undergo considerable molecular and cellular changes by remodeling their cytoskeleton and cell interactions with surrounding environment. Since we have seen that GASC can modify the motility of glioblastoma cells, we decided to get better insights into the interactions between GSC and GASC isolated from LGG and HGG [57]. By using time-lapse microscopy as well as atomic force microscopy and single cell force spectroscopy, we first demonstrated that, independently from the grade of the glioma of origin, GSC are softer than GASC, in agreement with their neoplastic features [57]. Subsequently we have shown that the adhesion strength of GSC on GASC appears to be significantly lower for cells derived from HGG with respect to those derived from LGG [57]. This is in line with the fact that HGG cells are characterized by a more infiltrative nature with respect to LGG. What was surprising is the fact that when GSC from HGG were cultured, in parallel, on GASC derived from LGG and HGG, they firmly adhere on GASC from LGG but not on those from HGG, suggesting that the grade of GASC plays an important role in modulating cancer cell adhesion, thus possibly affecting glioma cell migration, invasion and thus cancer aggressiveness [57].

*Altogether these results provide evidence that investigating cell adhesion and elasticity of both tumor cells and tumor-supporting cells can open the way to novel diagnostic tool and suggest novel therapeutic targets.*

### *9.3.3 GASC Are Endowed with a Prognostic Potential*

Since GASC showed a state of activation that did not change upon in vitro expansion, and the extent of the tumor-supporting ability increased with the grade of gliomas, we wondered whether GASC features could predict the clinical behavior of the tumor (Fig. 9.3). We decided to focus our attention on LGG, trying to define new criteria to prognostically stratify this heterogeneous clinical entity [7].

The study was articulated in two parts. We first identified the GASC-features distinguishing LGG from HGG and we inserted them in a score that was finally tested for its capacity to prognostically stratify 40 LGG patients in terms of overall survival (OS), malignant progression free survival (MPFS) and progression free survival (PFS).

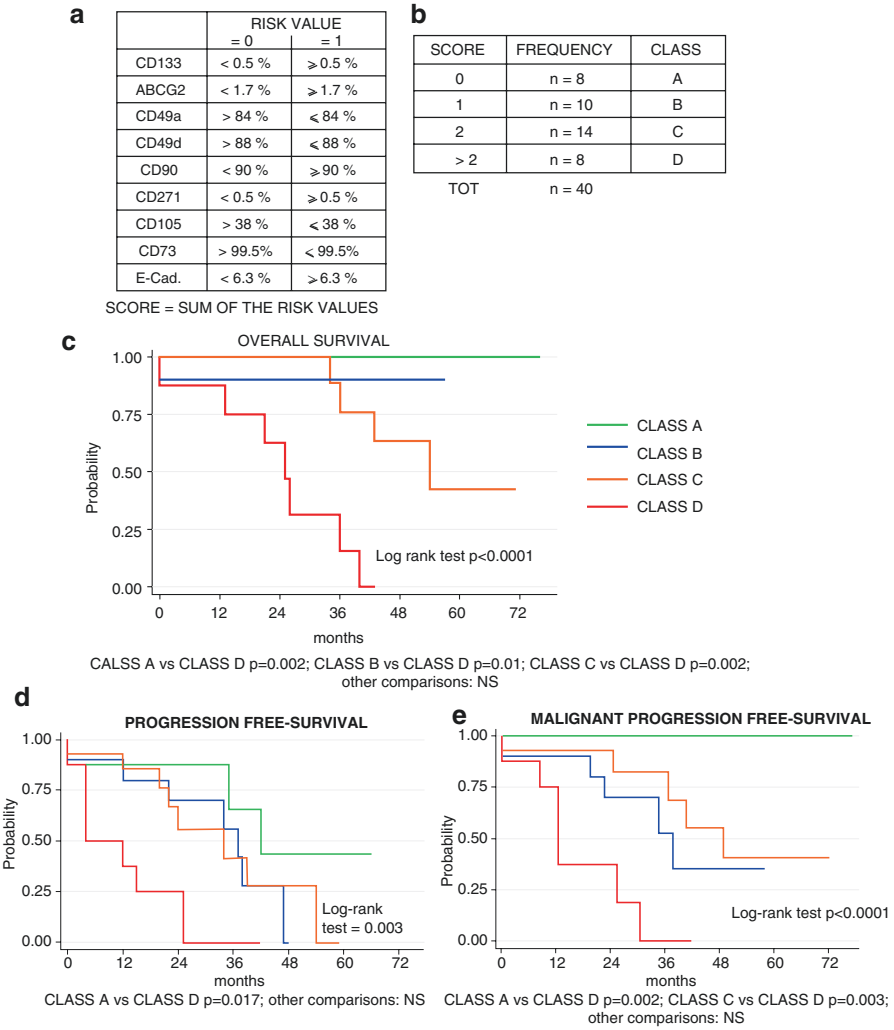


**Fig. 9.3** Prognostic value of the GASC-based score in LGG patients. (**a**) Parameters and cut-off value used to define the GASC-related score. (**b**) Distribution of the LGG patients in four GASC-classes, according to the GASC-score value. (**c**–**e**) Kaplan-Meier curves showing OS (**c**), PFS (**d**), and MPFS (**e**) in LGG patients stratified according to the GASC-based score. *Slightly modified by Bourkoula E, et al. Stem Cells. 2014;32:1239–53*

Comparing the features of GASC obtained from HGG and LGG and utilizing a ROC analysis, we selected nine parameters (among the surface proteins detected by flow-cytometry) significantly able to correctly classify the two groups and we determined the cut-off value able to discriminate the two populations (Fig. 9.3a). Of the nine parameters, five were more expressed (CD133, CD271, ABCG2, E-Cadherin, CD90) and four less expressed (CD49a, CD49d, CD105, CD73) in GASC from HGG with respect GASC from LGG.

We expressed the selected parameters as binary values creating a score based on the sum of these latter. This GASC-based score was indeed a number between 0 and 9, depending on the number of the GASC features similar to those obtained from HGG.

When the GASC-based score was assessed in a case study including 40 subsequent LGG-patients (median follow-up 36 months, range 13–76), we decided to stratify the patients in four classes (Fig. 9.3b). The 40 LGG were well characterized in terms of clinical (age, gender, extent of resection, subsequent adjuvant therapies) and histo-pathological (histotype, Ki67 expression, IDH1/2 gene mutation, 1p/19q co-deletion, MGMT-promoter-methylation) features.

Considering OS, PFS and MPFS, at the univariate analysis the GASC-based score was significantly associated with a worse prognosis, while the extent of tumor resection (EOR) and the presence of mutated IDH1 or IDH2 genes were protective factors. Importantly, the multivariate Cox analysis showed that the four classes' GASC-based score was the only independent predictor of OS and MPFS, while EOR was the only independent predictor of PFS.

It is interesting to underline that the surface proteins included in the GASC score essentially belong to three classes: stem cell antigens (CD271, CD133 and ABCG2), adhesion proteins (CD49a, CD49d and E-Cadherin) and mesenchymal markers (CD90, CD73 and CD105). Specifically, GASC obtained from patients with poor prognosis were characterized by an increase in stem cell-related markers, a down-regulation in integrin expression and a variable modulation of mesenchymal markers. Moreover, these markers seemed to identify distinct sub-populations whose specific role in the natural history of glioma deserves future investigations.

*Altogether, these results indicate that GASC are endowed with prognostic value, thus supporting the idea that this patient-based in vitro model could be helpful in a precision medicine approach aimed at customizing healthcare, with medical decisions, practices, and/or products being tailored to the individual patient.*

### *9.3.4 GASC as a Potential Cellular Model for Precision Medicine*

The precision medicine (PM) initiative sponsored by President Obama relies on the concept that prevention and treatment strategies must take individual variability into account [2, 69]. PM has become more realistic by the recent development of large-scale biologic databases (e.g. human genome sequence), powerful methods for characterizing patients (e.g. proteomics, metabolomics, genomics and diverse cellular assays), and computational tools for analyzing large sets of data [69]. Regarding cellular model, it is considered important by the National Cancer Institute (NCI), to develop new laboratory models of human cancer including human cancer cell lines and patient-derived tumor xenografts. These new models could help researchers in gaining new insights into tumor biology and better predicting patients' responses to cancer treatment [69].

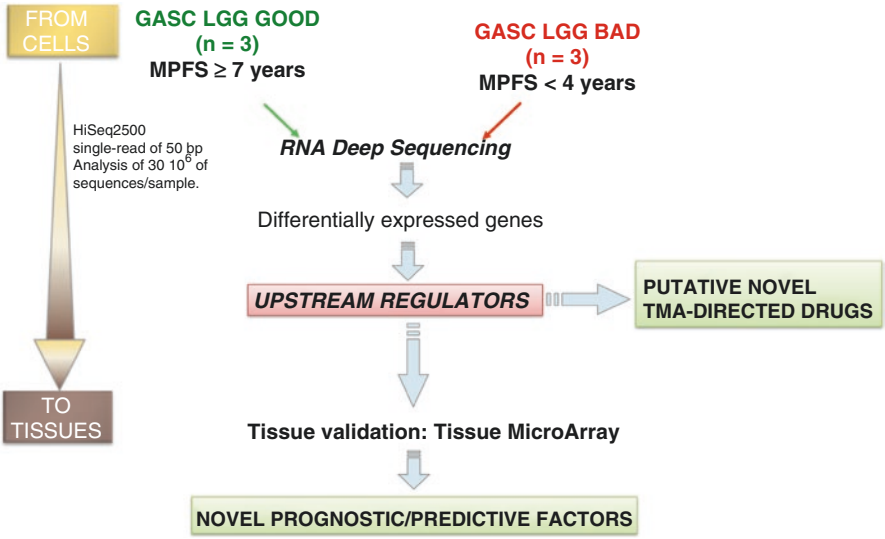


**Fig. 9.4** Experimental approach using patient-derived GASC to identify novel prognostic/predictive factors and putative TME-directed drugs

Since the difficulties in isolating GSC from LGG [70] and being GASC a strong predictor of LGG patients' OS and MPFS outperforming the state-of-the-art prognostic factors [7], we have decided to explore this patient-based model to identify novel prognostic/predictive factors and to devise new therapeutic strategies aimed at targeting glioma by "curing" the tumor stroma (Fig. 9.4).

At this regard, by using next generation sequencing techniques, we highlighted 81 genes and 15 miRNAs that distinguish GASC isolated from LGG with a good prognosis from those characterized by a rapid anaplastic transformation. Interestingly, most of the differentially expressed genes were related to an inflammatory and pro-angiogenic signature (unpublished data).

To facilitate the introduction of these new markers into the clinical routine, we started a project aimed at confirming the results, obtained at the cellular level, in a large case study including LGG tissues, by using immunohistochemistry, an ancillary technique currently used in all Pathology department. The proof of concept has been reached for one of these markers that resulted to be an independent predictor of both OS and MPFS (unpublished data).

Additionally, the above-mentioned analyses have also identified putative molecules and drugs that can act reverting the molecular pathways active in GASC obtained from LGG rapidly undergoing anaplastic transformation.

We intend now to provide evidence of whether, at least in vitro, it is possible to "cure" GASC by inhibiting their tumor-supporting function. Notably, stromal cells are optimal therapeutic targets for their genetic stability and lower potential to develop drug resistance [16, 41], although they can develop long-term resistance.

However, the possibility to have cell cultures can help in developing in vitro model to explore these phenomena.

*Altogether these results support the notion that GASC, being a patient-based model, can help in identifying biomarkers useful to predict prognosis and in devising novel therapeutic strategies aimed at interrupting the cross talk between tumor cells and their supporting stroma. Both properties of this cellular model can be instrumental at a precision medicine approach for LGG, an extremely heterogeneous clinical entity.*

## *9.3.5 GASC: Still Open Questions*

### 9.3.5.1 GASCs' Origin

The presence of GASC raises issues regarding their origin in humans. In fact, their phenotype share many antigens with tumor cells, making difficult to unequivocally identify the in vivo counterpart of GASC in a tissue. Additionally, lineage-tracing experiments from the cell-of-origin cannot be done in humans [71]. However, some hypotheses on the GASC origin/in vivo counterpart can be done.

Regarding a possible fibroblast origin, in analogy to the tumor-associated fibroblast present in the epithelial tumors, it has to be underlined that there is a limited presence of fibroblasts in the CNS and their proliferation has never been described in the course of pathology [72]. Instead, the cell type that characterizes the CNS' response to injury is represented by reactive astrocytes [73, 74]. Importantly, in murine models, non-neoplastic astrocytes could be converted, by the glioma microenvironment, into a reactive phenotype [75, 76] that could acquire stem cell features similar to GASC [77]. The activation of astrocytes seems to be mediated by an epithelial-to-mesenchymal like transition process [78], possibly regulated by the presence, in the tumor microenvironment of hypoxia and an increased myeloid cell number [79]. Unpublished data from our laboratory show that GSC-derived exosomes can indeed activate an epithelial-to-mesenchymal like transition process into cultured human astrocytes, which acquire stem cell properties.

Alternatively, GASC may derive from a population of perivascular mesenchymal stem cells endowed with both mesodermal and neuroectodermal differentiation capacities [80]. This opens the question regarding a possible connection between GASC and mesenchymal stem cells.

### 9.3.5.2 GASC and MSC

To date, the concept of "Mesenchymal stem cells" (MSC) is still a developing issue in terms of defining criteria, sites of origin, in vivo counterpart and function in normal and pathological conditions, including cancer. The demonstration of the existence of MSC into the brain opens the questions on the possible role of these cells in glioma and the relationship with GASC.

## MSC: Definition Origin and Function

In 1960s Friedenstein first isolated from murine bone marrow a population of plastic-adherent, fibroblast-like cells able to form clonal colonies in vitro (colony-forming unit (CFU)—fibroblast). These cells, described as self-renewing non-hematopoietic bone marrow stromal stem cells (BMSC), were also capable of osteogenic differentiation in culture, could generate bone when implanted in ectopic locations in vivo and presented high self-renewal ability in serial implants [81]. Later on, Caplan coined the term "mesenchymal stem cells" and gave a full description of MSC features [82]. Currently, minimal criteria to define a cell as MSC have been described. Specifically, MSC must be plastic-adherent when maintained in standard culture conditions, must possess a specific surface phenotype and must differentiate into osteoblasts, adipocytes and chondroblasts in vitro [56, 83].

Regarding the site of origin, the concept that the bone marrow was the solely tissue hosting MSC has been discarded as this population was found in many tissues, such as adipose tissue, dental pulp, amniotic fluid, umbilical cord, muscles and many others, including brain [84, 85].

Considering the in vivo counterpart of MSC, lately researchers focused their attention on the concept that MSC home close to the vasculature, under the form of pericytes and adventitial cells. This new hypothesis has opened a new branch of research [86]. Bouacida et al. used in vivo and in vitro assays to support the idea that pericytes can be considered precursors of MSCs [87]. This theory might be able to explain the reason of the presence of MSCs in all tissues.

Moreover, Da Silva Meirelles et al. described some of the similarities between MSCs and pericytes, e.g. isolation methods, immunophenotype, clonogenicity, in vitro and in vivo multipotency, capacity to influence the immune system [88].

The great effort in defining criteria and protocol for MSC culture and characterization relies on their possible clinical use [86, 89]. The major clinical application of MSC are mainly attributed to their ability: to home to sites of injury when injected intravenously; to differentiate into various cell types [90]; to secrete multiple bioactive molecules capable of stimulating recovery of injured tissues and reducing inflammation and to perform immunomodulatory functions [89, 91, 92]. In fact, major applications are the treatment of the graft versus host disease and the regeneration of injured tissues, such as bone lesions and infarcted myocardium [89]. To date, clinicaltrials.gov reports more than 400 on-going trials using MSC in different disorders, especially in the field of bone regeneration and myocardial infarction.

An emerging role of MSC in cancer has been recently described.

## MSC and Cancer

The role of MSC on tumor is still debated [93, 94]. MSC isolated from normal tissues present a tropism towards site of tumors and, while many studies have reported that these cells can support tumor progression and metastasis, others have shown that they can exert a tumor-suppressing function [93, 94]. Specifically, MSC can promote tumor growth by several mechanisms, including: differentiation into

tumor-associated fibroblasts; suppression of the immune response; promotion of the angiogenesis; stimulation of epithelial-to-mesenchymal transition (EMT); contribution to the tumor microenvironment; inhibition of tumor cell apoptosis; and promotion of tumor metastasis [93, 94]. Conversely, MSC can act as tumor suppressors by: increasing inflammatory infiltration; inhibiting angiogenesis; suppressing Wnt signaling and AKT signaling, and inducing cell cycle arrest and apoptosis [93, 94].

Conversely, MSC isolated from the tumor, invariably present tumor-supporting functions [95].

Possibly, these apparently contrasting results can be explained considering the existence of a dynamic co-evolution of both tumor and stromal cells [53]. Therefore, MSC, once reached the site of tumor recruited by the inflammatory microenvironment, can modify and be modified by the tumor cells and the resulting function (tumor-suppressing or tumor-supporting) is initially the results of several factors, including the cytokines secreted by MSC and interactions between MSC, host immune cells and cancer cells [94]. However, with time, tumor MSC will be definitely "educated" by the tumor microenvironment to support tumor growth, progression and metastasis by recruiting additional immunosuppressive cells, enhancing the fraction of cancer stem cells in tumors, promoting EMT, and stimulating tumor angiogenesis [95].

For this reason, studying how to stop the interactions among tumors, MSC, and the inflammatory tumor microenvironment could suggest new therapeutic strategies.

## Brain-Derived MSC and GASC: The Pericyte Connection?

As previously mentioned, MSC have been described in numerous tissues, such as bone marrow, umbilical cord, placenta, muscle, skin and periosteum as well as the central nervous system (CNS) [84, 96]. In line with the evidence that the in vivo location of MSC may be the perivascular niche and that MSC may actually represent a subclass of pericytes [65], Paul et al. identified for the first time a perivascular stem cell in the human adult brain. Isolated cells shared a mesenchymal and pericyte phenotype and had the potential to differentiate into mesodermal and neuroectodermal progeny [80], thus suggesting the existence in the brain of another stem cell population distinct to the neural stem cell pool [97, 98]. Pericytes are peri-endothelial vascular mural cells that form an incomplete layer on the abluminal surface of capillary endothelial cells. For many years, pericytes have been viewed as supportive vasculature cells involved in the regulation of capillaries blood flow and contributing to the blood-brain barrier [97, 98]. Currently, it has been demonstrated that pericytes play a role in angiogenesis, in matrix proteins and bioactive molecules synthesis, in vessel stabilization and in the regulation of vascular tone [97, 98]. These key-properties explain why pericytes could play a role in cancer progression and other brain diseases [97, 98].

As mentioned, the possibility that MSC could originate from a pericyte subset would adequately explain why MSC can be cultured from all tissues and why they could function as a source of stem cells for the regeneration of local

lesions. At this regard, it has been reported that pericytes play a role in post-injury neurogenesis [99–101]. Regarding the mechanism of origin of MSC from pericytes, Caplan suggests that adult pericytes become activated MSC when the vessel is damaged or inflamed [102]. These activated MSC act secreting a cascade of bioactive molecules that control the local immune cells as well as regeneration processes [102].

MSC have been isolated from both murine [103] and human gliomas [104]. In the murine model, infiltration of brain tumor (BT)-MSC correlated to tumor progression and BT-MSC increased the proliferation rate of the GL261 glioblastoma cells in vitro [103].

Similarly, glioma associated human MSC increased proliferation and self-renewal of GSC in vitro and enhanced GSC tumorigenicity and mesenchymal features in vivo [104] by secreting interleukin-6 which activates STAT3 in GSC.

Since the mesenchymal nature of GASC, that also express some pericyte markers such as CD146, it would be interesting to explore the hypothesis that the cell of origin of GASC would reside in the pericyte subset. The identification of the mechanisms underlying generation and activation of GASC from pericytes could then become a novel therapeutic target.

*Being still undefined the in vivo counterpart of GASC, the origin of these latter remain an open question. However, understanding which cells originate them and the mechanisms responsible for their activation would represent a novel therapeutic target within gliomas.*

## 9.4 Conclusions

The tumor-supporting stroma has gained much attention as a key player in tumor progression. However, protocols that are able to successfully isolate, from human tissues, cells representative of this tumor-supporting population are still new and pioneering.

GASC cell culture represents a patient-based in vitro model of the glioma microenvironment. GASC have revealed their clinical significance allowing a better prognostic stratification of LGG patients and this could, in perspective, improve the clinical management of this heterogeneous class of patients.

Moreover, the study of these cells can represent an innovative tool for devising new therapeutic strategies, even patient-targeted, aimed at disrupting the communication between glioma stem cells and their supporting stroma.

The study on GASC represent a truly expression of the “from bench to bedside” principle, as it furnish a patient-based cellular model that, together with molecular, neuroradiological and other clinical data, can help in tailoring optimal healthcare decisions to the individual LGG patients, within a so called precision medicine approach.

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# Chapter 10
# Molecular Imaging of Diffuse Low Grade Glioma

**Whitney B. Pope and Kevin Spitler**

**Abstract** Beyond defining tumor extent and anatomic location, recent advances in MRI and PET allow for the non-invasive physiologic, metabolic and molecular imaging of diffuse low-grade glioma. How this information can be best combined with detailed molecular characterization of tumors, in order to produce applicable markers of prognosis and response to therapy, remains to be determined. The impact on imaging of molecular features of gliomas including 1p/19q loss of heterozygosity (LOH) and the *IDH1* and *IDH2* mutations is discussed. Newer MR sequences and data mining techniques including diffusion and perfusion MRI and textural analysis may better stratify tumor prognosis and grade. Additionally, measurement of the oncometabolite 2-HG with MR spectroscopy appears clinically feasible, although the relationship to outcomes is yet to be determined. Lastly PET with amino acid tracers including $C^{11}$-MET, FET and FDOPA provide additional avenues of tumor characterization that are unfettered by the high background uptake of FDG. The future may be characterized by gains in predictive, rather than merely prognostic markers, that could help optimize patient outcomes. As more targeted therapies become available, it will also be critical to develop early response indicators that are acquired prior to change in tumor size. To date, many imaging biomarkers lack the rigorous validation necessary for clinical decision-making, but ongoing efforts could yield such data in the near future. As more is understood about the relationship between imaging and underlying molecular features of disease, we can continue to refine treatment strategies in a manner more precisely tailored to individual patients.

**Keywords** Diffuse low-grade glioma • Imaging • MRI • PET • 1p/19q • IDH • Perfusion • Diffusion • MET • FDOPA • FET • Textural analysis

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## 10.1 Introduction

Imaging is critical for glioma management because of its ability to noninvasively define the anatomic location and extent of disease. While conventional imaging techniques guide current treatment, multiple studies suggest molecular features of gliomas may be identified with noninvasive imaging, including physiologic MRI and amino acid positron emission tomography (PET). These advanced imaging techniques have the promise to help characterize underlying tumor biology including angiogenesis, mitotic activity, hypoxia and cell density and may provide important information that could be integrated into routine clinical practice in the near future.

In tandem with advances in imaging, the molecular characterization of low-grade gliomas (LGG) has continued apace. Of the numerous molecular alterations that have been described in these tumors, four have received particular interest due to their association with prognosis and treatment susceptibility. Of these, three are associated with longer survival: *IDH* mutations, 1p/19q deletion and *MGMT* promoter methylation, whereas the *TERT* promoter mutation is associated with markedly shorter longevity [1]. Development of noninvasive imaging biomarkers that reflect the status of these molecular features is an active area of investigation. The search for imaging correlates of both 1p/19q deletion and IDH-1 mutation has intensified and provided a large amount of data. While correlation between imaging features and MGMT promoter methylation has received substantial attention in glioblastoma (GBM), whether similar or different imaging correlates are present in LGG is unknown. Similarly, to date, little is known about the potential impact of the *TERT* promoter mutation on image findings. As more is understood about the relationship between imaging and underlying molecular features of disease, the opportunity arises to improve prognostic and predictive biomarkers that help refine therapeutic strategies in a more patient-specific approach.

## 10.2 Routine Clinical Imaging of LGG

Clinical imaging of brain tumors has been provided by MRI since the 1980s. Some of the first MR pulse sequences to be developed were T1- and T2-weighted images, followed by fluid attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) [2]. Currently, MRI sequences including T1, T2, FLAIR, T2* gradient echo, DWI and post-contrast T1-weighted sequences are all considered routine and are available on most clinical scanners. Although hampered by cost, complexity and limited availability, the use of PET scans has increased in recent years, allowing for unique metabolic information to be acquired that can benefit management of specific clinical situations. Although 2-deoxy-2-[$^{18}$F]fluoroglucose (FDG) PET has been the mainstay of cancer imaging in non-neurologic applications, amino acid PET tracers have been shown to be more suitable for depicting brain tumors [3].

On routine MRI, typical features of LGG are well-circumscribed T1-hypointense, T2- and FLAIR-hyperintense+masses which lack substantial contrast enhancement

and restriction of diffusion. Peritumoral edema is usually minimal or absent [4]. Routine MR images have high sensitivity for bulk tumor, but lack the ability to depict microscopic infiltration of surrounding brain parenchyma. Similarly, PET images typically depict LGG as regions of increased tracer uptake (for both FDG and amino acid tracers) compared to normal white matter, but are inadequate for identifying microscopic tumor spread [5].

## 10.3 Imaging Features of Oligodendroglioma Versus Astrocytoma

As oligodendroglioma and astrocytoma are the two most common types of LGG, the question arises as to whether it is possible to distinguish one from the other using conventional MRI. Unfortunately, oligodendrogliomas cannot be reliably differentiated from astrocytomas using routine imaging. However, coarse calcifications, a cortical-subcortical as opposed to central white matter location and frontal lobe involvement are all favorable for oligodendroglioma histology. The superficial location of some oligodendrogliomas also can lead to remodeling of the overlying skull. Mild enhancement, increased perfusion and increased FDG uptake on PET also are more suggestive of oligodendroglioma than astrocytoma [4, 5].

## 10.4 Imaging Correlates of Molecular Features of Oligodendrogliomas: 1p19q Loss of Heterozygosity

A defining molecular feature of oligodendroglioma is 1p/19q loss of heterozygosity (LOH) [6]. 1p/19q LOH refers to the loss of tumor suppressor genes at both the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). 1p/19q LOH is associated with favorable survival and response to chemotherapy [7, 8]. 1p/19q codeletion also is associated with reduced risk of pseudoprogression i.e., treatment-related changes mimicking tumor growth [9]. Meta-analysis indicates that isodeletion of 1p, more than isodeletion of 19q, conveys the survival advantage [10].

Given its importance as a molecular feature of oligodendroglioma, imaging correlates of 1p/19q LOH are being investigated. Analysis of routine MR images has uncovered an association between the appearance of tumor margins and 1p/19q allele status, specifically that indistinct tumor margins, particularly on T1-weighted images, is associated with 1p/19q LOH [11, 12]. One study found that 93% of tumors with well-defined borders had intact 1p/19q alleles [12] and another study [13] reported that 83% of oligodendrogliomas with 1p/19q LOH have indistinct borders. Although the presence of indistinct margins has good sensitivity for 1p/19q LOH, a substantial proportion (38%) of oligodendrogliomas with intact 1p/19q also had indistinct borders. Similarly, calcifications are more common in tumors with

**Table 10.1** Comparison of imaging markers associated with 1p/19q LOH versus intact alleles in grade II oligodendroglioma

| Imaging marker | 1p/19q LOH | 1p/19q intact |
|---|---|---|
| Location | Frontal lobe | Insular |
| Margin | Indistinct | Well-defined |
| T1/T2 signal | Heterogeneous | Homogeneous |
| Calcification | Common | Less common |
| Perfusion | Higher rCBV | Lower rCBV |
| PET tracer uptake | Increased FET, possibly increased MET | Not increased FET |

1p/19q LOH, although calcifications are found in 1p/19q intact tumors as well [14]. No association has been found between contrast enhancement and genotype in grade II tumors. However, 1p/19q LOH may be associated with absent enhancement in grade III tumors [15] (Table 10.1).

One method that might increase accuracy for oligodendrogliomas genotype detection is textural analysis. Textural analysis is based on the automatic quantification of variations in signal intensity patterns on MR images that are often not recognizable by visual inspection. This encompasses pixel inter-relationships and spectral properties of images that can encode heterogeneity, coarseness, borders, and transitions. These data are combined to develop a texture signature, which is then correlated with clinical features of interest, such as 1p/19q allele status [16]. Using S-transform-based texture analysis, Brown and colleagues found that T2-derived texture features could differentiate 1p/19q intact and deleted tumors [17]. After optimizing the cut-off values for T2 retrospectively, the authors report that a prospective analysis using the application of spectral frequencies yields an accuracy of greater than 90% for the detection of 1p/19q LOH. Thus this appears to be a substantial improvement in the ability to detect 1p/19q LOH over efforts based on visual inspection of conventional MRI. In fact, the authors tested this possibility by using blinded experts to classify tumor genotype based on the methods described by Megyesi and colleagues [11]; they found that visual inspection alone yielded a sensitivity of 0.70 and specificity of 0.63, which appears to be substantially less than that for textural analysis. The next step will be to determine if textual analysis can maintain a high degree of accuracy when astrocytic tumors are included in the patient population.

## 10.5 Advanced MR Imaging

Advanced imaging also is being used to detect molecular features of gliomas including 1p/19q LOH. The term “advanced imaging” is somewhat ambiguous but generally comprises techniques such as perfusion and diffusion imaging that can depict and potentially quantify aspects of tumor physiology, adding potentially valuable information to the anatomic data that is derived from standard imaging. Aspects of tumor physiology that are thought to drive aggressive behavior

including transformation to more malignant tumor phenotypes may have imaging surrogates. For instance, hypoxia can trigger an angiogenic switch leading to neovascularization and tumor progression. Hypoxia can be imaged directly or indirectly by several newer techniques including chemical exchange saturation transfer (CEST) MRI [18], 1-(2-Nitro-imidazolyl)-3-[18F]fluoro-2-propanol (FMISO) PET [19, 20] and proton and hyperpolarized C13 MR spectroscopy [21]. Perfusion imaging, which depicts aspects of blood flow to tumor tissue, can be used as a surrogate for angiogenesis.

Perfusion imaging is performed with MRI using a variety of methods including dynamic susceptibility contrast (DSC) and dynamic contrasted enhanced (DCE) techniques in addition to arterial spin labeling (ASL) [22]. Common perfusion metrics include relative cerebral blood volume (rCBV) measured by DSC imaging, Ktrans, a transfer coefficient that correlates with leakiness of the blood brain barrier derived from DCE perfusion, and cerebral blood perfusion (CBF) a measure of the amount of blood flow through tissue per unit time, which can be acquired with ASL imaging.

Diffusion weighted MR imaging is used to generate the apparent diffusion coefficient (ADC) value for voxels within tumor and brain. This measure of water diffusion correlates well with cell density, especially when little or stable amounts of edema are present (edema increases the ADC and thus can confound cell density measurements). In addition to overall diffusion, the preferential direction of water movement (anisotropic diffusion) may be determined using diffusion tensor imaging (DTI) [23].

PET scans can be used to measure glucose metabolism using FDG as a tracer, as well as cellular proliferation with 3′-deoxy-3′[(18)F]-fluorothymidine (FLT). Depiction of amino acid uptake as a generalized measure of cellular metabolic and protein synthetic activity also is possible with a variety of PET tracers. FDG PET for brain tumor imaging is limited by high background cortical uptake, which can mask tumor glucose metabolism. This limitation is not present for amino acid PET tracers. Thus amino acid tracers, while limited by availability, have recently gained ascendancy for the imaging of brain tumors [3].

## 10.6 Advanced MR Imaging for Detection of 1p/19q LOH

Given the limitations in accuracy provided by standard imaging, advanced MR imaging has been assessed as a non-invasive method to improve identification of 1p/19q loss in oligodendrogliomas. Methods examined include perfusion and diffusion MRI, as well as MR spectroscopy. Jenkinson and colleagues originally reported in 2006 that 1p/19q loss was associated with higher rCBV in a cohort of mixed tumor grade (II and III) and subtype (oligodendroglioma and oligoastrocytoma) [24]. Subsequently a group at the University of Pennsylvania [25] found that rCBV was elevated in tumors with 1p loss for grade II tumors, but not grade III tumors, which they later confirmed in a larger study [26]. Another group provided

independent confirmation in 2013 [27]. Analyzing perfusion data using histograms (rather than "hot-spot" analysis) may improve the ability to identify both tumor grade and 1p/19q LOH status as Emblem and colleagues were able to separate six patients with low grade oligo without 1p/19q LOH from 46 other patients with grade II and III gliomas (both oligodendrogliomas and astrocytomas) with 93% accuracy [28]. It remains unclear why elevated rCBV, which is generally a predictor of more aggressive tumor, is associated with 1p/19 LOH tumors, which have a better prognosis. And why this is association is present in grade II but not grade III tumors also remains a mystery.

The added value of diffusion imaging in identifying 1p/19q LOH is less clear and discrepant results have been reported. Jenkinson and colleagues found that 1p/19q intact tumors had higher maximum ADC, but ADC did not differentiate between subtypes or grades [29]. Fellah and colleagues reported almost the exact opposite, specifically that ADC can help distinguish tumor grade, but is not associated with 1p/19q LOH [27]. The authors posit that this inconsistency may be explained by the small number of patients [17] in the Jenkinson study or potentially by differences in diffusion imaging acquisition protocols.

Another approach to identifying tumor subtypes is to measure metabolite concentrations using MR spectroscopy. MRS is commonly used to quantify N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr). NAA is a marker of neural integrity. Choline is proportional to membrane turnover and has been shown to have a linear relationship with cell density in glioma [30]. Cr is a marker of energy storage, and is depleted in highly cellular tumors; therefore, the ratio of Cho/Cr ratio is commonly used to identify areas of greatest tumor burden.

MR spectroscopy has been analyzed alongside perfusion data to determine if the combination improves differentiation of genotypes [13]. Apparently the Cho/Cr ratio is slightly higher in 1p/19q LOH versus 1p/19q intact oligodendroglioma (grade II and III tumors), and a multivariate logistic regression model using maximum rCBV and metabolite ratios can slightly improve the accuracy of genotyping from 68 to 72%, a 4% gain. Similarly, although diffusion and perfusion imaging and MRS independently do not identify 1p19q LOH reliably, a multiparametric approach combining these modalities results in a 1p/19q LOH misclassification rate of 40%, slightly improved over the misclassification rate of 48% with conventional MRI sequences [27]. So to date, the value gain from physiologic imaging in determining 1p/19q LOH over standard MRI is marginal at best, and the misclassification rate remains unacceptably high.

## 10.7 IDH Mutation

The isocitrate dehydrogenase (IDH) mutation, an early mutation in gliomagenesis, has been identified in the majority of LGG, including both astrocytomas and oligodendrogliomas [31]. The IDH mutation is associated with a hyper-methylated phenotype and also results in the accumulation of the oncometabolite 2-hydroxy glutarate (2-HG) in tumor cells, providing a unique target for imaging.

### *10.7.1 IDH1 Mutation and Anatomic Imaging*

IDH1 mutant tumors tend to have sharp margins (less infiltrative [32]) and are more homogeneous and less contrast-enhancing [33] than IDH1 wildtype tumors. Grade II and III tumors with imaging evidence of necrosis are more likely to be IDH1 wildtype and have a worse prognosis than tumors lacking evidence of necrosis by MRI [34, 35]. Immunohistochemistry with MRI coregistration has demonstrated that, as with wildtype tumors, IDH1 mutant LGG extend beyond the margin of the T2 signal abnormality [36, 37]. To date no imaging features from standard MRI have been identified that can reliably identify IDH1 mutant LGG.

Emerging evidence indicates that the anatomic location of gliomas is not evenly distributed throughout the brain. IDH mutant glioma are frequently present in the frontal lobe at the rostral aspect of the lateral ventricles as well as in the insula [38]; both of these regions also raise the possibility of an association with neural progenitor cells in the subventricular zone as the origin of IDH mutant gliomas. Similarly, using a voxel-based lesion symptom mapping (VLSM) atlas of 146 low grade gliomas Wang and colleagues [39] found that 102 of the tumors contained the IDH1 mutation, and these tumors were statistically more likely to be found to be in contact with the SVZ and to have rostral extension into the frontal lobe [39]. Frontal lobe preference has separately been reported for oligodendrogliomas with the 1p/19q codeletion [40, 41], which is not surprising since these tumors are frequently IDH1 mutated [31], and the IDH mutation precedes 1p/19q codeletion [42]. Similarly, when gliomas are limited to the insula, they are frequently (90%+) IDH1 mutated, whereas insular gliomas with extension to surrounding regions (paralimbic gliomas) have a lower rate of IDH1 mutation (approximately 50%) [43, 44].

There also appears to be a relationship between LGG location and brain regions defined by function as LGGs are located preferentially in secondary functional areas (cortical regions immediately adjacent to primary eloquent regions), including the supplementary motor area (SMA) in addition to the insula [45]. Compared to GBM, involvement of the SMA or insula is approximately twice as common in LGG. In consideration of the similarities in the computational roles of the insula and SMA, it has been hypothesized that a similar neuron-glial network may be utilized by these regions and may share a similar susceptibility to low grade glioma tumorigenesis. The reason for higher prevalence of LGG within the SMA and insula remains to be determined; and the progenitor cells of the SVZ hypothesis may not favor inclusion of the SMA as a typical site.

### *10.7.2 IDH1 Mutation and Advanced Imaging: Hypoxia/ Angiogenesis*

Several lines of investigation suggest that IDH1 mutant tumors are less angiogenic than their IDH wildtype counterparts. Using MR imaging, the IDH1/2 mutation is associated with decreased CBV compared to wildtype tumors in both low and high grade glioma [46–48]. Kickingereder and colleagues report that using genotype/

imaging phenotype correlation the odds of an IDH mutation decrease by 69% for each one-unit increase in rCBV [47]. In that study, IDH1 mutant tumors also were found to express lower levels of angiogenic genes. The potential association between IDH1 and angiogenesis is further supported by in vitro studies. For instance, lactate production (a by-product of hypoxia, which in turn drives angiogenesis) is absent in in vitro models of IDH1 mutant LGG, but present in wildtype GBM cells [21]. Thus perfusion imaging may provide a useful non-invasive method that can help detect differences in angiogenesis between wildtype and IDH1 mutant tumors.

### *10.7.3 IDH Mutation and Diffusion Imaging*

Diffusion imaging also has been applied to studies investigating the potential impact of the IDH1 mutation on imaging. Although values overlap, higher minimum ADC is found in anaplastic astrocytomas with versus without the IDH1 mutation [38]. Only limited data is available on the relationship between diffusion imaging and IDH mutational status in LGG. Multiple diffusion metrics, including the ratio of maximal fraction anisotropy and ratio of minimal ADC, (thought to in part reflect decreased angiogenesis and edema), can be combined to identify IDH1/2 mutant oligodendrogliomas with >90% accuracy [49].

### *10.7.4 IDH1 Mutation and MRS for the Detection of 2-HG*

The IDH1 and 2 mutations result in the production of 2-HG, a chiral compound, similar to an amino acid. The (R) enantiomer is the species associated with the IDH mutation, and this molecule accumulates in IDH mutant tumors cells in high concentrations (5–35 mM) [50]. It was quickly realized after this discovery that proton MR spectroscopy could provide a non-invasive method to detect 2-HG, which consequently could be used to identify IDH1 mutated glioma. Furthermore, serially quantifying 2-HG levels, it was thought, might add value to standard MRI in determining treatment response as well as tumor progression and transformation.

In 2011, we were the first group to demonstrate that a technique called MR point-resolved spectroscopy (PRESS) could detect elevated 2-HG levels in gliomas with the IDH1 mutation (Fig. 10.1) [51–53]. We found that MRS data correlated fairly well with 2-HG levels determined by mass spectrometry of ex vivo samples, although there was some overlap in MRS-detected 2-HG levels between mutant and wildtype tumors (potentially false positives in the wildtype group). Our findings were quickly supported by data from several other groups for in vivo [54, 53] and ex vivo tumor specimens [55, 56]. Subsequently we unequivocally confirmed the ability of MRS to detect 2-HG using a murine flank xenograft model in which we compared IDH1 mutant- versus wildtype-transfected glioma models: 2-HG was detectable only in the tumors with the IDH1 mutation [57].

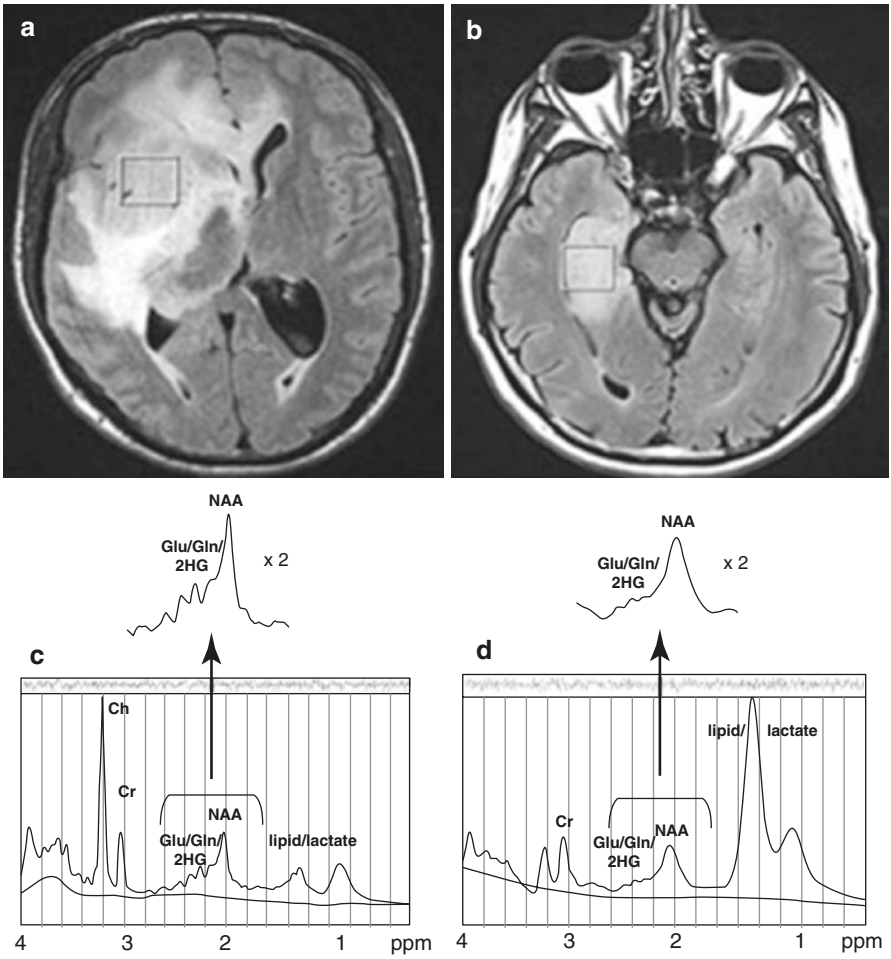


**Fig. 10.1** MR spectroscopy detects elevated 2-HG concentration in IDH-1 mutant glioma. (**a**) FLAIR image of IDH1+ glioma and corresponding spectrum (**c**) demonstrating 2-HG and overlapping glutamate and glutamine peaks which can be resolved with computer modeling for 2-HG quantification. (**b**) FLAIR image of IDH1 wildtype glioma lacking measurable 2-HG (**d**). From Pope et al., 2012, reprinted with permission from Springer Science and Business Media

### *10.7.5 Technical Limitations*

2-HG detection by MRS is hampered by overlying metabolite spectra, in particular that due to the structurally related molecules glutamate and glutamine. This can lead to false positive findings. Improved methods to separate the 2-HG signal from contaminating species include two dimensional correlation magnetic resonance spectroscopy (2D-COSY) [54] as well as difference editing [53]. Using 2D-COSY, a

sensitivity of 2 mM for 2-HG detection has been achieved. Others have reported a sensitivity of 1.5 mM, yielding essentially 100% accurate for identifying grade II and III wildtype versus IDH1/2 mutants [53]. To date, no other group has achieved this level of accuracy.

Another limitation of MRS for measurement of 2-HG in brain tumors is the requisite large voxel size, up to 27 $cm^3$ in some studies [54]. This can be problematic because smaller tumors may not entirely fill the voxel, leading to a dilution of tumor-associated metabolites due to incorporation of uninvolved brain parenchyma. The impact of small tumor size was demonstrated in a study in which 2-HG was detected by MRS in only 8% of small tumors (<3.4 mL) but in 91% of large (>8 mL) tumors, an impressive difference in sensitivity [58]. This may be a particularly important limitation following surgery when volumes of residual tumor can be quite small.

One way to improve separation of metabolite peaks is to use higher field strength magnets. This method led to the successful detection of 2-HG with an only 20 s acquisition time (studies using 3T typically have an acquisition time of 5–20 min) [59]. Other groups have also shown potential sensitivity gains for 2-HG detection using 7 Tesla (T) ultra-high field strength systems [60].

Another method developed to improve detection of IDH mutant tumors is to analyze multiple metabolite concentrations rather than 2-HG alone. Because glutamate levels are diminished in IDH1 mutant compared to wildtype glioma, models incorporating glutamate appear to improve sensitivity for the IDH1 mutation [61].

### *10.7.6 Clinical Utility of 2-HG Measurements*

As improved methods to non-invasively detect 2-HG levels in IDH1 mutant gliomas have been developed, attention has turned to the potential clinical utility of these measurements. De la Fuente and colleagues integrated MR spectroscopy into routine glioma imaging in 89 consecutive glioma patients [58]. In pre-op patients 2-HG levels corresponded to tumor cellularity, (an expected finding since it is the tumor cells that are producing 2-HG), but not with mitotic index or tumor grade. A significant limitation of the study was that the sensitivity of 2-HG detection in IDH1 mutant tumors was low—only 48%, apparently related to small tumor size in many of the enrolled patients. The authors report that, at least in one patient, reduction in 2-HG paralleled decrease in tumor volume during treatment. This is similar to another study which reported that 2-HG levels decreased in IDH1 mutant glioma patients after chemotherapy and radiation and that the volume of decreased 2-HG correlated with improved clinical status [62]. Survival data for this patient cohort is pending. Interestingly, change in FLAIR volume did not correlate with change in functional status. So the key question remains whether 2-HG measurements add value to standard MRI for detecting treatment benefit. One cautionary piece of data is that, at least in one report, there did not appear to be a survival difference between IDH1 mutant tumors with high versus low 2-HG [63]. Thus it is unclear how 2-HG levels, and therefore the drugs that target 2-HG production, impact patient outcomes.

## 10.8 Tumor Grading

Routine imaging suffers from poor accuracy in determining glioma grade [64]. Although in general GBM can be identified on standard imaging as ring enhancing lesions with evidence of necrosis and peritumoral edema, it is typically much more difficult to distinguish grade II and III gliomas, particularly when faced with a non-enhancing lesion with scant edema. Thus there may be a role for advanced imaging to identify LGG.

In oligodendrogliomas, the relationship between rCBV and tumor grade is unclear. Some have found no relationship [24], whereas other studies indicate a statistically significant correspondence between higher rCBV and higher tumor grade [26, 27]. A 76% accuracy for differentiating grade II and III oligodendrogliomas using a mean plasma volume derived from DCE MRI has been reported [65]. Discrepant conclusions may be due to the observation that, for unknown reasons, low grade oligodendrogliomas oftentimes exhibit focal areas of high rCBV [66] that may degrade the specificity of this metric [66]. Of note, CBV was a superior classifier of tumor grade compared to contrast-enhancement alone [66].

Falk and colleagues focused on identifying tumor grade in patients (n = 25) with suspected new diagnosed LGG (astrocytoma and oligodendroglioma), using both DSC and DCE perfusion MRI [67]. They found metrics for both modalities with moderate predictive ability for grade II versus III histology: DCE Ktrans skewness and rCBF both had accuracy of approximately 80%. DSC and DCE perfusion MR appear to be comparable in the ability to differentiate grade II and III gliomas [68]. Multiple other studies have assessed the ability of MR perfusion to separate tumors by grade, although a universal threshold has not yet been established [69–71].

ADC may help identify regions of higher tumor grade, and differentiate low from high grade gliomas. Accurate ADC-based grading is impeded by histological changes that can impact water diffusion such as mass effect from tumor and edema which do not necessarily correspond to a higher tumor grade. Advanced diffusion metrics derived from diffusion tensor imaging, which depict the relative direction of water motion, may improve the ability to assign tumor grade. One study found that diffusion tensor imaging, but not perfusion imaging, accurately discriminated low versus high grade non-enhancing glioma with a specificity of 92% and sensitivity of 87% [72].

The clinical utility of determining tumor grade by MRI is questionable, as most tumors proceed to biopsy or resection where the tumor grade and type will be definitively established histopathologically. Additionally, resected tissue provides the opportunity for full molecular characterization of tumors, which is becoming more critical to patient management decisions. However, some tumors may be located in areas that preclude biopsy due to unacceptable risk. Lastly, biopsies may undergrade tumors due to sampling error, i.e. not sampling the most malignant portions of the tumor. Thus there is a limited, but still impactful, role for imaging in identifying tumor grade [73].

## 10.9 Prognosis and Detecting High-Grade Transformation

LGG oftentime undergo transformation to higher grade (grade III and grade IV) tumors which usually signals a period of increased growth and treatment resistance, ultimately leading to the patient's death. Thus there is great interest in early markers of this transformation. Traditionally the development of contrast-enhancement in previously non-enhancing tumors is thought to be indicative of development of grade III/IV tumors. However, this simplistic approach may be inaccurate. For example, in a series of 108 grade II glioma, contrast enhancement as a marker for higher grade histology had a sensitivity of 92% but a specificity of only 57% [74]. Clearly, specificity needs improvement.

Neo-angiogenesis, i.e., microvascular proliferation, is a required step in the transformation of low- to high-grade glioma and may be detectable by perfusion imaging. Microvascular proliferation is typically absent in LGG and they usually have low levels of perfusion as measured by MR [75]. In 2001, Fuss and colleagues demonstrated that in patients with low-grade-astrocytoma (n = 25) treated with fractional stereotactic radiotherapy, tumors progressing prior to 42 months after radiotherapy had higher pretreatment rCBV than those that recurred later [76]. Subsequently, a seminal work by Law and colleagues assessed changes in perfusion in LGG as a marker of increasing tumor aggressiveness [77]. They demonstrated that among LGG, a CBV of 1.75 was discriminatory for time to progression and adverse outcome (Fig. 10.2). Over a 4-year follow up period, all LGG with CBV under 1.75 had nonsignificant growth. Time to progression (TTP) was 4620 days in

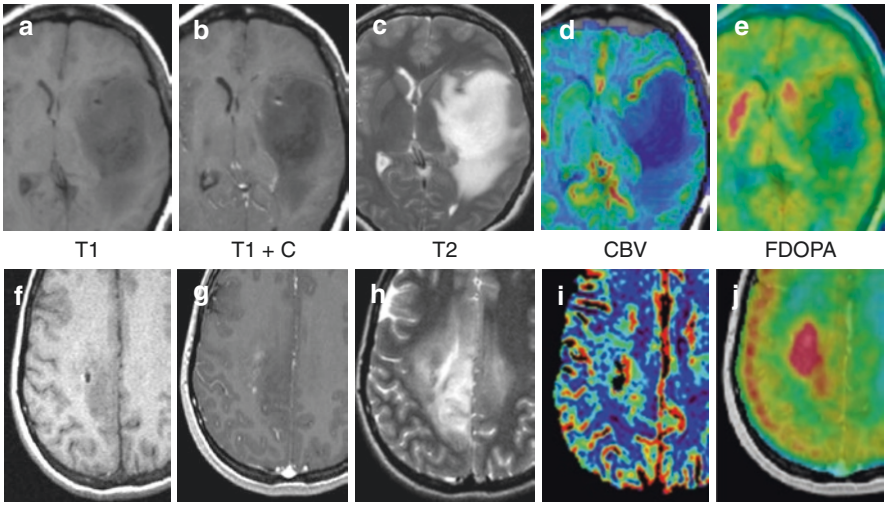


**Fig. 10.2** Multiparametric advanced imaging may help refine patient prognosis. (**a**–**e**) Grade II Astrocytoma, IDH1+, 1p/19q intact with low rCBV (<1) low FDOPA uptake (tumor: basal ganglia ratio <1) and long (>2 years) PFS survival. (**f**–**j**) Grade II Oligodendroglioma, IDH1+, 1p/19 LOH with elevated rCBV (>2), high FDOPA uptake (tumor: basal ganglia >1) and short PFS (<6 mos). Both increased rCBV and increased FDOPA uptake are associated with shorter survival in LGG

these tumors, whereas in LGG with rCBV >1.75, TTP was only 245 days. Importantly the authors did not find an association between contrast enhancement and time to progression. The association between elevated rCBV and diminished TTP in LGG was later confirmed by the authors in a multi-institutional study which included data from University College, London [78]. The London group also published a report specifically designed to test the hypothesis that longitudinal MR perfusion imaging predicts malignant transformation [79]. They found this was indeed the case in a study of patients with conservatively treated LGG that underwent malignant transformation, comparing the "transformers" to "non-transformers:" rCBV was essentially low and stable in non-transformers (around 1.5) but steadily rose to a mean of 5.4 in transformers. Substantial increases in rCBV could be detected up to 12 months prior to the development of contrast enhancement [79].

The University College London group also analyzed growth rate as a marker of malignant transformation [80], and compared it to rCBV and diffusion parameters [81]. They found that average growth rates were lower in non-transformers compared to transformers and that growth rates increased to a rate of 56% (by volume) per year in the 6 months before transformation. Furthermore, they showed that 6-month tumor growth was a better predictor of patient outcomes that perfusion- or diffusion-derived metrics.

MRS has been used to identify oligodendrogliomas undergoing anaplastic transformation as well. In a sample of 20 oligodendrogliomas followed for 30 months on average, Cho/Cr ratio>2.4 reliably identified anaplastic transformation, but only in patients without, and not with, 1p/19q LOH (Fig. 10.3) [82]. The number of transformers was only 6 in this study (4 without 1p/19q LOH), so caution regarding the conclusions is advisable. However, if replicated, this example is illustrative of how an imaging biomarker can be dependent on a tumor's molecular status. In a much larger study of recurrent (n = 111, 71 transformers) LGG combining both oligodendrogliomas and astrocytomas, MRS was combined with perfusion and diffusion data to determine if a multiparametric approach could help improve the ability to identify malignant transformation [83]. The best multivariate model incorporated Cr, Cho/NAA, diffusion parameters and the volume of T2 signal abnormality and was accurate in 76% of patients in identifying malignant transformation. Oligodendrogliomas were misclassified at a higher rate (35%) than astrocytomas (17%) or mixed gliomas (20%). It is unclear whether the high rate of misclassification for oligodendrogliomas was impacted by 1p/19 allele status as previously reported [82].

In addition to prognostic markers, markers that indicate treatment response are being sought. Since tumor-size change on standard MRI may take months to develop, early response markers of treatment efficacy could speed clinical decision making. To date few early markers of response for LGG have been developed. One avenue that may be productive is to assess metabolic changes with MR spectroscopy. A pilot study (n = 12) showed that serial changes in choline over 1 year paralleled changes in tumor volume for patients with LGG treated with temozolomide (TMZ) [84]. Decreased Cho/Cr and Cho/NAA ratios could be observed 1 month after treatment initiation with TMZ whereas standard MRI showed little

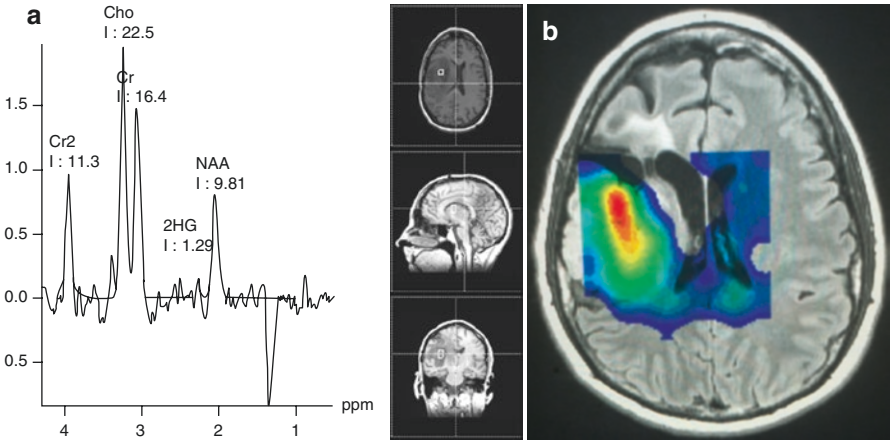


**Fig. 10.3** Single and multi-voxel MR spectroscopy of grade II astrocytoma, ID1 mutant, 1p/19q LOH. (**a**) Single voxel spectroscopy shows 2-HG resonance to the left of an abnormally low NAA peak, compatible with an IDH1 mutant tumor. (**b**) Multi-voxel spectroscopy with pseudocolor Cho (*red* = higher concentration) illustrating variable Cho within the tumor with the highest concentration in the central and anterior portion of the mass. In the single voxel spectroscopy (**a**) the Cho/Cr ratio is <2.4. A Cho/Cr ratio>2.4 has been associated with malignant transformation, but only in 1p/19q intact tumors (Bourdillon 2015 [72]). Cho (choline), Cr, Cr2 (creatine) NAA (N-acetyl-aspartate)

change [85]. Additionally, the mean relative decrease in choline at 3 months was predictive of outcome at 14 months. Perhaps most interestingly, change in the ratios of metabolites including Cho, NAA and Cr was predictive of relapsed tumor with a sensitivity of 60% and a specificity of 100%. Thus early response markers for effective LGG are limited, but could be highly impactful following additional validation.

## 10.10 PET Imaging

PET provides a non-invasive method to image tissue metabolism and has been extensively studied in brain tumors. Although most reports initially used FDG, a glucose analog, as the PET tracer, data using non-FDG-PET has become more common. In particular, the use of amino-acid tracers, which have increased uptake in gliomas of all grades, alleviates the problem of background cortical activity which is a substantial limitation of FDG [3]. Several studies have highlighted the superiority of amino acid tracers compared to FDG. For instance, it has been shown that $^{11}$C-methionine (MET)-PET is superior to FDG-PET for the detection of recurrence in low-grade glioma [86, 87]. $^{18}$F-fluoro-ethyl-l-tyrosine (FET), another amino acid tracer, has been shown to be superior to FDG in the diagnosis of patients with gliomas of all grades [88].

Amino acid PET also has been used to non-invasively assess tumor grade and prognosis. On dynamic FET-PET imaging, higher-grade gliomas tend to have rapid uptake followed by decreasing uptake (washout), while lower grade gliomas have ascending or plateau kinetics [89]. This technique classifies high and low grade gliomas with both sensitivity and specificity of at least 80% [89, 90]. Another interesting observation is that [1] tumors with homogeneous malignant uptake kinetics (i.e., washout kinetics) lacked low-grade regions and [2] tumors with homogenous benign uptake kinetic lacked high-grade regions. Thus, this method provides insight into the regional heterogeneity of tumor histology as well.

MET PET has also been investigated as a marker for prognosis, treatment effect and tumor grade. Ribom and colleagues found that high MET uptake was associated with shorter TTP in patients with LGG, an association driven by the predictive value in oligodendrogliomas rather than astrocytoma or mixed glioma [91]. They also found that only patients with high MET uptake appeared to benefit from surgical tumor resection [92]. Similarly, in a later study the same group reported that high MET uptake in pre-treatment LGG correlated with reduction in MET uptake in response to radiotherapy [93]. Unfortunately decrease in MET activity following therapy initiation did not appear to correlate with outcome [91]. More recently Takano and colleagues found that MET, unlike FDG, uptake is higher in non-enhancing grade III compared to grade II glioma, (yielding a sensitivity of 83% and specificity of 74% for identifying grade III tumors), and there was much longer PFS (64 v 18 months) in grade II patients with low MET uptake [94]. Conversely, MET uptake was not prognostic for patients with either grade III glioma or for patients who received adjuvant therapy. Thus MET uptake may be a prognostic biomarker for grade II glioma and may help distinguish grade II from III glioma, but its utility in predicting or detecting favorable (non-surgical) treatment response is questionable.

Inextricably linked to prognosis is the time to transformation into higher-grade tumors. Galldiks and colleagues found that for FET-PET the tumor-to-brain ratio and kinetic parameters both provided valuable information for the detection of malignant progression [95]. Specifically, a change in time-activity curves on FET-PET from a positive to negative slope paired with increasing FET uptake were prognostic of tumor progression. Similar findings were reported by others [90, 96]. Interestingly static FET-PET does not provide prognostic information [96, 97]. However dynamic, compared to static, FET-PET, is more useful in predicting recurrence of LGG [98]. Tumor uptake of both FDOPA [99] and the mitotic marker FLT [100] have both been shown to be associated with shorter survival and earlier tumor progression in LGG (Fig. 10.2), but the added value of dynamic PET imaging has so far been shown only for FET.

Static FET and FDG PET appear to have little power to discriminate molecular features of LGG in comparison to dynamic FET-PET. For example, in a cohort of 54 WHO grade II gliomas, no difference was found in static FET-PET in IDH1 mutant versus IDH1 wild type gliomas [97]. Similarly, no significant difference in IDH1 mutant versus wild type gliomas was seen with FDG-PET [101]. On the other hand, using dynamic imaging IDH mutations are frequent in tumors with

homogeneously increasing (90%) and focally decreasing (79%) time-activity curves, but are uncommon in those with homogeneously decreasing time-activity curves [90].

The ability of PET to reliably detect 1p/19q LOH has been investigated in multiple studies with somewhat conflicting results. In 2011, Shinozaki and colleagues reported that oligodendroglioma with 1p/19q LOH had lower MET uptake compared to those with intact alleles [102]. Conversely Saito and colleagues found that the 1p/19q LOH was associated with higher MET uptake compared to tumors without 1p/19q LOH [103]. In 2016, the Shinozaki group confirmed their earlier results in a larger cohort of patients (37 grade II and 29 grade III oligodendrogliomas), again finding that 1p/19q LOH was associated with lower MET uptake, in both grade II and grade III tumors [104].

Studies with FET-PET also have been performed. 1p/19q LOH is associated with higher FET in oligodendroglial tumors, but FET-PET does not well predict 1p/19q LOH in individual patients when both astrocytic and oligodendroglia tumors are combined, because high-grade astrocytic tumors also have high FET uptake [105]. In a study of only suspected grade II oligodendrogliomas using a dynamic FET-PET analysis, 1p/19q LOH is associated with a focally decreasing time-activity curve [90]. Higher FET uptake is also associated with 1p/19q LOH [97].

In addition to 1p/19q LOH, there also may be a relationship between amino acid PET uptake and other prognostic molecular features. For instance, in a study of 20 patients with grade II non-enhancing glioma, tumors with tumor/normal brain (T/N) MET uptake ratio of $\geq$1.6 were more likely to have MGMT promoter methylation above 3% [106]. No patients with T/N ratio of <1.6 had MGMT >3% [106].

Thus similar to MR, PET scans may be useful for noninvasively identifying tumor grade, prognosis and molecular features including 1p/19q LOH and MGMT promoter methylation. Optimal combinations of MR and PET data to maximize non-invasive imaging accuracy are being investigated, and may become better elucidated with the greater availability of MR-PET imaging systems.

## 10.11 Conclusions and Future Directions

The amount and complexity of data that can now be acquired to characterize LGG is much larger than ever before. Imaging, including MRI and PET, non-invasively and globally surveil tumors and can be used to reveal a variety of malignant processes that influence patient prognosis and potentially treatment susceptibility. However, methods to combine imaging and molecular information streams into actionable clinical paradigms remain underdeveloped. Advanced mathematical and other modeling may be required to optimally leverage this “big data”, and to more fully understand the interaction between imaging biomarkers and subclasses of tumors based on molecular features including 1p/19q LOH and the IDH mutations. These models also will need to be tailored to ongoing clinical developments such as targeted drug therapy. In general, there will be greater need for predictive, rather

than merely prognostic, markers for tumor therapy, in order to maximize clinical impact. The development of better early therapy response markers that can be acquired before changes in tumor size are apparent also is a critical unmet need. Lastly, as the number of important tumor subclasses grows, it will be ever more challenging for single institutions to generate patient cohorts large enough to allow for meaningful analysis. Continued multicenter collaborations in conjunction with standardized patient imaging protocols and post-processing methods will likely be a necessity for further progress in imaging biomarker development and validation.

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# Part III
# Clinical Aspects and Diagnostic Imaging

# Chapter 11
# Clinical Presentation in Diffuse Low-Grade Gliomas

**Anja Smits and Asgeir S. Jakola**

**Abstract** Due to the slow growth of DLGG with frequent involvement of eloquent areas and diffuse infiltration of subcortical pathways, the clinical presentation of patients with DLGG shows a large variety. The natural course of DLGG is considered to occur as a continuum with an initial silent period, followed by a symptomatic period characterized by new-onset seizures but without functional deficits, and a final period of malignant progression where focal deficits or increased intracranial pressure may occur. However, such a schematic view of the step-wise development of DLGG over time may be misleading. Recent literature gives support for a high prevalence of subjective complaints and minor cognitive deficits already during the silent phase of DLGG when tumor diagnosis is still unknown, suggesting that patients with incidental DLGG should be considered as "not yet diagnosed" rather than "asymptomatic". These insidious symptoms may be unrecognized but present and affect emotional and cognitive functions. Also, malignant tumor transformation can precede the development of clinical symptoms for long periods of time, indicating that the absence of progressive symptoms does not protect against malignant transformation. Not surprisingly, the feeble association between tumor-related symptoms and signs on one hand and the natural course of disease on the other makes traditional clinical surveillance ("watchful waiting") inadequate to detect important biological changes within DLGG. As the biological clock is about to change from a slow and continuous growth towards a more aggressive biology, there is a fine line between what is considered "too early" and what may be "too late" with respect to tumor treatment. A more comprehensive understanding of the tumor-related symptoms and

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signs at presentation, including how these parameters are correlated with molecular tumor characteristics, is a prerequisite for optimal clinical management.

**Keywords** Diffuse low-grade gliomas • Clinical symptoms • Disease onset • Epileptic seizures • Cognitive deficits

## 11.1 Introduction

Diffuse low-grade gliomas (DLGG) are slow-growing primary brain tumors. According to the WHO classification of brain tumors, DLGG consist of gliomas WHO grade II [1] that are characterized by extensive invasion but only low proliferation. DLGG occur mainly in adult life with a peak incidence around 30–35 years. The clinical course for patients with DLGG is very diverse but all tumors transform into high-grade gliomas and will eventually lead to death.

Most DLGG will demonstrate indolent behavior initially. Longitudinal studies using sequential MRI over time have demonstrated a linear expansion of approximately 4 mm/year in diameter of the bulky tumor mass during the entire time course before malignant progression occurs [2]. In parallel with the continuous expansion over time, tumor cells migrate diffusely along white matter pathways and have been demonstrated well beyond the radiological border [3, 4] (Fig. 11.1). By means of mathematical models it has been estimated that the invasion rate of glioma cells in the white matter is about five times higher than in the gray matter [5]. Given the limited plasticity of the white matter and the infiltrative character of DLGG, tumor resection of tumors with infiltration of subcortical pathways imposes a major surgical challenge.

More than 90% of all patients with DLGG are diagnosed during the symptomatic period and 70–90% of these patients have new-onset seizures as the first tumor-related symptom [6]. In general, seizure semiology reflects the specific location of the tumor with the somatotopic organization of cortical brain functions. Brain tumors give rise to partial (also called focal) seizures that occur with or without secondary generalized tonic-clonic seizures. The epileptic origin of partial seizures, in particular those originating from temporal or fronto-insular regions, may sometimes be difficult to recognize. Seizures may therefore go unnoticed for long time periods and it may not be until tonic-clonic seizures arise that patients seek medical ward.

Not all patients with DLGG present with new-onset seizures. DLGG are sometimes diagnosed incidentally in patients who undergo radiological examination for reasons or symptoms not related to the tumor [7]. This is in line with the natural course of DLGG that is traditionally considered to occur as a sequential three-step process; an initial silent period, followed by a symptomatic period, and a final period of malignant progression. From a clinical point of view, such a schematic view of the step-wise development of DLGG over time may be misleading. For example, in the silent phase with tumor diagnosis still unknown, insidious clinical symptoms may be present but unrecognized [8, 9]. Furthermore,

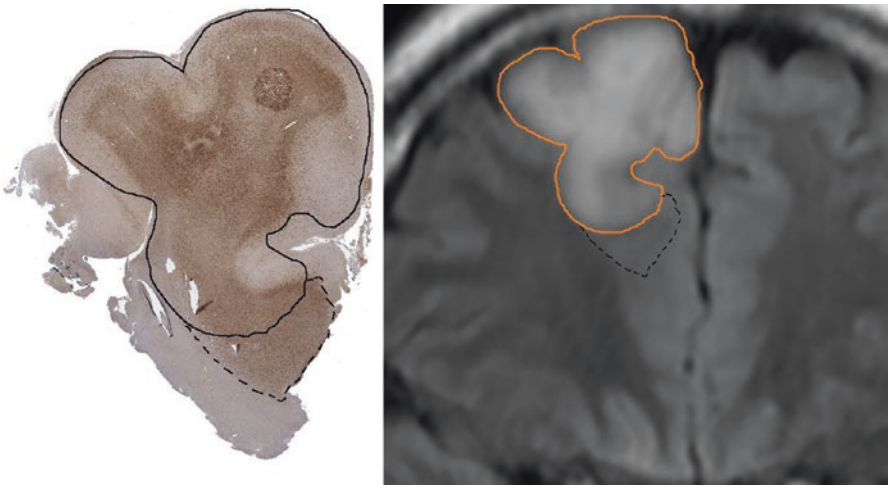

**Fig. 11.1** MRI of a patient with an oligodendroglioma WHO grade II in the right frontal pole. A right frontal lobectomy was performed with en-bloc removal of the tumor. Postoperative MRI confirmed that the tumor had been completely resected. An area with a high density of tumor cells was detected outside the radiological border. *Left*: An IDH1 image (with tumor cells brown-stained by the anti-IDH1-R132H antibody) showing the radiological border delineated by a *solid line* and the tumor cells outside the radiological border indicated by a *dashed line*. *Right*: The corresponding preoperative T2-FLAIR image with the radiological tumor border delineated by a *solid line* and the area with tumor cells missed on MRI delineated by a *dashed line* (from [4], J Neurosurg. 2016 Feb 26:1–12; reprints made with permission from the publisher)

malignant progression may occur prior to the development of neurological deterioration, indicating that the absence of progressive symptoms does not protect against malignant transformation [8].

Not surprisingly, the feeble association between tumor-related symptoms and the natural course of disease makes traditional clinical surveillance ("watchful waiting") inadequate to detect important biological changes within DLGG. As the biological clock of DLGG may change suddenly to reveal a more aggressive biology, there is a fine line between what is considered "too early" and what may be "too late" with respect to tumor treatment. In other words, regardless of when patients are diagnosed within this continuum, there is a need to systematically consider early surgical intervention in light of the favorable impact of this strategy over "watchful waiting" for long-term outcome [10]. Interestingly, a recent trial showed that chemotherapy was also associated with better outcome when delivered early compared to as a rescue therapy at the time of tumor transformation [11]. These data illustrate the fundamental changes in view over the years in favor of early and maximal safe treatment for these differentiated and slowly proliferating tumors, which can be considered as a paradigm shift. They also underline the importance of a more comprehensive understanding of tumor-related symptoms and signs at presentation, and how these parameters relate to the molecular characteristics of the tumor, which is the focus of this chapter.

## 11.2 Clinical Symptoms

### *11.2.1 Incidental DLGG*

It has been estimated that 3–10% of all DLGG are discovered incidentally, i.e. when radiological examination is performed for reasons unrelated to the tumor [12, 13]. In general, patients with incidental DLGG have smaller tumor volume, less frequent involvement of eloquent areas, and better performance score [14]. A recent study reported a high prevalence of subjective complaints but also of attention deficits and disturbances of working memory and executive function in patients with incidental DLGG, suggesting that these patients are to be considered as "not yet diagnosed" rather than "asymptomatic" [8]. It is not clear whether incidental DLGG constitute a specific subpopulation of tumors, and more studies are needed to clarify this important issue. In a retrospective case series of 23 incidental DLGG having surgical treatment, the majority consisted of IDH1-mutated, 1p/19q-codeleted oligodendrocytomas that in itself is a favorable prognostic subgroup [14].

### *11.2.2 Epileptic Seizures*

Partial seizures due to brain tumors are divided in simple partial and complex partial seizures. There is no impairment of consciousness in case of simple partial seizures, while patients with complex partial seizures experience varying levels of clouded consciousness. Simple partial seizures are most common in patients with high-grade gliomas, complex partial seizures are more frequent in DLGG. In general, complex partial seizures consist of an initial phase that precedes clouding of consciousness (patients will be able to recall and report these initial experiences), followed by involuntary movements called automatisms such as lip smacking, chewing or picking at clothes. However, epileptic symptoms may vary from one patient to the other and the separate seizure components cannot always be distinguished. As mentioned, partial seizures may go unnoticed for long time periods and patients seek medical ward first when a secondary generalized tonic-clonic seizure arises.

Seizure semiology reflects the specific tumor localization with the somatotopic organization of cortical brain functions. The most common location of DLGG is the frontal lobe. Asymmetric tonic seizures, characterized by tonic arm extension and elevation followed by forced head deviation to the side of the extended arm (often but not always contralateral to the tumor) are strongly associated with frontal tumor locations, especially with seizure origin in the supplementary motor area [15]. Partial Jacksonian motor or somatosensory seizures, examples of simple partial seizures, are related to tumor location in perirolandic areas. Other typical manifestations of frontal lobe seizures are speech arrest or motor agitation, the latter characteristically occurring at night or upon awakening in early morning, and in

patients with deeply seated frontal lobe tumors. This seizure type is sometimes mistaken for non-epileptic psychogenic seizures.

Temporal lobe seizures can be difficult to differentiate from frontal lobe seizures [16]. Patients with partial complex seizures due to temporal lobe tumors typically report characteristic symptoms consisting of déjà vu phenomena, visceral sensations such as epigastric rising, gustatory or olfactory auras. Auditory hallucinations, language or memory disturbances may also be part of temporal lobe seizures.

Seizures originating in the insular cortex may mimic temporal lobe seizures. In a series of 50 patients referred for preoperative evaluation of temporal lobe epilepsy, six patients with insular seizures had discharges on ictal EEG recordings that were distinct enough to allow differentiation from seizures with temporal origin [17]. In full consciousness these patients with pure insular seizures reported laryngeal discomfort with thoracic and abdominal oppression or dyspnea, unpleasant paresthesiae or warmth sensations in the face and extending to larger cutaneous territory, eventually followed by dysarthric speech and focal motor convulsions [17].

A less common location for DLGG is the occipital region. Patients with occipital lobe tumors may experience partial seizures consisting of positive visual symptoms such as flickering or blinking lights or visual disturbances such as micropsy and macropsy, but may also have visual field defects or blurred vision during seizure activity as in migraine.

### *11.2.3 Neurological and Cognitive Symptoms*

The majority of patients with DLGG do not show sensorimotor deficits at presentation or during the entire pre-malignant phase of the disease. Standard neurological examination of patients with DLGG in eloquent location at the time of diagnosis is therefore usually normal. The slow growth of DLGG allows for cortical adaptor mechanisms, leaving time to reorganize the brain [18]. This brain plasticity that is characteristic for DLGG does not or only to a very limited extent, occur in patients with fast growing brain tumors such as glioblastomas. As a consequence, patients with high-grade gliomas frequently show neurological deficits at presentation [19]. The plasticity of subcortical structures is however limited, and patients with DLGG that infiltrate subcortical connectivity may also suffer from early functional deficits. The prevalence of functional deficits in patients with DLGG at clinical presentation is probably underestimated. Indeed, it has been estimated that more than 90% of all patients with brain tumors has at least some cognitive impairment prior to therapy [20].

Neuropsychological examination prior to any treatment is the only way to decipher tumor-induced cognitive changes from treatment-induced cognitive deficits. Further, the presence of cognitive deficits is strongly correlated with the health-related quality of life of patients with brain tumors [21, 22]. To our mind, this clearly justifies the inclusion of neuropsychological examination as

part of the diagnostic procedure at disease presentation. Most of our knowledge on cognitive performance at the time of diagnosis comes from observational studies where cognitive function at diagnosis has been evaluated as baseline performance prior to treatment. Wu and co-workers compared neuropsychological function in patients with insular gliomas with a matched control group with non-insular gliomas and found frequent impairment in learning and memory in both groups [23]. Patients with insular tumors exhibited worse function in tests on naming [23].

In the elderly population of DLGG, sensorimotor deficits as well as cognitive impairment and language disorders at diagnosis are more often present while seizures occur less frequently as initial symptoms compared to younger patients [24]. These age-related differences in symptoms reflect a generally more aggressive tumor growth in the elderly population, favoring neurological and cognitive deficits over seizures in elderly patients with DLGG.

### *11.2.4 Mental-Health Related Symptoms*

Depression and anxiety in patients with DLGG at clinical presentation may be caused by the psychological stress of brain tumor diagnosis, by the tumor itself or by a combination of these factors. Importantly, preoperative depression was associated with shorter survival in patients with DLGG [25]. Patients with tumor location in the right hemisphere had higher anxiety levels than patients with left sided primary brain tumors [26]. Still, brain tumor sidedness does not seem to have a large impact on the overall quality of life [27]. Behavioral disorders with changes in personality do sometimes occur in patients with DLGG but are more frequently found in patients with glioblastomas [22].

Fatigue as a multidimensional symptom including concentration problems, reduced motivation and physical activity, is frequently reported by cancer patients. Fatigue as a symptom related to DLGG has been studied mostly with regard to treatment or in long-term survivors [28]. In this population, fatigue was a severe problem in a large proportion of patients, with highest levels in elderly patients and patients using anti-epileptic drug treatment [28]. Six out of 15 patients with incidental DLGG reported subjective complaints of tiredness [8]. Thus, tiredness and other insidious symptoms may occur already during the silent phase of DLGG, demonstrating once more that patients with incidental DLGG are not necessarily asymptomatic. It may be argued that such unspecific symptoms are just as common in the normal population and thus not necessarily caused by the tumor. On the other hand, it was reported that 36% of patients with DLGG encountered adjustments in work tasks or reduced workload already one year prior to tumor diagnosis, which is higher than expected in the normal working population [29]. These data suggest that disease-related psychological and/or neurocognitive symptoms may precede radiological tumor diagnosis and underscore the importance of a

comprehensive neurological and neuropsychological examination at initial visit to the clinic.

### *11.2.5 Implications of Symptoms for Clinical Management*

Since many patients with DLGG present with seizures and show normal function at routine neurological examination, many centers have practiced "watchful waiting" as their primary strategy [10]. Even though this strategy does not jeopardize short-term quality of life, the cumulative quality of life of patients may be severely impaired due to earlier malignant transformation and death [30]. It is also worth noting that medically refractory seizures, which are amongst the most disabling symptoms, may respond well to extensive surgery [31]. Thus, extensive surgery is a potent symptomatic treatment for the most important tumor-related symptoms at presentation and provides long-term benefits in terms of improved survival.

Concerning the optimal treatment strategy for incidental DLGG, it is currently difficult to decipher the apparent excellent results from surgical treatment of incidental DLGG from the effects of the beneficial molecular profiles of these tumors and lead-time bias [7, 12, 14, 32]. It should always be born in mind that brain surgery itself may cause morbidity in terms of neurological impairment, cognitive disabilities and impaired quality of life. Nevertheless, since incidental DLGG demonstrate similar growth dynamics as symptomatic DLGG, early intervention is likely to be beneficial and to contribute to better chance of radiological complete tumor removal [10, 33]. Even though more studies are needed on both short-term and long-term implications of early tumor resection, the adverse effects of surgery seem to be acceptable for patients with incidental DLGG. Based on the current knowledge, most patients should therefore be given the option and advice to undergo early resection regardless of symptoms at presentation.

## 11.3 Radiological Presentation

### *11.3.1 Morphological MRI: Characteristic Findings*

The RANO (Response Assessment in Neuro-Oncology) group for DLGG has provided criteria for the diagnosis and follow-up of non-enhancing tumors [34]. According to these criteria, morphological magnetic resonance imaging (MRI) is the imaging modality of choice for initial diagnosis with a protocol including non-enhanced and enhanced T1-weighted sequences, T2-weighted and T2-fluid attenuated inversion recovery (FLAIR) [34]. As such, MRI shows anatomical tumor location, tumor size, and contrast enhancement at presentation and is used to determine the individual tumor growth rate by repeated volumetric measurements over

time. In general, DLGG show MRI signal intensities with hypointensity on T1-weighted images and hyperintensity on FLAIR or T2-weighted sequences (Fig. 11.2). The absence of contrast enhancement after administration of gadolinium-based MR contrast agent is characteristic for DLGG, but has low specificity and low sensitivity to differentiate DLGG from anaplastic gliomas. Approximately 20% of DLGG enhance, whereas approximately one third of non-enhancing gliomas consist of high-grade gliomas [35, 36]. Especially low-grade oligodendrogliomas may show minimal to moderate patchy, multifocal contrast enhancement [37]. This has been reported in up to 50%, distinguishing oligodendrogliomas from other DLGG, and is thought related to the tight capillary network that is a histological hallmark of these tumors [37].

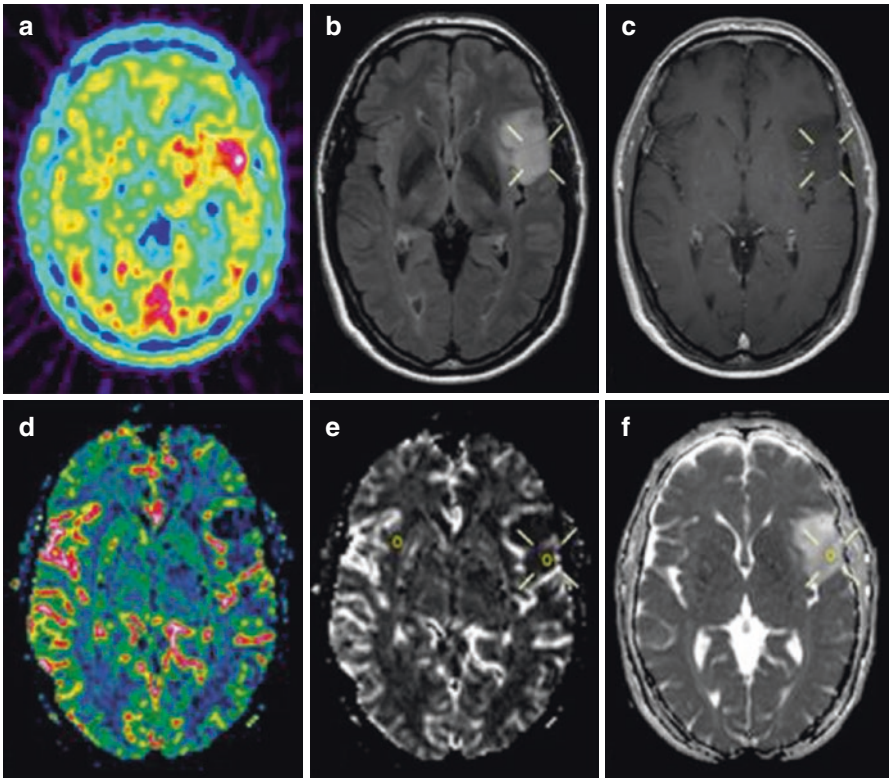


**Fig. 11.2** Preoperative $^{11}$C-methionine-PET and MRI of a patient with a left-sided frontal astrocytoma grade II. (**a**) PET study shows the hot spot area in the tumor (hot spot/cortex ratio 1.6). (**b**) T2-weighted FLAIR MRI shows a high signal intensity tumor. (**c**) T1-weighted contrast-enhanced MRI shows a non-enhancing hypointense tumor. (**d**) Perfusion-MRI with rCBV *color* map shows low perfusion in the tumor area. (**e**) Perfusion-MRI with rCBV *grey*-scale map shows low perfusion in the region corresponding to hot spot on PET. The region of interests in the tumor and the contralateral normal appearing *white* matter are shown. (**f**) Diffusion-MRI shows increased mean diffusion in the region corresponding to the hot spot on PET

### 11.3.2 MRI-Based Estimation of Tumor Extension

Morphological MRI tends to underestimate the extension of DLGG [37]. Previous studies by multiple biopsies have identified tumor cells outside the radiological border on FLAIR or T2-weighted MRI sequences [38]. A recent report using co-registration of histology with MRI in en-bloc removed DLGG demonstrated tumor cells at 1–2 cm outside the radiological tumor borders, defined as the normal-appearing brain on FLAIR or T2-weighted images, in all tumors [3] (Fig. 11.1).

### 11.3.3 Volumetric Assessment of Initial Growth Dynamics

The assessment of volumetric growth may provide valuable information for differential diagnosis, especially when non-tumorous lesions or more uncommon variants of WHO grade II tumors like gangliogliomas are considered. If the tumor grows similar to the often quoted 4 mm/year in diameter, the likelihood increases that the image finding indeed is a DLGG [40]. Also, the initial growth rate may provide valuable prognostic information in DLGG [41, 42]. For widespread clinical implementation, more studies of measuring volumetric assessment including the inter- and intra-observer variability of the manual or semiautomatic methods are welcomed.

### 11.3.4 Advanced MRI

Advanced MRI methods like perfusion (pMRI) and diffusion (dMRI) imaging, providing information on tumor vascularity respectively cellularity, are now valuable diagnostic tools in neuro-oncology (Fig. 11.2). The pMRI parameter maximal cerebral blood volume ($CBV_{max}$) reflects neo-vascularization and correlates with malignancy grade [43, 44]. DLGG lack microvascular proliferation and have generally lower regional CBV (rCBV) values than high-grade gliomas [45]. In clinical practice, pMRI of DLGG is still limited to visual interpretation of perfusion maps representing mean values of measured parameters. Oligodendrogliomas tend to have higher rCBV values than astrocytic tumors, due to higher cell density and typical dense capillary networks in oligodendrogliomas.

dMRI measures the random motion of water molecules in tissues, reflecting their microarchitecture. Tumor diffusion as measured by dMRI provides quantitative information about tissue water diffusion and correlates with tumor cell density [45]. Diffusion is decreased in malignant gliomas due to a higher cellularity with restricted motion of water molecules in the extracellular space. In spite of generally lower mean diffusion (MD) in high-grade gliomas than in DLGG, it is difficult to predict tumor grade by dMRI due to the marked overlap in MD values between gliomas of different histological subtype and grade [46].

Functional MRI can provide valuable preoperative information of functional areas in case of tumors with eloquent location but is still mostly restricted to specialized centers [47]. MR spectroscopy (MRS) is used to measure regional variations in neurochemistry and the concentration of various brain metabolites, which may be valuable for differential diagnosis from non-tumorous T2 hyperintensive lesions. Interestingly, MRS may allow non-invasive characterization of the IDH status of the tumor through detection of the metabolite 2-hydroxyglutarate, and provide a valuable tool for disease monitoring [48, 49]. Diffusion tensor imaging (DTI) is used to map the three-dimensional diffusion of water as a function of spatial location and able to estimate the white matter connectivity patterns in the brain in relation to the tumor. Concerning the diagnostic value of advanced MRI for DLGG in clinical practice, the RANO group concluded in their report from 2011 that dMRI, pMRI and MRS are used upon indication in individual cases while positron emission tomography (PET) may be considered for tumor grading [34].

### *11.3.5 Positron Emission Tomography*

PET is used to measure the metabolic activity of gliomas and has several clinical applications in neuro-oncology. Labeled amino acids like $^{11}$C-methyl-methionine (MET) are considered the molecule of choice for gliomas, although quantification of incorporation is more difficult compared to $^{18}$F-fluoro-2-desoxy-D-glucos (FDG) [50]. The superiority of MET over FDG for evaluating glioma is based on the low background uptake of MET in normal brain, providing good contrast with tumor uptake [51]. In accordance, MET is better than FDG in delineating gliomas. The amino acid tracer $^{18}$F-fluoro-ethyl-L-tyrosine (FET) has the advantage of a longer half-life, allowing transport of this tracer to other units. MET and FET show similar uptake intensity and distribution in gliomas, independently of blood–brain-barrier disturbance. In specialized clinical centers, PET with amino acid tracers, integrated with MRI, is recommended for patients who present with a presumed DLGG, and is of value for differential diagnosis, prognostic assessment prior to therapy and to obtain targeted biopsies in metabolic hot spots [36] (Fig. 11.2).

### *11.3.6 Radiological Appearance; Correlation with Molecular Markers*

There is a regional diversity of brain tumors and accumulating evidence that tumor location is closely associated with the genetic profile of the tumor and its precursor cells [52]. Molecular characterization of the cell of origin of gliomas will yield

important insights into the molecular evolution of gliomas. IDH1-mutated glioblastomas were predominantly located in the frontal lobe, surrounding the rostral extension of the lateral ventricles, suggesting that this region may be the cell of origin for IDH1-mutated gliomas [52–55]. In addition, several studies have reported a correlation between tumor location and 1p/19q co-deletions in oligodendrogliomas. Co-deleted oligodendrogliomas were most commonly located in the anterior part of the brain, whereas tumors with intact 1p/19q were more frequently found in the posterior part [56].

The insula is an anatomical structure that is of specific interest for DLGG. Around 20–25% of all DLGG originate in the insula, which is in contrast to high-grade gliomas that in only 10% have their origin in the insula [57]. The preposition of slowly growing tumors for the insula is not well understood [58]. The insula has traditionally been regarded as a simply visceral sensory region in the brain, but recent studies using functional MRI have revealed the complex role the insula plays in emotional awareness and perception of bodily functions and its tight connection with cognition [59]. It has been suggested that the natural course of insular gliomas is more indolent compared to other tumor locations [58]. In a recent report, paralimbic DLGG (involving frontal and/or temporal lobes as well as the insula) with IDH1 mutation differed significantly from paralimbic DLGG with wild-type IDH [60]. The 15 out of 22 IHD-mutated paralimbic DLGG in this study shared a less invasive growth pattern on MRI that was similar to the growth pattern of purely insular DLGG tumors, of which 18 out of 20 with IDH-mutations. The authors speculated that IDH mutations lead to compromised cell migration in gliomas, reflecting also the better outcome of IDH-mutated DLGG [61].

Signal intensities on MRI and the sharpness of the radiological border are also associated with loss of heterozygosity (LOH) of chromosome 1p/19q. Thus, oligodendrogliomas with co-deletion of 1p/19q have generally indistinct tumor margins, heterogeneous signal intensities and calcifications, although these radiological characteristics are not exclusively found in 1p/19q-deleted tumors and are also present in non-deleted tumors [37].

Figure 11.3 illustrates the typical indistinct and blurry radiological borders that are characteristically found in a proportion of DLGG. Interestingly, a correlation was recently reported between radiological tumor borders and the immune-related biomarker human leucocyte antigen-G (HLA-G) [54]. Tumors with high HLA-G gene expression were associated with larger volumes and blurred borders, and patients with these tumors were less likely to have undergone complete resections. Although the significance of the association between molecular subpopulations of DLGG and invasion patterns remains to be understood, these studies can provide important novel insights on tumorigenic mechanisms and provide a ground for biologically based therapies.

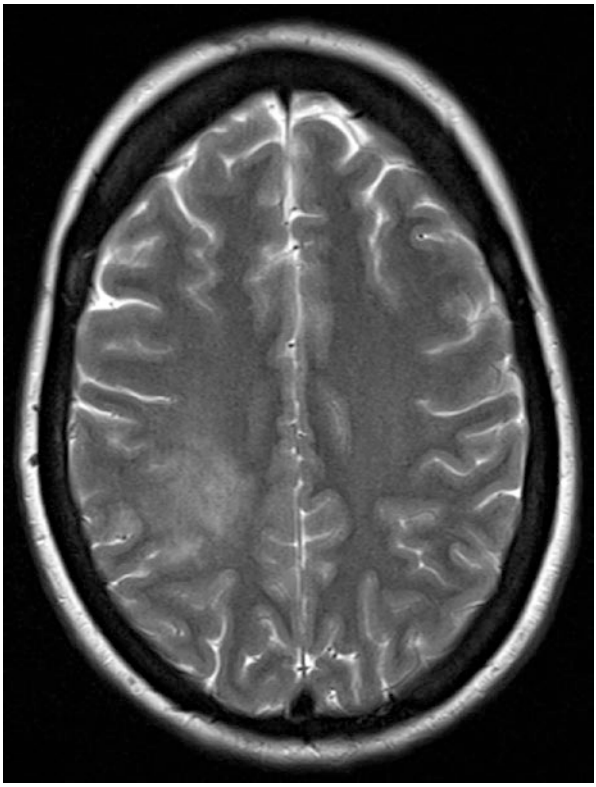

**Fig. 11.3** T2-weighted signal changes corresponding to a DLGG in the right hemisphere with extremely blurred and indistinct radiological tumor borders

## 11.4 Conclusions

Both the clinical and radiological presentation and the prognosis of patients with DLGG show a large variety. Regardless of when new-onset symptoms occur, surgical resection if provided in the low-grade phase of the disease, i.e. before malignant transformation, is the most effective therapy and should systematically be considered at presentation. The cornerstone in routine diagnostics is still morphological MRI, which also opens up for the assessment of tumor growth rates over time, providing prognostic information. The value of advanced imaging methods, in particular MRS and amino acid PET, to determine differential diagnosis (tumor versus no-tumor), molecular markers, focal hot spots in presumed non-enhancing DLGG and prognosis, is increasingly recognized.

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# Chapter 12
# Epilepsy and Diffuse Low-Grade Gliomas

**Johan Pallud**

**Abstract** World Health Organization diffuse low-grade gliomas (DLGGs) are highly epileptogenic primary brain tumors. Here, we will discuss the incidence and predictors of epileptic seizures and of seizure control, the pathophysiological epileptogenic mechanisms, the impact of oncological treatments on epileptic seizures, and their prognostic significance. Epileptic seizures occur in more than 90% of cases at diagnosis and their predictors are male gender, age, eloquent tumor locations and the presence of competitive other symptoms. Epileptic seizures progress together with drug resistance during the course of DLGG despite treatments and predictors of uncontrolled seizures are simple partial seizures, motor seizures, long duration from seizure onset to oncological treatment, temporal lobe, insular lobe and central area involvement. Epileptogenic foci are nested within the peritumoral neocortex infiltrated by sparse glioma cells and glioma-related epileptogenic mechanisms are multifactorial and intermixed. An excessive glutamatergic excitatory neurotransmission is induced by a high extracellular glutamate concentration resulting from a decrease in glutamate uptake and from an increase in glutamate release by glioma cells and by neighbouring non-tumor cells. An impaired GABAergic signaling is induced by reduced GABAergic inhibitory pathways and functioning and by pathological changes in neuronal chloride homeostasis that switch GABAergic signaling from hyperpolarizing to depolarizing. The short seizure dura-

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tion before surgery and the extent of resection are main predictors of postoperative seizure control in DLGG and a supratotal resection encompassing the epileptogenic foci in the peripheral neocortex surrounding the DLGG can improve seizure control. Last, epileptic seizure independently impacts DLGG prognosis, as both malignant progression-free survival and overall survival are longer in patients with a history of epileptic seizures.

**Keywords** Epilepsy • Seizure • Glioma • Isolated glioma cell • Glutamate • GABA • KCC2 • NKCC1

## 12.1 Introduction

Epileptic seizures are one of the most relevant symptomatic expressions of cerebral gliomas [1]. The origin and mechanisms of human glioma-related epilepsy are multifactorial, intermixed and dependent of specific mechanisms related to the tumor itself or to modifications of the peritumoral neocortex [2]. Epileptic seizure incidence varies with tumor subtype, grade and location and low-grade gliomas are more epileptogenic than high-grade gliomas [3]. Among them, World Health Organization diffuse low-grade gliomas (DLGGs) are one of the most highly epileptogenic [2, 3]. Indeed, epileptic seizures are the most common presenting sign, epileptic seizure history and control rates vary along the natural course of the DLGG, and impair its evolution [1]. However, both epileptic seizures and antiepileptic drugs predispose patients to cognitive impairments, a central concern during the comparatively long survival of DLGG, and may impact the oncological outcomes due to possible interactions with chemotherapy and possible direct oncological effects [4, 5]. The seizure control is often difficult to achieve by antiepileptic drugs and the application of oncological treatments (surgery, radiotherapy and chemotherapy) significantly helps [6]. The identification of predictors of epileptic seizure occurrence and control in patients with DLGG is essential to refine and adapt antiepileptic drugs and oncological treatments on an individual basis. The available literature contains sparse studies on that topic, including two monocentric studies of 332 and 508 patients, respectively [7, 8], a systematic literature review with meta-analysis, pooling 773 patients from 20 small-sized studies [9]. Though well conducted and interesting, the contribution of these studies is restricted to postoperative seizures control, lacks long-term follow-up, and heterogeneous data sources are used. A unique observational multicentric study of 1509 patients [1] reported a homogeneous data collection from an observational French multicentre DLGG database, allowing the assessment of the independent role and predictors of epileptic seizures on a long-term follow-up.

In this chapter, we will discuss the incidence and predictors of epileptic seizures along the course of DLGG, the pathophysiological epileptogenic mechanisms, the impact of oncological treatments on epileptic seizures, the predictors that may affect long-term seizure control, and the prognostic significance of epileptic seizures.

## 12.2 Epileptic Seizures at Diffuse Low-Grade Glioma Diagnosis

### *12.2.1 Definition*

According to the International League Against Epilepsy, the DLGG-related epilepsy can be defined as a history of at least one epileptic seizure due to the presence of an enduring alteration in the brain (i.e. the DLGG) [10]. There is no argument to consider clinics of seizure as a specific feature of DLGG and the intrication of neuropsychological disorders may render difficult the identification of a subtle focal seizure. Patients with a DLGG are supposed to present with localization-related seizure, depending on the localization of glioma [11]. Accordingly, patients present mainly with focal seizures (60–95%), with (50%) or without (50%) altered consciousness and with primary (<10%) or secondary (25%) generalized seizures [1].

### *12.2.2 Incidence and Risk Factors of Epileptic Seizures at Diagnosis*

Epileptic seizures are the most common presenting sign of DLGG, occurring in more than 80% of cases, and the most common sign at the time of diagnosis, occurring in more than 90% of cases [1, 3, 5, 6]. In the absence of oncological treatment, seizures frequently predate other symptoms and can remain the only one during many years, despite an actual DLGG growth on imaging follow-up [12]. It is known from cohort of patients with an incidentally discovered DLGG that epileptic seizures occur during the follow-up concomitantly to the glioma growth in the absence of oncological treatment [13]. Altogether, it appears that epileptic seizures are the primary symptom for DLGG in adults and progress during the natural course of the tumor.

Several factors influence the risk of epileptic seizures, explaining why seizure history and control rates vary among patients. Regarding patient-related risk factors, the risk of seizures decreases with the increase in age and increases with the male gender [1, 14]. Regarding glioma-related risk factors, tumor location influences the risk for epilepsy. The seizure risk is related to the proximity of the DLGG to the cortical gray matter and patients with deeply located tumors are less likely to present with seizures [12]. Tumors involving the frontal, temporal, insular and parietal lobes are more commonly associated with seizures than are occipital lesions. In addition, the DLGG proximity to eloquent cortex also increases seizure frequency [1]. This can be explained by the variation of DLGG subtype and of intrinsic epileptogenicity by cerebral lobe [1, 15]. Hence, paralimbic DLGG location, and particularly insular location is associated with an increased seizure risk [1, 16–19]. The risk of seizure increases with the tumor volume in DLGG, but not in gliomas of higher grade of malignancy, which is linked to the slow growth of the DLGG that allows the epileptogenic

mechanisms to develop [1, 18], but the presence of a mass effect or of edema does not impact the risk of seizures. Of note, in the specific subgroup of DLGG, the quantified tumor growth on imaging did not significantly differ in patients with and without seizures [1]. Histopathological subtype according to the WHO classification version 2007 is supposed to influence the risk of seizures: they are more common in oligodendrogliomas and in mixed gliomas than in astrocytomas [7]. However, in three large and recent series focused on DLGG, the histopathological subtype did not significantly impact the seizure risk [1, 8, 20]. The significance of molecular markers on the risk of seizures in DLGG is increasingly studied. The presence of a IDH1/2 mutation appears associated with a higher risk of seizures in DLGG [21–23]. No significant association between the presence of the 1p19q codeletion and the seizure risk has been observed [1, 24, 25] but one study suggested that the absence of a 19q deletion was associated with a higher risk of seizures in DLGG [25]. Two recent and large studies found no correlation between seizure risk and molecular markers, including p53 expression [1, 8].

Of note, in the largest studies dedicated to epileptic seizures in supratentorial DLGG in adults encompassing 1509 cases [1], independent and significant risk factors of epileptic seizures at diagnosis were the male gender, the age, anatomical and eloquent tumor locations and the presence of competitive other symptoms (neurological deficit, increased intracranial pressure). No significant association was observed for tumor volume, cortical involvement, quantified tumor growth on imaging, histopathological subtype, proliferation rates or the expression of biomolecular markers (including 1p19q codeletion, p53 expression, IDH1-R132H expression).

### *12.2.3 Incidence and Risk Actors of Uncontrolled Seizures at Diagnosis*

Although still debated, the International League Against Epilepsy commission on therapeutic strategies defines refractory epilepsy as an epilepsy that is not controlled by two tolerated and appropriately chosen and used antiepileptic drugs schedules whether as monotherapies or in combination [26].

The rates of uncontrolled seizures vary markedly in literature, from 15 to 50% in DLGG before oncological treatment [1, 7, 8]. This can be attributed to the time interval between first seizure and oncological treatment as it appears that the prevalence of epileptic seizures increases, together with those of uncontrolled epileptic seizures, during the tumor natural course before oncological treatment, from discovery to diagnosis [1]. Indeed, in a cohort of 208 patients with a histologically proven and untreated DLGG, uncontrolled epileptic seizures progresses despite antiepileptic drugs (from 13 at diagnosis to 39%) during a mean 34 months of follow-up without oncological treatment [1]. In addition, uncontrolled seizures progress during the tumor course, despite antiepileptic drug therapy and oncological treatment as illustrated in a large series: from 2% at imaging discovery, 15% at

histopathological diagnosis, 33% after first-line oncological treatment, to more than 40% at malignant transformation [1].

The main predictors of uncontrolled seizures at the time of diagnosis are the presence of simple partial seizures, the presence of motor seizures, a long duration from seizure onset to oncological treatment, a temporal lobe, an insular lobe and a central area involvement [5, 12, 14, 27]. A proliferation index >10% appears possibly linked to the risk of intractable seizures [8, 20].

## 12.3 Glioma-Related Epileptogenicity

The origin and mechanisms of human glioma-related epilepsy remain partially elucidated but gathering evidence suggests that glioma growth stimulates seizures, and that seizures encourage glioma growth. Epileptogenic mechanisms are multifactorial, intermixed and dependent of specific mechanisms related to the tumor itself, and to modifications of the peritumoral neocortex [1, 2, 28].

### *12.3.1 Cortical Foci of Glioma-Related Epilepsy*

Electrophysiological preoperative investigations with magnetoencephalography, surface electroencephalography, stereo-electroencephalography and intraoperative investigations with direct electrocorticography and transcorticography have shown that epileptic activities were recorded from the peritumoral neocortex and not from the glioma core [29]. Ex vivo electrophysiological explorations of spatially oriented human samples have shown that these activities arose mainly within the supragranular cortical layers [30, 31] of the peritumoral neocortex infiltrated by glioma cells [32–34]. Thus, in DLGG, the sites of epileptic activity are commonly at the frontier of glioma growth and arise from the interactions between the surrounding brain with a functional neocortex and the glioma per se. The peritumoral neocortex microscopically invaded by sparse glioma cells appears as the key structure for DLGG-related epileptogenesis (Fig. 12.1).

### *12.3.2 Intratumoral Epileptogenic Mechanisms*

Since a DLGG is a space-occupying lesion, which also permeates the surrounding functional brain with infiltrating and migrating glioma cells, it may contribute to produce epileptic activities by mechanical effects [2]. Mass effect and edema may induce microcirculation impairments by reducing cerebral perfusion responsible for focal ischaemic changes in the surrounding neocortex [35]. DLGGs that grow slowly and invade the surrounding brain may isolate and deafferentate cortico-subcortical local

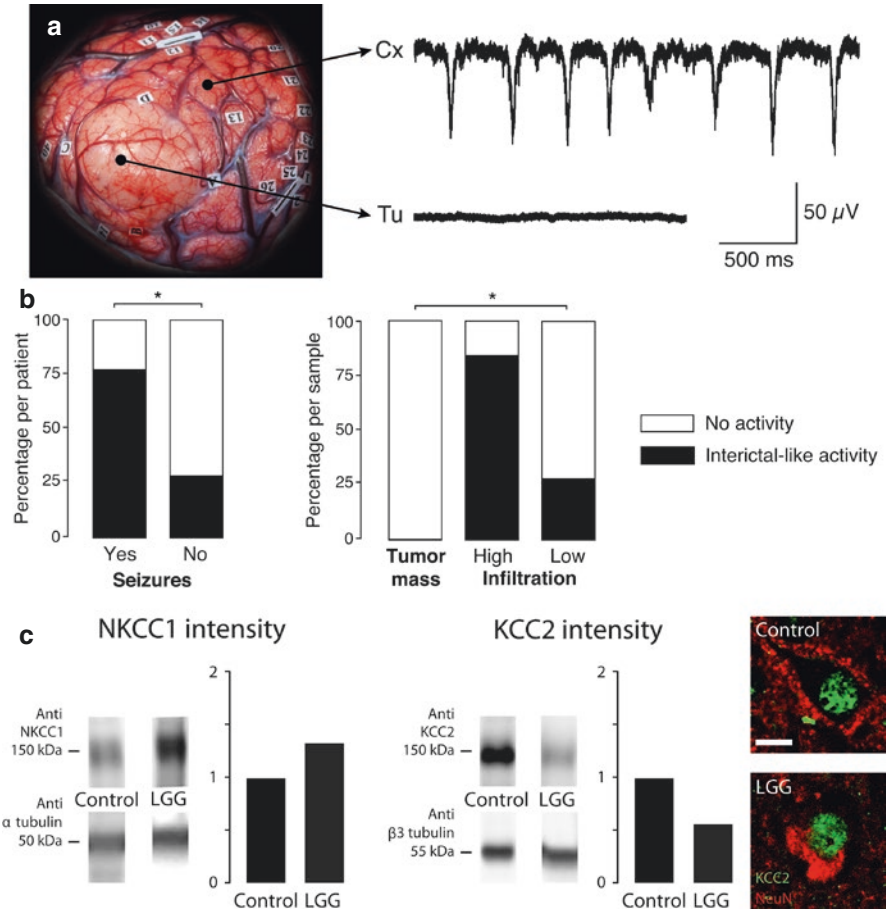


**Fig. 12.1** (**a**) Example of a *left* parietal diffuse low-grade glioma. Brain tissue specimens were sampled inside the tumor (Tu) and from the neocortex infiltrated by sparse glioma cells (Cx). Intraoperative field potential recordings demonstrated sponteanous interictal-like epileptiform discharges from the infiltrated neocortex adjacent (Cx) to the glioma core but not in the glioma core itself (Tu). (**b**) The proportion of patients or slices from which sponteanous interictal-like epileptiform discharges were (*black*) or were not (*white*) detected, grouped by history of seizures, and histopathological abnormalities (tumor mass vs. high tumor infiltration vs. low tumor infiltration by sparse glioma cells). (**c**) Western blots for Na-K-2Cl cotransporter 1 (NKCC1, *left*) and K-Cl cotransporter 2 (KCC2, *middle*) in control neocortex (control) and in neocortex close to a diffuse low-grade glioma (LGG). NKCC1 expression was normalized to a nonneuronal-specific marker, α-tubulin. KCC2 expression was normalized to a neuron-specific marker, β3 tubulin. Histogram representing NKCC1 protein quantification shows that NKCC1 is increased in the glioma sample as compared to controls. Histogram representing KCC2 protein quantification shows that KCC2 is decreased in the glioma sample as compared to controls. Representative images of KCC2 expression (*red*) with neuronal nuclear antigen (NeuN) marker (*green*). In control tissue (control), the fluorescence is distributed along the plasma membrane of the cells. In the diffuse low-grade glioma, the distribution of KCC2 in neurons in neocortex with a low tumor infiltration by sparse glioma cells is restricted in the cytoplasmic region with a loss of fluorescence along the plasma membrane of the cells. Scale bar, 5 mm

and distant networks, leading to epileptogenicity [33, 36]. Contrarily, high-grade gliomas that grow rapidly and induce neoangiogenesis, may provoke acute tissue damages such a haemorrhage or necrosis that may participate in epileptogenesis [36]. However in DLGG, the lack of significant correlations between seizures and tumor volume, mass effect, edema, necrosis, histopathological and molecular findings and the existence of a positive correlation between seizures, cortex involvement and tumor location argue for the implication of interactions between tumor and neocortex rather than intrinsic tumor properties alone in epileptogenicity [1, 2, 33, 35].

Structural reorganization and functional deafferentation with neuronal and glial losses, neurogenesis, reactive astrogliosis, neuronal, axonal and synaptic plasticity within the peritumoral neocortex have been described, resulting mainly in a reduction of inhibitory pathways and in an increase of excitatory ones [33, 35, 36]. Accordingly, magnetoencephalography has shown that gliomas interfere with normal brain function by disrupting functional connectivity of brain networks within peritumoral and distant brain areas [33]. Taken together, these findings suggest that such changes may induce alterations in local neuronal networks, leading to imbalance between excitation and inhibition and, eventually to epileptogenicity.

Glioma cells impact the surrounding environment by recruiting non-glioma cells (astrocytes, microglia, stromal cells) that provide resources and growth advantage to facilitate tumor progression by the mean of secreted factors (cytokines, growth factors, chemokines) and of extracellular communication. Glioma cells activate and attract the neighboring microglia that, in turn, can modulate glioma biology: activated microglia enhance glioma cells migration abilities by inducing the secretion of matrix metalloproteinases and glioma cells proliferation through the EGF/Pi3K/Akt pathway.

Although rarely observed in DLGG, the pathological disruption of the blood brain barrier exposes the brain to blood serum components, such as glutamate, fibrinogen and albumin, together with the release of vascular endothelial growth factor [37]. The vascular endothelial growth factor can induce edema and its subsequent mass effect and can alter the gap-junctions permeability [37]. The extravased glutamate participate to the sustained increase of its extracellular concentration. The perivascular astrocytes may uptake albumin, whom intracellular accumulation induces a downregulation of inward—rectifying $K^+$ (Kir 4.1) channels in astrocytes, resulting in reduced buffering of extracellular $K^+$. Further, fibrinogen and albumin can induce a reactive astrogliosis with an impaired clearance for extracellular $K^+$ and glutamate, leading to an increase neuronal hyperexcitability in the surrounding neuronal network. Finally, immunoglobulins themselves may be incorporated in neurons and affect their behavior.

### *12.3.3 Peritumoral Epileptogenic Mechanisms*

Glutamate homeostasis is impaired in the peritumoral neocortex. Glioma cells lack sodium-dependant excitatory amino acid transporters 1 and 2, leading to a decrease in glutamate uptake [33, 38], and highly express the system Xc- cystine glutamate

transporter, leading to a increase in glutamate release [38–41], both resulting in a poor regulation of glutamate homeostasis with highly elevated and sustained extracellular glutamate concentrations, up to 100 μm and up to tenfold higher than normal. In addition, non tumoral astrocytes and activated microglia of the peritumoral neocortex display impaired glutamate clearance abilities with reduced extracellular glutamate upload and with increased glutamate release [37]. In parallel, mutations of the isocitrate dehydrogenase genes are frequent in DLGG and they lead to conversion of isocitrate to D-2-hydroxyglutarate rather than to α-ketoglutarate [42]. Consequently, D-2-hydroxyglutarate accumulates in glioma cells and the extracellular space, where it is thought to act as a glutamate receptor agonist owing to its steric analogy to glutamate [28, 43]. In clinical practice, IDH mutations in DLGG are possibly associated with a high prevalence of epilepsy [1, 22]. Last, the glutamate extravased from blood due to blood-brain-barrier disruption participated to an increase in extracellular glutamate concentrations. Glioma epileptogenicity is thus related, in part, to an excessive glutamatergic excitatory neurotransmission. The excessive extracellular glutamate may induce seizures through the facilitation of pathological pyramidal cells synchronization [39] and experimentations on glioma-bearing mice confirmed that peritumoral neuronal hyperexcitability was attributable to glutamate release by glioma cells via the system Xc- cystine glutamate transporter [31]. In accordance, increased glutamate concentration and altered glutamate transporter expression have been shown to be associated with the presence of tumor-related seizures in patients harboring a glioma [40]. Gliomas utilize the glutamate as an "autocrine tumor growth factor" to gain a growth advantage as the released glutamate enhances glioma cells proliferation and invasion with neurotoxic, pro-invasive and proliferative effects [41]. These effects are increased by glioma cell overexpression of glutamate receptors, including metabotropic glutamate receptor (mGluR) types 2 and 3, N-Methyl-D-Aspartate (NMDA) receptors and $Ca^{2+}$-permeable α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [28]. Glutamate NMDA receptors on glioma cells increase motility of these cells [41]. NMDA receptor activation, which induces $Ca^{2+}$ inflow, increases glioma cell proliferation, and AMPA receptors that predominantly lack GluR2 subunit expression, allowing a $Ca^{2+}$ influx and overexpress GlutR1 subunit, resulting in an increase in glioma cells adhesion to extracellular matrix components, which have been shown to promote cell motility and invasion [39]. They also result in an activation of the glioma cell proliferation through the EGF/Pi3K/Akt pathway [44] and mitogen-activated protein kinase pathways [28]. The excessive extracellular glutamate can cause peritumoral neuronal excitotoxicity through the activation of NMDA receptors on neurons adjacent to the glioma, contributing to a glutamatergic-mediated cell death [31, 38, 39, 41], thus giving glioma cells the free space required for tumor expansion where neurons die.

GABAergic signaling is also involved both in glioma growth and epilepsy. GABA levels are higher in tissue around gliomas than in the tumor core [45]. Glioma cells express $GABA_A$ receptors that contribute to the cell volume changes required for glioma cells proliferation and migration [46]. The released extracellular glutamate downregulates neuronal and nontumoral astrocytes $GABA_A$ receptors [33, 37]

and the peritumoral neocortex presents reduced GABAergic inhibitory pathways with a loss of GABAergic interneurons [32] and a reduction of inhibitory synapses within pyramidal cells [47]. These alterations result in a weakening of the GABAergic inhibitory functioning within the peritumoral neocortex [31, 33, 37, 45]. Regulation of intracellular $Cl^-$ influences neuronal responses to GABA. In healthy mature neurons, intracellular $Cl^-$ is maintained at low levels by activation of $K^+$-$Cl^-$ transporter 2 (KCC2), which cotransports $Cl^-$ with $K^+$ out of cells, and repression of $Na^+$-$K^+$-$Cl^-$ transporter (NKCC1), which cotransports $Cl^-$, $Na^+$ and $K^+$ into immature neurons [28]. In this context, activation of GABA receptors causes $Cl^-$ influx that hyperpolarizes cells and inhibits neuronal activity. As in other non-glioma human focal epilepsies [48] where pathological changes in $Cl^-$ homeostasis can switch GABAergic signaling from hyperpolarizing to depolarizing, aberrant expression of KCC2 and/or NKCC1 is associated with gliomas and epileptic activity, and leads to accumulation of intracellular $Cl^-$, which contributes both to glioma proliferation and migration and epileptic activity [28, 34, 46]. The intracellular $Cl^-$ accumulation of glioma cells, up to ~100 mM and tenfold higher than normal, is actively maintained by the NKCC1 cotransporter [49], which is expressed in glioma cells at higher ranges in peritumoral cortex of gliomas than in controls through phosphorylation mediated by WNK3, which is controlled by the EGF/Pi3K/Akt pathway [34, 50, 51]. Both glioma cell division and migration require a fast volume cell reduction, which is operated by the efflux of $Cl^-$ from $Cl^-$ channels [46, 52] coupled to $K^+$ efflux from $K^+$ big-conductance channels, and draw water out of the cell through aquaporines [46]. All $Cl^-$, $K^+$ and water channels are abnormally and highly expressed in the cytoplasmic membrane of glioma cells and are spatially restricted to the leading edge of the cell and to the invadipodia. Neurons within peritumoral cortex are affected by such $Cl^-$ dysregulation were $Cl^-$ homeostasis is disrupted in about 60% of pyramidal cells [34, 53]. This disruption is caused by upregulated expression of NKCC1 and downregulated expression of KCC2 in these neurons [34, 50, 53, 54]. Such $Cl^-$ defects are responsible for depolarizing GABAergic effects that are observed ex vivo in the cortex surrounding human gliomas and that may favor epileptogenesis in this tissues [34]. Changes in the expression of $Cl^-$ cotransporters can be triggered by brain-derived neurotrophic factor (BDNF) that is released by glioma cells and activated microglia : BDNF increases expression of NKCC1 and reduces expression of KCC2 [2, 55]. In addition, a NMDA-mediated glutamate signaling also suppresses KCC2 expression, so aberrant extracellular glutamate in gliomas could exacerbate dysregulation of $Cl^-$ levels [37].

Astrocytes are also involved in $K^+$ homeostasis by extracellular $K^+$ buffering through Kir4.1 channels [56]. $K^+$ buffering is impaired in gliomas by a loss of expression of Kir4.1 channels in the plasma membrane of glioma cells that is required for cell proliferation [56]. The resulting high extracellular $K^+$ concentration together with other local perturbations, such as the alkalization of the peritumoral neocortex [35] and the alterations of the gap-junctions functioning [33, 35] may increase the excitability of the pyramidal cells. The mTOR signalling pathways, which can be dysregulated in gliomas, result from upregulation of Pi3K/Akt signalling, and mutations in PTEN [28]. Hyperactivation of the mTOR pathway affects

neuronal differentiation and migration, axonal and dendritic growth, neuronal excitability, upregulation of immature forms of the glutamatergic NMDA receptor GluN2C, and impairment of $Cl^-$ regulation [28].

## 12.4 Seizure Control by Oncological Treatments

Several studies have supported the beneficial role of oncological treatments (surgery, radiotherapy, chemotherapy) in seizure control of DLGG-related epilepsy. The impact of oncological treatments on seizure control are illustrated in Figs. 12.2 and 12.3.

### *12.4.1 Surgery*

Surgery allows seizure control in a significant proportion of diffuse DLGGs, including uncontrolled seizures. A recent systematic literature review [9] identified the extent of resection, the preoperative seizure control, and the short seizure duration before surgery as predictors of good seizure outcome after surgery. These results were reproduced in the largest studies dedicated to epileptic seizures in supratentorial DLGG in adults encompassing 1509 cases where age and extent of resection were independent predictors of postoperative seizure control while history of seizures at diagnosis, and parietal and insular locations were independent predictors of postoperative uncontrolled seizures [1]. Other predictors of postoperative uncontrolled seizures that were proposed are the presence of a preoperative neurological deficit, and the DLGG location within the central area [1, 5, 7, 9, 12, 57].

The extent of resection is the main predictor of postoperative seizure control in DLGG as illustrated in a large series of 1509 supratentorial DLGG were postoperative uncontrolled seizures occurred in 44% following biopsy, 40% following partial resection, 32% following subtotal resection, and 16% following total resection [1]. These results have improved as a result of the increased use of intraoperative mapping techniques, and awake surgery, which has made possible to increase the extent of resection according to functional boundaries while preserving the eloquent areas, but also to extend the indications for surgery within brain regions classically considered as inoperable such as the insular lobe or the rolandic area, both of these locations being highly epileptogenic [12]. It has to be noted that the intraoperative functional mapping using direct electrical cortical and subcortical stimulations under awake conditions does not increase the risk of early and late postoperative seizures [58, 59]. A major issue related to surgery, especially in paralimbic tumors, is that the epileptogenic zone can include significant extratumoral cortical areas, thus explaining why about 20% of patients still suffer from uncontrolled seizures postoperatively, even after a total tumor resection. In this setting, the removal of the putative epileptogenic foci beyond the tumor, including the hippocampal formation

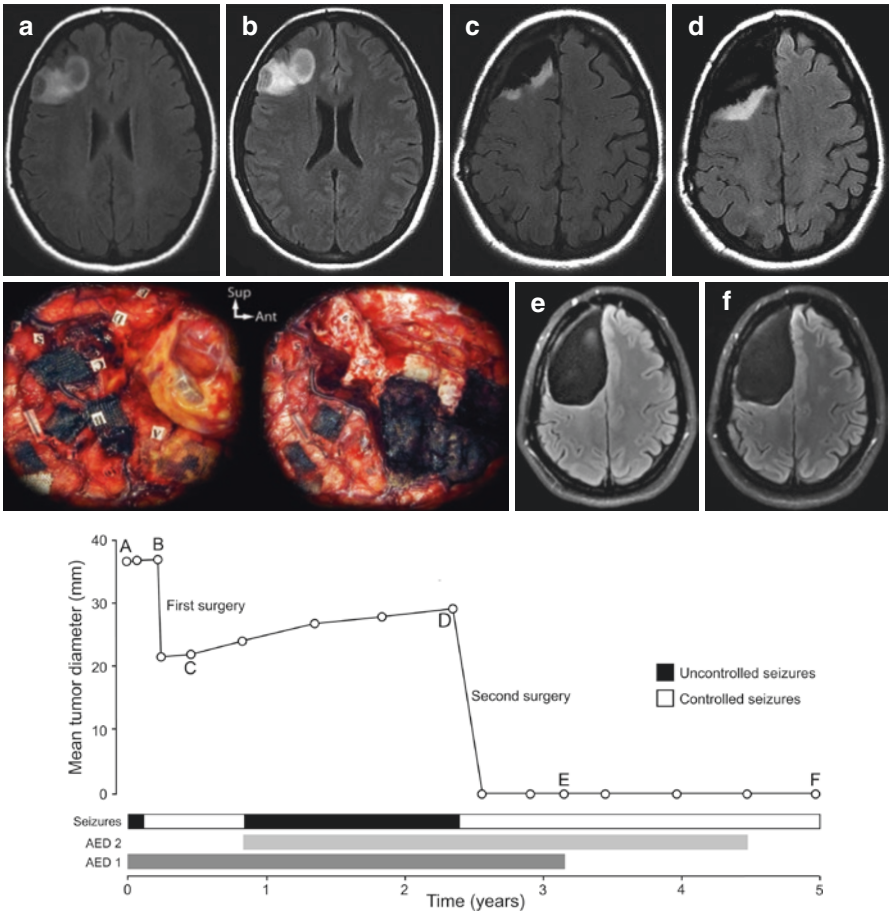


**Fig. 12.2** Example of the epileptic seizure history along the natural course of a diffuse low-grade glioma. The evolution of the radiographic mean tumor diameter is plotted over time. A 33-year-old right-handed female patient presented with partial motor and secondary generalized epileptic seizures controlled with one anti-epileptic drug and a right frontal non-enhanced mass with spontaneous growth on MRI (velocity of diametric expansion at 2.6 mm/year). A subtotal resection was performed under general anaesthesia and confirmed the diagnosis of a World Health Organization grade II oligodendroglioma. 5 months after surgery, epileptic seizures recurred, requiring the introduction of antiepileptic drug 2 and the residual tumor grew on MRI (velocity of diametric expansion at 3.8 mm/year). Epileptic seizures remained uncontrolled. A second surgical resection was performed using intraoperative functional mapping with direct cortical and subcortical electrostimulations under awake condition and allowed a supratotal resection beyond MRI-defined abnormalities (see intraoperative photographs before and after resection; each numbered tag represents an eloquent site at the cortical and subcortical levels). Following this second surgery, epileptic seizures were controlled, antiepileptic drug 1 was stopped at 6 postoperative months and antiepileptic drug 2 was reduced at 24 postoperative months. At last follow-up, the patient was seizure free and no glioma recurrence was observed.

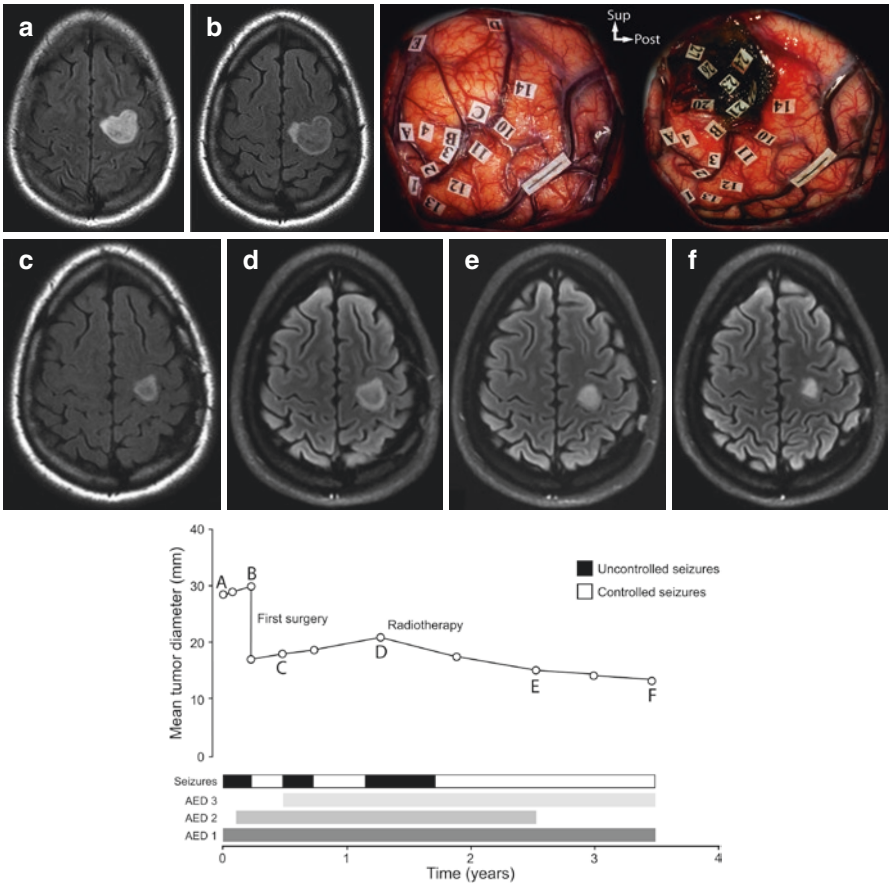


**Fig. 12.3** Example of the epileptic seizure history along the natural course of a diffuse low-grade glioma. The evolution of the radiographic mean tumor diameter is plotted over time. A 26-year-old right-handed female patient presented with simple partial motor epileptic seizures that remained uncontrolled despite two anti-epileptic drugs and a *left* frontal non-enhanced mass with spontaneous growth on MRI (velocity of diametric expansion at 7.4 mm/year). A partial resection was performed using intraoperative functional mapping with direct cortical and subcortical electrostimulations under awake condition and confirmed the diagnosis of a World Health Organization grade II mixed glioma (see intraoperative photographs before and after resection; each numbered tag represents an eloquent site at the cortical and subcortical levels). 5 months after surgery, epileptic seizures recurred, requiring the introduction of antiepileptic drug 3 and the residual tumor grew on MRI (velocity of diametric expansion at 3.4 mm/year). At one postoperative year, epileptic seizures recurred and remained uncontrolled despite three antiepileptic drugs. A conformational external radiotherapy was performed, allowing epileptic seizure control 9 months after radiotherapy and antiepileptic drug 2 arrest 2 years after radiotherapy. At last follow-up, the patient was seizure free and no glioma recurrence was observed. Of note, radiotherapy induced a reduction of the residual glioma as quantified with a velocity of diametric expansion at −3.6 mm/year.

for paralimbic DLGG, could lead to an improved seizure outcome [9, 17]. The emerging concept of supratotal resection (i.e., removing a margin beyond MRI-defined abnormalities until functional cortico-subcortical boundaries are reached) [60] for better seizure control has been proposed [61, 62]. It relies of the presence of epileptogenic foci in the peripheral neocortex surrounding the DLGG core and infiltrated by isolated glioma cells that can be removed through a supratotal resection beyond MRI-defined abnormalities [34]. Together with the extent of resection, the short seizure duration before surgery is a main predictor of good seizure outcome after surgery [1, 7, 9, 12, 14, 63].

Second-line surgery using intraoperative functional mapping can be useful for seizure control of DLGG in case of an initial partial removal [12, 19, 64]. A series has previously demonstrated that a re-operation using intraoperative functional cortical and subcortical mapping of DLGG located within eloquent area allowed both a better DLGG control and a better seizure control [64]. In this setting, a preoperative neoadjuvant chemotherapy can be discussed and preliminary studies are encouraging [65, 66]. Last, the use of intraoperative electrocorticography monitoring may further improve postoperative seizure control by identifying surrounding epileptogenic foci [67]. However, previous series led to inconclusive results whereas it is acknowledged that the cases in which electrocorticography were used were associated with more severe and refractory epilepsy [9].

Taken together, this suggests that the main prognostic parameters of seizure control after oncological treatment of DLGG include the extent of resection.

### *12.4.2 Radiotherapy*

Although observed in clinical practice, the impact of radiotherapy on DLGG-related seizures is supported by limited data [5, 68]. Stereotactic interstitial irradiation, which is no longer used for DLGG, allowed seizure control in 40% of patients and reduced seizure frequency in 50% of patients [69, 70]. Conventional radiotherapy has been reported to help seizure control in about 75% of DLGG patients with uncontrolled seizures [5]. A retrospective series of 33 DLGG demonstrated a reduction of 50% of more of the seizure frequency in 75% of cases following radiotherapy, 35% of patients had controlled seizures at 1 year post-radiotherapy [68]. Of note, seizure reduction usually begins early following radiotherapy and precedes the tumor shrinkage on MRI [68, 71]. The time to radiotherapy appears to impact the seizure control as the European Organisation for Research and Treatment of Cancer 22,845 phase III trial, which compared early radiotherapy versus observation and radiotherapy at “progression” in DLGG, demonstrated that 25% of patients who were irradiated had uncontrolled seizures, compared with 41% of patients who were not irradiated [72]. Of note, no difference in seizure control has been observed between high (59.4 Gy) and low (45 Gy) doses of radiotherapy [4, 73].

### 12.4.3 Chemotherapy

Concomitantly to the oncological efficacy, chemotherapy with alkylating agents appears to improve the seizure control of DLGG patients. Temozomide allows a reduction of the seizure frequency in 50–60% of patients, 20–40% of them being seizure free [5, 74–76]. A series of 39 DLGG demonstrated a reduction of 50% of more of the seizure frequency in 60% of patients following Temozolomide as compared to 13% in patients with antiepileptic drug therapy only [77]. A series of insular DLGG demonstrated a reduction of the seizure frequency in 100% of patients following Temozolomide, 14% of them being seizure free, as compared to 30% in patients with antiepileptic drug therapy only [19]. In this line, the emerging experience of preoperative neoadjuvant chemotherapy demonstrated a reduction of the seizure frequency in 90% of cases following Temozolomide, 50% of them being seizure free [65, 66]. Interestingly, following surgery and neoadjuvant Temozolomide, a reduction of the seizure frequency was observed in 100% of cases, 70% of them being seizure free [65]. Of note, no significant correlation between seizure response and 1p/19q codeletion has been reported so far [5].

PCV chemotherapy (procarbazine + CCNU + vincristine) allows a reduction of the seizure frequency in up to 100% of patients, up to 60% of them being seizure free [78]. A series of 33 DLGG demonstrated a reduction of the seizure frequency in 53% and a total seizure control in 31% of patients following PCV chemotherapy [79].

As a whole, alkylating agents appear as a promising therapeutic option to help the seizure control of DLGG in addition to the oncological impact, and possibly as a neoadjuvant treatment to improve the onco-functional balance of the surgical resection.

## 12.5 Prognostic Significance of Epileptic Seizures in Diffuse Low-Grade Gliomas

### 12.5.1 Epileptic Seizures and Progression

It is a common experience from clinical practice that recurrent seizures after an initial seizure-free period, that occurrence of new seizures, or that their increase in frequency in a patient with a treated DLGG is the first sign of tumor progression and warrants imaging investigations [11, 12]. It is speculated that altered seizure control reflects a change in tumor growth rate or the transformation towards a higher grade of malignancy, whereas seizure reduction (temporarily obtained by radiotherapy or chemotherapy) could represent a transient conversion to slower DLGG growth [12]. However, this has not been validated by a specific study that corretates seizure control and quantitative DLGG tumor growth rates on imaging.

Further supports for a causal relationship between changes in seizure control and DLGG progression come from a recent study on DLGGs in pregnant women [80]

and from electroencephalographic findings. The quantified tumor growth on MRI in these patients showed a significant increase in growth rate compared with corresponding prepregnancy measures, and 40% of the patients reported a simultaneous increase in seizure frequency. In addition, in glioma patients with an available electroencephalographic follow-up, glioma-related electrophysiological alterations are observed on EEG in about 100% of progressive gliomas.

### *12.5.2 Epileptic Seizures and Survivals*

The majority of studies on survival of patients with DLGGs provide support for a correlation between the presence of seizures at diagnosis and a more favorable outcome [1, 12]. In the largest study of 1509 supratentorial DLGG, a history of epileptic seizure at diagnosis was an independent protective prognostic parameter for overall survival: patients died at a mean time from histopathological diagnosis of 92 ± 69 months and 51 ± 38 months, respectively, for the subgroup of patients with and without a history of epileptic seizure at diagnosis [1]. The prognostic significance of epileptic seizures in malignant transformation is less documented but in the largest study of 1509 supratentorial DLGG, a history of epileptic seizure at diagnosis was a strong independent protective prognostic parameter for malignant transformation: it occurred at a mean time from diagnosis of 65 ± 55 months and 39 ± 28 months, respectively, for the subgroup of patients with and without a history of epileptic seizure at diagnosis [1].

Altogether, the occurrence of epileptic seizure independently impacted DLGG prognosis, as both malignant progression-free survival and overall survival were longer in patients with a history of epileptic seizures.

## 12.6 Key Points

- DLGGs are one of the most highly epileptogenic primary brain tumors, epileptic seizures occurring in more than 90% of cases at diagnosis.
- Predictors of epileptic seizures at diagnosis are male gender, age, eloquent tumor locations and to the presence of competitive other symptoms.
- Epileptic seizures progress together with drug resistance during the course of DLGG.
- Predictors of uncontrolled seizures are simple partial seizures, motor seizures, long duration from seizure onset to oncological treatment, temporal lobe, insular lobe and central area involvement.
- In DLGG, epileptogenic foci are nested within the peritumoral neocortex infiltrated by sparse glioma cells.
- The glioma-related epileptogenic mechanisms are multifactorial and intermixed.

- DLGG epileptogenicity is related to an excessive glutamatergic excitatory neurotransmission.
- Glutamate homeostasis is impaired in the peritumoral neocortex, leading to a decrease in glutamate uptake and to a increase in glutamate release, both resulting in a high extracellular glutamate concentration.
- Mutations of the isocitrate dehydrogenase genes lead to D-2-hydroxyglutarate accumulation that can act as a glutamate agonist.
- DLGG epileptogenicity is related to an impaired GABAergic signaling.
- The peritumoral neocortex presents reduced GABAergic inhibitory pathways and functioning.
- Neurons within peritumoral cortex of gliomas present $Cl^-$ homeostasis alterations with accumulated intracellular $Cl^-$ caused by upregulated expression of NKCC1 and downregulated expression of KCC2.
- These pathological changes in neuronal $Cl^-$ homeostasis can switch GABAergic signaling from hyperpolarizing to depolarizing.
- The short seizure duration before surgery and the extent of resection are the main predictors of postoperative seizure control in DLGG.
- Removing the putative epileptogenic foci beyond the tumor, including the hippocampal formation for paralimbic DLGG, could lead to an improved postoperative seizure control.
- A supratotal resection encompassing the epileptogenic foci in the peripheral neocortex surrounding the DLGG can improve seizure control.
- Second-line surgery using intraoperative functional mapping can improve seizure control of DLGG in case of a previous partial removal.
- The impact of radiotherapy on DLGG-related seizures is supported by limited data and seizure reduction precedes the tumor shrinkage on MRI.
- The time to radiotherapy but not the radiotherapy dose impacts the seizure control of DLGG.
- Chemotherapy with alkylating agents (Temozolomide, PCV) appears to improve the seizure control of DLGG patients.
- Preoperative neoadjuvant chemotherapy can be discussed in the management of DLGG for both oncological and epileptological purposes.
- Epileptic seizure independently impacted DLGG prognosis, as both malignant progression-free survival and overall survival are longer in patients with a history of epileptic seizures.

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# Chapter 13
# Quality of Life in Patients with Diffuse Low-Grade Glioma

**Martin Klein**

**Abstract** While surgery, radiotherapy, and chemotherapy alone or in combination are important therapeutic options in controlling growth of diffuse low-grade gliomas (DLGG), these same therapies pose risks of neurotoxicity, the most common long-term complications being radiation necrosis, chemotherapy-associated leukoencephalopathy, and cognitive deficits. Currently, there is no consensus on the treatment strategy for these tumors. Because of the relatively slow DLGG growth rate, these patients have a relatively long expected survival with radiographic and clinical stability.

Compared to traditional outcome measures like PFS and OS, evaluation of health-related quality of life (HRQOL), typically by use of questionnaires, may be considered time-consuming and burdensome by both the patient and the doctor. Besides, given the relatively low incidence of brain tumors and the ultimately fatal outcome of the disease, also for those harboring DLGG, the interest in HRQOL emerged relatively late in these patients. Moreover, the notion that the tumor and treatment may affect brain functioning and thus the patient's introspective abilities may complicate the use of patient-reported outcome measures.

The studies presented in this chapter describe outcomes of both single dimensional and multidimensional methods of studying HRQOL. Although only few studies incorporated HRQOL as primary outcome measure of interest, most studies have embraced the notion that an accurate assessment of HRQOL must be based on patient self-report.

In future trials, more sensitive measures of long-term cognitive, functional, and HRQOL outcomes on DLGG patients at important time points over the disease trajectory are needed to better understand the changing needs that take place over time.

**Keywords** Diffuse low-grade glioma • Neurosurgery • Radiotherapy • Chemotherapy • Health-related quality of life • Cognitive functioning

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## 13.1 Introduction

Diffusely infiltrating low-grade gliomas (DLGG) include astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas (WHO grade 2). Supratentorial DLGGs account for 10–15% of all adult primary brain tumors [1]. Most patients present between the second and fourth decades of life, and a seizure is the presenting symptom in about 80% of patients [2]. Mental status changes are present in 3–30% of patients at the time of presentation [3–5]. Older studies suggest that 10–44% have signs of increased intracranial pressure, such as headache and nausea, when first diagnosed [3, 4, 6], but with the now routinely used and widely available multimodal MRI sequences, the percentage of patients presenting with ICP will be rather 10% than 44%. Focal neurological deficits are present in 2–30% of patients [3, 7]. However, patients may also have normal neurological examinations.

Although their name might imply otherwise, most DLGGs result in considerable morbidity and inevitable death due to malignant transformation [8]. Management of DLGG is controversial because these patients are typically younger, with few, if any, neurological symptoms. Historically, when DLGG was diagnosed in a young, healthy adult, a commonly accepted strategy was a watchful waiting policy because of the proposed indolent nature and variable behavior of these tumors. There was also a belief that DLGGs did not necessarily transform into malignant tumors over time. However, the latter notion has been refuted by retrospective studies of the kinetics of glioma growth, that showed continuous tumor growth in the premalignant phase before anaplastic transformation [9]. Velocity of diametric expansion of the tumor is now known to be an independent predictor of long-term outcome in DLGG [10]. The majority of DLGGs progress to malignant gliomas with time and based on age, histology subtype, tumor diameter, tumor crossing the midline, and presence of neurologic deficit before surgery patients can be classified as either being at low- or high-risk [11], where in the latter group treatment may not be deferred. Adding to the complexity, patients with mutations of the isocitrate dehydrogenase genes (IDH1 and IDH2) have a much better prognosis than those lacking these molecular markers [12]. Additional favorable prognostic markers include co-deletion of 1p19q and promoter methylation of the methylguanine-DNA methyltransferase (MGMT) gene. The decision as to whether a patient with DLGG should receive resection, radiotherapy, or chemotherapy is based on these factors and evidently on patient preference. Since DLGGs are such a heterogeneous group of tumors with variable growth patterns, molecular, and histological characteristics, the risks and benefits of these treatment options must be carefully balanced with the data available from limited prospective studies.

The incidence of treatment-related late-delayed encephalopathy in DLGG patients is steadily increasing, not only because of improved survival, likely due to delaying malignant transformation, but also because of improved detection (neuroimaging and extensive cognitive function testing) and raised awareness among both physicians and patients.

## 13.2 Defining Quality of Life

The definition of health-related quality of life (HRQOL) is the level of performance in the major domains of life function as measured from the patient's perspective [13, 14]. The concept of HRQOL is not unidimensional, but instead covers a number of life domains, usually including physical, psychological, social, and spiritual domains [15–17]. For each domain, HRQOL may be perceived differently and be differentially weighted. Changes in one domain can influence perceptions in other domains. Thus, disruption in the physical domain is likely to affect the individual's psychological or social well-being.

HRQOL in DLGG patients has not been studied extensively and the methodological quality of most studies does not allow for drawing firm conclusions on how study outcomes regarding HRQOL may affect clinical decision-making. Although HRQOL is systematically assessed as part of EORTC brain tumor clinical trials, with 80% of the RTCs performed in high-grade glioma patients, only two out of the 14 identified RCTs, representing over 3000 glioma patients, sufficiently satisfied key methodological criteria to provide high-quality patient-reported outcome evidence [18].

Patient-oriented outcome measures, such as symptoms, physical functioning, and HRQOL, are most relevant for patients who cannot be cured of their disease. This is the case for most brain tumor patients for whom palliation of symptoms and the maintenance or improvement of HRQOL may become important goals early or late in the disease trajectory. Evaluation of treatment in brain tumor patients should therefore not only focus on survival improvement, but should be aimed at neurological functioning and at adverse treatment effects on the normal brain. In this respect, cognitive functioning is a highly critical outcome measure for brain tumor patients [19]. However, little is known about the relationship between cognitive functioning and HRQOL in these patients. This association was studied in 190 DLGG patients with stable disease at an average of 6 years after diagnosis by using neuropsychological testing and self-report measures of generic (MOS SF36) and disease-specific (EORTC BN20) HRQOL [20]. Performance in all cognitive domains was positively associated with physical health (SF36 Physical Component Summary). Executive functioning, processing speed, working memory, and information processing were positively associated with mental health (SF36 Mental Component Summary). Negative associations were found between a wide range of cognitive domains and disease-specific HRQOL scales. From this the authors conclude that in stable DLGG patients, poorer cognitive functioning is related to lower generic and disease-specific HRQOL. This confirms that cognitive assessment of LGG patients should not be done in isolation from assessment of its impact on HRQOL, both in clinical and in research settings.

## 13.3 Treatment and Quality of Life in DLGG

Major symptoms related to having a DLGG are the cognitive and physical changes that may be due to effects of tumor and treatment. Most patients present with seizures that are often medication refractory and furthermore have cognitive

dysfunction of various degrees, from mild dysfunction with good information processing and good performance to severe dysfunction with problems in most cognitive domains [19, 21, 22]. Neurological deficits also occur; in most cases, motor impairment limited to difficulties with function in the upper limbs [11, 21]. Many of these changes may alter the patient's ability to function in a work or home environment. In addition, the roles of the people closest to them usually change to adjust to the neurological deficits and treatment requirements. Consequently, informal caregivers of these patients experience reductions in their HRQOL [23]. Not surprisingly, patients' HRQOL and neurological functioning also affect the informal caregiver's HRQOL and feelings of mastery [24].

HRQOL in DLGG patients can be affected by the tumor, by tumor-related epilepsy and its treatment (surgery, radiotherapy, antiepileptic drugs (AEDs), chemotherapy, or corticosteroids), and by fatigue, cognitive deficits, depression and changes in personality and behavior [25]. Therefore, the remainder of this chapter will discuss the tumor and treatment effects on HRQOL of patients with DLGG. Since HRQOL is nowadays considered to be measured from the patient's perspective, the focus will be on patient self-reports rather than on (older) reports of physician's ratings of patient functioning.

### *13.3.1 Tumor Effects on Health-Related Quality of Life*

In addition to seizures, motor or sensory deficits, and increased intracranial pressure, DLGG patients can present with cognitive complaints and deficits that negatively affect HRQOL [26]. With this respect, it is important to note that patients with tumors in the dominant hemisphere tend to have more symptoms than those with lesions in the non-dominant hemisphere [27, 28]. Patients with DLGG furthermore tend to have more global cognitive deficits, unlike patients with stroke who tend to have lesion site-specific deficits. This may be explained by a diffuse growth of tumor cells infiltrating normal brain tissue [29]. Additionally, acute neurotransmitter changes and chronic degeneration of fiber tracts [30] caused by tumor and treatment-related damage to certain brain areas may impair neuronal responses in remote undamaged cortical regions (i.e., diaschisis). Given the increasing evidence for redistribution of neural function, particularly in DLGG, taking advantage of this property is becoming an important aspect of surgical management of these patients. As extensively discussed elsewhere in this book, a number of groups have endorsed a strategy pioneered by Duffau which takes advantage of surgery-induced plasticity for DLGG [31]. Evidently, deterioration in functioning usually occurs at the time of anaplastic transformation, which occurs in the majority of DLGG patients [9].

With regard to the effect of tumor volume, location, and histological grade on preoperative HRQOL a study of 101 successive brain tumor patients [32] was performed using the Nottingham health profile (NHP) and Sintonen's 15D scale [33]. Analyses showed tumor size not to be related to HRQOL scores. However, large tumors (>25 ml) were associated with poorer HRQOL than small tumors

(< or = 25 ml). Surprisingly, patients with tumors in the right hemisphere or in the anterior region had poorer HRQOL than those with tumors in the left hemisphere or posteriorly. From this study the authors [32] conclude that large tumors apparently damage several parts of the brain and/or raise intracranial pressure to a level that exceeds the brain's compensatory capacity. In this study tumors in the right hemisphere seemed to be related to poorer HRQOL, while other studies observed that patients with right-sided lesions perceived a better HRQOL [14, 27]. To add to the confusion and most likely due to methodological issues, two studies reported homogeneity of HRQOL of patients with right- and left-sided lesions [34, 35], another study reports a worse HRQOL in patients who have bilateral lesions [36] and one reports a better functional status (KPS) in patients with right-sided lesions, but without affecting HRQOL [37]. Awaiting analyses from large preoperative studies that systematically documented both HRQOL, information on tumor location, and on mood, since depressive symptoms are known to affect HRQOL ratings, definite conclusions regarding laterality of the tumor and HRQOL cannot be drawn.

In order to place HRQOL of DLGG survivors in an appropriate, interpretable context a healthy population control group, matched on key background characteristics such as age, sex and education is needed. In a 2011 study [38] related to a study by Klein et al. [26] 195 DLGG patients studied on average 6 years following diagnosis and initial treatment were compared with 100 hematological (non-Hodgkin lymphoma and chronic lymphatic leukemia cancer survivors (NHL/CLL) and 205 healthy controls, matched on age, sex and educational level. Generic HRQOL was assessed with the SF-36 Health Survey; condition-specific HRQOL with the Medical Outcomes Study Cognitive Function Questionnaire and the EORTC Brain Cancer Module. Objective cognitive functioning was assessed with a battery of neuropsychological tests. No statistically significant differences were observed between the DLGG and NHL/CLL groups in SF-36 scores. The DLGG group scored significantly lower than the healthy controls. Approximately one-quarter of the DLGG sample reported serious cognitive symptoms. Problems with vision and motor function were uncommon. Age (older), sex (female), number of objective cognitive deficits, and epilepsy burden were associated significantly with both generic and condition-specific HRQOL. Clinical variables, including time since diagnosis, tumor lateralization, extent of surgery, and radiotherapy, were not related significantly to HRQOL. From this the authors conclude that DLGG survivors experience significant problems across a broad range of HRQOL domains, most of which are not condition-specific. However, the cognitive deficits that are relatively prevalent among DLGG patients are associated with negative HRQOL outcomes, and thus contribute additionally to the vulnerability of this population of cancer survivors. Patients that remained stable (65 out of the initial 195 patients) for 12 years following diagnosis reported significantly worse physical functioning using the SF-36 Physical Component Summary and the physical functioning subscale at long-term than at midterm follow-up [39]. For this subgroup, further research is recommended to better aid patients in dealing with the consequences of DLGG.

The prognostic value of HRQOL was determined in a study by Mainio [40]. The postoperative survival of 101 brain tumor patients was followed from surgery (1990–1992) until the end of the year 2003. Depression was evaluated by the Beck Depression Inventory (BDI) and HRQOL with Sintonen's 15D scale [33] before operation and at 1 year as well as at 5 years after operation. The mean survival times in years were significantly related to tumor malignancy, being the shortest, 1.9, for patients with high-grade gliomas, while patients with DLGGs or a benign brain tumor had mean survival times of 9.1 and 11.6, respectively. At all follow-ups, depressed DLGG patients had a significantly shorter survival time, 3.3–5.8 years, compared to non-depressed DLGG patients, 10.0–11.7 years. A decreased level of HRQOL in DLGG patients was significantly related to shorter survival. These results suggest that depression and decreased HRQOL among DLGG patients are related to shorter survival at long-term follow-up. Decreased HRQOL may therefore serve as an indicator for poor prognosis in DLGG patients. This finding is in line with a meta-analysis [41] that indicates depression diagnosis and higher levels of depressive symptoms predicted elevated mortality of cancer patients. This was true in studies that assessed depression before cancer diagnosis as well as in studies that assessed depression following cancer diagnosis. Associations between depression and mortality persisted after controlling for confounding medical variables. Research is needed on whether the treatment of depression could, beyond enhancing quality of life, extend survival of depressed cancer patients.

### *13.3.2 Surgery Effects on Health-Related Quality of Life*

Surgery for brain tumors is used to establish the histological diagnosis and to alleviate neurological symptoms through the reduction of tumor mass. Data from multiple series have demonstrated the importance of aggressive surgical resection for improved outcomes in DLGG. In particular, increased volumetric extent of resection has been shown to directly improve survival [42–45]. The risks and benefits must be weighed carefully because the surgical intervention itself may result in a transient or permanent decline in neurological function [46]. Where the tumor involves critical functional regions of the brain (e.g., motor cortex or arcuate fasciculus), complete tumor removal would directly affect the patient's functioning and is thus not feasible. Surgical debulking is often recommended for any patient with increased intracranial pressure, neurological deficits related to mass effects, or uncontrollable seizures. It is important for the patient to understand that gross total resection does not mean the tumor has been completely removed. Surgery and perioperative injuries may cause neurological deficits owing to damage of normal surrounding tissue. However, most of these deficits resolved within 3 months, presumably owing to the plasticity of the normal brain [47]. Nonetheless, many neurosurgeons are hesitant to operate on patients with tumors in eloquent brain areas. Studies that use intraoperative image guiding and functional mapping in

patients with DLGG in eloquent brain locations showed that intraoperative electrostimulation mapping during awake procedures is the most reliable method for identifying eloquent regions [48, 49]. This is a safe, inexpensive, and reproducible technique that allows the identification of crucial (nonfunctionally compensable) structures at the level of the cortex, white matter pathways, and deep gray nuclei [50]. Nonetheless, surgery for glioma in eloquent areas can negatively affect neurocognitive functioning early after surgery. In a study [51] 28 patients with gliomas of the left hemisphere in language and non-language areas were assessed before and 3 months after surgery with a comprehensive neuropsychological test battery. The authors showed pre- and postoperative language, memory, and executive functioning to be worse than healthy controls. Postoperatively, a decline was found in language and executive functioning. Postsurgical change was determined by tumor location, with only patients with tumors in or close to language areas to have reduced language capacity. Tumor resection in language areas thus increases the risk of cognitive deficits in the language domain postoperatively. A comparable study into the subacute surgery-related changes in neurocognitive functioning in patients with left and right temporal lobe tumors yielded similar findings [52]. They showed patients with left temporal lobe tumor to have greater decline than patients with right temporal lobe tumor on verbal memory and confrontation naming tests. Nonetheless, over one-third of patients with right temporal lobe lesions also showed verbal memory decline.

A follow-up study [53], suggests not only that most patients will have recovered 1 year after surgery, but also that recovery of neurocognitive functioning, specifically regarding language, might take longer than 3 months, as is generally assumed.

As noted earlier, treatment for low-risk patients may be deferred [11] and a watchful waiting policy in these patients with suspected DLGG does not appear to have negative effect on cognitive performance and HRQOL [22]. HRQOL and cognitive status of 24 patients suspected of having a DLGG, in whom treatment was deferred, and 24 patients with proven DLGG, who underwent early surgery were compared [22]. These patients were matched with healthy control subjects for educational level, handedness, age, and gender. The two patient groups were also matched for tumor laterality, use of AEDs, and interval between diagnosis and testing. HRQOL and cognitive status were compared between the three groups. Both patient groups scored worse on HRQOL scales than healthy control subjects. Unoperated patients with suspected DLGG scored better on most items than patients with histologically proven DLGG. Cognitive status was worse in both groups than in healthy control subjects, but, again, patients with suspected DLGG performed better than patients with proven DLGG. A much larger study [54] compared biopsy and watchful waiting that was favored in one hospital to early resection guided with three-dimensional ultrasound that was favored in the other regarding HRQOL outcome. Using generic (EQ-5D) and disease specific (EORTC QLQ-C30 and BN20) questionnaires They found no evidence that an early aggressive surgical approach in long-term DLGG survivors is associated with reduced HRQOL compared to a more conservative surgical approach. This finding weakens a possible role for watchful waiting in DLGG.

### *13.3.3 Radiotherapy Effects on Health-Related Quality of Life*

Prior research has shown that conventional (photon) radiotherapy, the standard treatment for most patients with high-risk DLGG, has a favorable impact on survival, but may negatively affect neurocognitive functioning and thus HRQOL. The risk of permanent central nervous system toxicity owing to radiotherapy, which typically becomes detectable after an asymptomatic latency period, continues to influence clinical treatment decisions. Interindividual differences in sensitivity result in a certain variability of the threshold dose and preclude administration of a guaranteed safe dose, even in the current era of high-precision image-guided (photon) radiotherapy. The therapeutic index in the nervous system is low, because the radiation dose required for tumor control is very close to, if not higher than, the toxic dose for neighboring tissues.

In contrast to the early complications of radiotherapy, the so-called late-delayed encephalopathy is an irreversible and serious disorder. This complication follows radiotherapy by several months to many years and may take the form of local radionecrosis or diffuse leukoencephalopathy and cerebral atrophy. Cognitive disturbances are the hallmark of the diffuse encephalopathy [55]. The severity of cognitive deficits ranges from mild or moderate cognitive deficits all the way to cognitive deterioration leading to dementia. It is not hard to imagine that these limitations in functioning have profound effects on HRQOL.

A commonly overlooked late complication of cranial radiotherapy in adults is endocrine dysfunction caused by damage to the hypothalamic–pituitary axis. Only a few studies have been done in adults, and these indicate that most patients who have clinical or subclinical endocrine dysfunction also show a significant decrease in well-being [56]. Emerging data indicate that these effects might be reversed by growth hormone therapy that could have a role in improving cognitive function by interacting with specific receptors located in areas of the CNS that are associated with the functional anatomy of learning and memory, by affecting excitatory circuits involved in synaptic plasticity, and by its protective effect on the CNS, as exemplified by its beneficial effects in patients with spinal cord injury [57].

Taphoorn et al. [58] described HRQOL in 20 patients who had been treated with early radiotherapy and 21 patients who had undergone surgery or biopsy only. In addition, 19 patients with hematological malignancies were included as a control group. The patients were evaluated for HRQOL through an interview, a multidimensional questionnaire that included physical status, social status, overall well-being, and treatment experiences and through the Profile of Mood States. Results showed that patients with brain tumors, regardless of whether they had received radiotherapy, had greater fatigue, memory loss, lack of concentration, and speech disorders than the control group. Patients were less satisfied with their condition and felt more restricted in daily activities than the control groups.

In view of the long survival of patients with DLGG and retrospective data suggesting a decline in cognitive function after radiotherapy in these patients [26, 59–61], both the EORTC and the NCCTG did companion studies assessing HRQOL

outcomes. The randomized phase III trial EORTC 22844 [60] where low RT dose (45 Gy) was compared to high RT-dose (59.4 Gy) in DLGG after biopsy or surgery showed no difference in OS. A subset of patients answered questionnaires on physical, psychological, social, and symptom domains before radiotherapy and at various times after treatment. Comparisons between the high-dose and low-dose radiotherapy groups could be made for two time points: from the completion of radiotherapy to 6 months, and from 7 to 15 months after radiotherapy. During the initial postradiotherapy interval of 6 months, patients in the high-dose group reported poorer functioning and more symptoms than patients in the low-dose group. Significant differences were noted between the high-dose and low-dose groups for the symptoms of fatigue, malaise, and insomnia. During the 7–15-months after radiotherapy, significant differences favoring the low-dose group were noted in leisure time activity and emotional functioning. No significant differences between the baseline scores were seen. A phase III prospective randomized trial of low- versus high-dose radiation therapy for adults with supratentorial low-grade astrocytoma, oligodendroglioma, and oligoastrocytoma found somewhat lower survival and slightly higher incidence of radiation necrosis in the high-dose RT arm [62] potentially explaining why patients in the high-dose arm of EORTC 22844 experienced poorer HRQOL. A more recent study showed that although DLGG patients may have significantly lower scores on the Mental Component Summary of the SF-36 the use of radiotherapy was not consistently associated with lower HRQOL self-ratings [38]. Given the relatively long survival of considerable numbers of DLGG patients, the follow-up study of the Klein et al. cohort yields interesting results. At a mean of 12 years after their first diagnosis, this study [63] reports on the radiological and cognitive abnormalities in DLGG survivors with stable disease since the first assessment [26]. Of the 65 patients 32 patients (49%) patients had received radiotherapy and these patients had more attentional deficits at the second follow-up than those who did not have radiotherapy. Furthermore patients who had radiotherapy had poorer attentional functioning, executive functioning, and lower information processing speed between the two assessments. In total, 17 (53%) patients who had radiotherapy developed cognitive disabilities deficits in at least 5 of 18 neuropsychological test parameters compared with 4 (27%) patients who were radiotherapy naive. White-matter hyperintensities and global cortical atrophy were associated with worse cognitive functioning in several domains. These results suggest that the risk of long-term cognitive and radiological compromise that is associated with radiotherapy should be considered when treatment is planned. The findings of the previously mentioned study of the same group [20] that poorer cognitive functioning is related to lower generic and disease-specific HRQOL stresses this notion.

Relative to conventional (photon) radiotherapy, proton radiotherapy reduces entrance dose and eliminates the exit dose, with the advantage of sparing normal tissue, while having comparable biological effects on the targeted tissue as do photons. Although a few small studies show promising results [64, 65], whether this technique also compares favorably to photon therapy regarding neurocognitive functioning and HRQOL has to be demonstrated in large multi-center studies. Twenty patients were evaluated at baseline and at yearly intervals for up to 5 years

regarding neurocognitive functioning, mood, and functional status [64]. Overall, patients exhibited stability in neurocognitive functioning with those with tumors in the left hemisphere versus in the right hemisphere being more impaired at baseline on verbal measures. Greater improvement in verbal memory over time was seen in patients with left than with tumors in the right hemisphere. There was no change on average in the emotional well-being of patients over time and there was no significant decline in HRQOL over time following radiotherapy completion. The same group [65] demonstrated that while all 20 patients (median age, 37.5 years) tolerated treatment without difficulty, new endocrine dysfunction was detected in six patients. Since no follow-up studies on neurocognitive functioning have been performed beyond the median survival of these patients, no definite conclusions can be drawn as to the preferred treatment of these patients.

### *13.3.4 Effects of Medical Therapy on Health-Related Quality of Life*

#### 13.3.4.1 Antiepileptic Drugs

Patients with DLGG in the temporal lobe, parietal lobe, or cortex are at greater risk for seizures than those with tumors in the infratentorial or white matter location. Brain tumor patients that present with a seizure as a first symptom remain at an increased risk for recurrent seizures despite treatment with AEDs [66]. Apart from tumor type, tumor location, and peritumoral and genetic changes affect the mechanism of seizures in brain tumor patients [2]. The available data on the efficacy and tolerability of AEDs in tumor-related epilepsy are scarce and heterogeneous due to the different histologies, the pathophysiology of seizures, the natural history of the tumor, and concomitant treatments [67]. In a large study one or more AEDs were taken by 71% of patients with DLGG to prevent seizures [68]. Risks of side-effects of AEDs can add to previous damage by surgery or radiotherapy, and therefore appropriate choice and dose of antiepileptic drug is crucial. The older AEDs (phenytoin, carbamazepine, and valproic acid) are known to have behavioral effects [69] with patients on valproic acid cognitively performing better than patients on phenytoin [70]. Several newer AEDs (e.g., levetiracetam, topiramate, lacosamide) appear to have fewer adverse effects than the older agents, though additional comparisons between new AEDs are required to fully assess the cognitive side effect profile of these newer anticonvulsant agents. Levetiracetam in fact may have cognition-promoting characteristics, as has been shown in healthy individuals where executive functioning improved [71] and in patients [70]. The latter study showed that glioma patients using levetiracetam performed better on verbal memory tests than patients not using AEDs. In a case series analysis levetiracetam monotherapy [72] was shown to be safe and efficacious, with positive impact on HRQOL expressed by less worry about seizures, limited side-effects of levetiracetam, and ability to maintain social

functioning. Of the newer agents, topiramate is associated with the greatest risk of cognitive impairment, although this risk is decreased with slow titration and low target doses [73, 74].

The purpose of a study by Klein et al. [68] was to determine the impact of epilepsy and antiepileptic drug (AED) treatment on cognitive functioning and HRQOL in DLGG patients. One hundred fifty-six patients without clinical or radiological signs of tumor recurrence for at least 1 year after histological diagnosis and with an epilepsy burden (based on seizure frequency and AED use) ranging from none to severe were compared with healthy controls. The association between epilepsy burden and cognition/HRQOL was also investigated. Eighty-six percent of the patients had epilepsy and 50% of those using AEDs actually were seizure-free. Compared with healthy controls, DLGG patients had significant reductions in information processing speed, psychomotor function, attentional functioning, verbal and working memory, executive functioning, and HRQOL. The increase in epilepsy burden that was associated with significant reductions in all cognitive domains except for attentional and memory functioning could primarily be attributed to the use of AEDs, whereas the decline in HRQOL could be ascribed to the lack of complete seizure control. The authors concluded that DLGG patients suffer from a number of neuropsychological and psychological problems that are aggravated by the severity of epilepsy and by the intensity of the treatment.

A study by Struik [75] aimed at determining the prevalence and severity of fatigue in long-term survivors with a DLGG, and at analyzing the relationship between fatigue and demographic variables, disease duration, tumor characteristics, former tumor treatment modalities, antiepileptic drug (AED) use, self-reported concentration, motivation, and activity. Therefore, 54 patients with stable disease (age range, 25–73 years) who were diagnosed and treated more than 8 years ago were included in this study and completed the Checklist Individual Strength which is a questionnaire measuring fatigue. Thirty-nine percent of the DLGG patients were severely fatigued, with older patients being most affected. Severe fatigue was associated with use of AEDs, and with reduced self-reported concentration, motivation, and activity. No relation was found between fatigue and gender, histology, tumor laterality, disease duration, type of neurosurgical intervention and radiation treatment. Fatigue is perhaps the most common and potentially debilitating symptom experienced by cancer patients, including those with brain tumors, that have a significant negative impact on routine activities of daily living and diminish HRQOL.

#### 13.3.4.2 Chemotherapy

Final analysis of data of the RTOG-9802 trial indicates that DLGG patients receiving radiation therapy followed by six cycles of combination chemotherapy and who are younger than 40 years of age and have undergone subtotal tumor resection or who are 40 years of age or older, have a longer PFS and OS than patients who received radiation therapy alone [76]. No serious longer-term cognitive side-effects could be substantiated for compared with their baseline MMSE score, patients

treated either with radiotherapy alone or with radiotherapy plus chemotherapy had a significantly higher average MMSE score during the first 5 years after randomization [77]. As noted earlier [78], radiotherapy may be associated with subcortical white matter changes, which are associated with behavioral slowing. The fact that none of the MMSE items have time constraints might have contributed to the lack of demonstration of a clear trend toward cognitive worsening after radiotherapy chemotherapy in a significant proportion of patients or might have led to an underestimation of the actual radiation or chemotherapy effects. Furthermore, as is the case with the studies into the neurocognitive profiles after proton radiotherapy [64, 65], longer term follow-up is needed.

Potential late CNS neurotoxic side-effects of chemotherapy may be difficult to discern from radiotherapy, because a substantial number of DLGG patients treated with chemotherapy have already been treated with radiotherapy [79, 80].

One of the oldest studies in DLGG patients under chemotherapy has been performed by Mackworth et al. [81]. The sample, in which HRQOL self-reports with the KPS were collected, consisted of 195 patients seen in a neuro-oncology clinic. Most patients had undergone surgery and radiotherapy, and were presently receiving chemotherapy. The mean age of the patients was 41 years (range 12–75 years). The multidimensional questionnaire evaluated energy, social life, physical symptoms, cognitive and memory skills, freedom from depression, work, sex, and well-being. A composite HRQOL score was determined by using the areas that were significantly correlated with well-being. These areas were freedom from depression, good social life, energy, and freedom from symptoms. In this sample two thirds of the patients had a KPS score of 90–100. No relationship was found between the HRQOL scores and the KPS score of 90–100. Mean HRQOL scores decreased with a KPS score of <90. However, this relationship was not significant. Age was noted to be inversely related to the KPS score, yet age was not related to well-being. The patients who lived more than 1 year had significantly higher HRQOL and KPS scores than those who died within a year. Correlating the KPS scores to the HRQOL scores in this study was helpful because the KPS is used in daily clinical practice to assess functional status and crudely measure HRQOL. This study showed that patients with no disease symptoms, or patients who have only minor signs or symptoms of disease had a strong sense of well-being.

Chemotherapy in standard and intensified formulations of procarbazine, lomustine (CCNU), and vincristine was administered to nine symptomatic patients with low-grade oligodendrogliomas [82]. Eight patients were treated with chemotherapy at presentation and one was treated for a recurrence after radiotherapy had failed. All patients improved in seizure frequency and other neurologic symptoms or MRI criteria, or both. No patient deteriorated while in therapy and the responses were sustained without radiotherapy for a median of 35 months (range, 22–45) in all surviving patients treated at presentation. Chemotherapy was well tolerated; all patients developed myelosuppression, but only those receiving the intensified regimen required dose reduction or premature discontinuation of treatment. As with recurrent and anaplastic oligodendroglioma, low-grade oligodendroglioma responds to chemotherapy.

Brada [83] studied the efficacy of temozolomide in DLGG patients treated with surgery alone using MRI and clinical criteria. Following surgery, 30 DLGG patients received temozolomide 200 mg/m$^2$/day for 5 days at a median of 23 months after initial diagnosis, on a 28-day cycle, for a maximum of 12 cycles or until tumour progression. Median age was 40 years and median follow-up from entry into the study was 3 years. Objective response was assessed by 3-monthly MRI and monthly HRQOL and clinical assessment. Three patients had a partial response, 14 minimal response, 11 stable disease and one progressive disease. Of the 29 evaluable patients, three discontinued after four, five and six cycles and two after ten cycles. Nine patients progressed, five had evidence of transformation. The 3-year progression-free survival was 66%. Ninety-six per cent of patients with impaired HRQOL had modest improvement in at least one HRQOL domain. Fifteen of twenty eight patients (54%) with epilepsy had reduction in seizure frequency, of whom six became seizure free. In a related study 43 patients with DLGG (29 astrocytoma, 4 oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with temozolomide at the time of clinical and radiological progression [84]. Thirty patients (69.7%) had previously received radiotherapy; 16 (37.2%) had received prior chemotherapy. Clinical benefit was evaluated measuring seizure control, reduction in steroid dose and modification of KPS and Barthel index. Quality of life was assessed with the QLQ-C30 questionnaire. A complete response was observed in 4 patients, 16 partial responses, 17 stable disease and 6 progressive disease. Median duration of response was 10 months, with a 76% rate of progression free survival at 6 months, and a 39% rate of progression free survival at 12 months. A relevant clinical benefit was observed particularly in patients presenting with epilepsy. In a study where DLGG patients with only prior surgery were given temozolomide for 12 cycles HRQOL was assessed by the Functional Assessment of Cancer Therapy-Brain at baseline prior to chemotherapy and at 2-month intervals while receiving temozolomide [85]. Patients at baseline prior to chemotherapy reported higher social well-being but lower emotional well-being compared to a normal population. Mean change scores at each chemotherapy cycle compared to baseline for all HRQOL subscales showed either no significant change or were significantly positive.

Newer agents, such as signal transduction inhibitors, angiogenesis inhibitors, monoclonal antibodies, immunotoxins, and gene transfer therapies, as well as new approaches to drug delivery, such as drug-impregnated sustained-release polymers and convection-enhanced delivery, remain to be investigated in DLGGs.

## 13.4 Conclusion

The studies presented in this chapter described outcomes of both single dimensional and multidimensional methods of studying HRQOL. Although only few studies in DLGG patients incorporated HRQOL as outcome measure, current studies have embraced the notion that an accurate assessment of HRQOL must be based on patient self-report.

HRQOL in DLGG patients is affected by the tumor, by tumor-related epilepsy and its treatment, and by fatigue, cognitive deficits, depression and changes in personality and behavior. The multidimensional scales used to study changes in HRQOL studies in brain tumor patients address this notion and provide a more comprehensive view of what is important to the patient concerning living with their disease and receiving treatment.

In future trials, more sensitive measures of long-term cognitive, functional, and HRQOL outcomes on DLGG patients at important time points over the disease trajectory are needed to better understand the changing needs that take place over time.

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# Chapter 14
# Magnetic Resonance Oncometabolic Imaging in DLGG Beyond the Image

**Rémy Guillevin, Guillaume Herpe, and Carole Guillevin**

**Abstract** Increasing knowledge in both genomic-metabolic and magnetic resonance imaging fields have generated more and more data from year to the next. In addition to give accurate statistical analysis, mathematic tools appear mandatory to (1) allow parameter extraction from MR sequences; (2) provide comprehensive and coherent analysis biodynamic systems, as it is the case for diffuse low-grade glioma: to fit their metabolic evolution for predicting their malignant transformation.

**Keywords** MRI • Diffuse low-grade glioma • Oncometabolic imaging • Multinuclear spectroscopy • Texture analysis • Fractal analysis • Mathematical modeling • Radiomics

## 14.1 Introduction

During the last years, increasing knowledge in both genomic and metabolic fields, as well as the developments in magnetic resonance of the brain have lead to extensive works and studies about correlations between the two sets of data, and the MR parameters, which are increasing from year to year. Extensive analysis of the "image contents", giving "the parameters beyond the image", using different mathematical tools, have encountered a huge development. However, this dramatic increase of data needs also powerful tools to provide comprehensive, hierarchical and logical understanding of the links between them: that is the role of statistical analysis, which become more important every day. In addition, whatever the numbers of parameters, some of them will lack to complete the entire "puzzle" of in vivo metabolism of the tumor within the brain. Mathematic modeling appear more and more necessary to complete the blanks and organize them in a coherent system which may match with the previous knowledge and the data arising from experimental

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research. This text aims to highlight some aspects of actual and future potential of radiogenomics (i.e. the correlation between cancer imaging and genomic features) towards a more accurate diagnostic workup of brain gliomas and their follow-up.

## 14.2 Investigating the Signal Contents: A Key Role of Mathematic Tools

### *14.2.1 Investigating the Tumor Heterogeneity: Texture Analysis Fractal Analysis*

*Texture Analysis (TA)* Based on the general assumption that the glioma heterogeneity should constitute a biomarker of its aggressiveness, as it is correlated to the WHO grade [1], MRTA assesses the distribution of gray-levels within an image to obtain texture features of intra-lesional heterogeneity [2, 3]. The initial filtration step employs a Laplacian of Gaussian (LoG) band-pass filtration, which extracts and highlights image features at different sizes corresponding to spatial scale filter (SSF). Quantification of histogram (with and without filtration) was based on the parameter standard deviation (SD), which represents the width of the histogram or degree of variation from the mean pixel value (equation shown below)

$$SD = \left\{ \frac{1}{(n-1)} \sum_{(x,y)\in R} \left[ a(x,y) - \bar{a} \right] 2 \right\}^{1/2}$$

This type of analysis can be used on different MR sequences or CT slices. Yet, portrayed texture from necrosis, which may be important to detect during LGG transformation, may be extracted from ADC textural analysis, whereas TA of T1 post-contrast may provide accurate quantitation of intra-lesional heterogeneity. However, it should be noticed that several methods are used for this technique, and then the results may be difficult to standardize for appropriate comparison from one series to another. Particularly, the filtration step is crucial for removing image heterogeneity due to noise, thus leading to highlight biological important heterogeneity. In addition, the order (e.g. first or second) of histogram statistical parameters is determinant for the results. Last, other authors have selected different texture analysis parameters, such as entropy derived from ADC maps [4], or combining imaging features from several sequences and using support vector machines [5]. Then the reproducibility of these methods may be uncertain, leading to increase variability in interpretation. However, Brown et al. [6] demonstrated in a study of 55 cases of oligodendrogliomas that codeleted (1p19q) tumors had significant differences in the amplitudes of intermediate frequencies on both T1 and T2—weighted images, thus allowing high sensitivity and specificity (95%) discrimination. In a follow-up study [7], heterogeneous signal intensity on T2 images was associated with codeletion.

SWI-LIV: Grabner et al. developed a technique providing quantitation of hypointensities local image variance based on 7T SWI (Susceptibility Weighted Imaging) images analysis [8]. After segmentation and pre processing with intensity correction and rescaling the intensity image, the SWI Local Image Variance was calculated using the following formula LIV = $G(X^2)$-[G(X)]2 (X is the pre processed image and G represents a Gaussian low pass filtering). Significant differences in SWI-LIV values were found dependent on the IDH1 mutational status and type of MRI contrast-enhancement, thus leading to improve pre-operative assessment of DLGG.

*Fractal Analysis* The fractal dimension (FD) is a non-integer number that characterizes the morphometric variability of a complex and irregular shape [9]. Based on SWI images which underwent automated computation, extracting two quantitative parameters: the volume fraction of SWI signals within the tumors (signal ratio) and the morphological self-similar features (fractal dimension [FD]). The results can be then correlated with each histopathological type of glioma and increase the accuracy of initial diagnosis (e.g. between WHO II and WHO III and malignant transformation of DLGG).

*CEST Imaging or Molecular Imaging* Amide Proton Transfer -Chemical Exchange Saturation Transfer may also provide critical information about tumor response of glioma under chemotherapy. Although this is a recent new technique based on a specific sequence, with only few publications in our field, it represents the new trend of molecular-metabolic-physiological imaging by magnetic resonance [10, 11]. CEST contrast is obtained after applying a saturation pulse at the specific resonance frequency of an exchanging proton site. The saturated spin is transferred to bulk water, and then specific molecular information can be obtained [12], within a so called "negative contrast" [13]. In APT, chemical exchange between protons of free tissue water (bulk water) and amide groups (−NH) of endogenous mobile proteins and peptides. Those exchangeable protons are more abundant in tumor tissues than in healthy tissues [14]. Other previous reports demonstrated that the APT signal increased by 3–4% in tumor compared with peritumoral brain tissue and human brain tumor at 3T [15]. However, those chemical exchanges are dependant from other metabolic changes, as the reduction in intracellular pH after treatment with TMZ. This would also result in a decrease in APT signal because −NH proton exchange is known to be catalyzed by base [16], which is otherwise consistent with natural history of gliomas, as previously suggested in experimental and clinical studies [17, 18]. This point suggests that APT sequence may be used concomitantly with phosphorus spectroscopy for pHi monitoring.

The results of the different studies above-cited suggest that APT imaging may serve as a useful biomarker in glioma for monitoring treatment response during chemotherapy and follow-up after treatment, including for radionecrosis identification [19]. This can be implemented on a standard clinical scanner [15, 20].

### *14.2.2 Improving Data Analysis and Quantitation from Spectroscopy*

Some works have raised during last years with the aim of provide optimized quantitation of brain tumors metabolites detected by MR spectroscopy. However, it should be noted that comparable data from different imaging centers and then, from different series, is difficult to obtain because of the heterogeneity of scanners, which is particularly important in spectroscopy, as the signal is varying in huge amounts (until two folds) from 1.5T to 3T magnets for a metabolite considered [21]. This may lead to important errors for (1) differential diagnosis from DLGG to other tumors; (2) follow-up characterization, as the successive exams for a same patient may be performed in a same center alternatively on magnets with different magnetic field strengths. Moreover, the data post-processing is also heterogeneous as numerous softwares are available in many MR centers, whatever commercial, freeware or in-house, with different solutions for quantitation. Some interactive quantification methods for the single voxel spectroscopy (SVS) such as AMARES or VARPRO, bring user lots of repetitive and unbearable work. What's more, the quantitative result is hard to be reproduced because of the difference in user's prior knowledge and state. Therefore, the automatic quantification is required to replace the interaction quantification for the sake of more efficiency and robustness. In their paper, Dou et al. [22] present a new automatic quantitative approach based on the convex envelope (AQoCE), compared with LC Model used on Siemens magnets. This method leads to increase both specificity and sensitivity of MR spectroscopy, thus suggesting that automated processing of MR data may avoid intra individual variability [23, 24]. This kind of software is based on mathematical algorithms, which supposes to have local specific competencies. The results, while repeatedly provided with a rigorous method in a same center, may be difficult to compare with those arising from another center. The reproducibility of some interesting results may be then random. Moreover, spectroscopic parameters are integrated in a global multiparametric analysis including contrast enhancement, related cerebral blood volume, ADC values extracted from diffusion sequence. Thus, the UCSF team [24] recently published a study on 120 patients with recurrent DLGG. They found several multivariate models with similar accuracy for predicting the grade II and the malignant transformation to grade III or IV. Hence, this kind of tools within the "kinetic" approach they allow are used in routine in some centers with expertise in the field, for the therapeutic follow-up and when the surgical resection is not possible [24]. Moreover, new proton high resolution multivoxel sequences, so-called "Laser or Mega Laser", allow 3D metabolic mapping, including 2 hydroxyglutarate and glutamate, thus marking the tumoral spatial heterogeneity [25].

*Perfusion Imaging Combination of MR DCE and DSC Imaging* Many works have been published about the predictive value of malignant transformation of DLGG [26–28]. Combined acquisitions allowing comparison of vessel compartment and permeability may provide simultaneously parametric maps of CBV, Vp and K(trans).

In addition, the region(s) of highest value (hotspot) can be measured on each map, and compared with histograms of rCBV, Vp and K(trans), with global increased sensitivity of perfusion-weighted sequence [29].

## 14.3 From Biometabolic Model to the Genomic Through the Metabolic Signal

Numerous publications have emphasized a pro malignant role of metabolic enzymes as isocitrate deshydrogenase, succinate deshydrogenase and fumarate deshydrogenase [25]. The most investigated one until today, as the cytosolic isoform, named IDH1, is of interest because (1) its key-role in tumorigenesis; (2) the ability of proton MRS to detect and to quantify some of their metabolic counterparts (Fig. 14.1). Once mutated, the IDH1 enzyme leads to convert α-ketoglutarate to 2-hydroxyglutarate, which is identified to play a crucial role in the initiation of tumorigenesis in mutant IDH1 cells (please refer to the dedicated chapter in this

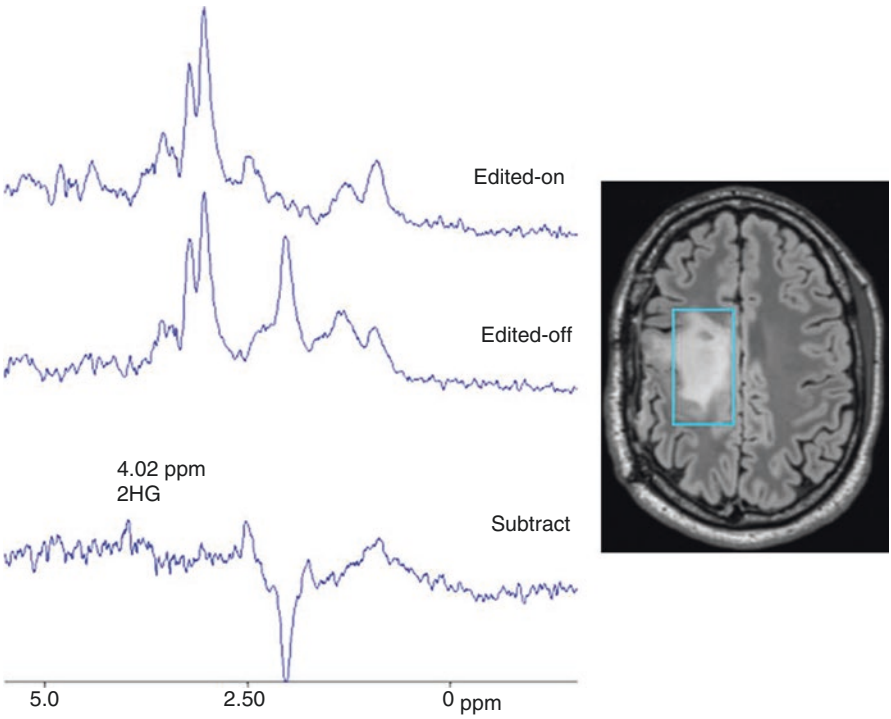


**Fig. 14.1** Glioma 2hydroxyglutarate editing: Suppressed spectrum (edited on), unsuppressed spectrum (edited off), edited spectrum of 2hydroxyglutarate (4.02 ppm) derived by subtraction of spectra (on-off)

book). Using point resolved spectroscopy within spectral difference editing from proton magnetic resonance spectroscopy, it is possible to detect and quantify 2-hydroxyglutarate resonance, a so-called oncometabolite, which accumulate [30]. Moreover, some authors have demonstrated the interest of longitudinal 2-hydroxyglutarate quantitation for monitoring treatment response in IDH1 mutant patients [31–33]. The authors developed a specific 3D sequence for over sampling the tumor and avoid difficulties due to heterogeneity. It is potentially available in centers with routinely use of proton magnetic resonance spectroscopy.

In their recent experimental works, Viswanath et al. [34] demonstrated that the IDH1 mutation may lead to a decrease of lactate production from pyruvate. They used multinuclear magnetic resonance spectroscopy, and especially $^{13}$C-MRS with dynamic nuclear polarization for pyruvate-lactate fluxes assessment, and $^{31}$P-MRS for steady-state assessment of intracellular pH and PCr. Furthermore, they showed that reduced flux of hyperpolarized [1-$^{13}$C] pyruvate to hyperpolarized [1-$^{13}$C] lactate could be due to reduced MCT1 and MCT4 expression in IDH1 muted cells. Increased intracellular pH in both type of cells was not modified by the drop of intracellular lactate.

Interestingly, the vascular counterpart of this "biochemical re-programming" is also accessible by MRI, during the same time of examination. Kickingereder et al. [30] provided a study in which they demonstrated that a one-unit increase in rCBV corresponded to a two-third decrease in the odds for an *IDH* mutation and correctly predicted *IDH* mutation status in 88% of patients. It has been established that increasing levels of 2 hydroxyglutarate leads to indirectly decrease of hypoxia-inducible factor 1-alpha, thus limiting angiogenic growing.

Whereas some of those results are obtained in experimental conditions with limited extrapolation to human- in vivo conditions, we must notice that they are partly consistent with theoretical conjectures expressed in previous papers [35, 36]. Yet, at this stage, before the recent knowledge assessing the links between genomic and metabolic modifications, alterations of MCT properties have been suggested by the previously published model. In this concept, glioma is considered as a general parametrical system evaluating in a viability domain, with specific ranges a value of each parameter [17, 35, 37]. Especially, high concentrations of Lactate (resulting from transport rate by MCT and pHi, are known to be not compatible with metabolic function of the parametrical system, e.g. the glioma (Fig. 14.2). This field of investigation seems to be at its beginning as the technical possibilities are increasing from year to year, especially in multinuclear magnetic resonance imaging, with the ability of studying different molecules according the nucleus studied, e.g. proton, phosphorus, carbon, sodium. Here is arising a new dimension of magnetic resonance, as metabolic one, which cross the link with the isotopic approach.

Moreover, this approach leads to interrogate potential therapeutic ways, based on MCT targeting, with potential therapeutic monitoring of a putative response using multinuclear spectroscopy.

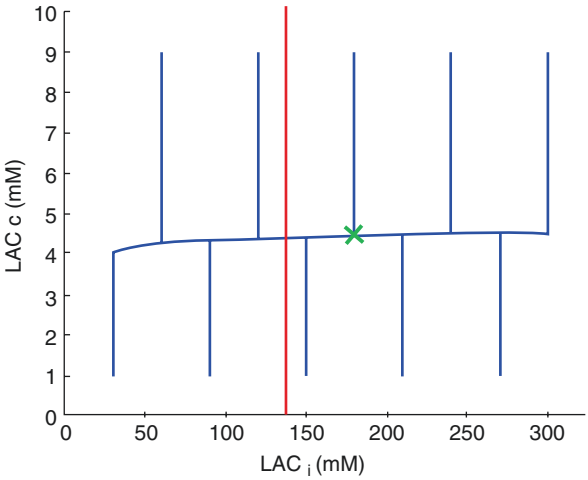


**Fig. 14.2** Impact of a significantly decrease of CBF. The *red line* represents the maximum limit of the viability domain, with maximal acceptable value of LACi

### *14.3.1 Which Sequences for Which Timing? The Challenge of Relevance*

Regarding all the possibilities provided today during brain MRI examination time, the key question of patient's compliance arises. Performing all the sequences abovementioned as well as morphologic and functional sequences may require much more than 1 h of scanning time. This not include post-processing which should not be taken into account for the patient's time. This is the case for texture or fractal analysis. Then the potential pertinence of each parameter from a dedicated sequence should be thoroughly considered within the therapeutic step of the patient. The improve of multivoxel proton spectroscopic sequences as Laser allow supplementary information during the same time without additional sequences, such as spatial distribution of 2 hydroxyglutarate and glutamate, both metabolites of importance for glioma monitoring, whatever they are under chemotherapy or not. Then, as stated before, periodic controls including those sequences must be performed to define the "kinetic–metabolic profile", especially during the initial phase of management (e.g. within the diagnostic time) and at each time of therapeutic commutation. Then the parameters may be integrated into the models to ensure the optimal follow-up. Amide Proton Transfert may provide additional information, especially about the glioma response under temozolomide or in the radionecrosis hypothesis. This sequence should be added into the imaging protocol during TMZ treatment. Phosphorus spectroscopy should also be used concomitantly as stated above, and is also recommended for monitoring (pre) malignant transformation, so-called "2 + grade", of DLGG. Because of their technical requirements, these last two sequences can be considered as "optional", dedicated to specific centers. More generally, as evoked in the spectroscopic section, requirements of both sequences acquisition and post-processing may lead to consider that oncometabolic imaging may be realized in centers with high specialization in brain tumor imaging.

## 14.4 Conclusion

Overview of the different aspects of metabolic imaging for glioma could be resumed as a new trend of brain tumor (and more, cancer imaging) so-called "mathematic-metabolic imaging" by MR or isotopic or both. This trend will have to deal with major issues, in the signal processing topic as well as in the mathematical tools development. Thus, the glioma (e.g. cancer) imaging management will require much more expertise which could not be limited to "radiology", but extended to mathematics and physic sciences, as a counterpart of increase of knowledge in genomic and metabolism.

The management of the DLGG "imaging" remains challenging for all sites. As stated below, a complete so-called metabolic imaging requires (1) a high-tech platform with appropriate team to use it; (2) a high level of standardization for acquisitions; (3) transversal competencies allowing appropriate exploitation of the information.

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# Chapter 15
# Positron-Emission-Tomography in Diffuse Low-Grade Gliomas

**Karl-Josef Langen, Marion Rapp, Michael Sabel, and Norbert Galldiks**

**Abstract** Contrast-enhanced MRI is currently the method of choice for the diagnosis of diffuse low-grade gliomas and provides an excellent depiction of structural changes in the brain. Nevertheless, the delineation of the tumor from normal brain tissue and non-specific abnormalities on MRI such as edema or treatment-related changes can be difficult. Positron-Emission-Tomography (PET) provides additional information on tumor metabolism and is helpful in many clinical situations. In particular, PET using radiolabeled amino acids has a wide range of applications and helps to solve a number of clinical issues. At initial diagnosis, amino acid PET may be helpful to estimate the prognosis of a low-grade glioma and to optimize patient counseling. Furthermore, the method improves targeting of biopsy and provides additional information of tumor extent, which is also helpful for resection planning and radiotherapy. In the further course of the disease, amino acid PET allows a sensitive monitoring of treatment response, the early detection of tumor recurrence, and an improved differentiation of tumor recurrence from treatment-related changes. In the past, the method had only limited availability due to the low number of PET scanners and the use of radiopharmaceuticals with a short half-life. In recent years, however, the number of PET scanners in hospitals has increased considerably. Furthermore, novel amino acid tracers labeled with positron emitters with a longer half-life have been developed and clinically validated which allow a more efficient and cost-effective application. These developments and the well-documented

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diagnostic performance of PET using radiolabeled amino acids suggest that its application continues to spread and that the method may be available as a routine diagnostic technique for certain indications in the near future.

**Keywords** Low grade glioma • PET • Amino acids • MET • FET • FDOPA

## 15.1 Introduction

MRI with its excellent soft tissue contrast, the high spatial resolution, and its multiplanar reconstruction capabilities is currently the method of first choice for the diagnosis of cerebral gliomas. Despite these unsurpassed properties of MRI, many problems in the diagnostic assessment of low-grade gliomas remain and a number of pivotal questions concerning the management of low-grade gliomas cannot be answered satisfactorily. Thus, at initial diagnosis, diffuse low-grade gliomas may exhibit only minimal changes in the brain tissue, which can hardly be distinguished from benign lesions. In larger tumors, the differentiation of glioma tissue from surrounding edema may be difficult, particularly when the tumor is not sharply demarcated from normal brain tissue due to diffuse tumor cell infiltration. Although commonly assigned as low-grade gliomas the course is clinically diverse and for some patients the disease has a benign course, whereas others experience rapid progression [1]. In the further course of the disease, the tumors may exhibit regional malignant progression, which is difficult to detect, especially when the blood-brain barrier (BBB) remains intact. In these patients with a heterogeneous tumor and intact BBB, biopsy guidance may be especially difficult. Monitoring of treatment response is another important factor to optimize individual treatment strategy where volume changes in MRI are just a very late sign. After treatment, postoperative or radiogenic changes in peritumoral brain tissue may result in contrast-enhancement on MRI that cannot be reliably distinguished from vital tumor tissue of recurrent glioma [2, 3].

Therefore, alternative imaging methods reflecting metabolic features of the tumor tissue have attracted the interest of neuro-oncologists for many years in order to facilitate the process of clinical decision-making in this challenging tumor entity. PET is a powerful method in Nuclear Medicine that has shown great potential for the diagnostic assessment of malignant tumors. The most widely used tracer for PET is $^{18}$F-Fluorodeoxglucose (FDG), which is accumulated in the majority of tumors due to an increased energy demand and consequently an increased glucose metabolism. FDG has been used for the evaluation of brain tumors since the early days of PET and a relationship of FDG uptake and tumor grade of gliomas and prognosis of cerebral gliomas has been reported in numerous studies [4]. In low-grade gliomas, however, FDG uptake is generally low and there is high FDG uptake in the surrounding normal brain tissue. Therefore, the usefulness of this tracer for low-grade gliomas is limited. In this chapter, the most promising PET tracers for the

**Table 15.1** Clinical applications of amino acid PET in low-grade gliomas

| | Clinical potential | References |
|---|---|---|
| Detection and differential diagnosis | + | [58, 63, 65, 66, 68] |
| Biopsy guidance | +++ | [54, 58, 59, 67, 69, 81–84, 154] |
| Tumor extent | +++ | [85–88, 90] |
| Grading of gliomas (static amino acid PET) | + | [41, 52, 58, 66, 87, 106] |
| Grading of gliomas (dynamic FET PET) | ++ | [52, 53, 55, 59, 107] |
| Prognosis | +++ | [35, 57, 114, 115, 155] |
| Malignant transformation | +++ | [51, 54, 59, 69, 84, 116] |
| Resection planning | +++ | [90–93, 156] |
| Radiotherapy planning | ++ | [101, 104] |
| Detection of recurrence | +++ | [120–123, 157] |
| Therapy monitoring | +++ | [134–139] |

**+** limited value, **++** helpful in a fraction of patients, **+++** high clinical impact

diagnostic assessment of low-grade gliomas will be reviewed. The chapter deals mainly with the application of radiolabeled amino acids owing to the ability of these substrates to pass the intact BBB and to depict brain tumors with a high tumor-to-background contrast. These tracers are well investigated, allow decisive diagnostic information in cerebral gliomas with respect to many clinical aspects, and are quite close to be established in routine clinical diagnosis (Table 15.1) [5–12].

## 15.2 Radiopharmaceuticals for PET in Low-Grade Gliomas

Today, the most widely used application of PET is the measurement of glucose metabolism with FDG in various types of cancer. In cerebral gliomas, FDG uptake is correlated with the degree of malignancy of the tumor (WHO grading) and with the patient's outcome [4, 13, 14]. Due to the high rate of glucose metabolism especially in the grey matter of the brain, however, it is difficult to distinguish glioma tissue from normal brain tissue by FDG-PET. While most high-grade gliomas WHO grade III and nearly all grade IV glioblastomas show an increased FDG uptake compared to the white matter, low-grade gliomas WHO grade II usually exhibit an indifferent or even a decreased FDG uptake (see Fig. 15.1). Therefore, FDG PET is not useful to delineate low-grade gliomas from the surrounding brain tissue.

Nevertheless, FDG PET has been shown to be useful to detect malignant transformation in low-grade gliomas and may therefore be useful for follow-up in low-grade gliomas [4]. The use of proliferation markers such as [$^{18}$F]3′-deoxy-3′-fluorothymidine (FLT) showed even a better correlation with the grade of malignancy and prognosis of cerebral gliomas than FDG uptake or MR spectroscopy [15, 16]. An image-guided biopsy study demonstrated that FLT is a useful marker of cellular proliferation that correlates with regional variation in cellular proliferation, but was unable to identify

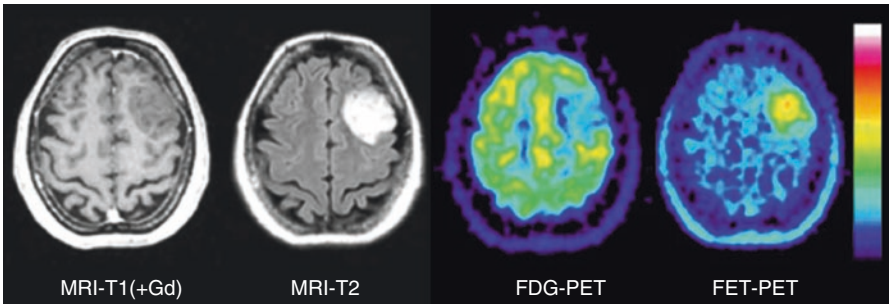


**Fig. 15.1** Astrocytoma WHO Grade II in the *left* hemisphere. The T1-weighted MRI after application of Gd-DTPA shows no contrast enhancement indicating an intact BBB and depiction of the tumor in the T2 weighted MRI is similar. FDG PET shows hypometabolism and is not helpful to guide biopsy. FET PET identifies a hot spot within the tumor and detects an optimal biopsy site

the margin of gliomas [17]. This is caused by the fact that FLT is not able to pass the intact BBB and accumulates usually in areas with contrast enhancement on MRI only [15, 18–20]. Therefore, portions of the tumor with an intact blood-brain barrier (BBB)—frequently present in low-grade gliomas—cannot be detected with FLT-PET. Furthermore, $^{11}$C-Choline or $^{18}$F-Fluoro-choline (FCH) has been used as a marker of cell membrane phospholipids in brain tumors and shows a significant correlation of uptake with the degree of malignancy in gliomas [21, 22]. Tracer uptake in areas with intact BBB is generally low but some studies have reported that FCH might be helpful to detect recurrent LGG in brain areas showing no contrast enhancement in MRI [23, 24].

Another interesting approach is to investigate the presence of intratumoral hypoxia using $^{18}$F-Fluoromisonidazole [25–28]. Hypoxia in tumors is a pathophysiological consequence of structurally and functionally disturbed angiogenesis along with deterioration in the inability of oxygen to diffuse through tissues. A PET study in patients with cerebral gliomas demonstrated areas of hypoxia in glioblastomas, but all investigated low-grade gliomas showed low uptake of $^{18}$F-Fluoromisonidazole [29]. This is not unexpected since tumor growth and angiogenesis in low-grade gliomas are still in a balance so that this approach is particularly attractive for the evaluation of high-grade gliomas.

A promising new target for brain tumor imaging is the mitochondrial translocator protein (TSPO), which is a component of the mitochondrial permeability transition pore and is strongly expressed by glioma cell lines [30]. In the recent past, PET imaging using TSPO ligands such as $^{11}$C-(R)PK11195 focused mainly on inflammatory brain diseases as an indicator of microglial activation but recent studies suggest a role of this method in the assessment of brain tumors [31–33]. A recent study has shown that TSPO expression may extend beyond the tumor margins in MRI and amino acid PET indicating an infiltration zone that exhibited tumor progression in the further follow-up of the patients [34].

At present, the best established PET tracers for the investigation of low-grade gliomas are radiolabeled amino acids of the class of large neutral amino acids such as [Methyl-$^{11}$C]-L-methionine (MET), O-(2-[$^{18}$F]fluorethyl)-L-tyrosine (FET) and 3,4-dihydroxy-6-[$^{18}$F]fluoro-phenylalanine (FDOPA) [5, 6, 9–12, 35, 36]. Because the uptake of these amino acids by both, the white and grey matter of normal brain tissue is relatively low, cerebral gliomas can be distinguished from the surrounding normal tissue with high contrast. It was long assumed that increased uptake of MET in brain tumors reflects an increased protein synthesis rate. Experiments in mice, however, demonstrated that an inhibition of protein synthesis did not influence the uptake of radiolabeled MET in tumors and brain [37] suggesting that alterations of amino acid transport rather than increased protein synthesis caused increased uptake in tumors. Furthermore, the predominant role of transport phenomena for increased amino acid uptake in gliomas is confirmed by the observation that PET using radiolabeled amino acids such as FET which are not incorporated into protein exhibit nearly identical results concerning brain tumor imaging as MET PET or FDOPA PET. Thus, a number of studies have shown that imaging of cerebral gliomas with MET, FET and FDOPA is rather similar [38–43]. Since FDOPA is a precursor of dopamine it shows also uptake in the striatum and can be used to trace the dopaminergic pathway in the nigrostriatal region to evaluate the presynaptic function in patients with neurodegenerative and movement disorders [44]. This property may cause problems in the delineation of gliomas affecting the striatum [12, 45].

The increased uptake of amino acids such as MET, FET and FDOPA by cerebral glioma tissue appears to be caused predominantly by increased transport via the transport system L for large neutral amino acids namely the subtypes LAT1 and LAT2 [46–50]. A recent study suggested that the trapping of FET within the cells is caused by the asymmetry of its intra- and extracellular recognition by LAT1 [48]. Nevertheless, there appear to be some differences in transport characteristics of MET, FET and FDOPA. FET shows different patterns of time-activity-curves in low-grade and high-grade gliomas [51–55] which could not be observed with MET or FDOPA [43, 56].

Since large neutral amino acids also enter normal brain tissue, a disruption of the BBB, i.e., enhancement of contrast media on MRI scans, is not a prerequisite for intratumoral accumulation of MET, FET and FDOPA (see Fig. 15.1). Consequently, uptake of these tracers has been reported in many low-grade gliomas without BBB leakage [5, 35, 57–60].

Most PET studies of cerebral gliomas have been performed with the amino acid MET [5], although the short half-life of $^{11}$C (20 min) limits the use of this technique to the few centers that are equipped with an in-house cyclotron facility. In contrast to MET, $^{18}$F-labelled amino acids (half-life, 109 min) such as FET and FDOPA can be transported from a cyclotron unit to multiple external PET centers. This enables a wider application of amino acid PET in clinical diagnosis. One of the best-established $^{18}$F-labelled amino acids is FET that can be produced in large amounts for clinical purposes like the widely used FDG [36, 61, 62].

Animal experiments have shown that FET, in contrast to MET, exhibits no uptake in inflammatory cells and in inflammatory lymph nodes but false positive uptake has been observed for MET, FET and FDOPA in human brain abscesses, demyelinating processes, near cerebral ischemia and hematomas [12, 63–65]. Therefore, increased uptake of the tracers is not specific for cerebral gliomas although increased amino acid uptake has a high positive predictive value for cerebral gliomas [66]. The report is focused on the clinical experiences with MET, FET and FDOPA, which are at present the best-validated amino acid tracers for PET.

## 15.3 Clinical Applications of PET in Diffuse Low-Grade Gliomas

### *15.3.1 Detection of Low-Grade Gliomas and Differential Diagnosis*

The diagnostic potential of amino acid PET to detect low-grade gliomas is limited since MET and FET exhibit increased uptake only in a fraction of about 60–80% of low-grade gliomas [6, 35, 57, 58, 60, 63, 65, 67–69]. The specificity of MET, FET and FDOPA PET for neoplastic lesions and especially in the case of low-grade gliomas is generally affected by possible tracer uptake in the area of benign processes such as hematoma, ischemia, traumatic brain injury, and acute inflammatory processes [5, 63–65, 70–73]. In the largest study to date evaluating MET PET in a consecutive series of 196 patients with suspected brain tumors, differentiation between gliomas and non-neoplastic lesions was correct in 79% using a threshold of the tumor/brain ratio of 1.47. Exclusion of high-grade gliomas (99 low-grade gliomas versus 24 non-neoplastic lesions) yielded a sensitivity of 67% and specificity of 72% for distinguishing low-grade gliomas from non-neoplastic brain lesions [6, 68]. The diagnostic performance of FET PET has been evaluated in a series of 174 newly diagnosed cerebral lesions with suspicion of glioma, which included 72 histologically confirmed diffuse low-grade gliomas [58]. In that study, the mean tumor to brain ratio (TBR) was 1.8 ± 0.5 in low-grade gliomas versus 1.4 ± 0.4 in nonneoplastic lesions yielding a sensitivity of 79% and specificity of 48% for distinguishing low-grade gliomas from non-neoplastic brain lesions. These results are similar to the observations in other publications in which low-grade gliomas, with the exception of oligodendrogliomas, presented with mean TBR in the range of inflammatory and other active (e.g., ischemic, traumatic) brain lesions [63, 65, 67]. Higher amino acid uptake in the subgroup of low-grade oligodendrogliomas and oligoastrocytomas according to the WHO classification 2007 [74] has been reported in several studies and is most probably related to the increased cellular and vascular density in this glioma subtype [52, 60, 75–77].

Taken together, the diagnostic accuracy of amino acid PET to detect low-grade gliomas and to differentiate suspicious lesions from non-specific uptake in non-neoplastic lesions is limited. Therefore, a histological evaluation of suspicious brain lesions by biopsy remains necessary under most circumstances.

### *15.3.2 Identification of an Optimal Site for Biopsy*

An important aspect of the diagnostic assessment of low-grade gliomas is the definition of areas with the highest cellular proliferation rates. Since the tumor biology is dominated by the most aggressive glioma parts, representative tissue samples are vitally important for histological tumor diagnosis, prognostication, and treatment planning. The ability of MRI to show the most rapidly proliferating portions of diffuse low-grade gliomas is limited, particularly when the tumor shows no contrast enhancement in MRI, which occurs frequently in low-grade gliomas. FDG and FLT PET are usually negative in low-grade gliomas and provide no information on regional heterogeneity of metabolic activity in these tumors. Radiolabeled amino acids exhibit increased uptake in the majority of diffuse low-grade gliomas and are helpful to optimize the targeting of biopsies and prevent the problem of non-diagnostic biopsies from non-specifically altered tissue (Figs. 15.1 and 15.2). Biopsy controlled studies have shown that MET and FET uptake correlate with microvessel and cell density in non-contrast enhancing gliomas [77–79]. Vascular density is a frequently described feature linked to early malignant transformation in gliomas [80]. A number of studies have compared the diagnostic potential of PET using FDG and MET or FET to identify metabolic hot spots in cerebral gliomas to guide biopsy [67, 81, 82]. These studies consistently report that regionally increased FDG uptake, if present, is congruent with that of increased MET or FET uptake but amino acid PET is generally more sensitive than FDG PET. A number of studies

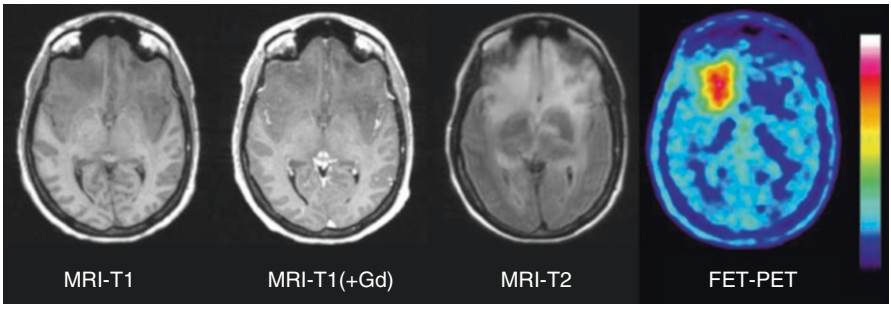


**Fig. 15.2** Astrocytoma WHO Grade II in the frontal lobe. T1-weighted MRI after application of Gd-DTPA shows no pathological contrast-enhancement and a tumor cannot be clearly delineated. T2-weighted MRI shows widespread abnormalities within the complete frontal lobe and is not helpful to depict the tumor. FET PET identifies a clear tumor with high tracer uptake in the lower frontal lobe

have evaluated the role of amino acid PET for biopsy guidance in the subgroup of low-grade gliomas. In a study with 32 patients that included 10 low-grade gliomas MET PET allowed the definition of a biopsy target in all low-grade gliomas while FDG showed increased uptake in only one of these tumors [83]. In a patient series of 22 histologically confirmed low-grade gliomas, FET PET identified a local maximum for biopsy guidance in 16 of the tumors (72%), while FDG identified a metabolic spot in only 2 (9%) of the low-grade gliomas [67]. Another study including 72 histologically confirmed diffuse low-grade gliomas, FET PET identified a local maximum in 79% of the tumors [58]. Other studies emphasize the role of kinetic analyses of FET uptake in low grade glioma [51, 54, 59, 69, 84]. Areas with an early peak in FET uptake followed by a descending time activity curve were associated with areas of malignant transformation and poor prognosis. Interestingly, a "malignant curve pattern" was also predictive for poor outcome if FET uptake in the suspicious brain lesion was low [51, 59, 69]. These data suggest that amino acid PET is a useful tool for identifying metabolic hot spots in low-grade gliomas to target biopsies. Furthermore, dynamic FET PET appears to provide important additional information on the aggressiveness of the tumors independent of the degree of tracer uptake. Nevertheless, it is not yet proven beyond doubt that the maximum concentration of amino acid uptake in low-grade gliomas corresponds to the most aggressive part of the tumor and further studies are needed to investigate this aspect (Fig. 15.3).

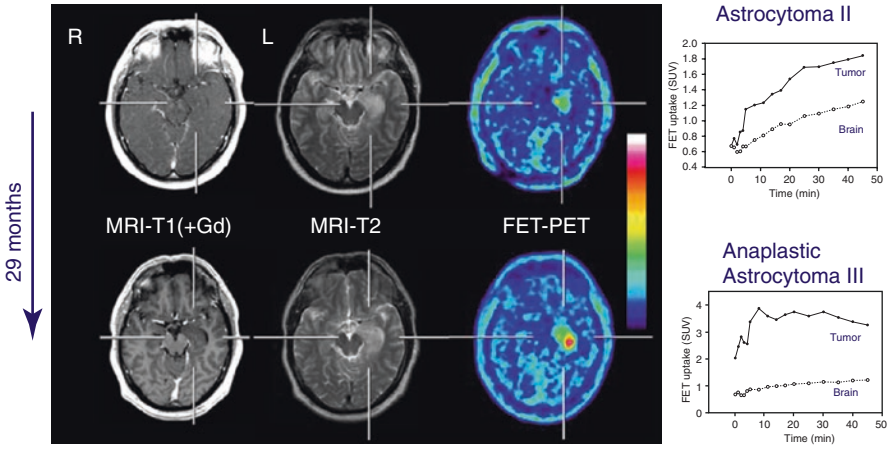


**Fig. 15.3** MRI and FET PET and of a patient with newly diagnosed histologically confirmed diffuse astrocytoma WHO grade II in right temporal lobe (*upper row*). T1 weighted MRI shows no contrast enhancement (*left*) and hyperintensity on T2-weighted image (*middle*) and slightly increased FET uptake (*left*). Time–activity curve on the right shows constantly increasing FET uptake. Twenty-nine months later (*lower row*), patient presented with malignant progression to WHO grade III astrocytoma associated with significant increase in FET uptake, discrete contrast enhancement and enlargement of hyperintensity on T2-weighted image. Dynamic evaluation of FET uptake (*right*) shows a "malignant curve pattern" with an early peak of FET uptake followed by declining time activity curve

### *15.3.3 Delineation of Tumor Extent for Treatment Planning*

Multiple studies in which the radiological findings were compared with the histological findings in tissue samples obtained by biopsy or open surgery have provided clear evidence that PET using radiolabeled amino acid detects the solid tumor mass of cerebral glioma tissue more reliably than either CT or MRI [81, 83, 85–88]. This is especially relevant for the non-enhancing parts of gliomas in MRI, which predominantly occur in low-grade gliomas. In a study exploring the potential of FET PET to image the extent of cerebral gliomas, 52 neuronavigated biopsies were taken from cerebral gliomas of 31 patients. Neoplastic tissue was found in 94% of biopsies in FET-PET positive areas, but only in 53% of the suspicious areas identified by MRI [87]. In that study, 12 biopsies yielded the histopathological diagnosis of a diffuse low-grade glioma and FET uptake was increased in all but one of the areas from which the biopsies were taken. In contrast, none of these areas showed contrast-enhancement on MRI. Another study investigated the role of FET-PET as a surrogate marker for accumulation of 5-aminolevulinic acid (5-ALA), which is used as a metabolic marker of malignant glioma cells for fluorescence-guided resection [89]. In that study, patients with 17 low-grade gliomas were included. FET was positive in 7 of the tumors while 5-ALA was observed in only one of the low-grade gliomas, which showed corresponding contrast enhancement. These data indicate that amino acid uptake in PET is a more sensitive indicator of low-grade glioma than 5-ALA fluorescence.

Since amino acid PET appears to be a valuable instrument to detect the solid tumor mass of cerebral gliomas, this technique has been used for resection planning. In a study evaluating integrated MET PET and MRI guided resection of 103 brain tumors, a large fraction of low-grade gliomas was included [90]. Resection planning in 59 low-grade gliomas demonstrated that the PET volume did not match the MR volume and improved the tumor volume definition in 88% of the cases. Similar results were reported in other studies for MET and FET PET which mainly included high-grade gliomas [91–93].

These data suggest that resection of low-grade gliomas guided by amino acid PET may increase the resection extent and thus the patients' survival. It needs, however, to be considered that MET, FET and FDOPA show increased uptake in only 60–80% of low-grade gliomas and that the resection of the tumors with low amino acid uptake cannot be improved.

The improved imaging of glioma tissue using amino acid PET has also been applied to improve planning of radiation treatment of brain tumors [94]. A number of centers have started to integrate amino acid imaging into CT- and MRI-based radiotherapy planning, particularly in high-grade gliomas and when high-precision radiotherapy is to be given or in the setting of dose escalation studies or for the re-irradiation of recurrent tumors [95–103]. Experiences with amino acid PET radiotherapy planning of low-grade gliomas are limited but indicate improved sensitivity in detecting postoperative residual tumor and a benefit for radiotherapy planning in patients with inconclusive MRI findings [104]. Improved outcome of the patients with radiotherapy planning by amino acid imaging compared with conventional therapy planning, however, has not yet been proven.

### *15.3.4 Glioma Grading and Prognosis*

FDG PET is considered as a relative accurate predictor of tumor grade and prognosis of cerebral gliomas and the detection of foci with increased FDG uptake in low-grade glioma is highly suspicious for malignant progression [13, 105]. The combination of FDG PET and multiparametric MRI may further improve the diagnostic accuracy to differentiate high-grade and low-grade glioma [14]. Most PET studies employing amino acids have shown that gliomas of different WHO grades overlap in their degree of amino acid uptake, so that the tumor grade cannot be reliably predicted with this technique [5, 19, 41, 52, 58, 87, 106]. A high potential to differentiate high-grade and low-grade gliomas has also been claimed for FLT, but FLT uptake goes along with BBB disruption and there is a high fraction of anaplastic astrocytoma without significant contrast enhancement on MRI which consecutively are negative in FLT PET [19, 20].

Using FET PET a number of studies have demonstrated that the evaluation of tracer kinetics in the tumors may be helpful to differentiate between high-grade and low-grade gliomas [52, 53, 55, 59, 107]. High-grade gliomas are characterized by an early peak of the time-activity curve around 10–15 min after tracer injection followed by a decrease of FET uptake. In contrast, time–activity curves slightly and steadily increase in low-grade gliomas of WHO grade II. Using dynamic evaluation of selected regions of the tumor, high-grade and low-grade gliomas could be distinguished with an accuracy of 70–90% in primary tumors as well as in recurrent tumors [52, 53, 59, 84, 107]. Furthermore, a recent study suggested that early static scans of FET uptake have a higher diagnostic accuracy for grading of gliomas than the standard 20–40 min scans but this approach did not reach the accuracy of dynamic FET imaging [108]. Studies using MET and FDOPA demonstrated that unlike FET PET, the time-activity curves of tracer uptake do not allow the classification of low- and high-grade gliomas [43, 56].

Considering gliomas of all WHO grades the prognostic significance of amino acid uptake remains a matter of controversy. Some studies seem to show that lower amino acid uptake especially in astrocytic glioma is associated with a better prognosis, but there is generally high uptake in oligodendroglioma despite their apparently better prognosis [5, 60, 75, 76, 109]. Recent studies suggest that dynamic FET PET [110], the “biological tumor volume” (BTV) as assessed by amino acid PET at primary diagnosis [111, 112] or textural parameters considering tumor heterogeneity may be important predictors of prognosis [113].

For patients with low-grade gliomas prognostication is an important factor for disease management. Some of these patients have a stable course with an excellent quality of life for many years or decades even without treatment, while others experience rapid tumor progression with malignant transformation to a high-grade glioma and a poor prognosis. A better identification of individuals with either a poor or a favorable prognosis is highly desirable to optimize patient counseling. A study with MET PET showed that these patients benefit from a surgical procedure only when increased amino acid uptake can be demonstrated [114]. In a series of 24

patients with low-grade gliomas, patients with a tumor/brain ratio >2.2 had a significantly shorter survival time than the patients with a tumor/brain ratio <2.2 [115]. Similarly, in a series of 50 patients with low-grade gliomas a SUV of FDOPA uptake >1.75 was an independent predictor of disease progression [35]. Another study indicated that the combined evaluation of FET-PET and MR morphology was a statistically significant prognostic predictor for patients with newly diagnosed low-grade gliomas [57]. Within a 7-year period, a group of 33 consecutive patients with previously untreated non-enhancing WHO grade II glioma were included in a prospective study. A baseline, both MRI and FET-PET were performed before histology in all patients on tissue samples by biopsy and a "watch and wait" strategy without further treatment was started. During the follow-up it turned out, that baseline FET uptake and a circumscribed versus a diffuse growth pattern on MRI were highly significant predictors for patients course and outcome: Those low-grade gliomas that were well delineated on MRI and showed no FET uptake had an excellent prognosis with long progression-free intervals, good clinical condition and late malignant transformation. In contrast, patients with low-grade gliomas with diffuse tumor margins on T2-weighted MRI and FET uptake had a poor outcome with early progression in combination with malignant transformation to a HGG, rapid clinical deterioration, and die earlier. A recent study in 54 gliomas of WHO grade II observed no correlation between FET uptake and progression-free survival but that analysis included 16 patients with recurrent tumors and comparison with other studies is difficult [60]. In any case, also low-grade gliomas with low FET uptake should be monitored carefully because also tumors without tracer uptake can harbor high-grade glioma tissue [59].

Recent studies have emphasized the role of kinetic analyses of FET uptake in the evaluation and follow-up of low-grade glioma [51, 54, 59, 69, 84, 116]. Areas with an early peak of FET uptake followed by a descending time activity curve in suspected low-grade gliomas were associated with areas of malignant transformation and poor prognosis. Interestingly, a "malignant curve pattern" is also predictive for poor outcome if FET uptake in the suspicious brain lesion is low [59, 69].

### *15.3.5 The Diagnostic Assessment of Recurrent Tumors*

Early detection of recurrent tumor is of particular interest. It is difficult to distinguish recurrent glioma from nonspecific post-therapeutic changes with conventional MRI alone, because pathological contrast enhancement may reflect either re-growth of tumor or reactive changes after radio- or chemotherapy [2, 117]. Furthermore, contrast-enhancement is usually missing in recurrent low-grade gliomas and MRI cannot differentiate between tumor, edema and nonspecific treatment-related changes, unless a mass effect or distinct bloating of cortex or other grey matter structures is seen [68]. Unfortunately, most publications in the literature have evaluated the role of PET in the detection of recurrent gliomas in groups with mixed WHO grades. The potential of FDG-PET in differentiating tumor recurrence from radionecrosis in high

grade gliomas is limited because of the higher frequency of non-specific uptake [118] and the performance of FLT PET is also limited [119]. Multiple studies have shown that MET-PET is highly sensitive to detect recurrent gliomas but the specificity for the differentiation of vital tumor tissue from non-neoplastic changes is not optimal and in the range of 70–75% [5, 120, 121]. The specificity of FET-PET for the differentiation of recurrent gliomas from non-neoplastic changes appears to be higher than that of MET-PET. In a study involving 45 patients (including 11 low-grade gliomas), the sensitivity and specificity of FET-PET for the detection of recurrent gliomas were 100% and 93%, respectively, compared with 93% and 50%, respectively for MRI [122]. A recent study in 124 glioma patients including 55 patients with low-grade gliomas demonstrated that the combined use of static and dynamic FET PET parameters differentiate progressive or recurrent glioma from treatment-related non neoplastic changes with an accuracy of 93% [123]. One study that focused on the role of FET PET as a diagnostic tool for detection of malignant progression in patients with low-grade gliomas reported that the combined analysis of FET PET parameters (i.e., changes of TBRmax, TTP, or time–activity curve pattern) yielded a significantly higher diagnostic accuracy for the detection of malignant progression than changes of contrast enhancement in MR imaging (accuracy, 81 vs. 63%; P = 0.003) [54]. Thus, especially FET-PET is considered as a valuable tool in differentiating recurrent tumor from non-neoplastic changes.

### *15.3.6 Monitoring of Radio- and Chemotherapy*

Imaging for radiological response assessment in low-grade gliomas is based on serial measurements of T1- and T2-weighted MRI. Low-grade gliomas usually show no contrast enhancement on MRI due to an intact BBB, and the diffusely infiltrative nature of these tumors makes the assessment of tumor boundaries difficult. Changes in apparent tumor size that are seen in MRI are taken as indicators of the response to therapy but this approach is limited by the difficulty in distinguishing vital tumor tissue and unspecific treatment effects. The feasibility and usefulness of PET for treatment assessment and follow-up in cerebral gliomas of all grades of malignancy after radiotherapy and chemotherapy have been explored in multiple studies and the diagnostic accuracy compared with conventional MRI is considered to be very efficient.

The current experience concerning treatment monitoring in brain tumors with PET is based mainly on the data obtained in patients with high-grade gliomas. Several studies evaluated the role of amino acid PET using MET, FDOPA and FET in patients with high-grade gliomas to monitor external fractionated radiation therapy [112], treatment effects during standard chemotherapy regimen, i.e., adjuvant temozolomide [124] or chemotherapy with procarbazine, CCNU, and vincristine (PCV) [125], dose-intensified chemotherapy with temozolomide [126], and experimental treatment such as intracavitary radioimmunotherapy [127], convection-enhanced delivery of paclitaxel [128], tyrosine kinase inhibitor treatment [129], brachytherapy [130] and antiangiogenic treatment with bevacizumab [131–133].

The currently available data suggest that a reduction of the tumor-to-brain ratio of amino acid uptake and the metabolic volume of high-grade glioma is a sign of a response to treatment.

Besides cytoreductive surgery, local radiotherapy is an important treatment option especially in patients with an astrocytoma WHO grade II. The possibility of late side effects of radiotherapy (e.g., neurotoxicity) in this group of patients with a much longer life expectancy makes it necessary to identify groups that benefit from early radiotherapy compared with those in whom radiotherapy should be delayed until the time of tumor progression. The role of MET PET has been evaluated in a small number of retrospective studies, mostly in comparison to FDG PET. Roelcke and co-workers evaluated the effects of postoperative external fractionated radiotherapy using MET and FDG PET in patients with an astrocytoma WHO grade II [134]. Tracer uptake was assessed by tumor to brain ratios during follow-up and at the time of first tumor progression, and was not significantly different in patients who received external radiotherapy after tumor resection (n = 13) in comparison to patients treated with surgery alone (n = 17). Different results could be observed in brachytherapy after implantation of $^{125}$I seeds. One year after seed implantation, FDG uptake did not change in patients with low-grade glioma, but a significant decline of MET uptake was detected [135, 136] indicating that MET PET may provide more information on therapeutic effects than FDG following brachytherapy. The different results of these studies may be explained by different follow-up times and radiotherapy modalities used in the study protocols.

In order to assess the response to chemotherapy using amino acid PET in patients with low-grade gliomas FET and MET PET was used in a prospective study to evaluate the response to an intensified temozolomide regimen in a series of 33 patients with low-grade glioma. Reduction of metabolically active tumor volumes, but not reduction of PET uptake ratios or MRI tumor volumes, correlated with improved seizure control following chemotherapy. A decrease of the active tumor volume of ≥80.5% predicted a progression free survival of ≥60 months and a decrease of ≥64.5% a progression free survival of ≥48 months. [137, 138].

In patients who showed a clinical response, a reduction of the metabolically active tumor volume after initiation of treatment could be observed in FET PET earlier than volume reductions on FLAIR MRI sequences (see Fig. 15.4). In a retrospective study the effect of PCV chemotherapy was examined using MET PET in seven patients with an oligodendroglioma WHO grade II [139]. Similar to the above-mentioned study, changes of tumor volume in MRI FLAIR sequences and metabolically active tumor volume derived from MET PET were monitored. MRI-FLAIR and MET PET provided concordant information on tumor to PCV treatment, but MET PET was found to be more sensitive for the assessment of PCV responsiveness.

The findings indicate the sensitivity of amino acid PET for detecting early treatment response in low-grade gliomas. Furthermore, the early identification of non-responders may help to minimize negative impact of chemotherapy on quality of life.

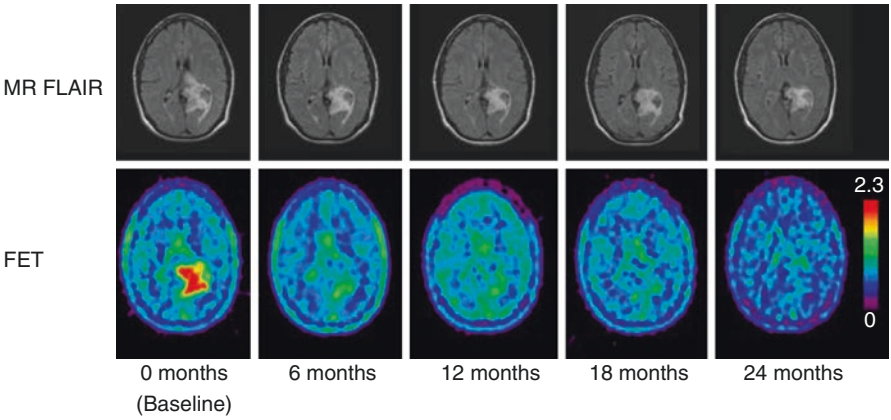


**Fig. 15.4** Patient with an oligoastrocytoma WHO grade II during chemotherapy with temozolomide. FET PET identifies response to treatment at an early stage of disease, while T2-weighted MRI remains ambiguous. With kind permission from Springer Science + Business Media: J Neurooncol: Early metabolic responses in temozolomide treated low-grade glioma patients, Vol. 95, 2009, Wyss et al. Fig. 2. Licence No. 2834741072095

## 15.4 Perspectives for PET in the Management of Low-Grade Gliomas

Diagnostic assessment of diffuse low-grade gliomas by PET using radiolabeled amino acids permits a more specific representation of the spatial extent of the tumors than is possible by conventional MRI alone. This has been shown to be advantageous for biopsy planning, tumor resection, and radiotherapy. Valuable prognostic information can be obtained at initial diagnosis, to detect malignant transformation during follow-up and the treatment response can be judged early in the course of treatment. Recurrent tumors can be differentiated from post-therapeutic changes with a high degree of specificity. Advanced MRI methods may also yield metabolic information that is markedly more specific than that obtainable by conventional MRI [140]. A recent meta-analysis has analyzed the role of advanced MR imaging with magnetic resonance spectroscopy (MRS), perfusion weighted imaging (PWI), diffusion weighted (DWI) and diffusion tensor imaging (DTI) in the management of adults with diffuse low-grade glioma [141]. Although these techniques are established and widely available for a longer period of time there is still not enough evidence to recommend the integration of either in standard diagnostic imaging protocols. The fact that amino acid PET is widely used in centers that also have full access to the spectrum of functional and molecular MR methods, emphasizes the additional value of amino acid PET beyond alternative MRI methods. The diagnostic accuracy of these techniques in comparison with amino acid PET remains to be investigated. First studies have

demonstrated the potential benefit of integrating fiber tracking by DTI and FET PET [142–144]. These studies indicated complementary information and more detailed understanding of peritumoral fiber tract alterations in gliomas, which are more complex as described so far.

A first comparative study of FET PET and PWI in 56 patients with cerebral glioma, showed higher TBRs and larger tumor volumes in FET PET than the maps of regional cerebral blood volume [145]. The spatial congruence of both parameters was poor and the locations of the local hot spots differed considerably. Similar results were observed in another study including 55 patients with cerebral glioma when comparing FDOPA PET and PWI [45].

The future will also be strongly influenced by the integration of PET and MRI in one imaging device [146–148]. The advent of hybrid PET-MRI systems offers a multimodal approach for the investigation of brain tumors and improved patient comfort due to a significant reduction in measurement time and improved spatial and temporal co-registration of PET and MRI data.

The scientifically documented utility of amino acid PET of low-grade gliomas seems to justify its introduction as a routine diagnostic technique for certain indications, but it remains to be confirmed that this will improve the overall quality of care. Initial studies have already evaluated the cost effectiveness of amino acid PET for target selection in gliomas and achieved promising results [149]. The guidelines of the European and the German Association of Nuclear Medicine for brain tumor imaging using labelled amino acid analogues have been published in recent years [150, 151]. The Response Assessment in Neuro-Oncology Working Group (RANO) which is an international effort to develop new standardized response criteria for clinical trials in brain tumors has recently recommended the use of amino acid PET in all stages of patient management, i.e., at primary diagnosis especially for the differentiation of equivocal brain lesions in MRI, after diagnosis for the definition of tumor extent for resection, biopsy and radiotherapy planning, in the early course of treatment to differentiate pseudoprogression and early tumor progression, at a later stage for the differentiation of radionecrosis and recurrent tumor and for treatment monitoring [10]. The logistical prerequisites for amino acid PET have become markedly less difficult to achieve in recent years with the introduction of FET PET. In Europe, MET PET has been replaced in many neuro-oncological centers by the more convenient PET tracer FET and the improved availability and high clinical interest in this method has led to more than 10,000 FET PET scans in some centers [152]. As the first country, Switzerland has approved FET PET for brain tumor imaging in 2014 [153].

The benefit of amino acid PET in cerebral gliomas appears to be well justified by its clinical utility since the costs of PET imaging are relatively small in relation to the expenses of local or systemic treatment approaches and, consecutively, the management of possible adverse effects. The information provided by amino acid PET assists to optimize the individual treatment strategy and to minimize negative impact of treatment approaches on quality of life.

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# Chapter 16
# Dynamics of DLGG and Clinical Implications

**Emmanuel Mandonnet**

**Abstract** Diffuse low-grade glioma are defined by a common morphotype on histological analysis. However, these tumors exhibit a wide heterogeneity in their degree of biological aggressivity, resulting in a large range of survival times. Several factors at diagnosis have been found to identify different subgroups of prognosis, but there is growing evidence that the intrinsic dynamics of the tumor—that can be evaluated over a short initial follow-up—plays a major role in predicting overall prognosis at an individual scale. We will review our current knowledge of DLGG dynamics on molecular, histological, radiological and clinical scales. In particular, we emphasize the importance of estimating the initial radiological dynamics from two successive morphological MRI. Finally, we describe how the spontaneous dynamics can be modified by the different treatment modalities, including surgery, chemotherapy and radiotherapy.

**Keywords** Diffuse low-grade glioma • Tumor dynamics • Tumor kinetics • Growth rate

The histological definition of diffuse low-grade glioma (DLGG) actually comprises a wide spectrum of tumoral behaviours. This apparent diversity of tumoral biodynamics, coupled to differing levels of sensitivity to treatments, explain the wide heterogeneity of DLGG survival. In this chapter, we propose to review our current understanding of DLGG dynamics, to study how to determine individual dynamics, and to analyze how this information can be integrated in the decision process of personalizing treatments sequences.

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## 16.1 Multiscale Multimodality Approach of Pretreatment Longitudinal Follow-Up

### *16.1.1 The Cellular and Subcellular Scales*

Despite considerable advances in the understanding of molecular biology in cancer, very little is known about the *sequence* of cellular and molecular events underpinning the tumorigenesis and tumor growth in DLGG. First, the cell of origin, if it exists, remains supputative (see Chap. 7). Second, the very first mutations leading to the transformation of the cells of origin, and then to the indolent proliferation in the initial low-grade phase, are also not elucidated. It is however believed that IDH mutation [1] is an early event in DLGG, preceding the 1p-19q codeletion in oligodendroglioma and the p53 mutation in astrocytoma, as shown in studies with biopsy samples performed longitudinally [2–7]. This is further validated by the recent discovery that Ollier-Maffucci patients, a disease that predispose to different kind of tumors, including IDH-mutated glioma, bear the same IDH-mutation in non-evolutive enchondroma and glioma [8]. In other words, the IDH mutation probably arise during embryogenesis, with a somatic mosaicism [9]. Because only 5% of Ollier-Maffucci patients will develop a glioma, either the mosaicism only rarely involves glial precursor cells, either the sole IDH-mutation is not sufficient to initiate tumorigenesis [8].

For oligodendroglioma, it has been recently shown that they exhibit a modest and stable somatic mutational load, CIC being the sole gene very frequently (close to 70%) mutated in tumors with IDH mutation and 1p-19q codeletion [10, 11]. On the contrary, in astrocytoma, tumors cells with p53 mutations acquire a growth advantage, with an increasing percentage of mutated cells on longitudinal samples [12], a phenomena that could contribute to increase the genomic instability over time, possibly through an early methylation of MGMT [13, 14], and later in time of DNMT1 [13]. This difference in genomic instability between 1p-19q deleted oligodendroglioma and p53 mutated astrocytoma has been further proven in a recent paper [2], that compared mutational landscapes between initial tumor and progressed tumor after malignant transformation (see mutational changes in supplementary figure S5 of supplementary S1 and time to progression in Table 1 of supplementary S2 of this article by Bai et al. [2]). A deeper understanding of this genomic instability requires an analysis in terms of phylogenetic trees, showing rather branching than clonal evolution [5]. Surprisingly, different p53, ATRX, CIC, or FUBP1 mutations are observed between the initial and recurrent tumors, as if those genes were specifically targeted by some yet undiscovered mutational mechanism. Interestingly, this branching phylogenetic evolution can be deciphered in the spatial structure of the mutational landscape, which reveals the different branching clones in different parts of the tumors [5]. Most interestingly, it has been shown that the same tree structure is shared by epigenetic and genetic spatial and temporal evolutions, proving the co-dependency of the these two levels of analysis [25]. Moreover, comparison of genomic and epigenomic landscapes between initial

tumors and their malignant progression counterparts allows to decipher events associated with malignant transformation, that include activation of the MYC and RTK-RAS-PI3K signaling pathways, alterations in cell cycle regulators such as CDKN2A-CDKN2B, upregulation of the FOXM1- and E2F2-mediated cell cycle transitions and epigenetic silencing of key developmental transcription factors [2]. Finally, it should be noted that most of studies focused on genetic changes observed at malignant progression, pointing out the need of more studies exploring the genetic dynamics between two longitudinal biopsies after repeated surgery [26] for a recurrent DLGG, before any malignant transformation.

### *16.1.2 The Histological Scale*

Historically, neuropathologists were among the first to attempt to picture some elements of glioma growth and invasion dynamics. Their analysis entirely relied on the ultimate snapshot of the tumor, i.e. the post-mortem specimen. This method enabled for example to describe the preferential extension of glioma along white matter tracts [27, 28].

Daumas-Duport introduced an histological classification of oligodendroglioma (low-grade astrocytoma does not exist in her classification, because astrocytes are interpreted as being always reactive to the oligodendroglial tumor), based on the spatial organization of the cells [29]: most low-grade glioma belong to the type III, composed of isolated tumor cells (ITC), while some others do exhibit both solid tumor tissue and ITC (type II). Interestingly, when endothelial hyperplasia and/or a contrast enhancement is observed on MRI with gadolinium [30], the tumor structure is always a mixture of solid tumor tissue and ITC (type II). This mixed architecture thus probably constitutes a more malignant stage of the disease. Of course histological analysis gives only a single snapshot of the dynamics, and one cannot know whether the type II arises later in time from a type III or from a type I (composed only by solid tumor tissue). However, the fact that there exist some foci of higher tumor cell density and minute microangiogenesis in about 15% of type III oligodendroglioma [29, 31] supports the idea that the transition from a type III towards a type II usually occurs, with a likely continuous transition between these two types. Moreover, it has been shown that ITC can be detected, at a very low density, outside the area of T2 hypersignal on MRI [32], confirming that there exists a cell density threshold of radiological visibility (see chapter on Biomathematical modeling by Mandonnet). This structure of low-density radiologically non-visible part of the DLGG could be named type IV. Thus, it can be hypothesized that surrounding areas of type IV progressively evolve towards radiologically visible type III, and within the type III zone, anaplastic micro-foci arise,[1] whose further growth and coalescence ultimately leads to a type II.

[1] We do not know whether this is a random process or whether some biological law governs the spatio-temporal dynamics of these events.

### *16.1.3 The MRI Follow-Up: A Three Periods Story*

#### 16.1.3.1 The Silent Phase

This phase corresponds to the "hidden" tumor life, from its biological birth to its clinical revelation (most often by a seizure). Very little is known about this part of the story. However, with the increasing availability of magnetic resonance imaging, these tumors are now more frequently discovered incidentally. Two series have been reported in the literature [21, 33], establishing that incidental DLGG present a continuous and spontaneous radiological growth during the silent period preceding their clinical revelation. Interestingly, growth rates were found very close to those reported in symptomatic patients, with a median growth rate at 3.9 mm/year in one study and 3 mm/year in the other [21, 33, 34].

These results suggest that the growth rate measured in a symptomatic patient is a good estimate of what it was during the silent phase. In other words, one can extrapolate backward in time the growth curve of the diameter, leading to an estimation of the radiological birthdate of the glioma, through the formula $d_0/v$, $d_0$ being the diameter at first MRI and v the estimated velocity of diameter expansion (VDE) during the silent phase. Of course, this procedure assumes that the dynamics properties of the glioma remained unchanged during the whole silent phase, a strong hypothesis which cannot be verified. However, it has been possible for a specific patient to show that the estimated date of the radiological birthdate was not unrealistic: in this case, an old MRI without any lesion was available, and the date of this MRI was indeed anterior to the predicted date of radiological birthdate [35].

#### 16.1.3.2 The "Low-Grade" Phase

Qualitative Follow-Up

Radiologically, the analysis of the tumor shape can already yield some information regarding the growth pattern of DLGG. Chen et al. [36] proposed a simple classification: tumors originating from the grey matter will remain bulky, without clear involvement of white matter while continuously growing (the so-called expansive growth), whereas tumors originating at the junction of grey and white matters will grow predominantly along the adjacent white matter fiber tracts. While we agree that some tumors looks radiologically much more bulky than others, we do not believe that DLGG remain restricted to the grey matter. They always invade the adjacent white matter, along the U-shape fibers, joining two successive gyrus. This radiologically bulky phenotype should not be confused with the histological Daumas-Duport type II: indeed, a type III DLGG may appear bulky on MRI (see example in [29]). Interestingly, we noted that in the course of the post-operative period, the radiological bulky phenotype might shift towards a more diffuse one (see Fig. 16.1).

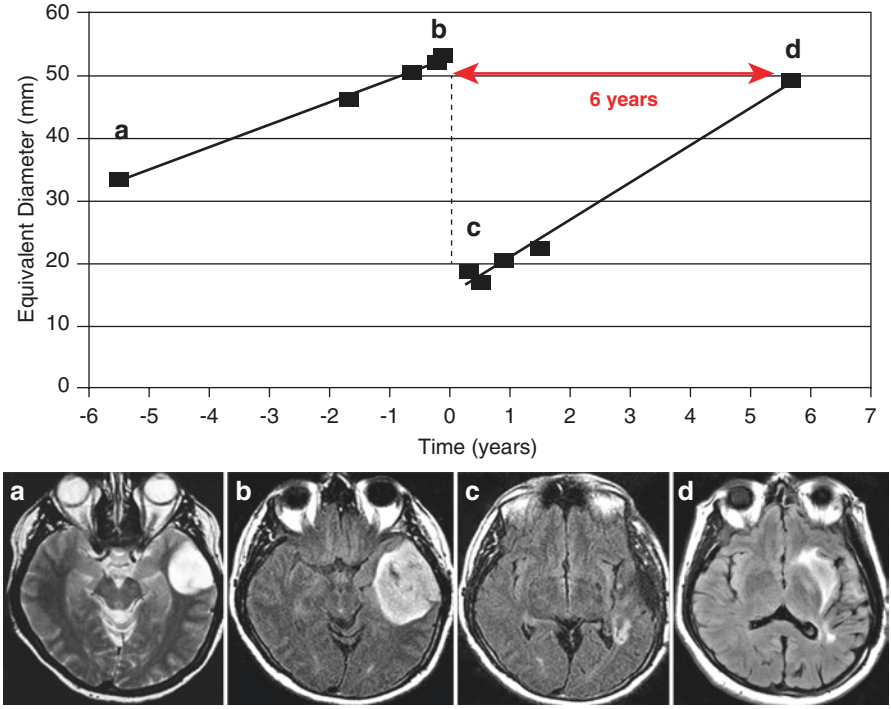


**Fig. 16.1** Illustrative case of pre- versus post-operative growth rates. Note that one can estimate the oncological gain of surgery: the re-evolution curve is translated by about 6 years. Note also the evolution of radiological phenotype, from bulky preoperatively to diffuse postoperatively

Several reports have also illustrated that the shape of DLGG on MRI is imposed by the architecture of white matter fiber tracts. It is indeed well known that projection or association pathways constitute a major road of tumor cells invasion for high grade glioma [27, 28, 37]. For DLGG, a similarity between the tumor shape and the anatomical description of fiber tracts has been reported [38, 39]: in particular, insular/paralimbic tumors may extend along the uncinate fasicuclus, the arcuate fasciculus and/or the inferior fronto-occipital fasiculus (IFOF) as well as the sagittal stratum (corresponding to the merging of IFOF and optic tracts).

Moreover, a longitudinal radiological study demonstrated on a series of 16 patients the preferential extension along these tracts [39], as it has been also confirmed by computational simulations based on a biomathematical model of tumor growth [40]. Of note, if it is clear that white matter pathways can facilitate tumor cells invasion within a tract, one could also imagine that the interface between two orthogonal pathways acts as a barrier against cells invasion. This phenomena has been less investigated in the literature.

Quantitative Follow-Up

The old belief that DLGG may alternate indolent and growing periods is still alive, although not supported by any relevant studies. A probable explanation is that a minor increase of tumor diameter is difficult to identify just by "eyeball" qualitative comparison of two consecutive MRI (see Fig. 16.2). Tumor diameter can be measured by different techniques, either with linear measurements of one, two or three diameters, or it can be deduced from a full 3D volumetric segmentation. It has been clearly evidenced that estimating tumor size by segmenting (manually or semi-automatically) each axial slice on a computer reduces greatly the intra- and inter-reader variability [41]. Indeed, as stated in [42]: "DLGG are often irregular in shape and grow anisotropically, resulting in poor reproducibility of area or volume estimation based on linear measurements." Moreover, a recent study reported that 3D volumetric segmentation are much less sensitive to head position in the MRI than 2D diameters [43]. The increasing availability of softwares allowing to perform segmentations on DICOM images (be they on dedicated stations in neuroradiology and radiotherapy department, in neuronavigations systems or even on PC—for e.g., Osirix, ImageJ,…) renders any other technique based on one, two or three diameters measurements oldfashioned [43]. Segmented volumes are then converted in diameters, by computing a *volumetry-based diameter ($d_V$)*:

$$d_V = \left(2 \times V\right)^{1/3}$$

Finally, the growth curve of this equivalent diameter can be plotted over time and the growth rate of the radiological diameter $d_V$, can be estimated for each patient from a simple linear regression, giving the Velocity of Diametric Expansion (VDE).

This methodology allowed to prove that DLGG are not radiologically stable. Mandonnet et al. [15] first showed quantitatively the spontaneous radiological growth of DLGG on successive MRIs in a subset of 27 histologically proven DLGG

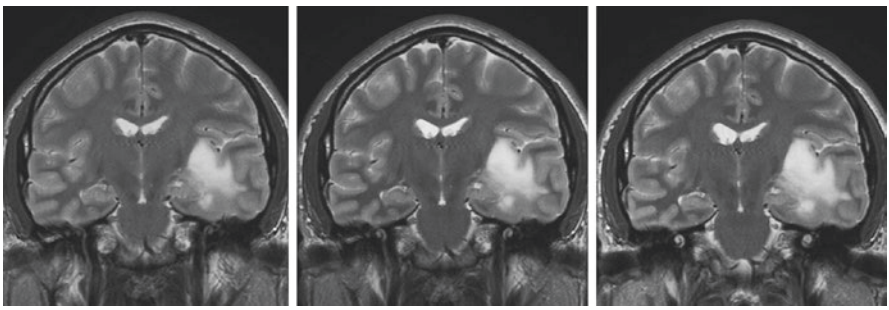

**Fig. 16.2** Eyeball versus quantitative estimation of growth. From *left* to *right*, three successive MRIs of the same patient, each separated by 9 months. Whereas growth is difficult to assess visually on two successive exams, quantitative measurements by full 3D segmentation reveal a 4 mm/year growth rates

**Table 16.1** Distribution of the velocity of diametric expansion in series of patients harboring a LGG, as reported by different groups

| Authors | Cases (n) | Median VDE (mm/year) | Range (mm/year) | Median follow-up (years) |
|---|---|---|---|---|
| Mandonnet et al. 2003 [15] | 27 | 4.1 | 2–8 | 4.75 |
| Pallud et al. 2006 [16] | 143 | 4.4 | 1–36 | 1.8 |
| Ricard et al. 2007 [17] | 39 | 4.76 | – | 3.6 |
| Brasil-Caseiras et al. 2009 [18] | 34 | Volumic increase | | 0.5 |
| Hlaihel et al. 2010 [19] | 21 | 3.65 | – | 1.9 |
| Peyre et al. 2010 [20] | 13 | 5.5 | 2.2–21.4 | – |
| Pallud et al. 2010 [21] | 8 | 3.3 | 1.1–3.7 | – |
| Goze et al. 2012 [22] | 64 | 3.5 | 0–24.3 | 0.8 |
| Pallud et al. 2012 [23] | 19 | 4.5 | 0.6–16.9 | 0.7 |
| Goze et al. 2014 [24] | 131 | 3.75 | 0–31.0 | 0.8 |

that were followed before oncological treatment. The average VDE was close to 4 mm/year, with a minimum at 2 mm/year. These initial results were confirmed by the same group on a larger series of 143 histologically proven DLGG, that ranged individual VDE from 1 to 36 mm/year [16], with a median VDE at 4.4 mm/year. In the series of Ricard et al. [17], the 39 patients with an available follow-up before chemotherapy also had a median VDE of 4.4 mm/year. Several independent groups have recently confirmed these results in series of patients harboring histologically proven supratentorial DLGG, as summarized in Table 16.1:

- Brasil Caseiras et al. [18] found that all patients exhibited a volume increase over a 6-month period (minimum of 1.9 mL) in a series of 34 patients. However, this group did not convert their volumic growth rates in terms of VDE, precluding to make any comparison with other series,
- Hlaihel et al. [19] reported a median VDE of 3.5 mm/year in a series of 21 patients,
- Peyre et al. [20] measured a minimal VDE of 2.2 mm/year in a subseries of 13 patients with an available follow-up before chemotherapy, with an average VDE at 5.5 mm/year,
- Pallud et al. [32] found that all of the eight studied DLGG with pre-treatment imaging follow-up experienced an increase of their diameter, the minimal VDE being at 1.1 mm/year, with a median value at 3.3 mm/year. The same group reported, on another series of 19 patients, a median VDE of 4.5 mm/year, with a minimal value of 0.6 mm/year [23],
- Goze et al. also reported a median VDE of 3.5 mm/year in a series of 64 patients [22], and more recently a median VDE of 3.75 mm/year in a series of 131 patients [24]. In these series, it seems that at least one patient presented a null VDE, but this could be due to the very short follow-up (median of 0.8 years, with a minimum of 0.25 years).

Finally, as already stated, two studies have evidenced a continuous growth of diameter in series of incidentally discovered DLGG:

– Pallud et al. [21] reported an average VDE of 3.9 mm/year in a series of 47 patients,
– Potts et al. measured volumic increase in eight patients with initial follow-up. After conversion to VDE [34], this yielded a value close to 3 mm/year.

Thus, these quantitative studies never reported a case of an indolent untreated DLGG with a stable tumor volume and a null VDE or a case of an untreated DLGG alternating indolent and growing periods. In summary, DLGG present a systematic, spontaneous and continuous radiological growth (although sometimes as slow as 1 mm/year), before any transformation into a higher grade of malignancy.

#### 16.1.3.3 The Transition Towards Higher-Grade

The transition towards a glioma of higher grade is a somehow unforseeable event, albeit unavoidable, in the natural history of a DLGG. It has been well proven that the greater the initial tumor volume (or its residue after surgery), the higher the risk of imminent anaplastic transformation. Whereas the reference definition of anaplastic transformation is based on the histological criteria of a grade III or IV glioma, it is now widely admitted that it can be also diagnosed by *the appearance in the longitudinal follow-up* of a new contrast-enhanced nodule on T1-gado MRI.

Several studies have shown that VDE greater than 8 mm/year on initial follow-up is highly suggestive of an imminent malignant transformation [16, 18, 24, 44]. However, for DLGG with an initial growth rate at 4 mm/year, it has never been shown whether malignant progression is preceded by an increase of the growth rate or not. This point will be further discussed in the chapter on biomathematical modeling. Advances in modern imaging methods,[2] including perfusion MRI and spectroscopic MRI, when performed at initial diagnosis, can yield valuable data regarding the anaplastic risk of an individual tumor [45], as detailed in the previous chapters (see Chap. 14). The aim of this paragraph is to put these results in a dynamic perspective and to emphasize what additional information can be gained from a longitudinal application of these techniques.

Perfusion MRI

Several studies have shown the interest of the value of rCBV max at the initial perfusion-weighted MRI in predicting malignant transformation or even overall survival. All studies evidenced a threshold value in the range 1.7–2.2 [46–49]. However, on an individual basis, the prognostic value is limited by the fact that

[2] PET imaging with different molecular markers will not be discussed here considering the limited number of longitudinal studies. We refer the reader to the PET imaging chapter for the interest of these technique in DLGG.

oligodendroglioma exhibits a greater rCBV max than astrocytoma [50–52]. One longitudinal study proved that an annual rate of rCBV max increase greater than 2/year is predictive for the appearance of contrast-enhancement within the next 6–12 months [46]. Thus, a high value and/or a rapid increase of rCBV max precede by 6–12 months the onset of contrast-enhancement.

Metabolic MRI

The advent of spectroscopic MRI enabled to measure non-invasively the concentrations of some molecules of metabolic interest, offering to track metabolic changes sustaining the transition towards malignancy. For example, it has been clearly shown that the choline levels correlates with increased cellular density and proliferation rate [53, 54]. To our knowledge, there are very few studies in the literature analyzing longitudinal datasets of spectroscopic MRIs for DLGG patients. Whereas for treated patients spectroscopic data seem to amplify the volumetric evolution [19, 55], studies in untreated patients provided diverging results regarding the possibility to predict anaplastic transformation (see [45] for a review). This can be explained by methodological limitations, like the variability of the spatial location of the ROI in the monovoxel technique [56]—a limitation that should be overcomed by the multivoxels technique [54]. An alternative explanation will be proposed in the chapter on biomathematical modeling.

With the discovery of high frequency of IDH mutations in oligodendroglioma, there has been a regain of interest for the study of glycolysis and oxydative phosphorylation in tumorogenesis. The lactate resonance is supposed to be a surrogate marker of a glycolytic switch, decoupling the glycolysis from oxydative phosphorylation in the tricarboxylic cycle [57]. Not surprisingly, no lactate resonance is observed for DLGG with a proliferation index inferior to 4%, whereas a lactate peak is detected when proliferation index is comprised between 4% and 8% [58]. Interestingly, the lactate resonance is no more evidenced for tumors with a proliferative index greater than 8%. As explained by a mathematical model [59–61], this could be linked to the combined effect of MCT overexpression (excreting lactate out of the cells) and increased cerebral blood flow, washing out the lactate through the capillaries. An alternative explanation would come from the theory of metabolic symbionts [57]: the lactate produced by glycolysis in hypoxic cells would be "recycled" by normoxic cells, through the transformation in pyruvate (then entering the tricarbonic acid cycle for oxidative phosphorylation). Hence, one should keep in mind a dynamic view of the tumoral metabolism when analyzing the lactate peak on spectroscopic MRI.

### *16.1.4 The Cognitive Follow-Up*

A striking feature of DLGG patients is that they do not have any focal neurological deficit. This means that brain networks plasticity can cope with lesions growing up to 4 mm/year, without any major consequence on motor or language function.

However, studies with extensive assessment of cognitive status have evidenced that healthy controls scored better than DLGG patients [62]. This holds true even in patients with incidental DLGG [63]. Hence, it can be suspected that the decline in cognitive status of DLGG patients is a continuous process during the silent and low-grade period, as for the MRI evolution. However, very few studies have focused on the longitudinal cognitive follow-up of "wait and see" cohorts. Indeed, only one longitudinal study has been published, showing a worsening in non verbal delay recall scores after a one year "wait and see" follow-up [64]. Of course, at malignant transformation, the brain plasticity capabilities are overwhelmed by the fast growing tumor (VDE greater than 8 mm/year). At that time, focal neurological deficits, together with an increased seizures frequency, are commonly observed. All together, one can assume that the tumoral dynamics (as measured by the VDE) should be correlated with the dynamics of cognitive deterioration: the higher the tumor growth rate, the faster the cognitive deterioration. This hypothesis would deserve more clinical studies.

## 16.2 Factors Influencing DLGG Growth Rates

First of all, the different DLGG histological subtypes (oligodendroglioma, astrocytoma, mixed glioma) do not exhibit significant differences regarding the radiological tumor growth rates, as previously demonstrated in several studies [16–18, 65].

Three studies have investigated the link between DLGG genetic subtypes. In the first one [17], it was shown that DLGG with 1p-19q codeletion grew significantly slower than DLGG without (median VDE at 3.4 mm/year), and that DLGG with immunohistochemical overexpression of p53 grew significantly faster than DLGG without (median VDE at 4.2 mm/year). The second study [22] confirmed that growth rates of DLGG are lower when 1p-19q codeletion is present, whereas IDH status does not influence growth rates, a result which has been confirmed recently by a third study on a larger cohort [24]. This suggests that the favorable outcome of 1p-19q codeleted patients might be in part related to a tumor inherently more indolent, and that on the contrary, the good prognostic value of IDH mutation could result from a better efficacy of treatments or a lesser risk of malignant progression.

Only one study investigated quantitatively the effects of pregnancy on the radiological growth rates of DLGG [66, 67]. The results showed that DLGG accelerated significantly their radiological growth rates during pregnancy, above levels detected either before pregnancy or after delivery in 75% of cases. These changes in tumor growth were associated with an increase in seizure frequency in 40% of cases and radiological and clinical changes during pregnancy motivated further oncological treatment after delivery in 25% of cases. These results also underline that young women with DLGG should be informed of the oncogenic role of pregnancy (see Chap. 30).

## 16.3 The Prognostic Value of Pretreatment VDE

The first study focusing on the prognostic significance of spontaneous MRI growth rates on overall survival was conducted on a retrospective series of 143 DLGG with measurements of the evolution of the diameter over time [16]. Overall survival was significantly higher in the low growth rates subgroup (median survival of 15 years for a VDE lower than 8 mm/year) than in the high growth rates subgroup (median survival of 5.6 years for a VDE at 8 mm/year or more).

The prognostic significance of spontaneous MRI growth rates on predicting progression into a higher grade of malignancy was addressed in two recent prospective studies. Brasil Caseiras et al. [18] proved in a series of 34 patients that "tumor growth within 6 months was better than baseline volumes, relative cerebral blood volume, or apparent diffusion coefficient in predicting time to malignant transformation in untreated DLGGs and was independent of other parameters". They found a threshold of 6.21 mL of growth within 6 months, with a mean time of progression of 3.91 years versus 1.82 years. However, the prognostic significance of the evolution of the tumor volume (and not diameter) over time may be a combination of two independent other prognostic factors, the initial tumor volume and the tumor growth rate [68]. Or stated differently, the same amount of volumic increase may correspond to a large tumor with a low growth rate (of diameter) or a small tumor with a high growth rate (of diameter) [68]. Thus, VDE, obtained by the evolution over time of the diameter (deduced from the total segmented volume V) appears as a more reliable parameter than the evolution of the tumor volume to assess selectively the prognostic significance of radiological tumor growth rates.

Hlaihel et al. confirmed these results and demonstrated that an elevated VDE higher than 3 mm/year was correlated with a greater risk of progression into a higher grade of malignancy, with an average VDE at 7.87 mm/year in transformers group versus an average VDE at 2.14 mm/year in non transformers group [19]. The VDE threshold at about 8 mm/year is thus as a strong predictor of both malignant progression-free and overall survivals.

## 16.4 Assessing Treatment Efficacy by Volumetry-Based Diameter Measurements: When Patients Can Serve as Their Own Controls

As DLGG are slow growing progressive tumors, with considerable variability in patient characteristics and therapeutic modalities, the accurate evaluation of the different oncological treatments efficacy constitutes a clinical challenge. Along with clinical response—particularly on seizure frequency—we will show that the quantitative assessment of the individual VDE by diameter evolution over time on consecutive MRI is a useful adjunct in the follow-up armamentarium.

### 16.4.1 Surgery

Using the VDE methodology, it has been shown in a retrospective study of 54 DLGG patients that radiological tumor growth rates remain unchanged after surgical resection [65] (see Fig. 16.1 for a typical case). This result reinforces the idea that the survival benefit of surgery is mediated by a cytoreductive effect, as already stated by several studies [69–73].

However, 2 patients of the 54 under study exhibited a decrease of their tumor growth rates greater than 3 mm/year whereas in 2 other patients, surgery failed to stop an ongoing anaplastic transformation, resulting in an increase of 3 mm/year on the tumor post-operative growth rates [65]. Thus, the precise quantitative assessment of VDE obtained pre and post-operatively by repeated measurements of the diameter would help analyzing the effects of surgical resection on an individual basis and should allow guiding the decision making of a postoperative oncological treatment.

Of note, *these results highlight the inadequacy of progression free survival as an endpoint in DLGG clinical trial*. Indeed, this notion is ill defined after surgery, as there is no progression free period in patients exhibiting a residual tumor after an incomplete resection.

### 16.4.2 Chemotherapy

Similarly, the tumor response to chemotherapy can be demonstrated quantitatively by tracking the diameter evolution. Ricard et al. [17] first quantified the tumor response after temozolomide chemotherapy in 107 DLGG. In addition, they evidenced different patterns of response, depending on the 1p-19q codeletion status:

- almost all patients exhibited an initial decrease of the diameter after temozolomide onset,
- the median VDE after temozolomide onset was −9.2 mm/year,
- tumor relapse occurred more frequently and earlier in tumors without 1p-19q codeletion.

A similar study was performed to quantify the tumor response after PCV chemotherapy in 21 DLGG. Peyre et al. [20] demonstrated that:

- tumor diameter decreased initially after PCV onset in all patients,
- the median diameter decrease after PCV onset was 10.2 mm/year, a value very close to the value reported by Ricard et al. [17] with Temozolomide,
- an ongoing diameter decrease in 20 of the 21 patients after PCV discontinuation that was prolonged more than 2 years in 60% of the DLGG under study.

These results demonstrate the same radiological quantitative response following TMZ and PCV chemotherapies. They challenge the idea that a prolonged duration of chemotherapy is necessary for treating DLGGs and raise the possibility of a

chemotherapy monitoring based on the quantitative changes of the tumor diameter over time. As a consequence, VDE changes could be used as a quantitative reproducible parameter for the assessment of the response to chemotherapy for DLGG, that is extremely difficult to judge using the Macdonald criteria [74] or the more recent RANO criteria—not based on objective volumetric calculation [42].

### *16.4.3 Radiotherapy*

In a recent study, VDE have been determined after radiation treatment. Pallud et al. studied a consecutive retrospective series of 32 adult supratentorial DLGG treated with first-line radiotherapy with an available imaging follow-up [23]. They demonstrated that:

- diameter decreases initially after radiotherapy onset in all patients during a mean 49 months,
- the median VDE after radiotherapy onset was −16.7 mm/year, a value close to those reported after chemotherapy,
- the post-radiotherapy VDE carried a prognostic significance on overall survival as the fast post-radiotherapy tumor volume decrease (VDE at −10 mm/year or faster) were associated with a significant shorter OS (median 47.9 months) than the slow post-radiotherapy tumor volume decrease (VDE slower than −10.0 mm/year) (median 120.8 months). One hypothesis would be that fast responders had a tumor with high proliferation rate. Once the radiosensitive cells have been killed, the tumor shrinks according to an equally high apoptosis rate. But the radioresistant clone will recur quickly, in keeping with a high proliferation rate. This phenomenon should be explored in a near future by biomathematical modeling. An alternative model has been proposed, that underlines the importance of edema draining in the evaluation of the response [75].

Finally, the actual distinction between tumor tissue and radiation-induced changes appears sometimes difficult to ascertain and could limit the assessment of tumor response after radiotherapy by morphological MRI.

## 16.5 Clinical Applications

The spontaneous growth rate on MRI being a strong prognostic factor, it is expected that their determination for each patient would help in the decision making process. This means that patients should get a second MRI before any oncological treatment, thus allowing the measurement of the VDE through the evolution of the diameter over time. This raises the issue of the intra- and inter-observers reproducibility in measuring the VDE and how the interval between the first MRI at radiological discovery and the second MRI before oncological treatment could influence the

reliability of the estimation. These issues have never been investigated. On one hand, a longer period would allow to enhance measurements reliability, but on the other hand, a too long period could put the patient at risk of progression to a higher grade of malignancy. Of course, in rare patients presenting with increased intracranial pressure and/or neurological deficit, treatment should be prompted, precluding to perform a second MRI after an observational period. On the opposite, for those DLGG incidentally discovered, an every 4 months follow-up has been proposed, with a threshold of VDE at 2 mm/year triggering surgical treatment [76]. In general, a 6 weeks interval would allow to detect those patients with a fast growing tumor (1 mm increase would correspond to 8 mm/year). If no evolution is found at 6 weeks, a 2–3 months follow-up further refines the estimation of the VDE, which is of importance for choosing the postoperative treatment.

Indeed, as there is currently no mean to cure the patient, the principle of DLGG management consists in optimizing the sequence of the different treatment options, including surgery, chemotherapy and radiotherapy, with the aim to delay malignant transformation (and death) while preserving quality of life [77]. From the datas reviewed in this chapter, it should be realized that DLGG is a dynamic disease, continuously evolving on molecular, histological, and radiological scales, and that moreover, the impact on the normal brain (epilepsy, cognitive dysfunctioning and re-functioning thanks to plasticity) is also dynamic. It naturally follows that selecting the treatment of a DLGG patient is *de facto* a dynamic process, meaning that the benefit/risk ratio of each treatment modality should be continuously re-evaluated all along the disease. In other words, the therapeutic strategy can only be recursive in essence (see Fig. 16.3). It cannot be overemphasized how much this school of care

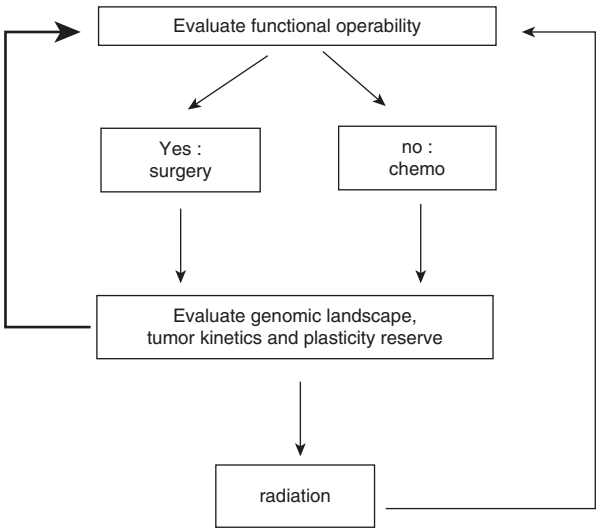


**Fig. 16.3** Recursive therapeutic strategy in DLGG. The (re)treatments are adapted to the dynamics of DLGG, on the basis of tumor kinetics, potential of neuroplasticity, and genomic landscape

is at the opposite from the current guidelines resulting from randomized studies. According to this orthodoxic view (the so called "evidence-based medicine"), only the genetico-histological initial diagnosis prescribes the treatment: radiotherapy and PCV for IDH-mutated 1p19 codeleted tumors, radiotherapy with concomitant and adjuvant temozolomide for IDH wild-type tumors, and radiation therapy for IDH-mutated without 1p19 codeleted tumors. We argue that this static view, which is an oversimplification reducing a multiparametric dynamic disease to a single attribute, can lead to overtreatment. Nevertheless, we acknowledge that large retrospective studies are needed to confirm the efficacy of a dynamic recursive strategy in comparison to those classical guidelines.

## 16.6 Conclusion and Perspectives

The better knowledge of DLGG radiological dynamics has greatly contributed to shift the treatment paradigm from a conservative one towards a proactive one. In the future, the dynamics on other scales should also be taken into consideration. Once a better picture of genomic, histological and cognitive dynamics would be gained, in addition to the radiological dynamics, an integrated view of DLGG dynamics should be analyzed for each patient. Then, treatment should be adequately selected for each patient dynamics, and adapted, all along the course of the disease, to dynamics changes.

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# Chapter 17
# Natural History and Spontaneous Prognostic Factors

**Roberta Rudà, Alessia Pellerino, and Riccardo Soffietti**

**Abstract** Low grade gliomas (LGGs) are a group of tumors with distinct clinical, histological and molecular characteristics. The most common presenting symptom is represented by seizures, that in MRI era occur in 70–90% of patients with low grade gliomas, and are medically refractory in about 50% of cases. LGGs typically affect young adults and are rare in elderly patients (>60 years). Occasionally, grade II glioma is discovered incidentally on brain imaging.

The natural history and patterns of care of LGGs have changed over time with an increase of survival, which is, at least in part, due to the earlier diagnosis afforded by CT and MRI. Overall the 5-year survival rates reported in recent randomized trials are in the order of 64–68%. A number of retrospective and a few prospective series have evaluated variables of potential prognostic significance in patients with LGG. Some of these factors have been fully validated: age >40 years, presence of neurological deficits and/or absence of seizures at onset, low performance status (Karnofsky <70), preoperative tumor diameter >4–6 cm, astrocytoma as histology, while others still need validation. Among molecular markers, 1p-19q codeletion and IDH 1 and 2 mutations are the most important prognostic factors, while some prognostic importance is attributed to ATRX loss and TERT mutation.

Based on the prognostic factors that emerged as significant after multivariate analysis among large, randomized multicenter trials, several prognostic scoring systems have been developed to identify subgroups of patients with different outcome (so called low and high risk groups).

**Keywords** Natural history • Prognostic factors • Age • Clinical presentation • Neuroimaging findings • Histology • Molecular markers • Prognostic scores

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## 17.1 Introduction

Low grade gliomas (LGGs) are a group of tumors with distinct clinical, histological and molecular characteristics. Although it is accepted that all grade I and II lesions according to WHO are low grade, the so called diffuse LGGs include only grade II tumors, that share similar invasive and malignant potential [1, 2]. Patients with LGG may survive for relatively long periods [3], but often progress to higher grade tumors, which are associated with neurological disability, and invariably fatal. Thus, reference to these lesions as benign gliomas has generally been abandoned. The widespread availability of MRI has resulted in an earlier diagnosis for many patients who have few or no symptoms and a normal neurologic examination.

The optimal management of patients with LGG is still controversial: for physicians caring for patients with LGG, the challenge lies between providing too much therapy too early or too little too late [4].

Some clinico-radiological and pathological factors are clearly correlated with outcome, while others are still a matter of discussion. The recent new WHO classification of grade II and III gliomas [5] has added molecular markers (IDH 1 and 2 mutations, 1p/19q codeletion, ATRX loss and TERT mutation) to the traditional histologic categories. More importantly, the use of these markers now stratifies tumors across WHO grade barriers into biologically and clinically meaningful subgroups [6]. However, one must be aware that so far almost all information on prognostic factors in the so-called "low grade gliomas" derive from studies on grade II tumors according to the previous WHO classification of 2007.

## 17.2 Natural History

The most common presenting symptom is represented by seizures, that in MRI era occur in 70–90% of patients with low grade gliomas, and are medically refractory in about 50% of cases [7]. There is no clear association between severity of epilepsy and behavior of the tumor. The advent of CT and MR imaging has shortened the duration and reduced the severity of symptoms at diagnosis. In a series of adult low grade gliomas, diagnosed between 1979 and 1995, 78% had seizures at presentation, 31% focal neurologic deficits, 29% headache, 11% cognitive or behavioral changes, and 9% papilledema, and the median interval between symptom onset and first imaging was 2 months [8].

Focal deficits, altered mental status or increased intracranial pressure can still be presenting symptoms, especially in diffuse tumors.

Low grade gliomas typically affect young adults, while they are rare in elderly patients (>60 years): however, few specific studies only have been performed in

this population [9–12]. Overall, about 8–10% of histologically verified LGGs occur at a 60 years of age or greater [11, 13, 14]. This value could be somewhat underestimated if one considers that elderly patients (particularly the very old ones) are less likely to undergo a biopsy when a suspicion of LGG is found on MRI. Kaloshi et al. [11] have compared the clinical, radiologic, pathologic and therapeutic data of a series of 62 patients older than 60 to those of 704 younger patients. The comparison between older and younger groups showed that elderly patients more often presented with a clinical deficit and a lower Karnofsky performance status. The lower frequency of seizures in the elderly (47 vs 85%) could be due to a more aggressive tumor growth favoring deficits over seizures. On MRI the mean tumor diameter was significantly larger, the tumors more often infiltrated both hemispheres through the corpus callosum, and contrast enhancement was about twice more frequent in the older than in the younger group. The histologic diagnosis was similar, including the ratio of oligodendroglial vs astrocytic tumors, and the same was suggested for 1p/19q codeletion. Not surprisingly, the older population had a lower rate of resection and radiation therapy; conversely, some series did not find differences in the rate of aggressive resections (≥90%) between the two age groups [15].

Rarely a grade II glioma is discovered incidentally on brain imaging although the detection of incidental gliomas will likely increase as access to brain imaging broadens worldwide. The rate of incidental WHO grade II gliomas is in the order of 3–4.9% [16–19]. Incidental grade II gliomas differ from symptomatic tumors in several respects [19, 20]. There is a female predominance, younger age and smaller tumor volume, being the tumors limited to one lobe in most cases, with rare involvement of corpus callosum and extremely rare contrast enhancement on MRI. These data could suggest that in the natural history of gliomas, incidental grade II gliomas may represent an earlier step of symptomatic GIIG. It has been suggested that an incidental discovery could be associated with a longer survival [19, 20].

The natural history and patterns of care of LGGs have changed over time with an increase of survival, which is, at least in part, due to the earlier diagnosis afforded by CT and MRI. Overall, the 5-year survival rates reported in recent randomized trials on surgery followed by radiotherapy are in the order of 64–68% [21, 22]. Up to 25% of patients survive for 20 years [3]. Nonetheless, the natural history of LGGs is one of progressive growth [23, 24] and eventual malignant transformation (50–70%) [8, 25–27]. The great variability in outcome for individual patients with LGG (survival ranging from less than 2 years to more than 20 years) depends on the combination of clinico-radiological, pathological and molecular factors.

A number of retrospective and a few prospective series have evaluated variables of potential prognostic significance in patients with LGG (Tables 17.1 and 17.2).

**Table 17.1** Spontaneous clinical and neuroimaging factors of unfavorable prognostic significance in low grade gliomas

| |
|---|
| *Fully validated in clinical trials* |
| • Age >40 years |
| • Presence of neurological deficits and/or absence of seizures at onset |
| • Low performance status (Karnofsky <70) |
| • Preoperative tumor diameter >4–6 cm |
| • Astrocytoma as histology |
| *Needing validation in clinical trials* |
| • Presence of contrast enhancement on MRI |
| • Preoperative and postoperative tumor volumes on MRI |
| • High speed of volumetric increase or velocity of diametric expansion (VDE) on MRI |
| • Elevated cerebral blood volume values (CBV) on MRI perfusion |
| • High uptake of aminoacids on PET. |

**Table 17.2** Prognostic value of molecular markers in low grade gliomas

| Markers | Method of assessment | Prognostic value |
|---|---|---|
| p53 mutation | PCR and immunohistochemistry | Minimal/absent |
| IDH 1 and 2 mutations | Immunohistochemistry/pyrosequencing | Prognostically favorable; possibly predictive with regard to radiotherapy or chemotherapy |
| 1p/19q codeletion | PCR, FISH | Prognostically favorable; possibly predictive with regard to radiotherapy and chemotherapy |
| MGMT promoter methylation | Methylation-specific PCR | Prognostic or predictive depending on treatment received or molecular subtypes |
| BRAF mutations | PCR | Unknown |
| ATRX loss TERT mutations | Immunohistochemistry/pyrosequencing | Still to be validated |

## 17.3 Prognostic Factors

### *17.3.1 Age*

Younger age is a well-established prognostic factor for survival [8, 28–30]. Early in the eighties Laws et al. [25], in a retrospective study involving 461 patients with LGGs treated at the Mayo Clinic, found that patients who were younger than 20 years had a 5-year survival of more than 80%, with a progressive decrease in survival of 60% to 35% for those in the 20–50 years age group and of less than 30% for those in the over 50 age group. The linear functional relationship between age and prognosis has been confirmed in large datasets from prospective randomized trials [15, 31, 32]. A cut point at 40 years has been more commonly found, but in the clinical practice this should not be interpreted as an absolute cut off value. A reluctance to undertake large resections (thus under-sampling a higher grade component of the tumor) in older patients could potentially contribute to a worse prognosis, even in patients with an imaging appearance of a low grade tumor. On the other hand tumor biology may differ in older patients, being the tumors inherently more aggressive. In this regard it has been reported that the proliferative index is higher and malignant transformation more frequent among patients with astrocytomas with an age >40–45 years [33]. Moreover, the proportion of gemistocytes in astrocytic tumors, that could be associated with a more aggressive behavior, increases with age [34]. Ultimately, although the biology behind the association of older age and worse outcome is still unclear, a possibility is that an age-dependent impairment of DNA repair mechanisms and the resulting acquisition of mutations may promote rapid progression after transformation occurs [35].

### *17.3.2 Clinical Presentation*

Clinical presentation is another strong prognostic factor, whether expressed as the presence of seizures, absence of neurological deficits or good performance status [25, 26, 36–40]. These factors are inter-related, e.g. neurologically intact patients who present with isolated seizures have a better performance status and prognosis. Moreover, patients who present with seizures tend to be younger and have smaller tumors than those without seizures [41–43]. It has been hypothesized that LGGs associated with epilepsy might differ biologically from LGGs of patients presenting with neurological deficits [44]. The duration of symptoms before diagnosis has been suggested as an independent predictor of time to recurrence [45]. The presence of an abnormal Mini-Mental State Examination (MMSE) has been found as a strong predictor of poorer progression-free and overall survival in a large dataset of patient treated with adjuvant radiotherapy [46, 47]. Seizure reduction has been reported as an early and consistent prognostic marker for progression-free (PFS) and overall survival (OS) after treatment with temozolomide [48].

### *17.3.3 Structural Neuroimaging Findings*

Conventional neuroimaging findings have some prognostic importance. A tumor diameter >4–6 cm [40, 49, 50] and a tumor crossing the midline [40] correlate with a short PFS and OS. Several investigators in nineties [27, 51, 52] have reported a tendency for larger tumors to behave differently with an earlier recurrence risk and/or greater tendency toward malignant transformation.

Tumor volume measurement on MRI has been increasingly used to study the relationships with outcome. Kreth et al. [52] found preoperative tumor volume greater than 20 ml to be of unfavorable prognostic significance, with the presence of midline shift being correlated with volume. In a recent study of hemispheric LGGs [53] greater preoperative and postoperative tumor volume was significantly associated with shorter malignant progression-free survival.

Growth rates, measured with different methods, are inversely correlated with survival [23, 54, 55] and early malignant transformation [24, 56, 57]. Among 143 consecutive patients with LGGs in adults, a median survival of 5.16 years was associated with a growth rate of 8 mm/year or more compared with a median survival of >15 years with a growth rate of less than 8 mm/year [54]. Other investigators have demonstrated that sequential measurements of LGG volume, by allowing a precise determination of growth rates, permits the identification of patients whose tumors are at high risk for an early malignant transformation [57]. Six-month tumor growth may also predict outcome in patients with LGGs [56]. However, the lack of widespread availability of volumetric assessments preclude their implementation in clinical trials thus far [58], although progress in imaging software is likely to make routine implementation possible in the near future.

The prognostic implication of contrast enhancement on either CT or MRI remains controversial. Contrast enhancement occurs when the blood-brain-barrier is disrupted and a lack of contrast enhancement more often suggests a low grade gliomas diagnosis [59]. However, contrast enhancement is reported in 15–50% of patients with low grade gliomas [21, 51, 60–62]. The finding that contrast enhancement is more commonly seen in high-grade gliomas has led many authors to infer that contrast-enhancing low grade gliomas represent a more malignant subset of low grade gliomas. Most articles on contrast enhancement and low grade gliomas derive from series in which both CT and MRI were used, and have concentrated on the relationships with survival, while there is paucity of information regarding the association with tumor recurrence and malignant transformation. The presence of contrast enhancement has been reported either as a negative factor for survival [30, 37, 63–65] or as without prognostic significance [8, 38, 66, 67]. Two recent papers have analyzed the prognostic significance of contrast enhancement in the MRI era, and the results are still somewhat different. In the experience of Chaichana et al. [61] at John Hopkins on 189 patients with LGGs who underwent surgical resection preoperative contrast enhancement was independently associated with decreased survival, increased recurrence and a trend toward increased malignant transformation in multivariate analysis. Five-year overall survival, progression-free survival and malignancy-free survival rates for

patients with contrast-enhancing versus non-enhancing tumors were 70 versus 85%, 32 versus 49% and 74 versus 90%, respectively. Notably in this series patterns of survival, recurrence and malignant transformation were not significantly different between contrast-enhancing fibrillary astrocytomas and contrast-enhancing oligodendrogliomas. Pallud et al. [62] reviewed 927 histologically proven (either after biopsy or resection) WHO grade II gliomas in the French Glioma Database, and found that the presence of contrast enhancement was not significantly associated with a poorer prognosis in multivariate analysis: median survival and surviving rates at 5, 10 and 15 years were 11.9 years, 79.1%, 68.5% and 27.8% for patients with contrast enhancement compared to 12.7 years., 83.2%, 60.3% and 44.3% for those without contrast enhancement. Conversely, in univariate analysis, the presence of a nodular-like pattern and a progressive contrast enhancement over time were statistically associated with shorter survival.

Overall, the persistent discrepancies among the different series can be accounted by several factors, such as a different rate of sampling errors leading to the inclusion of a variable percentages of high grade tumors and the absence of reproducible criteria to quantify the different degrees and characteristics of contrast enhancement prospectively. In this regard, it has been suggested that a quantification of the volume of substable contrast enhancement at baseline MRI could identify individuals at high risk for transformation [68].

### *17.3.4 Physiologic Neuroimaging Findings*

The emergence of physiological imaging techniques has added new perspectives for the prediction of outcome and malignant transformation in LGGs.

Proton MR spectroscopy allows the quantification of the levels of cellular metabolites: normalized creatine/phosphocreatine levels have been reported as significant prognostic factors for PFS as well as time to malignant transformation [69].

The measurement of relative cerebral blood volume (rCBV) derived from dynamic susceptibility-weighted perfusion contrast-enhanced MRI (DSC-MRI) could predict tumor behavior: a low rCBV correlates with longer PFS and OS [70, 71]. A longitudinal magnetic resonance perfusion imaging study was performed on conservatively treated LGGs to determine whether rCBV changes preceded malignant transformation as defined by conventional MR imaging [72]. In patients with non-transforming LGGs the rCBV remained relatively stable and increased to only 1.52 of normal tissue over a mean follow-up of 23 months. In contrast, patients with transforming LGGs showed a continuous increase in rCBV up to the point of transformation when contrast enhancement became apparent on conventional MRI. The mean rCBV was 5.36 at transformation and showed a significant increase from the initial study at 6 and 12 months before transformation. The measurement of rCBV correlates well with time to progression among low grade astrocytomas, while it is not useful in oligodendrogliomas, as these tumors have an abundant vasculature which is not a sign of malignant evolution.

According to a recent meta-analysis lower ADC values on MRI diffusion can predict a worse prognosis independent of tumor grade [73].

### *17.3.5 PET Findings*

PET with FDG is of limited value for prognostic purposes since LGGs show a low FDG uptake compared to the normal cortex. Conversely, PET with aminoacid tracers is more useful, as the uptake of tracers is increased in approximately two-thirds of patients with LGGs, and correlates with the proliferative activity of tumor cells [74, 75]. A low uptake of $^{11}$C-methionine has been initially correlated with longer survival [75–78] and among high-risk patients with LGG (as defined by the presence of 3–5 unfavorable clinical prognostic factors) those with high Met uptake had a worse outcome than patients with low Met uptake [79]. A reduction of tumor uptake following chemotherapy with temozolomide has been recently reported to occur earlier than standard MRI changes and significantly predict the duration of PFS, and to better correlate with seizure reduction [80]. Similarly to CBV values with perfusion MRI, the uptake of Met is physiologically relatively higher in low grade oligodendrogliomas compared to astrocytomas: thus, the prognostic value of PET Met seems restricted to astrocytomas.

PET with FET (18-fluoroethyltirosine) is similar to PET Met and has been reported with a similar prognostic value [81]. Moreover, dynamic $^{18}$F-FET PET can identify highly aggressive astrocytomas within the same WHO grade II category: tumors with decreasing time-activity curves manifested earlier tumor progression, malignant transformation as well as shorter survival [82, 83].

The prognostic value of uptake when employing tracers such as F-DOPA or FLT (18F- fluorothymidine) is still unknown.

### *17.3.6 Histology and Proliferation Markers*

Oligodendrogliomas have a better prognosis than astrocytomas, being oligoastrocytomas in between [8, 21, 31, 40, 84]. The median survival for patients with oligodendrogliomas is typically 10–15 years compared to 5–10 years for those with astrocytomas. Among diffuse astrocytomas the gemistocytic variant has a poorer outcome [85]. Some investigators have associated the clinical behavior and rates of proliferation of low grade astrocytomas with a different cellular lineage [86]: slow growing, cortically-based astrocytomas would be associated with a type 1 (protoplasmic) astrocytic lineage, whereas white matter astrocytomas would express antigens consistent with a type 2 (fibrillary) astrocytic lineage.

The difficulties in predicting the prognosis of low grade gliomas have led to the increasing use of proliferation markers as an adjunct to routine histological techniques. Historically, different methods have been used to estimate the proliferative

activity of low grade gliomas: silver staining of nuclear organizer regions (AgNORs) (a measure of ribosomal gene activity that correlates with the degree of tumor malignancy [87]; evaluation of proliferating cell nuclear antigen (PCNA) [88]; analysis of the S-phase fraction by flow cytometry [89, 90]; immunohistochemical investigation of bromodeoxyuridine and iododeoxyuridine labeling index [91, 92]. However, the most commonly used techniques up to date is the immunohistochemical evaluation of the MIB-1 monoclonal antibody to the Ki-67 nuclear antigen to stain cells undergoing active division. Several studies have reported an association between high Ki-67 labeling index (≥3–5%) and shorter survival [93–95], even if the independent prognostic value of Ki-67 has not yet been proven. It has been recently suggested that mitotic index could be significantly associated with outcome in IDH wild type tumors only [96]. Still unresolved issues are the best techniques, the inter-observer variability, the heterogeneity of Ki-67 within a tumor specimen, and the variability in cutoff values within the different studies [97].

### *17.3.7 Molecular Factors*

Positive TP53 mutation status (but not P53 overexpression/accumulation) was suggested to be an independent unfavorable predictor of progression-free and overall survival [98], but in contemporary studies from the German Glioma Network the P53 status was not associated with progression-free survival in tumors managed by surgery alone [99]. Accordingly, at present there is no need to know the P53 status for any clinical-decision.

IDH 1 and 2 mutations are the strongest prognostic factors in low grade gliomas: in particular patients without IDH mutations (30–35%) have a poorer survival compared to those with the mutation (65–70%) [99–101]. Conversely, the predictive value of IDH mutations respective to response to non surgical treatments is still to be proven [102].

1p/19q codeletion, that is commonly associated with the oligodendroglial phenotype and IDH 1 and 2 mutations, predicts longer overall survival [47, 103–106]. 1p/19q codeletion does not confer any prognostic advantage in terms of progression-free survival in patients with LGGs who received surgery alone [107]. Conversely, it could predict better response and longer progression-free survival in temozolomide-treated patients [24].

MGMT promoter methylation, which is commonly associated with IDH 1 and 2 mutations [108], could influence differently the progression-free survival depending on the treatment received, being a negative prognostic factor in patients with astrocytomas treated by surgery alone [109] and a positive prognostic factor in patients receiving temozolomide [110, 111].

The independent prognostic value of ATRX loss and TERT mutations is still to be defined.

BRAF mutations are rare in diffuse low grade gliomas; conversely, BRAF V 600E is found in approximately 60–70% of pleomorphic xanthoastrocytomas and

20% of gangliogliomas [112]. So far, there is no data on a prognostic relevance of BRAF mutations. Recently, the activation of the Akt-mTOR pathway has been suggested to correlate with a poorer outcome [113].

## 17.4 Prognostic Scoring Systems

Based on the prognostic factors that emerged as significant after multivariate analysis among large, randomized multicenter trials, several prognostic scoring systems have been developed to identify subgroups of patients with different outcome (so called low and high risk groups).

In the EORTC analysis [40] age >40 years, astrocytic tumor type, tumor size >6 cm tumor crossing the midline and neurological deficits at diagnosis had an independent negative prognostic value. A favorable prognostic score was defined as no more than 2 of these adverse factors and was associated with a median survival of 7.7 years, while the presence of 3–5 adverse factors was associated with a median survival of 3.2 years only. The EORTC prognostic score has been recently validated in database of NCCTG in US, and have yielded similar results [47]. However, in the American dataset the histology and tumor size had the maximal importance.

Another LGG preoperative prognostic scoring system has been developed at UCSF [49], based upon the sum of points given to the presence of 4 significant adverse prognostic factors (1 point per factor): location of tumor in presumed eloquent location; KPS score $\leq$80; age >50 years; tumor diameter >4 cm. Tumors with scores 0 or 1 had a 97% 5-year survival compared to 56% for those with score 4. This scoring system accurately predicted overall survival and progression-free survival in a multi-institutional population of patients [114].

## 17.5 Conclusions

Future clinical trials on lower grade gliomas will be designed based on molecular factors and not on traditional histological categorization as inclusion criteria. The hope is to be able to increasingly develop personalized treatment approaches in the daily clinical practice as well.

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# Part IV
# Functional Assessment and Interaction with the Brain

# Chapter 18
# Language, Cognitive and Emotional Evaluations

**Sylvie Moritz-Gasser and Guillaume Herbet**

**Abstract** Adults harboring a diffuse low-grade glioma (DLGG) present most of the time without evident cognitive disorders. Nevertheless, extensive and specific cognitive assessments often highlight disorders in cognitive functioning, especially concerning memory, attentional resources, and information processing speed, which may affect negatively quality of life. Therefore, whatever may be the chosen therapeutic option, cognitive functioning must be assessed longitudinally in all patients. Such a longitudinal assessment may provide significant information about tumor progression, on the one hand, and allow to put the bases of a cognitive rehabilitation program if needed, on the other hand.

Based on their strong experience in the care of DLGG patients, the authors thoroughly describe the different steps of the neuropsychological management.

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Cognitive, emotional and language perioperative assessments are reported, and different possible avenues of improvement are further discussed.

**Keywords** Diffuse low-grade glioma • Cognitive functioning • Language • Emotion • Assessments • Quality of life

## 18.1 Introduction

World Health Organization diffuse low-grade glioma (DLGG) is a premalignant, invasive and slow-growing brain tumor, occurring mainly in young adults, and most often diagnosed following an inaugural seizure [1]—although its incidental detection is currently increasing notably due to a widened access to neuroimaging [2]. Given this slow-growing character, patients with DLGG present most of the time without evident cognitive disorders, even when the tumor is located in functional areas for cognitive functioning, thanks to brain plasticity which allows cerebral functional reorganization. Nevertheless, extensive and specific cognitive assessments often highlight disorders in cognitive functioning, even in the case of incidental detection [3], especially concerning memory, attentional resources and information processing speed. These disorders, which may be caused by the tumor itself, but also by tumor-related epilepsy and by treatments [4], affect negatively patients' quality of life (QoL) [5]. Therefore, whatever the therapeutic option (surgery, chemotherapy, radiotherapy), cognitive functioning must be assessed longitudinally in all patients. Moreover, it seems that the longitudinal assessment of cognitive functioning might provide significant information about tumor progression [6, 7] and then might contribute to a better prediction of patients' survival [8, 9] as well as it may help clinicians in the selection of the most appropriate treatment to propose to the patient.

### *18.1.1 What Are Cognitive Functions?*

Cognitive functions interact with each other and encompass the so-called "higher functions", i.e. language, memory, attention and executive functions, to which we may add social cognition and emotional processes, and more "basic" functions such as visuo-spatial orientation, sensory-motor functions, praxis, and gnosis. Each cognitive function doesn't work in an isolated manner; cognitive functioning is possible thanks to the interaction between the different functions. This assertion is particularly true for language processing, because an efficient language functioning implies the integrity of attentional, executive and memory functions. As a consequence, if dividing cognitive functioning in several sub-systems is irreplaceable in order to understand the mechanisms involved in information processing, this division is quite artificial since all cognitive functions participate, with different degrees, in an efficient cognitive processing, whatever its modality. Therefore, when one studies a peculiar cognitive function, for

example language, one has to keep in mind that other functions are involved in the function under scrutiny. These considerations are essential in the assessment of cognitive functioning, and even more in cognitive rehabilitation (see Chapter by Herbet and Moritz-Gasser).

#### 18.1.1.1 Language

Although language is the mean to express our thought and to communicate, it's not a simple tool: it also allows conceptualizing the world and structuring thought. In other words, language is not reducible to speech, which is the motor planning and act of spoken language.

Language is processed following two poles, a productive one and a receptive one, in two modalities, spoken and written. There are different levels of processing: phonological, lexical, semantic, syntactic, to which must be added the level of communicating acts, called pragmatic level, which allows us understanding, particularly regarding implicit and metaphoric language.

Schematically, language processing involves a set of parallel processes interacting together, at different levels (Fig. 18.1). As mentioned above, to be efficient, these parallel processes depend on the integrity of other cognitive functions, namely attention, executive functions and memory.

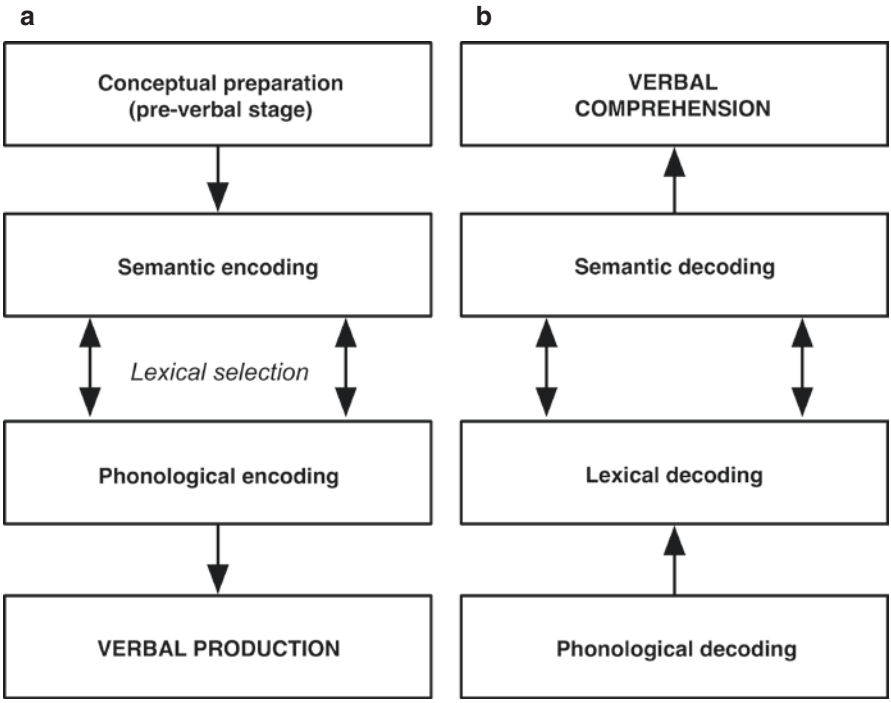


**Fig. 18.1** Schematic model of (**a**) spoken word production and (**b**) spoken word comprehension

#### 18.1.1.2 Memory

Thanks to numerous works in cognitive neuropsychology for over 30 years, consensual views and models of memory functioning have emerged. It is believed that memory is not a unitary system, but that it is composed of multiple independent systems nonetheless working in a relative interactive manner. A classical and well-accepted distinction is the one made between short-term/working memory and long-term memory. The former is involved in the temporary maintenance of information and its mental manipulation [10]. Numerous activities of daily life are constrained by the proper functioning of this memory. This can range from basic activities such as keeping in mind a telephone number to more complex cognitive tasks such as comprehension during reading, mental calculation, problem solving. Long-term memory is divided in two non-completely segregated subsystems [11]. It includes semantic and episodic memories. The former is highly involved in accessing the meaning of words, objects, people and facts but also in the apprehension of the whole world. The latter has an essential role in encoding and storing new information in a spatial and temporal given context. It is the basis on which our autobiographic memory (personal facts) is built.

#### 18.1.1.3 Attention

Attentional system is rooted in a long tradition in neuropsychology. It has been the subject of extensive experimental investigations during the last century. However, the term 'attention' remains difficult to define because it involves several phenomena. Numerous cognitive or anatomo-functional models have been proposed in the past. The more consensual in clinical neuropsychology is perhaps the model by Van Zomeren & Brouwer [12]. According to these authors, the attention system is characterized by two axes, which are themselves partitioned into two subcomponents. The first axe corresponds to attention intensity. It covers the notion of attentional arousal, vigilance and sustained attention. The second, the selectivity axe, includes the functions of selective attention (the capacity to select and orientate its attention on relevant information and to maintain it) and divided attention (the capacity to allocate attention on several sources of information). All the processes would be under the control of a more globalizing entity, namely the supervision attentional system, particularly involved during goal-directed behaviors (i.e. executive functioning).

Attention functions are crucial because they are the prerequisite to the functioning of all other cognitive functions.

#### 18.1.1.4 Executive Functions

Executive functions are defined as the set of processes which allows cognitive and behavior control. They are particularly involved when the subject has to adapt himself to a new or complex situation (carrying out no procedural tasks; problem

solving). Even though the term "executive functions" usually refers to a unitary concept, it includes a large number of sub-processes. Among these, the most prominent processes are action initiation, planning, organization, cognitive flexibility, cognitive control, emotion control or conflict monitoring. It is believed that their coordination makes possible the success of self-generated action or behavior [13], and efficiency in dealing with the environment intentionally. In the case of severe executive functioning disturbances [14], patients behave as if they were completely subject to environment (e.g. imitation behavior, lack of control and desinhibition, stereotypic actions, or perseverations).

#### 18.1.1.5 Social Cognition

Social cognition encompasses all psychological processes involved in the comprehension and the regulation of social behaviors. It includes a number of skills in which Theory of Mind (ToM) and empathy are the most representative. The former is referred to a unique form of metacognitive ability, which makes it possible to attribute mental states to oneself or others, like intentions, emotions, motives or beliefs [15]. ToM allows establishing causal links between behaviors and the hypothetical psychological reasons which have induced them [16]. For this reason, such a brain function is thought as one of the pedestal on which social cognition is supported, authorizing successful social relations and behaviors. As for empathy, it can be defined briefly as the ability to recognize and share an emotional experience [17–19].

These two social cognitive functions are very important for the appropriateness of behavior. For example, ToM disturbances are the cognitive landmark of a variety of neuropsychiatric or neurodevelopmental condition like schizophrenia or autism spectrum disorders [20]. A severe lack of empathy characterizes psychopathy or antisocial personality disorders [21].

## 18.2 Effects of Therapeutic Strategies on Cognitive Functioning

As mentioned above, surgery, chemotherapy, and/or radiotherapy constitute the main therapeutic options that may be proposed to DLGG patients, often completed by antiepileptic drugs. The effects of these different treatments on cognitive functions have been reported in several studies.

Concerning surgery, provided that tumor removal is performed in awaken conditions, allowing intraoperative brain mapping and maximal resection according to functional boundaries (see Chapters on Surgery for DLGG by Duffau), a transient worsening in cognitive processing is often observed. Most of these cognitive deficits (see below) resolved within 3 months [22], thanks to brain plasticity [23] which is presumably potentiated by the surgical act itself and by individualized cognitive rehabilitation.

Regarding radiotherapy, several studies showed that DLGG patients who received local radiotherapy experienced late-delayed (mean of 12 years after diagnosis) treatment-related disorders in cognitive functioning, especially in attentional functioning. Of note, these disorders were regularly associated with radiological abnormalities, compared with patients who were radiotherapy naïve [24, 25]. Moreover, a phase III trial showed that early radiotherapy has no impact on overall survival in DLGG patients [26]. Therefore, authors suggest that deferring radiotherapy treatment might be the most beneficial strategy to cognitive status.

Concerning chemotherapy, some authors have recently suggested that it might be a valuable therapeutic alternative in the management of patients with DLGG considered as inoperable (or not re-operable) because of an extensive involvement of eloquent areas, or because of invasion of contra-lateral hemisphere [27]. Interestingly, patients who benefited from this therapeutic strategy, namely neo-adjuvant chemotherapy followed by surgical resection after tumor shrinkage, presented with only slight cognitive disturbances, mostly related to glioma location [28].

## 18.3 Surgical Management of DLGG Patients

In any case, without treatment, malignant degeneration is invariably observed in DLGG. According to the guidelines of the European Association of NeuroOncology, surgical resection is now considered as the first therapeutic option for DLGG patients [29]. The extent of resection has been demonstrated to have a significant impact on the natural history of the disease, by delaying malignant transformation and increasing overall survival [30, 31]. Given that this lesion is preferentially located in brain areas involved in sensory-motor and language functions [32], this surgical management has to be led in awaken conditions, in order to check online patients' cognitive functioning (for which a significant inter-individual variability has extensively been reported) [33, 34]. This therapeutic (and not "wait and see") attitude allows achieving a challenge with two antagonist goals: to maximize the extent of resection while preserving functional areas, in order to increase patients' survival without inducing a worsening of their QoL—or even by improving it [35].

Therefore, the surgical management of DLGG patients has to be highly controlled and to follow a sequential succession of therapeutic stages well defined, that begins at the moment of the diagnosis and never ends (see Fig. 18.2). This dynamic strategy encompasses the involvement of a pluri-disciplinary team, which in the peri-operative period, is constituted by the neurosurgeon, anesthesiologist, speech-therapist and/or neuropsychologist, and nurses.

The speech-therapist and/or neuropsychologist have an important role to play in this management. They have to assess cognitive functioning of patients at different peri-operative times, in order to highlight their cognitive status and the efficiency of their own brain plasticity. To achieve this assessment, not only several objective tests but also subjective questionnaires and complaints inventory may be used. Moreover, the speech-therapist and/or neuropsychologist, who will be near the

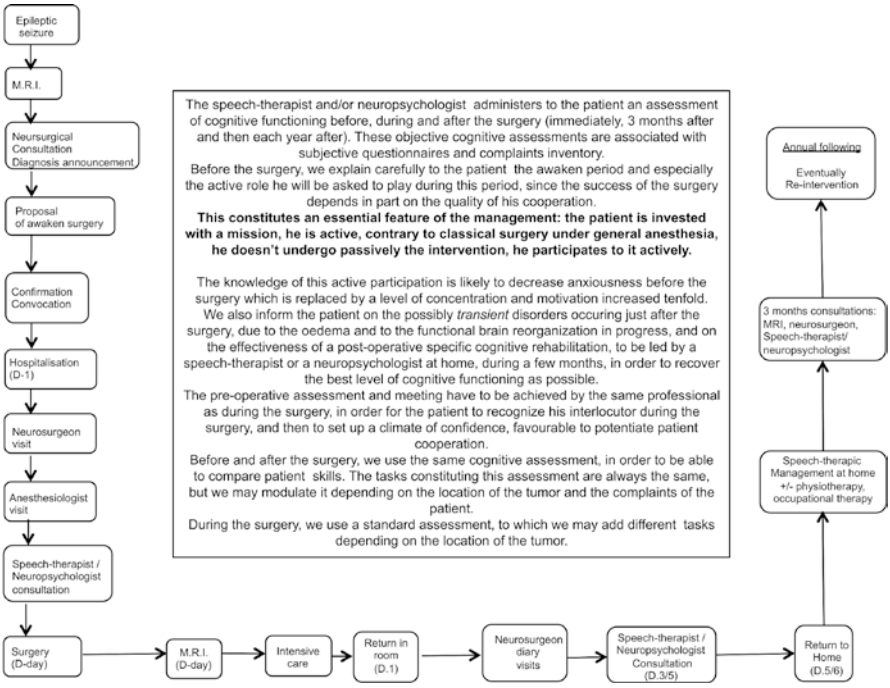


**Fig. 18.2** Longitudinal management of DLGG patients undergoing a surgical resection in awaken conditions

patient during surgery, have to explain clearly the modalities of the surgical procedure as well as the active role the patient, crucial to allow the neurosurgeon to achieve a successful resection. Indeed, the patient should be concentrated and motivated during all the awake period, to enable the neurosurgeon to establish relevant anatomo-functional correlations. This latter aspect of the management is as important as the assessment of cognitive functioning.

## 18.4 Choice of Cognitive Tests

It is obvious that the choice of cognitive tests depends on the goal of the assessment, that is, patient care (including peri-operative evaluations) *versus* patient longitudinal follow-up. Cognitive functioning assessment in the context of patient care must take into account several constraints: temporal constraints, on the one hand, especially concerning intra-operative assessments, and physical and psychological associated signs, on the other hand, due to the tumor itself, but also to reactive psychological distress and treatments—especially antiepileptic drugs (AED). Fatigue is the most reported physical associated sign, and it is correlated with reduced concentration, motivation and activity. There seems to be no relation

between fatigue and tumor laterality, or between fatigue and type of neurosurgical intervention (biopsy *versus* resection). On the other hand, fatigue is associated with AED use [36]. Psychological distress and mood disturbances associated with the disease may also lead to attention disorders and decreased motivation, and thus affect cognitive functioning [37]. In the context of patient care, we should get the most sensitive information as possible about cognitive functioning, independently of disorders induced by physical and psychological associated signs. For instance, in the context of pre-operative examination, we have to assess *present* (i.e. the day just before the surgery) patient cognitive functioning in order to understand his own brain functional organization and the efficiency of brain plasticity, to give in a way certain clues concerning the possible extent of resection. This pre-operative assessment must be performed in a given time, keeping in mind the understandable psychological consequences induced by the prospect of the imminent brain surgery. Now, extensive cognitive assessments are time-consuming and may fatigue the patient entailing biased results. Thus, cognitive assessments in the context of patient care should be in the same time individualized, sensitive, relevant, but not too long (ideally, each assessment should not exceed 1 h).

Cognitive functioning assessment in the context of longitudinal follow-up should be more extensive, because we are facing neither temporal constraints nor acute psychological distress. In this setting, the use of comprehensive series of tests, possibly administered during several sessions to avoid fatigue, is relevant and of great interest for many reasons: to understand accurately patients cognitive functioning, to put the bases of a possible cognitive rehabilitation, and to control its effects periodically. Of course, the tests used in this context have to be sensitive, valid and reliable. Moreover, longitudinal cognitive assessments should be administered with a sufficient delay between each other (at least 6 months), in order to avoid practice effects.

## 18.5 Cognitive Evaluation in the Context of Patient Care: Perioperative Assessment

The surgical management of a DLGG patient is highly controlled and it always follows the same temporal organization (see Fig. 18.2). Cognitive evaluations are administered 4 times peri-operatively: the day before surgery, during surgery, 3–5 days after surgery and 3 months after surgery. Then, cognitive functioning is assessed periodically.

### *18.5.1 Preoperative and Immediate Postoperative Assessments*

The same assessments (except subjective questionnaire and complaints inventory which concerns only the pre-operative assessment) are administered to the patient the day before the surgery and 3–5 days after. These assessments have to be very

sensitive in order to understand one's individual cognitive functioning, the effects of the tumor on neurocognition, the efficiency of functional brain plasticity (pre-operative time), the immediate effects of the surgery and surrounding edema on cognitive processing (post-operative time), with the goal to establish an individualized program of cognitive rehabilitation (see the Chapter by Herbet and Moritz-Gasser).

Preoperative meeting allows explaining to the patient the surgical procedure and the importance of his active participation, answering to his questions and ensuring him that his present cognitive functioning will be at least preserved, or even improved after surgery. Nevertheless, the patient and close parents must be informed that transient disorders (sometimes impressive) are frequently observed immediately after surgery, due to the resection, surrounding oedema and brain reorganization in progress. We must explain to the patient the transient character of most of these disorders, which will resolve in a few weeks. Moreover, the patient must be informed that he/she will benefit from a specific cognitive rehabilitation performed at home by a speech-therapist and/or neuropsychologist during at least 3 months, in order to potentiate this spontaneous brain reorganization, and then to maximize the recovering of the best level of QoL.

#### 18.5.1.1 Subjective Questionnaire and Complaints Inventory

Most of the time, before surgery, DLGG patients don't report cognitive symptoms, or only mild ones, which don't interfere with their daily life. Nevertheless, an extensive and specific cognitive evaluation highlights frequently slight cognitive deficits, especially concerning working memory and speed of processing [38, 39].

Indeed, if brain plasticity allows an efficient reorganization, thanks to the slow-growing character of DLGG, such a brain functioning implies consequently a new functional network entailing presumably a higher cognitive cost in information processing. Moreover, there are frequent discrepancies between objective disorders revealed by cognitive tasks and subjective disorders experienced by patients in their daily life. That's the reason why it is very important to ask the patient, before any objective assessment, about his complaints. Questions are very simple:

- Do you have complaints concerning your cognitive functioning?
- Are you full-working?
- If no, what are the reasons of decreasing your time of work?
- Is it difficult to mobilize your attention?
- Did you note any difficulties in elaborating projects, understanding orders, being concentrated on a task, participating in a conversation?
- Do you feel an important fatigue during or after such cognitive tasks?

It may be useful to ask the same questions to the close relations in order to compare subjective complaints and observed disorders.

#### 18.5.1.2 Language Evaluation

We use always the same battery of tests to assess language processing before and immediately after surgery, whatever the location of the DLGG (Table 18.1). This gold-standard assessment begins with the Edinburgh inventory [40] in order to specify patient handedness, and is then constituted by:

- An evaluation of the level of fluency and informativity of spontaneous speech,
- A timed naming task (DO 80), which consists in naming 80 black and white pictures [41]
- A fluency task (semantic and phonological), which consists in producing the highest number of words belonging to a given semantic category or beginning by a given letter, during 2 min [42]
- A timed non-verbal semantic association task (PPTT), which consists in matching two semantically related pictures [43].

It is worth noting that this assessment doesn't encompass a whole evaluation of language (e.g. BDAE [44, 45]. Indeed, we made the choice not to include this kind of whole examination, because we never observed, after more than 400 DLGG patients in the left hemisphere, lasting aphasic disturbances demonstrated by such a test. In other words, whole language evaluation such as BDAE, for relevant they are concerning other etiologies, are not sensitive enough for slight language disorders in DLGG patients, especially in the immediate pre-operative period.

Finally, we added a non-verbal semantic association task, because we estimated that the sole naming task didn't bring enough information on semantic processing.

Our assessment presents several advantages. Firstly, it is short (less than 1 h), it allows to study language functioning at all levels of processing (phonological, lexical, semantic, syntactic), in both modalities (written and spoken). Moreover, given that pre-operative assessment provides clues concerning the efficiency of functional reorganization and then concerning the possible extent of resection, we have to select pre-operatively some tasks that may be used easily intra-operatively—namely simple and sensitive tasks.

Of note, each task is timed: this procedure allows highlighting slowness in language processing. We give the same significance in responses accuracy as in responses time. A good response is an accurate one produced in a given time. Indeed, as mentioned, DLGG patient presents frequently with slowness in cognitive processing. In a recent study, we showed that there might be a link between naming speed and QoL [46]. Indeed, the return to professional activities after surgery seems to be correlated with lexical access speed. Therefore, in addition to the assessment of responses accuracy, we consider that the measurement of responses times should be systematically included in language evaluations.

Depending on tumor location, we may add some tasks to this basic language assessment: comprehension of metaphoric language, repetition of words and pseudo-words, reading and writing of words and pseudo-words.

**Table 18.1** Overview of (A) language assessments (B) other cognitive assessments

| Patient care (peri-operative assessments) | Patient longitudinal follow-up |
|---|---|
| Part A | |
| *Pre- and post-operative standard assessment* | |
| Subjective questionnaire/complaints inventory | Subjective questionnaire/complaints inventory |
| Handedness | Handedness |
| Fluency/informativity | Fluency/informativity |
| Timed naming task | Timed naming task |
| Fluency task | Fluency task |
| Reading task | Reading task |
| *Additional tasks depending on tumor location* | BDAE |
| Metaphoric language | Repetition |
| Repetition | Lexicality judgment |
| Reading, writing | Reading/writing |
| *Intra-operative assessment* | Token test |
| Semantic association task | Metaphoric, implicit language, prosody |
| Naming | Communication |
| Counting | Quality of life |
| Reading | |
| Repetition | |
| Dual task | |
| Part B | |
| *Pre- and post-operative standard assessment* | *Intellectual functioning* |
| Subjective questionnaire/complaints inventory | Verbal Comprehension, perceptive organization, working memory, processing speed (WAIS 4) |
| Speed of information processing | |
| Working memory | *Verbal and non verbal Memory* |
| Executive functioning (flexibility, inhibition) | Short-term and working memory (digit span test) |
| Motor and reflexive praxis | Episodic memory (RL/RI 16) |
| *Additional tasks depending on tumor location* | *Praxis* |
| Visuo-spatial cognition | Motor, ideomotor, reflexive, constructive |
| Social cognition, emotion recognition | *Visual gnosis* |
| *Additional tasks depending on tumor location* | V.O.S.P. |
| Voluntary movement | *Somatognosis* |
| Visuo-spatial cognition | Naming body parts |
| Visual fields | *Visuo-spatial cognition* |
| Dual-task | Line bisection, bell test |

(continued)

**Table 18.1** (continued)

| Patient care (peri-operative assessments) | Patient longitudinal follow-up |
|---|---|
| Social cognition | *Attention* |
| | Sustained attention, divided attention (T.E.A.) |
| | *Executive functions* |
| | Motor and verbal inhibition (Go-no-go and Stroop tests), shifting (T.M.T.), visuo-spatial planning (Rey's Figure), dual tasks (personal material) |
| | *Social cognition* |
| | Theory of Mind, social and moral reasoning, empathy |
| | *Emotion* |
| | Facial Emotion Recognition (Ekman's facial emotion recognition task) |

#### 18.5.1.3 Other Cognitive Evaluations

As concerning language, a short but sensitive evaluation of other cognitive functions is proposed before and immediately after surgery. This evaluation always includes an assessment of information processing speed, working memory, and, at the level of executive functioning, verbal or graphic auto-generation, cognitive flexibility and inhibition. Motor and reflexive praxis are also systematically reviewed. Depending on tumor location, visuo-spatial cognition, social cognition and emotion, including facial emotion recognition and Theory of Mind may be added to this basic evaluation. Post-operatively, if the patient does not reach his pre-surgical neurocognitive baseline, an individualized cognitive rehabilitation may be prescribed. Interestingly, patients may sometimes improve their performances on some tests despite the resection. This can be explained, at least partly, by the lifting of the mass effect possibly applied by the tumor on brain tissue or by the decrease of functional interferences induced by the DLGG within neural networks (see Chapter on Magnetoencephalography and functional connectivity by Douw et al.).

### *18.5.2 Intraoperative Assessment*

Here are described the different tasks used during surgical resection with intraoperative functional monitoring under awake condition.

#### 18.5.2.1 Language

During surgery, we assess the patient's cognitive and sensory-motor functioning, while the neurosurgeon applies direct electrical stimulations (DES), at the cortical and sub-cortical level (see Chapters on surgery for DLGG by Duffau). The role of

the speech-therapist and/or neuropsychologist is, in addition to motivate the patient and to explain him what he's asked to do, to note, to analyze and to interpret the most precisely and quickly as possible each disorder observed as well as to transmit this interpretation to the neurosurgeon—in order for him to perform a relevant cortico-sub-cortical individual brain mapping.

Moreover, to assess objectively the patient skills, the speech-therapist/neuropsychologist is never informed about when and where the DES are applied. With the aim to interpret the most accurately as possible patient behavior, we chose to always use the same intra-operative assessment.

To map language processes, the use of a naming task remains the gold standard. This task, which is easy to implement during surgery and especially adapted to patient positioning constraints (Fig. 18.3), is very sensitive to all levels of processing (Table 18.2). During electrostimulation, different kinds of impairments may be observed: speech arrest, dysarthria (disturbance of motor programming), anomia (disturbance of lexical retrieval), phonological paraphasia (disturbance of phonological encoding), semantic paraphasia (disturbance of semantic processing) or perseveration (disturbance of inhibitory control mechanisms) [47]. Beyond classical language-related cortical areas, the naming task enables to map the main associative

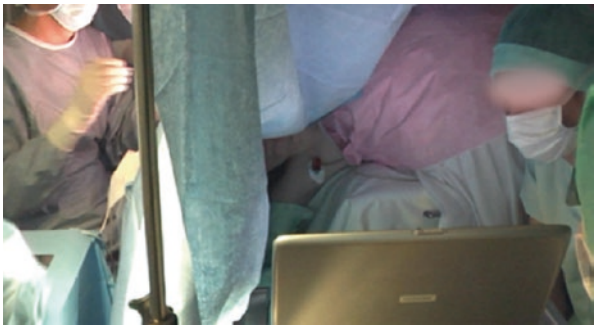

**Fig. 18.3** Positioning in the operating theater, showing the relative positions of the patient, the neurosurgeon, the speech therapist/neuropsychologist, and the computer screen

**Table 18.2** Different kinds of disorders observed during DES, reflecting the level of processing concerned

| Effect of DES (naming task DO 80) | Level of processing |
|---|---|
| Speech arrest | Motor programming |
| Anomia | Semantic encoding, lexical access, phonological encoding |
| Semantic paraphasia | Semantic encoding, lexical access |
| Phonological paraphasia | Phonological encoding |
| Dysarthria | Motor programming |
| Perseveration | Inhibitory mechanisms |
| Increased delay of response | Lexical access |

connectivities (i.e. the arcuate fasciculus for phonological processes, the lateral superior longitudinal fasciculus for articulatory processes, the inferior fronto-occipital fasciculus for semantic control processes and the inferior longitudinal fasciculus for lexical retrieval) and certain intralobar tracts such as the frontal aslant tract (speech initiation and control) [48, 49].

To intraoperatively assess the non-verbal semantic system (the naming tasks enables only to assess verbal semantics), we use also systematically a semantic association task (i.e. the Pyramids and Palm Trees Test). We have previously shown that this task is useful to map and preserve the direct ventral connectivity, especially the inferior fronto-occipital fasciculus in the left hemisphere [50].

When the tumor concerns the left occipito-temporal cortex, especially the visual word form area and its underlying white matter connectivity, it is necessary to map the different subprocesses involved in reading aloud. To this end, we typically use a reading task in which the patient is asked to read aloud different word categories, including regular and irregular words, and pseudo-words [51]. Depending on the structure stimulated, different neuropsychological disturbances can be observed. For example, stimulation of the anterior part of the visual word form area induces addressed phonology disturbances (irregular word reading) while stimulation of the posterior segment of the superior longitudinal fasciculus induces both addressed and assembled phonology disturbances (irregular words and pseudowords reading). Finally, to map brain areas involved in the motor implementation of automatic speech production, we always use a counting task consisting in counting aloud from 1 to 10 in loop.

#### 18.5.2.2 Other Cognitive Functions

Motor Cognition

Voluntary movement (i.e. the consequence of internal/endogenous activity) engages a set of highly sophisticated processes grouped under the term of motor cognition (i.e. intention to act, motor planning, motor initiation, action control, *etc*.). Impairment of motor cognition can lead to a variety of disabling disorders such as for example disturbance of bimanual coordination or ideomotor/motor apraxia. A way to basically control through the surgery all aspects of voluntary movement is to ask the patient to perform a simple double motor task engaging the upper limb: lower the arm and open the hand, then raise the arm and close the hand (the lower limb may be also concerned or both at the same time). In addition to control the velocity and the accuracy of the movement during all the surgery, this task enables to map under stimulation crucial areas for motor cognition [52]. Depending on the structures being stimulated, a wide range of manifestations can be observed. For example, stimulation of the supplementary motor area can lead to motor initiation disturbances. Other motor tasks can be performed to map more specific motor abilities. Regularly, we ask the patients to make coordinated movements with both hands [53, 54]—an ability especially crucial for certain professions (e.g. manual work, musician). It is also important to ask the patient to perform more complex movements to assess

fine-grained motor abilities such as drumming, or to perform reflexive praxis (e.g. imitation of meaningless movements) to evaluate movement planning.

### Spatial Cognition

Unilateral spatial neglect is a debilitating condition characterized by a failure to explore and allocate attention in the space contralateral to the damaged hemisphere [55]. It occurs mainly after a right lesion (especially when the lesion involves the right parietal lobe or the temporo-parietal lobes). This cognitive impairment has a major impact on quality of life by depriving the patient to resume a normal social and professional life.

A classical test to evaluate spatial neglect is the bisection line task [56]. For surgery, we have adapted this task in a touch-screen environment. The patient is asked to separate a line in two identical segments (i.e. find the middle of the line). The length of the line is 18 cm. If, during the time of stimulation, a significant rightward deviation is observed (typically 7 mm or slightly more if the patient present with a behavioral variability), the brain areas under scrutiny is considered as eloquent for visuo-spatial cognition. This task is especially useful to map the inferior and the superior parietal lobules and, most importantly, the dorsal white matter connectivity (i.e. especially the layer II of the superior longitudinal fasciculus) [57, 58]. Using this method, in our experience, none of our patients have presented a long-term spatial neglect although approximately haft of the patients with a right lesion has a transitory neglect in the immediate postoperative phase [59].

### Social Cognition

To avoid long-term postoperative social cognition impairments, we use an adapted version of a well-used mentalizing task (i.e. the Read the Mind in the Eyes Task [60]). We have indeed previously shown that patients with a resection of the pars opercularis of the right inferior frontal gyrus did not completely recover after surgery [61, 62], justifying the use of a new intraoperative task. This task has proven to be especially useful to functionally map the pars opercularis and the pars triangularis and their underlying neural connections in the right hemisphere [63].

### Visual Processes

Patients with large visual field defect, such as lateral homonymous hemianopia, have generally a poor functional outcome. In many countries, driving is formally prohibited and a lot of activities such as reading become arduous. To map visual connectivity and avoid the occurrence of long-term postoperative visual field defects, we use a simple protocol allowing to assess visual fields during surgery [64]. Specifically, with the vision being fixed at the center of the screen, patients are asked to name successively two pictures disposed in the two opposite quadrants knowing that it is

absolutely crucial to preserve the inferior quadrant (the superior being compensable). The position of the pictures is determined by the laterality of the lesion. Although direct electrical stimulation of visual pathways, especially the optic radiations, generally evokes a range a phenomena subjectively described by the patient himself (blurred vision, impression of shadow, phosphenes, visual hallucinations as zoopsia or metamorphopsia), the described task allows to have a more objective confirmation of the transitory visual disturbance induced (i.e. the patient cannot name the picture presented in the inferior quadrant contralateral to the lesion). Some indicators are also important to take into consideration during the assessment of visual fields, most notably the amplitude of visual saccades or the possible increase of naming response time in the visual field under scrutiny. It is also very important to regularly assess manually the extent of the visual field of the patient.

### High-Order Visual Processes

The inferolateral occipito-temporal cortex is reputed to broadcast critical information in the service of object recognition. Damage to this neural system may lead to visual agnosia. A simple way to map these high-order visual processes is to use a picture naming task. If a disturbance of object recognition is induced during electrostimulation, the patient generally commit a non-semantically related 'visual' paraphasia. Our group has previously shown that electrostimulation of the right inferior longitudinal fasciculus, connecting the occipital cortex with the temporal pole, can lead to such impairments [65, 66].

### Multi-Tasking

Numerous activities in daily life necessitate to process different matters at the same time. This crucial multitasking ability requires maintaining in working memory several task goals to be performed and concurrently allocating attention among them. During surgery, this higher capacity can be assessed by asking the patient to perform in the same time a regular movement of the upper limb and a naming task or a semantic association task in a coordinated manner. A multitasking disturbance is observed when the patient is no longer able to perform both tasks at the same time while the realization of each task separately remains possible. This impairment, to a lesser extent, may be manifested in a temporary desynchronization/lack of coordination between the two tasks.

### Other Cognitive Tasks

Patients may have a strong expertise in some cognitive domains due to their job or their hobbies (numerical cognition in a mathematician expert, working memory in a management assistant). In such cases, we can implement some specific tests to ensure the patient that he/she will recover a normal professional life after surgery.

For example, we regularly use a two-back task to assess working memory. This task consists in naming the picture viewed two trials before. For high-level patients, we can exceptionally increase cognitive load by asking the patient to name the picture viewed three trials before.

At several occasions, we have also used mathematical cognition tasks to assess basic mathematical operations. This is useful when the lesion is located in the left parietal lobule.

#### 18.5.2.3 Should We Introduce Other Tasks?

An issue frequently raised by our colleagues concerns the use of other cognitive/language tasks for the intraoperative mapping such as more fine-grained linguistic or memory tasks, or specific executive function tasks. It is a fair question. However, in our opinion, deciding to implement new tasks in standard practice involves several considerations:

(a) The cognitive tasks previously described appears to be sufficient to map both the main white matter connectivities and the cortical epicenters which are reluctant to brain plasticity [67].
(b) The used tasks must be necessary simple and easily workable given the constraints inherent to the electrostimulation procedure (stimulation duration: 4 s maximum), clinical context (intraoperative mapping cannot be too long), and surgery theater constraints (patient position).
(c) In connection with this, high-level functions such as for example certain executive functions particularly distributed at the anatomical scale are very difficult to map under stimulation (simultaneous contribution of multiple networks).
(d) The best onco-functional balance must be found: the first goal of surgery is to optimize the quality of the resection while preserving quality of life. Adding too many tasks might eventually affect the effectiveness of surgery.

In our opinion, giving an objective answer to this question necessitates to study longitudinally (i.e. before and after the surgery) patients' cognitive and language performances on a variety of behavioral paradigms. If patients do not recover efficiently and are impeded in their daily life functioning, it seems reasonable to think to the implementation of new well-controlled tasks. However, before doing this, we have to understand the pathophysiological mechanisms of the lack of recovery. Indeed, a number of factors can explain a lack of recovery after surgery such as the degree of infiltration of white matter connectivity, the preoperative functional status, and the inter-individual variability in the neuroplasticity potential, the socio-educational level, and probably the patients' personality.

#### 18.5.2.4 Cognitive Disorders Following Surgery

Most of the time, the immediate post-operative assessment (between 3 and 5 days after the surgery) highlights disorders related to the brain area which was removed. Nevertheless, these disorders are mainly transient, due to the post-operative edema,

maximal about 3 days after surgery. Moreover, the surgery itself induces processes of functional reorganization, which may spoil transiently the functioning of a given functional network. Apart from "site-specific" disorders (e.g. articulatory or initiation disorders after a resection close to motor planning areas), we may observe different kinds of language and other cognitive disorders. Thus, immediate post-operative clinical presentations are various and may go from slight disorders to broad impairments in different cognitive functions. In any case, patients present always with slowness in information processing and attentional disturbances.

This slowness in information processing is likely to be related to a disorder in working memory and executive functioning, rather than to a global psychomotor slowness.

Considering that, as mentioned above, language functioning has been checked at the end of awaken period, we are able to ensure the patient that immediate post-operative disorders are transient, even if sometimes impressive. Nevertheless, in order to potentiate spontaneous functional reorganization and thus to recover the best level of cognitive functioning in a short delay, all patients benefit from a specific and intensive program of cognitive rehabilitation, performed immediately after their return to home by a speech-therapist specialized in this management (see chapter on Functional rehabilitation in patients with DLGG by Herbet and Moritz-Gasser).

Three months after surgery, patients' neurocognition is re-evaluated. This assessment highlights the level of recovery and thus the efficiency of brain plasticity and speech-therapy management. Concerning language functioning, we always observe a clear improvement compared with immediate post-operative skills. Most of the time, the pre-operative level is reached.

Concerning other cognitive functions, attention, working memory and executive functions disturbances are common in the postoperative phase requiring a following specific cognitive treatment, although they are not systematic. Depending on tumor location, specific deficits can be observed, notably in the domain of social cognition and emotion. For example, resection of DLGG in the insular and the amygdala regions induce more often facial emotion recognition impairment, concerning disgust and fear, respectively (Fig. 18.4). When the lesion involves the posterior part of right inferior frontal gyrus, recognition of 'happy' emotion becomes sometimes transiently very difficult. Recognition of complex affective mental states (affective theory of mind) may also been disturbed (unpublished personal data). Another example is the problem of comprehension of intentions following mesial frontal areas removal, including the most anterior part of cingulate gyrus.

If the glioma is located in the inferior parietal lobule, or more generally at the level of the temporoparietal junction, transient spatial neglect may be observed (Fig. 18.5). This is also the case, to a lesser extent, when the resection involves the posterior part of inferior frontal gyrus.

Following a temporo-mesial lobectomy, transient severe disorders of anterograde memory may be observed. In some case, learning and retention of any new information is impossible. Although some degrees of slight disturbances may persist at 3 months, the initial dramatic disorders disappear almost completely in most cases.

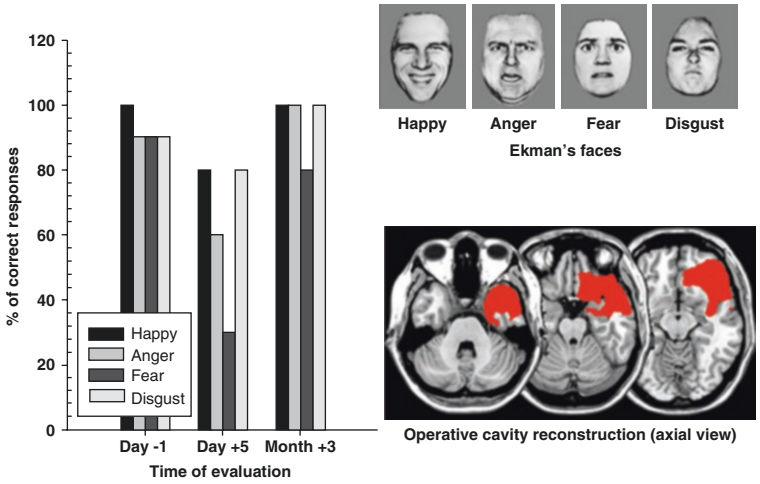


**Fig. 18.4** Longitudinal performances in recognizing basic facial emotions of a patient harboring a fronto-temporo-insular tumor. Results of this patient show a transient emotion recognition deficit, particularly for "fear" and in a lesser extent to "anger," immediately after surgery (Day +5)

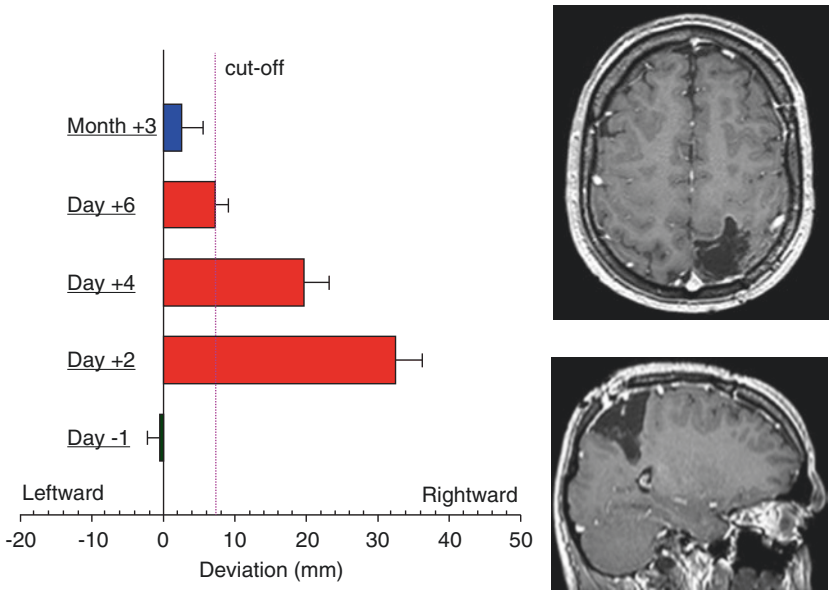


**Fig. 18.5** Longitudinal performances of a patient harboring a glioma in the right parietal lobule. This patient was operated on under local anesthesia. Line bisection test was used during the surgery to map the functional networks for visuospatial cognition. Although patient presented a severe spatial neglect 2 days after surgery (Day +2), it has already begun to decline during following evaluation (Day +4). Six days after (Day +6), performances were located just at the level of pathological threshold. Three months after, performances reached approximately the preoperative level, demonstrating that eloquent structures, especially the subcortical connectivity (i.e., superior longitudinal fasciculus in this patient), were preserved thanks to intraoperative testing (Unpublished personal data)

## 18.6 Cognitive Evaluations in the Context of Longitudinal Follow-Up

For an overview, see Table 18.1.

Whatever the therapeutic strategies, and whatever the location of the lesion, the assessment of DLGG patients cognitive functioning must absolutely be included in the context of medical longitudinal follow-up, for many reasons.

Firstly, our clinical practice shows that extensive and specific assessments always highlight at least slight disorders in cognitive functioning. Secondly, these cognitive assessments might provide significant information about tumor progression. Thirdly, the moment of these evaluations allows patients to set out cognitive complaints which cannot always been demonstrated by the tests proposed. Fourth, the highlighting of cognitive disorders during these assessments may lead the clinician to propose an individualized program of cognitive rehabilitation to the patient.

Thus, cognitive evaluation in the context of patient longitudinal follow-up must begin at the moment of the diagnosis, and it never ends. In this setting, in opposition to the peri-operative context, the use of comprehensive series of tests, possibly administered during several sessions to avoid fatigue, is relevant and of great interest. Follow-up evaluations should not have to be administered more than twice a year, with the goal to avoid practice effects. As far as possible, we may use standardized tests, but we can also use personal non-standardized specific tasks, which allow the comparison with patient specific skills between them over time.

We insist on the fact that these extensive follow-up evaluations should be performed in all patients harboring a DLGG and must begin at the moment of the diagnosis, even for patients who are candidate to a surgical management. In this latter case, the first evaluation will take place far before the surgery, and will not replace the immediate pre-operative and post-operative assessments described above.

### *18.6.1 Subjective Questionnaire and Complaints Inventory*

In addition to the complaints collection, standardized subjective questionnaires and scales may be used in order to assess the quantitative and qualitative level of communication, from the patient and close related point of view.

### *18.6.2 Language Evaluation*

In addition to the battery of tests presented in Sect. 18.5.1.2, we propose to assess language extensively, at all levels of processing, by administrating some or all of the following tests:

- Boston Diagnostic Aphasia Examination (BDAE), in order to have a baseline score at disposal
- Repetition of words and pseudo-words (phonological level)

- Lexicality judgment (lexical level)
- Reading and writing of words, irregular words and pseudo-words (phonological, lexical and semantic levels)
- Token test [68] (syntactic level)
- Information, similarities and vocabulary tasks from the WAIS 4 [69] (semantic level)
- Comprehension of metaphoric and implicit language, comprehension and production of prosody [70] (pragmatic level)
- Objective assessment of the qualitative and quantitative level of daily communication [71].

### *18.6.3 Other Cognitive Evaluations*

In this setting, an extensive cognitive examination is proposed. It is thought to assess all domains of cognitive and intellectual functions. Depending on tumor location, we may focus more specifically on particularly cognitive functions as, for example, numeric or visuospatial cognition if the tumors involves the left or the right posterior parietal cortex, respectively. However, an important basic assessment is common to all patients, whatever the location of the DLGG (see Table 18.1).

It is worth noting that, in the context of longitudinal follow-up, the first neurocognitive assessment is a crucial step in cognitive care because it will serve as a reference point for subsequent years.

Finally, we may add to these extensive assessments a questionnaire concerning QoL, in order to assess the impact of the DLGG and the therapeutic strategies on daily life [72, 73].

## 18.7 Psychological Support

If one of the fundamental roles of the speech-therapist/neuropsychologist is to assess as accurately as possible the neurocognitive functioning, as mentioned above, this is only a part of the management. The diagnostic announcement and the prospect of neurosurgical management may induce psychological distress. The loss of self-esteem is for example a fairly common problem after surgery. Moreover, even if the cognitive loss is generally low, it may be experienced as dramatic and may have a large rent on the psychosocial functioning and QoL of the patient (and his/her family) and, finally, it may lead to a depressive state. About this, it's well known that depression has detrimental effects on cognitive processes, in terms notably of memory by damaging natural plasticity (e.g. hippocampal plasticity) in healthy individuals [74, 75]. Another problem induced by depression is the inactivity and apathy often associated. After brain surgery, it is essential for the patient to resume quickly his daily activities (e.g. reading, crafts, outings, etc.). These environmental stimulations are needed to recover a normal functioning as quickly as possible, by

stimulating neural networks. Therefore, we have to take into account affective states and psychological distress, to be listening into patients' complaints and to carefully deal with them. Actually, we have absolutely to keep in mind that, even if cognitive status is widely correlated with QoL, especially with return to work, recovering a satisfactory level of QoL is not reducible to the recovery of a normal cognitive status.

## 18.8 Conclusion

In the context of perioperative patient care as well as in longitudinal follow-up, language and other cognitive evaluations are crucial in the management of DLGG patients. The neuropsychologist and the speech therapist, working in the same state of mind, have an essential role. They establish a real therapeutic alliance with the patient, which never ends. In the setting of longitudinal follow-up, extensive assessments of all the domains of cognitive functioning may be administered periodically, during several sessions if needed, to avoid fatigue. In the context of neurosurgical procedure, accurate and sensitive evaluations of neurocognitive functioning are administered before, during and after surgery, in order to assess the impact of the DLGG on cognitive functions and the efficiency of one's brain plasticity—and then to allow a maximum resection while preserving functional networks.

Whatever the context of evaluation is, its results allow to establish the bases of a relevant individual program of cognitive rehabilitation (when needed). In addition to these objective assessments, we include psychological support in patient care. Indeed, resuming a normal life is not reducible, from far, to the sole recovery of a satisfactory level of cognitive functioning, even if cognitive functioning contributes for a large part in QoL. Thus, in addition to objective cognitive assessments, subjective questionnaires, complaints collection, and psychological support should always be a part of DLGG patients care. Consequently, institutions and neurosurgeons should absolutely pay interest in these aspects of the management of DLGG patients, which are often neglected in practice.

If the management of these patients has dramatically improved in recent years, there is a long way to go. Some issues need to be further addressed. This is for example the case of possible changes of personal identity or personality after surgery. Indeed, it is not uncommon to observe some modifications in behaviors or more generally in decision-making in multiple settings (the patient being aware of this or not). This may range from simple irritability, easily manageable, to more problematic manifestations, such as lack or exacerbation of empathy, emotional indifference, changes in sexual conducts or others—sometimes related to social cognition disturbances. Although important behavior changes are rather the exception than the rule, it is nevertheless crucial to understand their conditions of occurrence. This challenging work can be accomplished in systematizing some types of psychological (e.g. premorbid personality) and cognitive (e.g. social cognition and emotions) evaluations before and after surgery. A better psychological characteriza-

tion of patients may help in anticipating postoperative behavioral abnormalities and, subsequently, may aid in deciding the prescription of postoperative behavioral therapy.

As a final note, it seems to be of first importance to develop in the future more studies dedicated to the effectiveness of neuropsychological rehabilitation in the context of DLGG surgeries. Although we know that cognitive and language rehabilitation is essential to pave the way toward a satisfactory level of recovery, controlled studies demonstrating the merits of this approach are lacking. The results of such studies could allow providing a better guidance for the postoperative management.

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# Chapter 19
# Task-Based and Resting-State Functional MRI in DLGG

**Alexandre Krainik and Jérôme Cochereau**

**Abstract** Since two decades, functional MRI (fMRI) using blood oxygenation level dependent (BOLD) signal has become the most popular imaging method to map cortical involvement during various tasks. This non-invasive technique is commonly used in clinical practice before neurosurgery and in cognitive neurosciences. Much technical and methodological efforts were conducted to improve fMRI feasibility and reliability. In patients referred for neurosurgical resection of diffuse low grade glioma, task-based as well as resting-state fMRI could be helpful to maximize treatment efficiency and safety by allowing a more extensive tumor resection and by limiting the risk of permanent neurological deficit. When compared to intraoperative electrical stimulation mapping (ESM), task-based fMRI of the sensorimotor system is convincing with a good reliability. When compared to WADA test, fMRI of the language system is reliable to determine hemispheric dominance. However, ESM reported discrepancies with task-based language fMRI at the local level. Regarding resting-state fMRI, even though it seems to represent a very promising technique, more validation studies are nonetheless needed before using this new method for surgical planning. In summary, besides methodological and behavioral differences across techniques, fMRI in clinical practice requires to fully master all aspects of fMRI, from image acquisition to processing, and be aware of various limitations to provide a fair and useful interpretation.

**Keywords** Functional MRI • Task-based fMRI • Resting-state fMRI • Diffuse low-grade glioma • Sensorimotor system • Language

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## Abbreviations

| | |
|---|---|
| ASL | Arterial spin labeling |
| BOLD | Blood oxygenation level dependent |
| CBF | Cerebral blood flow |
| CBV | Cerebral blood volume |
| CMRO2 | Change in cerebral metabolic rate of $O_2$ |
| CVR | Cerebral vasoreactivity |
| deoxyHb | Deoxyhemoglobin |
| DMN | Default-mode network |
| EPI | Echo planar imaging |
| ESM | Electrical stimulation mapping |
| fMRI | Functional magnetic resonance imaging |
| GRE | Gradient recalled echo |
| ICA | Independent component analysis |
| OEF | Oxygen extraction fraction |
| PET | Positron emission tomography |
| RS-fMRI | Resting-state fMRI |
| RSN | Resting-state networks |
| SE | Spin echo |
| WI | Weighted image |

## 19.1 Introduction

In the early nineties, functional MRI (fMRI) using blood oxygenation level dependent (BOLD) signal provided new insights into brain function. Ongoing technical developments quickly allowed to consider fMRI as a reliable and feasible tool to localize cortical activity in clinical practice and presurgical mapping. In two decades, fMRI became the most popular technique to depict regional functional anatomy in cognitive neurosciences. Meanwhile, methodologists and clinicians raised several concerns, questioning the wide acceptance of colorful maps displayed on 3D rendered brain, especially in clinical practice [1]. Indeed, presurgical mapping is the most challenging aspect in radiology.

Here, the images and their interpretation are expected to drive brain resection in diffuse low-grade gliomas, considering false positive activations that may limit the extent of tumor removal and false negative results that may lead to permanent neurological deficit. Thus, it is critical to master all aspects of task-based and resting-state fMRI, from image acquisitions to analyses, and be aware of its limitations to provide a fair and useful interpretation.

## 19.2 Task-Based fMRI in DLGG

### *19.2.1 BOLD MR Signal*

Most fMRI experiments in humans use blood oxygenation level dependent (BOLD) signal to map neural activity elicited by a set of appropriate tasks.

This task-related signal is a consequence of presynaptic neurotransmitter release that reflects local signaling, depending on relative inhibitory and excitatory input [2]. However the BOLD signal does not map directly the neural activity. In fact, BOLD signal relies on changes in blood oxygenation due to the oxygen consumption by neurons and the vascular response to neural activity.

First, the task-driven neural activity elicits a metabolic response that increases the $CMRO_2$. This leads to an increase of the oxygen extraction fraction (OEF) from the blood in the capillary bed. As oxyhemoglobin ($HbO_{2)}$ releases oxygen, the concentration of deoxyhemoglobin (deoxyHb) rises. Yet, deoxyHb is paramagnetic, responsible for microscopic magnetic susceptibility effect that accelerates transversal spins dephasing and decreases T2* signal. This early effect, that occurs within the first second after task onset and called the "initial dip" or "fast response", reflect the change of $CMRO_2$ [3]. The initial dip is inconstantly detected because of its low amplitude and its rapid onset. High field MR scan and high temporal resolution are required to identify the initial dip which is supposed to better reflect task-related neural activity using BOLD fMRI.

Second, the neural activity elicits the neurovascular coupling that increases the arteriolar diameter. This increases the cerebral blood flow (CBF) that exceeds the additional needs in glucose and oxygen by neurons. It also covers the drainage of catabolites, $CO_{2,}$ and heat. While CBF increases, the mean transit time of the blood through the capillary bed decreased and the oxygen extraction fraction (OEF) decreases. Thus, deoxyHb is washed-out and its concentration decreases. After 1–2 s, BOLD signal increases along a 5–8 s ramp to reach a "plateau" when then neural activity is sustained [4]. Therefore, the enhanced task-related BOLD signal is due to an excessive delivery of oxygenated blood out of proportion to the needs of oxygen by neurons.

Third, the increase of CBF leads to a massive inflow of blood in the venular compartment that passively inflates according to a "balloon model". This raise in cerebral blood volume (CBV) increases the concentration in deoxyHb at the voxel level that decreases the BOLD signal. This phenomenon is suspected to explain the "poststimulus undershoot" which lasts several seconds after the signal drops below the baseline [5, 6]. It is also advocated to explain the slow decrease of the amplitude of the plateau when a condition is sustained.

In fact, the effects of deoxyHb on the magnetic field are mostly detected in larger blood vessels, such as veins. The diffusion of water molecules contributes also to the extravascular magnetic susceptibility in increasing phase dispersion, especially

around larger veins. Thus, the increased dephasing of spins due to magnetic susceptibility shortens the T2*; and largest BOLD changes are identified near veins draining the activated area.

To minimize the spatial shift of the peak of BOLD signal to the veins, different techniques were proposed. Among these, spin echo (SE) T2-weighted images are more specific to BOLD signal originating from capillaries, because these images are less sensitive to the extravascular effect of the BOLD signal. This increase in spatial specificity is impaired by a decrease in sensitivity that requires higher static fields [5]. A calibrated-BOLD method has been proposed to better estimate $CMRO_2$ changes. It consists in measuring simultaneously BOLD and CBF with a combined BOLD and arterial spin labeling (ASL) technique. The BOLD calibration is performed under hypercapnia [7, 8] or hyperoxia [9]. Thus, the calibration relies on the vasoreactivity to mild inhalation challenges without change of $CMRO_2$. For a given CBF, neural-related BOLD signal is smaller than capnic-related BOLD signal. This difference corresponds to the signal drop due to the $CMRO_2$ [7, 10]. This approach to measure $CMRO_2$ using MRI has also been called quantitative fMRI. Other MR techniques have been proposed to perform fMRI using dynamic perfusion arterial spin labeling (ASL) [11, 12], and diffusion imaging [13]. Although attractive, these methods are still challenging and remain out of the current clinical practice.

Because of the poor sensitivity of MR signals to $CMRO_2$ changes, fMRI remains mostly based on vascular effects of neural activity. Such effects are indirect markers of task-related neurons involvement. Moreover, changes in basal perfusion and in functional properties of perfusion such as neurovascular coupling affect fMRI results. These aspects are critical in brain-lesioned patients. They should be estimated or at least be considered as a potential confounds in neurosurgical planning especially when results are inconsistent with clinical performance and regional functional anatomy.

### *19.2.2 Task Design*

Because MR signals are noisy and the amplitude of the BOLD signal changes is weak (1–5%), activation tasks are designed to perform cognitive subtraction with a conditional approach. Block-designed task alternating conditions requires for each condition to be maintained during a sufficient duration that allows the BOLD signal to reach a plateau (e.g. 15–45 s). For each condition, the number of stimuli, the duration of the blocks, and the number of blocks must be determined. Event-related design intends to explore single events scattered over time. Design optimization is required to obtain sufficient BOLD contrast [14]. Event-related design is less powerful in detecting response magnitude but more efficient at estimating the shape of the hemodynamic response [14, 15]. Moreover, the necessity to increase the number of stimuli remains an important limitation, especially in patients with increased risks of movements, fatigue, and poor performance. In clinical practice, block-designed paradigms are recommended.

### *19.2.3 fMRI Workflow*

Functional MRI is a feasible technique when the whole procedure is well-known and promptly conducted by technicians and neuroradiologists. Poor preparation and hesitations during data acquisition waste time, and may increase fatigue, anxiety, discomfort, movements, and poor performances. Thus, the fMRI workflow has to be optimized during preliminary tests, learned, and regularly conducted to be able to face incidental troubles. In practice, a MRI examination should not last more than 1 h. Data processing also requires preparation, especially in clinical practice, to allow the results to be provided and considered in due time for the patient care.

Before the examination, extensive explanations are necessary to obtain full cooperation. A preliminary training is needed. Instructions have to be clearly explained, and several re-explanations during the examination are needed. The installation must be comfortable with the head maintained within the coil. Specific devices are placed according to the stimuli (headphones, goggles or mirror …) and the expected responses (buttons, joystick …). Image acquisitions include both anatomical and functional volumes. Anatomical images usually consist in a 3D $T_1$-weighted gradient recalled echo (GRE) sequence covering the whole brain using a millimetric spatial resolution to coregister functional data. Functional images usually consist in single-shot GRE echo-planar-imaging (EPI) $T_2$*-WI covering the whole brain using voxels with a lower spatial resolution of 2–4 mm in each dimension. The echo time is adapted to the field strength. Such volume is acquired in 2–3 s depending on the number of planes scanned. The acquisition of this functional volume is repeated over time at a temporal resolution given by the time of repetition. Thus, this procedure provides a time-course of signal change for each voxel. During the functional acquisition, the subject has to follow the cognitive paradigm, and to avoid head motion.

Popular images postprocessing consists in statistical analysis based on the general linear model, which assumes that BOLD signals are a linear combination of regressors. Given to the experimental design, the stimuli presentation is convolved with a canonical hemodynamic response function to obtain a theoretical BOLD time-course for each condition. Thus, the regression analyses are conducted to estimate the causal relationships between theoretical and observed BOLD time-courses for each voxel. Statistical correction for multiple comparisons is highly recommended [16]. Now, such analyses could be computed in a real-time mode. These recent advances widely distributed by manufacturers allow estimating the quality of the examination.

### *19.2.4 Preoperative Brain Mapping in Clinical Practice*

Preoperative brain fMRI is daily performed to map cortical motor and language areas. Others functions such as memory are barely investigated using BOLD fMRI in low grade gliomas surgery, and their results lack validation. The main goal of

preoperative mapping is to clearly delineate functional areas at risk of permanent neurological deficit when lesioned. This risk is critical, especially in patients referred for low-grade gliomas with a long-term survival. Thus, false negative results are a major issue. In case of false positive results, fMRI brain maps may limit the extent of surgical resection.

#### 19.2.4.1 Sensorimotor System

According to the classical cortical representation of the primary sensorimotor system (SM1), primary motor activity is mainly located in the precentral gyrus while the primary sensory activity is mainly located in the postcentral gyrus contralateral to the movements [17]. A somatotopic organization is also present with representations of the foot in the paracentral gyrus close to the vertex, of the fingers close to the "handknob" a reversed omega portion of the posterior aspect of the central sulcus, and of the lips slightly above the subcentral gyrus. Indeed, knowledge in sulcogyral anatomy is always useful to identify the central sulcus and the adjacent gyri. However, the tumor may displace and distort classical landmarks such as the "handknob", giving fMRI an opportunity to localize cortical activity using paced movements to help presurgical planning. Selective delineation of the motor cortex or the sensory cortex is possible using conditional subtraction. However, clinical setup usually does not allow to elicit sensory activity independently. Therefore in daily practice, combined primary motor and sensory activities are identified along the central sulcus (Fig. 19.1).

In addition to primary sensorimotor cortex, secondary motor cortex involved in motor planning and motor onset such as the supplementary motor area (SMA) and the lateral premotor area are usually identified using simple paced movements. These activities are rather bilateral with predominance in the areas contralateral to the movements. In the SMA, a rostro-caudal somatotopy is also reported with representation the lips close to the vertical line passing through the anterior commissure and orthogonal to anterior commissure—posterior commissure plane. Foot representation is located posteriorly, adjacent to anterior aspect of the paracentral gyrus. Hand representation is located in between lips and foot representations [18] (Fig. 19.1). Again, conditional subtraction using mental imagery, modulation of movement preparation or complexity, could help to better distinguish primary from secondary motor areas. However, compromises are advocated to maximize fMRI feasibility in clinical practice.

These data were validated using several techniques. Similar results were obtained when compared to other techniques such as PET [19, 20] and magnetoencephalography [21, 22]. Confrontation with intraoperative electrical cortical stimulations demonstrated an accuracy of fMRI data within a 10–15 mm range [23, 24]. These slight differences are mainly explained by the sensory involvement using simple tasks contrasting paced movements versus rest, and the venous contribution of the BOLD signal. Additional validation was also obtained from surgical resection. Indeed, the

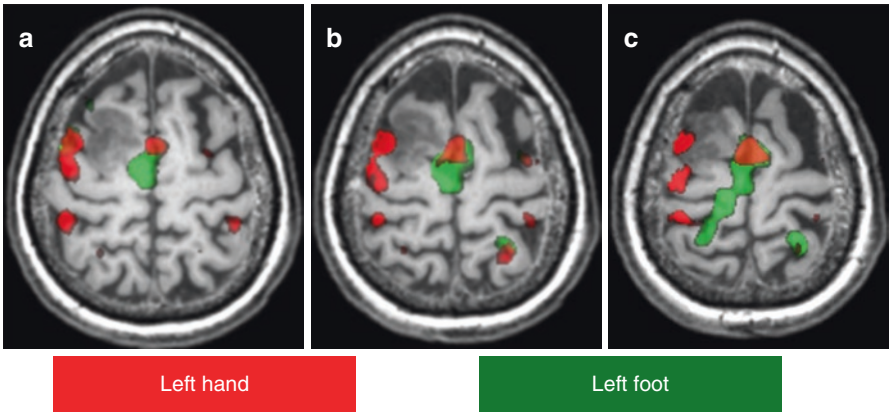


**Fig. 19.1 Motor fMRI.** A low grade glioma was located in the right superior frontal gyrus, anteriorly to the precentral sulcus. Presurgical fMRI shows primary sensorimotor activation of the *left* fingers in *red*, located along the precentral gyrus, posteriorly to the tumor (**a**–**c**). *Left* toes movements in *green* elicited activation in the paracentral lobule, posteriorly and medially to the tumor (**c**). SMA, adjacent to the medial aspect of the tumor was activated with an anteroposterior distribution, the activation related to hand movement was located anteriorly to those of the foot movements. A complete tumoral resection was performed, including SMA, and with respect to precentral gyrus. After surgery, a SMA syndrome was observed with a transient motor impairment of the *left* hemibody that recovered in a week

resection of the SMA activation was followed by a transient contralateral motor deficit that recovers within several days, the so-called SMA syndrome [25, 26].

While acute lesions of the primary sensorimotor areas are at risk of permanent neurological deficit, slow growing low grade gliomas are prone to elicit locoregional plasticity, involving adjacent areas and homologous contralesional areas, especially lateral premotor area and SMA able to facilitate recovery [26]. Considering rigorous quality check, well-known methodological and technical limitations of BOLD fMRI, cortical mapping of primary sensorimotor areas and SMA provided by BOLD fMRI may be helpful for treatment strategy and presurgical planning [27–29].

#### 19.2.4.2 Language System

Lesion-based and electrical stimulation mapping (ESM) studies demonstrated that the language system relies on a widespread cortico-subcortical network connected by subcortical fibers bundles.

The classical model inherited from the nineteenth century emphasized on an anterior motor area (Broca's area including posterior part of the inferior frontal gyrus and anterior opercular area) and a posterior sensitive area (Wernicke's area including posterior part of the superior temporal gyrus and posterior opercular area), connected by the arcuate fasciculus. This organization has a strong left hemi-

spheric dominance in the general population. Even though his simple model can explain some cases in clinical practice, fMRI may show additional area, such as the preSMA, especially using production task (Fig. 19.2). Indeed, surgical resection of activation located in the preSMA in the dominant hemisphere is associated with the occurrence of transient mutism [30].

The reliability of BOLD fMRI to determine hemispheric dominance, based on the calculation of a laterality index [31], was estimated by comparison with the selective intracarotid injection of sodium amobarbital, the WADA test that temporarily disables the hemisphere downstream [24, 32, 33]. This agreement argued to prone fMRI as a non-invasive technique able to determine hemispheric dominance for language instead of WADA test because of its greater comfort, lack of morbidity, lower cost, and higher availability.

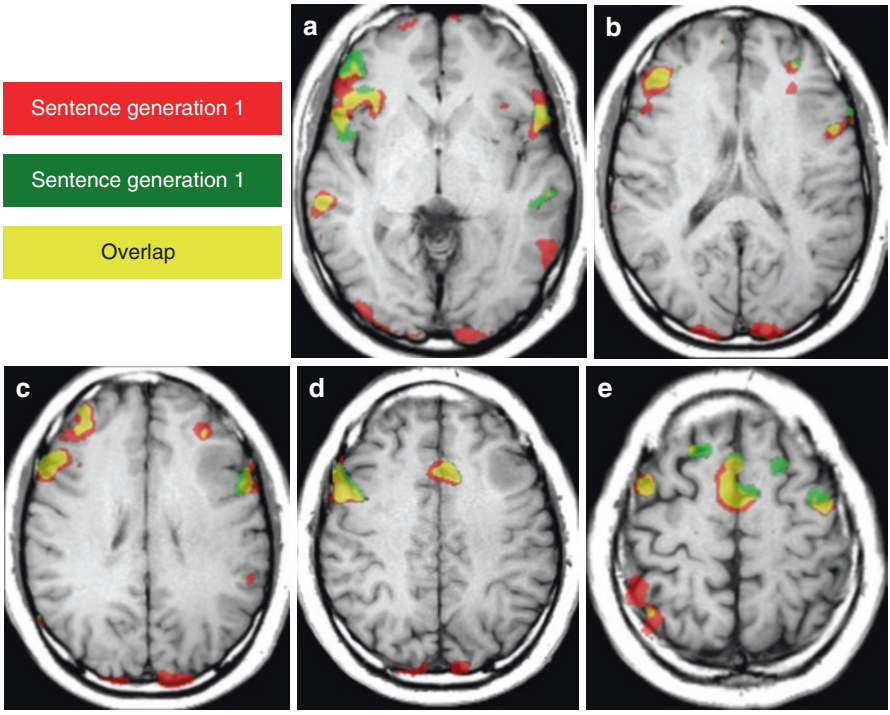


**Fig. 19.2 Language fMRI: Plasticity and reproducibility.** A low-grade glioma of the left middle frontal gyrus was revealed by seizure with speech impairment in a right-handed patient. Language fMRI using a covert sentence generation task repeated twice (activation maps using same statistical threshold are displayed in *red* (1st task), in *green* (2nd task); in *yellow* (*overlap*) shows reproducible anterior activations in both inferior frontal gyri (**a**, **b**), both middle frontal gyri (**c**–**e**), preSMA (**d**, **e**). Reproducible posterior activation was detected in the posterior part of the right superior temporal sulcus (**a**). The examination shows a *right*-hemisphere predominance for language with an activation of the left middle frontal gyrus close to the posterior-inferior aspect of the tumor. A complete tumoral resection was obtained with awake surgery and intraoperative electrostimulation mapping. No speech impairment was reported during and after surgery

In fact, ESM and numerous observations suggested that language organization was more complex, advocating for the necessity to update the classical model. Indeed, a dual stream of language is now proposed [34]. Inspired by the dual stream processing in the vision system, language system would rely on a dorsal stream for sensorimotor integration in the dominant hemisphere, and on a ventral stream for speech comprehension rather bilateral. Both streams would process neural inputs from sensory integration given by the Wernicke's area. The ventral stream would involve the ventral and anterior parts of both temporal lobes to perform speech recognition and representation of lexical concepts. The dorsal stream would consist in two pathways involved in driving phonological information to articulatory motor representations. The posterior part of the inferior and middle frontal gyri and the perisylvian temporo-parietal area would have a hemispheric predominance, left-sided in most cases [34].

Such a broader distribution of the language network is also supported by fMRI that provides multiple activation foci. In clinical practice, a set of block-designed paradigms is recommended to better identify anterior and posterior activation. This set may consist in sentence completion, word generation, speech comprehension [29, 30, 35, 36]. However, numerous discrepancies with ESM were reported [34, 37–39]. ESM remains the gold standard method using various tasks such as spontaneous speech, picture naming, and counting. As an alternative method, language fMRI mapping was obtained using several tasks involving speech production and comprehension. Language fMRI sensitivity ranged from 37 to 100% and specificity from 60 to 100%. fMRI false-negative rate, that decreased sensitivity and may lead to permanent deficit, would rather be associated with high-grade gliomas in line with data collected from motor tasks [40]. fMRI false-positive rate, that decreased specificity and may lead to an incomplete resection, would rather be associated with low-grade gliomas [38]. These differences might be explained by differences between covert tasks commonly used in fMRI to avoid head movement and overt tasks used in ESM, and by difference in spatial selectivity and functional sensitivity of each technique.

As a consequence of these considerations, fMRI results in language preoperative mapping remain questionable regarding presurgical goals with the needs to provide exhaustive mapping of critical areas, including spatial delineation with tumoral margins. Indeed, the variability of the fMRI maps remains significant despite of methodological attempts of standardization, cortical mapping does not provide information of essential subcortical structures to be preserved during surgery, fMRI is hardly able to distinguish critical areas from less essential areas regarding functional prognosis and oncological achievement.

In practice, fMRI of language system remains often limited to determine hemispheric dominance based on the sums of left and right-sided clusters that allow to calculate the laterality index, a way use to match the binary representation of language based on WADA test. This simplification barely reflects the multiple cortical involvement detected by fMRI using various tasks. Despite limitations, confrontations between fMRI and ESM will provide further insights in language processing.

### *19.2.5 Key Points in fMRI Interpretation*

Despite recent works using advanced imaging techniques; numerous limitations maintain BOLD fMRI far from being able to map directly neural activity in clinical practice. Besides reserves on the physiological basis of the BOLD signal and the cognitive subtraction approach, imaging resolutions are far out of the neural scales. Indeed, a standard voxel of 55 $mm^3$ (3–5 mm in each dimension) contains 5.5 million neurons, 2.2–5.5 × $10^{10}$ synapses, 22 km of dendrites, and 220 km of axons Additionally, a spatial smoothing twice larger than the voxel size is commonly applied [2]. The temporal resolution of 2–3 s is also far from having the neural millisecond scale, and multiple repetitions must be performed and averaged over time to reach a sufficient contrast between cognitive conditions.

Before addressing the most common issues in clinical fMRI interpretation, expected results and potential methodological and physiological confounds should be clear in mind. The whole procedure of data acquisition and analysis must be tested and validated prior to start clinical practice.

#### 19.2.5.1 Image Quality

Functional MRI is an imaging technique. Checking image quality sounds trivial. Contrary to conventional MRI, checking for the quality of the whole dataset is hard to perform in clinical practice. Indeed, a standard fMRI examination may, for instance, include 4 tasks acquired in 4 separate sessions of 100 volumes containing 40 slices, giving a total of 16,000 images to screen for artifacts.

Magnetic susceptibility artifacts mostly due to hemorrhage, calcifications, metal, and previous surgical procedures are common in neuro-oncology [41]. Beside these lesion-related artifacts, constitutional magnetic susceptibility artifacts due to important signal changes between air, bone, and tissue are detected near the skull base. Thus, fMRI of orbito-frontal, temporo-polar, and temporo-basal regions is difficult to perform using GRE-T2*. Such artifacts could be reduced using spin-echo T2-weighted images [42].

When present, these artifacts might be responsible of both false negative and false positive results. On the one hand, no reliable BOLD signal changes related to the activation paradigm can be extracted within a steady and homogeneous “black hole”. On the other hand, false activations are commonly observed on the margins of these artifacts due to subtle movements synchronous to the paradigm.

Recent advances in MR processing with real-time fMRI packages offer online reconstruction, to display native images and to superimpose activation maps. In such situation, it provides a better comprehension of the results during the examination, instead of suggesting another cause of abnormal results such as abnormal performance or movement that would require performing the task again.

#### 19.2.5.2 Image Position

In clinical practice, statistical maps calculated using BOLD images are usually overlaid onto an anatomical image to better depict the spatial relationships of the activations with the surrounding sulci or a lesion. To be valid, the superimposition is performed between datasets with similar geometric parameters or using software able to interpret potential change of position, angle and dimensions across volumes, appropriately. Coregistration can be easily checked by superimposing BOLD native images onto the anatomical image. Right-left orientation has also to be carefully checked. When necessary, manual coregistration must be conducted. Despite extensive care for spatial coregistration, a brain shift might occur during surgery and the removal of a space-occupying lesion. Thus, intraoperative fMRI has been proposed in addition to shift simulation implemented within the navigation system [43].

#### 19.2.5.3 Individual Performance

As other functional neuroimaging techniques, poor performance is a trivial cause of poor results. Indeed, the assessment of task-related neural activity relies on the appropriate perception of the stimuli and the execution of the task when required. The attention has also to be controlled across conditions and sessions. Indeed attention and fatigue modulate BOLD contrast [44]. Overly long paradigm should be avoided. In patients, experimental setup and design must be simple and feasible, limiting fatigue, task difficulty and speed. Thus, preliminary tests are necessary to estimate the appropriateness and the feasibility of the tasks.

Before fMRI, a full explanation of the tasks and of the fMRI time course must be given and sufficient training must be performed. During the examination, instructions ought to be re-explained and repeated before each run. A dedicated software is useful to send stimuli at specific onsets. Tasks execution should be monitored, at least visually for motor tasks. However, changes in force, amplitude, frequency, or preparation of the movement influence the results. In cognitive tasks, behavioral data can be recorded, using dedicated device to obtain specific answers. To study the hemispheric dominance for language, production tasks are robust and simple. Covert tasks are usually conducted because overt paradigms increase task-related movements and their control "non-language" condition is difficult to perform overtly. However, monitoring a covert task is particularly difficult. Again, real-time analyses are useful to estimate results, to repeat a task when necessary, and for positive reinforcement. To better estimate the relationship between the task execution and signal changes, recorded performances can be tested as a statistical regressor.

#### 19.2.5.4 Movements

Because of the brief duration of each image acquisition (<100 ms), movements artifacts within the image are unlikely. However in awake subjects, subtle movements are always identified across images along time. The motion amplitude and its

spatial coherence and synchrony with the paradigm may be responsible of significant signal changes [45]. In case of movements, most important signal changes are commonly detected along the parenchymal borders in voxels containing both brain tissue and cerebrospinal fluid. When these changes are synchronous with the task execution, long strips of false-positive activation are detected along the margins of the brain and ventricles. The borders of foci of magnetic susceptibility, such as hemorrhage or calcification with voxels containing both deep hypointensity and parenchymal hyperintensity, might also be associated with peripheral false-positive activation.

To minimize motion, subject must feel comfortable with the head maintained within the coil by adapted cushions. Paradigms must be tested to avoid excessive task-related movements and the overall duration of fMRI must be limited. Again, preliminary evaluation, explanation, training, dialog, and real-time analyses are precious to avoid excessive motion. After image acquisition, motion correction could be performed using spatial realignment. Statistical analyses might also estimate the confounding effect of head motion.

#### 19.2.5.5 Physiological Confounds

As previously mentioned, BOLD contrast relies on task-related changes in neural activity, perfusion, and blood oxygenation. This complex mechanism is modulated by basal conditions and physiological properties such as resting neural activity, oxygenation, neurovascular coupling, perfusion, and vasomotricity. Age, medication, pathology, capnia, nicotine or caffeine influence BOLD contrast [1, 5, 15, 46, 47]. These confounds need to be controlled in comparative studies across populations. Individually, brain lesions may influence locally BOLD contrast and may lead to inappropriate interpretation [1, 40, 48–57]. For instance, the vicinity of a tumor decreases adjacent activation even for a distance greater than 10 mm [40, 51, 53, 54, 57]. In preoperative fMRI, BOLD signal is impaired in patients with higher grade gliomas and meningiomas [40, 48, 50, 53, 54, 56]. However, inconstant impairment was reported close to low grade gliomas [40, 58].

As BOLD contrast impairment might underestimate the local neural activity, discordance in language lateralization has been reported when compared to the Wada test [44, 55, 57]. In fact, interhemispheric comparisons are flawed when unilateral lesion or vascular impairment is detected. In such cases, BOLD contrast should be at least tested [40, 52, 59, 60].

Besides oxygenation disorders near brain lesions, impaired vasomotor responses have been previously proposed to explain BOLD discrepancies [46, 47]. Schematically, pathophysiological alterations might be secondary to changes in: (1) the functional mechanisms that link a specific stimulus and a vasomotor response (neurovascular coupling in response to neural activity, vasoreactivity to circulating gases, and autoregulation to perfusion pressure); and (2) the quality of the hemodynamic responses that might be affected by loco-regional changes in basal perfusion and structural abnormalities of the vasculature.

A hemodynamic hypothesis would be supported by regional perfusion changes either due to the lesional vascularization, or to structural alterations of the surrounding brain vessels. In line with experimental data in healthy subjects showing that BOLD signal may decrease as CBV increases [5], local changes in basal perfusion have been advocated to explain BOLD contrast variations in patients with tumor [40, 51, 54, 58].

In brain-lesioned patients, quantitative fMRI using the calibrated-BOLD method seems to be a promising technique to better estimate the underlying neural activity. However, this method remains difficult to conduct in clinical practice. An alternative could be to estimate the quality of the BOLD contrast using hypercapnic challenge [40, 61]. Indeed, imaging of cerebral vascular reactivity (CVR) to CO2 change using BOLD signal has been tested, especially in patients with vascular disorders and false negative fMRI results [40, 60]. This approach provides BOLD maps that overlap 95% of the functional activation. In patients with stroke and tumors, regional asymmetries in eloquent areas detected on CVR maps were the best predictors for impaired motor activation [40, 52].

As BOLD fMRI aggregates evoked blood oxygenation and functional changes in brain perfusion, fMRI interpretation might remain difficult, especially in case of focal lesions that modify these parameters. Multimodal advanced imaging, including DTI to better detect peritumoral infiltration and edema, perfusion study with permeability and vessel size imaging, functional imaging of the perfusion using arterial spin labeling during vasomotor challenge, oxygenation imaging using MRI or NIRS, could be proposed to better interpret fMRI data in patients, and to better understand structural and functional changes near brain lesions.

### *19.2.6 Conclusions on Task-Based fMRI*

BOLD fMRI is regularly performed in clinical practice to map cortical activity of functional areas at risk of deficit before surgical resection of low grade gliomas. This technique relies on a solid biophysical framework. However, fMRI provides indirect evidence of cortical activity. Indeed, BOLD signals reveals tasks-related changes in oxygenation and perfusion. Interpretation must consider several constraints. As any imaging technique, the quality of native images must be sufficient to detect signal changes. Artifacts are common close to the skull base in the frontal and temporal regions, and in case of calcification and hemorrhage before and after surgery of brain tumors. The spatial and temporal resolutions of BOLD fMRI is far out of the range of neural scales. Activation foci with a centimetric interval of confidence should be considered. Repetition of simple tasks with a conditional approach is mandatory to reach significant and reliable signal changes, limiting fMRI to a non-ecologic investigation of brain activity. As any functional imaging technique, stimuli perception and tasks execution must be monitored. Real-time fMRI is helpful to provide immediate maps and to estimate overall quality check. Finally, changes in basal perfusion and in perfusion properties should be identified

especially when false negative results are suspected close to the lesion. Considering rigorous quality check, well-known methodological and technical limitations, BOLD fMRI may remain useful for treatment strategy and presurgical planning.

## 19.3 Resting-State fMRI in DLGG

### *19.3.1 An Introduction to Resting-State fMRI*

As mentioned above, most of functional neuroimaging studies focus on brain's response to a task or stimulus. However, the majority of brain's energy consumption arises from its activity at rest (95%) [62]. Spontaneous BOLD signal low frequency fluctuations are thought to arise from that baseline activity. Resting-state fMRI (RS-fMRI) focuses on spontaneous low frequency fluctuations (about 0.1 Hz) in the BOLD signal. An analysis of the frequency spectrum of RS-fMRI data demonstrated that low frequency fluctuations (defined as <0.1 Hz) contributed to more than 90% of the correlation coefficient between regions of the same resting-state network [63].

The functional significance of these fluctuations was first presented by Biswal et al. [64]. In this study, subjects were told not to perform any task. The authors identified a seed region in the left somatosensory cortex on the basis of block design fMRI. After determining the correlation between the BOLD time course of the seed region and that of all other areas in the brain, the authors found that the left somatosensory cortex was highly correlated with homologous areas in the contralateral hemisphere. The existence of synchronous spontaneous fluctuations between primary somatosensory and higher order areas was further confirmed by later studies [65, 66].

Several distinct networks have been identified at rest using BOLD signal temporal correlations defined as resting state networks (RSN). One of the most consistent RSN is the default mode network (DMN) [67], first identified from positron emission tomography (PET) data by Raichle et al. In this study, the authors found that consistent regions of the brain were activated at rest but decreased their activity when cognitive tasks were performed. Greicius et al. [68] identified the DMN using fMRI. Further studies have hypothesized that there are two opposing systems in the brain, one including the DMN and the other composed of attentional or task-based systems [69]. Those two systems have an anti-correlated functional connectivity.

Several other RSNs have been identified. The somatosensory network, studied first by Biswal et al., [64] includes primary and higher order motor as well as sensory areas. The visual network is highly consistent across various studies and spans much of the occipital cortex [63, 70]. An auditory network consisting of the Heschl gyrus, the superior temporal gyrus, and the posterior insula has been identified [66]. A language network that includes the so-called Broca's area and Wernicke's area,

but also that extends to prefrontal, temporal, parietal, and subcortical regions, has been described by using RS-fMRI [71].

RSNs involved in attentional modulation and cognitive control have also been identified. Two networks identified by using both RS-fMRI and task-based fMRI include the dorsal and ventral attention networks [72]. The dorsal attention network includes the intraparietal sulcus and the frontal eye field and is involved in the executive control of attention. The ventral attention network, which includes the temporoparietal junction and ventral frontal cortex, is involved in the detection of salient cues (those that stand out from their environment) [72]. The frontoparietal control network, which includes the lateral prefrontal cortex and the inferior parietal lobule, is thought to be involved in decision-making processes [73].

### *19.3.2 Reliability of RS-fMRI*

FMRI appears to be the ideal neuroimaging technique for the investigation of resting-state network characteristics. The spatial resolution is superior to other methodologies such as electroencephalography and magnetoencephalography, allowing for localization and separation of the various resting-state networks simultaneously. Significant correlations between variations in the power of electrophysiological activity in higher frequency bands (e.g. alpha and beta) and RS-fMRI signals have been demonstrated [74].

One weakness of RS-fMRI lies in an important difference between the analysis of spontaneous fluctuations and more traditional studies of task-evoked BOLD responses. In the latter, the timing and intensity of the task is known a priori and the responses of many trials are combined together to eliminate noise and to increase statistical significance [4, 75]. However, in RS-fMRI, functional connectivity is determined by measuring the temporal similarity of the BOLD time series in voxels using some metric, commonly the correlation coefficient. For example, in the original Biswal paper [64], voxels whose correlation coefficient passed a statistical threshold were deemed to be functionally connected, thus revealing common spontaneous fluctuations between left and right motor cortices. Since the two time series are measured simultaneously, any non-neural activity-related process that affects one or both time series will affect the measure of functional connectivity, thus yielding a spurious result. These RS-fMRI confounds can not only increase the apparent functional connectivity by introducing spurious similarities between the time series but they can also reduce the connectivity metric if differential confounds between regions are introduced. RS-fMRI confounds encompass the following physiological parameters: motion, cardiac and respiratory physiological noise, arterial $CO_2$ concentration, blood pressure, cerebral autoregulation and vasomotion [76]. In order to control those physiological confounds one can use two different RS-fMRI cleanup techniques: those utilizing external recordings of physiology and data-based cleanup methods that only use the RS-fMRI data itself [76].

Important issues to consider with regard to RS-fMRI are the test-retest reproducibility and inter-subject variability. Studies suggest that RSNs can be detected reliably across imaging sessions [77] and across different subjects [78] though there may be some loci of variability between subjects [79].

### *19.3.3 Functional Connectivity Maps: Technical Aspects*

The simplest technique is to extract the BOLD time course from a region of interest (called a seed region) and determine the temporal correlation between this extracted signal and the time course from all other brain voxels. This approach is widely used owing to its inherent simplicity, sensitivity and ease of interpretation [64]. However, it has some disadvantages. The results are dependent on the a priori definition of a seed region, multiple systems cannot be studied simultaneously and the extracted waveform may not be a true independent variable when assessing statistical significance. In response to these limitations other more sophisticated techniques for analyzing spontaneous BOLD data have been proposed.

Hierarchical clustering still requires a priori definition of seed regions [80]. However, instead of extracting the time course from just one seed region, the time courses from many seed regions are obtained and a correlation matrix is constructed. A clustering algorithm is then used to determine which regions are most closely related and which regions are more distantly related. This technique is useful to visualize the interaction between a large number of regions.

Independent component analysis (ICA) is perhaps the second most popular technique for analyzing spontaneous BOLD data [65]. This approach does not require a priori definition of seed regions. Instead, sophisticated algorithms analyze the entire BOLD data set and decompose it into components that are maximally independent in a statistical sense. Each component is associated with a spatial map. Some maps reflect noise components whereas others reflect neuro-anatomical systems. Because this technique is data driven and automatically isolates sources of noise, it holds tremendous promise and its use is increasing. However, there are still several challenges. First, results are highly dependent on the number of components one asks the algorithm to produce. Second, the user must determine which components reflect noise and which components look like neuro-anatomical systems, introducing a priori criteria for system selection.

### *19.3.4 Resting State fMRI and Low Grade Glioma Surgical Planning*

The use of resting state fMRI for the evaluation of spontaneous fluctuations in the BOLD signal has several benefits over traditional task-based fMRI. One important advantage of this method is that it can be performed even when the patient is unable

to cooperate with the functional task. This will enable us to perform fMRI mapping on many populations previously excluded from traditional task-based techniques such as young children, patients with cognitive impairments, and patients that are paralyzed, aphasic, or hard of hearing. Spontaneous fluctuations have been shown to persist under conditions of sleep [81] and different levels of anesthesia [82], thus a second advantage of this technique is that is can be performed in agitated patients and in young children under sedation. A third advantage is that one data acquisition can be used to study many different brain networks, thus possibly reducing the acquisition time when many systems are evaluated. This is in contrast to task activations which require dedicated data acquisitions for each function one is attempting to localize.

Practical and theoretical attractive aspects of RS-fMRI have resulted in several recent researches on its potential applications in surgical planning. Various approaches, either data driven [83, 84], parcellation [85, 86], or seed-based approaches [87, 88] have been used to map sensorimotor and/or language resting state networks and to compare it to intraoperative stimulation mappings results. Results from those studies suggest that sensorimotor networks identified with RS-fMRI are somehow comparable on the individual scale to the networks identified during surgery [84, 86–88] (see Fig. 19.3 for an illustrative case of intraoperative cortical stimulation compared with preoperative RSN). This supports the assumption that resting state networks correspond to functional networks involved in task performance [83]. However the interindividual variability of RS-fMRI accuracy in surgical planning is a matter of concern for clinical practice. To date, detection of resting state networks from data driven techniques, which are very attractive in a preoperative perspective because they don't require any a priori, depends on the

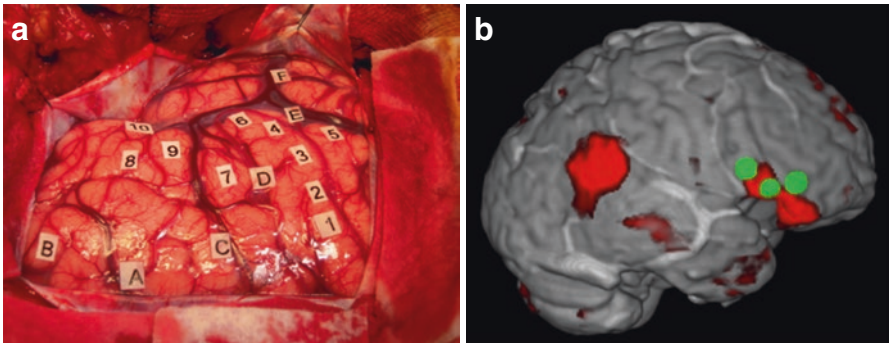


**Fig. 19.3** Illustrative case of eloquent language areas defined by stimulation mapping and RSN overlapping (**a**) Intraoperative photograph of a 40 year-old left-handed female's brain before resection. Tags n°7,8 and 9 elicited anomia during stimulation mapping. Tags n°1–6 elicited motor disorders when stimulated. Tag n°10 elicited mentalizing disturbances errors electrical stimulation. Lettered tags represent tumor boundaries defined using intraoperative ultrasound imaging. (**b**) Surface rendering of the patient's brain with language stimulation points represented with *green* 5 mm radius spheres. Language RSN extracted from an independent component analysis is represented in *red*

methodology employed in order to detect networks of interest. Sensorimotor network identification seems more robust than networks supporting higher order cognitive functions such as language. One explanation of that phenomenon is that functional connectivity within associative regions, including the main nodes of language, executive, and attention networks, are likely to be more variable than those within unimodal regions, such as visual and sensorimotor structures [89, 90]. Another limitation is the more difficult detection of language network from multiple components compared to sensorimotor network that is more easily delineated.

### *19.3.5 Additional Perspectives in the Use of Resting State Connectivity in Glioma Patients*

Studies in diffuse low grade glioma patients reported cognitive dysfunction in multiple domains (e.g., reduction of attention capacity, mood disorders as depression, or working memory problems), which is not easily attributable to local injury, thus suggesting a global impairment of neural networks induced by tumors [91, 92]. Hence some authors established correlations between changes in functional connectivity at rest and neuropsychological performances in glioma patients [93, 94]. Resting state networks connectivity changes could be used as a biomarker to determine patient's specific functional prognosis. Longitudinal follow-up using RS-fMRI could bring in the future valuable information on resting state networks reshaping after DLGG surgery along with recovery from neuropsychological deficits.

Recent studies established a correlation between decreased functional connectivity within the default mode network and WHO glioma grade, with a more impaired functional connectivity in higher grades [95–97]. The rapid growth of high grade gliomas compared to the slow evolution of low grade gliomas could explain that difference. Indeed, the huge plastic potential of the brain in low grade gliomas is obtained thanks to the slow evolution of those lesions, contrasting with the poor plasticity observed in acute lesions [98]. A higher functional connectivity within the default mode network might be correlated with a higher degree of plasticity.

### *19.3.6 Conclusion on RS-fMRI and Low Grade Glioma*

RS-fMRI is a very promising technique that could be used in a large range of clinical conditions especially in low grade glioma surgery. For example, it can be applied to patients with severe neurological deficits, as with a transient supplementary motor area syndrome [99], or altered states of consciousness, in order to investigate the functional connectivity changes when the patients experience such deficits. In addition, multiple functional networks are explored in a single short session

providing a complete overview of the whole cortical functional organization. It opens the door to new perspectives in terms of preoperative planning, functional evaluation, tumor grading and neurological/neuropsychological performance prognosis evaluation. *However, it should be underlined that, before using RS-fMRI in clinical practice, particularly for surgical planning, more validation studies are needed.*

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# Chapter 20
# Diffusion Magnetic Resonance Imaging in Diffuse Low-Grade Gliomas

**Sonia Pujol**

**Abstract** Diffusion MRI is the first non-invasive window on the organization of the human brain white matter. By linking the direction of diffusion of water molecules in the brain with the local orientation of white matter fibers, the technique has enabled *in vivo* exploration of the architecture of white matter pathways at the individual patient scale. Such a non-invasive brain mapping tool is of special interest in the management of diffuse low-grade gliomas (DLGG) which are invasive lesions that migrate along white matter fibers. In particular, diffusion MRI tractography techniques enable three-dimensional visualization of the spatial relationship of the tumor with white matter structures associated with sensorimotor, language, and visual function. White matter mapping could help neurosurgeons characterize tumor invasion and maximize the extent of resection while preserving fibers associated with critical function. However, the complexity of diffusion MRI data and the challenges inherent to the validation of the anatomical accuracy of tractography reconstruction remain barriers to the use of the technology as a standalone tool for neurosurgical decision-making. Multidisciplinary efforts that bring together neurosurgeons, neuroradiologists, neuroanatomists, and neuroimaging scientists are needed to lower this barrier so that the development and application of innovative diffusion MRI acquisition sequences and post-processing tools can become part of the brain mapping apparatus for the treatment and monitoring of DLGG. This chapter covers the basics of diffusion MRI analysis, and introduces the current performances and challenges of using the technique for the neurosurgical treatment of DLGG.

**Keywords** Diffusion magnetic resonance imaging • Tractography • Diffuse low-grade gliomas • White matter fibers

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## 20.1 Part 1: Basics of Diffusion MRI

### *20.1.1 Probing Brain Microstructure with Water Molecules*

Diffusion Magnetic Resonance Imaging (dMRI) provides a unique access to the neuroanatomy of the human brain at the individual patient scale. The technique uses magnetic field gradients to sensitize the MR signal to the random motion of water molecules in tissues [1]. The Brownian motion, which corresponds to the random movement of particles in a fluid, was first observed in 1827 by the botanist Robert Brown while looking under a microscope at pollen grains suspended in water. In 1905, Albert Einstein demonstrated that the observed phenomenon was the result of the collisions of the particles with individual water molecules in constant random thermal motion. In his seminal paper on the theory of the Brownian motion, Einstein linked the mean square displacement $<r^2>$ of a large number of particles from their starting point over a time $t$ to the diffusion coefficient $D$ of the suspended substance through the equation:

$$\left\langle \mathrm{r}^2\left(\mathrm{t}\right)\right\rangle = 6Dt \tag{20.1}$$

In this formalism, the distribution of square displacements of free water molecules is Gaussian, with the probability of displacing at a given distance from the origin being the same, independent of the direction in which it is measured. In biological tissues the diffusion of water molecules is hindered by intracellular and extracellular microstructures, such as cell membranes, myelin sheets and organelles. Thus, the mean square displacement per unit time is lower than in free water, and the distribution of molecular displacements deviates from the Gaussian law described in Einstein's equation. The apparent diffusion coefficient (ADC) was introduced to describe this deviation, and take into account the interaction of water molecules with the microstructures that restrict or hinder diffusion [2]. The calculation of ADC values in different brain tissues provides an indirect characterization of the underlying architecture of the brain at the microscopic level.

### *20.1.2 Measuring Diffusion Properties of Brain Tissue with MRI*

Diffusion MRI combines the physics of diffusion and the physics of MRI to enable the measurement of the displacement of water molecules in the brain. The spin echo effect discovered by Rewin Hanhn in 1950 and the subsequent mathematical and physical framework introduced by Carr and Purcell in 1954 opened up the possibility of measuring the diffusion coefficient of spin-labeled molecules. A few years

later, Stejskal and Tanner introduced the pulsed gradient spin echo (PGSE) sequence based on the addition of a pair of bipolar magnetic field gradients to a spin echo sequence, to sensitize the MR signal to the diffusion of water molecules [173]. In this formalism, the diffusion coefficient $D$ in a given direction $\hat{k}$ can be measured using two MR acquisitions: a diffusion-weighted acquisition with a pair of diffusion-encoding gradients oriented in the direction $\hat{k}$ and a baseline acquisition with the diffusion-encoding gradients set to zero. The signal intensity attenuation $S_k$ resulting from the application of the diffusion-encoding gradients is given by the equation:

$$S_k = S_o \exp\left[-bD\right] \tag{20.2}$$

where $S_0$ is the signal intensity of the baseline acquisition, $b$ is the diffusion-weighting factor, and $D$ is the diffusion coefficient. The diffusion-weighting factor, or so-called *b-value,* is calculated based on the amplitude of the magnetic field gradient pulses $G$, their duration $\delta$ and temporal separation $\Delta$, and the gyromagnetic ratio of hydrogen $\gamma$:

$$b = -\gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3}\right) \tag{20.3}$$

From Eq. (20.2), the apparent diffusion coefficient in the encoding direction $\hat{k}$ is expressed as:

$$ADC = -\frac{1}{b} \ln\left(\frac{S_k}{S_0}\right) \tag{20.4}$$

Since ADC values depend on the direction $\hat{k}$, diffusion-weighted imaging data are usually acquired sequentially using three or more orthogonal diffusion-encoding gradient directions and the measurements are averaged to obtain mean ADC values at each voxel.

In neuro-oncology imaging, ADC maps can be used to investigate pathological changes and monitor treatment [3]. The quantitative information provided by ADC maps can be complementary to invasive histopathology of tissue biopsy samples, which is the current gold standard for distinguishing among gliomas subtypes. However, ADC measurements cannot be used to diagnose a particular tumor due to the overlap between the tumor-specific ranges of diffusion values [4]. During treatment monitoring, the evaluation of changes in tumor ADC values before and after initiation of chemotherapy and radiation therapy has been investigated as a potential indicator of early tumor response [5, 6]. Such non-invasive quantitative imaging biomarker could aid physicians individualize treatment, minimize unnecessary systemic toxicity associated with ineffective therapies, and gain precious time [7, 8].

### 20.1.3 Quality Control of Diffusion MRI Data

Diffusion MRI pulse sequences use long and strong diffusion-encoding gradients that make the acquisitions very sensitive to involuntary patient movement, respiratory motion, and cardiac pulsation. Motion-corrupted diffusion weighted imaging (DWI) datasets can present ghosting artifacts and heterogeneous misregistration errors. A second major source of artifacts arises from eddy currents induced by the rapid switching of the diffusion-encoding gradient pulses. Eddy currents generate local magnetic field gradients that get combined with the diffusion-encoding gradients and result in ghosting artifacts that can lead to misinterpretation of the DWI scans. Finally, Echo Planar Imaging (EPI) sequences, the most commonly used diffusion MRI sequences in the clinics, are very sensitive to inhomogeneities of the static magnetic field $B_0$. These inhomogeneities produce EPI geometric distortion that can be important at the interface between bones and air-filled cavities, such as the sinuses and the auditory canal, as well as at the interface between brain tissues and air during intra-operative MRI acquisition.

Numerous techniques exist to prevent the apparition of image artifacts during the acquisition of DWI scans. These techniques include cardiac gating and head holders for motion-related artifacts, self-shielded gradient coils and proper calibration for eddy-current artifacts, as well as maps of the static magnetic fields and blip-up blip-down acquisitions for EPI distortion [9, 10]. Once a DWI scan is acquired, quality control of the raw images is an essential step before starting any post-processing pipeline. While visual inspection of each diffusion-weighted image can provide a quick detection of acquisition artifacts, the process is time-consuming and operator-dependent. In addition, image misalignment caused by patient motion across scans can be difficult to detect [11]. To overcome these limitations, several tools for quality control and automated artifacts correction of DWI data have been developed by the diffusion MRI research community. Most of these tools are available as open-source software packages, and provide useful resources to minimize the impact of artifacts encountered during clinical diffusion MRI acquisition [9, 12–14].

### 20.1.4 Diffusion Tensor Imaging

The diffusion of water molecules in the brain is sensitive to the underlying tissue microstructures [1]. In gray matter and cerebrospinal fluid, the displacement of water molecules is identical in all directions and the diffusion is isotropic. In white matter fibers, as myelin sheets and axonal membranes act as barriers, the displacement of water molecules is less hindered in the direction parallel to the fibers than in the direction perpendicular to their axis, and thus the diffusion is anisotropic [15]. Diffusion Tensor Imaging (DTI) was the first mathematical framework introduced

to model the anisotropic diffusion of water molecules in the brain [174]. In the tensor model, the signal attenuation $S_k$ resulting from the application of the diffusion-encoding gradient in the direction $\hat{k}$ is expressed at each voxel as:

$$S_k = S_0 \; e^{-b\hat{g}_k^t \mathbf{D}\hat{g}_k} \tag{20.5}$$

where $S_0$ is the signal intensity of the baseline acquisition, $b$ is the diffusion-weighting factor, $\boldsymbol{D}$ is the diffusion tensor and $\hat{g}_k$ is the unit vector describing the diffusion-encoding direction $\hat{k}$. The diffusion tensor $\boldsymbol{D}$ is a 3 × 3 symmetric matrix defined by six elements. Thus, a minimum of six diffusion-weighted acquisitions with six diffusion-encoding gradients oriented in non-colinear and non-coplanar directions is necessary to compute the tensor elements at each voxel. The diffusion tensor is then diagonalized to compute the three principal directions ($\hat{e}_1, \hat{e}_2, \hat{e}_3$), called eigenvectors, and the three diffusion coefficients ($\lambda_1, \lambda_2, \lambda_3$), called eigenvalues. The eigenvalues correspond to the apparent diffusivities along the eigenvectors, and the eigenvector associated with the largest eigenvalue corresponds to the direction of maximum diffusion. The eigenvectors and eigenvalues are rotationally independent, thereby DTI volumes are intrinsic to the brain structures being imaged, and are independent of both the orientation of the diffusion-encoding gradients used for the acquisition and the orientation of the patient in the MR scanner coordinate system.

Diffusion tensors can be represented using small graphical objects called glyphs in the shape of an ellipsoid. The diffusion tensor ellipsoid represents the isoprobability surface where a molecule of water placed at its center will diffuse [16, 17]. The axes of the diffusion tensor ellipsoid correspond to the eigenvectors and the length of the axes are proportional to the square root of the eigenvalues. The shape of the ellipsoid provides an intuitive visualization of the diffusion properties of different tissues: in anisotropic media, the diffusion tensor glyphs are either cigar-shaped or disk-shaped, while in isotropic media the glyphs are spherical. Color schemes were subsequently introduced to represent fiber direction from DTI data [18]. In directionally encoded color (DEC) images, white matter fibers oriented in the left-right direction appear red; fibers oriented in the anterior-posterior direction appear green; and fibers oriented in the superior-inferior direction appear blue. Through this representation, DEC maps derived from DTI data enable an intuitive identification of all major white matter association, commissural and projection pathways of the human brain.

In addition to the visual display of white matter fiber orientation, quantitative scalar parameters that measure different intrinsic features of anisotropic tissues can be computed from DTI data [17]. The most commonly used metrics are the mean diffusivity (MD), which is a measure of the amplitude of water diffusion, and the fractional anisotropy (FA), which quantifies the degree of anisotropy of diffusion, with values ranging between FA = 0.0 in isotropic media and FA = 1.0 in highly anisotropic tissue. Figure 20.1 shows an example of FA map, DEC map and diffusion tensor glyphs.

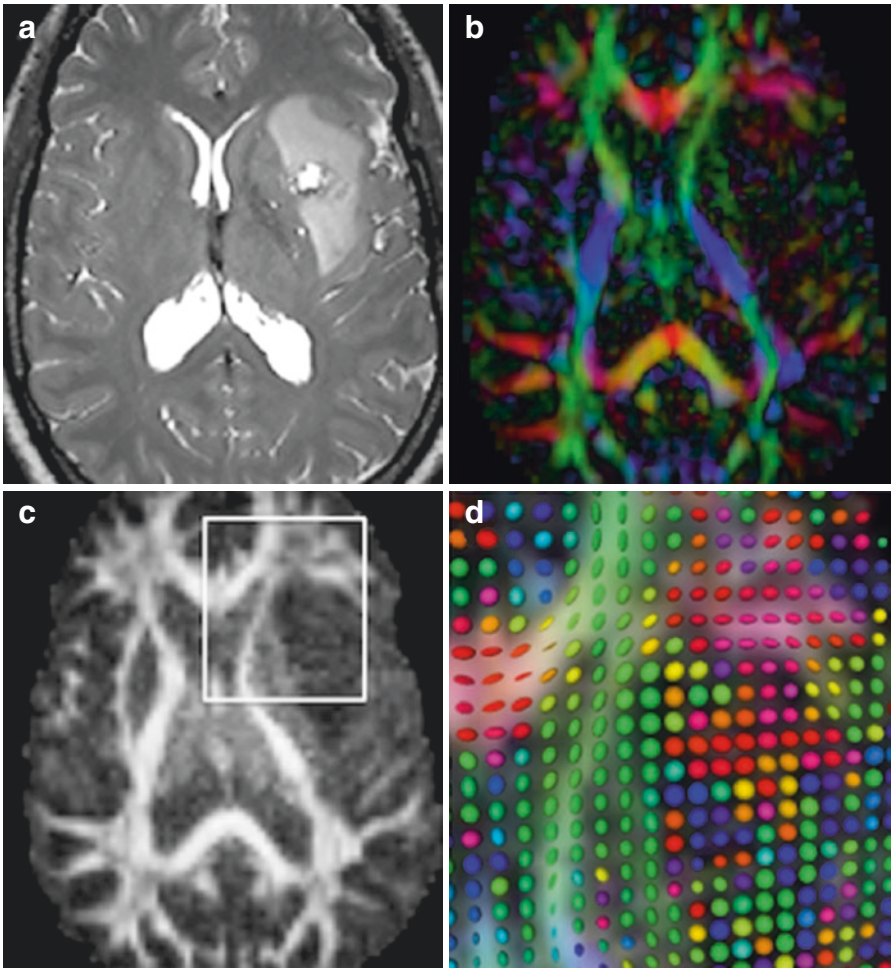


**Fig. 20.1** Pre-operative structural and diffusion MRI data in an astrocytoma grade II. (**a**) T2-weighted image; (**b**) Directionally encoded color (DEC) map; (**c**) Fractional Anisotropy (FA) map; (**d**) zoomed-in view of DTI glyphs superimposed on FA and DEC map. The view presented in (**d**) corresponds to the region of interest (*white*) outlined in (c).

Quantitative DTI data enable non-invasive evaluation of microstructural and physiological features of tissues [19]. Exploratory studies have investigated the use of DTI-derived metrics for the detection of peritumoral white matter infiltration in low-grade and high-grade gliomas [20–23] and the characterization of microstructural integrity in meningiomas and low-grade gliomas [24]. These preliminary findings suggest a potential role for quantitative DTI in the detection of tumor infiltration in regions that appear normal on conventional MR imaging, which could provide neurosurgeons clinically relevant information on tumor margins of

DLGG as tumor cells extend beyond radiological borders on FLAIR and T2-weighted images [25].

### *20.1.5 From DTI to HARDI: New Mathematical Models of Diffusion*

Diffusion Tensor Imaging provides an unprecedented opportunity to gain insights into the architecture of the human brain *in vivo*. While the tensor model provides a good estimate of fiber orientation in voxels where a single population of fibers exists, the model fails to characterize the diffusion in areas where fibers cross, bend, or fan. Modeling the diffusion of water in regions with complex fiber patterns is an active area of research, and numerous approaches have been developed in the past decade. These approaches can be broadly divided into two categories: model-based approaches and non-parametric algorithms [26].

Model-based approaches operate on a mathematical representation of the diffusion-weighted MR signal. Among these approaches are the multi-tensor models that represent the diffusion using a mixture of Gaussians, each representing a fiber population described by a single tensor model [26]. A constrained version of the multi-compartment model is the ball-and-stick model that decomposes the diffusion signal into an isotropic "ball" compartment and a number of completely anisotropic "stick" compartments [27]. Figure 20.2 shows examples of fiber crossings identified by the ball-and-stick model at the intersection between the pyramidal pathway and cerebellar tracts, and between the corona radiata and the superior longitudinal fasciculus. While the ball-and-stick model provides an elegant depiction of crossing fibers, the approach considers only a discrete set of fibers orientations and does not represent the orientation dispersion within the fiber bundles. The ball-and-rackets model was subsequently introduced to overcome this limitation and represent fanning geometries [28]. Other models such as the composite hindered and restricted model of diffusion (CHARMED) attempt at providing a physical description of the diffusion process in terms of hindered diffusion in the extra-axonal volume and restricted diffusion in the intra-axonal volume [29].

Non-parametric methods make no prior assumption on the molecular diffusion in a given voxel, and proceed by estimating the diffusion function directly. Such approaches include diffusion spectrum imaging (DSI) and q-ball imaging. DSI measures the diffusion function directly by sampling the diffusion signal on a three-dimensional Cartesian lattice [30]. In practice, DSI requires the acquisition of several hundred images and time-intensive sampling which are not compatible with clinical constraints. High angular resolution diffusion imaging (HARDI) sequences have been introduced as an alternative approach based on sampling in a spherical shell instead of a three-dimensional Cartesian volume [31]. The subsequent development of q-ball imaging, a model-independent reconstruction scheme for HARDI data, has enabled the depiction of fiber crossings both in deep white

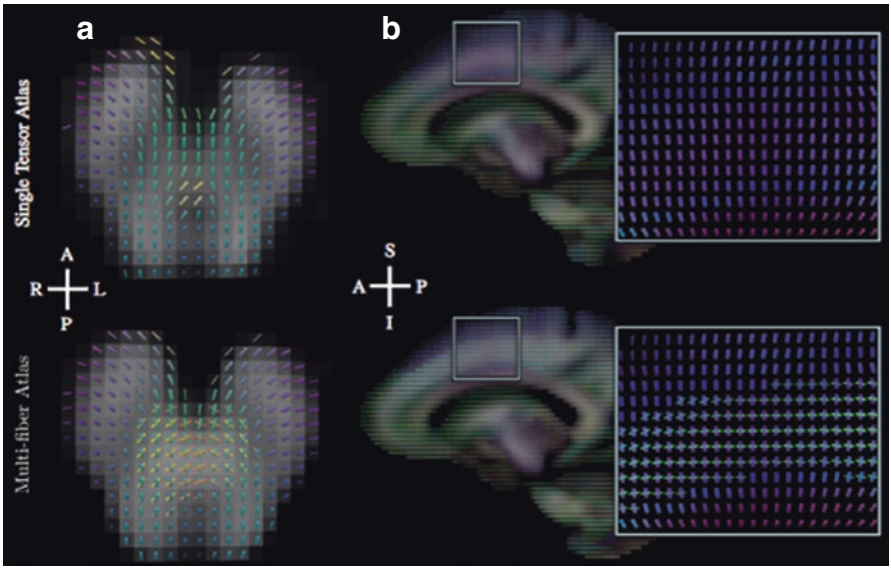


**Fig. 20.2** Single tensor and multi-tensor model of diffusion. The *top row* shows glyphs computed using a single tensor model. The *bottom row* shows ball-and-sticks glyphs computed using a multi-compartment model. The *left column* (**a**) shows an axial slice of the brainstem, demonstrating crossing fibers of cerebellar and pyramidal tracts. The *right column* (**b**) shows a sagittal slice demonstrating crossing fibers of the corona radiata and superior longitudinal fasciculus. (Source: [175])

matter pathways and at the subcortical margin [32]. Q-ball imaging computes a probability distribution on the sphere known as the diffusion orientation distribution function (dODF), and peaks in dODF are assumed to correspond to fiber orientations [32]. The computation of ODF initially performed using the Funk-Radon transform has been simplified using spherical harmonics [33]. Other approaches include spherical deconvolution methods that recover an estimate of the fiber orientation distribution function (fODF) [34], diffusion orientation transform (DOT) that calculates a variant of the dODF [35], and persistent angular structure MRI (PAS-MRI) that models the relative mobility of water molecules in each direction [36].

In addition to the multitude of sophisticated model-based methods and non-parametric algorithms for recovering multiple fiber orientations from diffusion-weighted images, novel approaches have recently been developed to estimate the microstructural complexity of dendrites and axons from clinical data. These approaches include neurite orientation dispersion and density imaging (NODDI) and multi-compartment microscopic diffusion imaging based on the spherical mean technique (SMT). NODDI use a tissue model that distinguishes three types of microstructural environment: intra-cellular, extra-cellular, and cerebrospinal fluid compartments [37, 38]. Multi-compartment microscopic diffusion imaging maps the neurite density and compartment-specific microscopic diffusivities unconfounded

by the effects of fiber crossings and orientation dispersion [39]. Such novel tools have the potential for providing new quantitative imaging biomarkers for the evaluation of complex tissues compositions associated with the progression of DLGG. A preliminary study on the feasibility of using multi-band diffusion weighted imaging data acquired at 7.0 Tesla to characterize gliomas has demonstrated the potential role of NODDI maps to provide a unique contrast within the tumor that is not visible in anatomical and DTI data [40].

### *20.1.6 Diffusion MRI Tractography Methods*

Diffusion MRI tractography provides a geometrical representation of the trajectory of white matter pathways in the human brain. The first tractography algorithms introduced in the late nineties reconstructed the trajectory of water molecules based on the assumption that the main eigenvector of the diffusion tensor is parallel to the principal fiber orientation at each voxel [42, 176]. Numerous fiber tracking techniques have since been developed and tractography algorithms can be divided into four categories: deterministic, probabilistic, global, and filtered. Deterministic tractography propagates a streamline until a termination criteria is reached. The initial fiber assignment by continuous tracking (FACT) algorithm uses a linear propagation approach [41]. Starting from a seed point, the technique consists in propagating a line by following the orientation of the main eigenvector of the diffusion tensor until a termination criteria based on an anisotropy threshold or a local tract curvature is reached [42]. The FACT approach has demonstrated anatomically faithful reconstructions of white matter pathways in voxels containing anisotropic fibrous tissues presenting with a single fiber orientation. However, in areas containing two or more distinct fiber populations, the diffusion tensor fails to accurately represent the orientation of the underlying white matter anatomy, leading to inaccurate tractography reconstructions. While the subsequent development of the tensor deflection (TEND) approach using the entire diffusion tensor has shown improved performance in fiber crossing regions, the algorithm underestimates the trajectory curvature for curved pathways [43]. In addition, both FACT and TEND algorithms propagate of a streamline based solely on the local diffusion information. Thus, a single error in the estimation of the principal direction of diffusion can propagate along the trajectory during the tracking process and lead to inaccurate tract reconstructions. The limitations of deterministic tractography algorithms have led to the development of probabilistic methods that introduced the notion of uncertainty in the tractography reconstructions [44].

Probabilistic tractography algorithms use the same tract tracing technique as deterministic methods, but propagate a large number of streamlines chosen from the distribution of possible fiber orientations from a given seed point. Each voxel is then assigned a probability that corresponds to the percentage of streamlines launched from the seed point that pass through that voxel [45–48]. Probability

maps provide useful information on the reproducibility of the tracking process, and give an indication of the level of confidence that can be assigned to the existence of a connection between two voxels given the data [27]. The combination of q-ball diffusion models and probabilistic fiber tracking has demonstrated improved sensitivity and predictive power to determine the course of white matter fibers when compared to deterministic approaches [49]. Building on whole-brain probabilistic tractography maps, super-resolution tract density imaging (TDI) can provide elegant depictions of white matter structures beyond the resolution of the diffusion weighted images [50]. However, probabilistic tractography images represent the percentage of tracts that reach a given voxel from the seed point, providing information on the repeatability of the tracking process, but not on the anatomical accuracy of identified pathways. As a result, probabilistic tractography results can be difficult to interpret since a reconstructed tract can be highly reproducible without being anatomically correct [51]. In addition, the choice of the threshold on the percentage of streamlines displayed to select between tract and non-tract voxels remains empirical and is a potential source of variability of the identified pathways.

Both deterministic and probabilistic tractography methods propagate streamlines by considering only directional information at the local level. Numerous ambiguities can occur in regions where multiple fiber populations cross, kiss, or bend, as well as in voxels close to grey matter or within tumoral tissue. Global tractography algorithms have been developed to overcome these limitations by solving a global energy minimization problem [52]. Global tractography methods aim at reconstructing the whole-brain fiber configuration that best explains the measured diffusion-weighted imaging data [53–56]. These sophisticated methods are gaining increasing popularity in the neuroscience community, but their long computation time and the difficulty in specifying prior knowledge criteria have hindered their rapid transfer to the clinics. Recent efforts to make global tractography more practical have demonstrated promising results for clinical applications [57]. Finally, novel filtered tractography algorithms have been introduced to simultaneously estimate a local fiber orientation and perform multi-fiber tractography [58]. These methods have been shown to reduce the diffusion model estimation error and improve the anatomical accuracy of the reconstructed tracts in complex fanning and branching fiber configurations [59]. Studies using a two-tensor filtered tractography technique have demonstrated the feasibility of reconstructing white matter pathways in peritumoral edematous regions [60].

The wide range and diversity of diffusion models and tractography methods developed by the medical image computing community in the last two decades represent a wealth of technical resources to advance knowledge on the architecture of white matter. The path of scientific discovery is likely to be accelerated through neuroscience research efforts such as the Human Connectome Project funded by the U.S. National Institutes of Health, which provides optimized high angular resolution diffusion-weighted imaging acquisition sequences and sophisticated brain mapping tools [61, 177]. New insights on the connectivity of the human brain hold

great promise to help advance clinical treatment of low-grade gliomas. Nevertheless, the numerous factors that influence tractography results, such as the choice of diffusion model, fiber tracking algorithm and parameters, and regions of interest for seeding, can make the interpretation of tractography results challenging. While diffusion MRI tractography enables unprecedented visualization of the location and trajectory of white matter fascicles at the individual patient scale, the tracts remain an indirect representation of the underlying white matter anatomy. A solid knowledge of neuroanatomy and an understanding of the current technical limitations of the different methods are essential for the correct interpretation of diffusion MRI tractography reconstructions.

## 20.2 Part 2: White Matter Mapping for the Individual Management of Diffuse Low-Grade Gliomas

The goal of brain tumor surgery is to maximize tumor resection while preserving eloquent cortical structures and associated subcortical white matter pathways. The extent of surgical resection of diffuse low-grade gliomas (DLGG) has a direct impact on progression free survival, malignant transformation and overall survival [178, 179]. Knowledge of the spatial relationship between the tumor and white matter pathways is critical for two reasons: first, any injury to white matter pathways can lead to permanent neurological deficit of the patient; and second, studies have shown that white matter bundles define the functional limits of surgical resection [62].

Pre-operative T1-weighted, T2-weighted and FLAIR MRI scans are an essential components of neurosurgical planning of brain tumor resection. However, conventional MRI presents some limitations in the depiction of the tumor margins and the relationship between the brain and the disease. Studies have shown that conventional MRI underestimates the extent of DLGG as the tumor cells invade beyond the margins visible on the scans [25, 63]. In addition, tumor cells migrate along white matter pathways, and conventional MRI data lack sufficient contrast to infer the architecture of the brain white matter. In that context, diffusion-weighted MRI and tractography reconstruction are promising tools to help infer the relationship between DLGG and white matter pathways.

Tractography reconstructions can provide three-dimensional visualization of the trajectory and integrity of white matter pathways involved in motor, vision and language function. When combined with functional information from pre-operative functional MRI (fMRI) and intra-operative direct electrical stimulation (DES), tractography has the potential to help understand the anatomo-functional connectivity of the brain at the individual patient scale. The following section introduces the current capabilities and limitations of tractography tools for delineating pathways associated with essential function for the individual management of DLGG.

### *20.2.1 Tractography Reconstruction of Motor, Language and Vision Pathways*

#### 20.2.1.1 Motor Pathways

The pyramidal tract is the principal white matter pathway that mediates voluntary movement in humans. Pyramidal fibers includes the corticospinal tract that controls the movement of the leg, torso, and arms, and the corticobulbar tract that controls the movement of the face and tongue [180]. Corticospinal fibers originate in the primary motor cortex, premotor cortex and supplementary motor areas and travel through the posterior limb of the internal capsule, cerebral peduncles, basilar pons, and medullary pyramid, before reaching the upper cervical spinal cord. Corticobulbar fibers arise in the lateral aspect of the pre-central gyrus, travel through the genu of the internal capsule and terminate in the nuclei of the pons and medulla.

Several DTI studies using single tensor deterministic tractography have shown the potential of the technique to depict the infiltration of the corticospinal tract in patients presenting low-grade gliomas near the motor and somatosensory motor areas [64–67] (Fig. 20.3). The detection of the presence of infiltrated or displaced corticospinal fibers based on the comparison of tractography reconstructions on the tumor side and on the contralateral side has been explored as a potential predictor of the extent of resection in glioma surgery [68]. Additional developments include the integration of pre-operative tractography reconstruction of the pyramidal pathway into neuronavigation systems for intraoperative visualization during glioma surgery [65, 69–71]. A prospective randomized controlled trial demonstrated the positive impact of using DTI-based neuronavigation in surgical resection of gliomas involving the pyramidal tract [181]. Other intraoperative use of tractography includes the generation of the trajectory of the pyramidal pathway from intra-operative DTI data, and the depiction of the displacement and deformation of the tract following tumor removal [72–74].

However, the reconstruction of the whole course of corticospinal and corticobulbar fibers from their origin to their termination is a challenge for most tractography algorithms. Standardized evaluation of deterministic, probabilistic, and global tractography approaches on patients presenting with a glioma near the motor cortex area have demonstrated that, while motor fibers projecting from the foot area can be easily identified, most methods fail to trace fibers arising from the hand and face area [75]. In particular, the intersection of the lateral portion of the pyramidal pathway with crossing fibers of the superior longitudinal fasciculus (SLF) that courses anteroposteriorly through the centrum semi-ovale poses a major difficulty to tractography methods [76]. Tractography seeding from intra-operative electrical stimulation sites corresponding to the wrist, forearm, and hand motor site showed an anterior and posterior diversion of the reconstructed tracts along the SLF [69]. A practical approach to solve this issue has been proposed based on the virtual removal of the SLF and tensor field replacement [77]. The approach demonstrated the feasibility of reconstructing the lateral projections of the corticospinal and corticobulbar tract from clinical DTI data [77]. Other attempts at overcoming fiber crossing issues

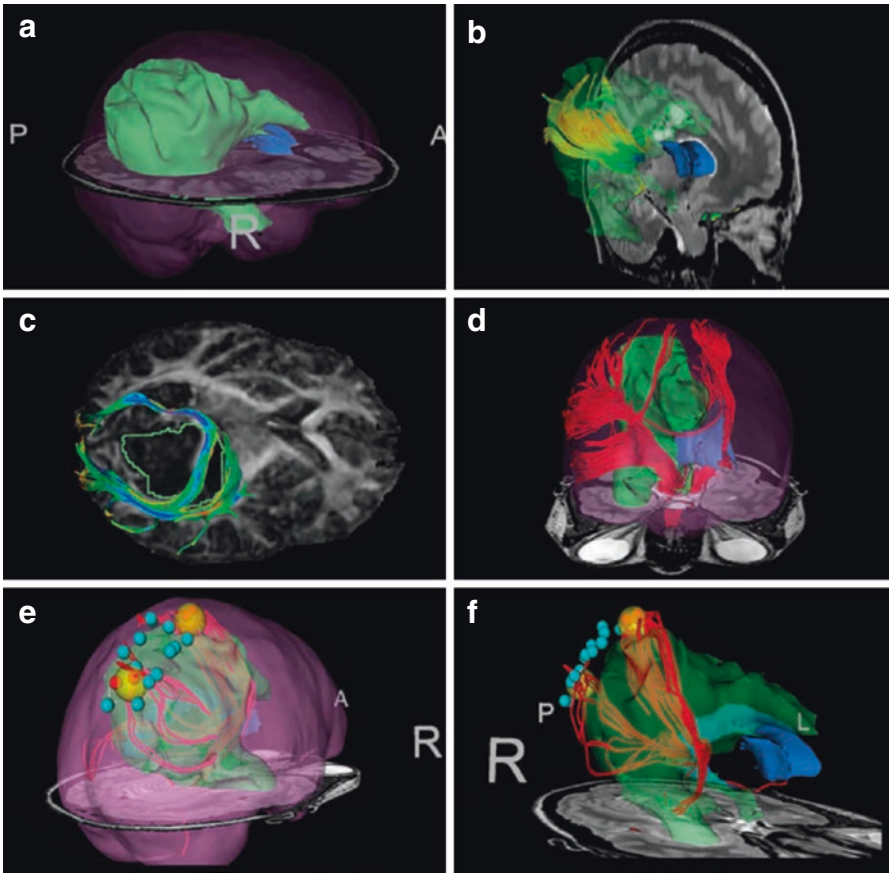


**Fig. 20.3** Multi-modal neurosurgical planning data on a large right fronto-parieto-occipital oligoastrocytoma WHO grade II. (**a**) 3D surface model of the tumor (*green*) with brain outline rendering (*pink*). (**b**) Tractography seeding within high-intensity T2-bright area demonstrates tracts within tumor region. (**c**) Manually seeded infiltrating and displaced tracts against the diffusion tensor imaging (DTI) fractional anisotropy map. (**d**) Region of interest seeding from cerebral peduncle to identify corticospinal tract. Seeding region was outlined on several T2-weighted slices, and tractography was seeded within this volume. (**e**) and (**f**), offline, postoperative tract seeding from intraoperative cortical stimulation locations (*red spheres*, positive). The *yellow spheres* represent enlarged seeding area around positive sites to seed DTI tracts that do not reach the cortical surface. (Source: [66])

in the centrum semi-ovale included the use of probabilistic tractography for the depiction of corticobulbar fibers from the face and tongue region [78], and two-tensor streamline tractography that showed improved performance when compared to single-tensor deterministic and probabilistic tractography methods [79, 80]. With the development of HARDI acquisition sequences, probabilistic q-ball tractography has demonstrated better sensitivity than deterministic and probabilistic DTI methods for the delineation of the lateral aspects of the corticospinal tract [81].

#### 20.2.1.2 Language Pathways

Language is one of the most complex functions of the human brain. The production, perception, and understanding of speech remains an active area of research in neuroscience. In this context, study of the connectivity of the human white matter using diffusion MRI tractography has the potential to provide critical insights into the language function [82]. In the modern model of language organization, the language network is composed of a dorsal stream for mapping acoustic speech sound to articulation and a ventral stream for speech comprehension and processing [83–86].

The phonological dorsal stream is composed of long white matter fibers running around the Sylvian fissure and connecting the frontal lobe to the temporal and parietal lobe. The dorsal pathway includes the arcuate fasciculus (AF) and the superior longitudinal fasciculus (SLF). The AF connects the pars opercularis and the ventral premotor cortex to the posterior superior and middle temporal gyrus. The SLF includes five subcomponents: the first three segments SLF-I, II, and III are horizontal fibers that connect the frontal region to the parietal lobe; the fourth subdivision corresponds to the AF and the fifth segment SLF-tp connects the inferior parietal lobe to the posterior temporal lobe [87]. The subcomponents SLF II, SLF III, AF and SLF-tp are involved in language processing [88].

The semantic ventral stream is composed of white matter fibers connecting the frontal lobe with the occipital lobe and posterior temporal lobe. The ventral pathway is divided between a direct pathway corresponding to the inferior fronto-occipital fasciculus (IFOF) and an indirect pathway formed by the uncinate fasciculus (UF) and the anterior inferior longitudinal fasciculus (ILF) [89, 90]. The IFOF is an associative white matter bundle that connects the orbitofrontal cortex and the dorsolateral prefrontal cortex with the parietal, posterior temporal and occipital lobes. The UF is an associative C-shaped bundle that connects the anterior temporal lobe with the medial and lateral orbitofrontal cortex. The ILF is an associative bundle that connects the temporal lobe to the occipital cortex. Recently, two white matter pathways have been investigated as additional white matter structures involved in language function: the middle longitudinal fasciculus (MdLF) connecting the inferior parietal lobule and the superior temporal gyrus [91, 92] and the frontal aslant tract connecting the superior frontal gyrus to the pars opercularis and pars triangularis in the inferior frontal gyrus [93, 94].

Tractography reconstructions of fibers of the ventral and dorsal route have the potential to provide clinically relevant information for planning the resection of gliomas in language areas [65, 95–99]. Figure 20.4 shows an example of tractography reconstructions of IFOF, ILF, UF, AF and horizontal and vertical portion of the SLF. Pre-operative tractography reconstructions of language pathways have been integrated to neuronavigational systems to provide intraoperative visualization of the tracts [98, 101]. During surgery, visualization of the trajectory of language tracts can be used to help guide intraoperative direct electrical stimulation (DES) [65, 95, 182] and reduce the number of DES needed to locate subcortical functional sites [98]. Visual display of language tracts overlaid on the operating microscope combined with intra-operative MRI data could help maximize the extent of tumor resec-


**Fig. 20.4** DTI tractography reconstructions of white matter pathways of the language network. The *figure* shows a 3D sagittal view of (*1*) Inferior Fronto-Occipital Fasciculus (*yellow*), (*2*) Inferior Longitudinal Fasciculus (*pink*), (*3*) Uncinate Fasciculus (*red*), (*4*) Arcuate Fasciculus (*orange*), (*5*) horizontal segment of the Superior Longitudinal Fasciculus (*purple*), (*6*) vertical segment of the Superior Longitudinal Fasciculus (*green*). The tracts are overlaid on a sagittal T1-weighted image for anatomical reference. (Source: [100])

tion with minimum postoperative morbidity [99, 101] (Fig. 20.5). In addition to depicting the trajectory of the language pathways, tractography reconstructions might provide clinically relevant information on white matter integrity based on the depiction of morphological changes, such tract displacement, partial infiltration or destruction [65, 67, 68, 102]. Finally, following surgery, tractography reconstructions of language pathways from post-operative dMRI data can be used to predict language recovery after tumor resection [103, 104]. A rating of disturbance based on altered fiber tractography (AFTD) has recently been proposed to evaluate the degree of white matter pathway injury in patients with gliomas [95]. Preliminary results on a small cohort of high-grade gliomas patients presenting with postoperative language deficit showed that AFTD ratings of post-operative tractography reconstructions of the SLF-t and AF have the potential to predict recovery of language function [95].

The majority of tractography reconstructions of language pathways for the resection of low-grade gliomas used deterministic streamline fiber tracking, with seed regions defined in anatomical scans or diffusion-encoded color maps. Several groups have investigated advanced tractography methods to overcome the technical limitations of single tensor deterministic tractography for mapping the complex topography of language pathways. These sophisticated approaches include global search approaches for reconstructing the trajectory of the AF and IFOF [105], two-tensor unscented Kalman filter tractography for tracing the AF through peritumoral edema [60], and a high-definition fiber tractography approach based generalized q-ball modeling, multiple intravoxel sampling, and multi-directional fiber tracking [106]. In addition, the use of HARDI data for white matter mapping of language pathways in neurosurgery clinics has recently been explored. Multidirectional fiber tracking from compressed sensing-based reconstruction of

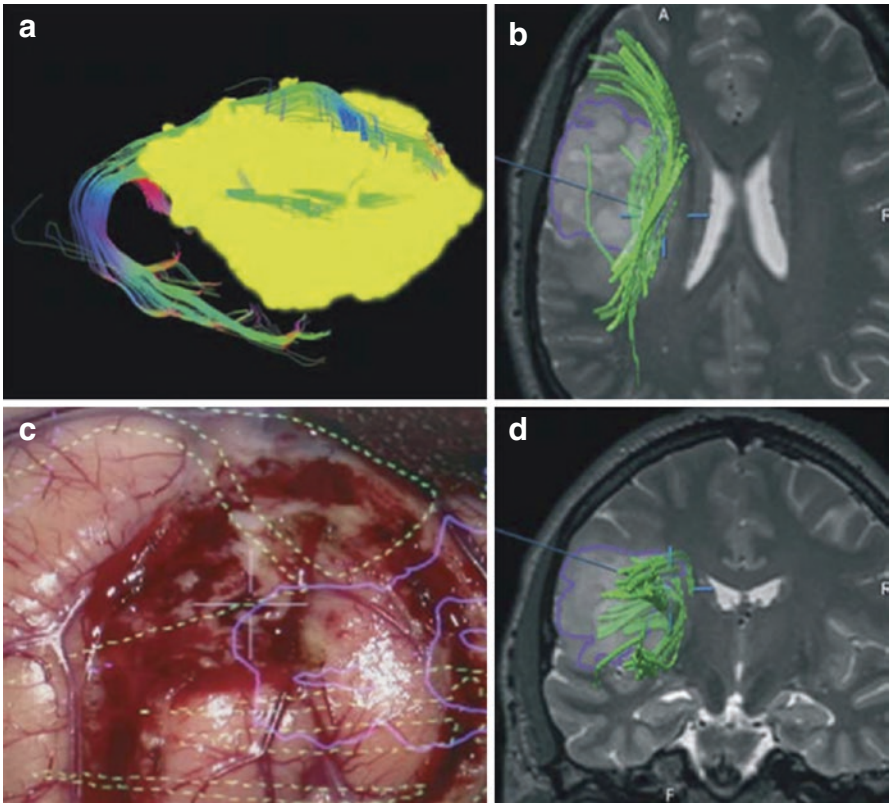


**Fig. 20.5** Intra-operative visualization of tractography results in diffuse low-grade astrocytoma. (**a**) Lateral right view of 3D surface model of tumor (*yellow*) and tractography reconstruction of language fibers (multi-color). (**c**) microscope view with outlines in heads-up display (tumor: *purple*, subjacent language pathways: *yellow*). (**b**) and (**d**) intra-operative axial and coronal T2-weighted image with segmented tumor (*purple*) and DTI tractography reconstructions (*green*). (Source: [183])

HARDI data demonstrated the feasibility to accurately reconstruct language tracts within clinical time constraints [107, 108]. An innovative tractography workflow based on residual bootstrap probabilistic q-ball tractography of the dorsal and ventral language pathways from HARDI data enabled the reconstruction of the multiple components of the AF/SLF complex as well as the MdLF and ILF on a large cohort of brain tumor patients [95].

#### 20.2.1.3 Visual Pathways

The optic radiation is composed of three bundles that connect the lateral geniculate body (LGN) to the primary visual cortex [180]. The posterior bundle has a straight course from the LGN to the occipital cortex. The central bundle makes an anterior

curve and courses along the wall of the atrium and the occipital horn of the lateral ventricle. The anterior bundle, or so-called Meyer's loop, makes a curve around the tip of the temporal horn, passes posteriorly around the lateral ventricles and converges on the lower lip of the calcarine fissure.

DTI tractography studies on healthy subjects have demonstrated the feasibility of tracking the optic radiation [109–112]. However, tractography reconstruction of the Meyer's loop presents technical challenges due the curved course and sharp turn of the bundle, as well as its close proximity to the uncinate fasciculus, inferior longitudinal fasciculus, and inferior occipito-temporal fasciculus. In addition, the high intersubject variability of the anterior extent of the Meyer's loop makes the prediction of its precise location in an individual patient difficult [113].

Studies have reported the added value of tractography reconstructions for gliomas near the optic radiation and optic [66, 114–116]. Exploratory approaches have been proposed for tracing the optic radiation, including increasing the number of diffusion sensitizing gradient directions [117], reducing the voxel size to 0.9 mm [118], and seeding from multiple fiducial volumes [119, 120]. A pilot study combining HARDI-based tractography with compressed-sensing techniques on patients presenting with a low-grade glioma in the left temporal lobe showed significant improvements of the reconstruction of the optic radiation when compared with DTI-based fiber tracking [107, 108].

### *20.2.2 Combining Tractography Reconstructions and Functional Data*

A challenge in DLGG resection is the preservation of cortical structures and subcortical white matter pathways associated with essential function. While diffusion MRI tractography provides a unique window on the architecture of the brain white matter, the information is purely anatomical. Tractography reconstructions depict the trajectory of a tract associated with motor, language, or vision, but they do not indicate to the surgeon whether the tract is still functional or not. Current techniques for mapping brain function include functional Magnetic Resonance Imaging and direct electrical stimulation. The following section examines how these techniques can be combined to the anatomical information derived from diffusion MRI tractography.

Functional Magnetic Resonance Imaging (fMRI) enables non-invasive localization of regions of the brain that are activated when a subject performs a task. The technique uses the blood oxygenation level dependent (BOLD) change as a surrogate marker for neuronal activity. BOLD maps can be superimposed on a high-resolution T1-weighted image to enable depiction of brain regions activated during motor, language, and visual tasks. Pre-operative fMRI activation maps have been used to identify eloquent cortex in the vicinity of gliomas [121, 122, 184]. The integration of fMRI and diffusion MRI has been performed using fMRI activation maps and subjacent white matter regions as seed regions for tractography reconstruction [64, 66, 123, 124]. Such integration could provide

clinically relevant information on the spatial relationship between functional cortical areas and their associated tracts. Since fMRI is non-invasive, data acquisition and analysis can be repeated at several time points for patient follow-up. However, the technique is sensitive to motion-related artifacts and signals from large draining veins [122]. In addition, both fMRI and tractography techniques provide only indirect surrogate markers of the location of eloquent tracts: activation maps derived from fMRI data represent blood flow and tractography maps derived from diffusion MRI data represent anisotropic water diffusion. The difficulty in validating fMRI and dMRI findings prevents the techniques from being used as stand-alone tools for clinical decision-making. Nevertheless, the integration of fMRI and dMRI data enables the evaluation of one technique against the other.

Intraoperative direct electrical stimulation (DES) is the gold standard to identify the location of cortical regions and subcortical white matter pathways associated with critical function prior to gliomas resection [62, 125–130, 185]. Cortical positive DES sites can be used as tractography seeds for the reconstruction of motor and language tracts [69, 131]. Visualization of the location and trajectory of white matter pathways provided by pre-operative tractography reconstructions might help guide to the location of subcortical DES sites during awake surgery [70, 98]. The comparison of pre-operative tractography reconstructions of language and motor pathways with intraoperative cortical and subcortical stimulation sites during awake mapping showed an acceptable, although not optimal, correlation between the tracts depicted as intact on tractography maps and the sites eliciting positive motor or language response during stimulation [65, 68, 81, 97, 132]. Similarly, studies in low-grade insular gliomas have reported an acceptable correspondence between the complete disruption of the IFOF, as displayed by pre-operative DTI tractography reconstructions, and the absence of eloquent function identified by intraoperative subcortical stimulation [133]. Thus, the depiction of tract integrity could help predict the presence or absence of response during intraoperative DES of subcortical areas. From a neuroscientific point of view, combining language disturbance elicited by electrical stimulation with anatomical information provided by DTI represents a unique opportunity to study the anatomo-functional connectivity of language [62, 94, 131]. Neurosurgical findings in patients presenting with a glioma in the frontal lobe have contributed to advance knowledge on the role the frontal-striatal tract and fronto-aslant tract in language function [94, 103, 104, 134].

### *20.2.3 Current Challenges and Limitations of Tractography*

Tractography is gaining increasing interest in the neurosurgical community due to the availability of diffusion MRI pulse sequences on most clinical scanners in Radiology departments, and the dissemination of fiber tracking tools integrated into commercial neuronavigation systems or available as open-source software.

However, converting the neuroanatomical information contained in diffusion MRI data into individualized patient maps remains a difficult task. The following section presents the current challenges and limitations of using tractography for neurosurgical decision-making.

As described in the first part of the chapter, anatomical regions where fibers cross, bend or fan pose a challenge to tractography techniques. While advanced diffusion models developed by academic centers have demonstrated improvement in the depiction of complex fiber configurations, most commercial tractography packages use the single tensor model, which cannot resolve fiber crossings in voxels with multiple fiber populations. The difference between the size of DWI voxels, in the order of a few millimeters, and the diameter of axons, in the order of a few microns, results in partial volume effects which can corrupt tractography results [135]. Diffuse low-grade gliomas pose an additional level of difficulty for fiber tracking as tumor infiltration can induce changes in the diffusion anisotropy properties of tissues that can confound tractography algorithms. As a result, some intact tracts within or at the periphery of gliomas can remain undetected by tractography algorithms.

The technical limitations of tractography tools can lead to two types of errors: false-negative tracts and false-positive tracts. False-negative tracts can be defined as anatomical fibers that a tractography tool fails to reconstruct. Examples of false-negative tracts are the missing lateral projections from the hand and face area of the pyramidal pathway [76]. False-positive tracts are artefactual tracts that do not represent an anatomical reality. Examples of false-positive tracts are descending corticospinal fibers crossing through the pons and ascending along the contralateral corticospinal tract [51].

The presence of false-negative and false-positive tracts poses several challenges to the neurosurgeon for the interpretation of diffusion MRI findings in pathological settings. When a portion of a tract appears to be missing, it is difficult to know if the tract is absent because the tractography tool cannot find it or because the disease has destroyed it. False-negative tracts can lead to inaccurate estimation of the size of critical white matter structures and result in permanent neurological deficit for the patient [136]. False-positive tracts can also have a detrimental effect on the surgical outcomes of DLGG resection as artefactual tracts can lead to a more conservative approach and thus lower the impact of surgery on the evolution of the disease [137, 138].

In addition to the difficulties posed by the interpretation of tractography reconstructions, the deformation of the brain due to gravity and loss of cerebrospinal fluid after craniotomy and dura opening creates a discrepancy between the location of the tracts displayed on pre-operative tractography maps and their actual location in the patient. The neurosurgeon must mentally compensate from the unpredictable shifting of white matter tracts following craniotomy [73, 74]. The use of intraoperative diffusion MR imaging data for updating tractography maps can provide a depiction of the location and trajectory of white matter pathways closer to the surgical reality [73, 74, 139, 140]. However, intraoperative tractography presents additional technical challenges as the interface between the open wound and the brain creates

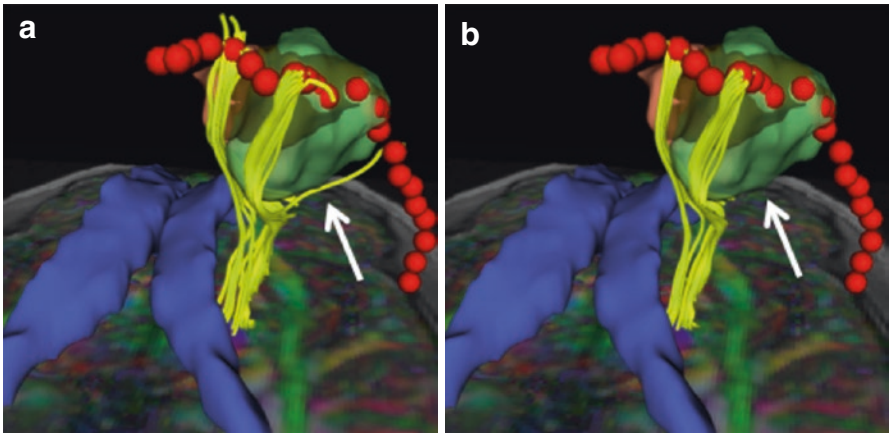


**Fig. 20.6** Impact of fractional anisotropy (FA) threshold on tractography results. The figure shows a dual 3D posterior view of the tractography reconstruction of pyramidal fibers (*yellow*) adjacent to a 3D surface model of an oligodendroglioma WHO grade II (*green*) and surgical cavity (*brown*). The tracts are seeded from pre-central gyrus sites (*red spheres*). Two different FA threshold values are used to terminate the tracking process: (**a**) FA = 0.10, (**b**) FA = 0.15. A peritumoral fiber ventral to the lesion is detected by the algorithm when the FA threshold is set to 0.10, and is not detected when the FA threshold is set to 0.15 (*white arrow*). An axial directionally encoded color map overlaid on a T1-weighted image and a 3D surface model of part of the lateral ventricles (*blue*) are displayed for anatomical reference

imaging artifacts that can corrupt tractography results, as well as practical challenges due to the limited time available for scanning patients during a neurosurgical intervention [141].

Tractography is the end-point of a complex image acquisition and post-processing workflow. The anatomical accuracy and the reproducibility of the tracts depend on multiple factors such as the parameters of the pulse sequence, the correction of diffusion-weighted images artifacts, the choice of the model of diffusion and fiber tracking algorithm, the segmentation of the regions of interest and the definition of the tract selection strategy. In addition, some steps in the workflow such as the manual delineation of regions of interest for seeding and the empirical choice of fractional anisotropy threshold for terminating the tracking process, are operator-dependent and introduce an additional source of variability in the results. Figure 20.6 illustrates the impact that a small change in a single parameter of the tractography workflow can have on the depiction of pyramidal fibers in the vicinity of a glioma. Studies have shown that the location of the seed regions as well as the choice of the FA threshold have a significant influence on tractography reconstruction in the vicinity of brain tumors [142, 143].

Different tractography methods can produce very different results. The lack of standardization of tractography parameters and fiber tracking strategies can result in a large degree of variability among tractography reconstructions. The comparative evaluation of different tractography methods for the reconstruction of white matter pathways on a common set of data acquired on healthy subjects have shown significant

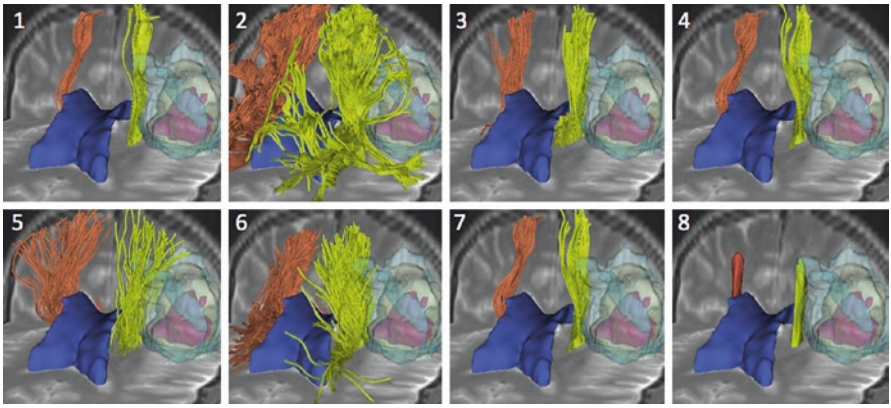


**Fig. 20.7** Variability of tractography results in the reconstruction of the pyramidal pathway. The mosaic image shows 3D anterior views of the pyramidal pathway reconstructed by eight tractography teams on a recurrent/residual anaplastic oligoastrocytoma WHO grade III. Each view presents the tracts (tumor side—*yellow*, contralateral side—*orange*) overlaid on an axial and a coronal T2-weighted image, along with 3D surface models of the tumor (*yellow*), necrosis (*pink*), edema (*light blue*) and lateral ventricles (*dark blue*). The teams are identified by a number, from 1 to 8, in the top left corner of each view. Source: DTI Challenge Project (http://dti-challenge.org)

differences among tractography results [186–188]. Standardized evaluation of tractography methods has shown that different tractography tools can produce very different outcomes when compared on clinical datasets acquired on gliomas patients [75]. Figure 20.7 illustrates the variability of tractography results obtained by eight tractography methods using different diffusion models, including single tensor, multi-tensor and q-ball, and different fiber tracking approaches, including deterministic, probabilistic, filtered and global, for the reconstruction of the pyramidal tract [75].

In summary, while diffusion MRI has the potential to provide clinical relevant information on the trajectory and integrity of white matter pathways in DLGG, tractography cannot be used yet a standalone tool to define resection boundaries [137, 138, 144]. Knowledge of the capabilities and current limitations of integrating tractography information into surgical planning for the resection of DLGG in eloquent cortical areas is essential to optimize surgical outcome and avoid postoperative neurological deficits in the patient [189].

## 20.3 Part 3: Perspective on the Clinical Use of Diffusion MRI for Resection of Diffuse Low-Grade Gliomas

Diffusion MRI tractography was originally designed as a clinical research tool. The mathematical models of diffusion and fiber tracking algorithms at the core of tractography applications rely on many assumptions, and the validity of tractography reconstructions for neurosurgical decision-support needs to be fully established.

This section describes the validation efforts that have been conducted to evaluate the performance of tractography methods, and introduces the potential of tractography for studying brain plasticity.

### *20.3.1 Validation of Diffusion MRI Tractography*

Diffusion MRI tractography provides geometrical reconstruction of the 3D trajectory of water molecules in the direction of less hindered diffusion. During the last decade, numerous complementary approaches have been developed to generate validation datasets that overcome the lack of a practical gold standard. These approaches include mathematical and physical phantoms studies, animal experiments, and post-mortem studies. Mathematical phantoms based on simulated DWI datasets enable rapid prototyping of complex fiber configurations and calibration of essential components of algorithm performance [145–148]. Ground truth datasets acquired on physical phantoms incorporate many of the image artifacts encountered during DWI acquisitions [149–151]. Thus, mathematical and physical phantoms provide critical testbeds to evaluate the accuracy and repeatability of diffusion MRI analysis tools when the ground truth is known. Validation experiments using neuronal tracers have been conducted on animals of different species. The experimental method is based on an *in vivo* injection of invasive tracers in an animal and a post-mortem histological preparation to reconstruct 3D images from a set of histological slices [152–155]. While the approach provides ground truth datasets, neuronal tracer experiments cannot be reproduced on humans. In addition, the agreement between a tractography algorithm and a tracer on white matter tracts of a particular animal species does not guarantee that the tractography method will be accurate on a human brain. Recent works in post-mortem validation using fluorescent carbocyanine dyes provide a novel methodology to compare histological and tractography data on human tissue [156]. Finally, post-mortem fiber dissection provides a very accurate description of the white matter neuroanatomy of the human brain [157, 158]. The recent technical developments in cortex-sparing fiber dissection techniques allow precise identification of the cortical terminations of white matter pathways [100]. The direct comparison between dissected tracts and tractography bundles provides insights into the accuracy of tractography techniques on human neuroanatomy [100, 159–162].

The validation of the accuracy of tractography methods for reconstructing white matter fibers in the presence of a pathology poses an additional challenge. DLGG infiltrate white matter pathways and can alter the diffusion properties of tissues. In that context, the performances of tractography methods need to be evaluated on clinical diffusion MRI data. Subcortical electrical stimulation during awake brain mapping for gliomas resection provides unique ground truth information on the location of white matter pathways at the individual patient scale. Studies

investigating the correlation between tractography findings and intraoperative subcortical mapping are crucial for the validation of tractography as a clinical decision-making tool [49, 65, 68, 71, 73, 74, 81, 97, 140, 190, 191].

Diffusion MRI tractography suffers from a lack of standardization. Clinicians face the challenge of selecting the appropriate tractography technique and parameters in the absence of ground truth, and researchers investigating novel tractography methods are confronted with the difficulty of validating tractography findings in a consistent manner. In order to address the situation, the DTI Challenge was initiated as a community-based effort to provide standardized evaluation of the performance of tractography methods on patient datasets [75, 192, 193]. The DTI Challenge has brought together an international working group of lead neurosurgeons, neuroradiologists and diffusion MRI scientists to evaluate tractography methods on a common set of data acquired on neurosurgical patients and help define guidelines and best practices on the use of tractography for neurosurgical decision-support (http://dti-challenge.org).

### *20.3.2 Perspective: Role of Diffusion MRI in the Study of Neuroplasticity*

DLGG are slow growing tumors that infiltrate white matter pathways. Neurological diagnostic evaluation shows the absence of deficit of critical function, such as motor or language, even if the tumor is located in so-called eloquent areas. This functional compensation results from the brain plasticity, which refers to the intrinsic ability of the brain to adapt and reorganize itself in response to tumor infiltration during the slow progression of the disease [163]. The concept of brain hodotopy has been introduced to describe the organization of the central nervous system as a set of dynamic and parallel networks composed of cortical epicenters ("topos") connected by subcortical pathways ("hodos") [164]. In this connectionist approach, neuroplasticity can be seen as mechanism in which the brain reorganizes functional maps by recruiting remote networks to compensate for the injury created by tumor infiltration. This reorganization has also been observed following neurosurgical resection of DLGG. Such phenomenon could be due to several factors, including the hyperexcitability caused by the surgical resection, an improvement of plasticity potential resulting from the reduction of epilepsy, and the continuous progression of the residual tumor [137, 138]. In this context, multimodal anatomical and functional data acquired during pre-operative planning, intraoperative mapping and post-operative follow-up of the surgical resection of DLGG contain a wealth of information on the capacity of the brain to reorganize itself. The analysis and interpretation of these rich sets of data can provide new insights into the neuroplasticity of the human brain and lead to improved clinical outcomes for the patient [137, 138, 165].

Studies have shown that functional cortical plasticity in DLGG can develop by recruiting local networks in the vicinity of the tumor, in distant regions in the ipsilateral hemisphere, or in remote areas in the contralateral hemisphere [164]. Perilesional reorganizations of language areas have enabled the resection of tumors located in brain regions that were classically considered inoperable, such as the Broca's area and Wernicke's area, without inducing permanent post-operative deficit [166, 167]. Transient post-operative deficits resolve quickly after the surgery, thus demonstrating the dynamic functional remapping of the brain induced by surgical resection. In addition, post-operative functional neuroimaging studies have demonstrated reorganization of the brain following DLGG surgery. This capacity of the brain to reorganize itself has enabled neurosurgeons to perform consecutive reinterventions to achieve subtotal resection [168, 169].

The preservation of white matter pathways is essential to maintain plasticity. Stroke studies have demonstrated that infraction of white matter tracts results in more severe neurological deficits than infarction in cortical regions [170]. In that context, tractography maps have the potential to provide complementary information to gain insights on the role of white matter pathways in neuroplasticity. White matter bundles of the dorsal and ventral stream, which constitute the subcortical components of the language network, are likely to play a critical role in neuroplasticity as they represent the infrastructure on which brain reorganization may occur [89]. Exploratory studies based on tractography reconstructionof the language tracts have investigated how the ventral semantic pathway could potentially compensate the role of the dorsal phonological pathway when the dorsal pathway is inhibited by a lesion [171].

A probabilistic atlas of functional plasticity has recently been developed based upon the retrospective analysis of neuroimaging and intraoperative DES data from a set of 231 patients who underwent complete or partial surgical resection of DLGG [172]. The atlas provides an unprecedented resource for studying the spatial distribution of neuroplasticity (Fig. 20.8). The analysis of the atlas data has demonstrated that the overall cortical plasticity of the human brain is high, except for primary motor, primary sensory and unimodal association areas, and that the subcortical plasticity is low [172]. The combination of functional subcortical stimulation findings and tractography data shows great potential to advance knowledge on neuroplasticity. Understanding how and on which pathway the function is displaced could help characterize the principles of plasticity of the human brain and provide critical insights for neurosurgeons to increase the extent of tumor resection without inducing any permanent deficit.

## 20.4 Conclusion

Diffusion MRI offers great promise for personalized white matter mapping in the individual management of diffuse low-grade gliomas. In recent years, considerable advances have been made in post-processing methods and tractography tools for

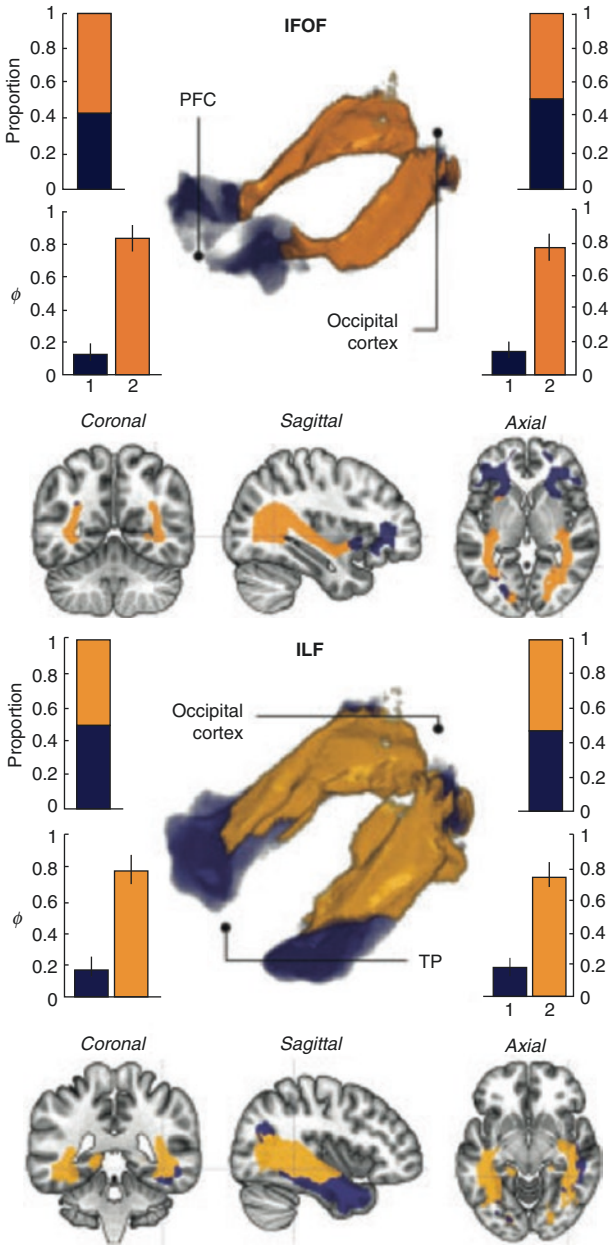


**Fig. 20.8** Tract-based cluster analysis of the functional plasticity of ventral associative white matter pathways. (**a**) Inferior Fronto-Occipital Fasciculus (IFOF), (**b**) Inferior Longitudinal Fasciculus (ILF), (**c**) Uncinate Fasciculus (UF). For each pathway, a 3D view of the functional plasticity map projected on the tractography reconstruction is presented along with 2D intersection with axial, sagittal and coronal FLAIR images. The upper histograms indicate the proportion of voxels in each cluster and the lower histograms represent the mean and standard deviation of the functional compensation index $\phi$ corresponding to the probability of stimulation-induced functional disturbance in the left and right hemispheres. (Source: [172])

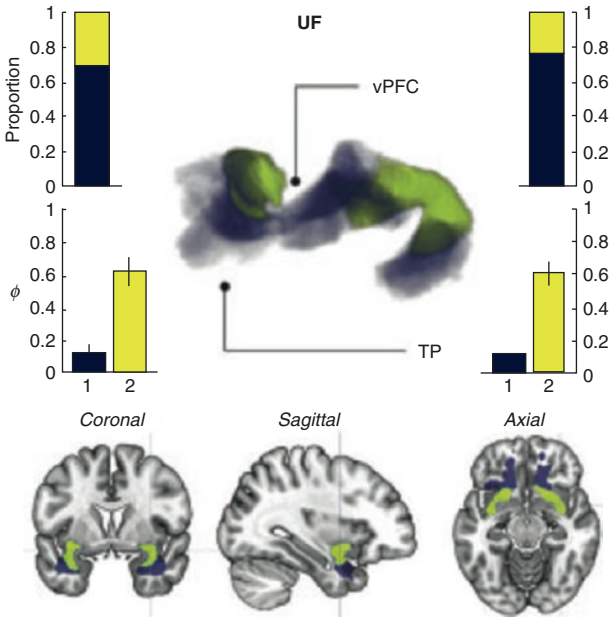


**Fig. 20.8** (continued)

inferring the trajectory of white matter pathways from diffusion MRI data. However, the interpretation of tractography reconstructions in the vicinity of gliomas is complex, and requires a solid knowledge of white matter neuroanatomy as well a clear understanding of the current limitations of tractography methods. Validation of tractography-derived findings will help establish the clinical utility and usability of the techniques so that tractography tools could become part of the brain mapping apparatus of the neurosurgeon. When combined with direct electrical stimulation, diffusion MRI tractography could help advance knowledge on brain neuroplasticity and improve clinical care of patients presenting with diffuse low-grade gliomas.

Clinical diffusion MRI for neurosurgical intervention is a young and multidisciplinary field which combines complex aspects of physics, biology, mathematics, neuroanatomy, neuroradiology and neurosurgery. The integration of knowledge and expertise from the individual fields is essential to translate diffusion MRI findings into improved patient care. This integration can be achieved through a close collaboration between research scientists developing novel diffusion MRI tools and clinicians using the tools to investigate white matter anatomy on clinical data. Joint multi-disciplinary efforts will help overcome the current limitations of the technology, and neurosurgeons will play a key role in the future advances of diffusion MRI for the individual management of diffuse low-grade gliomas.

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# Chapter 21
# Magnetoencephalography, Functional Connectivity and Neural Network Topology in Diffuse Low-Grade Gliomas

**Linda Douw, Jan J. Heimans, and Jaap C. Reijneveld**

**Abstract** Diffuse low-grade glioma not only impacts structural and functional connections in its direct vicinity, but also has a profound impact on the entire brain network. Magnetoencephalography (MEG) performed during a resting, task-free state is one of the methods that can be used to study functional connectivity. Frequency-specific analysis of functional connectivity further provides information on the topology of the brain network in terms of for instance efficiency, clustering and modularity. These network features are not only altered in low-grade glioma, also correlate with cognitive (dys)functioning and with the occurrence of epileptic seizures. Better understanding of the association between the tumor and the disruption of the neural network may in the future be used for diagnostic and prognostic purposes in low-grade glioma.

**Keywords** Low-grade glioma • Functional connectivity • Neural networks • Epilepsy • Cognitive functioning • Magnetoencephalograpy • Graph theory

## 21.1 Introduction

Much of what we know about the correlations between brain function and neuroanatomy is based on clinical observations. In the past, the neurological deficit demonstrated by a patient suffering from a focal brain lesion led to conclusions on the specific function of that particular brain area. However, nowadays we realize that the more complex a function, the larger the number of brain areas involved at the

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least, or the more difficult it is to localize the function at all. This is because lesions not only interfere with local cortical functioning but also with the connections between cortical areas. In other words, a focal cerebral lesion may cause a focal deficit but may also interfere with connections between widely distributed cortical areas. Thus, focal lesions cause large-scale alterations in network architecture and connectivity.

## 21.2 Structural, Functional and Effective Connectivity

Communication in the context of the cerebral network can be investigated in terms of structural, functional or effective connectivity. Structural connectivity refers to anatomical connections, and is often measured by using diffusion imaging. Functional connectivity is a more complex concept. Mathematically, it denotes any statistical association or dependency between two different parts of the nervous system [1]. Effective connectivity means that directed or causal relationships between elements exist. When the comparison with the European railway network is made, structural connectivity can be displayed by a map that contains all the local and international railways and gives an overview of the physical 'connections' between railway stations. However, such a map will not provide travelers with information on the train time schedules, duration of the trip or railway stations where trains have to be changed, while such information on functional connectivity is indispensable when planning a journey. Effective connectivity means that a person who travels from A to B, will be able to carry out an action in B, for example meeting another person or attending a conference, which would not have been possible if the journey would not have been made. It also implies that travelling from A to B is not necessarily the same as travelling from B to A.

Optimal knowledge not only on the precise location of eloquent areas but also on the connectivity between these areas (referred to as the 'connectome') will contribute to the possibilities of the neurosurgeon to achieve maximal resection of low-grade gliomas (LGGs). As has been demonstrated, conventional MRI underestimates the actual extent of LGGs [2]. The outcome of surgery might improve when the resection is extended beyond the region of MR defined abnormalities, while still avoiding critical functional areas (or 'functional hubs' in network terminology). For instance, Yordanova and colleagues analyzed the outcome of awake surgery with intraoperative functional electrostimulation mapping in 15 patients who underwent so-called 'supratotal' resections of LGG located in noneloquent areas in the left dominant hemisphere [3]. The results regarding recurrence rate show that anaplastic transformation and the need for adjuvant treatment occurred less often in these supratotally resected patients compared to patients who underwent standard total LGG resections, because the lesion involved eloquent areas. This study is a plea for an extension of surgical resection beyond the borders of MR defined abnormalities. The study also showed that 60% of patients who underwent supratotal resection had transient, postoperative clinical worsening, particularly of language function, but

they all recovered within weeks after surgery. Moreover, it appeared that epileptic seizures were under control after surgery, allowing a decrease or even cessation of anti-epileptic treatment.

It seems obvious that the favorable results of this study should be ascribed to the combination of supratotal resection and intraoperative mapping (and, of course, to the technical skills of the surgeons). However, the feasibility of such an approach as the standard of care is limited. Intraoperative electrical stimulation, although being the gold standard for the localization of functional areas, is a time consuming invasive procedure and the number of tasks that can be explored is limited due to fatigue. Moreover, there is an increased risk of epileptic seizures during stimulation. Therefore, the question arises whether the use of techniques that preoperatively provide insight into functional relations between brain areas may further contribute to the improvement of survival with preservation of function.

## 21.3 Methods of Measuring Brain Connectivity

The mapping of structural networks in the human brain should lead to a 'connectome' [4], which could be conceived as the description of all structural elements in the nervous system, and the links between them. Structural mapping can be done by means of diffusion tensor imaging (DTI), an MRI technique that makes it possible to image myelinated nerve fibers. Diffusion spectrum imaging (DSI) is another MRI technique, which is quite time-consuming to acquire and analyze, but offers the additional possibility of resolving multiple directions of diffusion within the white matter, thereby visualizing more details of the cerebral network. Alternative techniques to reconstruct structural brain networks based on standard anatomical MRI acquisitions, relying on the covariance of cortical thickness within a single subject, have also been used [5].

However, we need other techniques to elucidate how this structural network architecture supports functional interactions. Functional MRI (fMRI) is such a technique. It relies on hemodynamic correlates of neuronal activity. It has excellent spatial resolution, but—in contrast to electrophysiological techniques—poor temporal resolution.

Electroencephalography (EEG) and magnetoencephalography (MEG) do not rely on hemodynamic or metabolic fluctuations. Instead, these techniques provide us with a direct reflection of neuronal activity. For that reason, they have a much better temporal resolution than fMRI. On the other hand, their spatial resolution is in the order of millimeters or even centimeters.

MEG measures brain activity by detecting very small perturbations in the extracranial magnetic field that are generated by the electromagnetic activity of populations of neural cells. An advantage of the use of MEG over the use of fMRI in patients with brain tumors is that MEG is not influenced by the alterations in metabolism or blood flow of a specific brain area by the tumor or edema [6].

All regions of the brain show oscillatory magnetic activity and the correlation between these oscillations in different brain areas is a measure of functional interaction between these respective areas. These relations can be studied during specific tasks but also at rest, the latter of which will be the main focus in this chapter since it has the obvious advantage that it can be done without cooperation of the patient. Furthermore, the resting-state has been shown to contain a large amount of information, even on for instance motor function [7, 8].

Before we come to the thick of the network matter, let us first discuss which oncological mechanisms make it such that LGGs may affect functional connectivity at all. Some LGGs show predominantly 'invasive' behavior, whereas others have a more 'proliferative' growth [3]. Proliferative growth may result in local compression of brain structures, while infiltrative growth may cause destruction of tissue (cortical tissue, but also myelinated fiber tracks). Both types of growth may interfere with local and global connectivity of brain areas.

In order to investigate these connectivity profiles, time series of activity are first extracted from the MEG recordings, either per sensor, or per brain region after source reconstruction of the activity. Importantly, the skull and the scalp have no influence on the magnetic field measured outside the head and, for that reason the MEG signal contains less artefacts than the EEG signal. Another advantage of MEG over EEG is that it does not require a reference electrode, which makes it a more straightforward technique than EEG. With MEG it is more or less possible to 'look through the skull'. This renders MEG—in this respect—comparable to corticography. MEG and EEG both have the disadvantage of spurious coupling, which means that signals that are picked up by different electrodes or sensors may originate from the same (deep) source. This artefact could lead to an erroneous interpretation of similarity between signals, suggesting a certain degree of connectivity that, in fact, does not exist. Meanwhile, several analysis tools have been developed to overcome this disadvantage. Later in this chapter, we will give some more detailed information on these methods.

MEG signals, just like EEG signals, are categorized within frequency bands, which are often defined roughly as follows: delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz), beta (13–30 Hz), lower gamma (30–50 Hz) and upper gamma (50–80 Hz). After filtering the time series to these predefined frequency bands, the correlation between time series of different MEG channels or regions can be calculated. A measure for the functional connectivity between neurophysiological time series is the synchronization likelihood (SL [9]). This measure takes both linear and nonlinear coupling between time series into account and varies between 0 (total absence of synchronization) and 1 (total synchronization). A more recently defined measure of functional connectivity is the phase lag index (PLI ([10])). This measure also varies between 0 and 1, but takes only non-zero lagged connectivity between sensors/regions into account. This means that the usual problem of spurious coupling through common sources is mitigated.

## 21.4 Impact of Brain Tumors on Functional Connectivity and Network Architecture

One of our first MEG studies in patients with brain tumors was aimed at three questions: (1) is there a loss of functional connectivity (SL) in these patients, (2) if so, is this loss restricted to the region of the tumor or does it extend beyond these margins, especially to the contralateral hemisphere, and (3) is such loss of functional connectivity particularly found in the gamma band, which is a relevant frequency band for cognitive processes?

Indeed, we demonstrated that there was loss of functional connectivity in brain tumor patients in comparison to control subjects [11]. Moreover, there was no difference between the lesioned and the non-lesioned hemisphere in patients, which indicates that loss of connectivity was also present in the non-lesioned hemisphere. When the SL was computed in the gamma band, it appeared that the patient group showed decreased functional connectivity in comparison to control subjects. However, there was wide variance in level of connectivity within the patient group, with some patients showing no loss of connectivity at all, whereas other patients had an almost complete loss of connectivity in the beta frequency range. It is of interest to mention that abnormal findings were more frequently present in patients with left hemispheric tumors. Of course, it should be kept in mind that the global loss of connectivity that we observed in these patients could be a consequence of the presence of the tumor, but that most patients had also received radiotherapy and were being treated with anti-epileptic drugs (AEDs), both factors that have an established influence on cognitive functioning and, therefore, may also be supposed to affect connectivity [12, 13].

A next study addressed the question whether the network architecture—again within the predefined frequency bands—might be modified by the presence of a brain tumor [14]. This architecture was estimated using graph analysis, applied to the MEG recordings of the same group of 17 brain tumor patients. The time series were converted to a connectivity matrix consisting of 151 sensors (vertices) and the links between them weighted by their SL value, after which two parameters were used to quantify network topology: the clustering coefficient (C) and the characteristic path length (L [15, 16]). These two parameters characterize the architecture of a network in terms of ‘regular’ and ‘random’.

In short, the significance of these measures can be summarized as follows: C is defined as the likelihood that neighbors of a vertex are also connected. To compute the clustering coefficient of a certain vertex, the first thing that has to be done is to determine to which other vertices this one vertex is directly connected. These vertices, which are all one connection away, can be defined as the neighbors. The clustering coefficient is the ratio of all existing edges between these neighbors and the maximum possible number of edges between the neighbors. This means that C ranges from 0 to 1. When the clustering coefficient, as described above, is computed for all vertices of the network and then averaged, we can use this measure to scope the tendency of the network elements to form local clusters.

L is defined as the average of the shortest distance between pairs of nodes counted in the number of edges. Or, in other words, how many steps does it take on average to get from a particular node to any other node in the network? This measure indicates how well the network elements are globally integrated.

Relating these parameters to the earlier mentioned metaphor of the European railway system, travelling between cities in various countries is easier when long-distance (high speed) trains do not stop too often (low L), and when—starting from the railway stations where the long-distance trains do stop—local stopping trains frequently leave to various small interconnected stations (high C). So, using these two measures, we can resume our explanation of network theory as follows: regular networks are very clustered (high C), but it takes a lot of steps to get from one side of the graph to the other (high L). In contrast, random networks lack this high clustering (low C) while their path length is short (low L).

In our study, brain tumor patients were found to have values for local and long-distance couplings that differed significantly from the values of healthy controls [14]. With regard to local coupling, increases in the alpha, theta and delta bands were found. For long-distance connectivity, a significant decrease in beta and increases in alpha and delta bands were observed. The main results of this study confirmed the previous findings with respect to altered functional connectivity of the brain in tumor patients. Again, these alterations also involved intrahemispheric connectivity. Furthermore, the effects differed for the various frequency bands, with predominance for a decrease in high-frequency bands for long-distance connections and an increase in low-frequency bands for local connectivity. It is very difficult to give an unambiguous interpretation of these results, as the significance of the various frequency bands for local and long-distance connectivity remains largely obscure. The most affected long-distance couplings appeared to be the fronto-parietal interactions with decrease in both the gamma and beta connectivity, and an increase in connectivity for the delta band. This is relevant in light of a study reporting that in normal subjects, working memory and direct attentional tasks involve transient synchronization between frontal and parietal regions [17], but let us get back to the cognitive correlates of these findings later.

We also investigated changes in functional connectivity due to surgical treatment in 15 brain tumor patients [18]. The patients had various tumor histologies (low-grade gliomas, high-grade gliomas and meningeomas) and all underwent maximal debulking of the tumor. After tumor resection, functional connectivity appeared to have changed in a complex way. There was a decrease in long-distance interhemispheric connectivity in the theta band, possibly indicating normalization of the abovementioned increase thereof. Other patient related factors or tumor or treatment related factors had no influence on this change, so the effect must be attributed to the surgery itself or to the effects of surgery, i.e. reduction of tumor volume and edema and, subsequently, reduction of compression of brain tissue. Furthermore, the decrease in interhemispheric connectivity was most prominent in patients who were free of epileptic seizures postoperatively, indicating that tumor-related network changes go hand in hand with proneness to seizures. Another MEG

study offers additional insight into the mechanisms at play here. When comparing gliomas with different grades, low tumor grade was associated with higher theta band connectivity than high tumor grade [19], which may be attributable to several factors in addition to the obvious histopathological differences between LGG and HGG. Amongst others, epilepsy occurs more frequently in LGG than in HGG. Also, the slow-growing nature of LGG usually results in longer disease duration and probably more extensive plastic effects before diagnosis. From a cognition viewpoint, compensation is often hypothesized in the context of increases of connectivity. More effort and thus more connectivity might be necessary to reach adequate cognitive performance despite having a brain tumor, whereas healthy people do not need this extra connectivity effort. However, based on the current results, we cannot separate the correlates of epilepsy, cognition and/or compensation based on these studies.

## 21.5 The Small-World Phenomenon and Other Network Features

We have also analyzed the architectural properties of the cerebral network in brain tumor patients, according to the pioneering work of Watts and Strogatz [20]. We made use of the parameters 'C' and 'L'. Watts and Strogatz were the first to show that networks that combine a high number of local (short-distance) connections with a few (random) long-distance connections are characterized by high C and low L. Networks like this have been hypothesized to be optimal for information processing and are usually referred to as small-world networks.

Let us look into this optimal combination a bit more thoroughly. Network (or graph) theory originates from the fields of mathematics and sociology. The combination of these two has led to methods of analyzing all kinds of complex networks, including railway systems but also the human brain, by representing these networks in an abstract, theoretical figure called a 'graph'. The challenge of the study of networks is to find the universal parameters according to which all kinds of biological and social networks—including neural networks—can be defined. In general, networks combine two concepts: integration and segregation [21]. As mentioned before, the most optimally functioning networks have so-called 'small-world' characteristics, referring to an architecture that combines high clustering with long-distance connections. The consequence of such a topology is that all parts of the network that are seemingly remote from each other can be coupled through a few steps. This phenomenon in which both integration and segregation are present and which is characteristic for a complex network has been described in 1998 [20]. The authors proposed a very simple model of a one-dimensional network on a ring as depicted in Fig. 21.1. In the 'regular' network, each node (or vertex) is only connected to its neighbors. The number of connections per node represents the degree distribution of the network (k). Next, a few nodes are chosen at random with

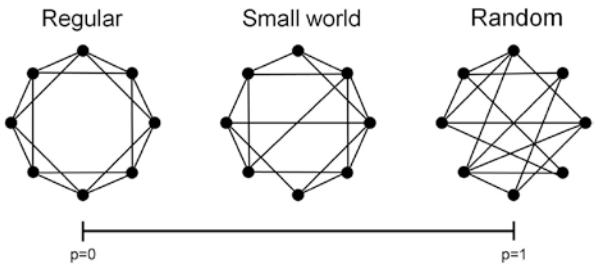


**Fig. 21.1** Three network types as described by Watts and Strogatz [20]. At the one end of the spectrum is the regular or ordered network. At the other end is the random network. In between the so-called 'small-world network' (from Heimans and Reijneveld [51])

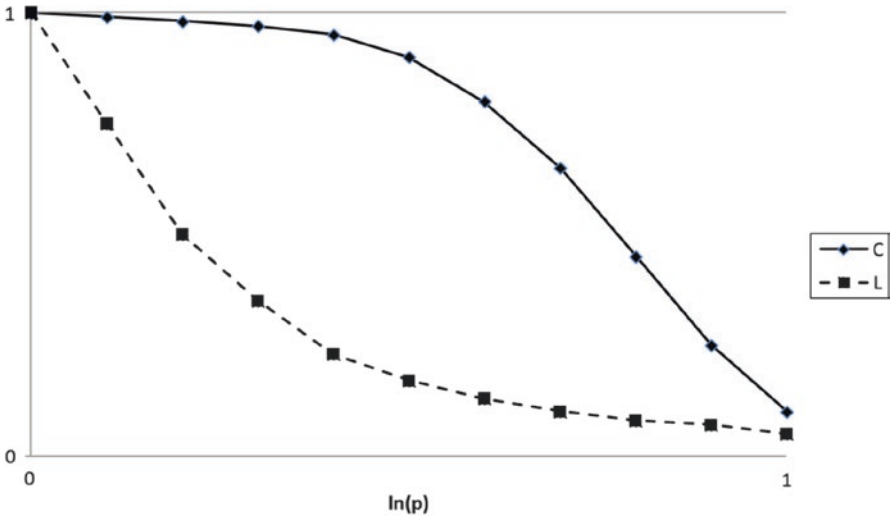


**Fig. 21.2** Graph illustrating different types of networks according to graph theory. When p = 0, the network is completely regular with high C and high L. When p is only slightly higher than 0 (which is the case when only a few edges are randomly rewired), the path length L drops sharply, while C hardly changes. At the other end of the graph the network is completely random (p = 1, low C, low L)

likelihood 'p', and these nodes are connected to other nodes (also chosen randomly). Now, with increasing p, more edges become reconnected and finally, when p = 1, the network is completely random. This model makes it possible to study all types of networks, ranging from completely regular (p = 0) to completely random (p = 1).

The intermediate between random and regular network architecture explains the small-world phenomenon. As mentioned above: 'C' and 'L' are the two crucial measures for the classification of a network on the continuum of regular to random. Interestingly, small-world properties already occur when p is only slightly higher than 0: now 'L' drops sharply, but 'C' hardly changes (Fig. 21.2). This means that a

regular network in which only a few connections are randomly rewired, suddenly combines high clustering with short path length, the small-world phenomenon. The combination of the parameters C and L makes it possible to define an index of 'small-worldness' [22]. All complex networks, varying from railway networks to the World Wide Web and from social to neural networks, show some degree of small-worldness.

In 28 healthy volunteers, the correlation between resting-state small-world network topology (measured with MEG) and cognitive performance was studied [23]. A higher 'small-world index', defined as the ratio between normalized clustering and path length, in the theta and lower gamma bands appeared to be related to a better cognitive performance. The clustering coefficient in the delta and theta bands was also positively correlated to global cognitive functioning. Moreover, the study showed that there was a gender difference in network topology: the female brain had a shorter average path length than the male brain, which indicates that the female brain has more efficient network architecture.

Modularity is another possibly relevant feature of the brain network; it quantifies to what extent a network can be optimally divided in internally correlated subnetworks or modules [24]. Furthermore, hubs are nodes crucial for information flow throughout the network. They can be defined in several ways, the simplest being determining which nodes have the highest number of connections. Conversely, the number of shortest paths passing a specific node reflects betweenness centrality as a measure of hubness. From a modularity viewpoint, connector hubs link different modules together, while provincial hubs only have high connectivity to nodes within their own module [25].

In an already mentioned study, we found significant differences in modularity between LGG patients and both healthy controls and HGG patients [19]. LGG patients displayed the most extensive modular disturbances, with more modular organization of their brain networks, and a decrease in integration between different modules, as compared to controls and HGG patients. But how do these alterations in the brain network relate to patients' functional status?

## 21.6 Correlation Between Network Disturbances and Clinical Functioning in Low-Grade Glioma Patients

We investigated network topology in relation to cognitive functioning in low-grade glioma patients [26]. Our hypothesis was that changes in the functional brain network are the intermediate between the impact of the tumor and the anti-tumor and anti-epileptic treatment on the one hand (this could be defined as 'input'), and cognitive performance (defined as 'output'), on the other hand. Seventeen LGG patients were selected for participation in the study. The patients had shown no radiological or clinical signs of tumor progression during the previous 6 months. The mean time

between diagnosis and this study was 8 years, with a range of one to 19 years. Seven patients had been treated with radiotherapy, and two patients had received prior chemotherapy (the combination of procarbazine, lomustine, and vincristine). Sixteen of 17 patients used anti-epileptic drugs (AEDs), and of these, six were free of seizures. We also included healthy controls (relatives of the participating patients or staff members of our hospital) to allow for comparisons. The patient group did not differ from the control group with respect to age, gender and educational level.

Cognitive performance was measured by an extensive standard testing battery, containing tests that reflect a wide variety of cognitive abilities, such as psychomotor function, executive (frontal) function, (selective) attention, mental processing speed, mental control, verbal learning, organization, memory, mental concentration, information processing and flexibility of verbal thought processes. It took between 60 and 120 min to complete this assessment. The data that were collected in this way were reduced to six cognitive domains (which are commonly used in neuropsychological research): (1) information processing speed, (2) psychomotor functioning, (3) attention, (4) verbal memory, (5) working memory, and (6) executive functioning.

We performed MEG recording during a no-task, eyes-closed resting-state (see Fig. 21.3). Magnetic field frequencies between 0, 5 and 80 Hz were recorded. From the entire recording of 10 min, four artifact-free samples of 13 s were selected by visual analysis. The SL was used as a measure of statistical interdependency between time series from all MEG sensors, and its values were calculated for every possible pairwise combination of MEG sensors for all frequency bands. MEG sensors were grouped according to their location in central, frontal, occipital, parietal, and temporal areas. Subsequently, three types of SL averages were calculated: (1) five interhemispheric between-area SLs, (2) eight (four per hemisphere) long-distance intrahemispheric SLs (frontotemporal, frontoparietal, parieto-occipital, and temporo-occipital), and (3) ten (five per hemisphere) within-

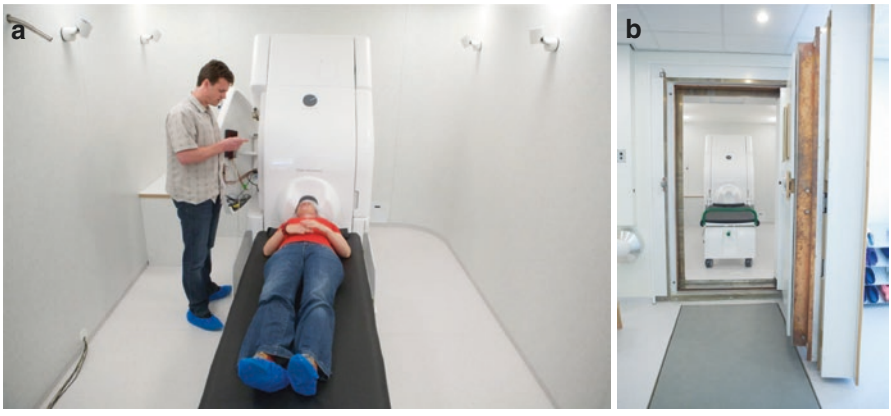


**Fig. 21.3** (**a, b**) The MEG system as used in the department of Clinical Neurophysiology of the VU Medical Center

area local SLs. The latter were a measure for short-distance connectivity, while the first two SL-types can be regarded as a measure for long-distance connectivity.

Regarding cognitive functioning, we found—as could be expected from the results of one of our previous studies [13]—that patients performed poorer than control subjects. This was the case for the overall measure of cognition as well as for psychomotor function, working memory, information processing speed, and attention. There were no significant differences for the domains of verbal memory and executive functioning. Regarding functional connectivity, long-distance functional connectivity was abnormally increased in the low frequencies in the patient group in comparison to the controls, corroborating our previous findings [11, 14]. Significantly decreased long-distance connectivity in patients was observed for intertemporal connectivity in the delta band and for interoccipital connectivity in the lower alpha band.

Obviously, the most important question was whether there was an association between cognitive performance and functional connectivity patterns. With regard to the previously mentioned disturbed cognitive domains, post-hoc regression analysis showed that increased long-distance and short-distance connectivity in the delta, theta and gamma bands was associated with decreased working memory, attentional functioning and information processing speed. It therefore seems clear that diminished cognitive performance is associated with pathologically increased connectivity, above all in the lower frequency bands (although the same was observed in the lower and upper gamma bands), for a number of long-distance connections. Again, it could be speculated that these changes indicate a compensatory mechanism in LGG patients: they might need an increase of synchronization in order to compensate for their diminished cognitive performance. However, this association may also indicate pathological 'disinhibition': local inhibitory connections are disrupted and this leads to slowing down and higher amplitude of oscillations and subsequently to increase of cortico-cortical connections. Anyhow, these findings strongly suggest that changes in resting-state connectivity are not simply an epiphenomenon, but may be relevant for the observed cognitive impairments in LGG patients, although the causal relation of the association remains unclear.

It must be stressed that the findings of this study regarding functional connectivity are not completely consistent with the findings of our earlier study [14], which is cited above. In that study we reported an increase in the low-frequency bands for the short-distance connections and a decrease in high-frequency bands for the long-distance connections. In that same study a decrease in the lower alpha band and an increase in the lower gamma band were found. It is—again—not clear how these conflicting results should be explained, but the different patient populations (LGG patients versus patients with a mixture of primary intracranial tumors) may lie at the root of these divergent findings.

Another study explored further details of network architecture and cognitive functioning in that same LGG patient group [27]. The PLI, which was also used in the aforementioned study [18], was used to generate connectivity matrices that could be converted into graphs. As mentioned before, the main advantage of the use

of PLI in this type of research is that it is less sensitive to volume conduction than other parameters of functional connectivity and it therefore measures 'true interactions'. Our hypothesis was that functional connectivity in LGG patients is diminished in comparison to healthy controls. Secondly, we expected to find a loss of small-world characteristics (by computing the clustering coefficient (C), the path length (L), and the 'small-world-ness' (S) which is based on the trade off between high local clustering and short path length) in the neural network of LGG patients, hypothetically combined with decreased cognitive performance.

Again, higher connectivity was present in the theta frequency band for short-distance connections and for interhemispheric connectivity. In the theta band, the clustering coefficient was significantly higher in the patient group than in the control group. In the beta band, the opposite was the case. Moreover, the patient group showed a loss of small-worldness compared to the control group.

In the delta and lower alpha bands, interactions between network characteristics and cognitive functioning (attentional tasks and executive functioning) were observed. In the delta band, a longer path length was associated with poorer executive and attentional functioning, whereas a higher degree correlation (which indicates to what extent the degree of a vertex is influenced by the degree of the vertices to which it is connected) was associated with better attentional functioning. In the lower alpha band, an interaction existed between network characteristics and verbal memory: increases in clustering coefficient and path length were associated with diminished verbal memory. Summarizing the results of this study, we showed that there was higher functional connectivity in the theta frequency band in LGG patients in comparison to controls and that there were differences in network organization. Moreover, these changes appeared to be associated with cognitive performance.

In the same vein, i.e. loss of overall integrity of the brain network being related to poorer cognitive functioning, we have also shown that increased modularity, i.e. possible disconnection between the modular subsystems of the brain, relates to poorer cognitive functioning in brain tumor patients [19]. Furthermore, using slightly different analysis methods, changes in functional connectivity within two resting-state modules were explored before and after resection in LGG patients, and related to changes in cognitive functioning [28] increased within the DMN and FPN after surgery. More importantly, these increases were related to better postoperative cognitive functioning in the domain of attention and executive functioning. Thus, tumor resection might normalize functional brain networks and improve patients' clinical outcome with respect to cognition.

Summarizing these results, it appears obvious that network configuration and functional connectivity are related to cognitive performance in (low-grade) glioma patients, as we recently posited in a review article [29]. Both increased and decreased connectivity within the various frequency bands may be demonstrated in the same patient, and these findings may again differ for long-distance and short-distance connections. Possibly, these nuances inform us about the clinical status of the individual patients, and may be used for clinical purposes in the future.

## 21.7 Assessment of Functional Connectivity and Clinical Applications

The aforementioned studies were primarily aimed at the investigation of general network disruption by glioma. A more direct approach to the use of MEG in glioma neurosurgical practice is also possible [30]. In this study, MEG was preoperatively used to identify the sensorimotor cortex. The MEG results were superimposed onto a three-dimensional MRI. The term 'magnetic source imaging' was used for this technique and a total of 50 patients with a variety of intracranial tumors, all located in the central region were examined and operated upon. The authors were able to distinguish sensory evoked fields and motor evoked fields in all patients. Sensory evoked fields were monitored by applying tactile stimuli to the thumb, the index finger and the little finger on the side contralateral to the lesion. For the registration of motor evoked fields, patients were asked to perform repetitive tapping with the contralateral index finger. Subsequently, the calculated cortical fields were used for image fusion with MRI. The procedure in which preoperative MEG findings are used for the optimization of neurosurgery is referred to as 'functional neuronavigation'. The main advantage of this procedure is that it allows preoperative assessment of the relation of the tumor with the sensorimotor cortex and thus makes it possible to predict the type of surgery needed in an individual case.

The quantitative comparison between preoperative magnetic source (MS) imaging and intraoperative sensory and motor mapping has been studied [31]. These authors found an MS imaging source localization accuracy of 12.5 mm and considered this to be " … a reasonable starting point in the preoperative planning of surgical approaches, resection strategies, and treatment options". MS imaging is considered as an aid to intra-operative cortical mapping in patients with intra-axial brain tumors.

An MEG-based approach to scope lesion localization with resting-state functional connectivity was used in 15 patients with unilateral lesions, one patient with bilateral lesions and 14 healthy control subjects [32]. Detailed analyses of connectivity were focused on the alpha frequency band. Significantly lower connectivity values were found in brain areas that were non-functional in comparison to contralateral tissue. This decrease was only observed in regions corresponding to a clinically functional deficit, rather than in the entire area of the tumor extension. These regions with diminished functional connectivity could reliably be resected. Moreover, patients in whom no connectivity deficit could be demonstrated or patients with increased connectivity in the tumor area suffered from transient or permanent neurological deficits after the resection. It is interesting to note that all patients, in comparison to control subjects, showed areas of scattered or diffuse decreased connectivity, but these were unrelated to tumor location, tumor volume or clinical deficits. This is in accordance with our own findings [11].

In a more recent study, this resting-state functional connectivity concept for use in clinical practice was further explored [33]. In 57 patients with a brain tumor near or within motor, sensory, or language areas, resting-state MEG recordings were

performed. Functional connectivity was estimated by means of 'imaginary coherence'. This is a measure that reduces the risk of overestimating the magnitude of connectivity as a consequence of crosstalk between voxels or common references. This method, like the PLI, makes use of the fact that phase similarities between time series that arise from a common reference or that result from volume conduction occur with zero time delay. The mean imaginary coherence between voxels in and around brain tumors, and the rest of the brain was compared to the mean imaginary coherence between contralateral voxels and the rest of the brain. A second comparison was made between the local cortical connectivity pattern in the tumor area and the results of intra-operative electrical stimulation. A very important finding of this study was that the cortical maps that were obtained with MEG showing decreased resting-state connectivity (this was the case in 7 out of 57 patients) had a negative predictive value of 100% for the absence of functioning eloquent cortex. On the other hand, if the functional connectivity in the tumor area was increased (which was the case in 42 out of 57 patients), a positive predictive value of 64% for the identification of language, motor or sensory cortex by means of intraoperative electrical stimulation was calculated. These results are encouraging and have stimulated further research on clinical applications of functional connectivity.

The potential clinical significance of these findings is obvious, but also limited at this point in time. Based on preoperative MEG findings, individual risk profiles may in the future be calculated before operation and this may have consequences for the planning of the surgical procedure, but this type of personalized medicine is not ready for the clinic yet. The extent of resection of low-grade gliomas still depends mainly on the results of intraoperative functional mapping, which includes also the stimulation of subcortical (white matter) structures [34, 35].

## 21.8 Epilepsy and Brain Networks in Low-Grade Gliomas

Epilepsy is the most common symptom in LGG patients and it accounts for a significant negative attribution to quality of life, especially when seizure freedom is not achieved with AEDs [12]. Tumor resection may contribute to seizure control; in a review on 773 patients from 20 studies, gross total tumor resection (compared to partial resection) appeared to be the variable that was most predictive of seizure freedom [36]. Another variable that indicated a favorable outcome in terms of seizure control was short duration of seizures (less than 1 year). The presence of medically refractory epilepsy before surgery, as well as the presence of simple partial seizures, was associated with poorer outcome. Consequences of these observations and the study described previously [3] are obvious: surgery should be aimed, whenever possible, at gross total resection, and operation should be performed as early as possible.

There is accumulating evidence that, apart from the ictal onset zone, the neural networks surrounding this zone and parts of the network even lying further remote are pivotal in the initiation, and particularly in the propagation of seizures [37, 38].

It is hypothesized that a loss of small-world network characteristics renders the brain more prone to seizures. Also, the presence of essential clusters of (pathological) connections in the network ('hubs') may play a role in the initiation and propagation of seizures [39]. The question then arises whether assessment of functional connectivity and neural network architecture with MEG may contribute to the planning of the surgical procedure of patients with LGG who also suffer from epilepsy.

What do we know about neural network configuration and epilepsy? The paroxysmal phenomenon of epilepsy is related to hyperexcitation of neurons, and this leads to synchronization of large neuronal networks during the seizure [40]. Various features of the cerebral network determine to what extent the network facilitates this transition. The more random a network, the more susceptible it is to whole system synchronization [41]. Furthermore, both epilepsy and brain tumors give rise to changes in connectivity that are most prominent in the theta frequency band. Moreover, epilepsy patients and brain tumor patients have neural networks that are characterized by a loss of small-world features.

We have studied the relation between functional connectivity, network topology, and epilepsy in a group of glioma patients [42]. We were particularly interested in the correlations between network topology in the theta band and epilepsy characteristics. The majority of the 17 patients that participated in this study suffered from a high-grade glioma. It turned out that increased theta band PLI was related to a greater number of seizures. This association was especially present within the temporal lobe and between the temporal lobe and other lobes. Assessments took place at two time points: (1) directly after surgery, and (2) 6 months later. There were no changes in network topology or connectivity over time. For this study the 'edge weight correlation' was used. This is a measure for the correlation between weights of neighboring edges, and neighboring edges are defined as edges that connect to the same vertex. A positive weight correlation indicates that transport over the network is increased. This could be beneficial for the functioning of the network, but it also increases the vulnerability of the brain to seizures, due to abnormally high synchronizability.

When further investigating the interplay between glioma, epilepsy and surgery, several studies suggest that the future may hold promising new methods of using network theory clinically. Firstly, unpublished research based on the 15 brain tumor patients previously described [18] shows that success of surgery in terms of seizure freedom goes hand in hand with increase of small-worldness [43]. In a later study, we again investigated the outcome of neurosurgery in terms of both network topology and epilepsy outcome in 20 lesional epilepsy patients, of which 15 had an LGG [44]. MEG was performed before and after surgery, after which a new analysis technique was applied to the PLI matrices. This so-called minimum spanning tree (MST) is a mathematical method that allows for extraction of the core network connections without setting parameters [45]. When investigating patients' pre- and postoperative networks using the MST, we found that only those patients that were seizure-free after surgery showed increased integration of the network, particularly in the low frequency bands.

However, these studies do not guide the neurosurgeon in his/her decision of which brain regions to resect. Very recent MEG works suggest that network theory may also be of use here. High frequency oscillations (HFOs) are potential biomarkers of the epileptogenic zone, but their resection does not invariably lead to seizure-freedom. This has lead to the hypothesis that in addition to an area of pathological HFOs, there may be a 'pathological hub' spreading the dysfunction across the entire brain [46]. Resection of these pathological areas may lead to greater success in terms of seizure freedom. Indeed, a recent study shows that MEG is able to pick up on the areas with HFOs, as well as possibly pathologically connected hub areas [46].

## 21.9 Future Research

In conclusion, MEG has proven to be a method that enables us to generate numerous relevant insights on functional connectivity and network characteristics, which are certainly useful in clinical practice as a base of knowledge. MEG has its limitations, such as the problem of volume conduction and a limited spatial resolution, but offers the unique possibility of studying neural network functioning in a non-invasive way. It is, therefore, the designated tool for the longitudinal study of network dynamics. In the specific case of the application of MEG for the study of LGG and LGG treatment a number of questions are relevant.

First of all, it is important to explore whether the combination of MEG with other modalities, such as fMRI, adds specific opportunities. Our research team has investigated the associations between different methods of scoping the brain network in healthy subjects [47, 48], but the use of its application in the setting of LGG remains to be elucidated.

In the second place, the value of preoperative MEG studies for the planning of surgical strategy in the treatment of LGG needs further attention. Both alpha band functional connectivity [32, 33] and pathological hub characteristics may be candidates for such an endeavor [46].

In the third place, the longitudinal monitoring of brain function with the help of MEG could provide us with valuable information on the dynamics of network architecture in an individual patient, possibly leading to tailored treatment strategies. The term 'natural plasticity' refers to the ability of the brain to redistribute functional maps. This implies that the brain is capable to reorganize itself which is crucial to the process of recovery after brain injury or stroke [49] But also slowly progressive lesions, such as LGG's, may give rise to significant functional reshaping [50] Longitudinal use of MEG in this patient category may reveal important findings on the plasticity of the cerebral network beyond the mechanistic insights obtained so far [18, 28, 44].

Hypothetically, preoperative MEG registration could serve as a 'baseline measurement'. During the postoperative period, follow-up MEG registrations may provide important information on the evolution of various network parameters, directly after the operation and, subsequently, during the process of recovery. The decision

to re-operate an LGG in an individual patient with the aim to further reduce tumor mass after initial recovery might be supported by postoperative MEG results that indicate favorable reorganization of the network. Also the influence of other treatment modalities, such as chemotherapy and radiotherapy, on functional connectivity of the brain could be monitored by repeated MEG registrations.

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# Chapter 22
# Interactions Between Diffuse Low-Grade Glioma (DLGG), Brain Connectome and Neuroplasticity

**Hugues Duffau**

**Abstract** The classical approach in neurooncology is to study the glioma first, with little considerations concerning the brain itself. Nonetheless, to define the optimal individualized therapeutic strategy for each DLGG patient, i.e. to optimize the "onco-functional balance", the understanding of the natural history of this chronic disease is not sufficient. One should also investigate the functional reorganization of the central nervous system (CNS) elicited by the glioma growth and migration. Indeed, due to strong interactions between DLGG and the brain, cerebral adaptive phenomena often occur to maintain neurological and cognitive functions. This neuroplasticity may allow the compensation of glioma spread and the preservation of quality of life—until the limits of plastic potential have been reached, leading then to seizures and/or neurological deficits. Here, the purpose is to analyze mechanisms underpinning neuroplasticity, based upon original insights issued from cerebral mapping and functional outcomes in patients who underwent awake surgery for DLGG. The ultimate aim is to tailor the individual management according to the dynamic relationships between DLGG course and neural remodelling. Remarkably, if early surgery is performed in patients with no or mild preoperative deficits, massive brain resection, including within the so-called "eloquent regions", can be achieved using intraoperative electrical cortical and subcortical functional mapping with no persistent neurological worsening. These results support a hodotopical anatomofunctional distribution of the brain, namely, a CNS organized in dynamic and interactive parallel large-scale delocalized networks, able to compensate for each other. Thus, neurooncologists should improve their understanding of brain connectome, because the subcortical connectivity should imperatively been preserved to allow plasticity, with the goal to elaborate new therapeutic strategies, such as multistage surgical approach—made

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possible thanks to cerebral remapping over years. In summary, cognitive neurosciences represent a valuable help to neurooncology. A better knowledge of brain plasticity in a connectomal account of neural processing enables a dramatic improvement of both functional and oncological outcomes in DLGG patients, and leads to the concept of a "personalized functional neurooncology".

**Keywords** DLGG • Neuroplasticity • Brain hodotopy • Brain mapping • Subcortical connectivity • Awake surgery • Functional neuro-oncology • Quality of life

## 22.1 Introduction

The traditional view in neurooncology is to study the tumor first, with little considerations concerning the host, namely, the brain itself. However, in order to define the optimal therapeutic management for each patient bearing a diffuse low-grade glioma (DLGG), the concept of "onco-functional balance" must be taken into account [1]. Indeed, while the understanding of the natural history of this disease is crucial, this is not enough. The adaptative reaction of the central nervous system (CNS) induced by the glioma growth and spread should also be investigated. In fact, dynamic interactions between the DLGG and the CNS may allow neuroplasticity phenomena, resulting in the compensation of glial tumor progression and in the preservation of quality of life—until the limits of plastic potential have been reached, leading then to seizures and/or neurological deficits [2, 3].

In this chapter, the purpose is to analyze mechanisms underpinning brain plasticity, based upon original insights issued from cerebral mapping and functional outcomes in patients who underwent awake surgery for DLGG. The aim is to switch from a localizationist model to a hodopical framework of neural processing. Such a connectomal account of brain organization results in tailoring therapeutic strategy according to the dynamic relationships between DLGG course and adaptatory cerebral functional remapping at the individual level [4].

## 22.2 The Concept of Neural Plasticity

### *22.2.1 History*

As early as the beginning of the nineteenth century, two opposite conceptions of the functioning of the CNS were suggested. Firstly, the theory of "equipotentiality" hypothesized that the whole brain, or at least one complete hemisphere, was involved in the practice of a functional task. By contrast, in the theory of "localizationism" (built on the basis of the "phrenology"), each part of the brain was supposed to correspond to a specific function. Progressively, the frequent reports of lesional studies

led into an intermediate view, namely a brain organized (1) in highly specialized functional areas, called "eloquent" regions (such as the Rolandic, Broca's and Wernicke's areas, early identified), for which any lesion gives rise to major permanent neurological deficits, and (2) in "non-eloquent" regions, with no functional consequences when damaged. Based on these first anatomo-functional correlations, and despite the description by some pioneers of several observations of post-lesional recovery, the dogma of a static functional organization of the brain was settled for a long time, i.e. with the unability to compensate any injury involving the so-called "eloquent areas". Nonetheless, thanks to regular reports of improvement of the functional status following damages of cerebral structures considered as "critical", this view of a "rigid" CNS was called in question in the past decades. Indeed, faced with a lesion of neural tissue, the brain can reallocate the remaining physiological resources to maintain a satisfactory level of function in a cognitively and socially demanding environment. Consequently, many investigations were performed, initially in vitro and in animals, then more recently in humans in order to study the mechanisms underlying these compensatory phenomena: the concept of cerebral plasticity was born [5]. Advances in functional mapping and neuroimaging techniques have dramatically changed the classical modular model for a new dynamic and distributed perspective of CNS organization, able to reorganize itself both during everyday life (learning) and after a pathological event such as a diffuse glioma. However, although there are some literature reports on cases of functional recovery or adaptation in various neurological context, the most persuasive body of evidence for the brain's astonishing, lesion-induced plasticity comes from the field of neurosurgery in general and the resection of DLGG in particular [6].

### *22.2.2 Definition and Mechanisms*

Neuroplasticity is a continuous processing allowing short, middle and long-term remodeling of the neurono-synaptic organization, with the aim of optimizing the functioning of neural networks—during phylogenesis, ontogeny, physiological learning and following lesions involving the peripheral as well as the CNS. Several hypotheses about the pathophysiological mechanisms underlying plasticity have been considered. At a microscopic scale, various mechanisms are suspected, including synaptic efficacy modulations, unmasking of latent connections, phenotypic modifications, and synchrony changes. Interestingly, many of them seem to involve glial cells in a direct or indirect manner: (1) direct manner: neurogenesis; gliogenesis; glial hypertrophy (possibly mediated by the interactions between astrocytes and neurons: indeed, the molecular and functional profiles of astrocytes could be regulated by the neurons, through the "sonic hedgehog" pathway); (2) indirect manner: through the regulation of synapse, as synaptogenesis (mediated by astrocytes) for the grey matter changes; increased glial cells density; increased myelination (mediated by oligodendrocytes); axonal sprouting (possibly involving NogoA which is mainly expressed by the oligodendrocytes); or vascular modifications for the white matter

changes. At a macroscopic scale, diaschisis, functional redundancies, unmasking of latent networks, cross-modal plasticity with sensory substitution and morphological changes are suggested to be implied. Moreover, the behavioral consequences of such cerebral phenomena have been analyzed in humans in the past decades, both in physiology—ontogeny and learning—and in pathology. In particular, the ability to recover after an injury of the nervous system—postlesional plasticity—and the patterns of functional reorganization within eloquent areas and/or within distributed networks, allowing such compensation, have been extensively studied [5].

In other words, cerebral plasticity can be conceived only in a dynamic and not rigid account of CNS organization. According to new theories, the brain is an ensemble of complex networks that form, reshape and flush information dynamically. Thus, reorganization could occur, based on the existence of multiple and overlapping redundancies hierarchically organized. These findings have testified that neuronal aggregates, beside or outlying a lesion, can increasingly adopt the function of the damaged area and switch their own activation pattern to substitute the lesioned structures while facilitating functional recovery following brain damage [4, 7].

In this context, the concept of the brain *connectome* has recently emerged. Its goal is to capture the characteristics of spatially-distributed dynamical neural processes at multiple spatial and temporal scales [8]. The new science of brain "connectomics", which aims to map the neural connections, is contributing both to theoretical and computational models of the brain as a complex system [9], and experimentally, to new indices and metrics (e.g. nodes, hubs, efficiency, modularity) in order to characterize and scale the functional organization of the healthy and diseased CNS [10]. In pathology, neural plasticity is nonetheless possible only on the condition that the subcortical connectivity is preserved [11], to allow spatial communication and temporal synchronization among large inter-connected networks – according to the principle of hodotopy (see below) [12, 13]. Indeed, although different patterns of subcortical plasticity have recently been identified, notably unmasking of perilesional latent networks, modification of the biological properties as changes in synaptic conductance boost, recruitment of accessory pathways, introduction of additional relays within neuron-synaptic circuits, and involvement of parallel long-distance association pathways, the real capacity to build a new structural connectivity ("rewiring") leading to functional recovery was not yet demonstrated in humans [14].

## 22.3 The Time Course of DLGG and CNS Reshaping

DLGG is a slow-growing tumor which progressively invades the brain over years. This slow time course of the disease explains why numerous patients with DLGG have usually only mild or even no functional deficit at diagnosis, despite the frequent involvement of the so-called eloquent structures [2, 15]. Indeed, it was recently shown that brain plasticity cannot be fully understood and fruitfully studied without considering the temporal pattern of the injury inflicted to the brain [3].

Therefore, in acute lesion such as stroke, even if many patients improved within the months following the damage, only around 25% of patients totally recovered [16], while more than 90% of patients with a DLGG (similar location than stroke) had a normal neurological examination (independently of the slight neurocognitive deficits often diagnosed thanks to an extensive neuropsychological assessment—see chapters by Moritz-Gasser and Herbet). Of note, the concept of "recovery" should be more clearly defined in the literature. Although this terminology should be reserved for a complete normalization of the neurological status, numerous authors talk about "recovery" in cases of partial functional improvement after brain damage. A standardization of the nomenclature is crucial to compare the results reported in the different series.

Interestingly, using a neurocomputational model based on a training of a series of parallel distributed processing neural network models, a recent work simulated acute versus slow-growing injuries [17]. The results showed a very different pattern emerging in the simulation of DLGG in comparison with the simulation of stroke, with slow decay of the links within the same subnetwork leading to minimal performance decline, in agreement with the patients literature. Moreover, at the end of the decay regime, the entire affected hidden layer could be "removed" on the simulation with no effect on performance—which closely matches the lack of major impairment from DLGG resection (see the two next chapters). It is likely due to the fact that abrupt stroke occasions rapid neuronal death, while DLGG initially spares neuronal tissue and thus gives time for cerebral remapping over the years. As a consequence, the functional status at the time of diagnosis might be a good reflect of the natural history of the disease, for example a relevant insight into the behavior of the glioma—which represents a crucial issue since these tumors are very heterogeneous.

## 22.4 Preoperative Functional Reallocation in DLGG Patients

Concerning the neural foundations of such functional compensation in DLGG before any treatment, the patterns of reorganization may differ between patients, a very important notion to know by the neurosurgeon with the goal to optimize both surgical indication and planning [18]. Indeed, preoperative functional neuroimaging has shown that four kinds of preoperative functional redistribution are possible, in patients without any deficit [2–4]. In the first one, due to the infiltrative feature of gliomas, function still persists within the DLGG, thus with a very limited chance to achieve a fair resection without inducing postoperative sequelae. In the second one, eloquent areas are redistributed around the tumor, thus with a reasonable chance to perform at least a near-total resection despite a likely immediate transient deficit—but with secondary recovery within a few weeks to months. In the third one, there is already a preoperative compensation by remote areas within the lesional hemisphere. Fourthly, a network of areas can be recuited in the controlateral hemisphere. In the two last patterns, the odds to perform a real total resection (or even a "supra-complete resection", see next chapter) of LGG are

very high, with only a slight and very transient deficit. Finally, these different patterns of reshaping can be associated. Therefore, in cases of brain lesions involving eloquent areas, plasticity mechanisms seem to be based on a hierarchically organized model, i.e., first with intrinsic reorganization within injured areas (indice of favorable outcome); second, when this reshaping is not sufficient, other regions involved in the functional network are recruited, in the ipsilateral hemisphere (close or even remote to the damaged area) then in the controlateral hemisphere if necessary [5, 19, 20].

In summary, as recently supported by magnetoencephalography study, a focal DLGG disturbs the functional and effective connectivity whithin the whole brain, and not only in the restricted area around the tumor [21] (see chapter by Douw et al.). Interestingly, these network dysfunctions are related to cognitive processing in DLGG patients [22]. Indeed, when objective neuropsychological and health-related quality of life assessment have been performed, visuo-spatial, memory, attention, planning, learning, emotional, motivational and behavioral deficits have regularly been observed in gliomas patients. These results show that brain plastic potential has limitations, which should be studied at the individual level. In other words, because surgical treatment itself may induce changes in large-scale functional connectivity [23], such knowledge of individual pattern of remapping should be taken into account, in order to elaborate personalized therapeutic management in DLGG patients [24].

## 22.5 Intraoperative Plasticity in DLGG Surgery

### *22.5.1 Intrasurgical Electrostimulation Mapping*

During surgery for gliomas, especially in “eloquent areas”, it has become common clinical practice to awaken patients in order to assess the functional role of restricted cerebral regions. The surgeon can maximize the extent of resection, and thereby improve the overall survival, without generating functional impairments, thanks to an individual mapping and preservation of critical structures [25, 26]. Therefore, the resection is not performed according to purely anatomic and oncological limits, but up to functional boundaries [27, 28]. Concretely, patients perform several sensory-motor, visuo-spatial, language, cognitive and emotional tasks, while the surgeon temporarily interacts with discrete areas within the grey and white matter around the tumor, using direct electrostimulation mapping (DEM). If the patients stops to perform the task or produces wrong response, the surgeon avoid removing the stimulated site [29, 30]. DEM transiently interacts locally with a small cortical or axonal site, and also non-locally, as the focal perturbation will indeed disrupt the whole subnetwork sustaining a given function [31, 32]. Thus, DEM represents an unprecedented opportunity to identify with a great accuracy and reproducibility, in vivo in humans, the structures that are crucial for brain functions both at cortical and subcortical (white matter and deep grey nuclei) levels [33].

### 22.5.2 Task Selection for Intrasurgical Cognitive Mapping

The optimal selection of the tasks used during intraoperative mapping is essential to preserve a normal life [34, 35]. For example, language mapping can be achieved to identify possible crucial epicenters in the right "non-dominant" hemisphere in left-handers or ambidextrous (and even in some right-handers), if language disturbances were detected on the preoperative cognitive assessment—even in cases of left-lateralization on functional MRI [36, 37]. The aim is to map the neural circuits underpinning the different but interactive sub-functions which should be preserved intraoperatively, by serving as boundaries of resection. DEM allows the mapping of many functions, such as movement (including control of bimanual coordination) [38]; somatosensory function [39]; visual function [40]; auditory-vestibular function [41]; spatial awareness [42]; language, including spontaneous speech and counting, object naming, verbal comprehension, writing, reading, syntax, bilingualism, language switching from one language to another (see [43] for a recent model of anatomo-functional connectivity of language based upon DEM); higher-order functions such as calculation, memory, attention, cognitive control, cross-modal judgement, non verbal comprehension [44–46]; mentalizing and consciousness [47–49].

### 22.5.3 Acute Functional Remapping During DLGG Surgery

Firstly, intraoperative stimulation mapping before resection can confirm the functional reshaping induced by the glioma, as supposed using preoperative functional neuroimaging [2]. It is nonetheless worth noting that recent studies comparing preoperative functional MRI with intraoperative DEM have demonstrated a low reliability of neuroimaging, in particular for language, with a sensitivity of only 37.1% and a specificity of only 83.4%—demonstrating that this technique is not reliable enough to be used in clinical routine [50].

Regarding intra-surgical plasticity, a very amazing observation concerns the existence of acute functional remapping triggered by the resection itself and taking place within 30–60 min of beginning the surgical act. This type of acute reorganization has been very well documented in the sensori-motor system. In several patients harboring a frontal lesion, although stimulation of the precentral gyrus induced motor responses only at the level of a limited number of cortical sites before resection, an acute unmasking of redundant motor sites located within the same precentral gyrus and eliciting the same movements than the previous adjacent sites when stimulated, was observed immediately following lesion removal [51]. Acute unmasking of redundant somatosensory sites was also regularly observed within the retrocentral gyrus in patients operated on for a parietal glioma. Furthermore, it was equally possible to detect a redistribution within a more larger network involving the whole rolandic region, i.e. with unmasking of functional homologuous sites located in the precentral gyrus for the first cortical representation and in the retrocentral gyrus for its redundancy (or vice versa) [52]. The most likely hypothesis

suggests that a local increase of cortical excitability allows an acute unmasking of latent functional redundancies (i.e. multiple cortical representation of the same function), via a decrease of intracortical inhibition [5]. In agreement with this idea, animal models have shown that focal brain damages induce large zones of enhanced cortical excitability in both the lesioned and the intact hemisphere [53]. Likewise, human studies have provided evidence that the level of intracortical inhibition is reduced in the damaged hemisphere in stroke patients [54]. Therefore, it is tempting to speculate that the latent redundant networks revealed by the resection process participate in functional recovery [55]. This idea fits well with the importance of adjacent reorganizations for behavioral recuperation.

## 22.6 Subcortical White Matter Tracts as a Limitation of Neural Plasticity

### *22.6.1 The Concept of Brain Hodotopy*

Although plastic potential is high at the cortical level, subcortical plasticity is low, implying that axonal connectivity should be preserved to allow postoperative compensation [4, 6, 11, 14, 33]. Indeed, lessons from stoke studies have thaught that a damage of the white matter pathways generated a more severe neurological worsening than lesions of the cortex. By combining cortical function and axonal connectivity, an updated model of CNS processing has recently been proposed, moving from a traditional "localizationist" model to a "hodotopical" framework [12, 13]. In pathology, according to this new concept, a topological mechanism (from the Greek *topos* = place) refers to a dysfunction of the cortex (deficit, hyperfunction of a combination of the two), whereas a hodological mechanism (from the Greek *hodos* = road or path) refers to dysfunction related to connecting pathways (disconnection, hyperconnection or a combination of the two). Thus, one should take into account the complex functioning of a large-scale distributed cortico-subcortical network to understand its physiology as well as the functional consequences of a lesion in this circuit—with possible different deficits depending on the location and the extent of the damage (e.g. purely cortical, or purely subcortical, or both) [12, 13].

Recently, probabilistic atlases of postsurgical residue and of functional plasticity were computed on series of patients who underwent resection for a DLGG on the basis of intraoperative electrical brain mapping [6, 11, 56]. The anatomo-functional correlations obtained by combining the intrasurgical functional data with postoperative anatomical MRI findings provided both a greater understanding of the functional limits of surgical removal, and new insights into the potentials and limitations of brain plasticity. Especially, these probabilistic atlases highlighted the crucial role of the axonal pathways in the reorganization of the brain after a lesion [6, 11, 56]. They provided a general framework to establish anatomo-functional correlations by computing for each brain voxel its probability to be left—due to its functional role—on the postoperative MRI. Their overlap with the cortical MNI template and

a DTI atlas offered a unique tool to analyze the potentialities and the limitations of inter-individual variability and plasticity, both for cortical areas and axonal pathways. It was observed as a rule a low probability of residual tumors on the cortical surface, whereas most of the regions with high probability of residual tumor were located in the deep white matter. Thus, projection and association axonal pathways seem to play a critical role in the proper functioning of the brain. In other words, the functions subserved by long-range axonal pathways seem to be less subject to inter-individual variability [57] and reorganization [6, 11, 56] than cortical sites. Consequently, these pathways define the surgical limits in the depth [33] and, since DLGG infiltrate these tracts [58]—which can explain why some patients may experience slight but objective neurocognitive disturbances on extensive neuropsychological examination performed before any treatment [59]—they constitute the main obstacle to radical surgical resection.

### *22.6.2 The Minimal Common Brain*

Two questions arise on why there is no or only very low inter-individual variability for subcortical structures [57] and why their resection cannot be efficiently compensated by plasticity phenomena [6, 11, 56]. For some of these areas, the explanation could be that they act as input or output areas: input sites convey or are the first relay of information entering the brain, whereas output sites are the last relay or the fiber tracts sending information outside the brain. These areas include the primary motor and somatosensory areas, the cortico-spinal and thalamo-cortical tracts and the optic radiations, that is, the projection fibers. These areas are mainly unimodal and probably organized serially. The absence of parallel alternative pathway explains the impossibility to restore their function after any damage [14].

For all other areas, their non-resectability should be analyzed within a network perspective. High-order cognitive processes are mediated by short- and long-range networks, with cortical epicenters connected by U-shaped fibers, associative and commissural pathways and a particular network topology (like the "small word" one) is required to allow proper synchronization between several distant areas [60]. The link between the function and the anatomy is not as simple as for input–output areas. In fact, a local lesion can disturb a whole network topology, which in turn could ultimately hamper the function sustained by this network. For example, subcortical structures like the inferior fronto-occipital fascicle (IFOF) and the arcuate fascicle (AF) are non-resectable because their lesion would cause so major changes in the network topology that the dynamical plasticity potential would be overwhelmed in both hemispheres. Interestingly, cortical functional epicenters that allow a plurimodal integration of multiple data coming from the unimodal systems, are considered as "hubs" in revisited models of cognition [61]. In a step forward, this integration may lead to the conceptualization, performed at the level of a wide network which includes these hubs. As a consequence, the hubs are interconnected by subcortical pathways, themselves crucial for brain function, such as AF and

IFOF which enables a direct communication between the posterior temporal and frontal plurimodal regions. The reproducibility of these results, despite the inter-individual anatomo-functional variability and plastic mechanisms, may lead to suggest the existence of a "minimal common brain", necessary for the basic cognitive functions—even if likely not sufficient for more complex functions such as multi-processing [11, 57]. This hypothesis is in good agreement with recent biomathematical models, analyzing the effect of a simulated focal lesion on the whole brain network topology [62]. For these areas, even biological plasticity—which has been shown to offer an axonal rewiring in animal models [63]—will fail on the long term to repair the connectivity needed to rebuild an effective network topology, hence a functional circuit [14].

In summary, these atlases shed new lights on the hodotopical organization of CNS, may be useful in predicting the likelihood of recovery (as a function of lesion topology), and thus give preoperatively an objective estimation of the expected extent of resection for DLGG resected under intraoperative stimulation mapping. In practice, this means that neurooncologists (especially neurosurgeons) should improve their knowledge concerning white matter circuitery. Therefore, beyond the well-known cortico-spinal (pyramidal), thalamo-cortical (somatosensory), and visual (optic radiations) pathways, subcortical connectivity subserving language, cognitive and emotional functions must be more extensively studied for each patient. As mentioned, DLGG is a tumor which migrates along the main projection, commissural and long-distance association bundles [58]. As a consequence, it is impossible to define the optimal therapeutic strategy against invasive glioma without understanding organization of the neural networks. Thus, cognitive neurosciences are closely related with neurooncology. In addition, beyond the clinical implications of the use of brain mapping technique during DLGG surgery (see the two next chapters), DEM also provides original data with regard to the circuits underlying sensorimotor, language, cognitive and emotional functions.

## 22.7 Anatomo-Functional Subcortical Connectivity Subserving Neural Functions: New Insights Into the Brain Connectome (Fig. 22.1)

### *22.7.1 Connectivity Underlying Sensorimotor Function*

Recent anatomo-functional DEM studies have changed our view of movement, that is, motor execution and control, away from a hierarchical organization and toward parallel and interconnected circuits. First, DEM have confirmed that the corticospinal tracts come from the primary motor cortex, run with a somatotopical organization within the corona radiata (with, from lateral to medial, the pyramidal tracts of the face, upper limb, and lower limb) and then within the posterior limb of the internal capsule (with, from anterior to posterior, the pyramidal tracts of the face, upper limb, and lower limb) before reaching the brainstem and the spinal cord [64]. Furthermore,

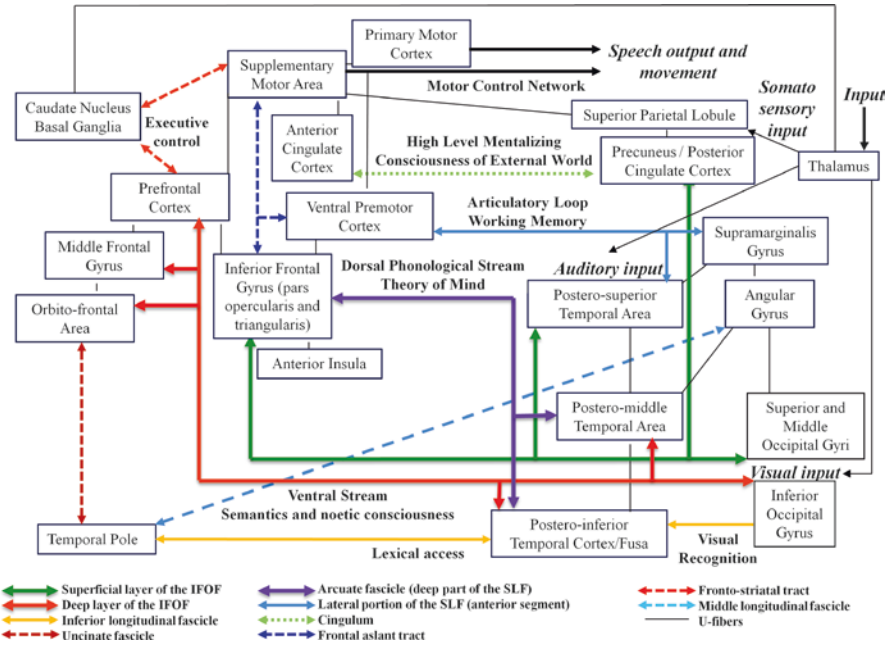


**Fig. 22.1** Proposal of a hodotopical model of functional connectivity in the human brain, with incorporation of anatomical constraints. This networking model was elaborated on the basis of structural-functional correlations provided by intraoperative direct cortico-subcortical electrostimulation mapping

the existence of an additional network involved in motor control was recently evidenced, eliciting movement arrest or acceleration when stimulated in awake patients, with no loss of consciousness [65]. The subcortical stimulation sites were distributed veil-like, anterior to the primary motor fibers, suggesting descending pathways originating from premotor areas known for negative motor response characteristics, and running to the head of the caudate nucleus, and possibly to the putamen through the external capsule: it seems that this motor control circuit is mediated by the fronto-striatal tract [66]. Furthermore, these white matter bundles underpinning movement control were somatotopically distributed. Indeed, stimulation of the fibers from mesial to lateral directions and from posterior to anterior directions evoked arrest of movement of the lower limb (mesially and posteriorly), upper limb(s), and face/speech (laterally and anteriorly) [67]. Further stimulation sites in the anterior arm of the internal capsule indicated a large-scale motor control circuit [65]. More recently, the first evidence of bilateral negative motor responses elicited by unilateral subcortical DEM has been reported. Such findings support the existence of a bilateral cortico-subcortical network connecting the premotor cortices, basal ganglia, and spinal cord, involved in the control of bimanual coordination [38]. Moreover, a DEM study that investigated the neural circuit mediating eye movements (involved in the control of the spatial orienting of attention), supported that the oculomotor tract originating from the frontal eye field might be a part of this motor control network [68].

Posterior thalamo-cortical somatosensory pathways and their somatotopy have also been investigated by DEM, which generate dysesthesias or tingling in awake patients [39, 64]. Interestingly, axonal stimulation of the white matter behind the central sulcus may also induce disturbances in movement control [65], possibly due to transient inhibition of U fibers within the rolandic region [69]. Moreover, in patients who experienced interference with movement during subcortical DEM, fibers that induced inhibition or acceleration were located immediately posterior to thalamo-cortical somatosensory pathways. Therefore, a thalamo-parietal connection distinct from somatosensory pathways is likely [69]. On the basis of these original DEM findings, the existence of a wide fronto-thalamo-parietal sensory-motor network has been suggested [65, 69].

### *22.7.2 Visual Tract*

The optic radiations arise from the lateral geniculate body in three bundles. The anterior bundle curves anterolaterally above the temporal horn (Meyer's loop) usually reaching beyond the anterior limit of the temporal horn and then loops backward along the inferolateral wall of the atrium. The middle bundle courses laterally around and turns posteriorly along the lateral wall of the atrium and the occipital horn. The posterior bundle courses directly backward, also along the lateral wall of the atrium and occipital horn [70]. Recently, visual pathways have also been mapped in awake patients. A protocol was recently proposed in which two images, located in opposite quadrants on the same computer screen, are shown to the patient. It is possible to generate a transient visual field deficit subjectively described by the patient, which is confirmed objectively with this test (only one of the two objects can be seen and, thus, described) during axonal DEM of the optic radiations [40].

Interestingly, DEM can generate either "negative effect" such as blurred vision or impression of shadow, or "positive effect" such as phosphenes in the contralateral visual field. In addition, complex responses such as visual hallucinations (e.g., zoopsia or distortion of pictures as metamorphopsia) have been described by patients during stimulation [71]. These findings might be explained by the fact that DEM of bundles joining the calcarine fissure evokes visual suppression (homonymous hemianopia), whereas DEM of fibres joining the association visual cortex for higher-order visual processing (outside the primary visual system) evokes visual illusion.

### *22.7.3 Connectivity Mediating Language*

On the basis of DEM findings, a dual model for visual language processing has recently been proposed, with a ventral stream involved in mapping visual information to meaning (the "what" pathway) and a dorsal stream dedicated to mapping visual information to articulation through visuo-phonological conversion [43].

These findings complete the seminal model by Hickok and Poeppel [61], which is a pure cognitive model that do not take into account anatomical constraints, especially with regard to the white matter tracts.

#### 22.7.3.1 Functional Anatomy of the Dorsal Superior Longitudinal Fascicle (SLF)/Arcuate Fascicle (AF) Complex

Fiber dissection in cadavers and DTI tractography studies in humans have investigated the structural anatomy of the SLF/AF complex [72, 73]. The different components of the perisylvian SLF were isolated and the tracts were followed until their cortical terminations. Three segments of the perisylvian SLF were detected: (1) anterior segment of the lateral SLF, that connects the supramarginal gyrus and superior temporal gyrus (in the region just posterior to the Heschl's gyrus) with the ventral portion of the precentral gyrus (ventral premotor cortex), (2) posterior segment of the lateral SLF, that connects the posterior portion of the middle temporal gyrus with the angular gyrus, and (3) long segment of the AF, deeply located, stemming from the caudal part of the temporal lobe, mainly the inferior and middle temporal gyri, that arches around the insula and advances forward to end within the frontal lobe, essentially within the precentral gyrus and posterior portion of the inferior and middle frontal gyri. Based on these original data challenging the traditional view, it was suggested that the fibers from the posterior part of the superior temporal gyrus are part of the anterior portion of the perisylvian SLF and not of the AF [72].

In awake patients performing a picture-naming task, cortically, phonemic paraphasias have been generated by DEM of the inferior parietal lobule and inferior frontal gyrus in the dominant hemisphere [74]. Axonally speaking, these phonemic paraphasias were evoked when stimulating the AF [74, 75], possibly associated with repetition disorders [76]. This is in agreement with the theory by Geschwind [77], who postulated that damages of this bundle would produce conduction aphasia, including phonemic paraphasias and repetition disturbances, and this supports the role of the sub-part of the dorsal stream mediated by the AF in phonological processing. Interestingly, the posterior cortical origin of the AF within the posterior part of the inferior temporal gyrus corresponds to the visual object form area [72]. Indeed, this region represents a functional hub, involved both in semantic and phonological processing dedicated to visual material [78, 79]. Therefore, phonological processing sustained by the AF is performed in parallel to the semantic processes implemented by the ventral route (see below). In addition to this direct dorsal route, the indirect dorsal stream composed of the lateral SLF is involved in articulation and phonological working memory, as demonstrated by DEM. Cortical areas eliciting articulatory disorders are located in the ventral premotor cortex, supramarginal gyrus and posterior part of the superior temporal gyrus [80, 81]. Axonally, stimulation of the white matter under the fronto-parietal operculum and supramarginal gyrus, laterally and ventrally to the AF, elicited anarthria as well [74, 81]. This bundle corresponds to the part III of the SLF according to Makris et al. [82]. Indeed,

this lateral operculo-opercular component of the SLF constitutes the articulatory (auditory-motor) loop, by connecting the supramarginal gyrus/posterior portion of the superior temporal gyrus (which receives feedback information from somatosensory and auditory areas) with the frontal operculum (which receives afferences bringing the phonological/phonetic information to be translated into articulatory motor programs and efferences toward the primary motor area) [72, 76, 81].

Using the same paradigm, DEM also supported that syntactic processing was mediated by delocalized cortical regions (including left inferior frontal gyrus and posterior middle temporal gyrus) connected by a sub-part of the left SLF. Interestingly, this sub-circuit is interacting but independent of the sub-network involved in naming, as demonstrated by a double dissociation between syntactic (especially grammatical gender) and naming processing during DEM. These findings support a parallel rather than serial theory, calling into question the principle of "lemma" [83].

#### 22.7.3.2 Functional Anatomy of the Ventral Route

The ventral stream connects the occipital, parietal and posterior temporal areas with the frontal lobe. This ventral route is referred by some authors as "extreme capsule fiber system" with reference to connectivity studies in the primate [84]. It seems nonetheless more adapted to talk about fascicles rather than "extreme capsule", because the latter only considers a discrete anatomical structure while the former considers actual neural pathways with their cortical termination, in a connectomal view of brain processing. Indeed, if one takes account of the sole subcortical region without any considerations regarding the cortical epicenters connected by these white matter fibers, this does not allow the understanding of the whole eloquent network.

Regarding structural anatomy, the ventral route is composed of direct and indirect pathways. The direct pathway is represented by the IFOF, that has never been described in animals, explaining the controversy about its role [46]. In humans, the IFOF is a ventral long-distance association bundle that connects the occipital lobe, parietal lobe and the postero-temporal cortex with the frontal lobe. Recent anatomic dissections combined with DTI have investigated the main course of the IFOF [85, 86]. From the posterior cortex, it runs within the sagittal stratum in the superior and lateral part of the atrium; it reaches the roof of the sphenoidal horn in the temporal lobe; it joins the ventral part of the external/extreme capsule and it runs under the insula at the posterior two-thirds of the temporal stem; then it joins the frontal lobe [85]. Two layers of the IFOF have been described [86]. The superficial and dorsal layer connects the posterior portion of the superior and middle occipital gyri, the superior parietal lobule and the posterior part of the superior temporal gyrus to the inferior frontal gyrus (pars triangularis and opercularis). The deep and ventral subcomponent connects the posterior portion of the inferior occipital gyrus, the posterior temporal-basal area including the Fusa (fusiform area at the occipito-temporal junction) and the posterior part of the middle temporal gyrus to the frontal lobe - orbitofrontal cortex, middle frontal gyrus and dorsolateral prefrontal cortex [85, 86].

In parallel, the ventral stream is underpinned by an indirect pathway, constituted by the anterior part of the inferior longitudinal fascicle (ILF) (running below the IFOF), that links the posterior occipitotemporal region (Fusa) and the temporal pole (TP), then relayed by the uncinate fasciculus (UF), that connects the TP to the basi-frontal areas by running within the anterior third of the temporal stem (in front of the IFOF) [85]. Of note, the posterior part of the ILF links the occipital lobe to the posterior occipitotemporal junction (visual object form area) [70, 79]. This means that this indirect route connects the occipital/Fusa to the orbito-frontal cortex - thus partially overlapped with the IFOF. Finally, while previously described in monkey, another pathway has recently been observed in humans, the middle longitudinal fascicle (MdLF), that connects the angular gyrus with the superior temporal gyrus up to the TP and courses under the superior temporal sulcus, lateral and superior to the IFOF [89].

In the awake patient, during picture naming, DEM of the IFOF, at least in the dominant hemisphere, elicited semantic paraphasias either associative (e.g. /key/ for /padlock/) or coordinate (e.g. /tiger/ for /lion/) in more than 85% of cases [90]. It did not matter what portion of the IFOF was stimulated (parieto-occipital junction, temporal, subinsular or frontal part) [43, 56]. These language disorders were mainly induced by stimulating the superficial layer of the IFOF. Interestingly, semantic paraphasias were never observed during stimulation of the dorsal route (SLF) [74]. Moreover, IFOF stimulation may also generate verbal perseveration [91], raising the question of its role in semantic control.

The functional role of the indirect ventral pathway is still debated. On one hand, this indirect route connects areas involved in verbal semantic processing such as Fusa and lateral frontal cortex [92]. Moreover, the major cortical relay between the ILF and UF is the TP, which is a hub, i.e. a functional epicenter enabling a pluri-modal integration of the multiple data coming from the unimodal systems (sub-served by ILF, UF and MdLF), explaining its role in semantics and its implication in semantic dementia when bilaterally damaged [93]. On the other hand, except for the posterior part of the ILF which is involved in visual recognition and reading [78, 79, 87, 88] and for which injury generates alexia [78, 79], the indirect pathway can be functionally compensated when unilaterally damaged [94–96]. This was also confirmed by language recovery following anterior temporal lobectomy in tumor and in epilepsy surgery [94, 97]. Even if very mild and selective deficit may persist, as concerning proper name retrieval after resection of the UF [98], or a more difficult lexical access after resection of the anterior part of the ILF combined with resection of the posterior part of the inferior temporal cortex [99], this is a good illustration of the concept of "subcortical plasticity", in which a sub-network (IFOF, direct pathway) is able to bypass another sub-network (indirect pathway) and to functionally compensate it [14, 96]. Similarly, DEM of MdLF and resection of its anterior part failed to induce any functional disorders [100], demonstrating that this fascicle converging to the TP can also be compensated.

In summary, DEM has enabled a re-examination of the classical Broca–Wernicke localizationist model of language. The new findings from axonal stimulation provide a distributed framework for future studies of language networks and

for management of patients with aphasia. This new model is based on multiple direct and indirect corticosubcortical interacting subnetworks involved in syntactic, semantic, phonological and articulatory processes. It offers several advantages in comparison with previous models, especially by explaining double dissociations during damage of the ventral versus dorsal stream (semantic and phonemic disorders, respectively). Also, it takes into account the cortical and subcortical anatomical constraints [43].

### *22.7.4 Connectivity Sustaining Visuospatial and Vestibular Processing*

In awake patients, axonal DEM of the ILF has generated contralateral visual hemiagnosia, supporting the existence of an occipitotemporal pathway connecting occipital visual input to higher-level processing in temporal lobe structures, in particular the fusiform gyrus [101]. These stimulation findings support a crucial role for the ILF in visual recognition, with specialization of this bundle for visuospatial processing in the right hemisphere and language processing in the left hemisphere.

Stimulation of a specific part of the SLF (called the SLF II) in the right hemisphere can produce spatial cognition problems. Indeed, DEM of this structure elicited rightward deviation in a line bisection test [42]. These data suggest that parietal–frontal communication is necessary for symmetrical processing of the visual scene. In other words, spatial awareness depends not only on the cortical areas of the temporal–parietal junction, but also on a larger parietal–frontal network communicating via the right SLF.

Finally, stimulation of another subcircuit in the right SLF can cause a central vestibular syndrome with vertigo, by disrupting the vestibular inputs assembled in the temporoparietal areas and the prefrontal cortex [41]. This finding demonstrates the role of the SLF in the network coordinating body posture and spatially oriented.

### *22.7.5 Connectivity Subserving Mentalizing*

Regarding the network sustaining mentalizing, namely, the theory of mind, crucial for emotion and social cognition, intraoperative DEM (that can interfer with the neural activity of mirror-related frontal areas by impairing mentalistic inferences) [47], combined with pre- and post-operative behavioral examinations showed that this function is made possible by parallel functioning of two subsystems. The first, low-level, of mentalizing accuracy of identification (mirror system, i.e. the ability to appreciate other people's emotions) is subserved by the AF/SLF complex; the second, high-level of inferential mentalizing, corresponding to

the attribution of mental states, is mediated by the cingulum [102, 103]. These findings, which constitute the first experimental data on the structural connectivity of the mentalizing network, suggest the existence of a dual-stream connectomal model, and could lead to a better understanding of disorders that affect social cognition, as autism [102].

### *22.7.6 Fibers Underlying Cognitive Functions*

DEM also evidenced the existence of an executive system (including prefrontal cortex, anterior cingulate and caudate nucleus) involved in the cognitive control of more dedicated subcircuits, as for example the subnetwork involved in language switching—itself constituted by a wide cortico-subcortical network comprising postero-temporal areas, supramarginal and angular gyri, inferior frontal gyrus and a sub-part of the SLF [104]. Moreover, the frontal aslant tract, that connects the pre-supplementary motor area and anterior cingulate with the inferior frontal gyrus, seems to play a role in language control, especially with regard to planning of speech articulation [66]. Therefore, DEM of this tract may evoke stuttering [105]. In the same vein, a cortico-subcortical loop involving the deep grey nuclei, especially the caudate nucleus, was also demonstrated as participating in the control of language (selection/inhibition), since DEM of the head of the caudate nucleus in the left hemisphere generated perseverations with a high level of reliability [106]. Anatomically, this cortico-striatal loop seems to be supported by the fronto-striatal tract [66].

DEM of the IFOF also induced non-verbal comprehension disturbances during non-verbal semantic association test—e.g. Pyramid and Palm Trees Test. The patients were not able anymore to make a semantic choice during DEM, with some of them still able to join a short verbal description of their feelings, like “I don’t know at all”, “what do I have to do?”, “I don’t understand anything” [46]. These comprehension disorders were mainly generated by stimulating the deep layer of the IFOF, and elicited a double dissociation: semantic paraphasia with normal non-verbal semantic choice during DEM of superficial IFOF and *vice versa* during DEM of deep IFOF. Thus, it was suggested that the existence of a superficial component involved in verbal semantics (see above) and a deep component involved in amodal semantic processing [46].

These data are in agreement with the cortical terminations of the IFOF (prefrontal, temporal-basal and parietal areas), that correspond with the cortical network involved in semantic control [86]. Consequently, from the new insights gained from axonal DEM, an original anatomo-functional model of semantic processing has been recently proposed, in which the crucial pathway is represented by the IFOF. In this model, visual information is processed at the level of the occipital and temporal-basal associative cortices, and auditory information is processed at the level of the temporal and parietal associative cortices. They are transmitted directly on an amodal shape to the prefrontal areas, which exert a top down control over

this amodal information in order to achieve a successful semantic processing in a given context. DEM of this fascicle generates a disruption of these rapid direct connections. The transient semantic disorganization observed when stimulating the IFOF would therefore be caused by a dis-synchronization within this large-scale network, interrupting simultaneously the bottom up transmission and the top down control mechanisms [46]. Thus, IFOF might play a crucial role not only in verbal and non-verbal semantic processing, but also in the awareness of amodal semantic knowledge, namely noetic consciousness. From a phylogenic perspective, because recent studies in the primate failed to identify this tract, one could suggest that the IFOF is the proper human fascicle. This multi-function fascicle allows human to produce and understand language, to manipulate concepts, to apprehend and understand the world (i.e. metalinguistics, conceptualization and awareness of knowledge) and it contributes to make the human what he is, with his infinite wealth of mind [46].

In the same spirit, axonal DEM has shown that disruption of the subcortical connectivity of the left posterior cingulate cortex reliably induced a breakdown in conscious experience [48, 49]. This acute phenomenon was mainly characterized by a transient behavioral unresponsiveness with loss of external connectedness (the patients described themselves as in a dream, outside the operating room). This finding suggests that functional integrity of posterior cingulate connectivity is necessary to maintain consciousness of the external environment. In other words, axonal DEM can open the door to the investigation of the connectomal anatomy underlying distinct levels of awareness, including the pathways involved in monitoring of the human level of consciousness related to semantic memory (noetic consciousness), as well as the pathways that sustain consciousness of the external world. Axonal DEM can also be used to explore the dynamic interactions between these subcircuits, and possible functional regulation of the intrinsic activity of these subcircuits by other subnetworks, such as the cingulothalamic system [48].

To sum up, these original insights provided by DEM strongly support the fact that cerebral functions are underpinned by extensive circuits comprising both the cortical epicenters and connections between these “hubs”, created by associating bundles of white matter [107]. In this hodopical model challenging the traditional localizationist view, neurological function comes from the synchronization between different epicenters, working in phase during a given task, and explaining why the same hub may take part in several functions depending on the other cortical areas with which it is temporarily connected at any one time. One step forward, it is crucial to consider that complex brain processes are possible only because of dynamic interactions exist between these parallel delocalized sub-networks, with different levels of sub-circuits recruitment according to the task required. Therefore, brain processing should not be conceived as the sum of several subfunctions. Rather, cerebral function results from the integration and potentiation of parallel (while partially overlapped) subnetworks, in a connectomal view of CNS functioning [33].

## 22.8 Cerebral Reshaping: Its Implications for (Surgical) Treatment of DLGG

Maximal surgical resection is the first option in DLGG (see next chapter). Consequently, it is important to be reliable in the preoperative estimation of the extent of resection. Interestingly, such prediction will directly depend on the involvement (or not) of subcortical pathway which cannot be functionally compensated (see probabilistic atlases of functional plasticity described above)—and this will lead to the selection of surgery as a first treatment or in contrast to give neoajuvant chemotherapy if the gliomas is too diffuse within the "minimal common brain" (see chapter by Duffau and Taillandier) [24]. Results of the neuropsychological assessment performed before any treatment will also participate in the investigation of the individual plastic potential. In other words, if the patient already experienced significant cognitive disorders and a fortiori neurological deficit, this means that limits of brain plasticity have been reached—preventing functional compensation. Such parameters should be incorporated in the surgical strategy with the goal (1) to extent the indications of resection in eloquent structures so far considered as "inoperable" (2) to maximize the extent of glioma removal, by performing the resection according to individual functional boundaries with no margin (3) while minimizing the risk of postoperative permanent neurological worsening or even by improving the quality of life [1, 30].

Thanks to the phenomena of preoperative and intraoperative plasticity, several surgical series showed that it was possible to undertake wide surgical resection of DLGG invading regions of the brain conventionally deemed to be inoperable. Extensive DLGG removals have therefore been carried out without causing permanent neurological deficits in the following "eloquent" brain structures (Fig. 22.2).

### *22.8.1 Resection of DLGG Within Broca's Area*

Surgical resection of DLGG within the pars opercularis and/or triangularis of the left inferior frontal gyrus can be performed without generating permanent language deficits [108–111]. Language compensation may be underlain by the recruitment of adjacent regions, primarily the ventral premotor cortex (vPMC), the pars orbitaris of the inferior frontal gyrus, the dorsolateral prefrontal cortex and the insula [108]. Indeed, it has recently been demonstrated that the left vPMC (located behind the pars opercularis) cannot be (totally) removed because it was in fact the final common pathway for speech - while Broca's area can be compensated after resection [81, 112]. Indeed, extensive neuropsychological examination following resection of Broca's area confirmed a complete functional recovery [109]. A transopercular surgical approach through Broca's area, even though not invaded by the tumor, has even been reported in insular DLGG in order to avoid splitting the Sylvian fissure

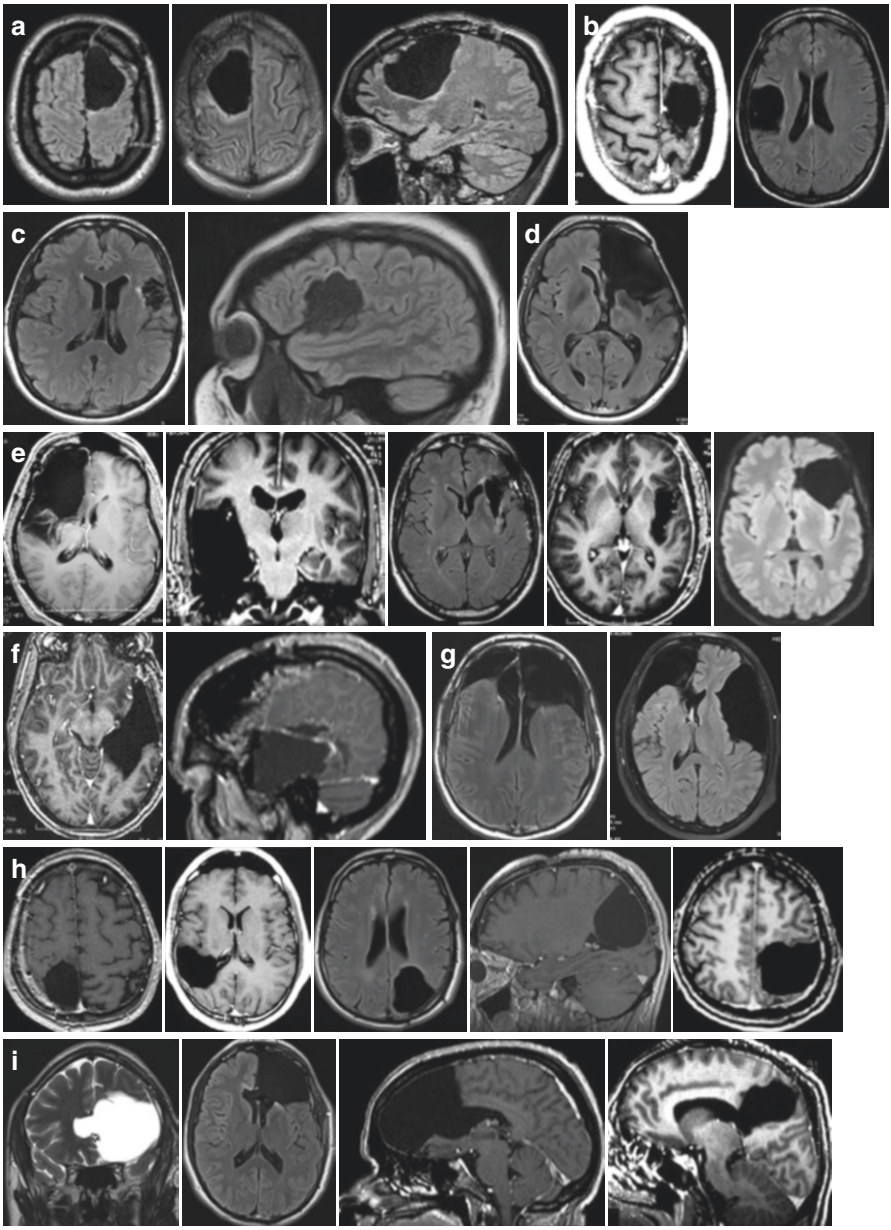


**Fig. 22.2** Examples of extensive glioma resections performed within the so-called "eloquent" areas using intraoperative electrical mapping, with preservation of the quality of life thanks to brain plasticity: (**a**) left and right supplementary motor areas; (**b**) left primary motor area of the hand ("knob of the hand") and right primary sensory-motor area of the face; (**c**) "Broca's area" and the rolandic operculum in the left dominant hemisphere; (**d**) entire left frontal lobe including "Broca's area"; (**e**) right paralimbic system, left insula and left operculo-insular complex; (**f**) left dominant temporal lobe, including "Wernicke's area" (posterior to the Labbé vein); (**g**) bilateral lesions; (**h**) parietal lobe in right (superior and inferior parietal lobule) and left hemispheres, including the primary somatosensory area; (**i**) corpus callosum, anterior or posterior part (splenium)

and therefore reducing the risk of vascular injuries: no persistent language deficits have been observed [113, 115]. Interestingly, a recent probabilistic map for crucial cortical epicenters of human brain functions, based on over 700 DEM data obtained in 165 consecutive patients who underwent awake mapping for DLGG resection, challenged the classical theories of brain organization by demonstrating that Broca's area is not the speech output area [115, 116].

### *22.8.2 Resection of DLGG Within Wernicke's Area*

The language compensation following resection of DLGG involving the posterior part of the left "dominant" superior temporal gyrus (and its junction with the inferior parietal lobule) could be explained by the fact that this complex function is organized in multiple parallel networks. As a result, in addition to the recruitment of areas immediately adjacent to the surgical cavity (e.f. the supramarginal gyrus), the long term reshaping could also involve progressive recruitment of remote regions within the left dominant hemisphere—such as the pars triangularis of inferior frontal gyrus or other left frontolateral regions—as well as controlateral sites in the right hemisphere because of transcallosal disinhibition [117]. Indeed, a recent study combining functional MRI and DEM evidenced the existence of a wide bilateral cortico-subcortical network able to compensate surgical resection of left Wernicke's area invaded by glioma [118].

### *22.8.3 Resection of Insular DLGG*

Despite a possible hemiparesis after right insular DLGG removal, likely because this region is a non-primary motor area, and possible transient speech disturbances following left dominant insular DLGG resection, all patients recovered in a personal experience—except in rare cases (2%) of deep stroke due to a damage of the lenticulo-striate arteries [114, 119–121]. QoL was even improved in about a third of patients who had epilepsy which was refractory to preoperative medical treatment, and in whom removal of the insular tissue (and even when necessary additional removal of the temporomesial structures), controlled the seizures. Moreover, it has been possible to remove the claustrum with no cognitive disorders (despite its role suggested in consciousness) in right non-dominant fronto-temporo-insular DLGG involving the deep grey nuclei [122]. The right striatum was also resected when invaded by DLGG without causing motor deficit or movement disorders, even after a long-term follow-up over 10 years: this compensation can likely be explained by a recruitment of parallel subcortical circuits such as pallido-luyso-pallidal, strio-nigro-striate, cortico-strio-nigro-thalamo-cortical and cortico-luysal networks [123].

### 22.8.4 Resection of DLGG Involving the Primary Sensory-Motor Area of the Face

Despite transient cerebral facial paralysis, the bilateral hemispheric cortical representation of this function explains why all patients have recovered [124]. However, if the insula is also invaded, a transitory Foix-Chavany-Marie syndrome may be produced with transient bilateral transient orofacial pharyngeal laryngeal paralysis [125].

### 22.8.5 Resection of DLGG Involving the Primary Motor Area of the Upper Limb

The "rigid" somatotopic organization of the homunculus needs to be replaced by a more dynamic vision of the functioning of sensorimotor areas, based on the fact that there are redundancies, both within the primary motor cortex and between the pre- and retrocentral regions (see above). Stimulation of the precentral gyrus can regularly produce somatosensory responses, whereas stimulation of the retrocentral gyrus may lead to involuntary muscle contractions or even to stop movement—indicating the existence of a complex central network and not a succession of discrete independent sites [53]. Unmasking of the latent subnetworks can therefore be demonstrated in real time in the operating theater, allowing sensorimotor maps to be reorganized within an hour and permitting more complete resection without causing deficit: these are short term plasticity mechanisms [54, 55]. Moreover, long-term redistribution effects (such as years later after the first operation) may also occur, optimizing tumor resection during a reoperation compared to the initial surgery, including surgery in the"knob of the hand" [117, 125, 126] (see below).

### 22.8.6 Resection of DLGG Within the Primary Somatosensory Area

Due to a dynamic organization of the whole central region referred to above, results using pre- and post-operative functional neuroimaging have suggested the possible recruitment of "redundant" eloquent sites around the cavity, within the postcentral gyrus, after removal of a DLGG involving the primary somatosentory cortex. This is in accordance with the intraoperative DEM data, showing unmasking of redundant somatosensory sites during resection, likely explained by the decrease of the cortico-cortical inhibition. In addition, recruitment of secondary somatosensory areas and/or posterior parietal cortex, primary motor area (due to strong anatomo-functional connections between the pre- and retro-central gyri), and controlateral primary somatosensory area may contribute to functional compensation to various degrees [117, 127].

### 22.8.7 Resection of DLGG Involving the Supplementary Motor Area

This resection generally causes a typical syndrome, with transient symptoms of akinesia (which may be complete) and mutism (particularly after surgery to the left supplementary motor area), which improves rapidly over around 10 days and then resolves after a few weeks (usually after intensive rehabilitation) [128, 129]. Pre- and postoperative task-based and resting-state funtional MRI has shown recruitment of the supplementary motor area and contralateral premotor cortex, as well as a modulation of the intra-hemispheric and inter-hemispheric connectivity, contributing to recovery [130, 131]. A more detailed cognitive examination however may reveal persistent subtle but objective long-term problems, particularly with complex movements and bimanual coordination [130]. For this reason, preservation of networks subserving movement control may be considered in some patients in order to preserve an excellent quality of life (in a pianist for example) [38, 65–67].

### 22.8.8 Resection of DLGG Involving a Subsection of White Matter Tracts

Interestingly, while neuroplasticity is constrained by subcortical connectivity (see above), some parts of white matter pathways can be resected with no severe permanent functional deficit. Indeed, this overall picture is more complex in some respects, as witnessed by the results of tract-based cluster analyses reported in a recent probabilistic atlas of functional plasticity [6]. In this study, the vast majority of individual tracts were generally divided into a subsection with a low and a subsection with a higher functional compensation index—suggesting that groups of fibres within the same tract differ in their neuroplastic potential. This confirms observations made in clinical practice. A telling example is the ILF, which connects the temporal pole to the occipital cortex and the occipitotemporal junction. Although the posterior part of the ILF is always functional for a set of cognitive processes (including reading aloud [79] and visual recognition [78]), its anterior part appears to abandon its functional role once infiltrated by a DLGG. These gradients of plasticity in the basal inferotemporal system can be analysed with regard to the connectivity patterns in the occipitotemporal area. In addition to projections from the ILF, this region receives widespread neural connections from the posterior segment of the SLF, the IFOF and the AF or even the vertical occipital fasciculus. Accordingly, one can speculate that the information broadcast by the ILF towards the temporal pole under normal circumstances could be redistributed via other connectivities if functional compensation is prompted by glioma growth [94, 96]. In the same vein, a part of the corpus callosum invaded by DLGG may also be removed with no morbidity [132].

However, as previously mentioned, in spite of these rare exceptions, the axonal connectivity should be preserved in the vast majority of cases, to allow the occurrence of neuroplasticity mechanisms within a wide bilateral cortico-subcortical circuit—also involving the deep grey nuclei and cerebellum, as recently evidenced by means of resting-state functional MRI before and after surgery for DLGG [133].

## 22.9 Postoperative Plasticity Evidenced by Serial Mapping: Towards a Multi-Stage Surgical Approach

Beyond preoperative and intraoperative reshaping of brain networks, postoperative plasticity also accounts for the resectability of areas for a long time thought as "unresectable". Again, these areas should be considered as nodes within a wide network: after their removal, the whole functional network will self-reorganize by dynamical and biological plasticity, and the function will finally be preserved. Indeed, the good clinical status 3 months after surgery (as evidenced by extensive neuropsychological testing) as well as the return to a normal life (including the return to work) in DLGG patients, argue for efficient plasticity mechanisms for these areas [2, 13, 18]. Such mechanisms induced by surgical resection within eloquent areas were also studied, by performing postoperative functional neuroimaging once the patient has recovered his preoperative functional status. In particular, several patients were examined following the resection of gliomas involving the supplementary motor area, which elicited a transient postsurgical syndrome (see above). Functional MRI showed, in comparison to the preoperative imaging, the occurrence of activations of the supplementary motor area and premotor cortex contralateral to the lesion: the contrahemispheric homologous thus participated to the post-surgical functional compensation [130, 131].

The price to pay to obtain such favorable functional results is sometimes to perform incomplete resection of the glioma, when the tumor invaded areas still crucial for the function [1]. A new concept recently proposed is to use more systematically such postoperative functional neuroimaging (task-based and/or resting state functional MRI), especially when the patient has totally recovered, since neuroimaging can be easily repeated due to its non-invasive feature, in order to compare the new maps to those obtained before surgery [4, 131, 133, 134]. Indeed, even if this method has some methodological limitations, subtraction between a pre- and post-operative acquisition may nonetheless shows a possible additional functional reshaping, due to (1) the resection itself (2) the postsurgical rehabilitation (3) the re-growth of the residual DLGG over the months or years (as before surgery). Such findings have led to propose a new strategy based on multi-stage surgical approach [134].

A better understanding of mechanisms underlying this postsurgical neuroplasticity was made possible thanks to experimentations in animals.

### *22.9.1 Experimental Observations in Animals*

Firstly, the possibility that functional recovery is modulated by kinetic factors has been addressed in a series of animal studies. The main idea behind these studies was to mimic the development of slow growing lesions by performing successive partial surgical ablations within a cerebral structure. These partial excisions were then compared to acute resections. In most experiments a control group was included. In this case several surgeries were performed but no cerebral tissue was removed ("sham" operation). Beyond some marginal disparities, the take-home message of all these studies is quite clear: the negative functional impact of large cerebral lesions is much smaller in progressive than acute lesions [3]. For instance, in rats, it was shown that major deficits were still present 36 days after an acute ablation of the entire somatosensory cortex. These deficits were absent when the same area was removed in two stages. In this case, the experimental rats could not be differentiated from a non-operated control group [135]. Another similar, and even more spectacular report, was provided by Adametz in cats [136]. The animals were submitted to a progressive (up to 8 surgeries) or acute resection of the midbrain reticular formation. In this latter case, the cats felt into deep coma and died within a few days after the surgery. In the former case, by contrast, complete recovery was found. The same type of dissociation was observed in monkeys. Acute ablations of the prefrontal cortex were found to induce functional deficits that were much more severe than those produced by serial lesions [137].

Probably, the most direct demonstration that functional recovery is directly influenced by the kinetic of the lesion inflicted to the brain has been provided by Patrissi and Stein [138]. These authors trained a group of rats to retrieve water alternatively located in the right or the left branch of a conventional T-maze. Following a period of training, the rats were divided in several sub-groups: (1) one-stage bilateral resection of the frontal cortex; (2) two-stage bilateral resection of the frontal cortex (one hemisphere per operation); (3) one or two-stage sham operations (control group). For the two-stage groups, three interlesion intervals were considered: 10, 20 or 30 days. The rats given sequential (two-stage) frontal lesions with either a 20 or 30 day interoperative interval could not be differentiated from the sham-operated controls. Animals with two-stage lesions produced 10 days apart exhibited substantial deficits when contrasted with the sham-operated, the 20 day or the 30 day two-stage groups. However, the two-stage 10 day animals performed significantly better than the one-stage rats. Similar results were found in other studies involving resections of the frontal cortex [139] and the superior temporal gyri [140]. In all these studies, the animals were reported to exhibit a complete recovery when the different surgeries were spaced by a sufficient interval. This interval varied from study-to-study but it was never smaller than 6 days. Whatever the interlesion interval, the level of recovery was always better for the multi-stage surgeries than for the one-stage operations.

Of course, the positive effect of sequential lesions on functional recovery depends strongly on the amount of tissue resected at each surgical stage. This was clearly

shown by Stein and colleagues in a monkey study involving the resection of the sulcus principalis. In this study, the total amount of tissue resected was kept constant. It was reported that four partial lesions performed three weeks apart produced a greater level of recovery than two partial lesions performed ten weeks apart [141]. This result pleads directly for the idea that the progressiveness of neural destruction is a key predictor of functional recuperation.

### *22.9.2 Application to Patients with DLGG: Towards Serial Surgery*

Interestingly, recent series demonstrated that such remapping was not a theoretical concept, but a concrete reality in humans [2, 18]. As mentioned, postoperative functional neuroimaging performed some months or years following surgery for DLGG in patients with a complete recovery clearly showed a new recruitment of perilesional areas and/or remote regions within the ipsilesional hemisphere and/or a recruitment of controlateral structures [118, 130, 134], with changes in the intrinsic connectivity [131, 133]. On the basis of these data, a second surgery was proposed in patients with incomplete resection, who continued to enjoy a normal life, before the occurrence of new symptoms (except possible seizures), only because the volume of the residual glioma increased [142]. The second surgery was also conducted using intraoperative cortical and subcortical DEM, in order to validate the mechanisms of brain reshaping supposed but not proven by preoperative functional neuroimaging, before to perform the additional resection [117, 134]. The preliminary results have supported the efficacy and the safety of such re-operation for DLGG not totally removed during a first surgery, due to their location within eloquent areas. Indeed, in a recent series, 74% resections were complete or subtotal (less than 10 ml of residue) following the second operation, despite no additional serious neurological deficit—on the contrary, with an improvement of the neurological status in 16% of cases. Again, the seizures were reduced or disappeared in 82% of patients who experienced intreactable epilepsy before the second operation. The median time between the two operations was 4.1 years, and all patients were still alive with a median follow-up of 6.6 years despite an initial incomplete resection. Therefore, these original data demonstrated that, thanks to mechanisms of cerebral plasticity, it is possible to re-operate patients with DLGG involving eloquent areas with a minimal morbidity and an increase of the extent of resection. Therefore, it was suggested to "over indicate" an early re-intervention, in order to anticipate the second surgery before malignant transformation [142]. Such concept of multi-stage surgical approach was particularly useful to optimize the extent of resection in traditional "critical" areas such as the Broca's area, Wernicke's area or Rolandic area (see above) (Fig. 22.2).

In addition, one can currently consider to perform also postoperative functional neuroimaging after rehabilitation, known to induce a significant improvement in

patients with brain tumors [143], and after recovery following a second surgery—in order to open the door to a possible third or even fourth resection several years after the previous operations. The goal is both to allow the patient to continue to enjoy a normal life as well as to increase the overall survival [1]. It is also possible to integrate surgeries within a dynamic therapeutic strategy including chemotherapy and radiotherapy, especially when a wide removal is not possible for functional reasons [24]. To this end, neoadjuvant chemotherapy was recently advocated in DLGG, with the goal to induce a shrinkage of the tumor before an operation or a reoperation [144]—but also possibly to facilitate functional brain reshaping (see chapter by Duffau and Taillandier) [24].

## 22.10 Conclusions: Neuroplasticity and the Concept of Onco-Functional Balance

Cognitive neurosciences represent a valuable help to neurooncology, by opening new avenues to elaborate original therapeutic strategies, and thus to improve both quality of life and median survival. It is time to switch from a modular to a hodotopical (delocalized) and dynamic model of CNS processing. Combination of serial peri-operative functional neuroimaging and intraoperative DEM has resulted in new individual and integrative models of functioning of neurono-synaptic circuits. Such networking models allowed a better knowledge of the dynamic potential of spatio-temporal reorganization of the parallel and interactive networks, namely the mechanisms of neuroplasticity—but also a better understanding of its limitation, mainly represented by the subcortical connectivity [4, 6, 11]. Indeed, for the first time in the history of neurosciences, DEM of the white matter tracts offers a unprecedented opportunity to investigate the function of the connectomal anatomy in humans. This original methodology, in which real-time anatomo-functional correlations are performed in awake patients, has provided new insights into the connectome underlying the sensorimotor, visuospatial, language and sociocognitive systems [33]. On the basis of these unique results in the literature, the first functional atlas of human white matter has recently been built [56]. In addition, interactions between these neural networks and multimodal systems, such as working memory, attention, executive functions and even consciousness, can be investigated by axonal stimulation. In this networking model, cerebral function results from the integration and potentiation of parallel, but partially overlapping, subnetworks [33].

In this comprehensive framework, surgical resection of DLGG in areas traditionally considered as “inoperable” is possible while preserving brain functions. Therefore, based on this new concept of a “hodotopic and plastic brain” [13], the next surgical goal in DLGG is to move towards personalized serial therapeutic managements [24]. The aim is to weight the value of the extent of resection versus the neurological worsening that could be voluntarily generated by a radical resection; that is, to study the “onco-functional balance” at the individual level [1]. In other

words, the benefit-risk ratio of different strategies of resection should be considered according to the brain structures actually invaded and by their plastic potential. To select the best candidates to (re)-operation(s), new bio-mathematical models could be helpful to examine the brain connectome, in order to attempt to predict *before surgery* the patterns of postsurgical remapping at the individual scale on the basis of the data provided by the preoperative functional neuroimaging [145]. The goal is to increase both the quantity of life and the time with a normal quality of life, based upon strong interactions between the tumor course, brain reorganization and multi-stage surgical approach adapted to each patient over time: this opens the window to the principle of "functional surgical neuro-oncology" [146]. Indeed, in the era of "evidence-based medicine", it is crucial not to forget "personalized-based medicine", taking into account the considerable interindividual anatomo-functional variability of the brain [57].

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# Part V
# New Insights into the Therapeutic Strategies for DLGG

# Chapter 23
# Surgery for Diffuse Low-Grade Gliomas (DLGG) Oncological Outcomes

**Hugues Duffau**

**Abstract** For many decades, surgery for DLGG was matter of controversy, mainly due to the fact that, in the classical literature, extent of resection (EOR) was not objectively assessed on post-operative MRI. EOR was usually based on the sole subjectivity of the surgeon, with no volumetric calculation of the residual tumor. In all modern series with objective measurement of the EOR on systematic postoperative T2/FLAIR-weighted MRI, a more aggressive resection predicted significant improvement in overall survival (OS) compared with a simple debulking or biopsy—by delaying malignant transformation. However, development of neuroimaging led neurosurgeons to achieve tumorectomy according to the oncological limits provided by preoperative or intraoperative structural and metabolic imaging. Yet, this principle is not coherent, neither with the infiltrative nature of DLGG nor with the limited resolution of current neuroimaging. Indeed, MRI still underestimates the actual spatial extent of gliomas, since tumoral cells are present several millimeters to centimeters beyond the area of signal abnormalities. Therefore, an extended removal of a margin beyond these MRI-defined abnormalities, i.e. a "supra-total" resection, was recently proposed, with a dramatic improvement of OS. Consequently, the actual aim is not to remove only the "top of the iceberg" visible on imaging, but to perform a radical resection of the brain invaded by a DLGG, on the condition that this part of the nervous system is not crucial for cerebral functions. Thus, biopsy should be reserved only in very diffuse lesions, such as gliomatosis-like, when at least a subtotal resection is not possible. Neurosurgeons should shift from a traditional view consisting of removing a tumor mass within the brain (image-guided resection according to oncological and/or anatomical limits) to the removal of a diffuse chronic tumoral disease invading neural networks. They should take the habit to

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perform a maximal resection up to the boundaries of brain functions, that is, functional guided-mapping resection by means of intraoperative electrostimulation in awake patients. To solve the traditional dilemma (OS versus quality of life) by optimizing the onco-functional balance (namely, *increased OS and better quality of life*), the new philosophy is to abandon the conservative wait-and-see attitude to evolve toward an early, radical, safe and invidualized "preventive functional surgical neurooncology".

**Keywords** DLGG • Surgery • Supratotal resection • Overall survival • Malignant transformation • Extent of resection • Functional mapping • Quality of life

## 23.1 Introduction

For many decades, surgery for diffuse low-grade gliomas (DLGG) was matter of debate. This was mainly due to (i) the poor knowledge of the natural history of DLGG (ii) the absence of objective calculation of the extent of resection (EOR) on postoperative MRI (iii) the fear to induce permanent deficits because of a frequent involvement of the so-called "eloquent brain areas" by this kind of tumor [1]. Indeed, DLGG usually occurs in young patients with no or only slight symptoms and who enjoy an active life. However, thanks to the technical advances in mapping methods, and above all, thanks to a better understanding of the dynamic neurobiology subserving brain processing (see previous chapter), the surgical risk has been dramatically reduced [2]. This issue will be extensively discussed in the next chapter about functional outcomes following surgery for DLGG.

Nonetheless, before to detail "how to operate?", it is first of all crucial to answer the main question "why to operate?". Here, the first goal is to review new insights into the natural history of DLGG. Furthermore, based upon this improved conceptual knowledge of DLGG behavior, the second aim is to emphasize the favorable impact of surgery on the course of this tumor, resulting in a paradigmatic shift from a conservative wait-and-see approach to a more aggressive surgical attitude. Indeed, in the modern series with objective calculation of EOR on postoperative MRI, a large amount of recent evidences have supported a significant role of surgery on overall survival (OS), by delaying malignant transformation, while preserving or even improving the quality life (QoL), in particular thanks to a better control of epilepsy [3]. The third aim is to analyze the refinement in surgical techniques, allowing the preservation of critical neural networks. Taken together, these data support a new philosophy in DLGG, in which the main goal is to change the behavior of this glioma, from a premalignant tumor to a chronic disease under control for many years (or even decades), thanks to early (and possibly repeated) treatments in patients enjoying a normal familial, social and professional life [4].

## 23.2 New Insights into the Natural Course of DLGG

While already described in previous chapters, it seems important to remind some crucial issues with regard to the behavior of this complex and heterogeneous tumoral disease.

### *23.2.1 Glioma Growth*

Unlike claims made in the classical literature, there is no stable DLGG. Objective calculation of growth rate (based on at least two MRIs 6 weeks to 3 months apart before any treatment) showed that all DLGGs had a constant growth during their premalignant phase, with a linear increase of the mean diameter (computed from the volume) around 4 mm a year [5–7]. This growth was observed not only in symptomatic patients, but also in incidental DLGG, discovered for independant reasons—as head trauma or participation in a research protocol (see chapter by Mandonnet et al. on DLGG Screening) [8]. *Therefore, the concept of "progression free survival" has no meaning* in untreated DLGG or following incomplete surgical excision, as by definition all DLGG progress continually (with a similar growth rate before and after partial resection [9])—except following complete excision or if it stabilizes as a result of chemotherapy or radiotherapy. In this context, the conventional radiological criteria initially proposed by McDonald [10], or more recently by the RANO group [11], are not appropriate for DLGG, as they only take account of the calculation of two diameters and not of volume (from which however the mean diameter can be deduced secondarily, see above) [12]. As a consequence, beyond OS, malignant progression-free survival should be prefered as a new endpoint for future trials in DLGG.

Furthermore, there is an inverse correlation between growth rates and survival in DLGG, showing that the mean velocity of diametric expansion is a better prognostic factor than the neuropathological examination performed according to the WHO neuropathological classification [13]. Indeed, among a series of 143 consecutive cases, Pallud et al. showed that a median velocity of diametric expansion of 8 mm/year or more was associated with a median survival of 5.16 years while a median survival of more than 15 years was seen with a gowth rate of less than 8 mm/year [13]. In the same vein, in a more recent experience with 407 DLGGs, during the follow-up (mean, 86.5 ± 59.4 months), 209 patients presented a malignant transformation, and 87 died [14]. Interestingly, the malignant progression-free survival and the OS were significantly longer in cases of slow velocity of diametric expansion (median, 103 and 249 months, respectively) than in cases of fast velocity of diametric expansion (median, 35 and 91 months, respectively; $p < 0.001$). In multivariate analyses, spontaneous velocity of diametric expansion as a categorical variable (4, ≥4 and 8, ≥8 and 12, ≥12 mm/year) was an independent prognostic factor for

malignant progression-free survival ($p < 0.001$; hazard ratio, 3.87; 95% confidence interval [CI], 2.67–5.52) and for OS ($P < 0.001$; hazard ratio, 4.62; 95% CI, 2.58–7.97). Velocity of diametric expansion is also an independent prognostic factor for OS as a continuous predictor, showing a linear relationship between OS and spontaneous velocity of diametric expansion (hazard ratio, 1.09 per one unit increase; 95%CI, 1.06–1.12; $P < 0.001$) [14]. Therefore, these studies demonstrate that the spontaneous velocity of diametric expansion allows the identification of rapidly growing DLGG (at higher risk of worsened evolution) during the pretherapeutic period and without delaying treatment. In addition, *growth rate is independent of the molecular status* [14, 15]. As a consequence, velocity of diametric expansion should be calculated for each patient before any therapy, in order to tailor the management according to the better understanding of the natural course of the disease at the individual level [7].

### *23.2.2 Glioma Migration*

Moreover, these tumors are migrating along the white matter tracts (U fibers, association, projection and commissural pathways) [16, 17]. Therefore, DLGG is not a "tumor mass", as regurlarly reported in the classical literature, but this is in fact an infiltrating chronic disease invading the central nervous system, especially within the subcortical connectivity. This is an important issue because these white matter pathways are known to be critical for brain functions [18, 19]. Indeed, in the new probabilistic atlases of functional plasticity elaborated from DLGG patients, these subcortical fibers showed a low level of interindividual variability [20] and a low level of plastic potential [21, 22] (see previous chapter by Duffau on "Interactions Between DLGG, Brain Connectome and Neuroplasticity").

As a consequence, diffusion of glioma cells along these bundles may induce cognitive disorders, due (at least partly) to a "disconnection syndrome" [23–25]. Indeed, mounting evidence now highlights the fact that disorders of executive functions, such as working memory, attention processes, learning or semantics, as well as emotional and behavioral disturbances are very common, although have long been underestimated [26–28]. These data demonstrate that the migration of DLGG along subcortical pathways can generate specific cognitive or emotional disturbances depending on the neural sub-network involved by the tumoral cells [25, 29, 30]. These mild but objective deficits are frequently observed when extensive neuropsychological assessments are performed at diagnosis, challenging the traditional view of "DLGG patients with a normal examination" (see chapter by Klein).

Thus, routine neurocognitive examinations with QoL assessment scales should now be achieved in all patients with DLGG, before (and after) any treatment, as the standard neurological assessment is ultimately too crude to be able to identify subtle deficits. Such a baseline assessment can be helpful for defining the best individualized management. Indeed, from a therapeutic point of view, glioma migration along

fibers can also limit the extent of surgical resection at the level of the axonal connectivity, in order to preserve brain functions [2].

### *23.2.3 Malignant Transformation and OS*

Last but not the least, DLGG will inulectably become malignant. Such transformation will lead to neurological deficit with a worsening of QoL and ultimately to death. In two EORTC (European Organization for Research and Treatment of Cancer) randomized multicenter trials involving more than 600 patients, in the subgroup of patients with a favorable prognostic score, the median survival was 7.7 years—whereas the in the subgroup of patients with a poor prognostic score, the median survival was only 3.2 years [31, 32]. As mentioned, accurate determination of growth rate allows the identification of patients whose gliomas are at high risk for early transformation [14]. Other clinical (age, neurologic and cognitive status, Karnofsky Performance Status—KPS), radiological (tumor volume, location and kinetics, metabolic parameters), pathological and molecular factors are also correlated with the risk of degeneration and OS, as already described elsewhere (see chapter by Rudà et al.).

To sum up, these data show that DLGG cannot be considered any more as a "benign" tumor, but as a premalignant cancer, with constant growth and diffusion within the central nervous system, and inevitable degeneration. Therefore, surgical and medical neurooncologists should definitely switch from a traditional "wait and watch" attitude to an early therapeutic strategy, with the aim of delaying malignant transformation and increasing OS, while preserving or even improving QoL [4]. In this state of mind, recent surgical series demonstrated that maximal safe DLGG resection played a crucial role on the course of this chronic brain disease.

## 23.3 The Impact of Surgical Resection in DLGG

### *23.3.1 The Classical Literature*

The actual role of surgery in DLGG was debated for many years. 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, with no volumetric measurement of the residue. Of note, this is unfortunately still true in very recent series [33]. Due to the invasive feature of DLGG, the residual tumor was doubtlessly underestimated in numerous studies, resulting in erroneous conclusions about the real benefit of surgery. Interestingly, recent comprehensive reviews of the literature have suggested that a more extensive resection of this tumor was correlated

with a more favorable life expectancy [34–36]. It was also demonstrated that the rate of surgical series observing a benefit of resection increased over time. In an analysis of ten studies since 1990 which have applied statistical analysis to examine the role of EOR in improving OS and delaying tumor progression among patients with DLGG, Sanai and Berger showed that the mean survival changed from 61.1 to 90.5 months with a greater EOR (i.e. subtotal resection versus gross total resection, respectively) [37].

### *23.3.2 Advances in Neuroimaging and Objective Assessment of Extent of Resection*

Currently, it is well admitted that T2/fluid attenuation inversion recovery (FLAIR)-weighted MRI is the only way to actually evaluate the postsurgical volume of (possible) residual glioma in routine practice. The best way to calculate pre- and post-surgical tumor volumes (and therefore EOR) with a high level of accuracy and reproducibility is to use dedicated and validated softwares (e.g. Myrian, Intrasense). It is nonetheless important to underline that isolated glioma cells cannot been detected by structural imaging and that the emergence of physiological/metabolic imaging techniques (diffusion-weighted MRI, perfusion-weighted MRI, MR spectoscopy, PET) will likely continue to improve the sensitivity of detection of residual disease [38].

### *23.3.3 The Modern Series*

#### 23.3.3.1 Impact on OS

Remarkably, in all recent series with objective postoperative evaluation of EOR on T2/FLAIR weighted-MRI, a more aggressive resection predicted a significant improvement in OS compared with simple debulking or biopsy. When no signal abnormality was visible on control MRI (complete resection), patients had a significantly longer OS compared with patients having any residual abnormality. Indeed, in the series by Smith et al. including 216 DLGGs, after adjusting for the effects of age, KPS, tumor location, and tumor subtype, EOR remained a significant predictor of OS (HR = 0.972; 95% CI, 0.960 to 0.983; $p < 0.001$), with an 8-year OS of 98% of patients who underwent complete resection [39]. Moreover, even in incomplete tumor removal (especially subtotal resection with a residual volume about $10 \pm 5$ cc), patients with a greater percentage of resection had a significantly longer OS. Furthermore, the survival was significantly better with at least 90% EOR compared with less than 90% EOR, whereas EOR of at least 80% also remained a significant predictor of OS [39]. In 156 DLGGs, Claus et al. reported that patients who underwent incomplete resection had 4.9 times the risk of death compared with those who underwent total

resection [40]. In 222 DLGGs with a median follow-up of 4 years, Duffau et al. found that 20.6% of patients with more than 10 cc of residue died, while only 8% of patients with less than 10 cc of residue died and no patients with complete resection died ($p = 0.02$) [41]. Yeh et al. demonstrated that EOR and postoperative KPS showed independent prognostic significance for OS using multivariate analysis in 93 consecutive DLGGs [42]. McGirt et al. observed that gross-total resection versus subtotal resection was independently associated with increased OS (hazard ratio, 0.36; 95% confidence interval, 0.16–0.84; $p = 0.017$) [43]. In 130 DLGGs studied by Ahmadi et al., extended surgery significantly prolonged OS [44]. In a study of 314 DLGG patients, Schomas et al. reported that the adverse prognostic factors for OS identified by multivariate analysis were in patients undergoing less than subtotal resection [45]. The same team has also recently confirmed that gross-total resection and radical subtotal resection were factors associated with improved OS in a series with 852 DLGGs [46]. In 190 DLGGs, Ius et al. demonstrated that patients with an EOR ≥ 90% had an estimated 5-year OS of 93%, those with EOR between 70% and 89% had a 5-year OS of 84%, and those with EOR <70% had a 5-year OS of 41% ($p < 0.001$) [47]. After stratification for eloquence of tumor location in order to correct for treatment bias, Gousias et al. confirmed that Kaplan-Meier estimates showed a consistent association between the degree of resection and improved survival [48]. Jakola et al. investigated survival in population-based parallel cohorts of DLGGs from 2 hospitals with different surgical strategies [49]. Treatment at a center that favored early surgical resection was associated with better OS (median survival, not reached) than treatment at a center that favored biopsy and watchful waiting (median survival, 5.9 years) [49]. One hundred fifty-three patients with diagnosed DLGG who had undergone resection or biopsy at Tokyo Women's Medical University between January 2000 and August 2010 were also analyzed: EOR was significantly associated with OS ($p = 0.0096$) in patients with diffuse astrocytoma [50]. In a recent retrospective series with 46 consecutive newly diagnosed low-grade astrocytomas stratified for IDH1, tumor resections were prognostic for OS in patients with ≥40% EOR (HR 1.08, $p = 0.007$)—persistent to adjustment for IDH1 [51]. The French Glioma Consortium published the largest surgical series of DLGG ever reported with more than one thousand patients, showing that both EOR and postsurgical residual volume were independent prognostic factors significantly associated with longer OS (Fig. 23.1) [52]. These results have recently been confirmed in another series of 1509 DLGGs by the same French Glioma Consortium [3]. In this experience, the OS was about 13 years since the first treatment and about 15 years since the first symptom, i.e. approximately the double of the OS reported in classical studies with no attempt to perform extensive resection [31, 32, 53, 54] or in series with only a biopsy [49]. Finally, Roelz et al. reported a 9-years near-randomized survey of surgery vs biosy [55]. In this series with 126 DLGG patients, 77 (61%) were initially managed by biopsy and 49 (39%) by resection. A significant survival benefit was found for patients with an initial management by resection (5-year OS 82% vs. 54%). The survival benefit of patients with initial resection was reserved to patients with a residual tumor volume of less than 15 cc. The authors conclude that maximum safe resection is the first therapy of choice in DLGG patients if a near-complete tumor removal can be achieved [55].

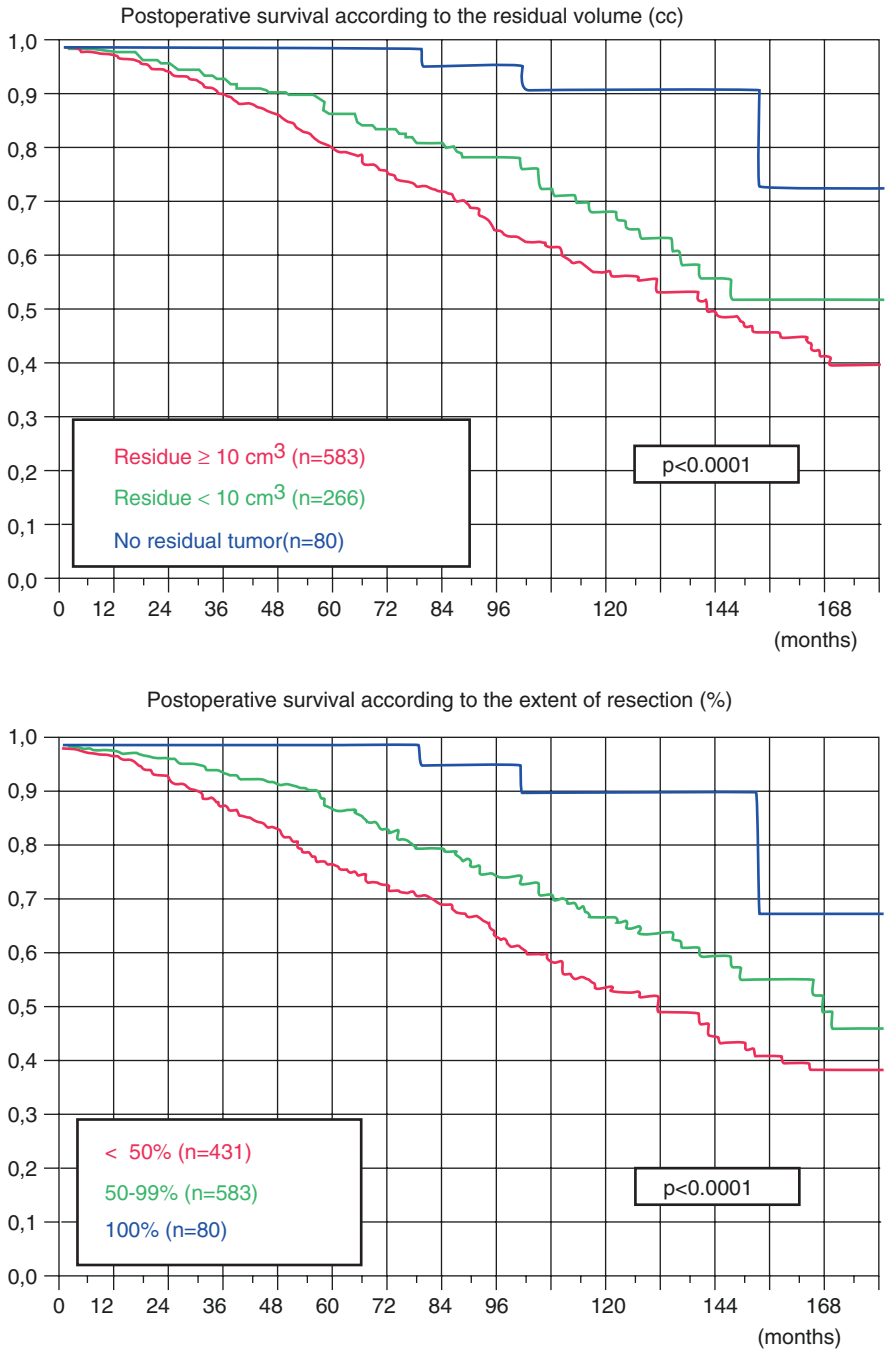


**Fig. 23.1** The largest surgical serie of DLGG ever reported, by the French Glioma Network, which demonstrated with an experience of 1097 patients that both the postsurgical residual volume (*upper*) as well as the extent of resection (*lower*) were independent prognostic factors significantly associated with a longer overall survival. Modified from [52]

Interestingly, the value of EOR was evident not only within the general hemispheric DLGG population, but also for specific DLGG limited to certain subregions, such as insular DLGG [56, 57].

#### 23.3.3.2 Impact on Malignant Transformation

Such an impact on OS is due to the fact that surgery delayed histological upgrading. It was demonstrated that the volume of residual tumor served as a predictor of malignant transformation [58]. In the recent series by the UCSF group 216 DLGGs, 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 0.995; p = 0.005) [39]. In an experience including 191 consecutive patients with DLGGs, Chaichana et al. also showed that gross total resection was an independent factor associated with malignant degeneration (RR 0.526, 95% CI 0.221–1.007, p = 0.05) [59]. Similarly, the French Glioma Consortium recently demonstrated that surgical resection was an independent prognostic factor associated with increased malignant progression-free survival ($p < 0.001$) [52]. Interestingly, as for OS, the value of EOR on malignant transformation was significant not only for the general DLGG population, but also for specific areas. For instance, the UCSF group showed that, within the insula, the interval to malignant progression of DLGG was longer in patients who had undergone greater resections [56].

Nonetheless, one could argue that the impact of EOR on malignant transformation and OS might be biased by a more favorable molecular pattern in DLGG amenable to a maximal resection. To examine this issue, the predictive value of 1p19q, IDH1, 53 expression and Ki67 index was recently investigated for the EOR in 200 consecutive DLGG patients (2007–2013) [60, 61]. Data were modeled in a linear model. The analysis was performed with two statistical methods (arcsin-sqrt and Beta-regression model with logit link). There was no deletion 1p19q in 118 cases, codeletion 1p19q (57 cases), single deletion 1p (4 cases) or19q (16 cases). 155 patients had a mutation of IDH1. p53 was graded in four degrees (0:92 cases, 1:52 cases, 2:31 cases, 3:8 cases). Mean Ki67 index was 5.2% (range 1–20%). Mean preoperative tumor volume was 60.8 $cm^3$ (range 3.3–250 $cm^3$) and mean EOR was 0.917 (range 0.574–1). Interestingly, the statistical analysis was significant for a lower EOR in patients with codeletion 1p19q (OR 0.738, p = 0.0463) and with a single deletion 19q (OR 0.641, p = 0.0168). There was no significant correlation between IDH1 or p53 and the EOR. Therefore, this study demonstrates in a large cohort of DLGGs that a higher EOR is not attributable to favorable genetic markers. *This original result supports maximal surgical resection as an important therapeutic factor per se to optimize prognosis, independently of the molecular pattern* [60, 61].

To sum up, early and maximal safe surgical resection is currently the first treatment in DLGG [4, 62].

### *23.3.4 Towards a Supratotal Resection of DLGG*

Despite this value of gross-total resection (MRI based) on malignant transformation and survival, a study using biopsy samples within and beyond MRI-defined abnormalities showed that conventional MRI underestimated the actual spatial extent of DLGG, since tumor cells were present beyond the area of MRI signal abnormalities, up to 20 mm—even when gliomas were well defined on MR images [63]. Interestingly, it was suggested that an extended resection of a margin beyond these MR imaging-defined abnormalities might improve the outcome of DLGG. Indeed, an original series reported that a "supratotal" resection—that is, resection extending beyond the area of MR imaging signal abnormalities (Fig. 23.2)—performed in 15 patients bearing a DLGG within "non-eloquent" brain regions avoided malignant transformation in a mean follow-up of 35.7 months (range 6–135) [64]. This series was compared with a control group of 29 patients who had "only" complete resection for a DLGG: malignant transformation was observed in seven cases in the control group but in no cases in the series of patients who underwent supratotal resection ($p = 0.037$). Furthermore, adjuvant treatment was administrated in 10 patients in the control group compared with one patient who underwent supracomplete resection ($p = 0.043$). However, 4 of 15 patients with supracomplete resection experienced recurrence [64].

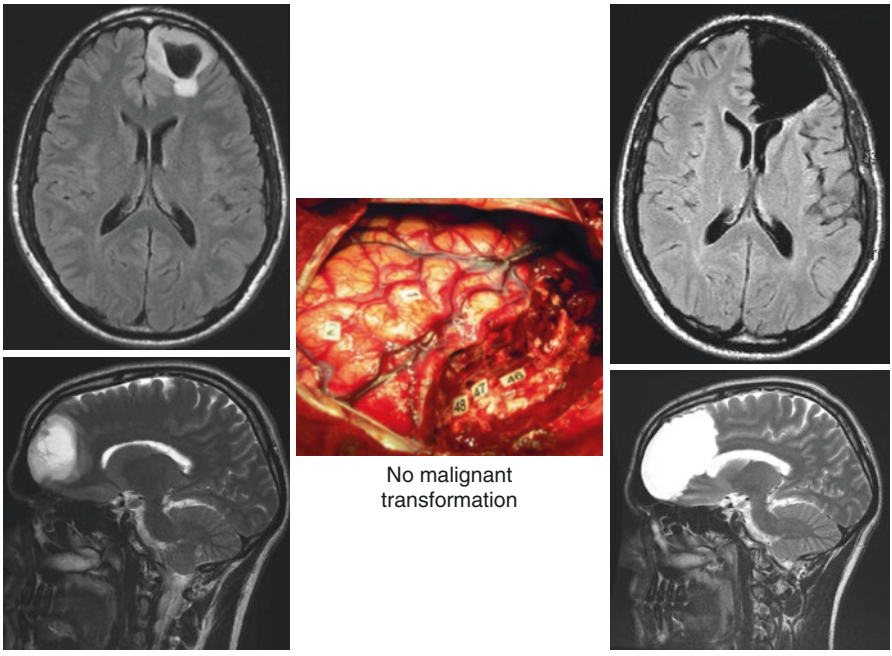


**Fig. 23.2** Supratotal resection performed according to functional boundaries detected using intraoperative cortico-subcortical electrical mapping. *Left*: preoperative MRI showing a left prefrontal DLGG; middle: intrasurgical photograph; *right*: postoperative MRI demonstrating that the resection was achieved beyond the FLAIR/T2-weighted MRI abnormalities. Modified from [64]

In a more recent series, sixteen consecutive patients who underwent supratotal resection for a DLGG with a long-term follow-up (minimum of 8 years after surgery) have been analyzed [65]. There were seven men and nine women (mean age, 41.3 years, range, 26–63 years) with a glioma (10 right and 6 left tumors) diagnosed because of seizure in 15 cases (one incidental discovery). The resection was continued up to functional cortical and subcortical structures defined by intrasurgical electrical mapping. All patients resumed a normal life after surgery (no neurological deficits, no epilepsy). No adjuvant treatment was administrated after resection. The mean duration of postoperative follow-up was 132 months (range, 97–198 months). There was no relapse in eight cases. Eight patients experienced tumor recurrence, with an average time to relapse of 70.3 months (range, 32–105 months), but *without malignant transformation*. Five of them have been retreated, with a reoperation (two cases), chemotherapy (three cases) and radiotherapy (two cases). All patients continue to enjoy a normal life. This is the first series demonstrating the prolonged impact of supratotal resection on malignant transformation of DLGG [65].

Nevertheless, the tumor relapse in 50% of cases is 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 the functional structures. It is worth noting that some patients had a relapse after only 18 months after supratotal resection, while other had no reccurence with 198 months of follow-up after the sole surgery [64, 65]. This could be explained by the fact that some DLGGs are more "invasive" whereas other DLGGs are more "proliferative". It is likely that surgery, in particular supratotal resection, in essence has a better chance of controlling the latter than the former. In the future, advances in physiological/metabolic imaging, closer to the neuropathological tumor infiltration as validated by new method of coregistration of histological and radiological characteristics [66, 67], might allow for better selection with respect to indications for supracomplete resection. Another useful method could be the new biomathematical models of proliferation and diffusion, based on at least two sets of MRI acquired 3–6 apart, before any treatment [68] (see chapter by Mandonnet). Therefore, the goal of supratotal resection is currently to avoid malignant transformation for a long period by reducing the number of peripheral tumoral cells and to delay the use of adjuvant therapy, without nonetheless (yet) claiming to cure patients with DLGG—except maybe in some selected cases with a more "proliferative" pattern and with an early diagnosis that permitted to take at least 2 cm of margin all around the glioma [64, 65]. This is the reason why a screening in the general population could be considered, because the rate of supramarginal resection is higher in series reporting removal of incidental DLGG (see the last chapter of this book by Mandonnet et al.) [69].

### *23.3.5 The Value of Re-operation(s)*

Due to the invasive nature of DLGG, relapse is thus possible after total or even supratotal resection, and continuous growth of the residual tumor is ineluctable after incomplete resection. Interestingly, in this setting, some authors provided argumentations in favor of the oncological impact of a second surgery. Schmidt et al.

analyzed the surgical results in a series of 40 patients re-operated for recurrent DLGG without other intervening therapy between surgeries. They provided evidence supporting that a gross-total resection was associated with an increased time to repeated surgery [70]. More recently, Jungk et al. confirmed that a greater EOR was prognostic for time to re-intervention (HR 0.23, p = 0.03) [51]. In a series of 130 DLGGs, Ahmadi et al. showed that extended surgical resection for non-malignant relapse (a total resection could be achieved in 53.1% of recurrent tumors) prolonged the OS significantly [44]. In the series reported by the French Glioma Consortium, subsequent surgical resection was an independent prognostic factor significantly associated with a longer OS [52]. Martino et al. also reported a consecutive series of 19 patients who underwent a second surgery for recurrent DLGG in eloquent areas [71]. A total or subtotal resection was achieved in 73.7% of patients during the reoperation, 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 (see previous chapter by Duffau) as well as by the first resection itself [72, 73]. In this series, the median time between surgeries was 4.1 years (range 1 to 7.8 years) and the median follow-up from initial diagnosis was 6.6 years (range 2.3 to 14.3 years) with no death during this follow-up period. As a consequence, due to a favorable benefit-to-risk ratio of such strategy, it was proposed to consider reoperation(s) in all recurrent DLGGs. Nonetheless, due to a high rate of malignant transformation histologically proven of 57.9% at reoperation, while the main goal of surgery in (recurrent) DLGG is to prevent degeneration, it was suggested to "over indicate" an early re-intervention rather than to perform a late surgery when histological upgrading already occurred [71].

## 23.4 The Limited Role of Biopsy in DLGG

Currently, the indications of biopsy are thus very limited in DLGG. First of all, this is due to the fact that by combining clinical and (dynamic) radiological data, the diagnosis of DLGG is typical in the vast majority of cases. Furthermore, the risk of undergrading is very high in biopsy. Indeed, Muragaki et al. have demonstrated that undergrading of WHO grade III gliomas occurred in 28% of cases [74]. This is explained by the huge intra-tumoral heterogeneity of DLGG, with the existence of frequent microfoci of malignant progression in the middle of the tumor [75] (see the chapter by Rigau). Finally, the surgical risk of MR-guided stereotactic biopsies is still around 2% of permanent deficits or death [76]. In practice, this means that 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-like and/or when at least a subtotal resection is not a priori possible [35]. To this end, in addition to the experience of the neurosurgeon, such a prediction of EOR can be optimized by the use of a resection probabilistic map [77] (see

the chapter by De Witt Hamer et al.). Such atlas, based on the computation of residual gliomas resected according to functional boundaries in a series of 65 DLGGs, allows a preoperative estimation of the expected EOR with a success rate of 82% [78]. This rationale, directly related to a distinct potential of brain reorganization according to the spatial location of the glioma—in particular with a lesser index of plasticity at the level of the white matter pathways, as detailed in the previous chapter by Duffau [21, 22]—may assist in decisions regarding surgical resection versus biopsy.

## 23.5 The Paradoxical Negative Effect of Neuroimaging in DLGG Surgery

Despite the valuable help of new methods of non-invasive neuroimaging in the diagnosis of brain tumors, these techniques of oncological and functional imaging have nonetheless also had a paradoxical negative impact on the surgical management of DLGG patients.

Indeed, development of neuroimaging led neurosurgeons to achieve a single tumorectomy according to the oncological limits provided by preoperative or intraoperative structural (in particular T2- and FLAIR-weighted MRI) and metabolic imaging (as perfusion or spectroscopy MRI). However, this principle is not coherent neither with the infiltrative nature of DLGGs nor with the limited resolution of current neuroimaging. This is due to the fact that, despite technical advances, MRI (or even PET scan) still underestimates the actual spatial extent of gliomas, since tumoral cells are present several millimeters to centimeters beyond the area of signal abnormalities [63]. Indeed, it is usually admitted that tumors appear on MRI only for cell densities above 500 cells/mm$^3$ [16]. Therefore, the first risk of oncological imaging, including neuronavigation or intraoperative MRI, is to result in premature interruption of resection [79]. In other words, if the DLGG is located in non-critical area, the current goal for many neurosurgeons is to remove only the MRI-defined abnormalities, without attempting to resect a margin around these signal abnormalities. Yet, as mentioned, recent studies have demonstrated that supratotal resection, i.e. resection beyond the MRI-defined abnormalities, enabled to avoid malignant transformation in DLGG for a long period [65]. Because tumoral cells have been identified in the margin removed around the hypersignal on FLAIR-weighted MRI, this means that resecting only the "tumor visible on MRI" is a loss of chance from an oncological point of view, when supramarginal resection was possible in DLGG involving non-eloquent regions.

On the other hand, from a functional point of view, image-guided resection is not logical in DLGG, knowing that critical structures may persist within the diffuse tumoral disease visible on FLAIR-weighted MRI. In other words, resecting solely the MRI-defined abnormalities for DLGG in eloquent areas does not prevent to generate permanent neurological deficit. Indeed, neurosurgeons have tendency to

believe that the data provided by functional MRI (fMRI) and diffusion tensor imaging (DTI) is the "absolute truth" with regard to the investigation the individual functional anatomy of the brain. This is the reason why a large amount of recent experiences is based on the exclusive use of functional imaging for the surgical indications and planning, as well as directly into the operating theater (preoperative data incorporated in a neuronavigational system or intraoperative fMRI/DTI) (for a review, see [80]). Yet, functional neuroimaging is not realiable enough at the individual level to be used in clinical routine [81] (see the next chapter by Duffau). Consequently, there is a risk not to 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 loss of chance from an oncological point of view. Furthermore, into the operative room, beyond the risk to damage crucial structures not identified by fMRI/DTI (due to their actual lack of sensitivity) and/or due to the brain shift increasing throughout the resection of voluminous gliomas (thus decreasing the reliability of the data provided by DTI), the dogmatic rule which emerged because of the poor accuracy of these techniques is to take 5–10 mm of margin around the presumed eloquent regions according to functional neuroimaging [82]. Again, such strategy is against the oncological goal, that is, to optimize EOR, whereas it was shown on hundreds consecutive patients with DLGG in critical areas that the resection could be pursued with no margin without increasing the rate of permanent morbidity (less than 2%) [83, 84]. Indeed, Gil Robles and Duffau showed that it was not logical to leave a small amount of tumor involving the cortex when the resection was already performed at the subcortical level into the contact of eloquent white matter pathways (according to the results of subcortical stimulation, see below), because this means that the cortical area not removed was in fact already disconnected and thus not functional anymore (Fig. 23.3) [85].

In summary, in spite of methodological developments based upon computer-aided surgery, and beyond the fact that these techniques are very expensive and not available in all departments of neurosurgery worldwide, no demonstrations have been made that the benefit-risk ratio of glioma surgery was significantly increased thanks intrasurgical neuroimaging. *Indeed, no series using such tools were able to show both an increase of overall survival and a decrease of postoperative morbidity* [86]. A single randomized controlled trial has been conducted to investigate the effectiveness of neuronavigation in resecting intracerebral tumors: no rationale for the routine use of neuronavigation to improve the EOR and prognosis has been demonstrated [87]. In the same way, a prospective randomized study using high-field intraoperative MRI in gliomas showed a significant increase of the EOR, but with nonetheless a high rate of new neurological deficits about 13% [88]—which is today not acceptable, because the rate of permanent worsening in series using intraoperative electrical mapping is about 3% [89] (see below). In other words, it is difficult to demonstrate the actual role of intraoperative MRI without comparing the outcomes with a control group based upon intrasurgical electrostimulation, and without evaluating both OS as well as QoL. However, such a study does not exist in the current literature.

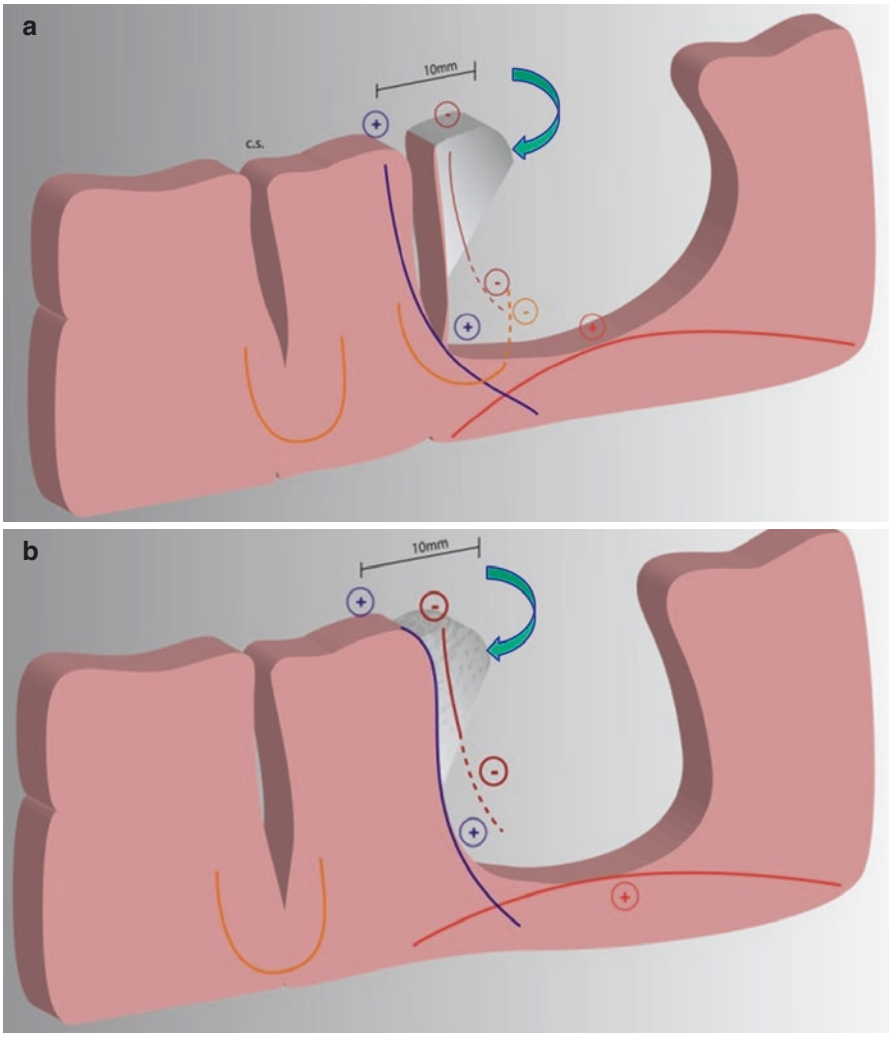


**Fig. 23.3** Schematic drawing showing two examples of a resection with margin, which should be avoided. (**a**) First, a tumor coming into the contact of a sulcus removed by leaving a 10 mm security margin from the positive cortical stimulation site (*Blue* +) (i.e. with no subpial dissection). If subcortical stimulation are performed, the projections fibers "vertical connectivity" will be identified at the bottom of the sulcus (*Blue* +, e.g. pyramidal tracts). The U fibers coming from the other side of the sulcus will also be tested throughout the resection (*Orange* −). At the bottom of the cavity, the "horizontal connectivity" or long distance assocation fibers (e.g. arcuate fasciculus) will represent the deep functional subcortical boundary (*Red* +) (no margin left around these tracts). Interestingly, the cortex invaded by the tumor (in *grey*, shown by the *blue arrow*) is functionally useless, since the resection has been pursued until the subcortical pathways have been encountered (*Blue* and *Red* +). Thus, the fibers arising from this cortex have been disrupted, as they do not respond to stimulation (*Brown* −). As a consequence, this cortex was disconnected and can therefore be removed with no functional risk. This is the reason why a subpial dissection should have been done since the beginning of the resection (**b**) The second illustration shows the same example in a case of an "intragyral dissection". Modified from [85]

## 23.6 Technical Considerations for Maximal Safe Surgical Resection of DLGG

### *23.6.1 The Conceptual Shift from an Image-Guided Surgery Towards a Functional-Mapping Guided Resection*

On the basis of these recent favorable oncological outcomes after DLGG resection, brain surgeons should change their mind, in order to operate the central nervous system involved by a chronic tumoral disease—and not by operating a tumor mass within the brain [1]. The goal is not to content with a single "tumorectomy", i.e. removal of the part of the glioma visible on neuroimaging, but to perform the most extensive resection of the parenchyma invaded by a DLGG, on the condition that this part of the brain is not essential for cerebral functions. In other words, the neurosurgeon should see first the brain, and not the glioma, to adapt his surgical procedure to the three-dimensional anatomo-functional organization of the connectome for each patient. Thus, both the philosophy and the technique within the central nervous system must be different from the surgical technique outside the brain, because surgical neurooncology is a cerebral networks surgery [90]. Indeed, the main principle in glioma surgery should be to tailor the resection up to individual functional boundaries, with no margin, to maximize the tumor removal while preserving eloquent structures [91]. In this setting, due to the major limitations of oncological and functional neuroimaging (see above), intraoperative electrostimulation mapping is the gold-standard in glioma surgery, because this is currently the sole method able to detect in real-time the cortico-subcortical neural networks crucial for brain functions—which should serve as limits to the resection [18].

Of note, one could consider that both methods, intraoperative MRI and electrostimulation mapping, are not antagonistic and could be combined in the operating theater. In fact, there is a conceptual issue (not a technical one) explaining why imaging-guided resection is incompatible with functional mapping-guided resection. The goal of imaging-guided resection is to remove the signal abnormalities on MRI. In contrast, the principle of functional mapping-guided resection is to stop only when crucial structures have been encountered. In practice, if there are discrepancies in information given by different tools when more than one intraoperative method is used—for example, intraoperative MRI demonstrating tumor but (sub) cortical mapping revealing proximity to functional tissue—the neurosurgeon should rely on stimulation mapping information. In this example, the surgeon should stop the resection to avoid permanent neurologic deficit [79].

### *23.6.2 Cortico-Subcortical Mapping: The Value of Function-Guided Surgery to Optimize the Onco-Functional Balance (Fig. 23.3)*

Here, the goal is not to accurately detail the methodology for awake surgery using stimulation mapping, which will be extensively described in the next chapter—as well as the functional outcome. However, it is seems important to undeline several key issues.

First of all, neurosurgeon has to keep in mind that, in physiology, there is a major interindividual anatomo-functional variability at the cortical level, in particular for cognitive functions such as language [20]—knowing that this variation can be increased in patients with slow-growing DLGG due to mechanisms of neuroplasticity [2, 72]. *This means that, even though anatomical landmarks remain important during cerebral surgery, they are definitely not enough*.

Therefore, it is crucial to benefit from a positive cortical mapping before to start the resection, in order to tailor it according to the distribution of the neural circuits, in this patient at this time. In other words, one should avoid a false negative (especially for methodological reasons) [84]. Indeed, since eloquent structures can be located within the glioma, the standard surgical principle of debulking tumor from inside to outside is not always safe in DLGG [92]. In the UCSF experience, 4 of 243 (1.6%) patients had a persistent new language deficit: all these four patients had no positive sites detected prior to their resections—"negative mapping" [93]. In another series with 309 patients who underwent surgeries with intraoperative electrostimulation, mapping was found to be negative in 109 cases, and 9% of these patients developed a long-term deficit [94]. Taylor and Berstein previously reported negative mapping in 70% of patients, with 3.6% of them who experienced a permanent neurological worsening [95]. Thus, negative mapping cannot guarantee the absence of eloquent sites and it cannot prevent persistent postsurgical deficit in all cases. This is the reason why other authors continue to advocate a wider boneflap in order to obtain systematic functional responses before the resection, by exposing at least the ventral premotor cortex which will generate articulatory disorders in all cases during stimulation, whatever the side [84, 96]. Of note, by using low intensity of stimulation (mean about 2.25 mA), electrocorticography is not mandatory to obtain a positive mapping and to limit the risk of intraoperative seizures—about 3% in a recent prospective cohort with 374 supratentorial brain lesions, with no aborted awake procedures [84]. In summary, "minimal invasive neurosurgery" means "minimal morbidity" and not "minimal boneflap size".

Another important issue is the preservation of the subcortical connectivity [1, 2]. Indeed, since DLGG are migrating along main white matter fibers, and because these tracts which subserve the connectome are crucial, as demonstrated using probabilistic atlases of neuroplasticity [21, 22], it is mandatory to identify and to preserve such pathways using subcortical stimulation throughout the glioma removal [18, 83, 90, 96, 97]. As a consequence, beyond electrical mapping, on-line cognitive monitoring should be performed in awake patients (whatever the hemisphere involved by the tumor, see next chapter by Duffau on "Surgery for DLGG: Functional Outcomes"), to check on-line whether no neurological and/or neuropsychological deficits are generated by the resection. To this end, strong real-time relationships are essential between the patient, the neurosurgeon as well as the speech therapist/neuropsychologist directly into the operating theater (see the chapter by Herbet and Moritz-Gasser). On the other hand, due to the fact that the patient can be tired following one to two hours of continuous task, it is recommended to start glioma removal directly into the contact of the eloquent structures detected using cortico-subcortical stimulation mappping, to avoit to waste time, and by disconnecting the part of the brain involved by the DLGG—rather than to "debulk" the tumor from

inside and then to come closier to the functional regions only at the end of the resection, when the patient is less cooperative. Indeed, once the invaded brain is disconnected according to the functional boundaries provided by the individual mapping, it is possible to remove it under general anesthesia since the on-line feedback of the patient is not necessary anymore [97].

Interestingly, 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 [77]. In addition, the EOR was increased [77]. These results are in agreement with previous studies which compared both functional and oncological outcomes in two consecutive series of DLGG removed without and then with intraoperative electrical mapping in the same institution [41]. Again, although functional mapping enabled to significantly increase the rate of surgeries within classical "unresectable areas", the rate of persistent worsening significantly decreased and the rate of total or subtotal resection significantly improved. Indeed, de Benedictis et al. described a series of 9 patients who underwent two consecutive surgeries for a DLGG [98]. 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 intrasurgical cortico-subcortical electrostimulation mapping defining the limits of resection. The first tumor removal was subtotal in three cases and partial in six cases, with a postoperative worsening in three cases. Following the subsequent awake surgery, postoperative MRI showed that the resection was complete in five cases and subtotal in four cases (no partial removal) and that it was improved in all cases compared with the first surgery ($p = 0.04$). There was no permanent neurological worsening. Three patients improved compared with the presurgical status. All patients returned to normal professional and social lives [98]. These original results demonstrate that awake surgery, known to preserve the QoL in patients with DLGG, is also able to significantly improve the EOR for lesions located in functional regions. Furthermore, the group of UCSF demonstrated in a series of 281 patients 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 tumor resection but also a significant improvement of long-term survival [99]. Finally, as mentioned, in a recent study, awake surgery was used for DLGG located in non-eloquent areas, with the goal to extend the resection beyond the visible part of the glioma on MRI. Because these "supratotal" resections prevented any malignant transformation in a mean follow-up of 132 months (range, 97–198 months), it means that the concept of functional mapping-resection can also be applied to non-eloquent regions with a significant value on the behavior of DLGG [64, 65].

To sum up, DLGG should be resected up to functional boundaries provided by intraoperative mapping *in all patients*, including when the glioma does not directly involve critical brain structures, because the rate of supracomplete resection and the oncological impact is greater in these cases.

### *23.6.3 Subpial Dissection and Vasculature Preservation*

Once functional areas have been mapped, another cornerstone in DLGG surgery is to preserve the whole vascularization, i.e. both arteries and veins, and thus to minimize the use of coagulation [100]. Surprisingly, while this technical point was extensively detailed for extra-axial neurosurgery, it received less attention for glioma resection. First of all, at the cortical level, the "in passing" vessels running at the surface of the tumor but not vascularizing it, which is the most frequent in DLGG, should be spared. The corticectomy must be performed on both sides of each vessel, with no vascular sacrifice. It is worth noting that in reoperations for glioma recurrence, sometimes several years following the first surgery, the cortical vessels preserved during the initial procedure were systematically found as still permeable—even in cases of bridging veins left within the surgical cavity [97].

In a second stage, the removal of the brain invaded by the glioma has to be continued using a subpial dissection. In other words, when the sulci which will represent the boundaries of the resection have been identified by electrostimulation cortical mapping, these sulci should not be opened, in order to preserve the vessels. Indeed, because the vessels are running within the sulci, if one tries to open them, the risk to damage the vessels is higher [97]. As previously mentioned, since the resection is performed with no margin around the eloquent structures, it means in essence that the buried cortex covering the other side of the sulcus is crucial for the function. Therefore, the consequence of possible arteries and/or veins coagulation would be an ischemia of this buried cortex, which will generate neurological deficit. On the contrary, subpial dissection with aspiration of the glioma but without coagulation allows the preservation of the vessels within the sulcus, and thus avoids any injury of the other side of the sulcus. This technique can be used for all sulci within the brain, including the Sylvian fissure. This is the reason why in insular/paralimbic DLGGs, it was proposed by several authors to remove the (frontal and/or temporal and/or parietal) operculae—even if not invaded by the tumor—to have an optimal access to the insula, rather than to open the Sylvian fissure, in order to minimize the risk of vascular damage [100–103]. Preservation of the pia-matter also avoids spasm, since there is no direct manipulation of the arteries. Indeed, long perforator arteries which supply the corona radiata may arise from the M2 segment of the middle cerebral artery. As a consequence, a deep stroke may also be due to a damage of the vessels in the Sylvian fissure [104]. Interestingly, the rate of permanent deficits in series with trans-opercular approach [100–103] is lower in comparison with series with trans-sylvian approach (see [104] for a recent review). Such strategy can also be applied for deep brain DLGGs in non-insular locations. Indeed, when a tumor is located near the depth of a sulcus, especially in presumed functional areas, it could seem logical to open the sulcus to reach the lesion. However, beyond the risk to damage the intra-sulcal vessels, thus with an increased risk of stroke, it should be kept in mind that the deep cortex that has to be crossed to reach the tumor might be eloquent, while not detected by the initial mapping performed at the level of the cortical surface. Therefore, it is safer to pass through the gyrus after

a corticotomy performed according to the results of the cortical mapping on the surface of the brain, with no vascular risk—on the condition nevertheless to continue to perform subcortical mapping throughout the trajectory within the white matter to reach the deep lesion [97].

In practice, it is possible to perform subpial dissection by using the aspirator or the CUSA, even if the former is safer, because the risk of damage of the pia-matter and thus of vascular injury maybe higher with the CUSA—which can also induce a transient inhibition of axonal condution [105]. When the pia is damaged, due to the surgical dissection or due to the tumor itself (especially in cases of re-operation), it is recommended to identify first the normal pia all around the portion which is damaged, and to converge on this point at the end of the resection. The last but not the least, the pia-matter also represents a very good anatomic landmark. When the deep part of a sulcus is identified at the end of a subpial dissection, it means that the resection arrives into the contact of the subcortical connectivity, and that it is time to start to perform electrical mapping of the long-distance association or projection white matter pathways (see next chapter by Duffau) [97]. Moreover, in the specific cases of insular/paralimbic DLGG, the deep part of the pia-matter buried within the anterior insular sulcus is very close to the lateral part of the anterior perforating substance, and may represent the end of glioma resection after the removal of the limen insulae—to avoid injury of the lenticulo-striate arteries—by identifying the inferior fronto-occipital fascicle that runs within the temporal stem [100, 106].

## 23.7 Conclusions and Future Prospects

Collectively, these data strongly argue in favor of achieving an early surgery for DLGG [4]. Thus, wait-and-see attitude must be definitely abandoned. Indeed, radical and safe resection, when possible, is the first therapeutic option to propose, as recommended by the current European Guidelines [107]. In front of this amount of evidence, a prospective randomized study is now unethical, while retrospective matched studies or prospective observational trials may be considered.

Resection for DLGG is a neural networks surgery [90]. In this state of mind, brain surgeon should be first a neuroscientist, in order to operate central nervous system according to eloquent cortico-subcortical individual structures made visible owing to the use of intraoperative direct electrostimulation mapping in awake patients (and not purely on the basis of oncological and/or anatomical landmarks, as in the classical literature) [108]. In other words, this resection should be functional-mapping guided, with no margin around the crucial circuits, i.e. with a resection pursued until functional boundaries have been encountered *and not before*, even for DLGG located within non-eloquent areas, in order to optimize EOR [91].

In order to better select the personalized therapeutic strategy and to improve the quality of patient counselling, resection probability map allowing preoperative estimation of residual volume for DLGG removal with intrasurgical functional map-

ping can been used [77, 78]. Such prediction of the postoperative residue according to the relationships of the glioma with critical neural networks may be useful to make the decision of surgical resection versus single biopsy followed by "neoadjuvant chemotherapy"—with the aim of inducing shrinkage of the DLGG and of opening the door to a subsequent surgery with a real chance to perform at least a subtotal removal (see the chapter by Duffau and Taillandier) [4, 109, 110]. To this end, biomathematical models of proliferation and diffusion, based on the acquisition of at least two MRIs 3 to 6 months apart, can also play a major role to predict the growth as well as the migration of the glioma [16, 68, 111] (see chapter by Mandonnet on "Biomathematical Modeling of the DLGG Behavior"). Such anticipation could be helpful to plan not only a first glioma resection but also a possible reoperation a few years later, with the goal to improve EOR while sparing critical circuits thanks to the mechanisms of neuroplasticity induced by DLGG progression (see previous chapter by Duffau) [73].

This new principle of "personalized functional neurosurgical oncology" [112] is based on the understanding and preservation of the brain connectome for each patient [2, 18, 86]. Such a conceptual shift has allowed to solve the classical dilemma in DLGG surgery, by increasing both OS and QoL. However, optimization of oncological and functional outcomes implies that DLGG patients should be referred in a more systematic manner in hyper-specialized centers, with multi-disciplinary teams specifically dedicated to the management of this rare entity. The next step will be to build a "preventive surgical neuro-oncology", by operating on asymptomatic DLGG patients, when the tumor is smaller and when the rate of total or supratotal resection can be significantly increased [113–115]. To this end, a screening policy for incidental DLGGs can be envisioned [69].

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# Chapter 24
# Surgery for Diffuse Low-Grade Gliomas (DLGG) Functional Ouctomes

**Hugues Duffau**

**Abstract** Early and maximal surgical resection is currently the first treatment in DLGG. Beyond oncological considerations, preservation of the quality of life (QoL) is a priority in DLGG patients with long survivals. For a long time, it was claimed that these patients had a no functional deficits. In fact, extensive neuropsychological assessments performed before any oncological therapy have found a high rate of cognitive disorders, even in DLGG incidentally discovered. This is due to the tumor progression that disrupts functional connectivity and/or epilepsy as well as anticonvulsants. Thus, these findings plead against a wait-and-see attitude, also for functional reasons. Moreover, because this chronic and diffuse tumoral disease often involves critical neural networks, it was thought that the chances to perform an extensive glioma removal were low, whereas the risks to induce permanent neurological deficits were high. To adapt the surgical procedure to the individual cerebral anatomo-functional organization, that can be highly variable from patient to patient—or even in the same patient over time due to brain reorganization induced by the slow growth of DLGG—neurosurgeons should see first the brain, and not the tumor. The use of the data provided by functional neuroimaging for surgical selection and planning has been proposed. However, this technique is not reliable enough to guide surgery, especially because it can not distinguish neural pathways crucial for brain functions from those which can be compensated after removal. Therefore, to talk about "radical safe resection" based upon neuroimaging is a non-sense. Here, the goal is to introduce an original concept in neuro-oncological surgery, that is, to achieve early resection of DLGG up to the individual functional limits, with no margin left around the critical structures, thanks to intraoperative electrical mapping and on-line neurocognitive monitoring achieved in awake patients. To this end, in addition to cortical mapping, it is crucial to map the subcortical connectivity, with

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the aim of preserving the networks underlying the "minimal common core" of the brain. This "hodotopical" workframe considering both cortical hubs and axonal pathways, opens the door to a paradigmatic shift in surgery, switching from anatomic/oncological-guided resection to functional mapping-guided resection—based upon an accurate study of brain connectomics and neuroplasticity in each patient. These conceptual advances have permitted an optimization of the benefit-to-risk ratio of surgery in DLGG patients, including in "eloquent areas" traditionally thought to be "unresectable", by improving significantly not only survival but also QoL—thanks to a preservation or even an increase of the neurocognitive scores as demonstrated by postoperative neuropsychological evaluation, and thanks to epilepsy control, related to the quality of resection. Thus, early maximal surgical resection should be performed not only for oncological but also for functional/epileptological purposes in DLGG—knowing that QoL is also a predictor of overall survival. With this in mind, stronger interactions between cognitive/behavioral neurosciences and oncological neurosurgery must be built. In other words, brain surgeons should also be neuroscientists, to open the door to "precision neuro-oncological surgery".

**Keywords** DLGG • Surgery • Awake mapping • Direct electrical stimulation • Anatomo-functional connectivity • Quality of life • Neuroplasticity • Neurocognition

## 24.1 Introduction

In the previous chapter by Duffau, it was demonstrated that the better understanding of the natural history of diffuse low-grade gliomas (DLGG) has participated in a renewed interest in surgery in the past decade. Indeed, rigorous studies based on objective evaluation of the extent of resection on postoperative MRI showed that surgery had a significant impact on both malignant transformation and overall survival in patients with DLGG [1–4]. As a consequence, because retrospective and prospective analyses support surgical intervention over watchful waiting [5], current guidelines recommend maximal safe resection as the first therapeutic option [6, 7]. From an oncological point of view, this paradigmatic shift should lead neurosurgeons not to content with a single "tumorectomy" (that is, to remove only the "top of the iceberg" visible on neuroimaging), but to switch toward an extensive resection of a chronic and diffuse tumoral disease of the brain—with the realization of a "supratotal" resection when possible [8, 9].

Of note, for a long time, the vast majority of glioma studies focused on overall survival but did not accurately analyze the quality of life (QoL) and the neurocognitive aspects. Nonetheless, due to an increased access to MRI, resulting in an earlier diagnosis, most of patients with DLGG experience no or only slight neurological deficit at time of the first imaging, usually performed because of inaugural seizures or even for independent reason resulting in incidental discovery (see the

last chapter by Mandonnet et al.) [10]. Thus, in addition to the optimization of extent of resection, preservation of the QoL—or even its improvement by controlling seizures in case of preoperative epilepsy—is currently a priority in (early) surgery for DLGG [11, 12]. On the other hand, due to the frequent location of DLGG near or within the classically so-called "eloquent" areas in a localisationist view of brain processing [13, 14], and due to the infiltrative feature of these tumor (poorly demarcated), it was claimed for several decades that the chances to perform an extensive glioma removal were low, whereas the risks to generate permanent neurological worsening were high. Indeed, many old surgical series have reported a postoperative rate of persistent and severe deficit between 13 and 27.5% (for a review, see [1]).

To solve this dilemma, i.e. to optimize the onco-functional balance of DLGG surgery [15], brain surgeon should change his philosophy as well as his technique, on the basis of a new concept, that is, to achieve surgical resection according to cortico-subcortical functional boundaries, and not to anatomic/oncological boundaries. In other words, the principle is first to understand the cerebral structural-functional organization at the individual level, because a major inter-individual variability has previously been demonstrated in healthy volunteers as well as in brain-damaged patients [16]. In particular, this variability is increased in cases of DLGG, due to phenomena of brain reorganization induced by the slow growth of the tumor [16–19]. Therefore, many arguments support the unpredictability of functional eloquence based on anatomic features alone and the fact that patients should not be considered ineligible for surgical intervention based on anatomic considerations alone (for a review, see [20]). Instead, neurosurgeons need to take advantage of mapping methods to create individualized maps and management plans. According to this principle, the ultimate goal is to remove a part of the brain invaded by DLGG, on the condition nonetheless that this part of the central nervous system can be functionally compensated—namely, with no negative impact on the QoL of patients [21].

This chapter reviews how a better understanding of cerebral processing, by means of intraoperative stimulation mapping in awake patients, has enabled a significant improvement of the results of DLGG surgery. To this end, in addition to cortical mapping, it is also crucial to map horizontal cortico-cortical connectivity (long-distance association fibres) and vertical cortico-subcortical connectivity (projection fibres), with the aim to preserve the networks underlying the "minimal common core" of the brain [22, 23]. Such a "hodotopical" workframe considering both cortical hubs and axonal pathways, opens the door to a paradigmatic shift in surgery, switching from image-guided resection to functional mapping-guided resection—based upon an accurate study of brain connectomics and neuroplasticity in each patient [19]. These original concepts have allowed an increase of the surgical indications for tumor located within eloquent areas traditionally considered as "inoperable" as well as a preservation, or even an improvement of the QoL—while optimizing the extent of resection as thus the overall survival (see previous chapter).

## 24.2 Presurgical Investigation of Neurocognition and QoL

The rate of neurological deficits is low in DLGG patients at the time of diagnosis, even though these tumors often involve the so-called "critical regions". This is explained by mechanisms of neural plasticity, made possible by the fact that DLGG is a slow-progressive disease (increase of mean diameter around 4 mm/year) [24], giving many years to the brain for functional remapping, with a recruitment of perilesional or remote areas within the ipsilesional and/or contralateral hemisphere (see the chapter by Duffau on "Interactions Between DLGG, Brain Connectome and Neuroplasticity") [25, 26]. The recent integration of these concepts into the therapeutic strategy has resulted in dramatic changes in the surgical management of DLGG patients, with an increase of surgical indications in "eloquent areas" while preserving QoL [27–29].

However, before to analyze postoperative functional outcomes, it must be underlined that detailed neuropsychological investigations performed before any treatment have revealed a high rate of cognitive deficits, despite a normal social and professional life in most of DLGG patients.

### *24.2.1 Baseline Neurocognitive Function Should be Assessed in a Systematic Way*

To determine the cause of changes in neurocognitive function following therapy for DLGG, it is necessary first to establish the effect of the tumor on the cognitive function of these patients at baseline. Indeed, mounting evidence now highlights the fact that, when an extensive neuropsychological evaluation is performed before any treatment, disorders of higher cognitive functions as executive functions, speed and information processing, language, visual-perception, reasoning, working memory, attention, learning or semantics, as well as emotional and behavioral disturbances are very common in DLGG patients [30, 31]. These subtle but objective deficits are frequently observed when extensive neurocognitive assessments are performed at diagnosis, challenging the traditional view which claims that DLGG patients have a normal examination (see the chapter by Klein). Even in cases of DLGG incidentally discovered, a recent study demonstrated for the first time in the literature that two thirds of patients reported preoperative subjective complaints, mainly tiredness (40%) and attentional impairment (33%). In addition, presurgical neurocognitive functions were disturbed in 60% of patients; 53% had altered executive functions, 20% had working memory impairment, and 6% had attentional disturbances [32].

This is the reason why a preoperative assessment of higher functions and health related QoL is now recommended in a systematic manner (see the chapter by Moritz-Gasser and Herbet). Such evaluation may have several interests: (1) to search possible subtle neuropsychological deficits not identified by a classical neurological examination (2) to adapt the strategy according to these individual results

(e.g. decision of neoadjuvant chemotherapy instead of surgery first in cases of very diffuse DLGG inducing important cognitive deficits) (3) to adapt the surgical methodology itself to the results of this assessment (e.g. to select intrasurgical tasks during awake surgery according to the results of the preoperative assessment) (3) to benefit from a presurgical baseline allowing a comparison with the postsurgical evaluation (4) and to plan a specific functional rehabilitation following the resection, which can induce a transient functional worsening.

Indeed, previous reports have shown that the presence of an abnormal baseline cognitive score is a strong predictor of poorer overall survival in DLGG patients [33]. The importance of baseline neurocognitive function is underscored by its inclusion as an independent determinant of outcome in the validated prognostic calculator analysis for patients with DLGG [34]. However, in spite of these reports, it is likely that more patients experienced cognitive disorders than described in the literature. This underestimation by neurosurgeon/neurooncologist is due to the fact that the identification of such "subtle" deficits is not possible using a single "standard clinical examination". Unfortunately, detailed neuropsychological evaluation was very rarely performed before (and after) DLGG surgery, especially when the lesion was located outside the so-called "language areas". As a consequence, the principle of a standardized examination of neurocognitive outcome has recently been proposed [35].

### *24.2.2 Mechanisms Underlying Cognitive Disorders Before Any Oncological Treatment*

A large proportion of DLGG patients are diagnosed following workup of a new-onset seizure. A study by Klein et al of 195 patients with DLGG showed that, regardless of "epilepsy burden", the patients with glioma had reduced cognitive function and health-related QoL compared with healthy controls [36]. DLGG patients who had the highest seizure burden demonstrated greater impairment, with decreased information processing, psychomotor functioning, attention, working memory capacity, and executive functioning. Although control of seizures was associated with a higher QOL, use of antiepileptic drugs was associated with worse cognitive performance in all domains except verbal memory. Therefore, both seizure and antiseizure medications have a negative effect on neurocognitive function in patients bearing a DLGG [36].

It is worth noting that, beyond epilepsy and its treatment, the tumor itself has negative impact on higher-order functions [37]. Recent investigations of brain resting-state functional connectivity, or no-task, "default network" state of brain activity, have identified differences between healthy controls and DLGG patients. Bosma and colleagues found significant differences between 17 patients with DLGG assessed with magnetoencephalography in conjunction with a battery of standard neurocognitive tests and 17 matched controls, in both long-range brain

synchronization and short-range brain synchronization that were mapped specifically to areas of working memory, attention, and information processing. Among the differences detected between the 2 groups was a modification in long-range connectivity in the resting-state of the DLGG patients. This finding was associated with worse working memory and attention deficits on neurocognitive tests. This means that the focal presence of low-grade tumor in the brain affects overall functioning by disrupting large-scale neural networks [38, 39].

In this state of mind, the new probabilistic atlases of functional plasticity elaborated from DLGG patients, subcortical fibers showed a low level of interindividual variability [16] as well as a low level of plastic potential [22, 23, 40] (see the chapter by Duffau on "Interactions Between DLGG, Brain Connectome and Neuroplasticity"). As a consequence, because DLGG are often migrating within the white matter tracts [41], diffusion of glioma cells along these bundles may induce cognitive disorders, due (at least partly) to a "disconnection syndrome" [42, 43]. For example, in a recent voxel-based lesion-symptom analyses on preoperative behavioral data in 31 DLGG patients, a significant relationship between semantic fluency scores and the white matter fibers shaping the ventrolateral connectivity was observed ($P < 0.05$ corrected). The statistical map was found to substantially overlap with the spatial position of the inferior fronto-occipital fasciculus (IFOF) (37.7%). Furthermore, a negative correlation was observed between semantic fluency scores and the infiltration volumes in this fasciculus ($r = -0.4$, $P = 0.029$) [44]. In the same vein, in another recent series with 93 DLGGs, each associative pathway's degree of disconnection (i.e. the degree of lesion infiltration) has been estimated in 93 DLGGs who benefited from behavioural tasks assessing mentalizing, that is, a key function in understanding and successfully performing complex social interactions. Interestingly, impairments in mentalizing were mainly related to the disruption of right frontoparietal connectivity. More specifically, low-level (theory of mind) and high-level mentalizing (inference of other's intentions) accuracy were correlated with the degree of glioma invasion in the arcuate fasciculus and the cingulum, respectively [45].

Taken together, these data demonstrate that the migration of DLGG along subcortical pathways can generate specific cognitive or emotional disturbances depending on the neural sub-network involved by the tumoral cells.

### *24.2.3 Evaluation of QoL*

In the same state of mind, and beyond the objective neuropsychological scores, it is essential to define what exactly means "QoL" for each patient, on the basis of his(her) job, habits, hobby and projects. The goal is to prioritize the brain functions which should be preserved throughout the resection, and to adapt the intraoperative tasks according to this preparatory discussion with the patient and his(her) family. For instance, it can be important to test different languages as well as language switching intrasurgically in multilingual patients, especially in translator; or to map

calculation in school teacher, spatial cognition in dancer, working memory in manager, syntax in writer, judgment in lawyer, mentalizing (empathy) in medical doctor, etc. [46, 47]. This means that intraoperative mapping should be personalized for each patient—in addition to standard tasks such as picture naming for lesions located within the "dominant hemisphere".

In conclusions, routine neurocognitive examinations with QoL assessment scales should be currently achieved in all patients with DLGG, before (and after) any treatment, as the standard neurological assessment is ultimately too crude to be able to identify subtle deficits. Such a baseline assessment can be helpful for defining the best individualized management, especially with regard to surgery. Indeed, from a therapeutic point of view, glioma migration along fibers can also limit the extent of resection at the level of the axonal pathways, in order to preserve brain functions [19, 23]. Last but not the least, the high rate of neurocognitive disorders existing before oncological therapy, due to disturbances of functional connectivity induced by the tumor progression, pleads against a wait-and-watch policy.

## 24.3 Preoperative Neuroimaging: Advances and Limitations

Although progress in neuroimaging have allowed a better knowledge of the natural history of gliomas (growth, invasion as well as malignant transformation) (see the chapter by Guillevin), paradoxically, it also led to several conceptual limitations.

### *24.3.1 Oncological Neuroimaging*

From an oncological point of view, as mentioned in the previous chapter, development of neuroimaging led neurosurgeons to achieve a single tumorectomy according to the boundaries provided by preoperative or intraoperative structural (in particular T2—and FLAIR-weighted MRI) and metabolic imaging (as perfusion or spectroscopy MRI). However, this principle is not coherent neither with the infiltrative nature of DLGGs nor with the limited resolution of current neuroimaging. Indeed, DLGG invades the brain beyond the abnormalities visible on imaging, with tumor cells present at a distance of 10–20 mm of the tumor boundaries defined by MRI [48]. This knowledge should led to perform larger glioma removal, at least in "non-functional areas", since "supra-complete" resection dramatically change the natural course of this tumor by avoiding malignant transformation [8, 9]. As a consequence, when DLGG is distant from eloquent structures, in essence, image-guided resection is a non-sense, because it could be possible in these cases to remove more tumoral cells while preserving the function, on the condition nevertheless to not constraint the resection according to the T2/FLAIR-weighted MRI—but according to functional boundaries (see below) [49]. Unfortunately, the integration of preoperative MRI into neuronavigation or the use of intraoperative MRI is based on a

reductionist concept, i.e. the exclusive removal of the signal-abnormality, with no attempt to increase the resection beyond these landmarks—even though they do not reflect the whole glioma disease. In other words, image-guided resection may decrease odds for patients with a DLGG away from neural networks crucial for brain functions, by resulting in premature interruption of surgery (see previous chapter by Duffau) [50].

On the other hand, from a functional point of view, image-guided resection is not logical in DLGG, because critical structures may persist within the diffuse tumoral disease visible on FLAIR-weighted MRI. In other words, resecting solely the MRI-defined abnormalities for DLGG in eloquent areas does not prevent to generate permanent neurological deficit [51].

### *24.3.2 Functional Neuroimaging*

In this context, the development of functional neuroimaging techniques such as functional MR (fMRI), white matter fiber tractography by diffusion tensor imaging (DTI) and transcranial magnetic stimulation has enabled the achievement of non-invasive mapping of the whole brain. Functional imaging is not however sufficiently reliable on an individual basis to be used in clinical practice, as it does not directly reflect cerebral functional reality, but provides a very indirect approximation based on biomathematic reconstructions—explaining why results may vary depending on the model used [52].

Indeed, comparison between fMRI and intraoperative electrophysiology have shown only 71% of positive correlations for motor function [53]. Poor correlations have also been observed concerning language (about 33%) [54], with a sensitivity around 66% [55]. More recently, by comparing preoperative language fMRI with intraoperative electrical stimulation mapping, Kuchsinski et al. calculated the sensitivity of fMRI at 37.1% and the specificity at 83.4% [56]. Therefore, in a review on this topic, Giussani et al. concluded that “The contradictory results of these studies do not allow consideration of language fMRI as an alternative tool to direct cortical stimulation in tumor located in language areas” [57]. In addition, fMRI could not distinguish regions which are essential for function (which must be preserved surgically) from regions of the brain which are involved but are not crucial for a given function (which may therefore be surgically removed as functional compensation may occur). Thus, this raises two risks of basing decisions on fMRI. The first one is not to select a patient for a procedure because of a false positive imaging result, with an oncologic loss of opportunity. This point was especially described for DLGG invading the insula or the so-called Broca’s area and Wernicke’s area, which have been removed with favorable outcome although these regions were a priori thought to be eloquent on the basis of functional neuroimaging [58–60]. Conversely, the other risk is to remove a DLGG from a region which was ultimately essential for function but not found on the preoperative fMRI because of a false negative result, with therefore a loss of functional opportunity [61]. With this in

mind, the concept of the lateralization index and dominant hemisphere for language is extremely dangerous. For instance, even if fMRI only detected under 10% active regions in a right-handed patient with a right hemisphere glioma, this "left dominance" does not however mean that the right side is not functionally crucial. It would simply need this critical epicenter to be located in the immediate proximity of the glioma for surgical resection based on fMRI results on the lateralization index in favor of the left hemisphere, to result in potentially irreversible crossed aphasia [62]. Consequently, Junck et al. have recently written that "fMRI is not ready for prime time in guiding glioma resection" [63]. Of note, beyond activation task-based fMRI, a recent study comparing intraoperative cortical stimulation mapping with preoperative resting-state fMRI in 98 DLGG patients showed that 96 ± 11% of sensorimotor stimulation were located within 10 mm from sensorimotor independent component analysis maps versus 92 ± 21% for language [64]. Furthermore, 3.1% and 15% of resected cortex overlapped sensorimotor and language networks, respectively. Thus, even though resting-state fMRI succeeded in some extent to distinguish eloquent versus resectable sensorimotor and language areas, these original results reveal a high interindividual variability of mapping accuracy and a rate around 80% in the detection of eloquent cortical sites, which is clearly insufficient to use resting-state fMRI on its own for preoperative cortical functional mapping. Further validation studies are needed to increase the reliability of this method for surgical planning, using in particular network automatic identification and/or subnetwork analysis [64] (see the chapter by Cochereau and Krainik).

Diffusion tensor imaging, which enables a tractography of the main white matter bundles to be carried out, needs also to be validated. In other words, neurosurgeons seem to forget that DTI is not a direct tool of visualization of the actual anatomy of fibers, but only an indirect reconstruction based on measuring the diffusion of water molecules. In fact, as reminded by Feigl et al., DTI results depend on (1) the acquisition of data (which themselves can vary by using different parameter settings for the scan sequences and by using scanners with different field strengths), (2) biomathematical models (e.g., deterministic vs. probabilistic fiber tracking), (3) the software programs [65]. In this state of mind, different reconstructions are found from distinct models and softwares by different teams using the same data, showing that tractography is neither reliable nor reproducible [52]. Indeed, an international working group of clinicians and scientists whose goal was to provide standardized evaluation of tractography methods for neurosurgery, the DTI Challenge, has recently been initiated [66]. In their first study, eight international teams from leading institutions reconstructed the pyramidal tract in four neurosurgical cases presenting with a glioma near the motor cortex. The evaluation of tractography reconstructions showed a great interalgorithm variability. Although most methods found projections of the pyramidal tract from the medial portion of the motor strip, only a few algorithms could trace the lateral projections from the hand, face, and tongue area. Therefore, because of disagreement among methods, this study suggests that there are still limitations to the clinical use of tractography for neurosurgical decision making [66] (see the chapter by Pujol).

Beyond algorithms, DTI reconstruction is also dependent on the physician who decides where to put the regions of interest. For instance, it is in essence impossible to build the middle longitudinal fascicle if this pathway is not voluntarily tracked, because little is known about it [67]. Therefore, its fibers will be wrongly incorporated within the superior longitudinal fascicle or the inferior fronto-occipital fascicle, with false results provided to the surgeon. Furthermore, when dealing with an abnormal or distorted fiber tract anatomy, in particular in brain tumors, the risk of erroneous DTI results is increased because diffusion properties may be affected by the lesion. By using neuronavigation and subcortical white matter stimulation in tumor patients, Kinoshita et al. showed that although they were able to visualize the pyramidal tract with DTI, the images failed to present the actual size of the fiber bundles [68]. These methodological pitfalls explain why correlation studies between DTI and intraoperative electrophysiology (direct subcortical electrostimulation, see below) have shown concordance in only 82% of cases [69]. Negative tractography does not formally mean that no crucial fibers are present within the glioma. In addition, DTI does not differentiate between efferent and afferent projections, thus it does not provide any information about the causality and directionality of the connections. It means that DTI is not able to give information about the eloquence of a specific white matter fiber: it can provide only indirect data about its structure [70]. Finally, a recent study that aimed to assess the utility of DTI in the surgical treatment of motor eloquent tumors demonstrated that tractography of pyramidal pathways did not influence the surgical planning or the intraoperative course [71]. Therefore, it is not at present reasonable to use tractography as the basis to determine indications for surgery or to plan the surgical procedure. Indeed, there are many risks of DTI, (1) to not select a patient for surgery while the tumor was actually operable; (2) to stop the resection prematurely, with a lower impact on the natural history of the disease; or (3) to cut eloquent pathways not detected by preoperative DTI [70].

With respect to transcranial magnetic stimulation, apart from the fact that this technique only examines the cortex and not subcortical connectivity, its specificity for language mapping is only 23.8%, with a positive predictive value of 35.6% [72]. Even for tumors located in or near motor cortex, a recent study showed that navigated transcranial magnetic stimulation had an objective benefit on the surgical planning in only one fourth of the patients [73].

Last but not least, the risk for young neurosurgeons who use functional neuroimaging regularly in the operating theater (incorporated into the neuronavigational system or acquired in real time with intrasurgical MRI) is to become dependent on neuroimaging. The danger is for them not to be able to operate in the brain without any intrasurgical neuroimaging, on the sole basis of their own mental imagery validated by online feedback provided by cognitive monitoring and stimulation mapping [50, 51].

In summary, neurosurgeons should be aware of the dangers of functional neuroimaging before applying its results both for preplanning and in the operating room [70]. In addition, the dogmatic rule which emerged because of the poor accuracy of these techniques is to take 5–10 mm of margin around the presumed functional

regions according to neuroimaging [74]. As already mentioned in the previous chapter by Duffau, such strategy is against the oncological goal, that is, to optimize extent of resection, whereas it was demonstrated in hundreds consecutive patients with DLGG in critical structures that the resection could be pursued with no margin left around the eloquent networks without increasing the permanent morbidity [49, 75–77].

Instead, functional neuroimaging should be considered as a research and didactic tool *outside the operating room*. Indeed, functional anatomy remains poorly known, and fMRI/DTI may play a role in the improvement of our understanding of brain connectomics. For example, combining functional information provided by intrasurgical electrostimulation mapping of the white matter tracts in awake patients and anatomic data from serial DTI is a new way to bring original insights to cognitive neurosciences [78], in particular for studying the mechanisms of cerebral plasticity [19]. DTI also is an excellent educational tool, especially because of the development of the atlas of human white matter tracts, which can be combined with functional atlas issued from intraoperative mapping [40]. Such a 3-dimensional representation of the eloquent pathways can be very helpful for training young neurosurgeons, neurologists, neuroradiologists, neuroanatomists, neurophysiologists, and even neuroscientists [79].

## 24.4 Intrasurgical Real-Time Cognitive Monitoring and Electrostimulation Mapping

Due to the major limitations of oncological and functional neuroimaging detailed above, *direct electrical stimulation mapping is currently the "gold-standard" when removing glioma* [80].

### *24.4.1 Limitations of Intraoperative Electrophysiological Monitoring and Extraoperative Mapping*

The technique of somatosensory and motor evoked potentials was extensively used in the past decades for intraoperative identification of the central region [81]. However, its reliability regarding the localization of the rolandic sulcus is not optimal, between 91 and 94%. Estimation of the overall sensitivity and negative predictive value of intrasurgical somatosensory evoked potential was evaluated around 79 and 96%, respectively [82]. Also, whereas the method of motor evoked potentials was improved, when recording compound muscle action potentials, only the monitored muscles can be controlled, i.e. there is an unability to detect and possibly avoid motor deficits in nonmonitored muscles. In addition, monitoring of muscle action potentials does not mean monitoring of complex movements,

bimanual coordination, action adapted to the environment, and intention to act, which is nonetheless the ultimate goal for the patient [83–86]. Above all, intraoperative evoked potentials cannot currently be used to map langague, executive functions or emotion, that is, higher functions crucial for the quality of life (for a review, see [87]).

Numerous authors have also proned the use of extraoperative electrophysiological recordings (electrocorticography) and stimulations via the implantation of subdural grids [88]. Using this method, the patient is in optimal conditions, in his room, to perform the tasks: this point is particularly important for children. Moreover, recent advances in the interpretation of the electrophysiological signal, such as electrocorticographic spectral analysis evaluating the event-related synchronization in specific bands of frequency, have allowed a better understanding of the organization of the functional cortex, and a study of the connectivity, in particular via the recording of "cortico-cortical evoked potential" [89]. However, beyond the research purpose, extraoperative electrophysiological mapping suffers from many limitations in practical surgical neuro-oncology. First, it is necessary to perform two surgical procedures, one to implant grids and a second to remove the lesion. In addition, there is still a risk of infectious complications due to the presence of subdural grids during several days. Above all, although this method was extensively advocated in epilepsy surgery, because it also allows detection of the seizure foci, only the cortex can be mapped: it provides no information about the axonal connectivity, i.e. it is not possible to map the subcortical structures [90]. Thus, this technique is not adapted to neurooncology, because gliomas migrate along the white matter bundles, and, as mentioned, these tracts represent the limits of neuroplasticity [22, 23].

### *24.4.2 Intraoperative Mapping Using Direct Electrostimulation (DES): The Gold-Standard*

Taking into account the limitations of the different mapping techniques described above, DES is the standard of care for glioma surgery—see a recent meta-analysis of the literature [80]. Except for tumors located within the motor structures, DES mapping is performed in awake patients. However, as previously mentioned, because movements and action are more complex than single muscle contractions, it is also currently recommended to map the motor function under local anesthesia with an active participation of the patient [84]. Indeed, in recent studies, the existence of a large fronto-parietal network involved in motor control, including bimanual coordination, has been demonstrated [84, 91, 92]. Its stimulation in awake patients, especially at the subcortical level, may induce unvoluntary arrest or acceleration of the movement of one or both hands, impossible to detect under general anesthesia with a single electrophysiological monitoring.

From a technical point of view, DES has extensively been demonstrated to represent an easy, reliable, reproducible, safe and not expensive method in numerous previous reports [1, 21, 76, 77, 87, 93, 94]. The main goal is to perform on-line anatomo-functional correlations, thanks to active interactions between the anaesthesiologist, speech therapist/neuropsychologist, neurosurgeon and the patient him(her)self. The principle is to use DES to mimick a focal and transitory virtual lesion, to obtain an individual functional mapping both at cortical and subcortical levels, and to test if a structure involved by a lesion is still crucial for the function, what is frequently observed in DLGG, especially at the periphery/depth of the tumor. It is thus possible to decide whether the brain area tested can be removed (or not), according to the induction of transient functional disturbances (or not) during its repeated stimulations [12, 15]. Indeed, DES of structure critical for brain functions generates a transitory disruption of the task performed by the patient, and this area (which is only a part of a more complex neural network) should be preserved. One of the major advantages of DES for brain mapping in adult patients is that *it intrinsically does not cause any false negatives*—if nevertheless the methodology is rigorously applied, as detailed below [95]. Indeed, DES is highly sensitive for detecting the cortical and axonal eloquent structures, and it also provides a unique opportunity to study brain connectivity, since each area responsive to stimulation is in fact an input gate into a large-scale network—rather than an isolated discrete functional site [26, 96].

The goal is now to detail the practical issues concerning an awake procedure as regularly performed in our institution [77, 97].

#### 24.4.2.1 Preoperative Preparation

The preoperative preparation for our institutional protocol is multidisciplinary and require at least 3 appointments per patient: with the neurosurgeon, anaesthesiologist, and speech therapist and/or neuropsychologist in charge of the preoperative, intraoperative, and postoperative cognitive testing (see the chapter by Moritz-Gasser and Herbet for a detailed description of this protocol). During these appointments, the patient and relatives are fully informed about the procedure modalities, their inherent risks and benefits, and the safety measures that might be undertaken. In particular, the sequence of events that would occur during the awake procedure and the moment at which patient cooperation would be required are accurately detailed.

The evening before the procedure, an oral sedative (zolpidem tartrate, 10 mg) is administered. The day of the procedure, no anxiolytic or sedative medication is given to avoid compromising the patient's cooperation during the awake phase. Anticonvulsants are administered as usual (i.e., with no systematic antiepileptic drugs in patients with no preoperative seizures), as well as a 400-mg dose of cimetidine.

#### 24.4.2.2 Operative Procedure: Practical Issues

Anaesthetic Management

Our institutional asleep-awake-asleep anaesthetic protocol has extensively shown its reliability and safety [97, 98]. Two intravenous lines are placed in the patient, who is monitored by a pulse oximeter, a noninvasive blood pressure monitor, electrocardiography, an end-tidal carbon dioxide partial pressure analyzer, and a respiratory rate monitor. Urinary catheters and temperature probes are used routinely. The position used is the lateral decubitus on a thick foam mattress. The head is placed in a Mayfield head holder, in neutral position with respect to the head-neck-trunk axis. The environmental temperature in the operating room is also controlled to avoid shivering, and a forced-air warming device is systematically used.

Total intravenous general anaesthesia with a laryngeal mask airway is used in the first asleep phase for all patients, using a target-controlled infusion of propofol and remifentanil to regulate the depth of anaesthesia and to facilitate ventilation, respectively. Noninvasive blood pressure monitor, pulse oximeter, electrocardiography, and respiratory rate monitor are used to monitor the patient. All patients receive ondansetron 4 mg, acetaminophen 1 g, and cefamandole 1.5 g intravenously for antibiotic prophylaxis. The scalp is infiltrated with local anaesthetic (20 mL lidocaine 2% with epinephrine) before placement of the Mayfield head holder and all along the skin incision, as well as at the level of specific regional anaesthesia points (e.g., temporal, supraorbital, or occipital nerve blocks). Once the craniotomy is performed, the temporal muscle and the dura mater are also infiltrated with lidocaine. Once the craniotomy is completed, the general anaesthesia is stopped at the surgeon's request and the laryngeal mask is removed when the patient opens his or her eyes. The examiner (speech therapist and/or neuropsychologist) is able to start working a few minutes after the patient is conscious and fully cooperative. The neurologic tests are then performed during whole cortical and subcortical mapping, as well as throughout the tumor resection. The anesthesiologist treat any discomfort, but no sedative medications and no antiepileptic drugs are administered during this phase. Again, the awake period end at the surgeon's request. General anaesthesia with intravenous propofol and remifentanyl is also used after the awake phase, for possible additional resection in noneloquent areas and closure [97].

Cortical Mapping

In all cases, bone flap and dura mater opening are wide enough to expose primary motor area and ventral premotor cortex, in order to obtain a positive mapping. Indeed, stimulation of the entire exposed cortical surface is achieved before the resection, which can be tailored according to the results of this individual functional map [77, 99]. Of note, some authors emphasized the value of "negative mapping" (no identification of eloquent sites) in the setting of a tailored cortical exposure [100–102]. However, a negative mapping is very dangerous in surgery of DLGG,

especially in non expert hands. Indeed, due to the fact that DLGG is poorly delineated, the limit of the resection will be essentially guided according to functional criteria. Because negative mapping can be due to false negative for methodological reasons, it does not guarantee the absence of eloquent sites. Thus, negative mapping cannot prevent persistent postsurgical worsening in all patients: 1.6–9% of permanent postoperative deficits have been reported in cases of negative mapping [100–102]. Therefore, we continue to advocate a wider boneflap in order to obtain systematic functional responses before the resection [77, 99]. *Moreover, a positive mapping might also allow an optimization of the extent of resection, since the tumor removal can be pursued until eloquent areas are encountered, i.e. with no margin left around the functional structures: this may result in supratotal resection* [49, 75].

In practice, a bipolar electrode with 5-mm spaced tips, delivering a biphasic current (pulse frequency 60 Hz, single pulse phase duration of 1 ms, amplitude from 1 to 4 mA, mean 2.25 to avoid seizures), with a maximum duration of stimulation of 4 s, is applied to the brain [77, 99]. Firstly, ultrasonography is used before any resection to identify the tumor limits and the main sulci and gyri. Next, speech and/or sensory-motor cortical mapping ares performed in all cases, over the ventral premotor cortex and/or primary sensory-motor area until a positive response is evoked (i.e., articulatory disorders eliciting a complete speech arrest while the patient is asked to count and/or induction of involuntary movements or paraesthesia in the contralateral hemibody and/or arrest of movement), indicating the optimal threshold of stimulation. The current of intensity is determined for each patient by progressively increasing the amplitude of stimulation in steps of 0.5 mA starting from a 1-mA baseline until a response was elicited. Once the threshold is defined, that current amplitude is used for the remainder of the cortical and subcortical mapping. The patient and the speech therapist/neuropsychologist are never informed when the brain is stimulated. No site is stimulated twice in succession, to avoid seizures. Each cortical site of the entire cortex exposed by the bone flap is tested 3 times. Indeed, it is admitted nowadays that 3 trials are sufficient to ensure whether an area is crucial for brain function, by generating disturbances during its 3 stimulations, and with normalization of the function as soon as the stimulation is stopped. Interestingly, recent series showed that the surgical procedure could be simplified, by avoiding the use of intraoperative electrocorticography despite an equivalent reliability of the electrical mapping, and without increasing the rate of seizures—or even with a decrease, that is, about 3% of partial seizures with no aborted surgery in a prospective cohort with 374 supratentorial awake surgeries [77]. If intraperative seizures occur, the speech therapist/neuropsychologist and/or anaesthetic team detect them. Stimulations are stopped, and the cortex is irrigated with cold Ringer lactate until cessation of seizures [103]. No anticonvulsants are administered. Once the patient is again able to perform cognitive tasks, resection is resumed.

It is worth noting that there is a limitation of trials and tasks required by the timing of the surgical procedure, because the patient is awake and can be tired at the end of the resection. In our protocol, intraoperative tasks include at least picture naming and a dual task (picture naming in concert with contralateral arm movement) while receiving systematic stimulation throughout the cortex [77].

Further tasks may be added according to the location of the tumor and QoL of the patient (defined on the basis of his or her job and hobbies, e.g., semantic association tasks, visuospatial tasks, judgment, mentalizing) [46, 47] (see below). Sites that induce errors or disturbances in the aforementioned functional tasks at 3 nonsequential stimulations followed by normalization after stimulation ceased are marked with numbered sterile tags on the cortical surface, and the specifics of the error are recorded (i.e., semantic paraphasia, speech arrest, dysarthria, and so on). A photograph was taken before resection to capture the cortical map.

Resection and Subcortical Mapping

After the completion of cortical mapping, the lesion is then removed by alternating resection and subcortical stimulation to identify critical pathways. Indeed, using the same parameters of stimulation as those applied at the cortical level, the functional fibers are followed progressively from the eloquent cortical sites already mapped to the depth of the resection [75, 99]. During the resection and stimulation of subcortical tracts, the patient continues with the same tasks, and the speech therapist and/or neuropsychologist analyze the functional disturbances in real time. To perform an optimized tumor removal while preserving eloquent areas, all resections are pursued until critical networks are encountered around the surgical cavity (i.e., resections are achieved according to functional boundaries). This means that there are no margin left around the eloquent structures, either within the gray or white matter [49]. As a consequence, when possible, the glioma resection is extended beyond the tumor's visible limits on preoperative FLAIR-weighted MRI [8, 9]. After lesion removal, a photograph of the subcortical maps is taken.

#### 24.4.2.3 Postoperative Course

After surgical procedure, all patients are admitted to intensive care unit for one night. Postoperative MRI is performed within the first 24 h. Immediate postoperative functional assessment, in which the same tests are used as were done preoperatively, was achieved 3–5 days after surgery and at 3 months. The KPS score is also evaluated 3 months after surgery. All patients receive systematic postoperative prophylaxis with antiepileptic drugs for at least 3 months, including patients with no preoperative seizures (usually levetiracetam 1 g/day) [104]. In the vast majority of cases, according to the results of the immediate postoperative examination, patients benefit from an early and intensive sensorimotor, speech, and/or cognitive rehabilitation after discharge [77].

### *24.4.3 Intrasurgical Real-Time Cognitive Monitoring and Test Selection*

The selection of the tasks administrated to the patient during surgery is crucial to preserve a normal life [12]. Intraoperatively, this means that, after asking to all patients to count, in order to detect the ventral premotor which systematically induces speech arrest or anarthria when stimulated (whatever the hemisphere) [105]—with the aim of identifying the optimal intensity threshold for the rest of the mapping (see above) [77]—the intraoperative testing should be adapted to each patient. Such a task selection should be made according to several individual parameters: job, hobby, handedness, results of the preoperative neuropsychological examination, location of the tumor and its relationships with the functional neural pathways [45, 46]. For instance, language mapping can be performed in order to detect possible language epicenters in the right "non-dominant" hemisphere in left-handers or ambidextrous (and even in some cases in right-handers), according to the results of the presurgical cognitive assessment—i.e. if language disturbances have been identified, even in cases of left-lateralization on functional MRI [62, 106]. The goal is to map the networks underlying the different but interactive sub-functions which have to be preserved intraoperatively—and which will serve as boundaries of the resection [26].

Indeed, DES allows the mapping of numerous brain functions:

- movement, which is not only the ability to contract a muscle, but which is a real cognitive function enabling to plan, execute and monitor a complex action, including bimanual coordination [84, 91, 92];
- somatosensory function: stimulation may generate dysesthesia/tingling described by the patient him(her)self intraoperatively, as well as movement disorders (e.g. arrest, acceleration) due to a deficit of haptic feedback [107];
- visual function: stimulation may elicite phosphenes, visual illusion, visual hemiagnosia and/or visual field deficit described by the patient, with a feedback made possible thanks to the presentation of two objects situated diagonally on a screen divided into 4 quadrants [108];
- auditory-vestibular function: in particular, stimulation may induce vertigo [109];
- spatial awareness: this complex function, which integrates the previous sensory-motor, visual and auditory-vestibular functions to allow a consciousness of the interactions between human body and the environment, can be mapped intraoperatively by using line bissection in order to avoid permanent hemineglect [78];
- language: beyond spontaneous speech and counting, object naming, verbal comprehension, writing, reading, syntax, bilingualism, language switching from one language to another can be tested throughout the resection—for a recent review, see [110];
- calculation: it is possible to map the circuits involved in different kinds of mental operation, as multiplication versus subtraction [111];

– non verbal understanding: it is crucial to map and to preserve this function (by using a semantic association task during DES), in addition to verbal comprehension, in order to enjoy a normal QoL, because this is an insight into noetic consciousness, i.e. the awareness that we know that we know [112];
– other higher-order functions such as attentional processing, cognitive control, cross-modal judgement may also be mapped using intrasurgical DES [113];
– mentalizing: preservation of emotional and behavioral processes is also very important to enable the patient to resume a normal familial, social and professional life. Insights into theory of mind and social cognition are now possible into the operating theater [114].
– the next step is to test consciousness during surgery [115].

As mentioned, due to the limitation of time during surgery, the goal is to prioritize the intrasurgical tasks according to the wishes of the patient, in order to preserve his(her) real QoL: in other words, the individual mapping must be personalized.

### *24.4.4 Intraoperative Subcortical Mapping Using DES: Detection and Preservation of the Neural Connectivity*

Another major issue is the use of subcortical electrical mapping throughout the resection, in order to map the axonal pathways critical for neural functions, in addition to the gray matter mapping allowing the identification of the cortical hubs before lesion removal [93, 94, 99]. Indeed, it is now possible to map the subcircuits underlying sensorimotor function, visuospatial and vestibular processing, the different subcomponents of language (articulation, phonology, semantics, syntax, pragmatic), cognitive and emotional processes, as well as to study the interactions between these large-scale networks throughout the resection [26, 40, 96]. Indeed, brain processing must not be conceived as the sum of several subfunctions. Instead, cerebral function results from the integration and potentiation of parallel (while partially overlapped) subnetworks, in a connectomal view of brain functioning [19].

Here, the aim is not to review the brain connectome, which has been extensively detailed in the chapter by Duffau on "Interactions Between DLGG, Brain Connectome and Neuroplasticity", but to remind that such subcortical connectivity should be preserved to allow postoperative recovery. Indeed, as for vascularization preservation (see previous chapter by Duffau on oncological outcomes), it is puzzling to note that intrasurgical subcortical mapping was very scarcely reported in glioma surgery, and that neurosurgeons began to demonstrate some interest for the white matter pathways essentially since the recent development of DTI—which is nevertheless not reliable enough, as already discussed [70]. Yet, recent probabilistic atlases of cerebral plasticity have demonstrated that the potential of functional reshaping was very low at the axonal level [22, 23]. This is the reason why neurosurgeons

should know very well the "minimal common brain", mainly represented by the white matter tracts, in order to detect these pathways with a high level of reliability into the operative room by means of axonal DES in awake patients [22, 40]. Interestingly, a better knowledge of these atlases of functional white matter bundles and brain plasticity is very helpful, not only to avoid postoperative permanent neurological/neurocognitive deficits, but also to predict before surgery the probable amount of postoperative tumor remnant [116, 117]—and thus to select the best patients for DLGG surgery.

To this end, even if DTI may represent an excellent didactic tool to learn this complex architecture [79], it is essential to go back to the laboratory to perform anatomic dissection on cadavers, especially concerning the white matter tracts using the Klinger's method [118, 119]. Indeed, new anatomic dissections of the subcortical pathways can be currently performed in the lights of data provided by axonal mapping, especially with regard to the cortical terminations of the subcortical fibers, which are still poorly known [96, 120, 121] (Fig. 24.1). Such a knowledge concerning relationships between brain structure and function can be successfully applied to the elaboration of new models of conation and cognition, as well as to a better understanding of the surgical anatomy. With this in mind, stronger interactions between cognitive/behavioral neurosciences and oncological neurosurgery must be built. In other words, brain surgeons should also be neuroscientists.

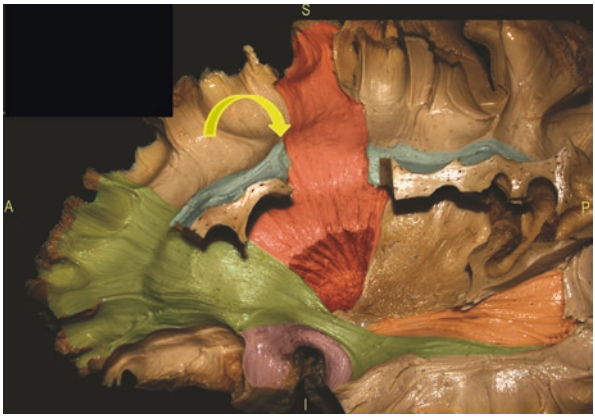


**Fig. 24.1** The main association and projection fascicles demonstrated in anatomic dissections were summarized and were colored for an easier recognition. *Green* = IFOF; *Violet* = uncinate fascicle; *Blue* = SLF/AF; *Red* = cortico-spinal tract; *Orange* = stratum sagittalis. (Left hemisphere; A, anterior; P, posterior; S, superior; I, inferior). According to this anatomy, the yellow arrow shows one of the major deep functional boundaries during glioma resection within the left frontal lobe, that is, the crossing between the left SLF/AF and the cortico-spinal tract. Modified from [121]

## 24.5 Mapping the Brain Connectome Applied to Surgical Functional Anatomy in DLGG

An improved knowledge of the connectomal organisation of the central nervous system, breaking with the classical localisationist model, is crucial to optimize the functional outcomes following DLGG resection. In other words, the principle of "hodotopy" is not only an esoteric concept, but also a useful tool for brain surgery, especially in neuro-oncology [122]. Here, the goal is to briefly summarize the different pathways which should be detected as functional limits of resection at the end of surgery for DLGG involving distinct cerebral regions (where DLGG is most frequently located)—in other words, to detail the surgical functional anatomy according to each glioma location.

### *24.5.1 Precentral-Frontal DLGG (Fig. 24.2)*

- Posterior limits: pyramidal pathways (with the risk to induce permanent deficit concerning complex movement such as bimanual coordination if the resection is pursued up to this cortico-spinal tract) and/or fibers involved in the control of movement and speech (i.e. fronto-striatal tract and frontal aslant tract in the left "dominant" hemisphere, respectively) if the patient wants a perfect recovery [84, 87, 91, 92].
- Deep limits: convergence of the anterior part of the superior longitudinal fascicle/arcuate fascicle (involved mainly in articulatory/phonological processing in the left hemisphere and mainly in the theory of mind in the right hemisphere, as well as in working memory bilaterally) [45, 76, 105] and of the anterior part of the inferior fronto-occipital fascicle (involved in semantic processing bilaterally, mainly verbal semantics in the left hemisphere and mainly the non-verbal semantics in the right hemisphere) [26, 112]. Of note, for mesio-frontal DLGG (e.g. within the supplementary motor area), the cingulum may be involved in high-level mentalizing [45]. The head of the caudate (involved in executive control) is also an important boundary in the depth [110].

### *24.5.2 Retrocentral-Parietal DLGG*

- Anterior limits: somatosensory pathways and/or fibers involved in the control of movement if the patient wants a perfect recovery of bimanual coordination [84, 107].
- Deep limits: lateral part of the superior longitudinal fascicle (involved in articulatory process) and posterosuperior part of the arcuate fascicle (involved in

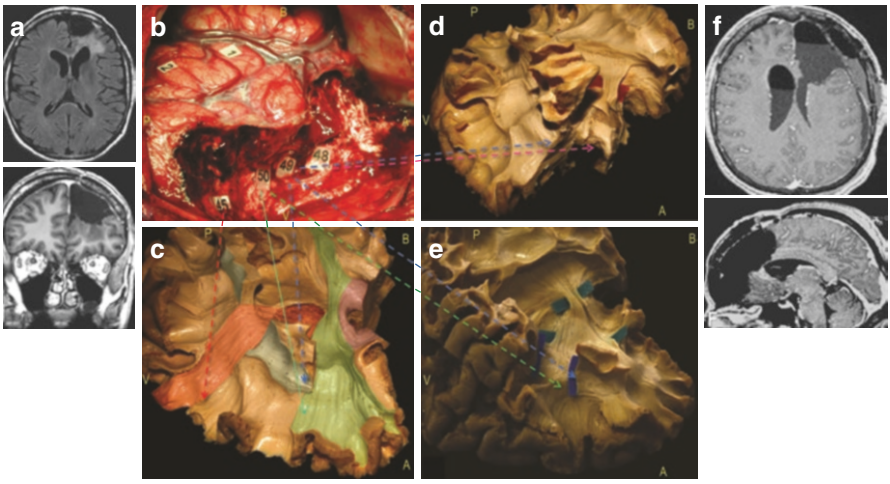


**Fig. 24.2** Illlustrative case of resection according to functional boundaries, concerning a patient who underwent a reoperation for a left dominant frontal DLGG (**a**). The first surgery was performed in another institution under general anaesthesia, achieving a partial resection. A second surgery was performed in our institution under direct brain mapping in awake conditions. The intraoperative picture shows the cortico-subcortical boundaries identified by DES (**b**). Reproducible speech arrests were induced at the level of the ventral premotor cortex (tags 1, 2). No further functional responses were elicited by stimulations of other frontal cortices, including the so-called Broca's area. The resection was extended up to the pars opercularis of the inferior frontal gyrus posteriorly, and to the precentral gyrus medially, with preservation of the supplementary motor area. The fronto-orbital and fronto-polar region was removed, reaching the head of the caudate nucleus in the depth. White matter critical components constituted the deep limits of the resection. Perseverations were induced by DES at the level of tag 48, phonemic paraphasias at the tag 49, semantic paraphasias at the tag 50, language and motor arrest at the tag 45 (**c**–**e**). The anatomical analysis of the subcortical pathways have been provided according to functional results of the DES in awake surgery. Tag 48, corresponding to the head of caudate nucleus (*pink arrow*), represents the deep limit of the lobectomy and is identifiable antero-laterally by means of the tip of frontal horn of the lateral ventricle (**d**); tag 49 refers to the SLF/AF stem running in the depth of the Inferior frontal sulcus (*blue tags*, *blue arrows*) (**c**–**e**); tag 50 represents the frontal fibers of the IFOF (*green tags*), crossing the superior longitudinal fascicle at the level of the pars opercularis and triangularis of the inferior frontal gyrus (*green arrow*) (**e**); tag 45 are the fibers coming from the supplementary motor area, including the fronto-striatal tract (*red arrow*) (**c**). The tumor was radiologically completely removed, as showed by the postoperative MRI (**f**). The patient fully recovered despite some transitory post-operative language disturbances and resumed a normal socio-professional life. (Left hemisphere; A, anterior; P, posterior; B, base; V, vertex). Modified from [121]

phonological processing and repetition, mainly in the left hemisphere) [105, 123]. Importantly, the part II of the SLF is crucial for spatial awareness in the right hemisphere [78]. The optic tracts may also be detected bilaterally, according to the wishes of the patient (who can accept to have visual field deficit—or not) [15, 108]. Of note, for mesio-pariteal DLGG (e.g. within the precuneus), the cingulum may be involved in consciousness [115].

### *24.5.3 Temporal DLGG*

- Superior and deep limit: the IFOF, involved in semantics (verbal semantics in the left hemisphere, non verbal and mentalizing in the right hemisphere) [110, 112, 120].
- Posterior limit: temporal part of the arcuate fascicle (vertical portion) [124]; the optic tracts may also be identified, if the patient does not accept visual field deficit [108].

### *24.5.4 Insular DLGG*

- Superior and posterior limits: dorsal stream (SLF/AF)
- Anterior (in the temporal stem) and inferior limits: IFOF
- Deep limits: somatosensory and motor pathways [125]

  *In all cases, these bundles should constitute the subcortical functional limits of the resection, in particular for large DLGG involving several lobes.*

  In summary, it is mandatory to map both horizontal cortico-cortical connectivity (long-distance association fibers) as well as vertical cortico-subcortical connectivity (projection fibers), with the goal to preserve the networks underlying the "minimal common core" of the brain [22, 23, 26]. Finally, it is worth noting that, for deep lesions, the shorter trajectory is not always the safer. In some cases, it can be more adapted to select a more complex surgical approach in order to avoid cutting functional pathways, on the basis of the results provided by intrasurgical cortical and subcortical mapping [122].

## 24.6 Functional Outcomes

In the past decade, brain mapping has led to an impressive improvement of functional and oncological results in DLGG surgery. Because oncological outcomes have already been detailed in the previous chapter by Duffau, here, the aim is to focus on functional results.

### *24.6.1 Increase of Patients Selection for Surgery in Eloquent Areas*

Firstly, patients who were classically not selected for surgery for a long time, on the basis of pure anatomical criteria (e.g. gliomas involving the precentral gyrus or the pars opercularis of the left inferior frontal gyrus), can now benefit from resection

with no dogmatic a priori against the surgical feasibility due to the tumor location. In particular, it was demonstrated that 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 [1, 126]. For example, surgical resection is possible with no permanent neurological worsening for DLGG located within the Broca's area, Wernicke's area, insula, and the central region (see previous chapters by Duffau) [17–19, 23, 25–29, 60]. In practice, this means that contra-indication for DLGG resection is essentially represented by very diffuse glioma "gliomatosis-like", especially when invading massively the subcortical white matter tracts or both hemispheres through the corpus callosum.

### *24.6.2 DLGG Surgery Preserves and Even Improves Neurological and Cognitive Status*

Secondly, despite an increased number of surgeries in critical regions, the rate of permanent neurological deficits is now significantly lesser than in the classical literature, thanks to awake mapping [1, 80]—i.e. less than 2% in the recent series using intraoperative stimulation. Interestingly, this rate of less than 2% of permanent deficits is very reproducible among the teams using awake mapping worldwide [76, 77, 101]. In comparison, in series which did not use awake mapping, the rate of sequelae ranged from 13 to 27.5%, with a mean around 19% (for a review, see [1]). Interestingly, 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 [80]. In addition, the extent of resection was increased [80]. In other words, despite a frequent transitory neurological worsening in the immediate postoperative period—due to the attempt to perform a maximal tumor removal according to cortico-subcortical functional limits using intraoperative mapping, leading to a specific functional rehabilitation (see chapter by Herbet and Moritz-Gasser)—*more than 98% of patients recovered the same status than before surgery after glioma resection within eloquent brain areas guided by functional mapping, and returned to a normal socio-professional life* [76, 77]. This is also true in very diffuse low-grade gliomas, when surgery was achieved following neadjuvant chemotherapy, that allowed a shrinkage of the peripheral tumoral invasion within the deep connectivity (initially not accessible to resection): global QoL was roughly preserved on the EORTC QLQ C30 + BN 20 (median score: 66.7%) in 10 DLGG patients who benefited from Temozolomide followed by surgery [127].

Of note, these excellent results do not mean that the patients do not experience postoperative subtle cognitive disorders. Indeed, when objective neuropsychological and health related QoL assessment have been performed after surgery, postoperative visuo-spatial, memory, attention, planning, learning, emotional,

motivational and behavioral deficits have regularly been observed (for a review, see [128]). Interestingly, a recent study showed that increased reaction time during naming task performed immediately after resection was significantly correlated to return to work [129]. However, one should remind that numerous neurocognitive deficits already existed before surgery, as demonstrated by baseline assessment (see above). Indeed, by comparing cognitive scores before and at 6 months after surgery in a series of DLGG patients, no worsening was found [112]. In the same way, Satoer et al. evaluated the issue of when is the best time to assess neurocognitive function following surgery [130]. These investigators used the same battery of tests before and at 3 months and 1 year following surgery of 45 patients with gliomas located in eloquent regions and compared the results with normal control subjects. The patients with glioma were found to have deficits in all cognitive areas at both baseline and after resection. However, they identified improvement in 2 areas of verbal fluency at the 1-year assessment, supporting both the need for longer duration follow-up of neurocognitive function in these patients as well as the possibility of latent networks of cognition that may be able to be activated over time [130]. Such postoperative improvement is in agreement with the experience reported by Teixidor et al., who performed a longitudinal cognitive investigation, in particular with regard to verbal working memory (vWM), before and after surgical resection of DLGG involving eloquent areas in eight patients [131]. Preoperatively, 91% of patients had vWM disorders. Immediately after surgery, 96% of patients had vWM worsening. At 3 months, following cognitive rehabilitation, among the eight patients examined, five recovered their preoperative vWM score, and three significantly improved it. Thus, these longitudinal follow-up studies show that DLGG surgery is possible not only without major long-term damage of cognitive functions, but also with an improvement of the preoperative cognitive status [131].

Interestingly, in the series by Satoer et al., extent of resection was no additional risk factor for cognitive outcome [130]. This is in agreement with the study by Jalola et al., who reported that, in long-term survivors with DLGG, an aggressive surgical approach does not lower health-related QoL compared to a more conservative surgical approach [132]. In other words, DLGG with preservation of neural networks does not go against the quality of resection and its impact on the natural history of the disease [133]. Again, this finding supports early and radical safe surgical resection, and pleads against watchful waiting in DLGG.

### *24.6.3 The Positive Impact of Maximal DLGG on Epilepsy*

As mentioned, epilepsy is frequent in DLGG patients, and it significantly impacts QoL: indeed, both epileptic seizure and antiepileptic drugs predispose patients to cognitive impairments [36, 134, 135]. Interestingly, in addition to its impact on survival, complete surgical resection is a predictor of epileptic seizure control, as demonstrated in two monocentric studies of 332 and 508 patients, respectively, and

a systematic literature review with meta-analysis, pooling 773 patients from 20 small-sized studies [134, 136, 137]. More recently, in the largest population of 1509 patients ever studied on DLGG in adults, the French Glioma Consortium reported that control of epileptic seizures and their medically-refractory status worsen during the natural course of DLGG; and that seizure control after oncological treatment is related to the extent of surgical resection: indeed, subtotal ($P = 0.007$) and total ($P < 0.001$) resections were independent predictors of total epilepsy control [138]. In addition, patients diagnosed with epileptic seizures and those with complete and early surgical resections have better oncological outcomes. Maximal surgical resection is thus required for DLGG, both for oncological and epileptological purposes.

In accordance with an emerging hypothesis regarding glioma-related epileptogenicity, no association between epileptic seizure history and histopathological findings, tumour growth speed and molecular correlates was found, suggesting that glioma-related epileptic seizures may not be triggered by specific intrinsic tumour properties [139]. Conversely, these data also demonstrated that tumour anatomical and functional locations were predictive of epileptic seizure incidence—especially tumor involving the insula or the central region [140]—suggesting that glioma-related epileptic seizures may be triggered by interactions between glioma and neocortex. Electrophysiological recordings and histopathological analyses support this hypothesis by demonstrating that epileptic seizures arise from the peritumoral neocortex and not from the tumour core and that infiltrated isolated glioma cells permeate the peritumoral neocortex [139]. Taken together, these findings support the realization of a supratotal resection (i.e., an extended tumor removal beyond the signal abnormalities on MRI) not only to avoid malignant transformation [8, 9] but also to improve seizure control and thus to optimize the QoL. Indeed, in DLGG patients who benefited from supramaximal resection, the rate of postoperative seizures was nil, with arrest of antiepileptic drugs or at least decrease of doses in all cases [9]. One step forward, Ghareeb et al. demonstrated the significant impact of hippocampectomy in patients with intractable epilepsy generated by a paralimbic DLGG, even if the glioma did not seem to invade the hippocampus on the preoperataive MRI [141]. Indeed, hippocampal resection allowed seizure control in all cases, with an improvement in Karnofsky Performance Scale score since all patients resumed their social and professional activities after surgery—while they were not able to work before surgery [141].

## 24.7 Future Directions: the Link Between Neuroplasticity and Repeated Resections

In the past decade, many observations of dramatic recovery following massive resection of brain regions invaded by DLGG have been reported [17, 18]. Such functional compensation was attributed to cerebral plasticity, namely, the continuous process allowing short-term, middle-term and long-term remodelling of

the neuronosynaptic maps, to optimize the functioning of brain networks (see the chapter by Duffau on "Interaction Between DLGG, Brain Connectome and Neuroplasticity") [19, 23]. Non-invasive task-based or resting-state functional neuroimaging allows the additional study of mechanisms of reshaping before and after surgical resection [142, 143]. Interestingly, longitudinal studies based on serial functional imaging after surgery showed new degrees of reshaping, as a probable consequence of both tumor removal and personalized postoperative functional rehabilitation. For example, functional neuroimaging performed following the recovery of a transient postsurgical supplementary motor area syndrome showed the compensatory recruitment of the contralesional supplementary motor area and premotor area [142], with changes in the intrinsic connectivity [143]. A "jump" of the perilesional activations was also reported following DLGG resection, for instance from the precentral sulcus to the central sulcus in tumors involving the premotor region, allowing the resection of the "knob of the hand" with no permanent deficit (Fig. 24.3) [144].

This better knowledge of plasticity phenomena has led to propose reoperation(s) when the resection was not complete at the end of the first surgery, due to the involvement of eloquent areas by the tumor. Thanks to functional reshaping (verified using intrasurgical awake mapping), it was possible to increase the extent of resection during a second and even during a third surgery, while preserving brain functions (Fig. 24.3) [144]. Therefore, this multistage surgical approach made possible DLGG removal in critical regions traditionally considered as unresectable, such as the central area, Broca's area, Wernicke's area, or the insular lobe [17–19, 23, 25–29, 60, 125].

Recently, such strategy has also been proposed in multicentric DLGG, a rare condition defined as widely separated gliomas in different lobes or hemispheres where there is no anatomical continuity between lesions. In a consecutive surgical series of 5 multicentric DLGGs, Terakawa et al. showed that gross-total or subtotal resection was achieved in all cases, using a single surgery in 3 patients and a 2-stage surgery in 2 patients [145]. Indeed, a single-stage resection of multiple lesions within different lobes may be performed if tumors are located in the same hemisphere. There was no mortality or permanent morbidity associated with surgery. The Karnofsky Performance Scale score ranged between 90 and 100 in all cases. Therefore, the authors concluded that multicentric DLGGs can be removed safely without inducing severe permanent neurological deficits and that surgery should be considered as the first therapeutic option for multicentric DLGG, as in solitary DLGG [145].

However, it is crucial to re-insist of the fact that these extensive resections with no or only slight neurological consequences can be achieved only on the condition that the essential subcortical connectivity is preserved. In other word, as mentioned, this is only possible in a connectomal view of brain organization (i.e. in dynamic and parallel distributed large-scale networks able to compensate themselves) and not in a "localizationnist" framework anymore (one area corresponding to one function) [19, 26].

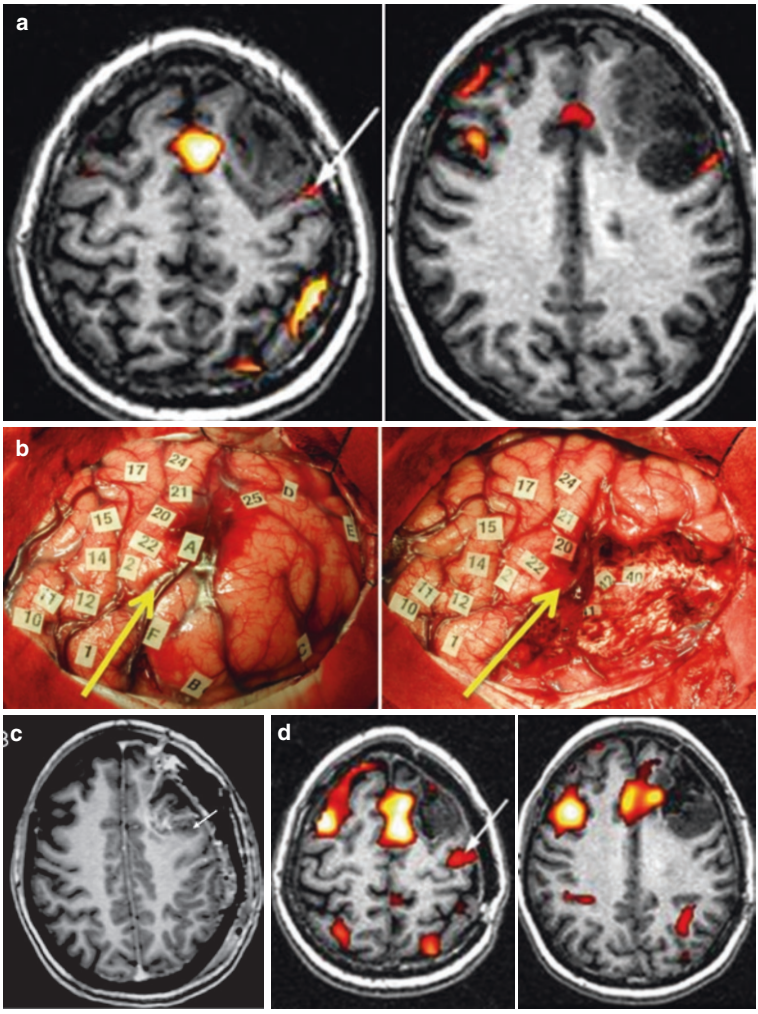


**Fig. 24.3** Illustration of the multiple-stages surgical approach (**a**) Preoperative fMRI in a patient without deficit, haboring a DLGG involving the left premotor area: activation was very close to the posterior part of the tumor, within the precentral sulcus (*arrow*). (**b**) Intraoperative views before (*left*) and after (*right*) resection of the glioma, delineated by letter tags. DES shows a reshaping of the eloquent maps, with a recruitment of perilesional eloquent sites, allowing a subtotal resection with nevertheless a posterior residue due to invasion of crucial areas (number tags). The yellow arrow shows the precentral sulcus, demonstrating that it was not possible to remove the part of the glioma involving the precentral gyrus (**c**) Immediate postoperative enhanced T1-weighted MRI showing the residue (*arrow*), in front of the precentral gyrus (**d**) Postoperative fMRI 4 years after the first fMRI, demonstrating a recruitment of the controlateral hemisphere, and the posterior displacement of activation previously located at the posterior border of the tumour, now within the central sulcus (*arrow*) (**e**) Intraoperative view during the second surgery, confirming the remapping, and allowing a more extensive tumor resection posteriorly, with no permanent deficit. Again, The yellow arrow shows the precentral sulcus, demonstrating that, this time, it was possible to remove a part of the glioma involving the precentral gyrus (**f**) Immediate postoperative axial FLAIR-weighted MRI (3 h after surgery) showing the improvement of the extent of resection within the left precentral gyrus, thanks to functional reshaping (the *red arrow* shows the central sulcus). The follow-up is now 11 years since the first surgery, with no reccurrence since the second operation, in a patient enjoying a normal social and professional life. Modified from [144]

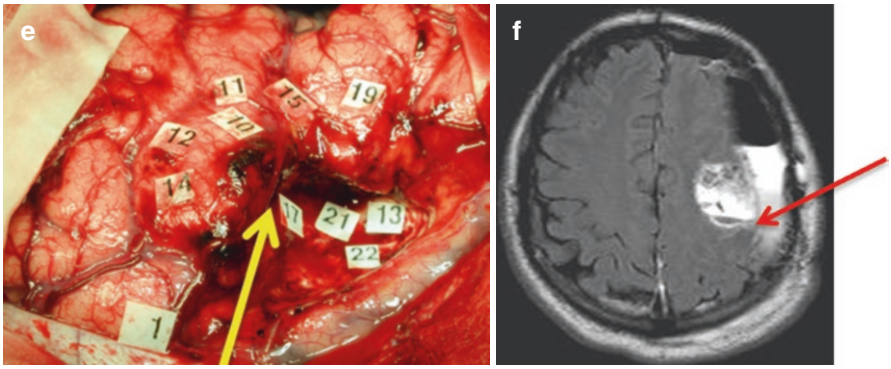


**Fig. 24.3** (continued)

## 24.8 Conclusions and Perspectives

Contrary to traditional belief, impaired neurocognitive function is extremely common in DLGG patients, including in cases of incidental discovery, due to the fact that the large-scale functional connectivity is disturbed by tumor growth and migration along the neural pathways. In addition, control of epilepsy and its medically-refractory status worsen during the glioma progression. Altogether, these recent findings plead against a wait and see policy, mainly advocated because of the theoretical risk of surgery. In fact, the QoL of DLGG patients regularly decreases during the natural course of the disease, resulting in more difficulties to restore QoL when surgery is proposed too late—no restoration of brain functions because the limits of brain plasticity have been reached, low chances to control intractable epilepsy.

In this setting, and thanks to recent technical and conceptual advances in brain surgery, the new standard is to achieve early and maximal (possible repeated) surgical resection(s) for DLGG according to functional (and not oncological) boundaries provided by real-time intraoperative neurocognitive monitoring and individual electrostimulation mapping both at cortical and subcortical levels, in a connectomal and plastic framework of cerebral processing. Such an early and radical functional-mapping guided resection has resulted in a preservation and even an improvement of neurocognitive scores as well as QoL of DLGG patients, in particular thanks to seizures control—directly related to the quality of resection. This means that extensive neuropsychological assessment should be achieved in a systematic way before and after each treatment, in particular to adapt a possible specific rehabilitation in the immediate postoperative period. In addition, such dramatic improvement of functional outcome has also led to better oncological results, with an optimization of the extent of resection, enabling a significant delay of malignant transformation and a significant increase of the overal survival (see previous chapter by Duffau). It is worth noting that functional and oncological issues are linked, since a worse QoL is related to a shorter survival.

*In summary, early maximal surgical resection should be performed in a systematic manner, both for oncological and functional/epileptological purposes in DLGG—knowing that QoL is also a predictor of overall survival.*

Recent stronger interactions between cognitive/behavioral neurosciences (which aim of studying the neural basis of cerebral functions, thanks to a combination between anatomy, functional mapping and cognitive models) and oncological neurosurgery, have participated to overcome the classical dilemma—extent of resection versus brain functions—by giving the possibility to become more ambitious, i.e. to solve the problem of the oncofunctional balance. This is only possible by defining precisely the needs of the patient and his/her family before surgery, in order to tailor the tasks administrated intraoperatively according to the actual QoL balanced with regard to the oncological purpose: for example, to map (or not?) mentalizing in a psychologist with a right temporal DLGG into the contact of the ventral (non-verbal) semantic stream mainly subserved by the inferior fronto-occipital fascicle (see the chapter by Mandonnet and Duffau on "The Oncofunctional Balance"). Of course, the decision should not be taken by the neurosurgeon, but by the patient him(her)self, on the basis of extensive explanations given by the expert team before to go to the operating theater. This means that, in order to counsel optimally the patient, brain surgeons must know the neural foundations underlying brain functions (not only with respect to movement or language, but also concerning higher-order functions as semantic control or theory of mind). In other words, neurosurgeons should be first neuroscientists, to build a "precision neuro-oncological surgery", based upon prevention and treatment strategies that take individual variability into account—not only by talking about proteomics, metabolomics or genomics [146], but first of all, *by taking into account the wishes of the patient, namely, the variability in the philosophy of life.*

The next step to open the door to prevention in DLGG is to propose a screening in the general population, allowing very early detection and surgery in incidentally discovered DLGG (see the last chapter by Mandonnet et al.). To this end, determination of a population at-risk in which MRI could be proposed (of course with the consent of the subject) might benefit from advances in the study of genetic risk factors. Indeed, from an oncological point of view, single nucleotide polymorphisms (SNPs) at 8q24.21 have been associated with increased risk of IDH-mutated gliomas [147]. In addition, with respect to functional aspects, accumulating evidence supports the contention that genetic variation is associated with neurocognitive function in healthy individuals and increased risk for neurocognitive decline in a variety of patient populations, including cancer patients. SNPs in genes in metabolism and cognitive pathways have been reported to affect high-order functions in different conditions such as temporal lobe epilepsy. Even subjects with no known neurologic disease perform more poorly on tests of memory and executive function if they are carriers of an "at-risk" variant alleles [148, 149]. For example, the epsilon 4 allele of APOE is associated with increased vulnerability to cognitive decline in brain tumor patients [150]. Recently, Liu et al. have demonstrated that polymorphisms in inflammation, DNA repair, and

metabolism pathways are associated with neurocognitive performance (memory, processing speed and executive function) in glioma patients before surgical resection [151]. Such original results could have implications for clinical practice, especially by targeting a subpopulation in which early detection of DLGG might be considered before neurocognitive dysfunction, in order to achieve larger and safer surgical resection.

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# Chapter 25
# Chemotherapy for Diffuse Low Grade Gliomas

**Luc Taillandier and Marie Blonski**

**Abstract** Diffuse low-grade gliomas are rare tumors. Therapeutic strategies have dramatically changed in recent years thanks to observational data, insight of some authors, retrospective studies and, incidentally, results of few phase III and II trials. Surgery has become the cornerstone of the treatment. Radiotherapy, because of its potential delayed neurotoxicity and the equivalent results in terms of survival whatever the timing of the treatment (early or late), is increasingly offered to patients with unresectable tumors (or tumor that can not be re-operated) and in case of progression after chemotherapy. Chemotherapy, subject of this chapter, has shown a clinical benefit regarding tumor progression for non-surgical patients, before or after radiotherapy: initial chemosensitivity almost constant, improvement of epilepsy and thus of cognition, preservation of quality of life (despite a possible transient alteration). Its articulation with surgery has been more recently discussed by allowing, thanks to tumor shrinkage, subtotal or total resection (whose impact on anaplastic transformation and survival has been demonstrated), in addition to potential effects on cerebral plasticity. It remains to show the direct impact on survival, to refine its risk-benefit ratio especially in the context of prolonged treatment with temozolomide or PCV and to develop further research from a neurological (impact on plasticity) and oncological (involved molecular pathways, identifying new therapeutic targets) points of view.

**Keyword** Diffuse low-grade gliomas • WHO grade II gliomas • Chemotherapy • Epilepsy • Quality of life • Survival

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## 25.1 Introduction

Diffuse low-grade glioma (DLGG) is a rare disease whose therapeutic concepts have profoundly been challenged these recent years [1].

Thus surgery, marginally considered until the 1990s, saw his place reinforced thanks to the development of neuroscience researches through the cortical and subcortical stimulations, awake surgery and functional imaging progress [2, 3].

Potential neurotoxicity of long-term conventional radiotherapy was stressed. This treatment is little used in the initial stages of the disease. Nevertheless, the timing of radiotherapy was again discussed after the publication of RTOG 9802 trial results [4] and concomitant issues concerning clinical trials focused on anaplastic oligodendrogliomas EORTC 26951 [5] and RTOG 9402 [6], while these studies have not exhaustively explored the long-term impact on neurocognition [7]. Recent technical advances allow considering a more focused therapeutic volume. It should so lead to new assessments with a clear evaluation of the ratio between expected benefits/potential risks according to different main locations [8].

Finally, chemotherapy, despite many theoretical limitations (intrinsic chemoresistance, difficulties to access tumoral site, low number of available molecules) gradually developed, first in case of progression after conventional treatments delivrance and then more precociously in the disease history and in close coordination with surgery. Over the past 5 years, this therapeutic modality has confirmed its role and benefit in DLGGs and has demonstrated its impact on survival. Despite its toxicity, a renewed interest of procarbazine + cecenu + vincristine association (the so-called PCV protocol) was mentioned.

These points will be developed below by considering the conceptual and historical bases, while highlighting the unresolved issues.

## 25.2 Current Practices

### *25.2.1 Conceptual Bases of Chemotherapy*

The place of the chemotherapy for DLGGs remains difficult to encircle. Many theoretical arguments can be opposed to the principle of prescription: subnormal blood brain or blood tumor barrier (low penetration of drugs), spontaneous chemoresistance of gliomas, very limited number of potentially active molecules.

Nevertheless, there are situations like tumor progression in case of patients with unresectable tumor previously treated by radiotherapy (RT) where chemotherapy (CT), in absence of therapeutic alternative, could be discussed or considered before anaplastic transformation.

The literature on the subject remains relatively poor.

For a long time, only the paper by Eyre et al. from the South Western Oncology Group (SWOG) served as a reference and discouraged all therapeutic inclinations. In fact, the SWOG conducted the first randomized trial concerning CT for DLGGs. It has compared RT alone versus RT plus lomustine based CT after subtotally/partial surgery or biopsy. No benefit was shown and the trial was prematurely terminated [9]. To date, it is difficult to consider this relatively old trial because of the associated methodological bias regarding the selected population (more specifically from a pathological and radiological point of view).

Cairncross and Macdonald have, the first, evoked the possibility of a real objective response for diffuse low-grade tumors within a series of aggressive oligodendrogliomas [10, 11]. Six years later, Mason was able to note 9/9 responders under Procarbazine + Cecenu + Vincristine association (PCV) [12] while Soffietti [13] reported 13/13 stabilised or respondered patients also under PCV.

Since then, few dozen articles have been published. There are mostly retrospective series that included most often a small number of patients (see below).

We will come back to some of these articles in the following chapters.

### *25.2.2 Available Data and Chronology*

The Table 25.1 adapted from Ducray [49] summarizes the literature on the subject. As we can appreciate, series are very heterogeneous in term of disease entities, time of illness, treatment modalities and evaluation of responses.

We can nevertheless confirm that, in recent years, regardless the growing role of surgery, we have seen a real interest in chemotherapy in the management of these tumors [51] (especially temozolomide and a new interest for PCV since published data concerning anaplastic oligodendrogliomas [5, 6] and RTOG 9802 trial [4] that compared 54Gy of radiotherapy (RT) with the same RT followed by adjuvant procarbazine, CCNU, and vincristine (PCV) chemotherapy in high-risk low-grade glioma).

This led to the creation of a dedicated European Task Force and to the establishment of recommendations recently published (and being updated). These recommendations clearly propose chemotherapy in specific situations to which we will return in the course of this article: “Chemotherapy can be useful both at recurrence after radiotherapy and as initial treatment after surgery to delay the risk of late neurotoxicity from large-field radiotherapy” [52].

We should nonetheless note that all except some published series have fewer than 50 patients. This low number of inclusions reflects the relative scarcity of the pathology but also the difficulties to include such patients in therapeutic trials probably because of the specificity of this particular tumoral entity (too heterogeneous for normative constraints of clinical trials) and the conceptual differences between major involved groups.

**Table 25.1** Review of literature on chemotherapy for DLGG

| Year | Authors and journal | N | Tumor type | Contrast enhancement (%) | Prior RT (%) | Prior CT (%) | Chemotherapy regimen | Response rate CR + PR/MR (%) | One year PFS (%) | Median PFS (month) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1996 | Mason et al. Neurology [12] | 9 | O | 33 | 11 | No | PCV | 66/NA | NA | 35 |
| 1998 | Soffietti et al. Neurosurgery [13] | 26 | 17O, 9OA | 73 | 42 | No | PCV | 62/NA | 80 | 24 |
| 1998 | Van den Bent et al. Neurology [14] | 52 | 43O, 9OA | 100 | 100 | No | PCV | 63/NA | NA | 10 |
| 2000 | Olson et al. Neurology [15] | 12 | O, OA | NA | NA | NA | PCV BCNU Cisplatine | NA | NA | NA |
| 2003 | Brada et al. Ann Oncol [16] | 30 | 11O, 2OA, 17A | O | No | No | Temozolomide | 10/48 | >90 | >36 |
| 2003 | Buckner et al. J Clin Oncol [17] | 28 | 17O, 11OA | 46 | No | No | PCV | 52/NA | 91 | NA |
| 2003 | Pace et al. Ann Oncol [18] | 40 | 4O, 10OA, 29A | 60 | 65 | 37 | Temozolomide | 47/NA | 39 | 10 |
| 2003 | Quinn et al. J Clin Oncol [19] | 46 | 20O, 5OA, 16A, 5PA | 70 | 15 | 22 | Temozolomide | 61/NA | 76 | 22 |
| 2003 | Van den Bent et al. Ann Oncol [20] | 32 | 17O, 11OA | 100 | 100 | 100 | Temozolomide | 22/NA | 11 | 3.7 |
| 2003 | Van den Bent J Clin Oncol [5] | 39 | 24O, 15OA | 100 | 100 | No | Temozolomide | 53/NA | 40 | 10.4 |
| 2004 | Higuchi et al. Neurology [21] | 12 | O | 50 | No | No | PAV | 58/NA | 100 | >60 |
| 2004 | Hoang Xuan et al. J Clin Oncol [22] | 60 | 49O, 11A | 11 | No | No | Temozolomide | 17/14 | 73 | NA |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2005 | Stege et al. Cancer [23] | 21 | 7O, 14OA | 21 | 24 | No | PCV | 19/57 | ND | >24 |
| 2006 | Catenoix et al. Rev. Neurol [24] | 7 | O, OA | 0 | No | No | PCV | 42/28 | 100 | >60 |
| 2006 | Duffau et al. J Neurooncol [25] | 1 | O | 0 | No | No | Temozolomide | 1/1 | 100 | NA |
| 2006 | Levin et al. Cancer [26] | 28 | O | NA | No | 28 | Temozolomide | 36/25 | 89 | 31 |
| 2006 | Ty et al. Neurology [27] | 7 | O | NA | 28 | No | PCV | 71/NA | 100 | >30 |
| 2007 | Lebrun et al. Eur J Neurol [28] | 33 | O | 22 | No | No | PCV | 27/NA | 90 | >30 |
| 2007 | Sunyach et al. J Neurooncol [29] | 24 | O | NA | No | No | PCV Temozolomide | NA | NA | 47 |
| 2007 | Kaloshi et al. Neurology [30] | 149 | 105O, 44OA+ A | 15 | No | No | Temozolomide | 15/38 | 79.5 | 28 |
| 2007 | Pouratian et al. J Neurooncol [31] | 25 | 15O, 6OA, 1A | 24 | No | 8 | Temozolomide 75 mg/m$^2$ – ¾ weeks | 24/28 | 72 | > 20 |
| 2007 | Ricard et al. Ann Neurol [32] | 107 | 82O, 20OA, 5A | | No | No | Temozolomide | 92% with initial decrease of MTD | NA | NA |
| 2008 | Tosoni et al. J Neurooncol [33] | 30 | 18O, 3OA, 9A | 0 | No | No | Temozolomide P 75 mg/m$^2$ – ¾ weeks | 30/NA | 73 | 22 |
| 2009 | Kesari et al. Clin Cancer Res [34] | 44 | 26O, 12OA, 6A | NA | 27 | No | Temozolomide P 75 mg/m$^2$ 7/11 weeks | 20/NA | 91 | 38 |
| 2009 | Kaloshi et al. Neurology [30] | 62 | 56O, 21OA, 23A | 0 | No | No | Temozolomide | – | – | – |
| 2009 | Taillandier et al. Neurosurg Focus [35] | 46 | O, OA, A | 0 | No | 1 | Temozolomide PCV | NA | NA | NA |

(continued)

**Table 25.1** (continued)

| Year | Authors and journal | N | Tumor type | Contrast enhancement (%) | Prior RT (%) | Prior CT (%) | Chemotherapy regimen | Response rate CR + PR/MR (%) | One year PFS (%) | Median PFS (month) |
|---|---|---|---|---|---|---|---|---|---|---|
| 2010 | Peyre et al. Neurooncol [36] | 21 | 15O, 4OA, 2A | 14 | No | No | PCV | 38/42 | 100 | 40 |
| 2010 | Kaloshi et al. J Neurooncol [37] | 20 | 21O, 4OA, 5A | 56 | No | 100 | Nitrosourea second line | 0/10 | 28 | 6.5 |
| 2010 | Houillier et al. Neurology [38] | 84 | 55O, 18OA, 11A | 0 | No | No | Temozolomide | – | – | – |
| 2011 | Blonski et al. J Neurooncol [39] | 10 | 6O, 2A, 2OA | 0 | No | No | Temozolomide | 10/10 | – | – |
| 2011 | Taal et al. Neurooncol [40] | 58 | A | 100 | 100 | No | Temozolomide | 54/NA | 25 | 8 |
| 2011 | Iwadate et al. J Neurooncol [41] | 26 | O, OA | NA | No | No | PAV | NA | NA | 93 |
| 2012 | Ribba et al. Clin Cancer Res [42] | 45 | 35O, 7OA, 3A | NA | No | No | PCV (n = 21) + Temozolomide (n = 24) | NA | NA | NA |
| 2013 | Blonski et al. J Neurooncol [43] | 17 | 13O, 2OA, 2A | 41 | No | No | Temozolomide | NA | NA | NA |
| 2014 | Kaloshi et al. J Neurooncol [44] | 38 | 18O, 8OA, 12A | NA | No | No | CCNU | 45/23 | 81 | 27.8 |
| 2014 | Jo et al. J Neurooncol [45] | 20 | 13O, 5OA, 2A | NA | No | No | Temozolomide | 5/40 | NA | NA |
| 2015 | Taal et al. J Neurooncol [46] | 38 | O, OA | NA | No | No | PCV | 47/13 | NA | 46 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2015 | Mazzocco et al. CPT Pharmacometrics Syst Pharmacol [47] | 77 | 56O, 16OA 5A | NA | No | No | Temozolomide | 100% with initial decrease of MTD | NA | 14.5 |
| 2016 | Koekkoek et al. J Neurooncol [48] | 53 | 14O, 7OA, 32A | NA | 71,7 | No | Temozolomide | 22% objective response at 6 months after temozolomide initiation 62% at 12 months 64% at 18 months | NA | 20 |
| 2016 | Baumert et al. Lancet Oncol [50] | 237 | 98O, 60OA, 79A | 50 | No | No | Temozolomide 75mg/m² 3/4 weeks | NA | NA | 40 (55 for IDHmt/ codel; 36 IDHmt/ non-codel; 23 IDHwt) |

Adapted from Ducray [49] and Baumert et al. [50]

*N* number of patients, *O* oligodendroglioma, *OA* oligoastrocytoma, *A* astrocytoma, *PA* pilocytic astrocytoma, *RT* radiotherapy, *CT* chemotherapy, *CR* complete response, *PR* partial response, *MR* minor response, *Temozolomide* 200 mg/m$^2$–5/28 days, *PCV* procarbazine + cecenu + vincristine, *PAV* procarbazine + acnu + vincristine, *NA* Not available, *IDHmt* IDH mutation, *Codel* 1p19q codeletion, *IDHwt* no IDH mutation

### *25.2.3 Types of Chemotherapy*

Two main modalities of chemotherapy were nowadays used for DLGGs: Procarbazine + Cecenu + Vincristine (PCV) association and temozolomide (TMZ), according to different patterns.

There are little variations in the reported dosages concerning the PCV combination used first by Gutin in 1975 [53] and Levin in 1980 and 1985 [54]. Classically, Cecenu is administered on day (D) 1 (110 mg/m$^2$), Procarbazine (60 mg/m$^2$) from D8 to D21 and Vincristine (1.4 mg/m$^2$–max 2 mg) at D8 and D29. A cycle is administered every 6 to 8 weeks. Intensified protocols have also been described but not used in DLGGs [55].

Temozolomide (TMZ) is, to date, the most widely used treatment. The conventional scheme proposes a daily dose of 150 mg/m$^2$ for 5 days during the first course. If it is well tolerated, the dose is increased to 200 mg/m$^2$/day for 5 days from the second course. Cycles last 28 days. Other plans, including intensified protocols, have been proposed. Lashkari et al. attempted to assess the impact of these different TMZ regimens on the treatment of DLGGs. They performed a systematic review of the literature and identified all the studies published in Pubmed, Embase and Cochrane databases that met the inclusion criteria. 18 studies and 736 patients were analyzed. Although there is possibly an indication that metronomic regimens of TMZ result in better "Progression Free Survival" (PFS) and response rate when compared with the conventional standard 5 day regimen, insufficient available data and study heterogeneity preclude any safe conclusions. Authors offer as conclusion that "well-designed randomized controlled clinical trials are needed to establish the efficacy of metronomic regimens of TMZ in DLGGs" [56].

To date, we can consider, mainly because of the good immediate tolerance and the respect for the quality of life (cf. infra), that temozolomide used with conventional doses remains the reference treatment.

PCV and temozolomide present a distinct profile of responses and toxicities (see below). Indeed, PCV is associated with a longer time to maximum tumor volume reduction, a longer duration of response and greater toxicity [36] whereas temozolomide is characterized by a shorter time to maximum tumor volume reduction, a shorter duration of response and lower toxicity [32] (see Sect. 25.4.7). To date, no randomized trial has compared the two drug protocols in DLGGs. A recent publication further refers to the interest (similar to PCV or temozolomide) of an old nitrosourea (cecenu) used in monotherapy [44].

## 25.3 Results

### *25.3.1 Chemotherapy, Volumes and Growth Rate*

The response assessment after chemotherapy for DLGGs remains a difficult and non-consensual issue.

For many years, MacDonald criteria, created to evaluate WHO grade III and IV gliomas [57] and based on two dimensional enhanced tumor measurements on computed tomography or magnetic resonance imaging (in conjunction with clinical and steroid dosage evaluations) were used for DLGGs after adaptation (especially by considering the two largest diameters on T2-weighted or FLAIR slides and not on injected images and by abandoning the reference to steroids). This procedure does not allow to objectively monitor the evolution of a tumor under treatment and clearly underestimates the number of responders. This was the case for many initially reported studies [16–18].

New recommendations were proposed [58]. These latter do not appear optimal by considering that "published studies that have compared calculations based on single, multidimensional and true volumetric measurements and the strength of their correlations with the outcome (PFS, OS) are absent and thus that evidence-based data for the preferred measurement system are not available". We disagree with this opinion (see the dedicated chapter), because we consider that the volumetric evaluation is absolutely necessary for monitoring DLGG patients receiving chemotherapy. Otherwise, the risk is to dramatically underestimate responses and thus to be in an absolute inability to properly monitor the treatment duration.

The papers by Hoang-Xuan et al. [22] and Ricard et al. [32] were the first most important considering the impact of chemotherapy on DLGGs. In the second one's, authors were, indeed, among the first to report a longitudinal real volumetric assessment in a population of 107 patients treated exclusively with temozolomide. The method of the three diameters technique (ellipsoidal approximation) was used to obtain volumes and mean tumoral diameters (MTD) [59]. During the treatment, they found that more than 60% of patients achieved a minor or partial response. At the onset of TMZ treatment, the MTD decreased in 92% of patients, demonstrating an early initial chemosensitivity: 38 of 39 patients who had a pre-, per- and post-evaluation of the MTD slope experienced a breakdown of the MTD growth curves after chemotherapy onset. After the initial phase of MTD decrease and despite continuous administration of TMZ, the tumors of some patients started to resume growth again whereas others continued to decrease. Tumor regrowth occurred in 16.6% of 1p-19q codeleted tumors and in 60.6% in non-codeleted tumors ($p < 0.0004$). Tumors over-expressing p53 had also a much greater rate of relapse (70.5% versus 25%). The evolution of the MTD was also tested after discontinuation of TMZ. The greater part of the population remains stable or sometimes continues to decrease despite the interruption of treatment. Nevertheless, a majority of tumors starts to grow again: 59% rate of MTD regrowth after a median follow-up of 200 days after TMZ discontinuation (range, 60–630 days).

Our group has also published a retrospective study concerning chemotherapy followed by surgical resection for DLGGs. The impact of chemotherapy on the tumor volume was estimated using Volume Viewer® software (General Electrics GE Healthcare, Milwaukee, WI, USA). For exams in which only printed images were accessible, a three diameters technique was used. We also demonstrated that chemotherapy induced a tumor shrinkage (median volume decrease of 35.6%) in 17/17 cases (ipsilateral in ten patients and in the contralateral hemisphere in seven patients) [43].

Peyre et al. [36] reported kinetics data concerning 21 patients treated with PCV protocol. During PCV treatment, all the patients presented a decrease of the mean tumoral diameter (MTD). During chemotherapy, the median MTD decrease was −10.2 mm/year (range, −23 to −1 mm/year). 20 of the 21 patients presented a persistent decrease after PCV discontinuation. The median duration of the MTD decrease was 3.4 years (range 0.8–7.7 years) after PCV onset and 2.7 years (range 0–7 years) after the end of PCV. At the time of maximal MTD decrease, the rates of partial and minor responses were 38% and 42%, respectively, according to adapted McDonald's criteria. PCV treatment is associated with a prolonged response even in patients with no 1p19q codeletion. Taal et al. confirmed these results in a retrospective series of 32 patients [46].

In the study of Kaloshi et al., they reported 38 patients treated with CCNU alone [44]. CCNU was delivered at the dose of 130 mg/m$^2$ every 6 weeks. The median time to obtain a radiographic response was 6 months and the maximum response was reached after a median of 12 months. 17 (45%) patients achieved a partial response, 9 (23%) patients a minor response, 8 (21%) were stable and 4 (11%) progressed. The maximal objective response rate was also 68%. Then, Kaloshi et al. analyzed growth kinetics in these 38 patients before, during and after CCNU treatment. During CCNU treatment, the median MTD decrease was −5.1 mm/year (range −8.9 to −1 mm/year) (after excluding patients with progression) [60]. The median duration of response was 1.7 years. Response was significantly longer in oligodendroglial tumors than in astrocytic tumors (median 2.8 years versus about 1 year, respectively, $p = 0.003$). The profile of CCNU response seems similar to PCV treatment. Otherwise, we have only limited data [37] on response rates after the restart of chemotherapy (low-grade stage) after a break of several months or years. It is thus difficult to provide guidance on this topic.

### *25.3.2 Chemotherapy and Epilepsy*

Seizures are the most common initial symptom in patients with DLGG. Their occurrence strongly depends on the tumor location including insular and central topography [61, 62]. Some authors have also suggested a link between IDH 1/2 mutation (frequent in DLGGs) and the onset of metabolic changes capable of promoting seizures [63].

For a long time, chemotherapy and irradiation were considered having just some minor beneficial effects on the patients' seizure disorder using the argument that overall 60–70% of patients may experience recurrent epilepsy during long-term follow-up [64].

The progressive development of this therapeutic modality, its conceptual changes (prolongation of treatment time) and more precise analysis of the impact of such therapy on seizures have radically changed the view of many authors. Thus, it is now considered (despite the usual difficulties with seizure quantification in retrospective studies) that (1) the negative course of seizure frequency was mostly correlated to tumor progression (2) surgery had almost always a favorable effect on

epilepsy (3) chemotherapy (such as radiation therapy) had a mostly favorable effect with acceptable tolerance [2, 65–67].

Seizure improvement is usually associated with radiological response. Nevertheless, some patients with a "stable disease" according to RANO criteria (defined by a FLAIR decrease inferior to 25%) reported significant seizure reduction [68]. Although it may be due to an underestimation of the response with this method, seizure reduction seems well to precede the radiological response given that a ≥ 50% seizure reduction at 6 months of TMZ initiation is associated with the occurrence of an objective MRI response (according to RANO criteria) at 12 months and 18 months. Likewise, seizure improvement seems to be independent prognostic factor for "PFS" and OS after 6, 12 and 18 months of TMZ onset [48, 69].

The improvement in seizure frequency during treatment with temozolomide seems, moreover, independent of antiepileptic drug adjustment [70].

An extensive experience with insular DLGGs (topography considered as the most epileptogenic) was also reported by our group. We confirmed the interest of a surgical removal and supported the role of chemotherapy from an epileptological point of view [35].

We need to address in this chapter, regarding the relationship between chemotherapy and DLGGs, the special place of antiepileptic treatments. Recommendations in this area are identical to the recommendations for all brain tumors. Most authors recommend first-line non-inducing drugs such as lamotrigine, levetiracetam or lacosamide [71, 72]. These new antiepileptic drugs seem better tolerated even if they are no more effective [67] The place of valproate remains debated. A clear efficiency is reported [72]. Combined antiproliferative activity through its inhibitory properties of histone deacetylase could improve survival as it was evoked for glioblastomas [73]. Nevertheless there are potential side effects (weight gain, thrombocytopenia, tremor, fetotoxicity) and enzyme inhibition may increase the hematologic toxicity of chemotherapy.

Finally, it seems possible to use amino acid Positon Emission Tomography to predict the impact of chemotherapy on epilepsy. The reduction of seizure frequency seems so well correlated with the reduction of metabolically active tumor volumes [74].

### *25.3.3 Chemotherapy and Cognition*

Cognitive functioning is correlated with quality of life, itself linked with return to work or to normal social life [75]. This point is absolutely crucial in general neuro-oncology and, still more, in the management of patients with DLGG. Approximately one quarter of patients with DLGG reported serious neurocognitive symptoms [76]. Neurocognitive deficits are far more frequent than previously thought and can be caused by the tumor itself, tumor-related epilepsy, treatments and psychological distress [52]. For some authors, the role of radiotherapy and chemotherapy in the treatment of DLGG remains controversial regarding their effect on survival and the development of neurotoxicity. 40 DLGG patients participated in the study of Correa et al. 16 patients had RT ± chemotherapy and 24 patients had no treatment. In this

series, RT ± chemotherapy, disease duration, and antiepileptic treatment contributed to mild cognitive difficulties. It is, however not possible in this work to isolate the precise role of chemotherapy alone in the toxicity [77]. The same team published a new paper with 25 DLGG patients who underwent neuropsychological evaluations at study entry, 6 and 12 months subsequently. Nine patients had RT ± chemotherapy prior to enrollment and 16 had no treatment [78]. Longitudinal follow-up showed that both disease duration and treatment with RT ± chemotherapy contributed to a mild decrement in non-verbal recall and in some aspects of executive functions and quality of life. In these two articles, the widespread use of combined strategies (radiotherapy + chemotherapy) makes difficult to analyze the specific contribution of chemotherapy in the cognition modulation. Our group [39] reported a retrospective work with a neuropsychological assessment (NPA) of ten patients who underwent a strategy with a first chemotherapy followed by functional surgery. Nine patients were right-handed and one left-handed. No one presented with premorbid intelligence deterioration. Three patients did not show any neuropsychological deficit. Seven patients failed at three or less out of the eighteen cognitive tests that were applied. The three others failed at least four tests. The main cognitive domains where deficits were observed concern episodic memory, especially verbal modality (five patients), and executive functions (five patients). Interestingly, the patients who did not continue to work were not the same who presented the most severe cognitive impairment. Our conclusion was that this combined strategy is highly likely to preserve cognitive function.

A recent observational study RTOG 0925 evaluated the "Natural History of Brain Function, Quality of Life, and Seizure Control in Patients in Supratentorial Low-Risk Grade II Glioma". The primary endpoint concerns neurocognitive functions assessed by four neurocognitive tests (which do not represent a robust and subtile neurocognitive assessment): Detection DET (psychomotor function), Identification IDN (visual attention), One Card Learning test OCTL (visuoperceptual learning and memory), Groton Maze Learning test GML (spatial learning and executive functions). Quality of life was measured by the EORTC QOL-30, EORTC QOL-BN20, EQ-5D questionnaires. Finally, seizure was analyzed using patient seizure diary. Results have not yet been published.

Donepezil could improve several cognitive functions (especially among patients with greater pretreatment impairments) in brain tumor survivors presented neurotoxic effects of radiotherapy [79]. Comprehensive neurocognitive rehabilitation has also demonstrated its benefit in DLGG patients [80]. The future researches have to develop systemic agents that allow to delay radiotherapy, to identify patients at major risk of neurotoxicity, to evaluate potential radioprotective agents [81].

### *25.3.4 Chemotherapy and Quality of Life*

As already mentioned, quality of life is correlated with cognitive functioning with, itself linked with return to work or to a normal social life [75]. Works on these three fundamental aspects of DLGG patient's evaluation are very rare. We know, generally, that female sex, epilepsy burden, and number of objectively assessed neurocognitive

deficits were associated significantly with both generic and condition-specific HRQOL [76]. The major impact of PCV on HRQOL is on nausea/vomiting, loss of appetite, and drowsiness during and shortly after treatment. There are few but severe no long-term effects of PCV chemotherapy. Majority of patients recover a "normal" state when they move away from the treatment period [82]. Some of them develop myelodysplasia or permanent sterility.

Liu et al. described the quality of life (QOL) of DLGG patients at baseline prior to chemotherapy and through 12 cycles of temozolomide. The Functional Assessment of Cancer Therapy-Brain (FACT-Br) was obtained at baseline (prior to chemotherapy) and at 2-month intervals under chemotherapy. Patients at baseline had higher reported social well-being scores (mean difference = 5.0; $p < 0.01$) but had lower reported emotional well-being scores (mean difference = 2.2; $p < 0.01$) compared with a normal population. Patients with right hemisphere tumors reported higher physical well-being scores ($p = 0.01$): 44% could not drive, 26% did not feel independent, and 26% were afraid of having a seizure. Difficulty with work was noted in 24%. Mean change scores at each chemotherapy cycle compared with baseline for all QOL subscales showed either no significant change or were significantly positive ($p < 0.01$). Authors concluded that DLGG patients on therapy were able to maintain their QOL in all realms. Patients' QOL may be further improved by addressing their emotional well-being and their loss of independence in terms of driving or working [83].

In our work concerning patients treated with presurgical chemotherapy [39], the Karnofsky Performance Scale (KPS) scores ranged from 80 to 100 (median 90) and were globally stable during the whole follow-up period. The main domain that presented with significant impairment in the QOL assessment was role functioning (feeling of independence and socio-professional life) with a median score of 66.7% (range 50–100). The global QOL score was preserved after chemotherapy and surgery for most patients with a median value of 66.7% (range 33.3 to 83.3%). Cognitive, emotional, physical and social well-being scores were also relatively preserved (median scores 83.3, 79.2, 100 and 100%, respectively). Among the general symptoms, the main complains were fatigue (median score 33.3% range 11.1–100%) and pain (median score = 16.6%, range 0–66.7%) due to different associated diseases like osteoarthritis and arteriopathy. Sleeping troubles (mean score = 20 ± 30.6%), financial impact (mean score = 23.3 ± 39.6%) and digestive troubles (mean score = 20 ± 30.6%) seemed to have a moderate influence on the QOL. No patient reached the cut-off of 15 in the inventory for signs or symptoms of depression (BDI) with a mean score of 8.7 ± 3.6. However, seven subjects showed a tendency for "mild depression", characterized by a score between 8 and 14.

We can therefore consider that TMZ alone or combined with surgery is able to maintain or even to improve the quality of life [84] and that PCV alters transiently the QOL, with a return to the "normal" situation when we move away from the treatment period.

We have to note that, nonetheless, more than one third of long DLGG survivors present an impaired quality of life (one or more Health Related Quality of Life scales) despite long-term post-therapeutic (including chemotherapy) stable disease [85]. It should make us particularly attentive about potentially incriminating thera-

peutic factors. It would also be interesting, in the future, to focus more specifically on the impact of chemotherapy on other quality of life parameters marginally explored like sexuality [86]. However, it could be difficult to specifically address the impact of each therapy given a multistage and individualized therapeutic approach in the current management of DLGG patients. Most studies have investigated the role of only one specific treatment without a global view of managing the cumulative time while preserving quality of life versus time to anaplastic transformation [84, 87]. Quality of life represents an individual and personal concept, which has to be taking into account and anticipate at each time of the management [88].

### *25.3.5 Chemotherapy and Survival*

To date, there is no direct evidence for DLGG patients that confirms the impact of chemotherapy on patients' survival. Only RTOG 9802 (randomized trial with RT alone or RT followed by six cycles of PCV for supratentorial adult DLGGs) and RTOG 0424 (phase II study of temozolomide-based chemoradiation therapy for high-risk DLGGs) trials demonstrated a benefit of chemotherapy on survival in "high-risk" DLGGs [4]. For RTOG 9802, median OS increased from 7.8 years to 13.3 years, with a hazard ratio of death of 0.59 (log rank: $p = 0.002$) [89]. For RTOG 0424, the 3-year OS rate was 73.1% (95% confidence interval: 65.3%–80.8%), which was significantly improved, compared to that of prespecified historical control values ($p < 0.001$) [90] (see Sect. 25.4.6.1). We know, however, that presumed eloquent location of DLGGs is an important but modifiable risk factor predicting disease progression and death [91] and that the risk of malignant transformation and subsequent survival may be predicted by pretreatment but also by treatment-related factors [92].

We are thus entitled to imagine that indirectly, this treatment modality may have an impact on patient survival.

In a retrospective selected series, seventeen patients considered at diagnosis or recurrence as "non operable" because of a functional areas infiltration or a too large contralateral extension, underwent temozolomide-based chemotherapy inducing tumor volume decrease immediately followed by a radical surgery. The median follow-up since initial radiological diagnosis was 5.9 years (range 1.4–11). The median time to malignant transformation was 99.6 months. We demonstrated that age, volume at diagnosis, 1p19q, IDH and MGMT promoter status had no impact on time to malignant transformation. Chemotherapy reduced tumor volume (median − 35.6%, range −61.6% to −5.1%) and significantly decreased the imaging tumor growth whatever 1p19q, IDH and MGMT status. We confirmed that a tumor volume decrease of more than 20% was significantly correlated with a lower postoperative residual tumor (median = 2 cc, $p = 0.04$), a greater extent of resection (whithout reaching statistical significance) and a better prognosis ($p = 0.04$). We thus concluded that, regardless of the molecular status, neoadjuvant chemotherapy could optimize surgical resection of DLGGs and could have an impact on their natural history and particular on the survival [43].

## *25.3.6 Tolerance*

### 25.3.6.1 Hematological Toxicity

The "PCV" association possesses a cumulative acute hematologic toxicity making difficult the administration of more than six courses. Previous papers provide evidence that nitrosoureas are leukemogenic in human beings and confirm observations that adjuvant chemotherapy with alkylating agents may increase the risk of leukemia [93]. In the paper of Boice et al. concerning adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU), the six-year cumulative mean risk of acquiring a leukemic disorder after treatment with semustine was 4.0 ± 2.2 per cent for an incidence rate of 2.3 cases per 1000 persons per year [94]. In a meta-analysis of five randomized clinical trials for adult patients with brain tumors, Greene et al. identified two of 1628 individuals who experienced acute nonlymphocytic leukemia after carmustine chemotherapy [95]. The risk of developing this complication was 24.6 times higher than expected [93]. Baehring et al. identified well-documented case reports and small case series of patients who developed therapy-induced myelodysplasia (t-MDS) and therapy-induced acute myeloid leukemia (t-AML) during or after treatment with alkylating chemotherapy for a primary brain neoplasm. Moreover, they performed a comprehensive review of the literature on the subject and noted that the overall incidence of primary MDS was estimated at 3–20 cases per 100,000 population with 10–15% of all MDS cases arising in patients exposed to chemo- or radiation therapy administered for other tumors [96]. It seems that t-MDS/t-AML risk among patients with brain tumors is maybe lower than in patients with other primary neoplasms [97]. Nevertheless, this observation may be linked to the often-reserved prognosis of the central nervous system tumors, not allowing the late haematological complications emergence. Perry et al. reported two cases of AML following therapy for malignant glioma and found 26 other examples of therapy related leukemia in adult and pediatric brain tumor patients (including 12 patients with malignant glioma). The median interval from treatment to diagnosis of AML was 31 months. Nine adult malignant glioma patients received all nitrosoureas and some of them as the sole chemotherapy. Authors concluded that "if regimens such as PCV continue to prove valuable in neurooncology the risk of leukemia will require integration into the clinical decision process" and recommended a search for "more effective therapy with minimal mutagenicity remains critical" [98].

The risk of late haematological complications with TMZ seems low compared with other alkylating agents like nitrosoureas mentioned above. An Australian team reported the cases of three patients treated with TMZ for a progressive glioma. These patients have continued the treatment respectively for 5, 7 and 8 years! No serious side effects were reported. Thus, it was often considered that most individuals receiving exceptionally large doses of alkylating agents over an extended period did not develop T-MDS/AML. This is true for patients receiving TMZ [99]. In contrast, Natelson et al. published a case report concerning a patient who had received

temozolomide as a single agent for treatment of malignant glioma and who developed t-MDS. After a literature review, authors suggested that the cumulative dose threshold (CDT) for temozolomide that could predispose to t-MDS and which may potentially lead to acute myeloid leukemia would be around 18,000 to 20,000 mg/m$^2$ [100]. The authors acknowledge, however, that the objective assessment of the real risk appears much difficult for tumors with a worse prognosis such as gliomas than for tumors associated with a long survival like Hodgkin's lymphoma, testicular cancer or breast cancer. They concluded that all alkylating agents, including TMZ, should be considered potentially leukemogenic when administered long term. Nevertheless, the risk of direct (progression or recurrence, malignant evolution) or indirect tumor complications (permanent deficit, seizures) or short latency adverse reactions to treatment (myelosuppression, opportunistic infection, encephalopathy due to radiation therapy) remains, at this day, much higher than the t-MDS/t-AML risk [96].

We have nevertheless to be careful with our prescription and to demonstrate in well-structured databases that prolonged use of alkylating chemotherapy until tumor progression or unacceptable toxicity is superior to treatment with a defined and limited number of cycles.

#### 25.3.6.2 Chemotherapy and Gonadotoxicity

Data concerning chemotherapy, DLGG and gonadotoxicity are almost non-existent. Alkylating chemotherapy containing procarbazine (and/or cyclophosphamide) causes prolonged azoospermia in 90–100% of men and premature ovarian failure in 5–25% of women under the age of 30 years [101]. We are also entitled to fear a marked gonadal toxicity of vincristine [102]. Thus, we can assume, although no specific published data, that the PCV association is clearly gonadotoxic. We so recommend (1) to warn patients of this possibility (2) to propose systematically a fertility preservation (easier in men than in women) (3) to avoid this association in patients wishing to preserve essentially their reproduction capabilities.

Concerning temozolomide, a retrospective study was published [103]. It concerns 24 female patients treated for a glioma. Fifteen patients had no fertility preservation and the remaining nine had a cryopreservation of embryos with or without an oocyte cryopreservation. Four patients are or have been pregnant (delivery, spontaneous miscarriage, pregnancy in the group of preserving fertility and a current pregnancy in the group where no fertility preservation has been achieved). The conclusion of the authors is that temozolomide is not totally gonadotoxic. Paternities have also been reported after temozolomide [104]. We could apply the two previous recommendations (information, fertility preservation) when a TMZ-based chemotherapy is needful in the course of a DLGG and when the patient wishes to preserve its reproduction capabilities while integrating the concept of a likely lower toxicity compared with that seen with nitrosoureas.

#### 25.3.6.3 Other Toxicities

The peripheral neurological risk of vincristine cannot be neglected. There is currently no way to prevent it [105]. The risk of lung fibrosis with cecenu is also a parameter to be integrated during the establishment of such a combined therapy with cecenu [106]. Otherwise, patients under the PCV association complain frequently about an intense asthenia and/or about a loss of weight [82].

Temozolomide induced hepatitis can be particularly severe, especially the cholestatic form [107].

## 25.4 Open Questions

### *25.4.1 How to Evaluate the Benefit of Chemotherapy*

For more objective assessment of the impact of chemotherapy, it is conventional in neurooncology to use parameters such as overall survival and progression-free survival.

Overall survival is sensitive to all instituted treatments including "salvage" therapies. In this type of disease, treatments are often multiple and repeated. That makes difficult to analyze the specific impact of a given treatment (chemotherapy in our case) on survival. Progression-free survival could be an interesting parameter to use if and only if (1) there is longitudinal and rigorous volumetric assessment (2) these morphological parameters are associated with quality of life data [108]. The same remark can be made for the classical time to malignant transformation.

It was recently pointed out that clinical trials for DLGGs "need to consider other measures of patient's benefit such as cognition, symptom burden, and seizure activity, to establish whether improved survival is reflected in prolonged well-being" [58] should move in this direction also emphasized by Klein and colleagues "the multidimensional scales used to study changes in HRQOL studies in brain tumor patients provide a more comprehensive view of what is important to the patient concerning living with their disease and receiving treatment" [109].

### *25.4.2 How to Monitor the Treatment (Response Assessment)*

To date, most radiologists and physicians analyze the images and decide the direction of treatment for gliomas and especially DLGGs via a side-by-side comparison of images. This procedure can be considered as very imperfect and even dangerous. It was indeed clearly demonstrated that automated change detection and image subtraction are superior to side-by-side image comparison for brain tumors in general [110] and more obviously for DLGGs [111].

In the same manner, the majority of dedicated centers simply monitored patients with conventional MRI without volumetric assessment and a fortiori without multiparametric examinations able to assess tumor cellularity, hypoxia, disruption of normal tissue architecture, changes in vascular density and vessel permeability [112]. However, today, these parameters seem absolutely essential [113].

RANO criteria [58] for DLGGs seem not appropriate to monitor treatment and follow-up. Detailed volume assessment is crucial in slow-growing tumors like DLGGs. Indeed, it may be difficult to highlight a tumor growth in this kind of tumors. RANO criteria correspond to a two-dimensional evaluation (the product of the two perpendicular diameters) whereas three-dimensional evaluation, is clearly superior and more accurate. 3D volumetric tumor measurement represents the gold standard [111, 114, 115]. In our group, we have demonstrated that manual MRI segmentation of DLGG tumor volumes (Osirix® free software) was reproducible, independently of the practitioner, nor the medical specialty or experience [116]. Volumetric assessment is also feasible in clinical practice.

Finally, some authors have attempted to model the response to chemotherapy in order to predict the response to treatment. Results have to be confirmed and stated in the future [42, 47, 117].

### *25.4.3 Links Between Chemotherapy and Clinico-Radiological Factors*

There are several factors clearly related to the prognosis of DLGGs. These factors formed the "EORTC scoring system" [118] or the "UCSF LGG prognostic scoring system" [119] by combining different parameters (1) location of tumor in presumed eloquent cortex (UCSF) (2) tumor crossing the midline (EORTC) (3) presence of neurological deficit (EORTC) (4) Karnofsky Performance Scale score < or =80 (UCSF) (5) age > 50 years (UCSF)/ > or =40 years (EORTC) (6) maximum diameter (> or =6 cm for EORTC/ >4 cm for UCSF) and (7) histology (astrocytoma histology subtype for EORTC). Patients that combine two or more factors are classified in the high-risk group for the EORTC scoring system. For UCSF, the stratification of patients is based on scores generated groups (0–4) with statistically different OS and PFS estimates ($p < 0.0001$, log-rank test). It has more recently been shown by a multivariate analysis constructed on the basis of two European Organisation for Research and Treatment of Cancer radiation trials for low-grade gliomas that tumor size and MMSE score were significant predictors of OS whereas tumor size, astrocytoma histology, and MMSE score were significant predictors of "PFS" [120]. Finally, Gorlia et al. validated prognostic models and prognostic calculators [121] after pooling data from two large studies. The presence of baseline neurological deficits, a shorter time since first symptoms (>30 weeks), an astrocytic tumor type and tumors larger than 5 cm in diameter were negatively influenced both "PFS" and OS.

It is so far difficult if not impossible to determine whether these factors are only prognostic factors or predictors of treatment response, including chemotherapy response.

Dynamic Susceptibility-weighted Contrast-enhanced perfusion imaging can identify progression and can also predict treatment failure during follow-up of DLGGs with, for some authors, the best diagnostic performance [122].

Concerning spectroscopy, Murphy et al. reported in 2004 that there was interest to evaluate the reduction in the tumour choline/water signal in parallel with tumour volume change and that this marker could reflect the therapeutic effect of temozolomide [123]. In addition and very interestingly, Guillevin et al. demonstrated that the mean relative decrease of metabolic ratio $-\Delta(Cho/Cr)(n)/(Cho/Cr)(o)-$ 3 months after the start of a TMZ-based chemotherapy was predictive of tumour response over the 14 months of follow-up. The (1) H-MRS profile changes more widely and rapidly than tumor volume and represents an early non-invasive predictive factor of outcome under temozolomide-based chemotherapy [113].

### *25.4.4 Links Between Chemotherapy and Pathological Phenotype*

The diagnostic criteria, in particular for oligoastrocytoma but also for "simple" astrocytomas or oligodendrogliomas, are highly subjective [124]. Most authors have proposed to go beyond the pathological (morphological) classification by including other criteria, notably molecular, to refine the prognostic significance of the diagnosis [125, 126]. Due to these important limitations of the morphological analysis of DLGGs, it was difficult to build clinical trials for chemotherapy.

The WHO classification of Central Nervous System tumors has been revised in 2016 [127] and integrates molecular parameters in addition to histology. Thus, IDH and 1p19q status are now used to define diffuse astrocytomas and oligodendrogliomas. Oligoastrocytomas "are now designated as NOS (not otherwise specified) categories, since these diagnoses should be rendered only in the absence of diagnostic molecular testing or in the very rare instance of dual genotype oligoastrocytoma". For instance, we think that these modifications will not changed our attitude in daily practice in DLGGs, especially in chemotherapy decision making. Indeed, as we mentionned previously (Sect. 25.3.5), chemotherapy could induced a significant tumor volume reduction whatever molecular status, at the individual level [43, 45]. A positive point is that this modified classification incites to systematically perform molecular analyses, although there is no precision concerning the technique for 1p19q assessment (loss of heterozygosity LOH or fluorescence in situ hybridization FISH or comparative genomic hybridization CGH). However, in this new classification, a diagnosis of glioblastoma GBM is retained even without necrosis on histological analysis of oligodendrogliomas, leading to an overdiagnosis of GBM in DLGGs harboring anaplastic micro- or macrofoci, as defined by Pedeutour-Braccini

et al. [128] Finally, this new classification will not solve the problem of the heterogeneity of DLGGs and it will be again difficult to draw conclusions from the various series to be published.

### *25.4.5 Links Between Chemotherapy and Molecular Biology*

To date, biomarkers most commonly identified and used in DLGGs comprise: IDH 1/2 expression (isocitrate deshydrofenase 1/2), 1p19q status, TERT (telomerase reverse transcriptase) promoter mutation, presence of G-CIMP (glioma-CpG island methylation phenotype), MGMT (methylguanine methyltransferase), ATRX expression (alpha thalassemia mental retardation X-linked).

Before talking about chemotherapy, the prognostic role of molecular markers after surgery alone could be discussed. Thus, even if the concept of "Progression Free Survival" (PFS) after partial surgery in the context of a DLGG is highly questionable, Hartmann et al. [129] considered that no molecular marker was prognostic for this endpoint after surgery alone using multivariate adjustment for histology, age, and extent of resection. Kim et al., on their side, screened 360 WHO 2007 grade II gliomas for mutations in the IDH1, IDH2, TP53 genes and for 1p/19q loss and correlated these factors with clinical outcome. TP53 mutation was considered as a significant prognostic marker for shorter survival ($p = 0.0005$) and 1p/19q loss for longer survival ($p = 0.0002$) while IDH1/2 mutations had not prognostic value ($p = 0.8737$). Their conclusion was that "molecular classification on the basis of IDH1/2 mutation, TP53 mutation, and 1p/19q loss has power similar to histological classification and avoids the ambiguity inherent to the diagnosis of oligoastrocytoma" [124].

Data regarding chemotherapy are partly contradictory. Iwadate et al. have treated 36 consecutive low-grade oligodendroglioma patients (postoperative residual tumors or recurrence after total resection) by a modified PCV based chemotherapy-preceding strategy and without radiotherapy. In this study, 1p and 19q status was analyzed by fluorescence in situ hybridization. 1p/19q co-deletion was observed in 72% of cases. There was no significant association between 1p/19q co-deletion and chemotherapy response rate. No significant difference has been found as well in terms of survival: median PFS of 121 months for 1p/19q-deleted tumors and 101 months for non-deleted tumors (logrank test: $p = 0.894$). Recurrent tumors were also well controlled by chemotherapy irrespective of 1p/19q status [41]. Following the work of Hoang-Xuan et al. [22] and in contrast, Kaloshi et al. reported a retrospective single center observational study with 149 consecutive patients. The median number of TMZ cycles delivered was 14 (range 2 to 30). Seventy seven patients (53%) experienced an objective response (15% of partial response, 38% of minor response, 37% of stable disease and 10% of progression). The median time to maximum tumor response was 12 months (3 to 30 months). The median "PFS" was 28 months (95% CI: 23.4 to 32.6). Material for genotyping was available for 86 patients. Combined 1p/19q LOH was present in 42% of the cases. Co-deletion was

significantly associated with (1) a higher response rate ($p < 0.02$) (2) a longer objective response to chemotherapy ($p < 0.017$) (3) a longer PFS ($p < 4.10^5$) and 4) a longer overall survival ($p < 0.04$) [30]. The same team, through Houiller et al. reported a series of 271 patients with a DLGG in which 84 patients were treated up-front. IDH (1 or 2) mutations were found in 132/189 patients (70%). IDH mutation and 1p-19q codeletion were associated with a prolonged overall survival in multivariate analysis ($p = 0.003$ and $p = 0.004$). 1p-19q codeletion, MGMT promoter methylation, and IDH mutation ($p = 0.01$) were also correlated with a higher rate of response to temozolomide. Inside the untreated subgroup, 1p-19q codeletion was associated with prolonged "progression-free survival" (this concept is, again, highly questionable in an untreated population) in univariate analysis whereas IDH mutation was not [38]. Our understanding of the problem may also be informed by the work of Ochsenbein et al. 22 patients with histologically verified DLGG (WHO 2007 grade II) were treated with temozolomide (TMZ) for tumor progression. LOH 1p and/or 19q correlated with longer time to progression but not with radiological response to TMZ. The volumetric response to chemotherapy analyzed by MRI and time to progression correlated with the level of MGMT promoter methylation [66]. Data on tumors considered as pure astrocytomas are likewise difficult to interpret. In the study of Taal et al. concerning temozolomide-based chemotherapy, MGMT promoter methylation and IDH1 mutations were not correlated with "PFS" but the interval between the first symptom and the start of the TMZ was significantly ($p = 0.02$) longer in the patients with a methylated MGMT promoter and with IDH mutations ($p = 0.01$) [40].

The reported results appear thus contradictory. Although at a population level, there is a quite pronounced correlation between 1p19q deletion (and a smaller correlation between MGMT promoter methylation or IDH1 mutation) and response to chemotherapy, it appears today absolutely impossible to consider the indication of chemotherapy on this sole argument at an individual level. We have previously shown [32] that 1p19q codeletion was primarily a marker of the duration of response and not a marker of response. In the case of a presurgical chemotherapy continued under a strict volumetric monitoring until obtaining a plateau, depriving patients of such a strategy (which can potentially change the natural history of the disease by allowing to move toward a possible subtotal resection not originally envisaged), seems to us a significant error [43, 45].

The Cancer Genome Atlas (TCGA) Research Network realized a large-scale and multidimensional molecular analysis of 293 WHO 2007 grade II and III gliomas [130]. Three molecular subgroups were individualized and were correlated to clinical outcome. First, concerning DLGGs with IDH mutation and 1p19q codeletion, results have confirmed the occurrence and coexistent mutations of CIC (62%), FUBP1 (29%), NOTCH1 (31%) and TERT promoter (96%). Second, concerning DLGGs with IDH mutation and no 1p19q codeletion, TP53 mutations were identified in 94% and inactivating alterations of ATRX in 86%. Moreover, in DLGGs with IDH mutation, the first event in gliomagenesis corresponds to IDH mutation and acquisition of the glioma CpG island methylation phenotype (G-CIMP, a specific pattern of widespread DNA hypermethylation) and is followed by either 1p19q

codeletion or TP53 mutation. Third, DLGGs with no IDH mutation (wild-type IDH) presented a clinical and genomic profile, which strikingly resembles of primary GBM: mutations in seven genes were associated with this subgroup and five of these genes have been reported to be mutated in glioblastoma (PTEN, EGFR, NF1, TP53, PIK3CA). Olar et al. confirmed in their review the importance of IDH mutations and 1p19q codeletion in gliomagenesis and in determining outcome. These two molecular alterations allowed determining DLGG subgroups. But, the predictive role (response to chemotherapy) of new markers such as ATRX, TERT, CIC, FUBP1 is not clearly defined and need to be validated [131], even if new prognostic algorithms were proposed [132].

In the same way, temozolomide induced resistance with driver mutations in the RB and AKT-mTOR pathways (which could be the cause of malignant progression to secondary GBM) was mentioned in the early 2010s [133, 134]. New results from the same team suggest that tumor cells with methylated MGMT may undergo positive selection during TMZ treatment in the context of MMR deficiency [135]. These points should be specified on prospective clinical series.

We must, in all cases, further analyze prospective and retrospective series to better understand the role of prognostic factors related to the host or to the tumor including new molecular markers optionally in correlation with the mitotic index [136] and how a therapeutic modality or a strategy combining several modalities could modulate the impact of these spontaneous prognostic parameters [137, 138].

### *25.4.6 When to Treat*

To date only four large randomized trials in patients with low-grade glioma have been published. They allow concluding that early radiotherapy does not improve overall survival and support alternative approaches like chemotherapy without providing evidence on the timing of chemotherapy [52]. We have previously emphasized the heterogeneity of the various reported series concerning chemotherapy. Often, within the same study, patients could be included before or after the anaplastic transformation of the tumor. To be very convenient, prescriptions at the "low-grade" stage can theoretically be proposed (1) in case of progression after surgery (regardless the quality of debulking) and radiotherapy (2) for non operable progressive tumor and before radiotherapy in order to delay radiation and so radiation induced cognitive impairment (3) in case of progression after a first line surgery if reoperation can not be immediately considered and before either surgery if the volume reduction obtained with chemotherapy allows it (4) upfront in order to allow, in case of volume reduction, a surgical procedure before radiotherapy.

Only one randomized trial has been achieved. It compared primary temozolomide versus radiotherapy in "high-risk" DLGGs (EORTC/NCIC 22033/26033) regardless of the initial surgical status, in case of active treatment requirement other than surgery. Data concerning survival are not yet available. Median "PFS" was not significantly different in the two groups (radiation therapy versus chemotherapy).

Concerning molecular DLGG subgroups, there were no significant treatment-dependent differences in "PFS" for patients with IDH mutation plus 1p19q codeletion and for patients with no IDH mutation. Patients with IDH mutation and no 1p19q codeletion seems to have a longer "PFS" when treated with radiation therapy (HR 1.86 [95% CI 1.21–2.87]). Nevertheless, some elements could be discussed: 1) 50% of the patients in each arm (relatively frequent and unusual for DLGGs) presented contrast enhancement (that could predict anaplastic transformation despite a central pathological review) at the initiation of the treatment 2) surgical treatment was considered not to be feasible (based on which criteria ? as assessed by an expert neurofunctional neurosurgeon ?) 3) response assessment was appreciated according to a bi-dimensional perpendicular product that is questionable [50].

#### 25.4.6.1 Chemotherapy After Surgery and Radiation Therapy

Historically, the first prescriptions of chemotherapy [12, 13] were made after standard surgery and radiation therapy, which were unambiguously considered as the reference treatments while chemotherapy was considered as less or not effective. Clinical and radiological responses were clearly observed [12, 13, 18, 19, 139].

Can we nevertheless draw from these publications that chemotherapy is able, at this time of prescription, to modify enough the natural history by delaying, for a given time, the evolution of the disease including the anaplastic evolution? Is the impact of post radiation chemotherapy, considering the duration of response more or less important than before the radiotherapy? More or less important before malignant transformation than after? Does it allow the patient to maintain longer a high quality of life in comparison with earlier (pre-radiotherapy) or later (after anaplastic evolution) prescription of chemotherapy?

It is difficult if not impossible to answer these questions. This point will, indeed, depend on many parameters: tumor volume, tumor heterogeneity, time of the disease where radiation therapy was performed, time from the end of radiotherapy, type of chemotherapy or duration of this one… It is also very difficult to assess the type of response evaluation (both clinically and radiologically) in the various published papers. The majority of reported series does not relate real reproducible parameters. The limited retrospective data (which constitute the majority of available data) on all of these parameters does not help to get a clear vision of the real impact of chemotherapy at this time of the disease.

Nevertheless, a phase III prospective study was conducted by the RTOG group (9802 trial). This is the only phase III trial that raised the question of the role of adjuvant chemotherapy in DLGGs. Inclusion criteria of this trial were related to presumed high-risk patients with a residual tumor after surgery or an age over 40 with any extent of resection. Patients were stratified by age, histology, Karnofsky performance status, and presence or absence of pre-operative contrast enhancement (suggesting that an unspecified proportion of patient had anaplastic transformation!). They were randomized to radiotherapy (RT) alone (54 Gy/30 fractions) versus RT followed by 6 cycles of standard dose PCV [4]. We often find in the literature statements such

"adjuvant use of PCV-chemotherapy in high-risk patients failed to improve progression-free and overall survival in comparison with radiotherapy" [140].

Initial results of this study contradict significantly this assertion and were published in 2012 [4]. Two hundred and fifty one cases were indeed included in the study between 1998 and 2002. 60% of the patients in the RT arm presented contrast enhancement and 65% in the RT + PCV arm (we must so clearly consider that this study concerns mainly anaplastic gliomas!). Median "PFS" time and 5-year "PFS" rates for RT versus RT + PCV were 4.4 years versus not reached ($p = 0.06$) and 46% versus 63% (log-rank, $p = 0{,}005$), respectively. Median OS time and 5-year OS rates for RT versus RT + PCV were 7.5 years versus not reached ($p = 0.33$) and 63% versus 72% (log-rank, $p = 0.13$), respectively. Beyond 2 years, the OS and PFS curves separated significantly favoring RT + PCV patients. For 2-years survivors (n = 211), the probability of OS for an additional 5 years was 74% with RT + PCV versus 59% with RT alone ($p = 0.02$) with comparable data for "PFS" (66% with RT + PCV versus 37% with RT alone, $p < 0.001$). Finally, the hazard ratio for RT + PCV versus RT was 0.52 for death ($p = 0.02$) and 0.45 for progression ($p < 0.001$). The mature results of the RTOG 9802 trial have been published this year [89]. Median follow-up was 11.9 years. Median "PFS" and median OS for RT versus RT + PCV were 4 years versus 10.4 years ($p < 0.001$) and 7.8 years versus 13.3 years ($p = 0.003$). The hazard ratio of death was 0.59 (log rank, $p = 0.002$). It is noteworthy that 77% of patients who progressed after RT alone received salvage chemotherapy [141, 142].

The main merit of this study is to demonstrate the interest of chemotherapy on survival. However, the main criticism is based on the lack of an arm "chemotherapy alone". Otherwise, at this day, we have no accurate data concerning quality of life and cognition on long-term follow-up. Only evolution of the Mini-Mental State Examination (MMSE) has been reported [143] with no significant decline in MMSE between the two arms, over time (through 5 years of follow-up). Authors concluded that the addition of PCV chemotherapy to RT improves "PFS" without "excessive cognitive function detriment" over RT alone. These results have to be taken with caution. Indeed, MMSE is not a sensitive and subtile tool. In this study, they considered a significant MMSE score decline as a decrease of more than three points (!), which is not a detailed assessment. Moreover, the compliance rates of MMSE collection decreased over time, with only 35% collected in RT + PCV arm and 41% collected in RT alone at five years of follow-up, although there were no significant differences in compliance rates between arms. Longer follow-up is also needed to assess quality of life and cognitive impacts according to the potential long-term neurotoxicity of radiotherapy and given the long survival of DLGG patients.

We must specify that another phase III was initiated by the ECOG group as "E3F05 Trial" in 2009 [51]. This trial randomized temozolomide (concurrent and adjuvant every 28 days for 12 courses) plus radiotherapy versus radiation alone (once daily 5 days a week for 5.5 weeks—28 fractions). The primary objectives were to determine whether the addition of temozolomide to fractionated radiotherapy improved the "PFS" and OS of patients with symptomatic or progressive

DLGGs. The design of this trial could fear an excess of delayed neurotoxicity. Indeed, patient enrollment was suspended as of February 3, 2014 due to updated findings from the RTOG 9802 trial. The E3F05 trial will not be completed.

Finally, a randomized phase II analyzed the place of temozolomide as an adjuvant treatment (RTOG 0424 trial). High-risk DLGGs (at least 3 risk factors: age ≥ 40, tumor diameter ≥ 6 cm, tumor crossing midline, astrocytoma subtype, pre-operative neurological function status >1) were treated with RT (54 Gy in 30 fractions) and concurrent and adjuvant temozolomide. Outcomes were compared to those of historical controls [118]. From 2005 to 2009, 129 patients were included. Median and minimum follow-up examinations were 4.1 years and 3 years, respectively. The 3-year OS rate was 73.1%, which was significantly improved compared to that of prespecified historical control values ($p < 0.001$). Median survival time was not reached. Median "PFS" and 3-year "PFS" were 4.5 years and 59.2%, respectively. Grade 3 and 4 adverse events occurred in 43% and 10% of patients, respectively. Nevertheless, management of DLGGs has changed since 2000s, with a more aggressive strategy characterized by initial surgical removal if possible. Was it relevant to compare these results to historical data? We have again and again to note that no quality of life and cognitive data are available [90].

So, these last years, two studies demonstrated a benefit of chemotherapy on survival in "high-risk" DLGG patients. Nevertheless, this "high-risk" population is also at risk of developing late toxicity given precisely to these risk factors (age > 40 years, large tumor volume to be irradiated…). We think that initial chemotherapy (after presenting to an **expert** functional neurosurgeon about a possible surgical removal) should be discussed at the individual level, even in "high-risk" patient, in order to reduce the tumor volume and by the same, in order to reduce the potential irradiation volume and therefore the risk of toxicity. It remains to define precisely what constitutes a "high-risk" patient.

Some authors [141, 144–146] have proposed a similar management for "high-risk" DLGGs and anaplastic gliomas (especially for 1p19q codeleted gliomas), according to the comparable results and outcome of the three trials of RT + PCV [4–6]. It is not surprising that the results of RTOG 9802 and EORTC 26951 trials are similar. Indeed, 60 to 65% of patients presented contrast enhancement in the RTOG 9802 trial (whereas maximally 15–20% of DLGGs were reported to enhance faintly gadolinium, in the literature), which is compatible with an anaplastic transformation.

Likewise, some gliomas in the EORTC 26951 have been possibly classified as anaplastic gliomas whereas anaplastic microfoci have been completely removed which could modify the outcome. Thus, populations in RTOG 9802 and EORTC 26951 trials are heterogeneous.

Finally, we suggest:

1. that all patient have to be presented to a neurosurgeon with expertise in tumor resection and utilization of intra-operative cortical/subcortical mapping and functional awake surgery, before any therapeutic decision,
2. that "high-risk" DLGGs have to be better defined,

3. that it is too earlier to adopt and to generalize RT + chemotherapy as first line in DLGGs, in the absence of (a) data concerning long-term quality of life and neurocognitive follow-up and according to heterogeneous populations in the trials,
4. trial having evaluated a single arm with initial chemotherapy and radiotherapy at progression (provided that no reoperation can be considered),
5. to propose a personalized and individual treatment strategy (rather than a "generalized" forever defined treatment) under a clinical (including quality of life) and volumetric monitoring with sequential treatment to consider for each patient, at each evaluation.

Some authors considered that "concerns on delayed radiotherapy associated delayed neurotoxicity may be less decisive in view of the superior survival of patients treated with initial radiotherapy followed by chemotherapy, and the absence of any trend toward increased survival in patients initially managed by chemotherapy only" [144].

We disagree with these reflexions. It is essential to take into account quality of life, quality of survival and neurocognitive functioning [108]. Indeed, must we absolutely improve survival with the risk to impact quality of life and cognitive functions (with impossibility to return to work, to drive, to have a normal social life, to live independently….)?

Everybody knows patients who certainly have a well control of the disease but also a major toxicity induced by radiotherapy with severe impact on their daily life. Long-term neurocognitive decline induced by radiotherapy has been well demonstrated [8]. Despite improvement in brain RT techniques, late neurocognitive deficits may still emerge. This supports an approach in which RT is delayed as long as this is safely possible, especially when one considers old trials (not enough mentioned) showing no difference in terms of survival between early or delayed radiotherapy [147]).

It does not seem reasonable to propose an aggressive treatment (combining RT + chemotherapy) to a population that a priori has a spontaneous better prognosis with long survival (especially patients harboring 1p19q codeletion), given the risk of late toxicity [148]. The reasoning would try to climb down the treatment for these specific patients. However, the ongoing CODEL study (a randomized phase III trial of radiotherapy versus TMZ alone versus radiotherapy with concomitant and adjuvant TMZ for patients with 1p19q codeleted anaplastic glioma) has been modified to include "high-risk" (as defined in RTOG 9802 trial) DLGG patients with 1p19q codeleted and to realize RT followed by PCV. Results will be available in several years (and possible a decade). This study will not compare TMZ and PCV, since all patients will be irradiated.

Moreover, although the IDH mutation and 1p19q codeletion subgroup is associated with a better prognosis, it also appears that this group is also heterogeneous (in terms of prognosis, pathological, trasncriptomic and immunophenotypic studies). It is questionable to generalize a treatment to a population that seems ultimately heterogeneous despite a-priori a better prognosis. These elements reinforce the notion of a personalized therapeutic strategy. Therapeutic decision could not be simply summarized to a molecular signature [149, 150].

The challenge also consists "to define when an aggressive treatment improves survival without impacting quality of life or neurocognitive function and when an effective treatment can be delayed in order to preserve QOL without impacting survival" [138]. We do not denigrate that radiotherapy is an effective oncological treatment. The hardest part is to determine the best time to carry out this treatment, neither too early (to avoid long-term side effects) nor too late (at glioblastoma stage). These risks and benefits must be balanced in strategy decision, at each time.

#### 25.4.6.2 Chemotherapy Before Radiotherapy

Chemotherapy for Non-surgical Tumor

Some locations (e.g., primary motor area, tumor infiltrating deep connectivity), multifocal tumors or "gliomatosis like" aspects remain forever non-surgical. These tumors are evolving as much as the other gliomas, clinically and radiologically. A primary chemotherapy course has to be discussed because, especially in the case of multifocal tumors or gliomatosis, volumes to be theoretically irradiated remain at risk of high cognitive toxicity. Data from the literature remain, again, rare and affect mainly the gliomatosis. We know that chemotherapy (temozolomide or "PCV") can be effective in terms of symptoms and volumes [151]. The main question concerns the duration of temozolomide treatment for long responders. Can we continue the treatment for a very long time (even several years) when chemotherapy is (1) well tolerated (2) able to produce a volume reduction and stability or do we fear the risk of late complications related to it (myelodysplasia, induced leukemia) [152] or induction of malignant phenotype in some tumors (see above)? There is to date no formal response. The question must clearly asked by analyzing the risk/benefit ratio with on one side a tumor often with pejorative prognostic factors and on the other side a low risk at a medium term of complications.

Articulation Between Chemotherapy as First Line Treatment and Surgery

Our group reported the first case of a complete surgery made possible thanks to an initial chemotherapy. This patient was initially diagnosed because of seizures. He benefited from a first partial conventional resection. The tumor continued logically to grow with an invasion of the controlateral hemisphere via the corpus callosum. A temozolomide-based chemotherapy was then prescribed and allowed a regression of the controlateral extension. Post chemotherapy surgery was performed with intraoperative functional mapping and allowed a complete resection without sequelae [25]. The patient now continues to enjoy a normal life more than 10 years of follow-up since the first surgery (without radiotherapy). Spena et al. reported the same strategy for a patient and concluded that this new therapeutic approach of chemotherapy followed by surgery can offer safer and more radical surgical resection while improving the quality of life of the patient [153].

We then published a series of ten patients who benefited from a presurgical chemotherapy. In all cases we observed a tumor shrinkage that made possible the resection of these initially inoperable tumors. All the patients were secondarily evaluated from a cognitive and quality of life points of view. We demonstrated that the combined treatment was (1) feasible, (2) efficient and (3) well tolerated with few cognitive deficits (mostly related to the tumor location) and with a good quality of life [39]. Martino et al., also within our group, reported a series of 19 patients who benefited from two operations separated by at least 1 year. Nine of these patients received chemotherapy before the second operation that allowed a subtotal or total resection in 14/19 cases. After the second operation, 16/19 patients improved or stabilized their clinical situation, while in 14/17 cases, seizures were reduced or disappeared. Therefore, the authors concluded that chemotherapy did not prevent or even favored a second operation [154].

We described in Sect. 25.3.5 our series of selected seventeen initially non-operable patients who underwent temozolomide-based chemotherapy. Here, we just would like to point out that chemotherapy was able to reduce the growth slope in all 17 cases whatever the molecular status, and that the quality of surgery was directly related to the magnitude of response to chemotherapy. TMZ appears thus as a way to optimize surgery and an additional way to potentially modify the natural history of this disease [43].

Another retrospective series reported 20 patients treated with neoadjuvant temozolomide [45]. They analyzed anticipated extent of resection EOR before chemotherapy and 3 months after TMZ completion. The anticipated EOR was defined as: [(total tumor volume—unresectable tumor volume)/total tumor volume] × 100. The anticipated EOR was defined on anatomical criteria (not on functional criteria). Mean tumor volume decrease was −32.5% ($p < 0.001$) (comparable to the median tumor volume decrease 35.6% in our study of 17 patients). Mean pre-treatment anticipated EOR was 67.2% versus 71.5% at 3 months post-treatment. They did not find statistically significant improvement in anticipated EOR with a mean change from baseline of 4.3% ($p = 0.10$). Interestingly, the mean tumor volume decrease was −26.9% for patients with 1p19q codeletion versus −37.4% for patients with no codeletion ($p = 0.46$). So, the mean change in anticipated EOR was 3.06% for patients with 1p19q codeletion versus 7.09% for patients with no codeletion ($p = 0.45$).

The case described in our first publication presented a-priori "high-risk" DLGG (tumor deemed unresectable, more than 40 years old), with IDH mutation and no 1p19q codeletion. According to the results of RTOG 9802, this patient should have been treated with radiotherapy plus PCV as first line. And according the preliminary results of EORTC 26033, this patient should have been treated with RT. Finally, this patient have been operated on with a great EOR 92% (pre-treatment tumor volume of 57 $cm^3$ and post-treatment tumor volume of 8 $cm^3$). As we know, surgical removal of DLGGs has clearly demonstrated its benefice on survival. In conclusion, we can not prevent a patient from initial chemotherapy only on molecular and pathological criteria. We must, as we have suggested it above, discuss the strategy with an expert functional neurosurgeon, case-by-case, at each time of the follow-up of DLGG patients.

## *25.4.7 How Long to Treat (Efficacy versus Potential Toxicity)*

### 25.4.7.1 Temozolomide

Duration According to Volumic Evolution

The article that can argue, at best, this question about the duration of chemotherapy is that of Ricard and colleagues [32] we talked about earlier. In this paper, the great majority (92%) of patients experienced initial decrease of the mean tumoral diameter after initiation of temozolomide. Ricard et al. found a clear correlation between 1p19q codeletion or absence of p53 overexpression and the duration of the response. Under chemotherapy, the volume is better controlled in codeleted patients (while recognizing that the maximum duration of temozolomide was 24 months). Otherwise, a majority of the patients resumed their progressive growth within a year after discontinuation of the chemotherapy. This observation of Ricard et al. raises the question of the validity of an arbitrary interruption of treatment in patients whose mean tumoral diameter (MTD) is still decreasing when the a priori fixed number of chemotherapy courses has been reached. Should treatment be pursued as long as the MTD continues to decrease (or stabilize), knowing that this option should be balanced with the potential long-term toxicity of prolonged treatment? Alternatively, should we abbreviate chemotherapy to four to six cycles to prevent formation of drug resistance? In this case, can we be certain that the tumor will remain sensitive to the treatment resumed after several months of interruption? Outside volume aspects, must we incorporate other parameters in the longitudinal follow-up of patients? We know that H MRS imaging 3-dimensional volumetric maps of choline (Cho) over creatine (Cr) is more accurate in DLGGs for the detection of glioma progression in comparison with conventional magnetic resonance imaging (MRI) and clinical symptoms [113, 155] and that the (1) H-MRS profile represents an early predictive factor of outcome over 14 months of follow-up under temozolomide [113]. It appears so obvious that, in the future, we will focus on a multimodal monitoring.

Duration According Tolerance

We know that prolonged administration of adjuvant temozolomide is safe and can be favorable for patients with anaplastic gliomas [156]. Other authors have nevertheless a more pessimistic view highlighting the fact that 15 to 20% of patients (in a high-grade glioma population) treated with TMZ develop clinically significant toxicity, which can leave further treatment unsafe [157]. This point was developped in Sect. 25.3.6.

Chemoresistance Induction?

Johnson et al. [133] have suggested a risk of novel mutations induced by chemotherapy (TMZ) in DLGG patients. These mutations could lead to a malignant dedifferentiation. Nevertheless, these preliminary results (we have already discussed this

point) have to be confirmed on a large population and long-term impact has to be studied.

#### 25.4.7.2 PCV

As described in the Sect. 25.3.1, Peyre et al. [36] reported a series of 21 DLGG patients with a prolonged response to PCV. The mean duration of the MTD decrease after PCV onset was 3.4 years (0.8–7.7). The mean duration of the MTD decrease after the end of PCV was 2.7 years (0–7). According to adapted McDonald's criteria, the rates of partial and minor responses were 43% at the end of PCV but 80% at the time of maximal mean tumoral diameter decrease, which occurred after a median period of 3.4 years after PCV onset. This prolonged impact of treatment is to be balanced against the increased toxicity of the association mainly during its administration [82] and also sometimes after, via lung, gonadic and hematological long-term complications (cf. supra). Nevertheless, PCV protocol allows to delay radiation therapy, especially in 1p19q codeleted tumors (for 6.2 years versus 2.6 years for non codeleted tumors), given the prolonged response induced by PCV (MTD decrease more than 6 years in Taal et al.). Indeed, 10-year "PFS" was 34% for codeleted tumors in the study of Taal et al. [46].

Kaloshi et al. reported 38 patients who were treated with CCNU alone. A prolonged response was specified especially in oligodendroglial tumors. The profile of CCNU response is similar to PCV.

### *25.4.8 Retreatment with Chemotherapy*

Taking again temozolomide for a patient initially responder with this drug and after an interruption for a given period can possibly be discussed even if the data are very rare [158]**.** The alternative way may be based, in this configuration (TMZ pretreatment) and in the absence of other possible therapeutic modality, on the prescription of a nitrosourea. The results reported by Kaloshi et al. appear nevertheless disappointing. The authors have indeed described a series of 30 patients treated with a Nitrosourea-based chemotherapy for low-grade gliomas failing initial treatment with temozolomide. Response rate was 10% (3 minor responses achieved in non-enhancing tumors). Tolerance was considered as acceptable. Median PFS was 6.5 months. Median OS from start of salvage treatment was 23.4 months. Chromosomes 1p/19q codeletion was not predictive for objective response to salvage treatment but correlated with a better PFS ($p = 0.02$). The conclusion of the authors was that salvage NU chemotherapy provides disappointing results in TMZ-pretreated DLGGs. They recommend in priority conventional radiotherapy, especially in DLGGs that display contrast enhancement at progression [37].

Platinum salts [159] or CPT11 [160] seems also to have a modest effect. Therefore, the development of new drugs is highly desirable.

Better understanding of the DLGG pathogenesis will allow the development of personalized management strategies. Indeed, potential more effective targeted therapies (BRAF serine/threonine kinase gene; the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) network, IDH) emerge in specific trials. IDH inhibitors seem promising [161], with further development ongoing in glioma, as well as immunotherapy. These therapies may be used either alone or in combination strategies.

## 25.5 Conclusion and New Horizons

A DLGG is a tumor that, in the absence of treatment, shows a continuous growth resulting, usually within a few years and through a *crescendo* evolution of tumor aggressiveness, in life threatening. During the initial period, contrary to a classical belief, this tumor entity alters so much quality of life through, most often, the existence of cognitive disorders and *crescendo* socially debilitating epilepsy. The idea of an initial "simple" monitoring ("wait and see" attitude) should definitely be abandoned in favor of an active therapeutic strategy implying the preservation of the core neurological sensory-motor and visual functions, but also the cognition, language and emotional abilities, and thus the quality of life. In recent years, we have very clearly seen an improvement of the surgical component of care. It has been shown that the extent of surgery had a major impact on the delay before anaplastic transformation and survival itself. Under the development of functional surgery (cortical and subcortical stimulations, intraoperative awakening), percentage of patients undergoing a subtotal or total excision has increased considerably. At the same time, morbidity was significantly reduced with a mortality tending to zero. Meanwhile, indications of early radiotherapy were reduced because of inducing late treatment risks, mainly related to cognitive disorders. In this chapter, we saw that chemotherapy could also take place in the armamentarium. Currently, two strategies remain advisable: monochemotherapy by temozolomide or PCV type association (vincristine + procarbazine + cecenu). Temozolomide offers the advantage of a better tolerance to short and medium term (hematologic, gonadal and general parameters). Serious complications (myelodysplasia, leukemia) remain exceptional. The limit is clearly based on tumor regrowth in the months following discontinuation of therapy, inciting to discuss an extension of the treatment duration. PCV is somewhat more toxic when administered. Serious haematological complications also exist. Nevertheless, it provides tumor control over long periods up to several months or years after treatment discontinuation.

In all cases, we now know that chemotherapy (1) allows a volume decrease in the vast majority of cases (2) improves the neurological symptoms, in particular epilepsy and cognition (3) indirectly improves "PFS" and OS. We have also shown that this treatment could make "the bed of surgery" allowing the realization of subtotal or total excision, of which we know the impact on survival and quality of life. We are thus entitled to imagine, although we have not formally demonstrated it, that

chemotherapy could improve directly or indirectly the survival of patients, while preserving or even improving the quality of life. Much work remains, however, to be performed. Two major prescription frames seem to be well considered (1) tumors (at diagnosis or progression) for which surgery could be discussed in case of a more or less volume reduction eventually associated with a redistribution of functional areas able to afford a subtotal or total resection (2) tumors that will remain, with regard to their topography and or extension (gliomatosis like, multifocality, deep connectivity infiltration) forever inoperable. In both cases, there are, to date, many unanswered questions regarding (1) timing of the prescription (after demonstrating a lesional scalability with two successive MRI at 3 or 4 months of interval? later in the disease, after a period of "wait and see" with the risk of being confronted with a bulkier tumor having accumulated a greater number of genetic abnormalities potentially promoting a chemoresistance?) (2) decision-making criteria for prescription assistance (pathological, molecular or radiological predictors of chemosensitivity or chemoresistance criteria? parameters to exclude patients who are at risk for serious side effects like myeloysplasia or induced leukemia?) (3) the specific strategies (conventional temozolomide? intensified temozolomide? PCV? Alternative treatment in case of progression after PCV and temozolomide for a tumor remaining a real WHO grade II glioma? If so which one?) (4) Duration: when to operate after a chemotherapy has been established? From the time when the tumor seems, based on probabilistic maps [58] able to benefit from subtotal resection? When the tumor stabilizes from a volumetric point of view, which implies the necessity of close volumetric monitoring? In the event of a definitive inoperable tumor, how long to continue temozolomide if the choice fells on this molecule? In case of well hematological and general tolerance, until the tumor is at least stabilized? For defined periods and if so, how long? After discontinuation, by repeating the treatment at a new documented growth, can we be certain of the chemosensitivity persistence?

Furthermore, it is obviously important to continue basic research, both from neurological and oncological point of view. Neurologically, as well as for surgery, we must, again and again, better assess the impact of our treatment strategies, for each topography and each patient on cognitive, language and emotional impairments and on the capabilities of the brain to redistribute itself, with chemotherapy alone or in combination with parallel strategies of speech therapy and cognitive rehabilitation. Oncologically, a better understanding of energy processes or cellular and molecular mechanisms will allow the development of specific therapeutic targets able to extend the rather limited armamentarium at our disposal [162, 163].

Despite the relatively low number of DLGGs, this adventure remains exciting by itself, but also in that it will be able to open up original concepts declinable for a number of other entities, starting with WHO grade III and IV gliomas.

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None.

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# Chapter 26
# Radiation Therapy in the Treatment of Low Grade Gliomas

**Hunter Boggs and Minesh Mehta**

**Abstract** Radiotherapy is used to treat gross and microscopic disease in low grade glioma. This chapter will address controversies of dose, timing, techniques, recent advances in the field and the benefit of systemic therapy. With the advent of molecular classification, current understanding of the role and benefit of radiotherapy in this diverse population is rapidly changing.

**Keywords** Radiotherapy • Conformality • Timing • Dose • Genomic and molecular classification

## 26.1 Introduction

While few deny that radiotherapy has been a mainstay of therapy for high-risk low grade gliomas, controversies regarding the timing, dose, modality, use of concurrent systemic therapy, and target volume determination continue to this day. Some of these controversies stemmed from our inability to adequately and accurately characterize this very heterogeneous group of malignancies, with significant variability in survival. Historically, categorization of gliomas was based primarily on pathologic features such as mitotic number, nuclear atypia, endothelial proliferation, and necrosis [1]. Further prognostic subcategorization utilized clinical factors such as extent of resection, size of the tumor, and age of the patient. These variables are the primary determinants of which patients maximally benefit from adjuvant

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radiotherapy and systemic therapy and form the basis for current radiotherapeutic decision making.

The discovery of molecular markers such as *IDH1*, *1p-19q* codeletion, *TERT*, and *TP53* has changed the landscape of low grade glioma classification. These markers are not only strongly *prognostic* of survival and progression, but are increasingly seen to be *predictive* of which therapy may offer maximal chance of cure. By incorporating molecular signatures into the grading of gliomas, the 2016 WHO classification system upends sole reliance on traditional histopathologic categorization [2]. As such, groups that were previously staged together, (such as low grade oligoastrocytomas) are now understood to potentially respond to treatment very differently based on their genetic and molecular profiles. For instance, an *IDH* mutated, *1p19q* codeleted oligoastrocytoma is distinct from an *IDH* wild type oligoastrocytoma. These reclassifications are blurring the potentially artificial distinction between WHO grade II and grade III gliomas.

While the developing understanding of molecular classification for gliomas represents an important elucidation of a heterogeneous group of malignancies, it has enormous and as yet uncertain implications for radiotherapy. Current treatment paradigms for low grade glioma are based on randomized studies and primarily utilize clinical factors, such as age and extent of resection to determine who may benefit from adjuvant local and systemic therapies. The report of long term results of Radiation Therapy Oncology Group (RTOG) 9802 resulted in a new standard of care in the management of high risk low grade glioma patients [3]. Differences in survival and progression were initially not appreciated in the original reporting of results in 2012, but with continued followup, survival curves clearly separated, illustrating a definitive benefit of adding PCV chemotherapy to radiotherapy for high risk LGG [4]. It is evident that certain groups of patients in RTOG 9802 demonstrated poor response to any adjuvant therapy and unfortunately died early, regardless of treatment approach. This resulted in the initial failure of the survival curves to separate. The remaining patients likely had molecular profiles that responded differentially to alkylating agents. The answer to why these survival curves only separated after many years is the key to understanding optimal adjuvant therapies for LGG.

This chapter will discuss the history and controversies of radiotherapy in low grade glioma. In addition, future directions incorporating evolving radiotherapeutic approaches based on molecular classification will be discussed.

## 26.2 Dose of Radiation Therapy

The first randomized study evaluating radiotherapy for LGG attempted to answer the benefit of dose escalation. EORTC 22844 (also known as the “Believers Trial) randomized 379 patients with low grade astrocytoma, oligoastrocytoma, and oligodendroglioma to adjuvant radiotherapy to a dose of 45 Gray (Gy) or 59.4 Gy [5]. All treatments were delivered in 1.8 Gy per fraction. Completely resected grade I

pilocytic astrocytomas were excluded. All patients either underwent resection if possible, or biopsy alone. When comparing the low dose arm to the high dose arm, there was no difference in 5-year OS (58 vs 59%, respectively), or PFS (47 vs 50%, respectively). Extent of resection was the strongest predictor of outcome. A subsequent quality of life analysis demonstrated that patients in the high dose arm reported lower emotional functioning and greater levels of malaise and fatigue [6].

The second dose escalation trial was conducted by the NCCTG and later included the RTOG and ECOG, to assist in completing accrual [7]. This Intergroup trial randomized 203 patients with WHO grade 1 and 2 astrocytoma, oligoastrocytoma, and oligodendroglioma to 50.4 Gy or 64.8 Gy in 1.8 Gy delivered per fraction. Again, pilocytic astrocytomas were excluded. When comparing the low dose arm to the high dose arm, again there was no difference in 5 year OS (72% and 64%, respectively) or time to progression (58% and 52%, respectively). Grade 3 or higher radiation necrosis was also higher in the high dose arm (2.5 and 5%).

In contrast to the previously mentioned studies which demonstrated no benefit of doses over 45–50.4 Gy, retrospective evidence by Leighton suggests that doses <50 Gy are potentially associated with inferior prognosis in patients with incomplete resection [8]. Olson et al. examined 106 patients with LGG who were treated between 48–65 Gy and did not find dose to be a significant predictor of survival [9]. Both RTOG 9802 and EORTC 22845, which did not attempt to answer the question of radiotherapeutic dose, utilized a standard dose of 54 Gy in 1.8 Gy per fraction [4, 10].

In light of these findings, radiotherapeutic doses ranging from 45 to 54 Gy appear to be effective, safe, and well tolerated in LGG patients and are currently recommended in the absence of a higher grade component.

## 26.3 Timing of Radiation Therapy

EORTC 22845 (also known as the "nonbeliever trial") randomized 314 patients with supratentorial low grade astrocytoma, oligoastrocytoma, and oligodendroglioma and incompletely resected pilocytic astrocytomas to early radiotherapy versus radiotherapy at time of progression. Exclusion criteria included optic nerve gliomas, brainstem gliomas, third ventricular gliomas, and most infratentorial gliomas as well as completely resected pilocytic astrocytomas. The primary endpoint of this study was OS and PFS. Overall survival was similar between the immediate radiotherapy and "wait and see" arms (7.4 vs 7.2 years, respectively; $p = 0.872$), but median progression free survival was significantly improved in the immediate RT group (5.3 vs 3.4 years, respectively; $p < 0.0001$). In the "wait and see" arm, 65% of patients received salvage radiotherapy. Of the patients who progressed, there was no significant difference in the rate of high grade transformation between the immediate and delayed RT arms (72 vs 66%, respectively) [10].

Interestingly, the rate of seizures, which is likely a marker for symptomatic intracranial recurrence, was significantly higher in the delayed RT arm vs the immediate RT arm (41 vs 25%, respectively; $p = 0.0329$) [10].

This study has been interpreted differently by "believers" and "non-believers" in immediate radiotherapy. Non-believers reference the lack of survival difference and equivalent efficacy of salvage radiotherapy to immediate RT. By delaying RT as long as possible in this often young patient group, it is argued, detrimental long term side effects of radiotherapy may be postponed or even omitted in a subset of patients. Believers argue that no meaningful quality of life endpoints were assessed in this trial, thus rendering ineffective the claim that earlier RT contributes to inferior QOL. Tumor progression is associated with inferior cognition and quality of life [11]. This is also evidenced by the increased seizure rate in the delayed RT group. Because evaluation with MRI was not required, patients were often understaged. Central pathology review demonstrated that 26% of patients had high grade tumors, although this was well balanced between the arms. Extent of surgical resection was evaluated by the surgeon intraoperatively with no post-operative imaging required [10].

In an attempt to determine which patients were more likely to benefit from adjuvant RT, Pignatti et al., examined clinical prognostic factors that were associated with increased risk of progression and decreased survival. In a post hoc analysis of EORTC 22844 and 22845, they found that pure astrocytoma histology, age $\geq$ 40, tumor $\geq$6 cm, tumor crossing midline, and baseline neurologic deficits were poor prognostic factors. Presence of more than two of these factors was associated with decreased median OS (3.7 vs 7.8 years) [12]. Other series have also demonstrated the powerful negative prognostic significance of age $\geq$ 40. Medberry et al., showed that median survival was 6.75 years in patients <40 and 1 year in patients with LGG diagnosed age $\geq$ 40 [13]. This was also demonstrated by Piepmeier et al., who found patients aged <40 years had a median survival of 8.7 years compared to 4.9 years in older patients [14]. Numerous series have identified extent of resection as an important prognostic factor as well [14–16].

RTOG 9802 defined high risk LGG as age $\geq$ 40 and any extent of resection and age < 40 and subtotal resection or biopsy. Patients that met these criteria were randomized to the immediate intervention arm of RT ± PCV. Patients not meeting high risk criteria were observed [4]. At present, patients who meet high risk criteria for 9802 are reasonable candidates to offer immediate as opposed to salvage radiotherapy. In the future, molecular and genomic characteristics will likely provide better insight as to which LGG should receive immediate adjuvant therapy.

The data are less clear regarding immediate adjuvant therapy for patients who do not have high risk LGG (i.e. age $\leq$ 40 and surgeon defined gross total resection). Shaw et al., examined patients who were enrolled on the observational arm of 9802 and found that overall PFS rates at 2 and 5 years were 82 and 48%, respectively. Predictive factors for poorer PFS included preoperative tumor diameter $\geq$ 4 cm, astrocytoma or oligoastrocytoma histology, and post-operative residual $\geq$1 cm as determined by MRI. Patients with 1–2 cm of residual disease had a 68% recurrence rate; >2 cm of residual disease was associated with an 89% recurrence rate [17]. These patients may potentially benefit from post-operative radiotherapy given their high propensity of recurrence.

## 26.4 Radiation and Chemotherapy

Current understanding of the role of systemic therapy in low grade gliomas has radically shifted with the practice changing long term results of 9802. Previous studies, such as the Southwest Oncology Group (SWOG) trial, which randomized patients with LGG to RT alone or in combination with lomustine, failed to demonstrate a survival advantage with the addition of systemic therapy. Ten year overall survival in the lomustine arm was 40% compared to 20% in the observation arm ($p = 0.7$) [18]. While this was statistically insignificant, this trial failed to meet accrual goals. In addition, short followup may have failed to capture long term benefits of systemic therapy that were demonstrated in later trials.

As mentioned previously, long term results of RTOG 9802 have altered current understanding of the benefit of chemotherapy in LGG. This study randomized 251 patients age ≥ 40 and any resection or age < 40 with less than surgeon defined gross total resection to adjuvant RT (54 Gy in 28 fractions) alone or RT followed by 6 cycles of adjuvant PCV (procarbazine, CCNU, and vincristine). The primary endpoint was overall survival. On initial report, there was no statistically significant difference in OS (63 vs 72%), but PFS was significantly improved with the addition of PCV (63 vs 46% at 5 years; $p = 0.005$) [4]. With extended followup, however, the median OS advantage of adjuvant PCV became significant (13.3 vs 7.8 years, $p = 0.03$). Interestingly, the OS and PFS did not begin to separate until after 2 years, which explains the nonsignificant difference in OS on the initial report in 2012. It is thought that perhaps *IDH1* non mutated and *1p19q* non codeleted tumors showed resistance to addition of alkylating agents, thus the initial failure of the curves to separate. These patients, who have a poorer prognosis than their mutated counterparts, were likely censored early which allowed the differential benefit of alkylating agents on the remainder of the population to become evident. In the long term followup of RTOG 9802, an attempt was made to differentiate benefit of chemotherapy by *IDH1 R132H* mutant status. While there was a pronounced difference in PFS and OS between the arms in the mutated subgroup, there were not enough wild-type *IDH1* patients to categorically determine the presence or absence of benefit to adjuvant PCV. When differentiating response by histology, both oligodendroglioma and oligoastrocytoma demonstrated a significant improvement in OS and PFS with the addition of PCV. Astrocytoma histology showed a trend for OS benefit ($p = 0.06$) in the PCV arm, however the absolute number of patients were relatively small. It is important to note that the differential benefit of PCV on histopathologic and molecular subgroups was an exploratory and hypothesis generating analysis. Thus at present there is not an identified subgroup of high risk low grade gliomas who did not benefit from PCV. Molecular classification remains strongly *prognostic*, but not yet *predictive* in low grade glioma [3].

Stupp et al. established the benefit of the oral alkylating agent temozolomide (TMZ) when given concurrently with RT in patients with high grade glioma [19]. TMZ has a more favorable route of administration and side effect profile compared to PCV. Thus, current investigation is aiming to establish the efficacy of TMZ in the

LGG population. RTOG 0424 was a single arm phase II trial which examined TMZ concurrent with RT followed by adjuvant TMZ for up to 12 cycles in 129 patients who had LGG with 3 or more risk factors for recurrence as per the Pignatti criteria (discussed in the previous section) [20]. Patients received 54 Gy in 30 fractions. Compared to historical controls, the addition of TMZ resulted in an increase in 3 year OS from 65 to 73.1% ($p < 0.001$) [20].

However, the efficacy of TMZ vs PCV in this population is unclear. The NOA-04 trial randomized grade III patients to RT or chemotherapy with PCV or TMZ. The study incorporated a crossover design for patients who failed initial therapy. So, patients who failed RT received chemotherapy and vice versa. TMZ had less toxicity than PCV. After median followup of 54 months, there was no difference in PFS or OS, but followup was short and the crossover design resulted in many patients receiving both RT and chemotherapy [21].

The CODEL trial is a currently accruing Phase III randomized trial examining RT followed by PCV vs RT + TMZ followed by TMZ vs TMZ alone with RT at progression in 1p/19q co deleted grade II and III patients. This trial was initially only open to patients with anaplastic glioma. After the results of the 9802 trial, this trial has now been expanded to include patients with low grade glioma, provided that they are 1p19q codeleted and meet high risk criteria as per RTOG 9802. Of note, the TMZ only arm has closed due to decreased OS and PFS compared to the immediate RT arms [22]. Results of the CODEL trial should provide insight into the equivalence of TMZ to PCV in lower grade glioma [23].

## 26.5 Target Volume Delineation

The conventional ICRU naming standard of Gross Tumor Volume (GTV), Clinical Tumor Volume (CTV), and Planning Target Volume (PTV) are used. Preoperative and postoperative MR imaging including the T1 post gadolinium enhanced, T2, and Fluid Attenuation Inversion Recover (FLAIR) sequences should be fused to the treatment planning CT. As these tumors do not typically enhance with gadolinium administration, the FLAIR and T2 weighted sequences are often the most useful. The advantage of FLAIR over T2 is the ability to suppress hyperintensity from CSF and extracellular fluid to aid in more accurate tumor delineation [24]. GTV includes any residual tumor on postoperative MRI as well as the post-operative bed. CTV expansion accounts for subclinical tumor spread and is typically a 1–2 cm margin around the GTV. Natural barriers such as dura, bone, brainstem and orbital structures may not need to be included if there is no clinical concern for spread to these regions. CTV expansion often does not cross midline unless there is a nearby natural route of spread such as the corpus callosum. Expansion to PTV is based on institutional standards but typically ranges from 3–5 mm based on immobilization, reproducibility, and presence of image guidance.

There are few studies addressing the appropriate CTV margin in LGG. Recommendations are derived from early clinical trials in LGG as well as

extrapolation from high grade glioma patterns of failure studies and clinical trials examining appropriate CTV margins [24]. Paulino et al., retrospectively evaluated 39 children who received radiation for LGG. CTV margins examined were either 1.0 cm around the GTV, 0.5 cm around the CTV, or a dose painting method whereby a 1 cm CTV received 50.4 Gy and the GTV received 41.4 Gy. There were seven failures, all of which occurred in the highest dose region. This suggests that CTV margins over 1.0 cm (and perhaps over 0.5 cm) may not be necessary. In the pediatric population, Marcus et al., prospectively evaluated fractionated stereotactic radiotherapy, which utilizes increased image guidance and immobilization to decrease the treated margin. Of the 81 patients that were treated, 50 had low grade astrocytoma. Margins included no CTV and a 2 mm expansion around GTV to form PTV. Mean dose delivered was 52.2 Gy in 29 fractions. There were no reported marginal misses in this report [25]. This trial was limited by a lack of a randomized arm and precision radiotherapeutic delivery which is costly, time consuming, and impractical when administered over prolonged treatment times in older populations. At present, reduction of CTV margins in radiotherapy naïve adult LGG is considered experimental should be evaluated prospectively [26].

## 26.6 Radiation Therapy with Photons: 3D–Conformal Radiotherapy, IMRT, Stereotactic Radiotherapy and Radiosurgery

The majority of low grade gliomas are treated with three-dimensional conformal radiotherapy techniques with the goal of the 95% isodose line covering 95–100% of the PTV. Typically, multiple non coplanar beams are used with the purpose of decreasing the amount of high dose in the brain outside the PTV. Beam shaping is performed using a multi leaf collimator (MLC). The advantage of 3D CRT over more advanced modalities is often better target coverage with decreased risk of marginal misses [27]. A potential disadvantage is the inability to spare high doses to nearby critical structures in certain anatomic locations.

Intensity modulated radiation therapy (IMRT) uses an inverse planning algorithm to modulate the high dose region to more tightly conform to the PTV. This is potentially beneficial particularly in complex shaped infratemporal, peri-chiasmatic, or peri-orbital tumors that have the potential to deliver excess dose to the cochlea, retina, brainstem, and optic apparatus. In large or multifocal tumors, high dose to the uninvolved brain may also be decreased. One disadvantage of this technique is increased integral (or low) dose that is spread around to the uninvolved normal brain. Another concern is the potential for marginal miss due to the sharp dose gradient outside the PTV. As mentioned in the last section, a retrospective analysis of 39 pediatric LGG patients receiving IMRT revealed no failures outside the high dose volume. This suggests marginal failures are likely not an issue with IMRT provided careful target delineation [26].

Stereotactic radiotherapy (SRT) and radiosurgery (SRS) utilize precise image guidance, immobilization, and treatment delivery techniques to deliver high doses of radiotherapy per fraction while employing small PTV margins. SRT is often delivered in 5 treatments, while SRS is given in a single treatment. Due to established safety of fractionated radiotherapy to doses of 45–54 Gy as well as the relative tolerance of most at risk normal structures to the dose, SRS and SRT are not considered standard treatment in LGG patients without previous radiotherapy. In addition, the large CTV margins required for LGG due to microscopic spread often result in treatment diameters that are not safe for large doses per treatment fraction. Roberge et al., analyzed 21 patients who received hypofractionated SRT for newly diagnosed low grade gliomas. A typical dose was 42 Gy, delivered over six fractions. While OS rates were comparable to other published results (71% at 10 years), three out of twenty one patients suffered late post-RT toxicity. Due the small number of patients in this study as well as selection bias for smaller tumors (median tumor diameter was 2.0 cm) and lack of prospective comparisons, SRT and SRS are not widely recommended for non-recurrent LGG in the adult population [28]. As mentioned in the previous section, SRT with 2 mm margins around gross disease was prospectively evaluated in pediatric LGG patients. Maximum tumor diameter was 5 cm. The treatment was well tolerated and all local recurrences occurred in the high dose arm. Unlike most SRT reports, this study employed conventional fractionation, and thus did not address the safety of giving larger doses per fraction over a shorter amount of time [29]. Nevertheless, highly conformal and precisely delivered radiotherapy that utilizes very steep dose gradients is a reasonable consideration in pediatric patients with small tumors where minimization of neurotoxicity is a concern.

In the recurrent or previously irradiated setting, SRS and SRT appear to be reasonable options. Safe doses of single fraction radiosurgery were established in RTOG 90–05, which evaluated patients with brain metastases or recurrent gliomas who had received prior partial or whole brain radiotherapy. Maximum tolerated doses were 24 Gy for tumors ≤2.0 cm, 18 Gy for tumors 2.1–3.0 cm, and 15 Gy for tumors 3.1–4.0 cm [30]. Appropriate therapy for recurrent gliomas will be discussed in a future section.

## 26.7 Proton Therapy

Given the concern for integral dose to the brain and hippocampus resulting in long term neurocognitive deficits, there has been mounting interest in the utility of proton radiotherapy to treat low grade gliomas. Unlike photon therapy, which continues to distribute exit dose far beyond the radiotherapeutic target, unique physical characteristics of protons result in maximal distribution of dose at a prespecified depth with virtually no exit dose observed. This phenomenon, termed the Bragg Peak, results in distribution very little integral (or low) dose to regions of the brain beyond

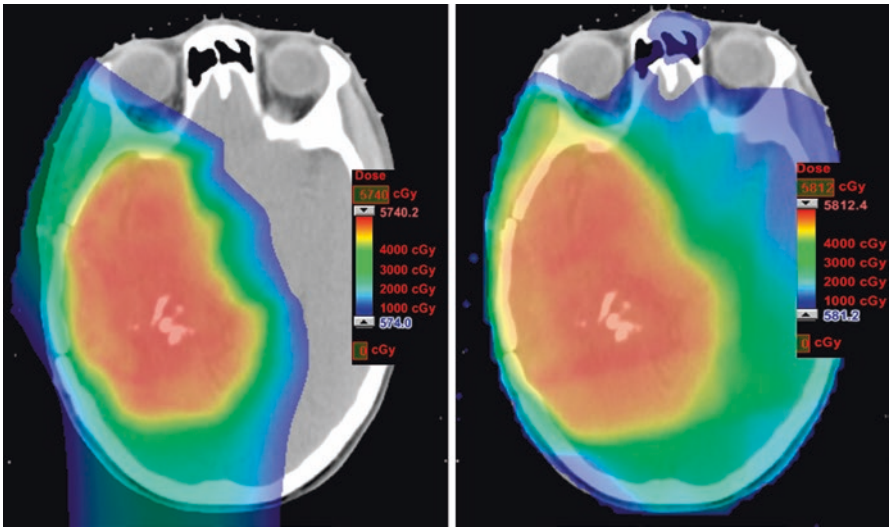


**Fig. 26.1** Proton radiotherapy plan (*left*) compared to a photon plan with IMRT (*right*). The proton plan demonstrates decreased low dose spill (green and blue colorwash) compared to the IMRT plan

the target. This is potentially of great benefit in the low grade glioma population given that these patients are often young and have prolonged life expectancies. Figure 26.1 shows comparative radiotherapy plans between protons radiotherapy and IMRT in a patient with anaplastic oligodendroglioma. Low dose spill to the brain outside of the PTV is drastically reduced with the proton therapy plan. Although no published randomized data comparing photon and proton radiotherapy for LGG currently exist, there are smaller series demonstrating the safety and potential dosimetric advantage of protons.

Greenberger et al., examined outcomes in 32 pediatric LGG patients who received proton radiotherapy. The GTV with a 3–5 mm expansion for PTV was treated to a mean dose of 52.2 $Gy_{RBE}$. PFS at 6 and 8 years was 89.7 and 82.8%, respectively. Overall, there was not a significant decline in neurocognitive status, but patients age < 7 and with significant dose to the left temporal lobe were more likely to suffer decline [31]. Dennis et al., performed a dosimetric exercise in LGG patients and demonstrated an estimated increased risk of secondary malignancy with IMRT compared to protons by twofold [32]. Shih et al., performed a cohort study of 20 adult patients treated with proton therapy for LGG (54 $Gy_{RBE}$ in 30 fractions) and found a PFS rate of 85% at 3 years which dipped to 40% at 5 years. There was no overall decline in neurocognitive functioning or quality of life over a 5 year interval [33]. There are 2 currently accruing single arm phase II trials assessing endocrine and neurologic sequela in LGG patients treated with proton therapy [34, 35]. At present, proton radiotherapy is a reasonable option in young children where dose to the hippocampus and temporal lobe may be spared compared to IMRT.

## 26.8 Measuring Response to Radiotherapy

While robust response assessments tools have been validated in high grade glioma patients, standardization of response criteria in low grade glioma patients has been more difficult. This is due in part to the relative rarity of LGG compared to HGG and the variability of radiotherapy timing after definitive resection. Accurate assessment of response to radiotherapy is vital in order to distinguish between recurrence, radiation necrosis, or pseudoprogression. The Response Assessment in Neuro-Oncology (RANO) group published response assessment guidelines in LGG and defined progression by the following: (1) increase in enhancement or development of new lesions, (2) 25% or more increase in T2 or FLAIR abnormality from baseline in the presence of stable or increasing corticosteroid dose, (3) clinical deterioration in the absence of decreasing steroid dose or reasons not clearly attributable to the tumor. Radiographic response of the T2 or FLAIR abnormality compared to baseline imaging is the major differentiator between measuring complete response (no abnormality), partial response (≥50% reduction in area of the tumor), minor response (25–50% reduction) and stable dose (<25% reduction or <25% growth) [36].

Ducray et al., examined tumor response kinetics in 39 LGG patients after radiotherapy. Median tumor diameter (MTD) decrease was observed in 37 out of 39 patients and duration of MTD was 1.9 years. Patients whose tumors expressed *1p19q* codeletion demonstrated a longer duration of MTD decrease (5.3 vs 1 years respectively). MTD was found to occur in two phases: an initial rapid decrease followed by a second more gradual phase of decrease. Patients with an initial rapid MTD decrease of over 7 mm/year had an inferior prognosis and shorter MTD which is likely due to more biologically aggressive disease [37].

Approximately 20% of LGG patients develop pseudoprogression after radiotherapy. Lin et al., found that presence of a *1p19q* codeletion in radiated oligodendroglioma and oligoastrocytoma patients conferred a 10 fold *decrease* in the risk of developing pseudoprogression. This is in contrast to high grade glioma, where MGMT methylation is associated with an *increased* risk of pseudoprogression [38]. While the mechanism behind this is not entirely clear, pseudoprogression is thought to be possibly correlated to p53 expression, which is typically overexpressed in MGMT methylated high grade gliomas and underexpressed in 1p19q codeleted low grade gliomas [39].

## 26.9 Reirradiation for Recurrent Tumors

When recurrence is suspected, a biopsy is recommended when safe. In a report from Mayo Clinic, 51 previously irradiated LGG patients with suspicion of recurrence underwent biopsy of which 9% were found to either have radiation necrosis or radiation induced sarcoma. Approximately 2/3 of patients found to have recurrent glioma had transformation to high grade tumors [40]. Systemic therapy alone is a valid

treatment option for recurrent tumor after radiotherapy, particularly if the interval from radiotherapy is short, the recurrence is near previously irradiated critical structures, or if the area of recurrence is very large. In chemotherapy naïve patients, salvage systemic therapy appears to be beneficial, particularly in *1p19q* codeleted tumors [41]. However, the efficacy of salvage systemic therapy in patients who received TMZ or PCV initially is less clear [42].

Decisions regarding which patients are ideal for reirradiation should be made as part of a multidisciplinary discussion and take into account expected toxicity of treatment and life expectancy. To decrease the risk of radiation necrosis, often concurrent and adjuvant bevacizumab are used with reirradiation [43].

SRS and SRT are often utilized in previously irradiated patients due to the need to avoid large areas of high dose. In addition, concern for failure outside the gross tumor volume is reduced in patients with recurrent disease, thus justifying the need for reduced or no CTV margins. Ideal candidates for these techniques would include well localizable disease on imaging and low volume area of recurrence. The group from University of Pittsburgh reviewed their experience in treating recurrent grade II astrocytomas and oligodendrogliomas with single fraction radiosurgery. The astrocytoma population was treated to a median dose of 14 Gy and had a 5 year PFS of 54%. Predictors of improved PFS included tumor volume < 6 cc and doses ≥15 Gy [44]. The oligodendroglioma population was treated to a median dose of 14.5 Gy and had a 5 year PFS of 82%. Patients with *1p19q* codeletion had improved PFS [45]. It is important to understand that these are small retrospective studies and only a subset of patients received prior irradiation.

Fogh et al., published results of 22 patients who received salvage reirradiation for LGG. The GTV (without a margin for PTV) was treated to a median dose of 35 Gy in daily fractions of 3.5 Gy. Clinical improvement was noted in 50% of patients [46]. This schema was also evaluated prospectively in high grade glioma patients as part of RTOG 1205, with final results pending [47].

Combs et al., examined 63 patients with recurrent low grade glioma who received reirradiation using fractionated SRT. Median dose was 36 Gy given in 2 Gy daily fractions prescribed to the tumor and a 1 cm margin. Median PFS was 12 months and OS was 24 months with no serious toxicities reported [48].

## 26.10 Brainstem Gliomas

Brainstem gliomas are more commonly diagnosed in the pediatric patients. High grade brainstem gliomas are often found within the pons and present as a diffuse infiltrative mass often involving large portions of the brainstem [49]. Lower grade lesions tend to present as more focal and dorsally exophytic [50]. Often brainstem LGG have an indolent clinical course followed by sudden onset of cranial nerve palsies. Due to the eloquence of the brainstem, definitive fractionated radiotherapy is the mainstay of treatment. The standard dose is 54 Gy delivered in 1.8–2 Gy fractions. Studies investigating altered fractionation including

hyperfractionation with dose escalation and hypofractionation have not demonstrated a benefit over conventionally fractionated radiotherapy [51, 52]. GTV is optimally defined on T2 or FLAIR imaging with a 1–1.5 cm margin added to form CTV and an institutional margin for PTV. Combs et al. examined fractionated SRT in adults with brainstem glioma (median dose 54 Gy using 1.8 Gy per fraction). Eight percent of patients received FSRT for re-irradiation. CTV margin was not used. Treatment was well tolerated with a median OS of 81 months and median PFS of 52 months [53].

## 26.11 Future Directions and the Impact of Molecular Classification

Perhaps no other malignancy is currently undergoing a more radical change in classification than gliomas. Passaw et al. performed a molecular analysis of grade II-IV gliomas and found that *TERT* mutation (which encodes telomerase), *IDH* mutation, and 1p/19q codeletion were powerful predictors of survival. So called "triple positive" patients had the highest survival. On multivariate analysis, "triple negative" patients had a hazard ratio for death of 3.74, while *TERT* mutation alone conferred a hazard ratio of 11.74. Anaplastic histology conferred a more modest hazard ratio for death of 1.49, when compared to grade 2 tumors [54]. The Cancer Genome Atlas Research Network performed genomic analysis of grade II and III gliomas and found *IDH*, *1p/19q*, and *TP53* status to be more predictive of outcomes than grade. In fact, LGG histologies that were IDH wild type had molecular and clinical behavior patterns similar to glioblastoma [55]. This has enormous implication for therapy. RTOG 9402 randomized patients with grade 3 gliomas to either RT or PCV followed by RT. On initial report, no survival benefit was seen. However upon longer followup, there was a profound survival difference in the *1p/19q* codeleted subgroup favoring PCV (14.7 vs 7.3 years respectively). These results mirror those of RTOG 9802 and underscore the similarities of behavior of grade 2 and grade 3 gliomas in subsets that harbor beneficial mutations [56]. Many have taken to referring to grade 2 and 3 gliomas with a favorable molecular profile as "lower grade gliomas." Future trials may enroll so called "triple negative" or *TERT* mutated lower grade gliomas in trials evaluating glioblastoma patients, given that traditional therapies are proving less effective in this population. Conversely, patients whose molecular profile confers the longest disease free survival interval may be more suited to treatment deintensification. In regards to radiotherapy, this latter group of patients is the most likely to suffer long term neurocognitive effects of radiotherapy given their long life expectancy. These are potentially the ideal patients to receive proton radiotherapy. A randomized trial addressing the benefit of proton therapy in this group is currently under development through NRG Oncology.

It is important to understand that treatment stratification based on molecular profiling has not yet been reported prospectively. Examinations of predictive and prognostic capabilities of *IDH, TERT,* and *TP53* have only been examined retrospectively

or as an unplanned subgroup analysis of prospective studies. Thus, outside the auspices of a clinical trial, genomic classification should not be used to guide clinical decision-making.

Current understanding of low grade glioma is changing at a rapid rate. Perhaps the reason that the role of radiotherapy has been so poorly understood is that our understanding of the biology of this disease has been limited. It is imperative that the field of radiation oncology understand the new landscape of molecular classification in order to better tailor adjuvant therapies to patients.

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# Chapter 27
# Functional Rehabilitation in Patients with DLGG

**Guillaume Herbet and Sylvie Moritz-Gasser**

**Abstract** A relevant and ethical management of DLGG patients can't refrain from taking into account cognitive disorders and proposing, if need be, a specific program of cognitive rehabilitation, to allow patients recovering—or maintaining—the best level of quality of life as possible. The slow-growing and infiltrating character of DLGG makes their associated cognitive disorders particularly amenable to rehabilitation, by potentiating or even constraining the mechanisms of functional brain reorganization within complex large-scale neural networks.

**Keywords** DLGG • Cognitive disorders • Cognitive rehabilitation • Distributed inter-connected networks • Functional brain reorganization • Neural plasticity • Quality of life

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## 27.1 Introduction

Patients with DLGG may present with functional impairments in various degrees, following especially lesion location and size, disease course and treatments. The term "functional" encompasses everything related with human functioning. Here we will focus on non-pharmacological rehabilitation of cognitive functioning, its efficacy and its consequences on the level of Quality of Life (QoL). Sensory-motor rehabilitation is managed either by physiotherapists, occupational therapists or even by orthoptists, for example in case of hemianopia. As mentioned in our previous chapter, cognitive functioning encompasses language, attention, memory, executive functions, to which we may add social cognition.

Recent advances in therapeutic strategies allow increasing significantly the duration of survival in patients with brain tumor. Nevertheless, during these disease-free periods, most of the patients experience cognitive disorders, which may negatively influence the QoL. Moreover, given that DLGG occurs mainly in young adults, with busy socio-professional activities, a relevant and ethical management of DLGG cannot refrain from taking into account cognitive disorders, whatever their importance and their origin. Indeed, cognitive disorders, which may go from slight ones to broad impairments in different cognitive functions, might be caused not only by the tumor itself, but also by related epilepsy and treatments [1]. Disorders may be related to the location of the tumor as well as to disconnection mechanisms between functional networks induced by probable disturbances in functional connectivity due to the tumor [2]. Thus, disorders are often diffuse, and not necessarily as they would be predicted by tumor location. Moreover, these disorders are different, for a given location, from those secondary to strokes [3]. Therefore, in the context of patient care as well as in the context of longitudinally follow-up, we absolutely have to assess periodically the cognitive functioning of DLGG patients (see Chap. 18) and to propose, if need be, a specific program of cognitive rehabilitation, in order to prevent or treat cognitive disorders. It is worth noting that we may propose this program not only in patients with cognitive disorders highlighted by cognitive assessments but also in those who have subjective complaints concerning cognitive functioning, even if not objectivable by neuropsychological evaluations.

Although studies on cognitive rehabilitation have already a long history in neuropsychology, from the early twentieth century in the aftermath of World War I [4], its efficiency is currently a wide matter of debate because, despite early and sometimes intensive therapies, cognitive or neurologic disorders may persist chronically [5]. Several lines of explanation can be advanced to account for this lack of positive outcomes, from methodological, institutional to more neurophysiological considerations. With regard to the latter, it was long believed that the poor functional recovery could be explained by a limited potential of the brain to compensate from lesions [6]. However, observations from DLGG patients show in an exemplary manner that this statement may not be true. Indeed, it is now well acknowledged that cognitive disturbances are limited in patients harboring a slow-growing tumor, despite sometimes extensive lesions and resections [6]. Among the most striking clinical observations, it has been, for example, demonstrated that extensive frontal lobecto-

mies did not induce any cognitive or behavioral dysexecutive syndrome [7] or that the surgical excision of Broca's area, a brain region thought yet as crucial for language processing, did not induce permanently a productive aphasia [8, 9]. These provocative findings have led to revise the conception according to which the potential of brain plasticity is relative in the case of brain injury as not allowing a complete and efficient recovery. In the same way, they have challenged the conventional conceptions of neuropsychology which are not able to explain these important functional reorganization phenomena. For this reason, alternative view of anatomo-functional organization, according to which brain function is the result of functional orchestration and integration of large-scale and distributed networks has emerged. The heuristic value of this framework is much higher to account for functional plasticity than the functional specialization framework.

If studies focusing on functional rehabilitation in patients with brain tumor are scarce, especially concerning cognitive rehabilitation (and even more concerning language rehabilitation), the few we found underline that rehabilitation interventions are associated with significant improvements in functional status (for a review, see [10–17]). These improvements in functional outcomes induced by rehabilitation justify, following some authors, the *delivery of rehabilitation services to brain tumor patients* [18, 19].

## 27.2 Theoretical Approaches and Mechanisms of Recovery

Cognitive rehabilitation encompasses all the modalities of nonpharmacological interventions to treat or prevent cognitive disorders. These interventions are administered to the patient by a speech-therapist and/or a neuropsychologist. Two kinds of mechanisms underlying the recovery of cognitive functioning are described in the literature: compensation and restoration [20–22]. Their effectiveness has been addressed in several studies, concerning different brain injuries (traumatic, strokes, and more scarcely tumors) [23, 24]. Compensatory and restorative processes participate both in functional brain reorganization, and may be induced by different strategies of cognitive rehabilitation. These different settings may be divided in two groups.

In the setting of compensation strategies, patients are taught to make use of external and internal strategies in order to bypass their cognitive disorders. Thus, they learn to achieve a given cognitive task in a different way as before by reorganizing functional networks in intact brain areas, close or distant to the lesion [25].

In the setting of restoration strategies, patients are taught to retrain specific cognitive skills thanks to repetitive stimulation, in order to restitute at least partially the prior cognitive functioning. Thus they learn to achieve the same behavior in a similar way as before, by enhancing residual functional capacities [26].

In any case, these strategies are not mutually exclusive, and actually, the mechanisms of recovering induced by the use of these different strategies remain unclear, certainly because no program of cognitive rehabilitation is based exclusively in one or the other strategy.

What one has to keep in mind when managing a patient with cognitive disorders is that, on the one hand, cognitive functions interact with each other and that, on the other hand, a given cognitive deficit may be induced by a disturbance of different functional overlapping brain systems [27]. Then we assert, borrowing from Luria's thought [28], that a relevant and appropriate program of cognitive rehabilitation may be outlined only with a specific and accurate cognitive assessment. Indeed, we have to be able to highlight intact kinds and levels of cognitive functioning as well as damaged ones, in order to plan a program of cognitive rehabilitation. Moreover, this clinical highlighting must be confronted with theoretical models of cognitive functioning, to understand at what level the disturbance is located.

The brain is by nature highly plastic. In humans, development, rapid learning or quasi-spontaneous flexibility toward environment are perhaps the most striking and visible evidence of this high potential in normal circumstances. In neurophysiological terms and at the macroscopic level, this means that the neural networks sustaining brain functions, although their general skeletons are probably already formed in childhood [29], are constantly modified and reshaped as one goes along the experience [30, 31]. This continuous process allows us to maintain and even improve the quality and the efficacy of our interactions with the environment. The brain is a dynamic evolving entity.

In the case of brain injury, trying to take full advantage of natural brain plasticity is the basic principle on which cognitive rehabilitation is based. In this context, the notion of plasticity slightly differs since it refers to the capacity to the brain to compensate for lesions. But, in many ways, plasticity induced by the lesion looks like natural plasticity [32]. In this sense, intensive cognitive or behavioral training is thought, at least to some extent, to constrain what the brain does naturally. Findings from natural plasticity studies in animals and humans have demonstrated that the acquisition of a new skill or the development of a cognitive expertise induced morphologic changes in the brain, sometimes very rapidly, minute-scaled [33, 34]. Furthermore, neuroanatomical reorganizations (i.e. rewiring) have been identified after brain injury in humans [35], facilitating probably the functional recovery [36]. This means that the brain is not hardwired but can be, in some extent, "rewired" [37]. How to help the brain to change or even to create new neural representations to support brain functions following damage is a key issue for cognitive rehabilitation.

## 27.3 The Particular Case of DLGG Patients

### *27.3.1 Slow-Growing Tumor as a Paradigmatic Model to Study Functional Plasticity*

Concerning the particular case of cognitive rehabilitation in DLGG patients, we have to keep in mind the slow-growing and infiltrating character of DLGG, which make their associated cognitive disorders particularly amenable to rehabilitation. Indeed, on the one hand, by infiltrating cortical and sub-cortical structures, the tumor

may destroy some of them but also only displace others and then residual function may be maintained [3, 38]. On the other hand, by growing slowly, the tumor induces a reactive reshaping and reorganization of functional networks [39]. It is precisely this key feature that may explain why cognitive or neurologic disorders can be more easily compensated as one goes along the disease compared to acute events like stroke [6]. In this respect, neurophysiological studies are really informative. Studies using functional magnetic resonance imagery (fMRI) paradigms have demonstrated different patterns of functional reorganization at the cortical level, showing that the brain recruits alternative areas not previously implied for the expression of cognitive function. Among these functional strategies, ipsilateral, perilesional, as well as homonymous contralateral recruitments have been described (for a review, see [6]). In this context, DLGG offers a unique and exciting opportunity to better understand both the dynamics underlying functional plasticity and the neural implementation of cognitive processes, valuable data for cognitive rehabilitation.

Thus, cognitive rehabilitation might on the one hand enhance residual functional capacities, and, on the other hand, potentiate the spontaneous functional brain reorganization.

### *27.3.2 Linking Cognition to Functional and Anatomical Connectivity*

The dynamic and holistic organization that assumes functional plasticity finds its corollary in the studies of cerebral connectivity in normal brains. For over than 10 years, new technics of data analyses more and more sophisticated, from functional and morphologic imaging, have emerged. In this setting, the idea according to which the brain is composed of complex large-scale neural networks became dominant. However, this view was already present in the middle of last century with Daniel Hebb [40] who suggested that high-level human functions are determined by the activity of complex neural networks composed of local and distant areas across the whole brain.

Data from spatial reconstruction of anatomical connectivity by means of diffusion tensor imaging, a technique that measures the diffusion of water molecules through cerebral tissues, is perhaps the best illustration of this complexity. The visualization of connections between distant brain areas via the multiple white matter bundles (projection or association fascicles, U-shaped fibers) is really demonstrative about this organization [41]. Although these data are by nature anatomic and give no direct functional information, studies using direct electrical stimulations during awake neurosurgery [39], which induce transient disconnection syndrome, have proved their essential role for the complete and normal expression of functions. In neuropsychology of strokes, injury of these subcortical fascicles can provoke severe cognitive disturbance, hardly compensable [42, 43]. In this context, it has been proposed that these subcortical structures are crucial for functional plasticity [44, 45]. If so, we should find structural changes of these white matter fascicles in

reaction to tumors and neurosurgery, and correlate their markers (i.e. fractional anisotropy and mean diffusivity) to cognitive functions. However, to the best of your knowledge, there is for the moment no study with DLGG patients in which structural integrity and changes have been assessed in a systematic manner by the means of a longitudinal design (pre-/postsurgical). As a consequence, this type of structural plasticity remains to be demonstrated in the framework of this brain pathology. Yet, recently works in the field of the surgery of refractory temporal epilepsy are very interesting in this respect. For example, the team of Duncan [46] has found, using a pre-/postsurgical design, DTI, and language assessment, a correlation between the score obtained in verbal fluency after the surgery, and an increase of fractional anisotropy in several regions including subcortical structures such as corona radiata. In other words, these results show that the degree of language recovery is related to structural changes implying some white matter pathways. These provocative data, by demonstrating for the first time that we can call functional subcortical plasticity, open exciting perspectives in the field of brain tumors.

In addition to the fact that DTI can be combined with functional data like cognitive scores, other methods are particularly promising, especially those implying functional connectivity computing, to track the phenomena of plasticity induced by the tumor and its resection. Functional connectivity (FC) is defined as "the correlation between spatially remote neurophysiological events" [47]. This means that temporal statistical interdependencies can be found between several cortical areas composing the neural networks sustaining cognitive functions.

In several studies, abnormality of FC has been correlated with cognitive disorders, demonstrating that temporal desynchronization (hypo- or hypersynchronization) between distant brain areas is particularly deleterious for functions. It is for example the case in neurodegenerative diseases where several and distinct patterns of functional alteration within the different networks can be found and linked to neuropsychological phenotypes (for a review, see [48]). For example, memory loss has been related to FC decrease in Alzheimer's disease [49]. In the field of brain tumor and traumatic brain injury, several works have studied the impact of brain damage on FC (see Chap. 21). Bartolomei and colleagues [2] have shown using resting MEG (magnetoencephalography) paradigm that synchronization was altered in a population of patients harboring a brain tumor. In a subsequent study, using the same experimental design, cognitive disturbances were shown to be correlated to abnormality of FC [50]. Very recently, FC-based resting MEG at the level of the tumor was evaluated before brain surgery. It was found that decrease resting-state FC was highly predictive to the lack of functionality of this region as evaluated by means of direct electrical stimulation during awake surgery, suggesting that FC is a good measure of the integrity of brain functions [51].

In the same vein, patients with TBI show altered FC [52]. Nakamura and colleagues [53] demonstrated using a resting-state fMRI that just after the injury rsFC was disturbed and that, during recovery, this disturbance tended to normalize. A more recent study showed that cognitive complaints were predictive of altered FC in the default mode network in semi-acute TBI patients [54]. Furthermore, Castellanos and his team [55] have evaluated FC-based rsMEG in a population of TBI patients. Data were recorded immediately following the traumatic event and after a specific cognitive rehabilitation program. The authors found that neuropsychological performances

significantly improved after treatment. Interestingly, this cognitive recovery was correlated with the reorganization of neural networks as indexed by the comparison between the pre- and posttreatment. These results suggest that functional recovery is related to the reorganization/reconfiguration of neural networks.

## 27.4 Aims of a Cognitive Rehabilitation

### *27.4.1 Clinical Aims*

Of course, the main goal we aim to reach when proposing a cognitive rehabilitation is to bring the patient to recover a satisfactory level of cognitive functioning. The question is as follows: what is a *satisfactory* level of cognitive functioning? We think that there is no unique answer to this question and that it depends on the patient, his personality, and his expectations. Thus, the program of cognitive rehabilitation has to be established taking into account not only the objective assessments of cognitive functioning but also the subjective complaints and the expectations of the patient. In this state of mind, we approve and recommend applying the following proposal, borrowed from Kurt Goldstein's works [56–58], a precursor of great influence in cognitive rehabilitation:

- Recognition of the individuality of patients
- Need for standardized assessments, and recognition of their limitations
- Importance of working with the problem of fatigue
- Careful observation of patients' response to the program
- Importance of periodical reevaluations and long-term follow-up
- Need to connect cognitive rehabilitation to personal and socio-professional activities.

The relevance of taking into account the patient in his wholeness, and not only in his cognitive functioning, has been confirmed in a more recent study [59].

Moreover, the patient has to be informed about our objectives and how we project to reach them, in order to establish a real therapeutic alliance.

### *27.4.2 Understanding Functional Network Reshaping to Constrain Brain Plasticity: A New Door to Cognitive Rehabilitation*

Taken together, the observations mentioned above suggest that brain injuries impact the functional coupling and integration between distant brain areas and that this alteration can be related to cognitive disorders. However, some results in studies with TBI patients show also that the spontaneous reorganization of neural networks is correlated in some extent with cognitive improvement. More interesting, cognitive rehabilitation with significant functional outcomes helps the brain to reorganize its functional networks [54]. Although these seminal results remain to replicate,

they are particularly promising for cognitive rehabilitation. Understanding the dynamic of neural network reorganization and the optimal functional reconfigurations may have several important implications for the elaboration of cognitive rehabilitation strategies (e.g. which networks should be targeted).

If the first studies concern mainly patients with TBI, we believe that the field of slow-growing tumors may provide crucial data on how the brain can maintain a functional homeostasis, despite extensible lesions. As mentioned above, cognitive disorders in DLGG patients are classically limited before the surgery, what is particularly challenging for the brain. Through a specific cognitive management, these same patients recover most of the time after the surgery on the condition that functional structures are preserved, especially some elements of subcortical connectivity [60, 61] essential in maintaining functional communication between distant brain areas. Consequently, how the brain changes the typology of its neural networks to continue sustaining brain functions despite extensive lesions and resections is an important step in cognitive neurosciences, both at the fundamental and clinical level.

In this setting, coupling brain functional and anatomical connectivity analyses with neuropsychological assessments in a pre-/postsurgical experimental design is essential to shed light on the neurophysiological underpinnings of what may be the optimal functional reorganizations. VBM-based and dTI-based analyses, if correlated with cognitive profiles, can provide valuable information on cortical and subcortical structural plasticity and how this latter is related to a good recovery at the behavioral level. Functional connectivity analyses at rest or during behavior tasks are essential to grasp the functional interactions between brain areas within neural networks and their efficiency for cognitive functions. These systematic analyses can allow, after a time, to find neurophysiological markers of optimum recovery.

It could help, at the clinical level, to anticipate, for example, the risks of cognitive decline after the surgery and to plan *a priori* hyper-individualized cognitive rehabilitation programs adapted to individual functional architectures identified previously as at risk. It could otherwise incite clinician neuropsychologist/speech therapist to implement, in some patients, preoperative cognitive training to constrain functional networks to reshape in a better way and minimize cognitive disturbances after the surgery. More indirectly, this knowledge could participate to the fine-grained selection of cognitive tasks for cognitive programs, in the extent that they will be known to stimulate the desired functional networks.

## 27.5 Functional Rehabilitation in the Context of DLGG Patient Care: Peri-Operative Rehabilitation

### *27.5.1 Postoperative Rehabilitation*

In the context of perioperative DLGG patient care, a postoperative cognitive rehabilitation has to be systematically administered to the patient. Indeed, as detailed in our previous Chap. 18, most of the time, the immediate postoperative cognitive assessment (between 3 and 5 days after the surgery) highlights disorders related to

the brain area operated on [39] but also related to disconnection mechanisms between functional networks [2]. Immediate postoperative clinical presentations are various and may go from slight disorders to broad impairments in cognitive functioning.

Even if these disorders are mainly transient, due to the postoperative edema, and probably to the functional reorganization in progress induced by the surgery itself, which may spoil transiently the functioning of a given functional network, all patients should benefit from a specific and intensive program of cognitive rehabilitation—performed right from their return at home by a speech therapist specialized in this management in order to potentiate spontaneous functional reorganization and thus to recover the best level of cognitive functioning as possible in a short delay.

Apart from "site-specific" disorders (e.g. articulatory or initiation disorders after a resection close to motor planning areas), we may observe different kinds of language and other cognitive disorders. Concerning language, the immediate postoperative assessment may highlight typical clinical presentations of various types of fluent and nonfluent aphasia. In any case, patients present always with slowness in information processing, associated with attention, memory and executive functioning disorders.

Thus, in contact with the professional who managed the inpatient, and thus administered cognitive evaluations (see our previous chapter), the specialized speech therapist establishes an individualized program of rehabilitation, depending on cognitive disorders highlighted by the immediate postoperative evaluation.

In all cases, the program of cognitive rehabilitation will be *intensive* and *specific*, at least during the 3 months following surgery. As much as possible, one should plan five sessions weekly, of which duration will depend on patient fatigue.

This program will first focus on the most prominent disorders observed. For instance, in the case of an akinetic mutism due to resection of the supplementary motor area, we will retrain intensively motor initiation of speech. But simultaneously, we will propose to the patient compensation training and retraining of attention, memory and executive functions skills. Indeed, clinical studies [14] showed that improving the functioning of other cognitive functions may enhance the recovery of a given damaged function. This assertion is easily explainable by the fact that all cognitive functions interact with each other, and that an efficient cognitive processing is possible, thanks to the involvement not of isolated brain areas but of parallel and distributed cortico-subcortical networks.

Alternatively, it is conceivable that, for some patients, additional therapies might be added. There is a growing literature on the use of transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (TdCS) to improve functional outcomes, notably in patients with focal lesions like strokes. Some benefic effects have been significantly obtained for motor, language and visuospatial functions (for a review, see [62, 63]) even if further controlled studies are needed to assess the effects of these techniques.

From this perspective, given that tumors impact on functional connectivity and integration in patients, especially in those presenting with cognitive disorders, it could be interesting to cumulate TMS sessions and cognitive stimulations to con-

strain the brain to reshape neural networks that have been identified previously as dysfunctional. TMS may have a relative long-term effect on the functionality of a given brain region. In this state of mind, it is reasonable to think that the transitory inhibition of dysfunctional networks during cognitive stimulations might help the brain to recruit alternative networks, to remap its connections in an alternative manner, and thus to accomplish the cognitive processes required to success the tasks during cognitive training. This might be a good strategy for some patients before the surgery.

As mentioned above, the aim of the program of cognitive rehabilitation will be the best recovery as possible of cognitive functioning, following patient expectation. Thus, periodical (twice a year) reevaluations of cognitive functioning and subjective complaints will be administered to the patient.

The end of cognitive rehabilitation will be decided, in common with the therapist and the patient, when both of them will consider that the best level of QoL is reached, thanks to cognitive recovery, and/or, eventually to the use of compensatory strategies (e.g. use of external aids, mnemonics, diaries, computer, prevention of distractions, and adaptation of the environment…).

It is worth noting that the therapist has to listen the complaints of the patient. Indeed, even if cognitive evaluation highlights normative scores, he/she has to consider the level of satisfaction of the patient regarding his QoL, including social and familial relations, return to work, and personal activities.

### *27.5.2 Toward a Preoperative Rehabilitation?*

In some cases, depending on the results of the preoperative cognitive evaluation and on the location and the volume of the tumor, it may be useful to propose a program of cognitive training to DLGG patients before surgery, in order to constrain functional networks to reshape in the best way and to prevent cognitive disturbances that may occur after surgery—in such a way that postoperative recovery might be the more complete and rapid as possible, by preparing the functional networks that will be the most suited to sustain cognitive functioning.

## 27.6 Functional Rehabilitation in the Context of Longitudinal Follow-Up

Of course, cognitive rehabilitation is not only intended for patients who undergo a surgical management. It has to be considered also in the setting of longitudinal follow-up, depending on the results of periodic cognitive assessments and complaints inventory, with the same aims as those mentioned above, to allow patients maintain ing the best level of QoL as possible.

## 27.7 Conclusion: Toward a Hyper-Individualized Approach of Cognitive Rehabilitation

Cognitive rehabilitation is an essential step in the clinical care of patients with brain injury. In the case of DLGG surgery, it helps the patient to reach its pre-surgical status and, even sometimes, to improve it and to resume the most quickly as possible a normal socio-professional life. To be the more efficient as possible, functional rehabilitation in DLGG patients has to be led keeping in mind both the interconnectivity of cognitive functions as well as the brain functional organization in parallel and distributed interconnected networks. The slow-growing and infiltrating character of DLGG makes their associated cognitive disorders particularly amenable to rehabilitation. Its main goal is to enhance residual functional capacities, to potentiate spontaneous functional brain reorganization, and even to constrain some patterns of neural functional reshaping by proposing specific programs of rehabilitation to each patient—depending on the results of cognitive assessments and complaints inventories, in order to allow them recovering the best level of quality of life as possible. Neuropsychological profiles have to be precisely delineated before and after the surgery in a systematic manner. By this method, we will be able in the future to better understand and anticipate at the individual level the risks of cognitive surgery after-effects. These predictive data will help us to put forward hyper-individualized strategies of cognitive rehabilitation and also to build more adapted tests for awake surgery, especially for high-order cognitive functions.

Advances in cognitive neuroscience will be probably crucial in this clinical endeavor. Brain plasticity sciences have extensively learned from clinic of DLGG. By inducing impressive functional reshaping, DLGG can be seen as an exemplary paradigm to study and understand the principles that govern both functional plasticity and anatomo-functional organization of neural networks underlying cognitive functions. In a modern view, higher-order cognitive functions are thought as the result of sophisticated interactions between complex long-range and distributed cortico-subcortical neural systems. It is precisely this holistic organization that might explain the important functional reorganization phenomena in the case of slow-growing lesions such as DLGG. In this setting, the major development of data analyses from functional and morphological imaging, by extracting more and more precisely the temporal and spatial characteristics of such neural networks, will open new doors to cognitive rehabilitation. Indeed, coupling multimodal imaging with fine-grained cognitive evaluations in a pre-/postsurgical design will allow determining the efficiency of functional reconfigurations, so that we can target more specifically the networks to be stimulated by intensive cognitive therapies. In this state of mind, seminal works on functional connectivity in the field of brain pathology, particularly with patients with strokes, traumatic brain injuries, or brain tumors, have offered interesting results. It is well known that brain injuries alter functional links between distant and local brain areas and that this alteration can be correlated to cognitive disorders. We also know that the

efficiency of cognitive rehabilitation programs may induce a reorganization of functional connectivity. Given that DLGG patients show little or sometimes no cognitive disorders, this patient population appears to be of major interest to reveal the neurophysiological underpinnings of efficient brain plasticity mechanisms across the whole brain.

Functional rehabilitation will probably take advantage of the rapid advances in cognitive neurosciences which will help to a better care of the patients, notably in the DLGG population. The treatment of cognitive disorders is a specific and accurate exercise that requires an individualized approach that is time-consuming. Its efficacy is guaranteed by expert clinicians with large knowledge in clinical neurosciences. In this state of mind, it requires an institutional structuration in order to allow a maximal efficacy. It means that medical institutions should develop specific departments dedicated to cognitive rehabilitation.

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# Chapter 28
# New Individualized and Dynamic Therapeutic Strategies in DLGG

**Hugues Duffau and Luc Taillandier**

**Abstract** Diffuse low-grade glioma (DLGG) is a chronic tumoral disease that ineluctably grows, migrates along white matter pathways, and progresses to higher grade of malignancy. Rather than a "wait and watch" policy, a therapeutic attitude is currently the gold standard, with early radical safe surgery as the first treatment. Indeed, intraoperative mapping in awake patients, with maximal resection up to functional boundaries, is significantly associated with a longer overall survival (OS), while preserving or even improving quality of life (QoL). However, most of traditional studies have investigated the impact of only one specific therapy (e.g. impact of surgery, or radiotherapy, or chemotherapy) on OS, without a comprehensive view of the whole management strategy on the patient's cumulative time with preserved QoL versus time to malignant transformation. Here, our goal is to switch towards a more holistic concept, based on the anticipation of a personalized and long-term multistage therapeutic approach, with on-line adaptation of the strategy over years using feedback issued from clinical, radiological and histomolecular monitoring at the individual level. This dynamic and multistage approach challenges the classical strategy by proposing earlier therapy, by repeating treatments, and by reversing the traditional order of therapies (e.g. neoadjuvant chemotherapy if at least subtotal surgical resection is not possible, no early irradiation), to improve both OS and QoL. Neuro-oncologists should tailor their management strategy during the follow-up on the basis of real-time oncological control and functional outcome. Thus, we propose new personalized strategies dealing with the interactions between the natural course of DLGG, reaction neuroplasticity, and onco-functional

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modulation induced by serial treatments. The ultimate aim is taking measures to delay malignant transformation as long as possible, while giving DLGG patients a real life that includes planning for their long-term future (e.g. such as deciding whether to have a baby). This philosophy supports an individualized, functional, and preventive neurooncology.

**Keywords** Diffuse low-grade glioma • Surgery • Chemotherapy • Radiotherapy • Individualized management • Multistage therapeutic approach • Quality of life

## 28.1 Introduction

Recent technical and conceptual advances in cognitive neurosciences, neuroimaging, genetics, and treatments have revolutionized our knowledge of DLGG, leading to the seminal principle of personalized management. Indeed, in previous chapters, it was emphasized that DLGG is not a tumor mass in the brain, but a progressive and invasive disease diffusing within the central nervous system. This aggressive tumor grows continuously [1], migrates along the white matter tracts [2], and inevitably progresses to a higher grade of malignancy, even for incidentally discovered DLGG [3], leading to neurological deficit and ultimately to death. As a consequence, the "wait and watch" policy should definitely be abandoned to evolve towards an early therapeutic attitude in order to delay malignant transformation. In other words, the goal is to transform a premalignant tumor in a chronic disease under control. Such an active attitude should be adapted to the complex biological course of DLGG at the individual level. However, in the classical literature, the majority of studies have investigated the role of only one specific treatment (e.g. impact of surgery, radiotherapy, or chemotherapy) without taking a global view of managing the cumulative time with preserved QoL versus time to malignization. Moreover, when different therapies have nonetheless been combined, a rigid therapeutic protocol (e.g. surgery followed by radiation plus PCV in incomplete resection in patients younger than 40 years of age and in patients who are 40 years of age or over, whatever the extent of resection) has been applied to DLGG patients, as it was a homogeneous group, usually with no attempt to adapt the sequence of therapies to each patient [4].

In this chapter, our goal is to switch towards a more holistic concept, based upon the anticipation of a personalized and long-term multistage therapeutic strategy, with an on-line adaptation of the management over the years using feedback provided by clinical, radiological and histomolecular monitoring at the individual level [5]. This dynamic approach challenges the classical policy with respect to different issues: by administrating earlier treatment, by repeating therapies (e.g. 2–4 surgical resections spaced by several years, or periods of 12–18 months of chemotherapy by Temozolomide spaced by periods of single

follow-up), and by reversing the "classical order" of treatments (e.g. neoadjuvant chemotherapy followed by surgery after tumor shrinkage, no early radiotherapy), with the ultimate aim not only of increasing the OS but also of preserving (or even improving) the QoL. To this end, the oncofunctional balance of the whole multimodal therapeutic strategy should be carefully evaluated—and not only the impact of each isolated treatment on the sole OS independently of the functional status of the patient [6, 7]. This means that neuro-oncologists should tailor their management attitude during the follow-up on the basis of real-time oncological control and functional outcome. Indeed, the patient's neurological and neurocognitive status can be preserved thanks to (1) cerebral plasticity mechanisms enabling compensation of the glioma progression and compensation of the effect of the different treatments taken alone and together (2) the selection, with a similar efficacy, of the best tolerated treatment, at the right time, for the right patient [2]. In other words, we propose a new personalized and recursive management dealing with the dynamic interactions between the natural history of the DLGG, the reaction brain reorganization and the oncofunctional modulation induced by serial treatments.

## 28.2 Towards Personalized Multistage Therapeutic Strategies in DLGG (Fig. 28.1)

The first step in the management of DLGG patient is to precisely study the glioma course and its possible consequences on neural functions. Thus, it is essential (1) to objectively calculate the volume of the tumor and its growth rate on two consecutive MRIs at least 3 months apart (or 1.5 month apart in cases with poor prognostic factors) before any treatment because both parameters are correlated with overall survival [8], (2) to accurately investigate the location of the glioma both at cortical and subcortical levels, especially by analyzing its relationships with neural pathways [9], and (3) to achieve extensive neurocognitive examination, even in DLGG discovered incidentally [10], with the aim of adapting the intrasurgical functional mapping, which increases the extent of resection while preserving QoL [11, 12]. All these considerations have already been detailed in previous chapters, and will be not discussed here. Nonetheless, it is important to insist on the fact that this baseline is crucial for elaborating a personalized strategy: indeed, starting therapy too rapidly without this initial functional and dynamic radiological assessment will result in a loss of precious information—preventing to anticipate a long-term optimal management at the individual scale. Of note, this delay (a few weeks before to treat) does not represent a risk in itself in this specific phenotype of DLGG, since this is in essence a slow-growing tumor (conversely to glioblastoma in which treatment should be performed immediately).

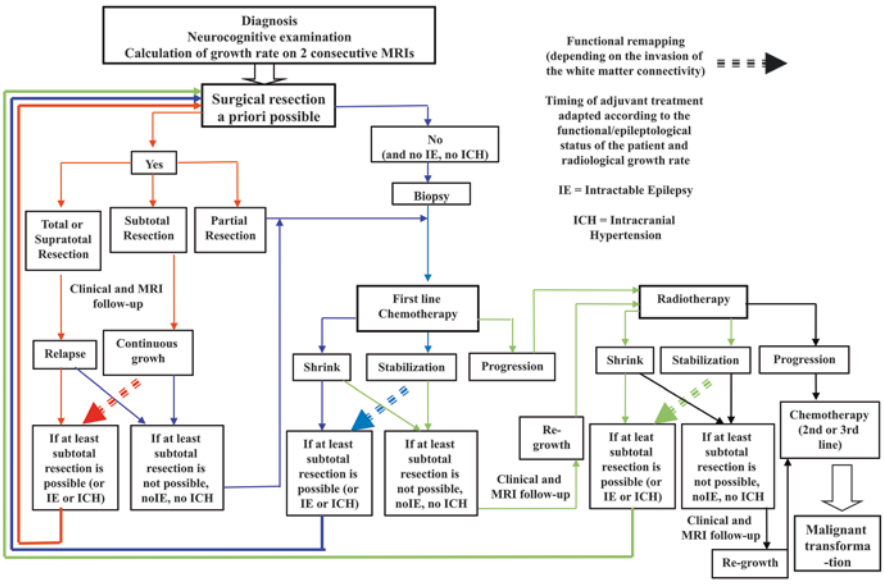


**Fig. 28.1** Personalized dynamic multimodal therapeutic strategy in DLGG, with the goal to prevent malignant transformation while preserving quality of life

### *28.2.1 The Multistage Surgical Attitude*

As extensively demonstrated in the chapter by Duffau on "Surgery for DLGG: Oncological Outcomes", surgical resection is the first option in DLGG—as recommended by the European Guidelines [13] as well as by the National Comprehensive Cancer Network [14]. Indeed, radical surgery has a significant impact on OS by delaying malignant transformation [15–18] while preserving or even improving the QoL thanks to the use of awake mapping [19–22].

Nevertheless, it is worth noting that DLGG patient cannot (yet) be cured by surgery, even in cases of "supratotal" resection. Yordanova et al. [23] and Duffau [24] reported that excision of a margin around the FLAIR-weighted signal abnormalities prevented malignant transformation (with no postoperative adjuvant therapy). Yet, some patients experienced a relapse within the year following supramarginal resection, likely due to isolated tumoral cells still present far beyond the glioma visible on MRI [25]. Indeed, with a mean duration of postoperative follow-up of 132 months (range, 97–198 months), 50% of patients experienced tumor recurrence, with an average time to relapse of 70.3 months (range, 32–105 months)—once again, without malignant progression [24]. This issue should be extensively explained to the patient and his/her family at diagnosis with the goal (1) to inform him/her about the fact that additional treatment(s) will be administrated regularly over the years, and (2) to improve, in parallel, him/her compliance: indeed, this actual "honest information", very well accepted by the patient, allows build trust that will last throughout the management of this chronic disease.

In other words, following an initial maximal safe surgery, i.e. function-guided resection (see the chapter by Duffau on "Surgery for DLGG: Functional Outcomes"), there is a high risk that DLGG will recur following several years, possibly after (supra)complete resection—and *a fortiori* in all cases following subtotal resection (i.e. with a residue less than 10–15 cc) [15, 17, 18]. Interestingly, the growth rate of residual glioma, voluntarily left for functional reasons, that is, to preserve QoL, will be similar to its presurgical kinetics [26]. Thus, thanks to the linear progression of the mean diameter of DLGG, one can predict at the individual level when the volume will reach about 15 cc, which represents the threshold for a higher risk of malignant transformation. As a consequence, a second "preventive" treatment can be proposed just before to reach this threshold, but not in the preceding years, in order (1) to not use prematurely (limited) therapeutic options, which will be very useful in the future (2) to preserve QoL of patient by limiting the administration of too much treatment(s)—for example by avoiding early radiotherapy, due the high risk of delayed cognitive disorders preventing to enjoy a normal life (see below) (3) while controlling the tumor by preventing progression towards a higher grade of malignancy, and thus by significantly increasing the OS [5]. Regarding the timing of second (or third, or fourth) surgery, we have reported a series of 19 DLGGs patients who underwent reoperations: 11 tumors had progressed to high-grade glioma in a median time between the two surgeries of 4.1 years. As a consequence, since there was no permanent morbidity associated with re-operations, we have suggested to "over-indicate" an early re-intervention rather than to perform a late surgery when the tumor has already transformed into a malignant glioma [27].

In this spirit, reoperation should be considered as a priority, on the condition nonetheless that at least subtotal resection can be achieved. Such a "multistage surgical approach"—beginning with initial tumor removal up to functional boundaries, followed by a period of several years, and then a second surgery with optimization of the extent of resection while preserving QoL—is possible, even in so-called "eloquent areas", thanks to mechanisms of brain remapping induced by (1) the first surgery itself (2) the postoperative functional rehabilitation (3) the slow re-growth of the DLGG [28, 29]. Regular neuropsychological examinations as well as serial functional neuroimaging can provide helpful information for predicting the extent of resection during a second (or even third or fourth) surgery, in the philosophy of a recursive surgical attitude [30, 31]. The goal remains to reduce the glioma volume in order to prevent progression to a higher grade while preserving QoL (or even improving it, e.g. by controlling seizures) owing to repeated resections. Thus, the onco-functional balance of surgery can be optimally found for each patient only if the strong relationships between the DLGG course and the cerebral adaptation phenomena are taking into account (see chapter by Duffau on "Interactions Between DLGG, Brain Connectome and Neuroplasticity").

On the other hand, we should insist again on the fact that a significant oncological benefit of surgery was actually demonstrated only when the resection was at least subtotal, that is, leaving a postoperative residual volume less than 10–15 cc [15, 17, 18]. Consequently, when the glioma is very diffuse, namely with huge invasion of the "minimal common brain" (that is, the cortico-subcortical structures

which cannot be resected whatever the patient due to limitations of brain plastic potential, see [32, 33]) and/or with bi-hemispheric infiltration, it is possible to predict using probabilistic atlas before any treatment whether the surgical removal will be only partial—thus with no or only mild oncological impact [34, 35]. In these specific cases, there is no indication to perform surgery first (or reoperation if a subtotal resection was already performed several years before, followed by tumor relapse with a very diffuse pattern)—except (1) in patients with pharmacologically intractable epilepsy, because even partial resection may allow a relief of seizures, especially when the insula and/or mesiotemporal structures are involved [36] (2) in rare cases of intracranial hypertension. In other words, in these invasive DLGG and at this moment, alternative nonsurgical therapies should be envisioned.

### *28.2.2 The Role of Chemotherapy in a Dynamic Multimodal Therapeutic Approach*

As already described (see the chapter by Taillandier and Blonski on "Chemotherapy for DLGG"), whatever the protocol used (PCV versus Temozolomide), chemotherapy may diffuse in the entire brain, i.e. even in critical areas, without inducing functional (neurological and cognitive) deficits [37]. This means that this therapy is perfectly adapted in cases of widely invasive DLGG, typically when (re-)operation is not possible. If one or multiple surgeries have previously been achieved, chemotherapy can be considered when the tumor re-grows with a volume reaching 10–15 cc (the same threshold as discussed regarding re-operation), and when it invades critical structures which cannot be functionally compensated (such as the subcortical white matter connectivity which constitutes the minimal common brain and/or in cases of bilateral extension, see above) [5]. As a consequence, the timing of adjuvant chemotherapy is strongly dependent on the glioma growth rate calculated before and after surgery, based upon regular control MRI performed at least every 3–6 months. The aim is at least to stabilize the DLGG, while preserving QoL, that is, to give chemotherapy before the occurrence of neurological deficits. To this end, Temozolomide is generally preferred, because of fewer adverse effects. In other words, the principle is to control the tumor volume, in order to delay malignant transformation, in patients who should continue to enjoy a normal life [7]. Indeed, QoL does not seem to change over time while patients are receiving Temozolomide. For example, in a recent series, Liu et al., compared of DLGG patients at baseline prior to chemotherapy and through 12 cycles of Temozolomide [38]. Mean change scores at each chemotherapy cycle compared with baseline for all QOL subscales showed either no significant change or were significantly positive ($p < 0.01$). Authors concluded that DLGG patients on therapy were able to maintain their QOL in all realms. Patients' QoL may be further improved by addressing their emotional well-being and their loss of independence in terms of driving or working [38]. Interestingly, we have also shown that, in patients with intractable seizures, chemotherapy was able to improve QoL by

controlling seizures, thus leading us to give earlier Temozolomide in these specific cases [39].

Furthermore, chemotherapy may also induce a shrinkage of DLGG [37, 40]. In fact, tumor regression with negative growth rate is very common under chemotherapy (see the chapter by Mandonnet on "Dynamics of DLGG and Clinical Implications"). Indeed, over 90% of DLGG patients experienced initial decrease of the mean tumor diameter [41]. It is likely that this rate was underestimated in the traditional literature, because the classical McDonald's [42] and RANO criteria [43] are not adapted to monitor DLGG, especially under treatment, because they are not sensitive enough. First, it is crucial to achieve objective measurement of 3D volume and not only of two diameters (size) in this kind of invasive tumor (because it is well known that glioma can migrate in one specific direction along white matter pathway) [2]. Secondly, velocity diameter expansion, which is calculated by comparing the evolution of mean diameter (computed from the volume) over time on consecutive MRI scans, is more objective and sensitive at the individual level rather than to wait for the increase or decrease of 25% of the size of the glioma—which is an arbitrary threshold with no demonstrated value. Of note, even in high-grade gliomas, it was shown that, based on the high degree of intra-observer variability, tumor measurements producing an increase in bidimensional products of >25% can routinely be obtained solely by chance [44]. Consequently, the RANO criteria are not sensitive enough to monitor the actual impact of chemotherapy, in comparison with quantitative analyses of glioma volume and kinetics.

In this context, when glioma shrinkage objectively calculated is significant, especially with regression of the tumor invasion within critical structures, chemotherapy may open the door to a subsequent surgery [45]. This original concept of "neoadjuvant chemotherapy" in neurooncology may be envisioned after previous surgical resection(s) when the DLGG recurred with a more invasive pattern, or as the first therapeutic option at the time of diagnosis in very diffuse gliomas—mimicking a gliomatosis [37, 40]. In these particular presentations, a surgical biopsy is recommended to benefit from neuropathological as well as molecular diagnosis. With respect to QoL, in our work concerning patients treated with presurgical chemotherapy, the Karnofsky Performance Scale (KPS) scores ranged from 80 to 100 (median 90) and were globally stable during the whole follow-up period. The global QoL score was preserved after neoadjuvant chemotherapy and subsequent surgery for most patients with a median value of 66.7% (range 33.3–83.3%). Cognitive, emotional, physical and social well-being scores were also relatively preserved (median scores 83.3, 79.2, 100 and 100%, respectively) [37].

Therefore, this dynamic strategy shows that serial multidisciplinary discussions are crucial over years for each patient, because a treatment which seemed impossible (e.g. surgical resection because a too invasive pattern of DLGG) several months or years ago can become possible thanks to a shrinkage elicited by Temozolomide. In other words, it is not reasonable for a tumor board to give a "rigid and definitive" decision regarding the resectability of a DLGG, due to strong links between glioma behavior, neuroplasticity, and treatment(s): such an equilibrium is dynamic and can be modified by administrating the right therapy at the right moment in a given

patient, potentially leading to a subsequent surgery initially thought to be impossible [5]. We should nonetheless acknowledge that the question concerning the potential for chemotherapy to induce brain plasticity remains unanswered: such a crucial issue should be investigated in the near future.

When chemotherapy allows (only) stabilization of the glioma volume, without opening the door to a (re-)operation, the duration of Temozolomide is still a matter of controversy (PCV is stopped in all cases after a maximum of 4–6 cycles). Indeed, it is currently very difficult to predict the DLGG course after interruption of chemotherapy, since different patterns have been observed: continuation of shrinkage [46], prolonged stabilization, or rapid re-growth [41]. Several parameters for monitoring should be taken into account in order to solve this problem at the individual level. Firstly, with the goal of preserving QoL, chemotherapy must be stopped if it is (or if it becomes) poorly tolerated. Nevertheless, when the patient has no adverse effects, oncological considerations should be the major criterion. Secondly, radiologically, the tumor volume is again one of the most important prognostic markers of malignant progression free survival and survival [15, 17]. Thus, if the volume is more than 15 cc, the tendency is to give Temozolomide longer, because the risk of malignant transformation is higher—and thus the need to stabilize DLGG at this stage is much more crucial in comparison with a smaller glioma (with a volume less than 10–15 cc). Thirdly, the velocity diameter expansion before administration of chemotherapy is a major criterion. Pallud et al. demonstrated that the growth rate was a significant prognostic marker of OS [8]. Therefore, for DLGG with a higher growth rate (especially more than 8 mm/year), chemotherapy should be administrated earlier and longer. Fourthly, neuropathological parameters can also be taken into account, in particular when micro-foci of malignancy have been detected within a DLGG [47], leading to interrupt Temozolomide later—especially in bigger and rapid-growing DLGG. Even though molecular markers might also been useful [48], it seems today difficult to determine the timing of adjuvant treatment on this sole factor. Indeed, Hartmann et al. considered that no molecular marker was prognostic for "progression-free survival" after surgery alone using multivariate adjustment for histology, age, and extent of resection [49]. In addition, it was not yet demonstrated that molecular biology had a good predictive value of chemosensitivity. Results concerning tumor response according to the molecular status are contradictory in the recent literature (see the chapter by Blonski and Taillandier on "Chemotherapy in DLGG"). Although some teams showed that 1p-19q codeletion, MGMT promoter methylation, and IDH mutation ($p = 0.01$) were correlated with a higher rate of response to temozolomide [50], others found that tumors were also well controlled by chemotherapy irrespective of molecular profile—especially irrespective of 1p/19q status [51]. In our experience, 1p19q, IDH and MGMT were not predictive of radiological response under chemotherapy [40]. In summary, even though at a population level, there are some preliminary results pleading in favor of possible relationships between molecular status and chemosensitivity, it is nonetheless currently too early to consider the indication of chemotherapy on this sole argument at an individual level. Of note, significant correlations between 1p19q status and delay of relapse after interruption of Temozolomide have been reported, supporting the

fact that molecular profile could be a marker of the duration of response and could be useful to decide when to stop Temozolomide [41]. Fifthly, metabolic imaging can also be considered to predict efficiency of chemotherapy on DLGG and to monitor patients under Temozolomide. Indeed, Guillevin et al. [52] found that the proton magnetic resonance spectroscopy profile changes more widely and rapidly than tumor volume during the response and relapse phases, and thus represents an early predictive factor of outcome over 14 months of follow-up.

To sum up, the most important parameters to decide when to administrate chemotherapy are (1) the impossibility to (re)operate DLGG due to an invasion of the white matter connectivity (that is, invasion of the minimal common brain with limitation of plastic potential); (2) QoL of the patient, knowing that intractable epilepsy can lead to propose chemotherapy earlier because it can help to control seizures; (3) the residual tumor volume and its growth rate. In this setting, prospective studies are now mandatory to optimize the management of DLGG under chemotherapy, especially in order to evaluate the possible benefit-to-risk ratio of new protocols alternating periods of 6–12 months with Temozolomide broken by periods of single clinical and radiological follow-up. It is likely that biomathematical modelling for each DLGG could bring precious additional information in the near future (see the chapter by Mandonnet on "Biomathematical Modelling of DLGG Behavior"). In all cases, our decision regarding chemotherapy, as concerning surgical resection(s), should be based upon an evaluation of the onco-functional balance, e.g. the possible efficacy and risk of this treatment at this moment in this patient weighted by the risks of tumor progression at short, medium and long terms [5].

### *28.2.3 When to Irradiate DLGG?*

One prospective randomized trial has strongly demonstrated that early radiotherapy had no impact on overall survival [53]. Although "progression free survival" was significantly increased, one should acknowledge that this issue has no any interest for the patient, for whom the goal is to leave longer and better. In fact, not only the survival was not improved, but in another study by Douw et al., the QoL was worsened due to late cognitive disturbances induced by irradiation [54]. Indeed, at a mean of 12 years after their first diagnosis, long-term survivors of DLGG who did not have radiotherapy had stable radiological and cognitive status. By contrast, of the 65 patients, 32 patients (49%) with DLGG who received radiotherapy showed a progressive decline in attentional functioning, they had poorer executive functioning and lower information processing speed—even those who received fraction doses that are regarded as safe (≤2 Gy). In total, 17 (53%) patients who had radiotherapy developed cognitive disabilities deficits in at least five of 18 neuropsychological test parameters compared with four (27%) patients who were radiotherapy naive. Moreover, white-matter hyperintensities and global cortical atrophy were associated with worse cognitive functioning in several domains [54]. These results suggest that the risk of long-term cognitive and radiological compromise that is

associated with radiotherapy should be considered when treatment is planned. Furthermore, conversely to surgery and chemotherapy, radiotherapy cannot be regularly repeated due to potential neurotoxicity. On the basis of these objective data, one could be surprised to see that many DLGG patients have nonetheless continued to be irradiated on an early phase of the disease. Indeed, in the era of "evidence-based medicine", it is puzzling to note that on one hand, clinicians claim that they would like to benefit from more Class I evidences, but on the other hand, that they do not apply the recommendations when such data have finally been obtained.

For example, in a recent study by Buckner et al. [4] comparing radiotherapy versus radiotherapy plus PCV, that showed that survivals are longer among DLGG patients who received combination chemotherapy in addition to radiation therapy than among those who received radiation, there was no arm with chemotherapy alone (without radiotherapy). This means that, in the design of the study, all patients younger than 40 years of age with incomplete resection and patients who are 40 years of age or over, whatever the extent of resection, were dogmatically irradiated—regardless the results of the two randomized trials mentioned above. In addition, in this series, the extent of resection was not objectively calculated by performing volumetric assessment before and after surgery, but it was based upon the subjectivity of the operating neurosurgeon [4]. In other words, one of the most important (even if not the most important) therapeutic prognostic factor in DLGG was not quantified, introducing a major bias in this trial based upon extent of resection to enrol the patients. Moreover, as previously noticed, radiation can induce subcortical white matter changes, which are associated with behavioral slowing [54]. Yet, in the study by Buckner et al. [4], the QoL was evaluated by using only a mini-mental status examination (MMSE), which was initially dedicated for patients with dementia and not for DLGG patients who enjoy a normal life in the vast majority of cases. Furthermore, none of the MMSE items have time constraints. In addition, longer term follow-up is needed. Indeed, it has been demonstrated that post-irradiation cognitive decline is generally delayed [54]. Nonetheless, this basic cognitive assessment was performed only within the 5 years following radiotherapy (in patients living more than 10 years) [4]. Therefore, due to these major methodological limitations, that resulted in an underestimation of the actual radiation effects, there is no demonstration that radiotherapy is safe. Regarding the efficacy, the sole objective message of this study is that the administration of PCV increases the survival, thus supporting the impact of chemotherapy on the history of DLGG: but it does not prove a possible effect of radiotherapy by itself on the OS. Finally, using the age as a main criterion in the design of this trial is questionable, in particular by differentiating patients under or above the threshold of 40 years. Indeed, in the widest series ever reported on DLGG patients, by the French Glioma Consortium (REG), an independent spontaneous factor of a poor prognosis was an age $\geq$55 years (and not 40 years) [17]. Moreover, Reuss et al. [55] have recently shown that the analysis of the age impact on survival in three independent series including a total of 1360 adult diffuse astrocytic gliomas with *IDH* mutation revealed no difference. Stratification of patients in four age groups, 18–29, 30–39, 40–49 and over 50 demonstrated a trend ($p = 0.067$; log-rank test) for patients over 50 exhibiting a poorer

outcome. They concluded that differences in age and survival between A II(WHO2007) and AA III(WHO2007) predominantly depend on the fraction of *IDH*-non-mutant astrocytomas in the cohort [55].

Yet, it is worth noting that despite these numerous limitations, Buckner et al. [4] proposed to give radiotherapy plus PCV in all DLGG patients younger than 40 years of age with incomplete resection (regardless the volume of the residual tumor) and patients who are 40 years of age or over, whatever the extent of resection, as a standard protocol that must be applied in a systematic manner without taking into account the crucial parameters detailed in the previous paragraph—as the QoL of the patient (especially the existence of seizures or not), the fact that the resection (if incomplete) was subtotal or partial (over 15 cc), the growth rate calculated before and after surgery, and so forth. In other words, this kind of dogmatic protocol is against the principle of personalized medicine: nonetheless, it is applied by many departments of neurooncology all over the world…

In fact, based on the objective data of the current literature, early radiotherapy (before or after surgical resection) does not represent a valid therapeutic option in new strategies that aim to optimize the cumulative time with preserved QoL while preventing malignant transformation. Even patients with high-risk DLGG receiving adjuvant temozolomide demonstrated a high rate of radiographic stability and favorable survival outcomes while meaningfully delaying radiotherapy [56]. In particular, patients with 1p/19q codeletion are potential candidates for omission of adjuvant radiotherapy [56]. As a consequence, irradiation should be kept in reserve for progressive DLGG that cannot be (re-)operated and that has recurred under chemotherapy (that is, with positive velocity expansion diameter despite Temozolomide) [5]. Of note, at that time, it is still possible to combine radiotherapy and PCV, with no loss of chances according to the "current recommendations" discussed above.

Indeed, as noted earlier, because the goal in DLGG patients is to avoid malignant transformation while preserving QoL as long as possible, it does not seem reasonable in this "preventive" mind to wait for a too long time before irradiating patients with growing DLGG not controlled by alternative therapy: in this case, radiotherapy must be proposed before the tumor has already evolved towards a higher grade of malignancy. In addition, besides its possible oncological impact, radiation may also have potential benefit on intractable epilepsy [57]. In this spirit, Pallud et al. showed that after radiotherapy in a subset of 33 DLGG, all patients demonstrated a tumor volume decrease (negative velocity diameter expansion, mean −16.7 mm/year), with a significant longer OS for slow responders [58]. Such data lead to propose, in fast responders, an earlier post-irradiation re-treatment. Although a (re-)operation could be considered following DLGG shrinkage, one must be aware about a higher rate of cognitive disorders (personal unpublished data). This is due to a limitation of the brain plastic potential. Indeed, radiotherapy is known to increase apoptosis, to decrease cell proliferation and to reduce stem/progenitor cell differentiation into neurons within the neurogenic regions (especially in the subventricular zone) [59, 60]. Furthermore, radiation can also induce white matter tracts changes, limiting the possibilities of functional compensation, because the "minimal common brain" (i.e. the part of the brain with a low potential of neuroplasticity) is mainly composed of

subcortical pathways [32, 33]. Consequently, a new line of chemotherapy is the best option to consider in cases of DLGG relapse after radiotherapy. However, it is worth noting that, thanks to technical advances, re-irradiation might be possible in selected patients. In particular, the place of radiosurgery remains to be defined, for instance by performing stereotactic radiotherapy on the occurrence of a very focal enhancement, especially when the FLAIR-hypersignal remains stable [61]. Of note, whatever the technical advances in radiotherapy, in particular regarding its accuracy, one should keep in mind that, after maximal resection achieved according to functional boundaries, in essence, adjuvant radiotherapy will be delivered at the level of neural networks crucial for brain functions, especially the subcortical connectivity: this is the reason why there is a high risk of cognitive decline whatever the methodology of radiation used.

In summary, due to the lack of demonstration of significant impact of early radiotherapy on global survival, and because of its high risk of long-term cognitive disorders, radiation should not be considered as a first therapeutic option in DLGG patients.

## 28.3 Conclusions

The current concept for DLGG patients is to anticipate (before neurological or even cognitive worsening) a personalized, multimodal and long-term management strategy from the diagnosis (both in symptomatic as well as in incidental discovered DLGG) to the malignant stage of the disease, with on-line therapies adjusted over time on the basis of regular functional feedback and radiological monitoring. For instance, although a complete surgical resection was not achievable during a first surgery due to the invasion of structures still critical for brain functions, such a total resection can become possible later owing to mechanisms of neural networks reorganization and/or following a shrinkage induced by adjuvant chemotherapy. In other words, we propose new individualized strategies dealing with the interactions between the natural course of DLGG, reaction neuroplasticity, and onco-functional modulation induced by serial treatments. Our recursive therapeutic philosophy breaks with the traditional attitude, by proposing a holistic and dynamic tailored strategy rather than by deciding dogmatically to administrate a protocol on the basis of few selected criteria statistically validated but with no value at the individual level (e.g. the arbitrary definition of "high risk DLGG patient" partly based upon an age over 40 years). Indeed, it seems questionable to apply a similar therapeutic protocol to all patients belonging to a same "subgroup" defined by only a few parameters (as the molecular pattern), without seeing the full picture at the individual level. Thus, the risk of guidelines based on the WHO classification is in fine to evolve against the deep concept of precision medicine, because one cannot define a patient solely in terms of tumoral molecular profile. Indeed, as mentioned by Boggs and Mehta (see the chapter on "Radiotherapy in the Treatment of DLGG"): "It is important to understand that treatment stratification based on molecular

profiling has not yet been reported prospectively. Examinations of predictive and prognostic capabilities of *IDH*, *TERT*, and *TP53* have only been examined retrospectively or as an unplanned subgroup analysis of prospective studies. Thus, outside the auspices of a clinical trial, genomic classification should not be used to guide clinical decision-making." Rather, in DLGG patients, in whom the survival is today significantly longer (with median survivals between one to two decades) thanks to an earlier and serial therapeutic management allowing to delay/prevent malignant transformation, QoL should become the first endpoint. In this state of mind opening new avenues to individualized, functional and prophylactic neurooncology (eventually by envisioning a screening in the general population to diagnose DLGG at an earlier stage), the ultimate aim is to give to human beings bearing DLGG a real life that includes planning for their long-term future—such as deciding whether to get a loan to buy a house or to have a baby.

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# Part VI
# Prospects

# Chapter 29
# Emerging Therapies for Diffuse Low Grade Glioma

**James Wright and Andrew Edward Sloan**

**Abstract** Because of the intractable nature of diffuse low grade gliomas, which always progress into higher grade, malignant gliomas, there is increased interest in the use of newer and alternative approaches in addition to conventional approached including surgery, chemotherapy, and radiotherapy. These emerging treatments include several technologies for thermal ablation and improved drug delivery as well as immunotherapy and nutritional or "alternative" therapies.

**Keywords** Laser interstitial thermotherapy • Stereotactic laser ablation • High intensity focused ultrasound • MRI-guided high-intensity focused ultrasound • Radiofrequency • Convection enhanced delivery • Immunotherapy • Nutritional therapy • Alternative therapies • Ketogenic diet

## 29.1 Introduction

The roles of conventional imaging, surgical approaches, cytotoxic chemotherapy, and photon radiotherapy in the treatment of diffuse low grade glioma have been addressed in other chapters in this textbook. The purpose of this chapter is to address

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emerging treatments for these tumors including emerging surgical approaches to complete both thermal tumor ablation and improved drug delivery; immunotherapy, and nutritional, or “alternative” therapies.

## 29.2 Thermal Therapy

There are four distinct types of thermal therapy which have recently been explored for thermal ablation of brain tumors including low grade gliomas. These include laser interstitial thermotherapy (LITT), high frequency focused ultrasound (HIFU), radiofrequency ablation, and cryotherapy. The goal of the first three is to induce coagulative necrosis of the tumor by heating it to ~42–45°C. Likewise, the goal of cryotherapy is to induce focused cooling of the tumor to create ischemic necrosis for the purpose of tumor ablation. Interestingly, two of these approaches, LITT and HIFU are also being developed to improve delivery of anti-tumor agents by utilizing the thermal disruption of the blood brain barrier induced by therapy to deliver these agents precisely to the tumor. This section will focus on thermal ablation, while use of LITT and HIFU related to improve drug delivery will be addressed separately below.

### *29.2.1 Laser Interstitial Thermotherapy (LITT)*

Laser interstitial thermotherapy (LITT), sometimes known as Stereotactic Laser Ablation (SLA) or MR-Guided laser interstitial thermotherapy (MRgLITT) is an emerging minimally invasive treatment modality designed for thermal ablation of various types of lesions. Early use focused primarily on extracranial pathology, but it has been utilized for difficult to access or unresectable intracranial lesions since 1983, though until recently intracranial use was confined to research subjects at a few centers [1]. However, the recent development of MRI-compatible lasers with software for near real-time MRI thermometry by two commercial vendors [2, 3], one with a robotic probe driver [3] has facilitated more precise and convenient treatment and the technology has become more widely utilized.

The vast majority of the gliomas treated using LITT have been high grade gliomas (Grade III–IV), but as the technology and indications have continued to evolve, and the costs and complications associated with LITT decrease [4], there is increasing interest in applying this technology to other types of lesions as well including low grade gliomas. Several series have reported treatment of low grade glioma in adults, but these are primarily retrospective in nature, provide little detail about pathology or location, and focus primarily on technical aspects of the procedure, with little outcome data [5–8]. A recent paper reported a retrospective results of a series of nine difficult to access pediatric low grade gliomas [9]. Although most were grade I pilocytic astrocytomas, at least two were diffuse tumors which appeared decrease in volume for more than a year post-operatively,

with only one complication (11.1%). However, given recent improvements in both software and delivery systems, promising preliminary results, and increasing acceptance with both two main neurosurgical journals devoting special issues on this technology within the last year [10, 11], it is expected that indications for LITT will continue to expand and will likely include treatment of low grade gliomas. However, at present, further studies are required to show outcome benefit or equivalence of this therapy as a treatment modality for diffuse low-grade glioma.

### *29.2.2 High Intensity Focused Ultrasound (HIFU)*

High intensity focused ultrasound (HIFU), sometimes called MRI-guided high-intensity focused ultrasound (MRIgFUS) or abbreviated as HUFUS, uses focused ultrasound to thermally ablate intracranial lesions, create precisely localized disruption of aberrant functional tracts, or disrupt the blood brain barrier at very specific locations improve drug delivery. The technology for HIFU in the late 1980s and early 1990s required that the patients undergo craniectomy pre-operatively so that the ultrasound would not need to penetrate the skull [12, 13]. One early of 17 patients included 14 with low grade gliomas treated with CT and ultrasound demonstrated safety, but little demonstrable clinical efficacy [12]. Subsequent studies primarily focused on high grade gliomas (anaplastic astrocytomas and GBMs) [13]. However, this approach appears to have fallen out of favor for more than three decades likely due the need for craniectomy and lack of demonstrable efficacy. However, recent advances in the technology have enabled the procedure to be performed non-invasively for GBM in the MRI after craniectomy to create a bone window [14, 15], and more recently, through an intact skull in cadavers [16] then in patients with deep GBMs up to 2.5 cm in diameter [17]. While current studies of HIFU are early stage trials for patients with brain metastasis [18], multiple preclinical studies are currently ongoing. HIFU was approved by the FDA for treatment of essential tremor in July 2016, and additional studies are planned which will eventually include diffuse low grade glioma [19].

### *29.2.3 Radiofrequency Ablation*

Radiofrequency ablation has demonstrated safety and efficacy over many years in the generation of neurolytic lesions for the treatment of trigeminal neuralgia. In the last decades, there has been anecdotal use of radiofrequency to treat both extracranial and intracranial lesions, though no large case series have been reported [14, 20]. Recent case reports have demonstrated efficacy in the treatment of hypothalamic hamartomas [21, 22]. Until recently, the technology could only create small lesions and not been MRI compatible, thus limiting application in patients. However, recent

studies have demonstrated that radiofrequency can create lesions up to 3 cm in large animals [22, 23] and units compatible with low-field MRI imaging have been demonstrated making future applications for gliomas of all grades likely in the future.

### *29.2.4 Cryotherapy*

Cryotherapy has proven efficacy for the treatment of extracranial tumors particularly liver metastasis, where a minimally invasive approach has similar efficacy to open surgery with minimal blood loss. Until recently however, while cryotherapy demonstrated efficacy in the creation of intracranial lesions in large animal models [24], the technology was not MRI compatible which hindered intracranial applications. Recent MRI compatible units have demonstrated the ability to create lesions in porcine brain with near real-time MRI imaging with minimal toxicity [25]. Preclinical studies are currently underway though no current studies have been announced for low grade gliomas [26, 27].

## 29.3 Surgical Approaches to Improving Drug Delivery

The anatomical properties of the central nervous system lead to unique challenges in drug delivery. Many chemotherapeutic agents have significant systemic toxicities that limit the doses that can safely be given. In addition, most have minimal penetration of the blood–brain barrier which limits their efficacy in the treatment of intracranial tumors. Thus, numerous approaches have been designed to bypass the blood brain barrier to improve drug delivery. These include: (1) placing drug directly into the brain using polymers, Intrathecal administration of therapeutic agents and CED; (2) modifying the blood-brain barrier directly using methotrexate, mannitol, HIFU or LITT or (3) design of drugs which better penetrate the blood–brain barrier. Polymers are FDA approved for GBM (i.e. Gliadel wafer) but have rarely been utilized for low-grade glioma. Intrathecal administration of therapeutic agents bypasses the blood–brain barrier, but distribution outside the ventricles is limited by diffusion and thus this approach has some efficacy for leptomeningeal disease, but limited efficacy for intraparenchymal tumor [28]. Design of novel chemotherapeutic approaches is covered in other chapters. Here we will focus on CED, HIFU, and LITT.

### *29.3.1 Convection Enhanced Delivery (CED)*

Convection-enhanced delivery (CED), first described in 1994, relies on convection, also referred to as bulk flow, to distribute a molecule through brain tissue by driving the agent through stereotactically placed catheters driven by positive

pressure gradients to enhance the natural distribution that occurs via diffusion [29]. CED has primarily been implemented in the delivery of chemotherapeutic agents for malignant gliomas. From 1997 to 2010, 13 stage I/II trials and a single phase III trial evaluated the use of conjugated immunotoxins (N = 8), conventional chemotherapeutics (N = 2), radioantibodies (N = 1), a lysosomal vector (N = 1), a genetically engineered virus (N = 1) and an immunologic oligonucleotide (N = 1) for the treatment of high grade gliomas [30, 31]. Unfortunately, despite preliminary evidence from the earlier phase II studies, the phase III study failed to demonstrate efficacy [32]. Challenges include uncertainty about the optimal agent to be delivered, optimization of cannula design, optimization of trial design (i.e. intra-tumoral vs intracavitary), optimization and guidance for canula placement, as well as assessing catheter placement, reflux, and drug delivery. CED has also been utilized for pediatric patients with diffuse intrinsic pontine gliomas (DIPG) with similar challenges [33, 34]. Since the failure of the phase III trial in 2010 [32], the field has been "on hold" and the first new trails have recently opened for GBM. Though CED has not been thoroughly studied for use in the treatment of low grade gliomas, it offers promise for the future as a way to deliver therapeutic agents directly to brain tumor tissue without inducing systemic toxicity and trials of CED for low grade gliomas will likely be performed if success is noted in the treatment of current high grade gliomas.

### *29.3.2 HUFU-Mediated Drug Delivery*

In addition to ablating tumor with thermotherapy, there is active investigation into use of HIFU improved drug deliver to intracranial gliomas either by transiently and specifically breaking down the blood–brain barrier, or by activating various chemotherapeutic agents local using HIFU [14, 35]. An ongoing study to assess the efficacy of HIFU in disrupting the blood–brain barrier is currently underway in Canada for patient with malignant brain tumors, and this is an active area of preclinical investigation [18]. At present, there is no data demonstrating efficacy of this approach, and as noted earlier, the focus is currently on malignant gliomas. However, if this approach proves to be efficacious, it will likely also be applied to low grade gliomas.

### *29.3.3 Use of LITT to Improve Drug Delivery*

A recent study demonstrated that LITT disrupted the blood–brain barrier in patients undergoing LITT for GBM for up to 6 weeks [36]. A new series of studies designed to capitalized on this LITT induced breakdown of the blood brain barrier is currently ongoing [37].

## 29.4 Immunotherapy for Low Grade Glioma

There is great current interest in immunotherapy for gliomas driven by promising preliminary results in patients with high grade glioma [38]. A recent review of the literature through December 2012 demonstrated little evidence for the efficacy of immunotherapy or tumor vaccines for patients with low grade glioma [39]. However, recent studies demonstrated immunological and clinical responses in adults with low grade glioma with improved progression-free survival of greater than 67 months [40]. Similarly, a recent case report of a dog with a spontaneously occurring gemistocytic astrocytoma, a type of low grade glioma with similar behavior in humans and dogs, demonstrated that vaccination not only induced a cellular immune response, but induced neurological improvement as well as complete resolution of the tumor for over 450 days [41]. Similarly, peptide specific immune responses as well as clinical responses have been demonstrated after peptide vaccine of children with low grade gliomas [42] including DIPGs and other brain tumors [43] which provides preliminary evidence for the efficacy of immunotherapy and tumor vaccines for patients with low grade glioma.

## 29.5 Nutrition and "Alternative" Therapy for Low Grade Glioma

A recent report revealed no level I or Level II evidence supporting the role for nutrition or nutritional therapy for the treatment of low grade glioma. However, minimal Level III evidence addressing the role of nutrition and alternative therapies for the care of low grade gliomas.

Since this time, there have been several studies providing anectodal evidence that a low carbohydrate or ketogenic diet might improve survival in patients with malignant gliomas and perhaps low grade gliomas [44]. In addition, a single center retrospective study of 182 patients demonstrated that persistent hyperglycemia was independently associated with decreased survival, increased recurrence and increased malignant degeneration even after excluding all patients with diabetes and those on continued post-operative steroids [45]. Data obtained from a modified food-frequency questionnaire administered as part of a population based study suggested that the influence of anti-oxidants on survival was inconsistent [46]. Self-reported moderate intake of fat-soluble lycopene was associated with poorer survival compared to low or high intake. Conversely, moderate intake of folate, was associated with greater survival. Assessment of actual plasma concentrations of the various nutrients assessed in the study was not performed. This adds to the complexity of understanding the role of various nutrients since differences in absorption may vary both among various nutrients as well as between individuals.

While no evidence for the efficacy of alternative or targeted therapies was identified, one group reported the results of questionnaires returned by 621 of 939 patients surveyed at six Neuro-Oncology centers in Germany [47]. This study revealed that more than 40% of patients with low grade gliomas self-reported using complementary therapies. In general, there were significant differences in usage seen with respect to age (younger > older), gender (female > male), and education (higher educational level > lower educational level). However, analysis was aggregated among all gliomas and it was not possible to assess the differences in these practices between patients with different grades or histologies of glioma. Most patients appeared to use complementary therapies *in addition to* rather than *instead of* conventional treatment, and did so in the belief that they were doing something to complement the care of their physician, rather than because of distrust of their physician. However, data for all grades of gliomas were aggregated in this analysis and thus motivations and beliefs of patients with low grade gliomas could not be specifically assessed. Given the study methodology, it is likely that the 40% figure represents an underestimate of actual practice.

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# Chapter 30
# Pregnancy and Diffuse Low-Grade Gliomas

**Sophie Peeters and Johan Pallud**

**Abstract** Improvements in the management of World Health Organization diffuse low-grade gliomas (DLGG) have resulted in overall better survival and better quality of life. As a result, the number of women considering pregnancy despite a DLGG diagnosis will increase. However, clinical evidence suggests that pregnancy impacts the evolution of DLGG: a tumor progression occurs on imaging during pregnancy in more than 75%, clinical deterioration occurred in about 40% of cases, and oncological treatments may be needed after delivery in more than 40% of cases. With regards to a woman harboring a DLGG who envisions a pregnancy, or when a possible DLGG is discovered in a pregnant patient, it is advised to take on a multidisciplinary approach to management. Clinically, the recommendations are: (1) careful and frequent neurological follow-ups during pregnancy and after delivery; (2) MRI follow-ups with quantitative assessment of the glioma during gestation; (3) rigorous obstetrical monitoring. In addition, it is recommended to counsel the patient that: (1) no definite guidelines exist; (2) completion of the pregnancy is feasible with the birth of a healthy baby; (3) pregnancy may accelerate DLGG growth, may exacerbate clinical deterioration, and may prompt oncological treatments earlier than in the DLGG population; (4) pregnancy possibly increases the risk of transformation of the DLGG towards a higher grade of malignancy; (5) the potential need for oncological treatment during pregnancy has serious known hazards for the fetus; and (6) there are potential problems associated with seizure control in addition to risks of congenital abnormalities from anticonvulsant therapy.

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**Keywords** Diffuse low-grade glioma • Pregnancy • Imaging progression • Delivery

## 30.1 Introduction

Recent improvements in the management of diffuse low-grade cerebral gliomas (World Health Organization (WHO) grade II gliomas), particularly for the IDH-mutated and 1p19q co-deleted oligodendrogliomas, have resulted in overall better survival and better quality of life [1–8]. As a result, with longer periods of disease control, along with the fact that female gender and young age are considered positive prognostic factors [6, 9], the number of women considering pregnancy despite a diffuse low-grade glioma diagnosis will only be increasing [10, 11]. Furthermore, though gravidity does not appear to influence one's risk of developing a glioma, pregnancy may lead to their discovery by influencing the natural evolution of these gliomas [4]. Gliomas in pregnant patients impose a double risk to both the fetus and the mother. Thus, treatment options are naturally more limited than in the general population due to the presence of a fetus who is very susceptible to most oncological treatments. The ideal timing of treatment is also not always realistic since, in order to ensure the best possible maternal and fetal health, the pregnancy must be brought as close to term as possible. The theoretical goal in these scenarios is to treat the mother as well as if she was not pregnant all the while avoiding additional risk to the fetus.

Presently, the possible interactions between diffuse low-grade gliomas and pregnancy have yet to be carefully examined [4]. Nonetheless, past studies have shown certain trends and correlations of glioma characteristics related to pregnancy. These include increased seizure frequency, increased tumor volume and growth rate, and transformation towards a higher grade of malignancy in pregnant versus non-pregnant glioma patients [12, 13].

In this chapter, we will discuss the mutual interactions between pregnancy and diffuse low-grade glioma evolution, as well as propose a tentative management approach based on trimester and time of diagnosis of the glioma with regards to the pregnancy.

## 30.2 Effect of a Glioma on Pregnancy

The potential impact of a glioma on pregnancy is difficult to assess as the symptomatic management (antiepileptic drugs) and the oncological treatments may interact synergistically with the glioma on the course of the pregnancy and on the *in utero* development of the child. The typical symptomatic presentation of this patient population is epileptic seizures. There seems to be a pattern of clinical deterioration during pregnancy, mostly in seizure frequency, that typically resolves postpartum for 27–44% of the patients (Table 30.1) [14]. In addition, a high rate of preterm deliveries and cesarean deliveries has been reported in pregnant women harboring a glioma [4, 12, 15, 16] and termination of pregnancy may be performed to conduct the

**Table 30.1** Changes occurring during pregnancy in patients harboring a diffuse low-grade glioma (DLGG)

| Citation | Number of DLGG (WHO grade II) | Clinical changes | Radiological changes | Increase in grade of malignancy |
|---|---|---|---|---|
| Daras et al. | 3 | Seizures (n = 1), Neurological deficit (n = 2) | Tumor recurrence (n = 3) | Yes (n = 3) |
| Isla et al. | 2 | Seizures (n = 2); Neurological deficit (n = 1) | Not detailed | Not detailed |
| Peeters et al. | 32 | Seizures (n = 17); Neurological deficit (n = 2); Increased intracranial pressure (n = 4); None (n = ?) | Imaging progression quantified on MRI follow-up (n = 28) | Not observed |
| Zwinkels et al. | 9 | Seizures (n = 3); Cranial nerve deficit (n = 1); None (n = 6) | Yes (n = 2); No (n = 7) | Not detailed |
| Yust-Katz et al. | 14 | Seizures (n = 7), Headache (n = 1), Neurological deficit (n = 1), None (n = 5) | Tumor progression (n = 4) out of the 8 cases diagnosed prior to pregnancy | Yes (n = 3) out of the 8 cases diagnosed prior to pregnancy |

necessary oncological treatment for the patient. In a study of 52 cases of gliomas during pregnancy (including 32 diffuse low-grade gliomas), all but two patients (one termination for fetal reasons, one termination for oncological reasons) had uneventful pregnancies with deliveries at a mean term of 38.4 weeks, including nine preterm deliveries [14]. The deliveries, all uneventful, were conducted through both a vaginal method and cesarean section in about 45.5% and 54.5% of cases, respectively, without specific reasoning for one mode of delivery over the other [14]. The rate of cesarean sections in those patients was high compared to the general population, which is in accordance with previous studies that encourage cesarean sections, predominantly in cases with a risk of increased intracranial pressure at the time of delivery [2–4, 11]. No study has published any poor developmental outcome with regards to the children born to mothers with a glioma. In all studied cases, albeit with limited follow-up, the babies were healthy, including the few cases that received radiotherapy and chemotherapy during the first trimester [2, 3, 10, 14, 17].

## 30.3 Effect of Pregnancy on a Glioma's Natural History

The possible impact of pregnancy on a glioma's behavior can be observed in clinical practice. It may result in clinical and morphological changes, possibly leading to additional oncological treatments.

Gliomas diagnosed during pregnancy are revealed by inaugural signs predominantly during the second or third trimesters of pregnancy [2–4, 18, 19], and patients with a glioma known prior to pregnancy may suffer from clinical deterioration during pregnancy [4, 13, 20]. However, the clinical presentation itself of gliomas during pregnancy appears comparable to the symptomatic picture outside the context of gravidity [1, 21, 22]. Indeed, seizures have been shown as a common presenting or worsening symptom for diffuse low-grade gliomas during pregnancy [3, 4, 10–12, 17, 21, 22] and have raised concerns regarding the risks of uncontrolled seizures and possible status epilepticus [4]. Beyond seizures, pregnancy has been reported to exacerbate neurological symptoms, which may precipitate an obstetrical emergency [4, 12, 15, 16]. Furthermore, concurrent eclampsia, although an extremely rare event, may initially mask the diagnosis of an underlying glioma presenting with seizures; it may also trigger the glioma to become symptomatic, through vasogenic cerebral edema, lowering the seizure threshold [16, 17].

In addition, pregnancy can induce morphological changes that are difficult to assess due to the lack of contrast-enhanced MR imaging during pregnancy. However, the quantitative analysis of the glioma growth over time can be performed easily by performing serial measurements of T2-weighted or FLAIR abnormalities over time, including during pregnancy, using a methodology previously described [23]. A previous study demonstrated in a subset of 12 WHO grade II gliomas that pregnancy increased the quantified imaging glioma growth rates in 75% of cases concomitantly with an increased seizure frequency in 40% of cases. The latter prompted further oncological treatment after delivery in 25% of cases [10]. Another study of 18 WHO grade II and III gliomas has shown that tumor progression on MRI follow-up, despite no quantitative measurement, occurs during or immediately after pregnancy in 44% of cases [11]. The change in tumor growth rates during pregnancy is illustrated in Fig. 30.1. Interestingly, a recent study noted an imaging progression, quantified as the imaging glioma growth rates, in more than 85% of total cases, with rates up to double as high during pregnancy compared to before pregnancy in more than 70% of total cases [14]. Hence, contrary to the dogma that pregnancy has not convincingly been shown to accelerate glioma growth [1, 2], the clinical deterioration and radiological tumor progression observed in this patient population, although transient in most cases, can prompt intrapartum oncological treatment. In this particular series 18% of patients with a glioma diagnosed during pregnancy were incited to get oncological treatment during their pregnancy, 70% of those patients received treatment shortly after delivery, and 25% of the patients with a glioma known prior to pregnancy [14]. Lastly, besides clinical deterioration and imaging progression, according to Daras et al., pregnancy may also lead to a transformation to a higher grade of malignancy in some of these patients [13]. Altogether, these findings clearly suggest a link between pregnancy and glioma progression, thus raising concerns for women with diffuse low-grade gliomas considering childbearing.

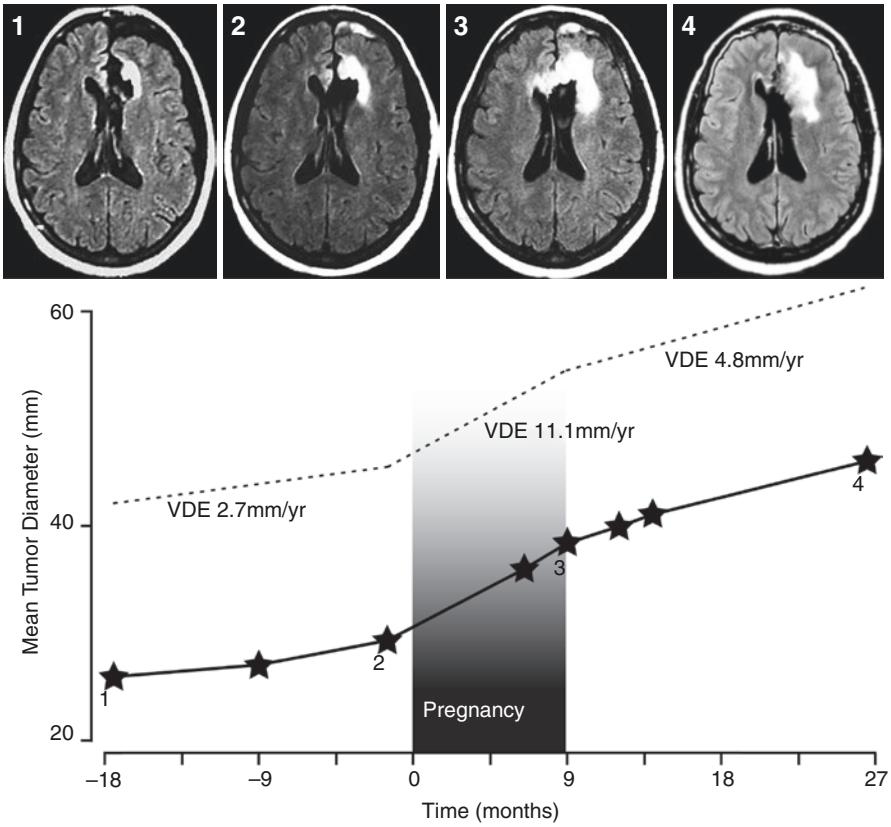


**Fig. 30.1** Example of the evolution of glioma mean tumor diameter (mm) over time before, during (*grey bar*) and after pregnancy in a left frontal diffuse low-grade oligodendroglioma treated by subtotal surgical removal 27 months before pregnancy. Before pregnancy, the residual tumor grew continuously, with a velocity of diametric expansion of 2.7 mm/year. During pregnancy, the tumor growth rate increased, with a velocity of diametric expansion of 11.1 mm/year. After delivery, the velocity of diametric expansion decreased to 4.8 mm/year without adjuvant oncological treatment

## 30.4 Possible Mechanisms and Hormonal Factors Involved in Pregnancy-Related Effects on a Glioma's Natural Evolution

The underlying mechanisms responsible for a glioma's clinical and radiological changes observed during pregnancy remain unknown. One certainty, according to Ducray et al., is that the clinical worsening observed with pregnancy cannot only be explained by increased intracranial pressure since the latter tends to remain constant until delivery [1]. Three main hypotheses, possibly intermixed, can be suggested as responsible for the clinical and radiological worsening observed during

pregnancy: immunological tolerance, steroid-mediated glioma growth, and hormone-mediated glioma growth [1, 13, 24, 25].

Possible interactions of pregnancy with gliomas have to do with the potential influence of sex hormones, which can cross the blood-brain barrier, and with physiological gestational changes [10, 13]. Specific steroid binding activity can be cancerous through activation of downstream expression of genes involved in cell growth, cell cycle progression and metastasis [13]. The levels of androgen, progesterone, and estrogen receptors seem to vary depending on glioma subtype and grade [13, 26, 27]. The presence of pregnancy-induced hormonal changes may lead to fluid retention, increased vascular volume, and peritumoral edema that may exacerbate an intracranial mass effect [1, 2, 10, 17, 28]. Some of the estrogen and progesterone receptors are cytosolic proteins [17]. Thus, they may mediate an increase in cellular dimensions through intracellular fluid retention, thereby contributing to tumor growth [17]. In addition, progesterone enhances glioma cell growth in humans [29] and expression of progesterone receptors increases with glioma grade as well as with invasion and migration markers [15, 27, 30]. Additionally, progesterone receptor positive gliomas have been shown to demonstrate high levels of Ki-67 expression [13, 27]. However, late manifestation of these gliomas, mainly during the second and third trimesters, would assume that the changes observed with pregnancy are likely related to more than just progesterone [17].

Contrarily, Cowppli-Bony et al. and Anic et al. found that low estrogen levels, whether earlier age at menarche, hormone replacement therapy, or oral contraceptive use, were consistently correlated with a decreased risk of tumor progression [25, 31]. The hypothesis behind these findings being that estrogen triggers growth inhibition and apoptosis in glioma cells through a multitude of mechanisms including cell cycle inhibition, decreased intracellular glutamate toxicity, and aromatase-mediated downregulation of astrocyte-derived TGF-beta1 and melatonin neuroprotection [25, 32, 33]. Furthermore, estrogen is also crucial to proper brain development during the gestational period, with a possible role in gliogenesis at that time [33]. Also noteworthy is that secretion of placental growth hormone at the maternal-placental interface stimulates secretion of growth factors, such as insulin-like growth factors, known to play a role in the proliferation and migration of glial cells, as well as secretion of pituitary gonadotrophins which also have receptors on tumor cells [4, 28]. Insulin-like growth factors 1 and 2 regulate and strongly stimulate glial cell migration and glioma growth [34, 35]. Peeters et al. found positive immunoexpression for insulin-like growth factor 1 receptor in 44% of pregnant patients with a diffuse low-grade glioma [14]. Though expression rate increased with WHO grade of malignancy, no clear correlation with glioma evolution during pregnancy, specifically clinical worsening and/or radiological progression, could be highlighted [14]. Of note, the latter study failed to find positive expression of estrogen, progesterone or growth hormone receptors in 20 diffuse low-grade gliomas of pregnant patients [14]. Results on the strict correlation of hormone receptors and tumor progression related to pregnancy remain inconclusive and no consensus has yet been reached.

## 30.5 Prognostic Factors and Survival Trends

A set of spontaneous prognostic factors in patients with diffuse low-grade gliomas has been isolated. The main estimated clinical, radiographic, or histopathological, predictors of both decreased survival without progression requiring oncological treatment, malignant-free survival and overall survival include male gender, older age (>40 years old), detrimental functional status (Karnofsky Performance Status <70), non-epileptic presentation (increased intracranial pressure, neurological deficit), absence of seizures at onset, non-frontal or parietal tumor location, large tumor size at diagnosis (>6 cm), tumor crossing the midline, rapid growth rates on MR follow-up (velocity of diametric expansion >8 mm/year), contrast enhancement (nodular-like or ring-like pattern), increased cerebral blood volume, presence of lactates and lipids on MR spectroscopy, astrocytic tumor subtype, high proliferative index, absence of 1p-19q codeletion, and absence of IDH1/2 mutation [36–43].

Interestingly, despite the previously discussed pregnancy-related effects on gliomas, pregnancy does not seem to markedly alter the outcomes of patients harboring a diffuse low-grade glioma. A recent retrospective cohort study on prospectively collected registry data identified 53 women who gave birth while harboring a diffuse low-grade glioma and showed that pregnancy does not seem to impact the overall survival in pregnant patients, compared to the control population of 247 women who did not give birth after the diffuse low-grade glioma diagnosis [44]. According to Peeters et al., no difference was found in progression-free survival between patients diagnosed with a WHO grade II glioma prior to pregnancy and those diagnosed during pregnancy [14]. Suggesting that early diagnosis does not give these patients a significant advantage with regards to time to tumor progression, and thus time of diagnosis and possible pre-pregnancy oncological treatment do not necessarily improve survivals. Therefore, whether a diffuse low-grade glioma was discovered prior to or during pregnancy should not impact the decision of when and how to treat the patient. Such outcomes could possibly be explained, or at least influenced, by the selection of female patients envisioning a pregnancy while harboring a glioma, including young age, good overall condition, tumor control at the time of pregnancy, and oncological treatments previously administered. In addition, the fact that female gender was isolated as a positive prognostic factor for diffuse low-grade gliomas cannot be ignored.

As previously mentioned, presence or absence of certain hormonal receptors and genetic markers can have some implications for patients' prognosis. However, possibly due to a shorter follow-up, no associations were found between survival without progression requiring oncological treatment or overall survival and presence of histopathological markers and molecular alterations in diffuse low-grade gliomas during pregnancy [14]. Negative alpha-internexin and positive p53 immunoexpression were associated with at least double the radiological growth rates during pregnancy compared to the values before pregnancy [14]. In addition, along with high insulin growth factor 1 receptor expression, those markers tend to be associated with higher tumor grade [14]. Next, an increase of the radiological growth rates during gravidity correlated with prompted oncological treatments immediately postpartum. Thus, low

grade gliomas with positive alpha-internexin, negative p53 expression, and low levels of insulin growth factor 1 receptor should be expected to have a smaller pregnancy-related increase in radiological growth rates, less likelihood of requiring oncological treatment promptly after delivery, and potentially a better overall prognosis.

## 30.6 Management Recommendations

Pregnancy makes oncological guidelines complicated as not all oncological treatments are approved for use in pregnant women. Despite controversy, different case series have reported pregnant women undergoing almost all combinations of oncological treatment types. In addition, management strategies are complicated by a variety of clinical and social factors [2, 14]. Consequently, these factors only allow for the assembly of an imperfect, practical, work-up plan for pregnant patients harboring a supratentorial diffuse low-grade glioma, using a multidisciplinary approach [1, 2, 4, 45]. An algorithm, adapted from Peeters et al., is proposed for management of the pregnancy in a patient diagnosed with a diffuse low-grade glioma prior to gravidity and during the pregnancy [14] (Fig. 30.2).

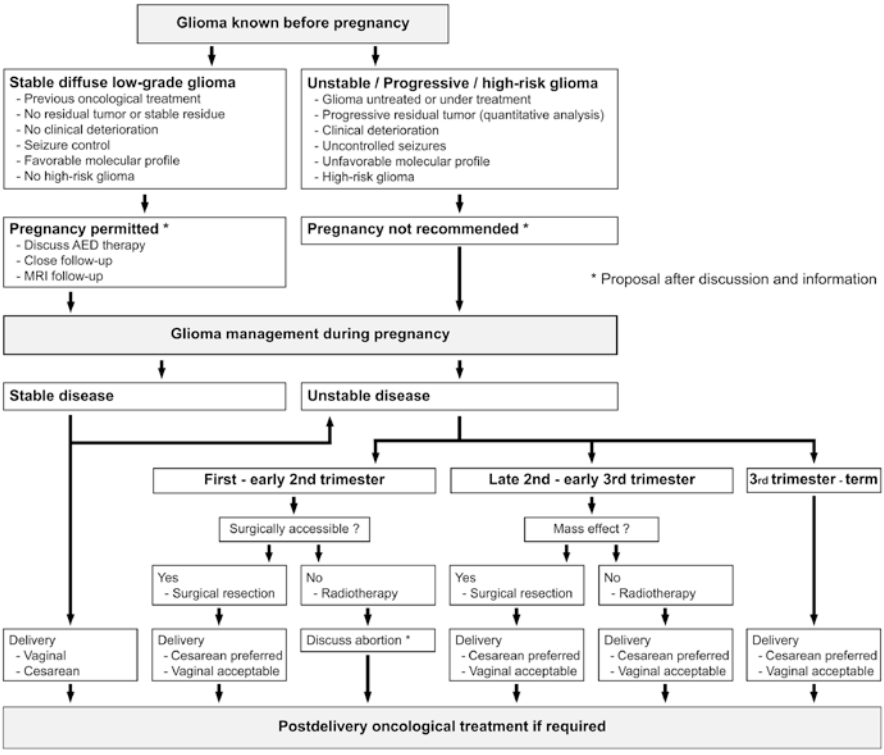


**Fig. 30.2** Algorithm of a management proposal of pregnancy in a patient with a diffuse low-grade glioma

Most importantly, the patient should have the best available treatment for their disease. The management itself will depend on the severity of the symptoms, the tumor size, location and histopathology, the patient's gestational age, and, last but not least, the patient's wishes [1, 28]. A watchful waiting policy is proposed for women diagnosed with a suspected diffuse low-grade glioma in their first and early second trimester [17, 18, 24, 45–47]. Clinical series have previously shown that the pregnancy achievement was possible in such condition without worsened oncological outcomes for the patient, as illustrated in Fig. 30.3. Indeed, results from a retrospective study confirm the feasibility of a watchful waiting policy in stable patients as 82% of the patients with a glioma discovered during pregnancy remained untreated until delivery, including 14% of preterm planned deliveries allowing a more prompt oncological treatment [14]. If required, and based on successful series of cases, there appears to be no clear contraindication to neurosurgical intervention

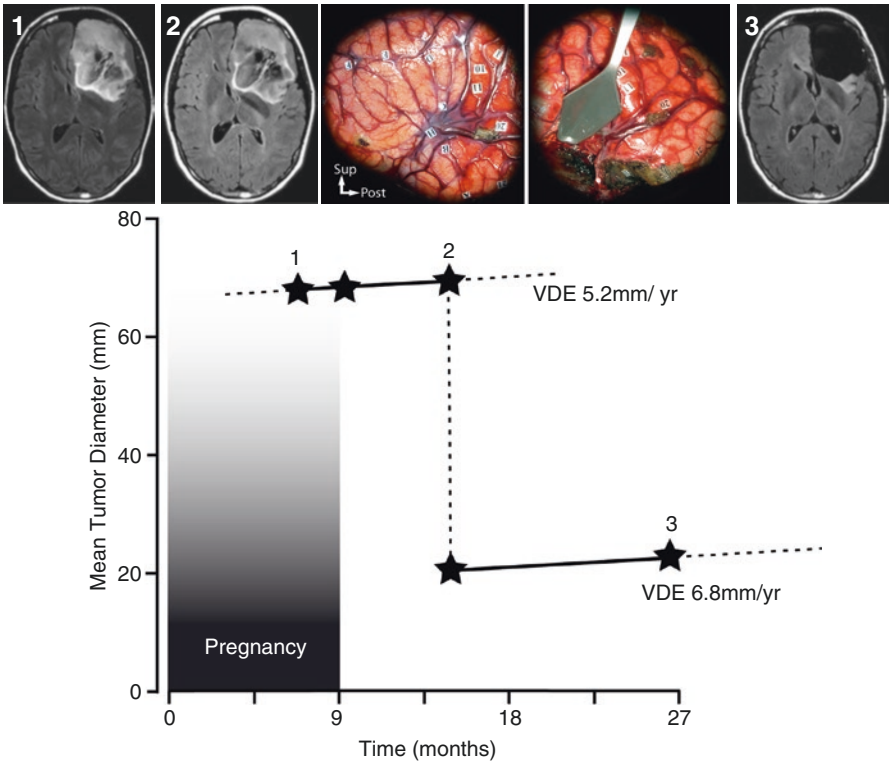


**Fig. 30.3** Example of the evolution of glioma mean tumor diameter (mm) during pregnancy (*grey bar*) and after delivery in a left fronto-temporo-insular diffuse low-grade oligodendroglioma revealed by epileptic seizures at 31 weeks of pregnancy and managed conservatively until planned delivery through caesarean section under general anaesthesia. A functional-based resection using direct electrical cortical and subcortical mapping under awake condition was performed 7 months post-delivery allowing for a subtotal surgical removal. During pregnancy and after delivery before surgery, the tumor growth rate demonstrated a velocity of diametric expansion of 5.2 mm/year. After subtotal surgical removal, the residual glioma grew at 6.8 mm/year without adjuvant oncological treatment (Table 30.1)

for intracranial neoplasms during pregnancy, as is the current preferred management for non-pregnant patients. Similarly, results from a retrospective study confirm the feasibility of safe surgeries in pregnant patients, as five patients underwent safe surgeries, with or without adjuvant treatment, during the first, second or third trimesters [14]. For the patients who are stable but in their late second and third trimester, gestational advancement to term should be considered. Then, delivery is an acceptable option prior to oncological treatment for the women with progressing neurological signs [1, 24, 45, 47].

For unstable patients, urgent neurosurgery is the standard of care for first and early second trimester patients. For unstable patients in their late second trimester to term, a cesarean section followed by urgent neurosurgery is recommended, though some studies discuss the possibility of performing a craniotomy prior to the delivery [17, 46, 47]. The administration of chemotherapy and/or radiotherapy during pregnancy is not required in front of a diffuse low-grade glioma but raises questions when faced with gliomas of a higher grade of malignancy [14].

## 30.7 Conclusions and Practical Implications

Clinical evidence suggests that pregnancy impacts the evolution of supratentorial diffuse low-grade gliomas. With regards to management, prudence is required when interpreting the potential guidelines for pregnancy in women with a supratentorial diffuse low-grade glioma, due to low statistical power and number of these studies. Nonetheless, based on a synthesis of previous observations, several points can be emphasized [2, 4, 10, 13, 14]. When a woman harboring a diffuse low-grade glioma envisions a pregnancy, or when a possible diffuse low-grade glioma is discovered in a pregnant patient, counseling her and her partner is recommended, informing them that: (1) knowledge on the question is scarce and no definite guidelines exist; (2) completion of the pregnancy is feasible with the birth of a healthy baby; (3) pregnancy may accelerate diffuse low-grade glioma growth, may exacerbate clinical deterioration, and may prompt oncological treatments earlier than in the diffuse low-grade glioma population; (4) no data confirm that pregnancy impacts the survival but pregnancy possibly increases the risk of transformation of the glioma towards a higher grade of malignancy; (5) the potential need for oncological treatment during pregnancy has serious known hazards for the fetus; (6) there are potential problems associated with seizure control in addition to risks of congenital abnormalities from anticonvulsant therapy; (7) the timing and choice of obstetrical interventions matter; (8) some intense oncological treatments may impact the child's growth and development. For all cases, it is strongly advised to take on a multidisciplinary approach to management [4, 10]. Clinically, the recommendations are: (1) careful and frequent neurological follow-ups during pregnancy and after delivery; (2) routine MRI follow-ups with quantitative assessment of the glioma during gestation; (3) rigorous obstetrical monitoring.

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# Chapter 31
# Biomathematical Modeling of DLGG

**Emmanuel Mandonnet**

**Abstract** In this chapter, we review recent advances in biomathematical modeling of glioma growth, based on the proliferation-diffusion equation. We show how the computational simulations from this equation can be compared with real tumor evolution on MRI and how these simulations progressively integrate more realistic anatomical knowledge, improving the accuracy of the virtual tumor evolution. The Achilles' heel of this model comes from the lack of quantitative relation between cell density and abnormal signal on conventional MRI, although future methods could overcome this limitation by taking advantage of multimodal sequences. In its simplified version, the model offers a practical way to monitor tumor dynamics, by estimating the velocity of the tumor front. We also envision applications to the management of DLGG, regarding model-based personalization of treatment sequence and evaluation of treatment efficacy in clinical studies. Finally, we propose a three pathways model of malignant progression. One of this pathway has been mathematically modeled by the proliferation-invasion-hypoxia-necrosis-angiogenesis (PIHNA) system of equations. We show how this model leads to the important concept of kinetics grade, which is complementary to the usual histological grade.

**Keywords** Biomathematical modeling • Diffuse low-grade glioma • Computational models • Malignant progression

## 31.1 Introduction

Since the pioneering work of Murray and Alvord in the 1990s [1–3], there has been an increasing interest for biomathematical modeling of glioma growth. It is remarkable that the proliferation-diffusion model initially proposed by these authors still constitutes the core of elaborated approaches more recently developed. The specific

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case of low-grade glioma could be especially favourable for modeling purpose, as their biological behaviour seems to be relatively constant during the "low-grade" phase. Moreover, since «watch and wait » policy has been until recently a standard recommendation in many centers, series of patients radiologically monitored over several years can be retrospectively collected, and serial MRI data sets before any treatment are available for comparison with model predictions.

In this chapter, we will give a brief overview about the proliferation-diffusion equation and explain the difficulties in personalizing the model based on serial MRI images. We will also detail current and future clinical applications, with special emphasis on the key approximations that should be improved in future works. Finally, we will also discuss why the complex problem of modeling the malignant transformation constitutes a real challenge.

## 31.2 Modeling the Low-Grade Period: The Challenge of an Image-Based Personalized Model

### *31.2.1 Modeling Proliferation and Migration of Glioma Cells: From a Mathematical Equation to Computational Simulations*

On a biological point of view, the behaviour of glioma cells is two fold: proliferation and migration. Mathematical models translate these two characteristics into an equation. The variable in the equation is a coarse-grained tumor cell density (c), which represents the average concentration of tumor cells in each cubic millimeter of the brain. The generic form of the equation, initially introduced in the 1990s [2, 3], is the following:

$$\frac{\partial c}{\partial t} = \rho c + \nabla.\left(D \nabla c\right)$$

that is, evolution with time of tumor cell density (c) at each position in the brain = proliferation (ρc) + diffusion (∇.(D∇c)).

The direct problem consists to compute this equation numerically, on a digital brain template, for given values of ρ and D. The results of the simulations give the evolution over time of maps of tumor cell density (see Fig. 31.1). The template is usually a generic atlas. Over the past decade, advances has been made in integrating a more precise anatomy in this atlas (see Fig. 31.1): whereas the very first templates were built from a 2D CT scan [2, 3], just outlining the brain surface and the ventricles, more recent works are based on 3D-MRI atlases (on which CSF, white and grey matter segmentations are performed [4]), eventually including detailed white matter architecture via DTI sequences [5, 6]. In that case, the D in the equation should read as a tensor of cell diffusion, which can be

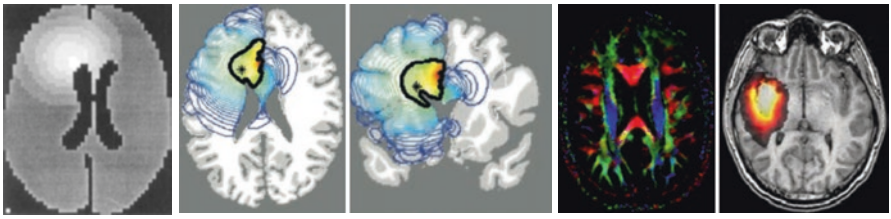


**Fig. 31.1** Advances over a decade in the anatomical accuracy of the simulations. The very first templates in 1995 were built from a 2D CT scan [2, 3], just outlining the brain surface and the ventricles. More recent works in 2000 were based on 3D-MRI atlases (on which CSF, *white* and *grey* matter segmentations were performed [4]). Finally, in 2005 detailed *white* matter architecture via DTI sequences was eventually included [6]

built from the tensor of water diffusion, introducing a factor $r$ of anisotropy increase between the two tensors. Diffusion images from an individual healthy volunteer are used [5, 6], but future studies could rely on a tractographic atlas or incorporate own patient DTI MRI. Whatever the elected template, it is of utmost importance that an expert validates its anatomical accuracy. For example, as explained in [6], a wrong segmentation of the subarachnoidal spaces can create artificial bridges of grey matter, especially between the frontal and temporal operculum, leading to unrealistic growth patterns in the simulations. In an effort to correct such inaccuracies, an expert-validated mask of subarachnoidal spaces has been recently built, that greatly improves the veracity of the virtual growth patterns [7].

### *31.2.2 The Visibility Threshold Hypothesis*

The tumoral cell density, which is the variable in the proliferation-diffusion model, is not directly measured on MRI. One has to make the reasonable and simple assumption that the tumor is visible on flair MRI at the condition that tumor cell density is above a given value (visibility threshold). Hence the link between simulated and real tumors relies on the comparison between the thresholded isocontour on cell density maps and the effective contours of the tumor on MRI. Unfortunately, there are very few datas in the literature about the value of this visibility threshold. Only one study correlating histological analysis with hypodensity on CT suggested a value of 8000 cells/mm$^3$ [1]. Actually, current studies on this topic suggest that the MRI flair hypersignal is not only dependent on the cell density but is also correlated to the intra- and extra-cellular water content [8]. Hence, it should kept in mind that the visibility threshold hypothesis is a strong approximation, and that most of the following results will be based on this assumption.

### *31.2.3 Model-Based Assessment of Tumor Dynamics*

To go a step further towards clinical application, one needs to solve the inverse problem [9], that is to identify the pair of parameters ρ and D specific to a given patient, resulting in the best fit between simulations and a dataset of longitudinal MRIs of the patient. This field of research is also called model personalization. In a first approximate solution of this problem, it can be shown that the proliferation-diffusion equation states that the velocity of expansion of the visible front is a constant given by $2\sqrt{(\rho D)}$ (see Fig. 31.2). In other words, the slope of the linear evolution curve of tumor diameter is given by $4\sqrt{(\rho D)}$, where the diameter $d = (2 \times V)^{1/3}$ is computed from the volume V. Note that V is estimated by full 3D-segmentation of the hypersignal on flair sequences. Thus, rather than expressing growth rates in terms of volumetric doubling times (which is the standard method for exponentially growing tumors), one should focus on the slope of diameter growth curves. Recent studies on low-grade glioma kinetics thus enabled to estimate the growth rate of tumor diameter (the so called velocity of diametric expansion, VDE) for individual patients. The average VDE is about 4 mm/year [10], leading to a value of ρD close to $9 \times 10^{-6}$ mm$^2$ day$^{-2}$. Hence this formula is a very simple and convenient way to estimate individually the product ρD from longitudinal MRIs. Finally, quantitative histological analysis could potentially allow to infer

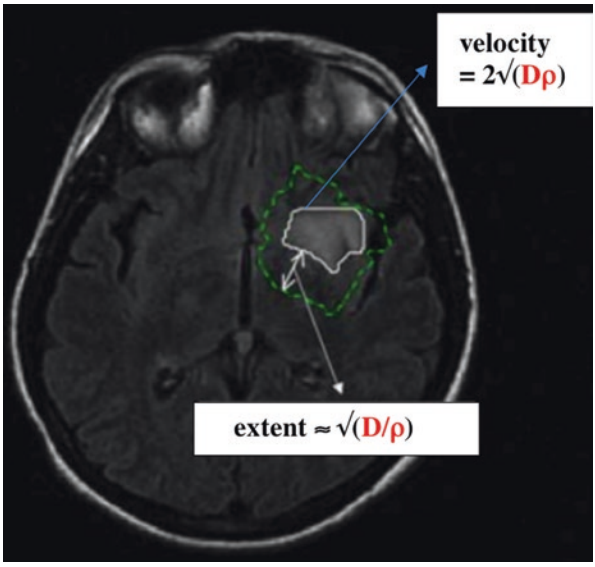


**Fig. 31.2** The role of the product Dρ and the ratio D/ρ. The two contours come from the simulation of a patient case. The *thick white* contour corresponds to the threshold of cell density visible on MRI. The velocity of this visible tumor front is given by the formula $2\sqrt{(D\rho)}$. The *dotted line* is the contour corresponding to a cell density five times smaller than the threshold. The extent of the non-visible tumor part is tuned by the ratio D/ρ

the ratio D/ρ: the steepness of the cell density decrease at the tumor margins can be linked to this ratio D/ρ [11]. Surprisingly, there are very few data in the literature on such quantitative histological measures.

More sophisticated tools are currently under development [12, 13], that will allow to estimate the optimized values of parameters minimizing the difference between real and simulated time series of segmented contours. This inverse problem is numerically highly challenging and even not always solvable given the paucity of datas (patients undergo usually two or three MRIs before treatment). At best, one can identify the two products $\rho D_w$ and $\rho D_g$, $D_w$ and $D_g$ being the diffusion coefficients in white and grey matter respectively [13]. From this latter study, one can conclude that image-based model personalization will not be achievable in clinical practice, unless one can find an imaging modality that would be indicative of cell density. In this spirit, some authors proposed a method in contrast-enhancing DLGG, assuming that T1-gado and Flair contours correspond to two isolines of distinct visibility thresholds of cell density. They used the two-thresholds method for estimating the ratio D/ρ [14] and the aforementioned method of velocity of diameter expansion to compute the product Dρ. Their results will be discussed in the next paragraph, but it should be kept in mind that there is no evidence that T1-gado and Flair contours are correlated with distinct levels of cell density.

Finally, any image-based personalization implies the segmentations of the tumor on successive images, which is a time consuming task. Hence, this method should be combined in the future with automated tools of segmentation.

### *31.2.4 Parameters Values for DLGG*

For low-grade glioma, values for parameters were initially extrapolated from the values found for high grade glioma and expected to be centered around 0.438/year for ρ and around 4.75 $mm^2$/year for D [1]. A range of values has been proposed by Harpold et al. [15], with ρ between 1 and 10/year and D between 10 and 100 $mm^2$/year. In a paper aiming to estimate the individual tumoral birthdates in a large series of DLGG glioma, a range of values for ρ and D was found, which significantly differed from the one previously proposed [16]. A first paper attempted to estimate D and ρ by eyeball fitting of a real patient evolution with simulated images. The best fit was achieved for the values ρ = 0.438/year and D = 3.65 $mm^2$/year [6], which lies within the domain found by Gerin et al. A very recent study estimated D and ρ on a series of 14 patients with DLGG showing an area of contrast enhancement by using the two-threshold method [17]. While some of the values fall between the expected range, some others were more suggestive of a grade III, as it could have been anticipated given the presence of a contrast enhanced area. All results are summarized on the log-log plot on Fig. 31.3.

For the anisotropic version of the equation, it has been found that the ratio *r* of anisotropy of the tensor cells has to be increased about ten fold compared to the

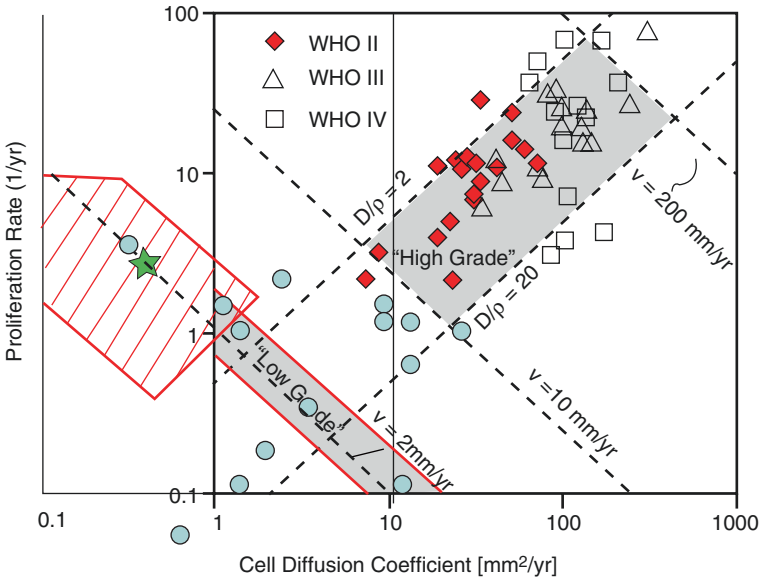


**Fig. 31.3** Numerical values of D and ρ in a log-log plot. This diagram has been first discussed by Harpold et al. [15]. The diagonal v = 2 mm/year corresponds to those glioma with a constant product Dρ, with a VDE of 4 mm/year, which is the average value for DLGG. *Red diamonds* correspond to the values found by Ellingson et al. [20] for WHO grade II glioma. Their values are probably irrelevant, as they fall within the expected range for high-grade glioma. The values found by Gerin et al. [16] in the *red dashed area* are correctly centered around the diagonal with a VDE equal to 4 mm/year (i.e. v = 2 mm/year), but with values of the ratio D/ρ smaller than predicted by Harpold et al. Note that the *green star*, corresponding to the DLGG simulation performed by Jbabdi et al. [6], falls within the values found by Gerin et al. The *blue circles* correspond to values found in DLGG with contrast enhancement [17]

anisotropy given by the tensor of water diffusion measured on DTI, reflecting the well known propensity of glioma cells to migrate longitudinally rather than orthogonally to the axonal pathways [6]. This value was indeed needed to reproduce finely the shape of the tumor (which was known to be correlated with the shape of the white matter fasciculus [18]).

### *31.2.5 Virtual Imaging: Seeing Beyond the Visible*

Interestingly, the ratio D/ρ controls the extent of non-visible part of the tumor (i.e. the number of cells located in areas with a cell density lower than the visibility threshold): the higher the ratio D/ρ, the greater the radiologically non-visible part of the tumor [19] (see Fig. 31.3). Although such virtual imaging could be potentially powerful, its practical interest is currently limited, for the two previously mentioned reasons: the lack of reliability of the visibility threshold hypothesis, and the

challenging problem of determining the personalized values of ρ and D for each patient. Should such limitations be overcome, important applications would result, for surgical decision making and for designing radiation therapy margins.

## 31.3 Future Methods of Model Personalization

### *31.3.1 Apparent Diffusion Coefficient: The Missing Link Between MRI and Cell Density?*

Ellingson et al. proposed in 2011 an elegant and powerful method to estimate 3D individual maps of proliferation and diffusion parameters from at least three longitudinal diffusion weighted sequences [20]. The key assumption is an inverse linear correlation between ADC and cell density (ADC = αc + β, α being negative). These authors have indeed found a negative correlation between cell density and apparent diffusion coefficient, measured from diffusion weighted sequences [21]. Assuming this relation, one can fully inverse the proliferation-diffusion equation, with ρ(x) and D(x) as the unknown variables (ρ(x) and D(x) are the proliferation and diffusion coefficient, that can vary with position x). Three successive ADC maps are nevertheless required, to estimate the time derivatives terms in the equation. The results give nice color maps for proliferation and diffusion, showing spatial changes of these parameters. However, the link between cell density and ADC is not that clear, as ADC changes can be observed in relation to demyelination, edema, and disruption of normal brain architecture [22, 23]. This might explain why the values found by these authors for ρ and D in low-grade glioma are not consistent with the values estimated by the aforementioned approach based on longitudinal morphological follow-up (see Fig. 31.3).

### *31.3.2 Towards Integration of Longitudinal Multimodality Imaging in the Model*

Spectroscopic magnetic resonance imaging also offers a means to estimate cell density and/or proliferation rate of a DLGG, and to get a rough estimate of their spatial variations using multivoxels techniques [24, 25]. Similarly, indices derived from DTI sequences (p and q values, fiber density, …) could also be linked to the cell density in the invasion part outside the flair hypersignal. Hence, this information could potentially be used as inputs for the model personalization process. Promising methods, using a Bayesian framework, are under development to integrate these multimodality imaging and to manage the uncertainty inherent to these experimental data [26]. However, the key point in these methods still relies on the mathematical links between cell density and multimodal imaging parameters

(ADC, Cho/NAA, CNI, p & q in DTI, …), and more efforts should be devoted to their determination.

## 31.4 Future Applications of Personalized Models

### *31.4.1 Model-Guided Optimization of Treatment Sequence*

Assuming that the inverse problem has been solved—i.e. one is able to personalize the model based on (multimodal) MRI—treatment sequences can be simulated on the virtual tumor of the patient, allowing to select an optimized scheme for each patient. For example, it has been suggested that the benefit of gross total resection for tumors with high values of D/ρ is limited, since a lot of isolated tumor cells would be left even after a radiologically complete resection [27]. One study tested this idea in the context of glioblastoma, and found indeed in a large series of more than 200 patients that no survival benefit of complete resection versus biopsy was observed for patients with high values of D/ρ [28]. However, another study failed to replicate these results [14], proving that the personalization method (based on the hypothesis that T1-gado and Flair extent delineates two isolines of high and low cell density respectively) is not reliable (which does not come as a surprise, since it is well known that flair extent in glioblastoma may result from inflammatory or vasogenic edema, rather than from tumor cells only).

In the same vein, the model would predict that a supra-radical resection of high D/ρ tumors would dramatically increase the delay of recurrence [27]. Identifying these patients would be an essential step, as this information is another parameter to include in the evaluation of the onco-functional balance (see chapter on onco-functional balance by Mandonnet et al.).

Thus, the combined use of patient-specific simulations with tools of preoperative functionally-based prediction of extent of resection [29, 30] could assist the decision making process of surgery versus another oncological treatment (chemotherapy, radiation therapy). To this end, the effect of chemotherapy and radiation therapy should also be included in the model. Some attempts have already been done for modeling radiotherapy in high grade glioma [31, 32], but the validity of such models is not well established. Moreover, the prolonged effect of chemotherapy and radiation therapy in DLGG [33–35] warrants to develop specific models of DLGG response to these treatments [36, 37].

### *31.4.2 Model-Based Evaluation of Treatment Efficacy*

The evaluation of treatment efficacy in DLGG is in itself a real challenge. The usual methodology of evidenced-based medicine that prevails in other fields of oncology, i.e. randomized studies comparing two treatment arms, is inadequate for DLGG

(in their true low-grade period), given the very long survivals of these patients [38]. Moreover, most patients will ultimately also receive the treatment of the other arm, thus precluding to analyze separately the effect of each treatment. Personalized models can play an important role to quantify individual treatment response: for each patient, simulations can act as its own virtual control. Hence, response can be defined at any time as the difference between real (measured) tumor diameter in the patient under study and simulated (predicted) tumor diameter in its untreated virtual clone. In its simplified version, this method consists in comparing the slopes of tumor diameter growth curve before and during treatment.

### *31.4.3 The Backward Extrapolation*

Simulations can also be used to estimate the real biological birthdate of a DLGG, which is anterior to the radiological birthdate estimated by a simple backward linear extrapolation (see chapter on dynamics of DLGG). It can be shown that, within some approximations of the proliferation-diffusion model, a corrective term of 20/v has to be added to the radiological birthdate [16], v being the velocity of diametric expansion (VDE). Applying this principles to a series of 144 patients, it has been found that patients could be classified roughly in two groups: a group of patients with low velocities (v between 1 and 4 mm/year) and a group with high velocities (v between 4 and 8 mm/year). For the low velocity group, patients are about 15 years of age at estimated biological onset, whereas for the high velocity group, patients ages are centered around 25 years of age [16]. Even if these results should be considered very cautiously given the strong underlying hypothesis of the model, they could help to identify different molecular signature of these two groups of tumors and to target age groups for a screening policy (see chapter screening).

## 31.5 Modeling the Transition Towards Higher-Grade

The transition towards a glioma of higher grade is a somehow unforeseeable event, albeit unavoidable, in the natural history of a LGG. It has been well proven that the greater the initial tumor volume (or its residue after surgery), the higher the risk of imminent anaplastic transformation. Whereas the reference definition of anaplastic transformation is based on the histological criteria of a grade III or IV glioma, it is now widely admitted that it can be also diagnosed by *the appearance in the longitudinal follow-up* of a new contrast-enhanced nodule on T1-gado MRI.

Considering that there is no neoangiogenesis in grade II glioma, we conclude that innate vascularization of the brain parenchyma (probably combined with an optimized metabolic scheme) is able to fulfill the energetic needs of a tumor growing up to 4 mm/year.

On a fundamental point of view, three distinct pathways can lead to the onset of neoangiogenesis (which is the major criteria of malignant transformation):

1. A genetic mutation (or the cumulative effect of several mutations or any changes at molecular scale) can directly drive the building of neo-vessels, irrespective of the hypoxic state of the cells (as it can be observed in the model of tumorigenesis of hemangioblastoma in Von Hippel Lindau patients),
2. Without any additional molecular changes, due to the progressive growth of the tumor, cells can enter an hypoxic environment (decrease of available energetics/oxygen resources per cell), triggering the neo-angiogenic cascade,
3. A genetic mutation (or the cumulative effect of several mutations or any changes at molecular scale) can induce the appearance of a more aggressive cellular behaviour (regarding proliferation rate and/or migration ability), which in turn will lead to an hypoxic focus within the tumor (increase of energetics/oxygen needs per cell).

This three pathways model could explain why longitudinal imaging can fail to anticipate malignant progression. For example, in pathways (1) and (2), the VDE of the tumor measured on the flair images should not increase before the onset of contrast-enhanced nodule. An increase of the VDE should precede the appearance of the contrast-enhanced focus only in pathway (3), as reported by two different studies [39, 40]. Similarly, spectroscopic imaging, which is based on surrogate marker of cell density and/or proliferation (i.e. choline increase, NAA decrease, or Cho/NAA ratio increase), might not be able to predict anaplastic transformation in pathways (1) and (2). In the pathway (1), one would indeed not expect an increase of such markers, as the cellular density and the proliferation rate remain stable despite onset of contrast-enhancement; and in the pathway (2), the increase in cellular density would be not significant enough to be detected by choline and NAA changes. Only in pathway (3) would changes in these compounds be an early marker of anaplastic shift. Of note, recent genomic and epigenomic studies [41–45] give support to pathway (3) in IDH-mutated tumors.

Moreover, this classification could also be of importance regarding treatment selection. It would be expected that surgery is of crucial importance to stop pathway (1), and to a lesser extent to refrain the progression in pathway (2). Pathway (3) would rather require chemotherapy or radiation therapy, as it is likely that the change in cellular behavior has also spread to the cells in the radiologically non-visible part of the tumor.

Interestingly, micro-environment-driven progression has been modeled, within the framework of the proliferation-invasion-hypoxia-necrosis-angiogenesis (PIHNA) model [46]. This model builds upon the proliferation-diffusion model, adding two other populations of cells: hypoxic and necrotic cells, as well as concentration of angiogenic factors and neo-vessels. Normoxic cells evolve towards hypoxic cells at a rate proportional to the concentration of cells and to the proliferation $\rho$. Hypoxic cells generate angiogenic factors, which in turn lead to an increase of vessels density. The advantage of this model is that it allows quantitative comparison with some histological immunomarkers, like the density of HIF1-$\alpha$ positive cells or the density of

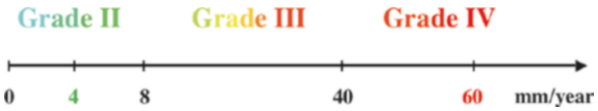


**Fig. 31.4** Kinetics classification. The range for grade II is based on the results from Pallud et al. [47]. The range for grade IV comes from the work of Wang et al. [47]. Note that a grade IV kinetics might present at diagnosis with histological characteristics of an histological grade II (at the condition the ratio D/ρ is high, hence the cell density quite low)

VEGF positive cells. The drawback of this approach is that several new parameters are introduced, the values of which are poorly known. As an interesting result, it is shown that a glioma with a product Dρ in the typical range of a glioblastoma (corresponding VDE around 40 mm/year) can exhibit, at initial diagnosis, histological features of a grade II glioma at the condition its ratio D/ρ is very high. Of course, within the next 3 months, histological characteristics of a glioblastoma arise in the simulated tumor. The authors interpret this simulated tumor as a «secondary glioblastoma». We do not share this opinion, as the initial value of D and ρ were typical of a glioblastoma from the beginning. In other words, the tumor is a *de novo* glioblastoma, but due to the high ratio of D/ρ, the cell density was not high enough to generate hypoxic focus triggering the neo-angiogenesis cascade during the first months of growth. In our view, these tumors correspond to «false» grade II (because of high VDE) despite true histological characteristics of grade II: they belong to the 10–15% of histological grade II glioma with an initial VDE higher than 8 mm/year as described in a series of 143 patients [47]. This underlines the importance of a kinetics grading based on VDE, independently of the histological grading (see Fig. 31.4).

## 31.6 Conclusion

Biomathematical modeling applied to glioma is still in its infancy. But the joined advances of computational modeling and multimodal MRI should offer in a near future powerful tools enabling to build realistic patient-specific virtual tumors. This would open new avenues to develop model-based virtual imaging, and to progress towards the individual optimization of treatment planning.

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# Chapter 32
# Resection Probability Maps of Glioma

**Philip C. De Witt Hamer, Emmanuel Mandonnet, and Hugues Duffau**

**Abstract** Resection probability maps capture the surgical treatment decision to stop glioma removal for many patients. This quantitates and explicates the extent of resection per voxel in the brain for a patient cohort from a single surgeon, a surgical team, an institute, or a group of institutes. This information may be useful for a new individual patient to make decisions on patient selection for resective surgery or for the application of advanced techniques to determine where to stop the resection. It may be used for surgical planning and postoperative evaluation of residual tumor. Furthermore, patient cohorts can be compared to pinpoint differentially resected regions in the brain to facilitate discussion by experts to improve surgical decision making. The processing of resection probability maps consists of collecting imaging data and related clinical data, segmenting of tumor outline before and after treatment, registering patient MRIs to a standard brain space, and statistical analysis of two or more resection probability maps.

**Keywords** Diffuse low-grade glioma • Surgery • Extent of resection • Probability map

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## 32.1 Purpose of Resection Probability Maps in Glioma Surgery

The aim of resective surgery of a glioma is a maximal safe tumor removal. For this, maximizing the oncological benefit by tumor load reduction is balanced with maximizing the odds for preservation of functional integrity by avoiding interruption of essential brain circuits. Hence, the neurosurgeon optimizes the surgical plan between these two goals for each patient. The most important surgical decision is when to stop tumor removal. If stopped too soon, then not enough tumor is removed, so that the tumor will recur earlier, which demands second treatment, while the patient will die sooner. If stopped too late, then too much tumor-infiltrated functional brain is removed, so that brain function deficits occur that will be permanent and render the patient's quality of life poor. Brain location of the tumor is the key parameter for this decision making, which is complicated by imperfect understanding of the brain and its compensation mechanisms. Other patient characteristics are also important for this decision making, such as age, neurological symptoms, general condition, comorbidity, anticipated glioma grade and type, and personal preferences of the patient and the neurosurgeon based on beliefs, attitude, and philosophy.

At present neurosurgeons learn when to stop tumor removal on a case-by-case basis, building an implicit mental image to which a new case will be compared. What is needed is a framework that captures neurosurgical knowledge from experts and that pools patient data for the neuro-oncological community to ensure the best practice for all patients with diffuse gliomas. The problem is that standards are lacking to determine the quality of glioma surgery for an individual patient or a group of patients. Likewise, a common framework is lacking to quantitatively compare decisions between individual neurosurgeons or neurosurgical teams.

In attempting to quantitate the quality of glioma surgery, several outcome measures have been considered. To measure the oncological benefit the percentage of patients with a low residual tumor volume, e.g. less than 10 mL, or high extent of resection, e.g. 'gross total' or 'subtotal', or the time to progression or overall survival have been reported [1–6]. To measure the preservation of functional integrity the percentage of patients with a neurological deficit or the group average score of cognitive domains have been reported [7, 8]. Although informative, the interpretation of these measures remains ambiguous for a number of reasons. First, definitions are not standardized and vary widely. For instance: 'gross total resection' has been defined as absence of MRI T2 hyperintensity to diameter residuals of up to 10 mm [9–13]. Second, outcome measures such as survival times and neuro(psycho)logical performance may depend more on tumor specifics, such as IDH1 mutation status and loss of heterozygosity of 1p19q, and secondary treatment, such as second surgery, radiotherapy, chemotherapy and inclusion in clinical trials, than on the quality of the first surgery. This complicates a valid interpretation of the quality of neurosurgical care. Third, bias from selection of patients for resective surgery can have a major impact on these measures. For instance, a very conservative approach to the indication for a glioma resection could result in an artificial excellent outcome for a highly selected subset of less complex cases.

Many techniques have been introduced to improve surgical outcome by more precise and less burdensome local treatment. Some techniques have been developed to maximize tumor removal, such as image-guidance of MR spectroscopy images and PET [14, 15], intraoperative MRI [16], intraoperative ultrasound [17], and 5-ALA fluorescence [18]. Other techniques have been developed to preserve functional integrity by localizing brain function, such as functional MRI [19], DTI [20], magnetoencephalography [21], transcranial magnetic stimulation [22], and grid electrode implantation [23]. Yet other techniques may serve both goals, such as intraoperative stimulation mapping [24]. Surgical teams vary widely in the application of these techniques based on limited evidence, availability, mechanistic reasoning, and expert opinion. This introduces considerable treatment variation in the field. Consequently the field should benefit from a method to explicate the differences in surgical decision making to pinpoint the discussions between surgical teams and experts.

The underlying question is whether a 'perfect cut' exists for any patient with a glioma. Resection probability maps capture the concept of resectability in patient cohorts on a voxel-wise basis throughout the brain [25–28] (Fig. 32.1). This facilitates the comparison of resection results without brain location bias, and without any presumption for the functional or anatomical organization of the brain. Resection

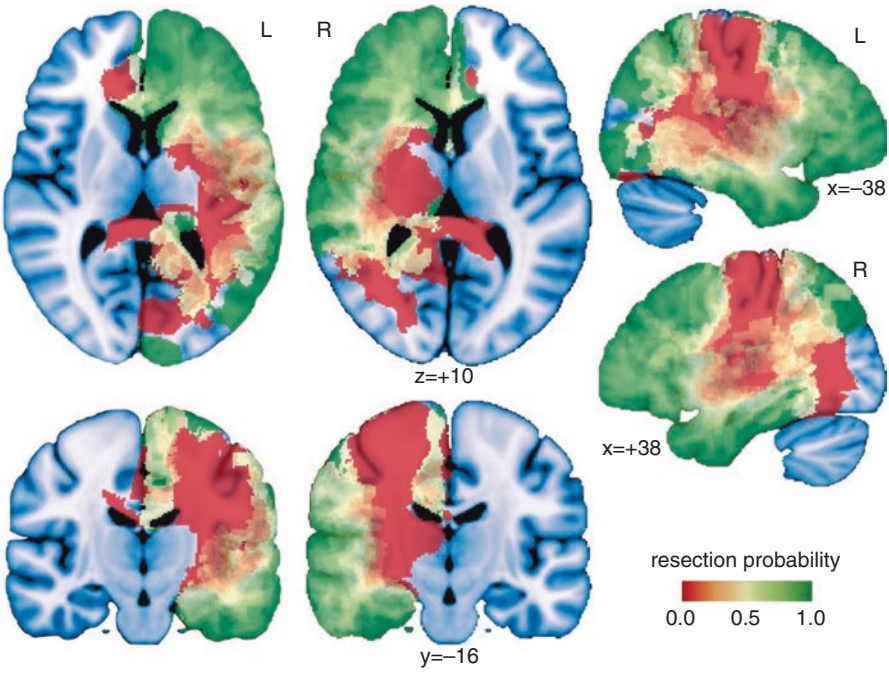


**Fig. 32.1** The resection probability map in three orthogonal sections for left-sided and right-sided nonenhancing gliomas based on 234 patients. The color legend corresponds with the resection probability as indicated. The x/y/z coordinates refer to MNI152 standard brain space

probability maps can be considered a step towards ‘brain tailored’ surgical treatment for patients with a glioma. So that, brain regions within patients should be identified for more and less radical resection. Such improved selection of patients and brain regions could bring more effective tumor removal, less loss of brain function and less costly treatment.

## 32.2 Examples of the Use of Resection Probability Maps

Resection probability maps could both serve individual patient care and evaluation of patient groups. None of these applications have been evaluated in clinical practice, but may prove to be useful for evaluation and ultimately improvement of the quality of care for patients with a glioma.

### *32.2.1 Individual Patient Care*

For the individual patient, indication for surgery, surgical planning and postoperative evaluation may be enhanced by relating the tumor location of an individual patient with aggregated results of other patients, which can be a resection probability map for instance based on best practice or based on previous institutional experience.

#### 32.2.1.1 Patient Selection

The decision to advice a patient to have resective surgery for a glioma depends on several factors, including symptomatology and anticipated reduction of symptoms, radiological diagnosis of grade and type, patient condition, age, comorbidity, tumor size, tumor location, and anticipated resectability. In many institutions treatment decisions are made in a brain tumor board meeting with professionals from different disciplines taking part in a structured discussion on the arguments in favor of and against a number of treatment alternatives. The treatment options with the arguments provided by the board meeting are discussed afterwards with the patient, who ideally comes to a ‘shared treatment decision’. Sometimes explicitly, but oftentimes implicitly the attending neurosurgeon evaluates the resectability as anticipated extent of resection or expected residual volume based on a mental reference map of similar cases and sometimes non-invasive functional mapping. The result of this evaluation differs between teams, between neurosurgeons, and between moments in time for a single neurosurgeon. Unfortunately, this estimation cannot be fully objective, and many neurosurgeons may rather overestimate than underestimate the extent of resection. This inherently biased view could be made more objective using

a resection probability map that quantitates the resectability for each location of a new patient's tumor, indicating the regions that will most likely be resected and which regions will likely not be resected as was reported in 2007 [25]. In this study, the extent of resection was predicted in being more or less than 10 mL for 82% of 65 patients.

The board meeting discussions can be sharpened further by the choice of the reference resection probability map. With accumulating patient information on resections, it should be possible to relate with reference maps of a single neurosurgeon, a neurosurgical team, a regional or national best practice standard or even a international leading team.

Some interesting arguments for treatment decisions can be expected from this type of evaluation. For instance, in case a new patient presents to a less experienced surgical team and this new patient's tumor contains regions that are universally resectable ('green') compared to a reference map of other teams, then it may not be necessary to refer this patient with a less complex glioma to a more experienced neuro-oncological team. And the patient can likely be operated without or with intraoperative stimulation mapping in case a resection beyond the tumor delineation on MRI ('supracomplete') is considered. As another example, in case a new patient's tumor has regions with a resectability of around 0.5 then surgical treatment may benefit from more advanced techniques such as intraoperative stimulation mapping to determine the functional limits of the resection (Fig. 32.2). Yet, in case a new patient's tumor has regions that are largely unresectable ('red'), then it may be the best option to advice the patient to have a biopsy and other treatment such as chemotherapy and/or radiotherapy. Obviously a minimal threshold of resectability to profit from resective surgery remains elusive, although a partial resection of less than 50% of resection or a residue larger than 10 mL was indicated to have no or minimal impact on survival [1]. However, in case resective surgery is indicated such as for seizure control or reduction of mass effect, than a limited resection could be considered using the resection probability map information.

#### 32.2.1.2 Surgical Planning

Once the decision has been made for resective surgery, the information from a resection probability map may be incorporated in the planning of the surgery along other image-guided techniques. So that the likelihood of resection can be incorporated in a surgical plan in addition to DTI tracking of white matter pathways, functional MRI or magnetoencephalography of brain regions involved in a specific task, and MRI SWI imaging of perforating arteries.

Intraoperatively image-guided navigation can project all regional information including resectability on the surgical field to enhance the surgical decision making at various stages of the resection.

The information on resectability can be used as an educational tool for residents and fellows to steepen their learning curves in successful glioma surgery by con-

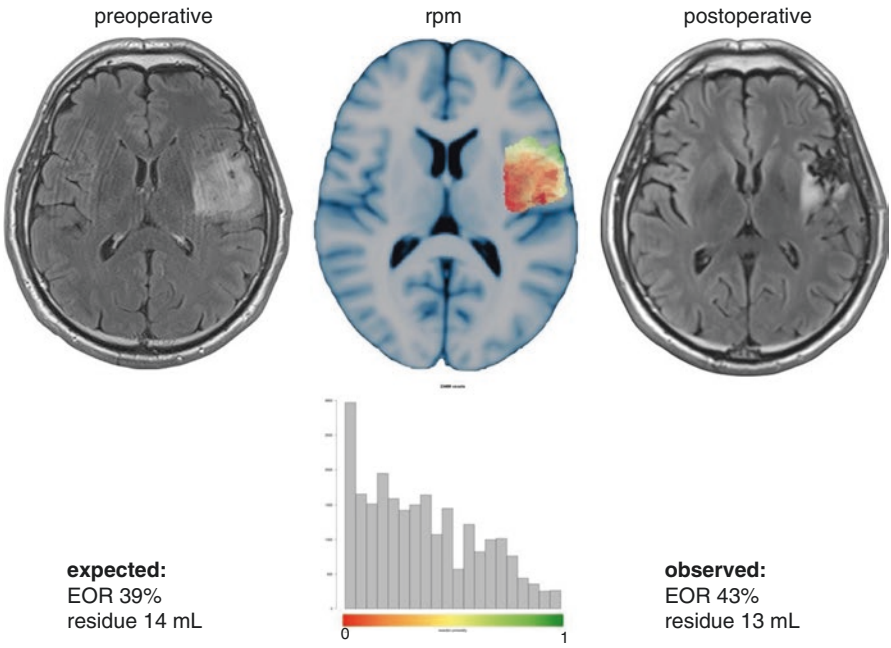


**Fig. 32.2** An example of preoperative prediction of the residual volume and the expected extent of resection for a patient with a nonenhancing glioma. One axial section is shown at the same level in the resection probability map for only voxels corresponding with this patient's tumor location. The postoperative MRI after 3 months is shown on the right, while this patient had surgery without resection probability map information. The histogram plots the resection probabilities of the voxels at the tumor location with corresponding expected surgical results and observed surgical result after measurement on the postoperative MRI

tinuously answering the question whether to stop a resection based on what was done in other patients by other neurosurgeons. For instance, a less experienced neurosurgeon can be warned during resection that a critical region is approaching because the resectability drops according to previous surgical decisions by others as captured by the resection probability map.

#### 32.2.1.3 Postoperative Evaluation

After the resection of a glioma the neurosurgeon can have a notion of the expected residue based on experience. A glioma cannot be completely resected at a cellular level. At best the imaging indicates the absence of tumor residue because microscopic disease remains undetectable, sometimes referred to as gross total resection. A postoperative MRI is customarily made to determine the residue more objectively. The neurosurgeon's estimate and the observations on MRI do not necessarily comply with each other [29, 30]. The postoperative MRI is usually

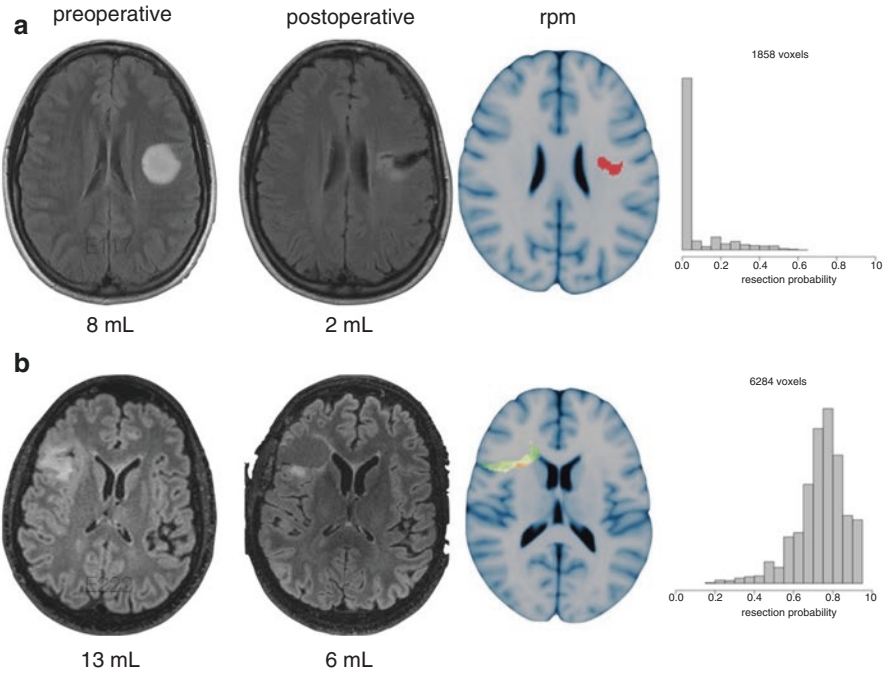


**Fig. 32.3** An example of postoperative evaluation of the residual volume. (**a**, **b**) demonstrate resections of nonenhancing gliomas of similar pre and postoperative volume. (**a**) can be considered a favorable surgical result with remaining voxels with low resectability in the patients that contributed to the resection probability map. (**b**) can be considered a less favorable surgical result with remaining voxels with high resectability in other patients

qualitatively reviewed by the radiologist and neurosurgeon and sometimes the residual volume is measured. Using the resection probability map the residual tumor can be quantitated in relation to surgical results in other patients for instance a best practice map (Fig. 32.3). So that the quality of the resection can be quantitated. Furthermore, relating the postoperative evaluation to the surgical results of an experience glioma surgeon from another surgical team may enhance the distribution of this expert's knowledge. This has been demonstrated for the first time in a series of patients who had resection of low-grade glioma in Paris by a starting surgical team [31].

Of course the interpretation of tumor residue versus postsurgical artefacts can be ambiguous. For instance, postsurgical diffusion restriction as a result of hypoperfusion has to be taken into account and should not be misinterpreted as postoperative residue [32, 33].

Residual glioma tissue on postoperative MRI is frequently observed, in particular after resective surgery for T2/FLAIR hyperintense diffuse infiltrative gliomas. In the ideal situation infiltrative tumor residues are only present in brain regions associated with an unacceptable risk of functional decline. In practice, however, postoperative residues can have several explanations. Intentional residues need to be

discerned from unintentional residues. First, intentional residues involve regions where glioma tissue cannot be removed because critically functional structures have been infiltrated, such as the corticospinal tract or the optic radiation. Extending the resection to these regions would result in permanent neurological deficits. Second, intentional residues involve regions where fragile and critical vasculature is surrounded by glioma, such as the lenticulostriatal arteries at the medial margin of insular gliomas. Extending the resection beyond these arteries could result in deprived vascularization and irreversible ischemia of critically functional regions, such as the internal capsule, resulting in permanent neurological deficits. Third, intentional residues can involve regions nearby critically functional structures. A safety margin of infiltrating tumor tissue is then accepted, anticipating on avoidance of transient neurological deficits. For instance, for patients of higher age or requiring undelayed adjuvant therapy a temporary loss of function may be deemed unacceptable. Avoidance of transient neurological deficits is based on the hypothesis that postresection edema, contusion and reversible hypoperfusion at the margin of the resection cavity will not involve the critical functional regions. Fourth, unintentional residues can occur because glioma tissue has not been recognized during surgery. Attempts to distinguish infiltrative glioma tissue from normal brain during surgery rely on microscopical appearance, tissue consistency, (functional) anatomical context, image-guided ultrasound navigation, and intraoperative MRI. Each of these techniques is subject to false negative observations, which is why the authors stress that glioma resections should rather be optimized using intraoperative stimulation mapping to extend up to functional regions. Fifth, unintentional residues can also occur because of early cessation of surgery, resulting in a multistage procedure. This includes prolonged postictal loss of function after epileptic seizures induced by stimulation mapping, patient fatigue, or loss of patient cooperation, loss of orientation by the surgeon, unexpected longevity of the procedure, or anesthesiological circumstances. This should largerly be avoidable in teams with expertise based on applying inatraopetive stimulation a routine basis.

### *32.2.2 Patient Cohorts*

Individual patient results can be aggregated at the level of a surgical team, an institution, or geographical regions in resection probability maps to compare resectability. This could serve as quality evaluation at a higher level to facilitate discussions on the best practice care for patients with a glioma. One example is the comparison of two surgical teams treating low-grade glioma patients with similar surgical techniques with similar resection results [27].

Given the variation in techniques to maximize tumor removal and to preserve functional integrity, treatment variation between teams is likely. The application of these techniques depends on availability (intraoperative MRI, magnetoencephalography, PET imaging), expertise (electrostimulation, motor evoked potentials), and opinions based on limited evidence (microscope, cusa settings, neuronavigation).

Perhaps more important than technological variation is a diversity in arguments, concepts, ideas, and sometimes dogmas in the field of glioma surgery. On the one hand this diversity facilitates development and improvement, on the other hand this can result in different outcome for patients.

Obviously the extent of resection is only one perspective on quality of care, but resection probability maps provide an instrument to compare surgical achievements without brain location bias. This is not an endpoint, but a starting point for discussions on quality of neurosurgical care between professionals. This instrument could pinpoint the discussions between teams to more clearly define the border between brain regions where resections should proceed and brain regions where resective surgery should be avoided. It is clearly not a goal of resection probability maps to push neurosurgeons towards 'more green maps', but to have them become aware of the surgical decision where to stop a resection. The more interesting brain regions that may or may not be compensated and consequently may or may not be resectable are those regions with intermediate resectability. These brain regions are amenable to plasticity in some but not all patients. A better definition, understanding and prediction of this plasticity facilitates better surgical decision making in individual patients ([34]).

Furthermore, it should be stressed that surgical decision making does not only depend on brain location, but on many other factors, such as symptoms, anticipated symptom reduction by a reduction of mass effect, radiological diagnosis of grade and type, patient condition, age, comorbidity, and tumor size. Ultimately, the synthesis of all this information translates into well-informed surgical decision making by experts. The instrument of resection probability mapping could add meaningful and comprehensive brain location information to this process.

## 32.3 Method

Resection probability maps can be processed from routine clinical MR images. The processing consists of several steps requiring user interaction. These steps include: (1) collecting and storing of MRI dicoms, (2) segmenting of 3D tumor objects in each patient, such as preoperative tumor and postoperative residue, (3) registrating patient space to a standard brain space, (4) comparing single case results with a probability map based on a patient cohort and comparing one probability map with another probability map.

### *32.3.1 Collect Imaging Data*

The first step is to identify patients that meet the requirements for inclusion in a probability map analysis. As this depends on the pertinent research question, this is beyond the scope of this text, but the quality of the results largely depends on the

quality of this patient identification. Selection bias can be minimized by a good patient registry. For instance for a patient to be included in a universal best practice probability map several requirements should be met. Such as having a favorable functional outcome status according to standardized definitions, perhaps including cognitive performance and/or employment return in addition to neurological tests. And having a favorable oncological outcome according to standardized definitions, such as being alive at 6 years after diagnosis ([35]).

Second, the MR images of these patients should be acquired. Several characteristics can be discerned on different imaging protocols. Standardized imaging protocols are beneficial to standardize further processing [36]. However routine clinical imaging with T2/FLAIR- and T1-weighted imaging before and after gadolinium enhancement usually suffice for glioma detection. The noise from diversity of imaging protocols between institutions is likely less than the noise from other aspects of the processing, such as tumor delineation or patient to standard brain space registration.

Third, for legislative purposes it is important to strip the patient imaging files from any identifying information as early in the processing as possible. Numerous anonymization software packages are available providing from basic to advanced customization. In practice, not all MR image files are created equal and anonymization requires a dedicated template filter for each specific manufacturer's scanner. On the one hand all identifying information should be discarded, while on the other hand all necessary imaging information, such as calibration and information on dimensions and orientation should be preserved. Examples consist of the MIRC DICOM Anonymizer (http://mircwiki.rsna.org/index.php?title=The_MIRC_DICOM_Anonymizer#Accessing_the_Anonymizer_Configurator_for_a_Storage_Service), custom matlab extension packages (http://nl.mathworks.com/help/images/ref/dicomanon.html), or DicomCleaner (http://www.dclunie.com/pixelmed/software/webstart/DicomCleanerUsage.html).

Fourth, clinical MRIs are acquired and stored in dicom file format (http://dicom.nema.org). In many image processing software packages the NIfTI file format (http://nifti.nimh.nih.gov) is preferred or required. Several tools are available to convert from a stack of 2D dicom files to one 3D nifti file, such as extension packages for Matlab (https://www.mathworks.com/matlabcentral/fileexchange/42997-dicom-to-nifti-converter--nifti-tool-and-viewer), SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) or MRIcron from Chris Rorden (http://people.cas.sc.edu/rorden/mricron/index.html).

Fifth, after this preprocessing a file archive has to be constructed to store the data. This can be quite a tedious task depending on the level of structure that is required. A low level solution is a straightforward folder structure. The advantage is simplicity, but the disadvantage is limited searching and sorting options. A high level solution is a full feathered pacs server storage, such as available open source from Osirix [37] (http://www.osirix-viewer.com/PACS.html#PACS), Orthanc (http://www.orthanc-server.com/index.php), Conquest (https://ingenium.home.xs4all.nl/dicom.html) or XNAT [38] (https://www.xnat.org). This allows for scripted query and export of data, but specific expertise in installation, security and maintenance is required.

### *32.3.2 Segment Tumor Outlines*

The next step is the identification of the tumor or residue on the images. The result is a 3D volume of voxels consisting of either 0s where there is no tumor or 1s at tumor locations, a socalled binary volume. Again a standard is lacking.

The most accepted strategy is the manual segmentation of tumor on sequential 2D patient images by an expert in radiology. This is very time consuming and can take several hours per scan. Another difficulty is that segmentation in one direction, for instance on axial sections, does not render an acceptable segmentation in another direction, coronal or sagittal, so that a lot of editing is necessary. Furthermore even between experts agreement on tumor segmentation can diverge considerably with DICE scores between 75–85% [39–46]. When resources are limited this is not always a realistic strategy for a dataset. A standard interpretation for glioma delineation on images is lacking. In general, for glioblastoma the T1-weighted images are used for tumor measurement, while acknowledging the underestimation of non-enhancing tumor elements. For low-grade and anaplastic gliomas the T2/FLAIR-weighted images are used. Two standards have been proposed for MRI assessment of glioma. First, standardized criteria for MRI response assessment have been postulated by the Response Assessment in Neuro-Oncology Working Group to apply in clinical trials of low-grade [47] and high-grade glioma [48]. Responses are categorized in four classes based on tumor diameter changes. Second, a standardized feature set (VASARI) was developed to characterize glioblastoma on MRI using 24 imaging characteristics based on the Visually Accessible Rembrandt Images [49, 50] (VASARI Research Project) (https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project). Both standards were not developed for the purpose of volume segmentation, but to address a specific clinical need. Furthermore, the interobserver agreement has not been systematically assessed for these standards. At the other end of the spectrum is a fully-automated segmentation. This has been attempted by several imaging teams as Multimodal Brain Tumor Image Segmentation (BRATS) benchmark challenge [39] evaluating 20 segmentation algorithms to delineate gliomas. The ideal fully-automated algorithm should be rapid, accurate, reproducible and scriptable for this purpose. No single automatic algorithm seems to outperform the manual segmentation of experts so far. Although several algorithms rank high in the benchmark tests, such as BraTumIA [51, 52] and GLISTR [53]. Automatic segmentation relies of a model of normal brain image measurements and the likelihood that image measurements deviate from normal due to tumor. This is a notoriously difficult task for several reasons. First, detection is based on relative intensity differences between abnormal and normal tissue that are smooth and obscured by artefacts and anatomical structures. Second, tumors vary considerably in location, size, and infiltration, so that a priori assumptions on abnormal tissue cannot be too strong. Third, normal brain structures can be grossly distorted or altered in signal by tumor and/or treatment effects, so that a priori assumptions on normal tissue cannot be too strong either. Fourth, the nor-

mal brain model can be optimized for a dedicated imaging protocol, but it is difficult to extrapolate any model to another environment with different scanners and protocols.

In between fully-automated and manual segmentation algorithms are many semi-automatic strategies that guide the user in a more rapid, more reproducible manual segmentation. These have been reviewed [54–56]. Three generations of semi-automatic algorithms are discerned. The first generation includes simple image analysis such as intensity thresholding and region growing. The second generation adds uncertainty models, such as tissue classification and supervised or unsupervised cluster analysis, as well as optimized boundary tracing techniques, such as the 'snake', 'fuzzy connections' or 'watersheds'. The third generation includes data driven a priori knowledge, such as atlas-based segmentation or shape modeling. Examples of popular open source software packages that provide semi-automatic tumor segmentation algorithms are Osirix [37] (http://osirix-viewer.com), ITKsnap [57] (http://www.itksnap.org/pmwiki/pmwiki.php?n=Main.HomePage), and Slicer [58] (https://www.slicer.org).

### *32.3.3 Register MRIs*

The next step is to align the patient MRIs so that brain locations of tumors and residues can be compared between patients. Conceptually the transformation is determined from the patient's individual brain space to a standard brain space. This transformation is then applied to the binary tumor segmentations that were outlined in patient brain space.

At each step several options are available, while the best selection for each step remains undetermined for images of glioma. This should be optimized in a trial and error approach for each specific research question and for every dataset. Major decisions consist of the sequence of registrations, the registration algorithm with its parameters, and the standard brain space atlas.

For the purpose of resection probability maps both the preoperative and postoperative tumor volume is segmented. These segmentations are derived from separate MRI sessions of the same 'subject'. Each MRI set can be registered to standard brain space separately directly (two subject-to-atlas registrations) or indirectly by first determining an intersession registration for the same patient from the postoperative set to the preoperative set and second a patient to standard space registration (one intra-subject and one subject-to-atlas registration). Sometimes the preoperative tumor volume is estimated from the postoperative imaging by adding the resection cavity to the postoperative tumor volume [25, 26]. This may avoid a separate registration step for the preoperative MRI session but typically in the case of removal of brain tissue beyond the preoperative tumor volume, as in supracomplete resections, the interpretation can become ambigu-

ous. Many open source registration algorithms are available. A comprehensive effort to benchmark customary algorithms has been done for normal brain of adults [59, 60] and of children [61]. These algorithms have not been evaluated for lesioned brains. For normal brains no single algorithm performed best. Highly ranked algorithms were: ART, SyN, IRTK, and DARTEL. Some of these are available as standalone application, others are distributed in software suites such as Slicer [58] (https://www.slicer.org). Each application comes with its own parameters and optimal settings. It is typical to use sequential registration steps with incremental complexity: translation, rigid, affine, and deformable registration. The registration of lesioned brains may be improved by the lesion masking feature. This essentially cancels out the intensity information at the lesion from the calculation of the registration. The optimal settings for various parameters may be different between datasets from different scanners and from different scan sessions. Usually a tradeoff is required between time and accuracy. Depending on these settings and hardware resources, a typical registration of one patient's MRI to standard space could take approximately 10–60 min. Standard brain space is by no means 'standardized'. Many atlases have been developed that could serve as common reference frame [62]. The classical stereotactic space was established by Talairach [63], that was devised for stereotactic procedures in deep-brain structures. Other atlases are based on a single indivudual's brain that has been scanned many times, such as Colin27 [64]. This atlas is a very precise representation of this single brain but it does not capture anatomical variability. Other atlases have aligned normal brain MRIs of many individuals aiming to capture anatomical variability, such as MNI305, MNI152, and ICBM452 [65–67]. These atlases mainly differentiate in the numbers of individual brains and the methods for alignment, either linear or non-linear.

Resection probability maps should be distinguished from lesion segmentation map. Resection probability maps are constructed from lesion maps of preoperative tumor and postoperative residue combined. Lesion load maps have been reported for untreated low-grade glioma [68] and glioblastoma [69]. Besides tumor segmentations, lesion load maps have been constructed for other pathology as well, such as multiple sclerosis [70], Alzheimer's disease [71], and stroke [72, 73].

### *32.3.4 Comparing Probability Maps*

The comparison of resection probability maps has only started to emerge. It should be discerned from a number of statistical imaging analysis techniques that may seem similar but that are in fact not. Comparing probability maps is dissimilar from functional MRI analysis that contrasts blood-oxygen-level dependent hemodynamic responses between two behavioral conditions [74, 75], voxel-based

morphometry that compares gray matter segmentations between two patient groups [76], and voxel-based lesion-symptom mapping that seeks structure-function associations [77].

One approach to statistical comparison of resection probability maps is voxel-wise calculation of the difference in resectability between two patient groups (Fig. 32.4). For this purpose a test statistic has to be chosen. When comparing two extents of resection between two cohorts, this comes down to the comparison of two ratios. Several test statistics apply, such as a chi-square test, fisher's exact test [27, 69], or a randomization test with the difference between the ratios [78–80]. A number of difficulties arise.

First, a straightforward test for one voxel is repeated for all voxels in the brain (approximately 1.5 million for a standard brain at 1 mm resolution). This can considered heavy multiple testing. Many techniques have been described to accommodate this. Some techniques are very conservative, such a Bonferroni correction [79]. Other techniques are less strict and calculate the socalled false discovery rate [78, 80–82].

Second, the measurements for one voxel location cannot be considered independent from another voxel location. More specifically neighbouring voxels probably autocorrelate considerably, while measurements between more distant voxels may be considered independent at some point. One approach to adapt this is to use threshold-free cluster enhancement, in which clusters rather than voxels are analyzed [83–85].

Third, the power of a test is not evenly distributed over voxels [86]. Despite relatively large patient cohorts of hundreds of patients, at a voxel only a small subset of the patients in these cohorts have had a tumor. Many voxels will contain information from only few patients, rendering the test less powerful to detect any difference in

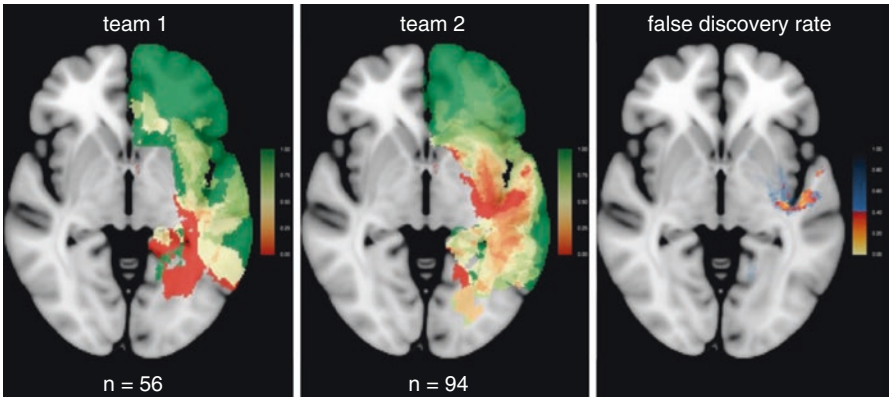


**Fig. 32.4** An example of comparison of two resection probability maps from different surgical teams who applied similar surgical techniques to the number of patients plotted in the figure. Only very few differentially resected brain regions are identified after statistical analysis with false discovery rates below 20%

resectability, than in voxels with information from many patients. This distribution depends on the preferential locations for glioma, the nature of which is uncertain. Typically the frontal and temporal lobes are the origin of glioma more frequently than the parietal and occipital lobes. A minimally acceptable number of patients per voxel has to be determined. So far we have arbitrarily restricted the analysis to brain regions that were resected in at least three patients.

## 32.4 Roadmap

The roadmap towards successful application of resection probability maps consists of three steps: collection of informative data, development of software tools to process and analyze these maps, and acceptance of the concept of resection probability maps by the neuro-oncological community. Ideally a reference map should be build with cases from multiple institutions having a favorable oncological and functional outcome after a quality check. This reference map should be accessible as best practice map for teams globally. The users should be able to use simple tools to upload cases and get meaningful results for individual patient care and for patient cohort comparison. Whether this concept is valuable as quality indicator to evaluate and improve neurosurgical care for patients with a glioma remains to be determined by the neuro-oncological community.

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# Chapter 33
# The Concept of Onco-Functional Balance in the Management of DLGG

**Emmanuel Mandonnet and Hugues Duffau**

**Abstract** Nowadays, management of DLGG is conceptualized as a multi-stages therapeutic sequence of the different treatment modalities that are surgery, chemotherapy, radiation therapy and concomitant radio-chemotherapy. The timing and order of the sequence steps has to be fitted to each patient, taken into consideration both tumor and patient's characteristics. The aim is to optimize *both* survival *and* functional status, in order to give to patients the best chances to enjoy a normal life all along the duration of this chronic disease. Consequently, the onco-functional balance of each treatment modality has to be updated all along the evolution, with the goal to select the best treatment at each step, while keeping also in mind the next step. In other words, one needs to be one step ahead. Indeed, the overall efficacy of a treatment cannot be assessed per se, as it will depend on its integration in the whole sequence.

At the first level, one needs to be able to evaluate the oncological benefit and the functional risk of each treatment type, independently of its integration in the sequence. At the second level, the same balance has to be reevaluated in the global view of a recursive multi-steps approach. We thus propose in this paper to systematically review how to estimate the onco-functional balance for surgery, chemotherapy, and radiation therapy, successively on these two levels.

**Keywords** Diffuse low-grade glioma • Surgery • Chemotherapy • Radiotherapy • Onco-functional balance • Multistep therapeutic approach • Quality of life

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## 33.1 Introduction

The treatment of diffuse low-grade glioma (DLGG) is currently conceptualized as a multi-steps sequence of the different treatment modalities that are surgery, chemotherapy, radiation therapy and concomitant radio-chemotherapy. The timing and order of the sequence steps has to be fitted to each patient, taken into consideration both tumor and patient's characteristics. The aim is to optimize *both* survival *and* functional status [1], in order to give to patients the best chances to enjoy a normal life all along the duration of the disease (that is more than 10 years given recent advances [2–6]). Consequently, the onco-functional balance of each treatment modality has to be updated all along the evolution, with the goal to select the best treatment at each step, while keeping also in mind the next step [7]. In other words, as for chess games, one needs to be one step ahead. Indeed, the overall efficacy of a treatment cannot be assessed per se, as it will depend on its integration in the whole sequence. Hence, the very same extent of resection has a different value in a slow growing tumor, allowing a repeat surgery after a couple of years of full cognitive recovery [8], or in a fast growing tumor—requiring in the next step a chemotherapy or a radiation therapy because of a low plasticity reserve resulting from the fast growth [9]; or the same response to temozolomide will have a different impact whether it is complemented (hopefully synergistically) or not by a surgery or a radiation therapy.

At the first level, one needs to be able to evaluate the oncological benefit and the functional risk of each treatment type, independently of its integration in the sequence. At the second level, the same balance has to be reevaluated in the global view of a recursive multi-steps approach. We thus propose in this paper to systematically review how to estimate the onco-functional balance for surgery, chemotherapy, and radiation therapy, successively on these two levels.

## 33.2 First Level: Onco-Functional Balance of Each Treatment Applied Alone

### *33.2.1 Surgery*

#### 33.2.1.1 Detecting Situations of High and Low Oncological Benefit

In DLGG, it is now widely accepted that there is a minimal extent of resection under which surgery has little if any influence on survival. This minimal extent can be measured as a range of values for both percentage of resection and absolute residual tumor volume, rather than an absolute cut-off. The seminal paper reported that there was no benefit if the residue was greater than 10 cc [10], leading to the usual definition of subtotal resection, while a recent study found a threshold at 15 $cm^3$ [11]. Further studies confirmed that survival advantage occurs only if the percentage of

resection is large enough, with threshold found at 40% [6] and 50% [3] of the initial volume. Most importantly, there is a gap in survival advantage when the resection is complete [3, 6], or even better, supracomplete [11, 12].

In summary, the oncological benefit can be roughly categorized in three groups:

- high benefit for (supra-)complete resection;
- very mild benefit if residue greater than 10–15 $cm^3$ or resection lower than 50%. It is worth mentioning that it is the lack of oncological impact of a too partial resection that motivated the proposition of neo-adjuvant chemotherapy in that situation [13];
- intermediate oncological benefit in any other situation.
- Importantly, for cases of intermediate and very mild benefit, the true final benefit will be highly dependent not only on tumor spatial heterogeneity (removal of a "hot spot", see next paragraph) but also on the interaction with other treatments in the whole sequence (see second part).

#### 33.2.1.2 Specific Situations of Potentially low Oncological Benefit

Beyond the well-known situation in which the surgical resection was very partial, there is a second under-recognized situation in which the oncological benefit of surgery is expected to be of limited value. It corresponds to "false" DLGG, which are in fact highly diffuse glioblastomas (see chapter on biomathematical modeling by Mandonnet). In their initial phase of low density, such glioblastoma really look like DLGG, as there is a low cell density and no contrast enhanced area. They can be detected nevertheless, due to their high growth rate (velocity of diametric expansion >8 mm/year), by an unexpected size increase on a second MRI performed 6 weeks after the first one. Unless a supracomplete resection is feasible, surgery, even complete, will leave behind a high proportion of tumors cells [14], with a high proliferation rate. Hence, only treatments targeting tissues beyond the visible tumor margins—hence a combination of chemotherapy and radiation therapy—could potentially stabilize such tumors. A typical example is given on Fig. 33.1.

#### 33.2.1.3 Specific Situations of Potentially High Oncological Benefit

It is now well recognized that DLGG might exhibit spatial heterogeneities [15]. New imaging techniques enable to detect such heterogeneities. In particular, dynamic $^{18}$F-FET-PET allows to identify foci of decreasing time-activity curves, that correlate with histological grade [16]. Similarly, the role of perfusion imaging to detect such hot spots is still investigated. Therefore, although this has not be proven, it can be anticipated that removal of such malignant foci within an otherwise DLGG could improve oncological benefit of surgery, even though the entire glioma was not completely resected.

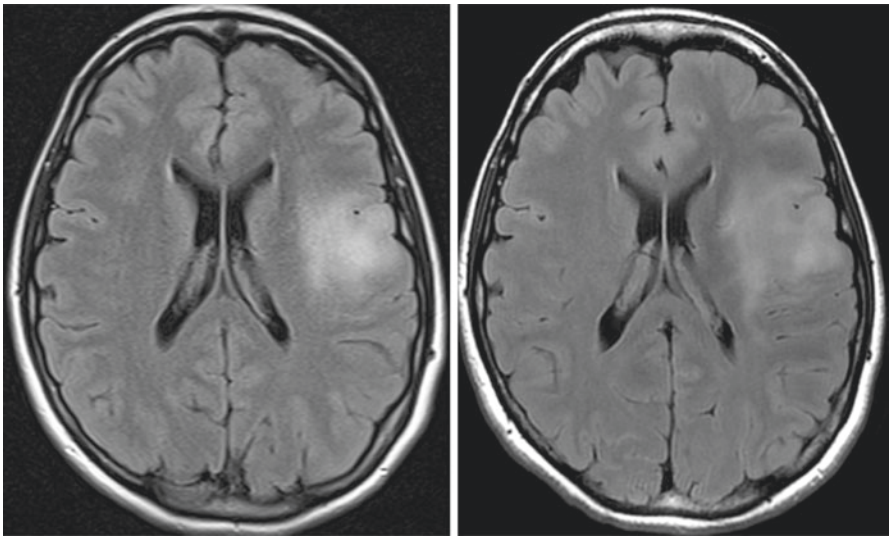

**Fig. 33.1** Axial FLAIR-weighted MRI showing a typical illustration of a "false DLGG", which is in fact a highly diffuse glioblastoma. In its initial phase of low density (*left*), such a glioblastoma really looks like DLGG, as there is a low cell density and no contrast enhanced area. However, due to an unexpected size increase on a second MRI performed 6 weeks after the first one (*left*), corresponding to a high growth rate (velocity of diametric expansion >8 mm/year), the diagnosis of "false DLGG" can be made before to obtain histo-molecular results. In this case, because a (supra) complete resection is not feasible due to an invasion of the subcortical connectivity, resection will leave behind a high proportion of tumors cells, with a high proliferation rate. Hence, only treatments targeting tissues beyond the visible tumor margins—hence a combination of chemotherapy and radiation therapy—could potentially stabilize this tumor. As a consequence, the onco-functional balance is low in this example

Finally, epigenomic and genomic landscapes and their evolution in the course of glioma growth are being progressively deciphered [17–20]. Such studies evidenced a branching pattern rather than clonal evolution. Importantly, the different branches are located in different spatial spots in the tumor [19, 20]. Thus, it can be anticipated that a better modeling of this genomic evolution could allow to identify a hot spot within the tumor bearing a branching clone of higher aggressiveness. Surgical removal of this specific area could result in enhanced oncological benefit, even if the resection is partial.

#### 33.2.1.4 Factors Influencing Functional Risk

It has been shown that awake surgery with intraoperative neurological and neuropsychological testing and monitoring greatly reduces the functional risk of DLGG surgery [21]. Nevertheless, it should not be forgotten that immediate postoperative cognitive evaluations report a deterioration in most of patients, with a (quite) complete recovery after 3 months of intensive rehabilitation. It is acknowledged that this

full cognitive recovery is made possible by the plasticity of distributed networks [8]. But the *sine qua non* condition for network normalization by postoperative plasticity is the surgical preservation of a minimal core of long-range connectivity [22–24], including but not limited to superior, middle and inferior longitudinal systems, inferior fronto-occipital fasciculus, cingulate fasciculus, frontal aslant tract, and callosal fibers. Such axonal pathways are essential to maintain the small-world topology of brain networks [25]. Therefore, these functional white matter tracts should be imperatively identified by direct subcortical electrostimulation mapping in all DLGG patients, whatever the tumor location, and they should serve as limits of surgical resection [26].

Considering that the neuronal areas per se of this core of connectivity are safely controlled thanks to intraoperative monitoring, small deep arterial infarcts remains the major source of damage of the long-range connectivity. Statistical map of diffusion hypersignal with decreased ADC (an MRI signature of acute ischemia) after glioma resection is lacking, as well as the functional correlates of such small strokes depending on their topography. It can be hypothesized that any stroke encompassing the minimal common brain [23] (i.e. the basic core of associative connectivity), would impact high level cognitive functions.

Moreover, for a similar insult of the connectome, the degree of recovery will vary from one patient to another, depending on their level of plasticity reserve. Hence, estimating the functional risk of a given patient means evaluating its plasticity reserve, which is currently not straightforward. First of all, a slight deterioration in some of the preoperative cognitive scores reflects that neuroplasticity has already spent much of its reserve. Interestingly, preoperative infiltration by glial cells of the connectivity of the ventral stream has been shown to correlate with a decrease of semantic fluency scores [27]. In other words, preoperative infiltration by the glioma of the minimal core of connectivity can hamper the reshaping processes of networks reconfiguration, precluding a fully effective functioning. This preoperative infiltration of the connectome has also to be taken into account regarding postoperative plasticity. Let us consider for example the effect of ILF resection on lexical access [28]: the degree of recovery could differ depending on the degree of preoperative infiltration of the other associative tracts involved in this function (inferior fronto-occipital fasciculus, long direct segment and short posterior segment of arcuate fasciculus [22]). This would be especially true in a fast growing glioma, because the axonal dysfunction induced by glioma infiltration has an impact on the process of neuronal synaptic reweighting underlying network normalization. In the same vein, postoperative radiation therapy on a residue left in the connectome could seriously compromise the chances of recovery [29].

Finally, age is a major factor of plasticity potential: as age increases, plasticity decreases. Surprisingly, there are no study in the literature reporting the influence of age on cognitive recovery after awake surgery of DLGG. In our experience, we observed that after 55 years of age, recovery took longer (between 8 and 18 months) in comparison to younger patients (for example, median time to work resumption of 4 months in [30]).

#### 33.2.1.5 The Definition of Functional Risk: A Personalized Assessment

Since postoperative cognitive evaluations are performed on a routine basis, our knowledge of the impact of surgery on high-level functions has greatly improved, leading to a better preoperative personalized estimation of functional risk [31]. To this end, the importance of the preoperative patient interview cannot be overemphasized. Patient should clearly formulate his wishes regarding which kind of functions should be primarily preserved. This will depend on its way of life, including profession, hobbies, and social interactions [32]. For example, it has been recently recognized that proper names retrieval is frequently impaired after left dominant temporal lobectomy [33, 34]. In any profession requiring a high level of proper names retrieval (for example when you need to deal with a lot of client names), such deficit precludes work resumption—while for some other patients, such a deficit would not affect quality of life. Another example is provided by fine motor functions : it has been reported that resection of SMA glioma without identifying networks of motor control [35–37] results in long lasting trouble in bimanual coordination [30, 38]. Again, such deficit goes unnoticed for some patients, while it would dramatically impact the professional life of a musician or a tennis player. In a similar way, the ecological consequences of the resection of optic radiations (causing an hemianopia) is not of the same importance whether the patient absolutely needs to drive or not [7]. In the same state of mind, the level of cognitive control (i.e. executive functions) can be set preoperatively with the patient, and intraoperative task can be personalized accordingly. Several tasks requires a high cognitive load, including but not limited to, dual task, working memory tasks, or TMT part B. Preserving such high-level cognitive capabilities is probably more important for a manager than for a cleaning lady. The same principles apply to emotional functions, like mentalizing. The read the mind in the eye task allows to identify the low-level network of mentalizing [39], and it is anticipated that preserving this network is of utmost importance for patients with a profession requiring a high level of empathy, like medical doctor.

Finally, there is a controversy regarding the possibility to offer a complete resection that would come together with a high risk of neurological deficit [40–42]. Resection of tumors involving the anterior perforated substance (APS), usually insular or paralimbic gliomas [43], is a paradigmatic example of this ethical issue. Complete resection of the APS comes with a very high risk of hemiplegia. Surgeons agreeing with the moto “primum non nocere” would definitely not go beyond the functional responses elicited in the external capsule covering the APS, thus giving up to resect the tumor part within the APS. In this tumor location, some other surgeons plaid for informing patients about the two options (safe resection with suboptimal oncological benefit versus maximizing oncological benefit at the price of hemiplegia) and offer them to get involved in this decision, that is, to accept (or not) severe permanent deficit in order to increase the extent of resection. However, it is questionable whether the patient can objectively imagine how he could enjoy life with an hemiplegia and/or a marked cognitive deficit—because cutting the temporal stem to reach the APS will also induce definitive higher-order disturbances (in addition to the motor deficit related to the injury of the lenticulo-striate arteries when removing the APS itself), especially

due to a damage of the inferior fronto-occipital fasciculus, even in the right hemisphere [44].

#### 33.2.1.6 The Functional Benefit of a Surgical Resection

Functional improvement after resection of DLGG have been reported [30, 45, 46]. Among other explanations, this could be due to the relief of mass effect or to the better reorganization of brain functional networks after tumor removal [47]. Moreover, the positive impact of resection on epilepsy status should not be overlooked [48]. It has been suggested that resection of temporo-mesial structures could be offered for epilepsy control even if not infiltrated by the glioma [49]. This functional benefit (which might be of utmost importance given that seizure control is the key parameter allowing patients to keep their driving license) has to be weighted with the functional risk of verbal memory decline, which is a well known consequence of temporo-mesial structures removal.

Importantly, the functional risks of the surgery should also be weighted in comparison to the spontaneous evolution of the DLGG. Indeed, as reported above, in absence of any surgery, there is a progressive cognitive decline all along the natural course of the disease, related to the infiltration of the minimal common brain. Of note, in a old series, it was claimed that with an endpoint at 4 years, surgery was cognitively more risky than wait and watch management [50]. However, this result might be out of date, considering that surgery was not performed under awake mapping at that time. In addition, even assuming that this would be still valid nowadays (which is very unlikely taken into account the favorable neurological and neuropsychological outcomes when using intraoperative awake mapping [45, 46, 51–54]), a 4-years time-point is not enough to draw any conclusion, considering that median survivals have now reached more than 10 years. In fact, any surgery that would delay the infiltration of the connectome should help to delay cognitive decline. Hence, (supra-)complete resection while preserving the minimal core of connectivity provides a functional advantage compared to wait and see. On the contrary, if a residue is left within the infiltrated connectome, the functional advantage of surgery is only provided by the oncological advantage, that is by delaying malignant transformation. Indeed, it has been shown that the residue will grow at the same speed as before surgery [55], meaning that in this situation, the connectome infiltration will not be delayed by the surgery compared to wait and see.

### *33.2.2 Chemotherapy*

#### 33.2.2.1 Oncological Benefit

The oncological role of chemotherapy has been recently proven: median survival in patients treated with PCV concomitantly to radiation therapy was 13.3 years versus 7.8 in patients treated with radiation therapy alone [2]. Unfortunately, this study

suffers so many flaws that its clinical utility is questionable. First of all, there is no information regarding the timing of the treatment. The abnormally high rate of contrast enhancement (between 60 and 65% in comparison to 15% in reference series of DLGG [3]) strongly suggests that many patients have been in fact initially monitored under a close wait and watch attitude, and included in the study only after onset of contrast enhancement. Moreover, it is not stated if this survival advantage is only observed in 1p19q codeleted patients. Indeed, the very same result was previously reported in grade III glioma [56, 57], with the additional result that the effect was only significant in patients with 1p19q co-deleted tumors. Nonetheless, as stated in [57], "Our data underscore that 1p/19q codeletion status is a marker, not a mechanism of sensitivity to PCV plus RT", meaning that this parameter cannot be used to drive a therapeutic decision on an individual basis. Moreover, in any of these studies, the role of extent of resection was not appropriately accounted for. Subgroup analysis based on extent of resection objectively assessed on postoperative MRI would have been of paramount importance to individualize treatment decision according to this major prognosis factor [3, 6]. Last but not least, this trial comes without any relevant data regarding the functional status of patients. Indeed, in the long-survival arm (median survival = 13.3 years), we would expect a significant cognitive decline, subsequently to long-term adverse effect of irradiation. However, no cognitive assessment has been performed beyond 5 years of follow-up [2].

Otherwise, in the preliminary results of EORTC 22033 trial, even though it has been suggested that progression free survival is lower in patients with non-codeleted 1p19q tumors treated with upfront temozolomide rather than radiation therapy, no data has been reported regarding overall survival, preventing to draw any conclusion [58].

All in all, current knowledge supports the idea that PCV and temozolomide have a strong oncological benefit in 1p19q codeleted tumors (which is in accordance with previous studies reporting volumetric decrease under these regimens [59, 60]), and that there might be a synergistic effect with concomitant radiation therapy.

#### 33.2.2.2 Functional Benefit

In terms of functional benefit, it is well known that chemotherapy can reduce dramatically the seizure frequency [61, 62]. Last but not least, it is obvious that temozolomide is so much better tolerated than PCV. It is striking that only 56% of patients could end the PCV protocol in the RTOG 9802 trial [2]. Hence temozolomide might be the best choice for optimizing the onco-functional balance at first line of chemotherapy.

Nevertheless, several questions remain unsolved: is there a loss of oncological benefit if a first line of chemotherapy is administered upfront, with the concomitant chemo-radiation kept for recurrence? If no, what is the optimal timing of first line of chemotherapy after the discovery of the DLGG: right after or delayed? Is there a

difference in oncological benefit between PCV first line followed by temozolomide plus radiation at recurrence versus temozolomide first line followed by PCV plus radiation at recurrence?

### *33.2.3 Radiation Therapy*

Current data on the real oncological benefit of radiation therapy are scarce. Indeed, it has been shown that in terms of survival, there is no benefit of early versus late radiation therapy in DLGG [63].

From a functional point of view, long-term adverse effects have been well described [64]. This study found a significant cognitive decline 7–10 years after irradiation, compared to a well matched population of DLGG patients without any irradiation. Currently, the factors that would allow to predict these late adverse effects in order to improve our evaluation of onco-functional benefit of radiation therapy are poorly known: are they related to age and cardiovascular parameters? to the volume of irradiation? to the location of the irradiated area, especially within or outside the minimial common brain—i.e. not only irradiation of the hippocampi but also irradiation of the functional white matter tracts? Interestingly, a recent series showed that diffusion tensor imaging can predict cognitive function deficit following partial brain radiotherapy for DLGG, in particular with an increased radial diffusion at the end of radiotherapy able to significantly predict decline in verbal fluency 18 months after irradiation [29].

Last but not least, short-term adverse effects are poorly described in the context of DLGG. Only a very recent paper reported a 20% rate of pseudoprogression [65], with a median delay of 12 months (range 3–78 months). In this study, no clinical symptoms were attributed to these pseudoprogressions, but one can fear that such reactions would be harmful whenever the irradiation targeted a residual tumor left by the surgeon for functional reasons.

These combined data about lack of survival benefit of early treatment and late onset of adverse effects grounded the recommendation to postpone radiation in DLGG whenever survival is expected to be greater than 7–10 years [66].

## 33.3 Second Level: Onco-Functional Balance of Treatments Integrated Within a Whole Sequence

Beyond the onco-functional balance intrinsically related to a given treatment, the choice of a treatment modality should be reevaluated in light of its interaction with associated treatments in the whole sequence. In this part, we propose to review some of these interactions.

### 33.3.1 Surgery as a Potentiating Neoadjuvant Treatment of Surgery

After a first surgery, brain networks reorganize, thanks to the plasticity, that is enhanced by intensive rehabilitation. Consequently, a delayed second surgery can be proposed, as functional limits have been pushed away from the boundaries of previous resection cavity, allowing to achieve greater extent of resection the second time while preserving brain functions [8, 67, 68]. Such a strategy can be envisioned only if plasticity mechanisms can take place. One condition is that the tumor growth is slow enough. In this perspective, the importance of assessing postoperative growth rates of residue cannot be overemphasized. The second condition is that the initial residue was left in a cortical epicenter outside of the deep core of connectivity. Such a cortical epicenter can be compensated after the first surgery thanks to network reshaping, while a residue within the connectome is much less likely to undergo such "functional silencing".

### 33.3.2 Surgery as a Potentiating Neoadjuvant Treatment of Chemotherapy

To our knowledge, little is known about the benefit of reducing the tumor volume with the hope to increase the benefit/risk ratio of chemotherapy. However, one could speculate that, if chemotherapy can result in a stabilization of DLGG, the risk of malignant transformation will be significantly decreased if the tumoral volume under control by temozolomide or PCV is reduced by surgery first—especially when the postoperative residual volume is less than 10–15 $cm^3$.

### 33.3.3 Chemotherapy as a Potentiating Neoadjuvant Treatment of Surgery

It has been proven that temozolomide can be proposed in a neoadjuvant setting [13, 69–71]. The goal is to reduce the tumor volume, up to the point that resection can be made at least subtotal (i.e. with a significant survival benefit). It is expected that this combination could be advantageous on a functional point of view: the response to chemotherapy should be correlated with a cognitive recovery, itself correlated to a normalization of functional connectivity. Even though this has not yet been demonstrated, there is nonetheless another argument in favor of this hypothesis. Computer modeling envision seizures as a signature of plasticity saturation [72]. Hence the reduction in seizure frequency under chemotherapy might be associated with a revival of plasticity, thus optimizing the surgical conditions. Accordingly, a study showed that cognitive status was very

good in patients treated by neoadjuvant temozolomide, followed by surgical resection [70].

There is another rationale for this completion surgery. It has been suggested that temozolomide, by inducing DNA mutations, might contribute to the malignant transformation [73]. The surgical removal of a temo-induced aggressive clone can thus potentiate the chemotherapy.

Of note, this neoadjuvant chemotherapy can be applied at re-evolution of a residue left at first surgery, in particular if this residue is growing too fast (and thus impeding optimal remodeling of functional networks by plasticity): this could reopen the door to a second (or even third) surgical resection.

### *33.3.4 Chemotherapy as a Potentiating Adjuvant to Radiotherapy*

As reported above, survival is better when chemotherapy follows immediately irradiation. There is a synergistic effect, that is not observed if the chemotherapy is administered later in time. Nevertheless, the trial by Buckner et al. did not address the question of starting first with chemotherapy alone, and delaying radiation therapy at a later stage [2]. Long-term results of the EORTC 22033 should provide some elements of response in the future.

### *33.3.5 Chemotherapy and/or Surgery as a Potentiating Neoadjuvant Treatment of Radiation Therapy*

Because the risk of late toxicity increases with the volume of irradiation, it is anticipated that tumor volume reduction will restrain functional risk of radiation therapy. To the best of our knowledge, there is no data linking long-term cognitive damage to the volume of irradiation. However, the location of the targeted area might be more important than its volume: stronger adverse cognitive effects are expected for irradiation of a residue located within the deep connectome [29].

### *33.3.6 Postoperative Adjuvant Wait and Watch or Adjuvant Active Treatment?*

Finally, after a first surgery, the main question will be to compare the onco-functional balance for postoperative wait and watch versus chemo and/or radiation therapy at the individual level. Indeed, it is not adapted to apply a similar protocol to each patient, as for example radiotherapy and PCV in all patients over 40 year-old or with

incomplete resection, as dogmatically written by Buckner et al. [2], without any consideration for the personalized onco-functional balance. Furthermore, it remains to be proven that there is no synergy between radiation therapy and chemotherapy in a chemo-naive patient that would not be found after a first chemotherapy exposure, meaning that concomitant treatment would improve both overall survival and area under the quality of life curve.

## 33.4 Conclusion

DLGG constitutes a particular case of cancer, because of the plasticity of brain networks—whereas plasticity of cancer cells is a hallmark of any cancer. On one hand, tumor progression will impact the connectome (hence the brain functions). On the other hand, treatments can prevent tumor progression, but will also interact (positively or negatively) with the connectome, independently of their anti-tumor effect. The goal of DLGG management is to select the optimal timing and order of many treatments, with the dual goal to delay malignant transformation and to prevent connectome infiltration as long as possible. This strategy is quite complex to implement, as we have shown that beyond the role of each individual treatment, second order effects (and probably third order effects, not discussed in this chapter) can potentiate the effect of one given treatment. A recursive approach can serve as a guide, keeping in mind that the choice at each time step should take into account both past treatments, current parameters (age, cognitive and epileptic status, tumor volume and kinetics, genomic landscape), and future anticipated treatments. Obviously, the standard methodology of randomized studies cannot be used to evaluate the efficacy of such strategies. Large-scale databases should be developed to this end.

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# Chapter 34
# The Origins of Diffuse Low-Grade Gliomas

**Amélie Darlix, Catherine Gozé, Valérie Rigau, Luc Bauchet, Luc Taillandier, and Hugues Duffau**

**Abstract** The improved understanding of the natural course of diffuse low-grade gliomas (DLGG) has allowed a paradigmatic shift in their management, from a "wait-and-see" attitude to an early, individualized and dynamic therapeutic strategy. However, optimization of this management requires a better understanding the origins of DLGG. To date, the origins and etiologic factors of

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DLGG are mostly unknown. Beyond some data, yet limited, regarding the temporal and the cellular origins of DLGG, the mechanisms and risk factors involved in DLGG are poorly known. A way to better understand the mechanisms involved in the genesis of DLGG is to study their spatial distribution, both within the brain and at the geographical level. Indeed, some hypotheses regarding the mechanisms involved may be speculated from these distributions. It is interesting to note that DLGG have preferential locations within the brain, mostly within the so-called “functional areas”. On the basis of strong relationships between DLGG development and the eloquence of brain regions frequently invaded by these tumors, we propose a “functional theory” to explain the origin of DLGG. In addition, it can be hypothesized that the biological pathways involved in the genesis of DLGG may differ according to the tumor location, as anatomo-molecular studies showed significant correlations between the DLGG locations and tumor genetics, with a higher rate of IDH mutation and 1p19q codeletion in frontal tumors. The cellular and molecular mechanisms of such “molecular theory” will be reviewed in the present chapter. It is also interesting to note that the geographical distribution of diffuse WHO grade II and grade III gliomas is heterogeneous at the international and national levels, suggesting possible environmental risk factors. We will thus also discuss this “environmental theory". Finally, we will briefly summarize the current knowledge on genetic susceptibility in gliomas. All of these crucial issues very well illustrate the close relationships between the pathophysiology of gliomagenesis, the anatomo-functional organization of the brain, and personalized management of DLGG patients.

**Keywords** Diffuse low-grade gliomas • Anatomo-molecular correlations • Eloquent areas • Brain–tumor interactions • Ultrastructural mechanisms • Oligodendroglial progenitor cells • Subventricular zone • Environmental risk factors • Genetic susceptibility

## 34.1 Introduction

To date, the origins and etiologic factors of diffuse low-grade gliomas (DLGG) are mostly unknown. There is, however, a few data regarding their temporal origins. Indeed, because the DLGG growth rate is constant during the initial premalignant symptomatic period, it was possible to extrapolate backwards in time, leading to the approximate glioma date of birth in early adulthood (around 20 years of age) [1–3]. This suggests that DLGG arise more likely “ex nihilo” rather than from a preexisting congenital lesion. Interestingly, the median age at diagnosis is quite homogeneous across countries despite some variations in incidence.

Beyond these data on temporal origins, the mechanisms and etiologic factors involved in the genesis of DLGG are still poorly known. To this point, it is noteworthy to mention that the implication of one unique etiologic factor for all DLGG is unlikely, as these tumors represent a heterogeneous entity. Indeed, recent refinement of the biomathematical model, based on a differential equation describing the diffusion–proliferation process, has enabled the identification of two types of DLGG: the first type are very slow-growing tumors that appear during adolescence, and the second slow–growing tumors that appear later during the young adult period [3]. These different DLGG subgroups thus attest of the heterogeneity among DLGG and of the complexity of DLGG genesis.

The aim of this chapter is to review the possible mechanisms underlying the genesis of DLGG. One way to better understand the mechanisms involved in the DLGG genesis is to study their spatial distribution, both within the brain and at the geographical level (at the international and national levels), as some hypothesis regarding the mechanisms may be speculated from these distributions.

Indeed, it is interesting to note that DLGG have preferential locations within the brain, mostly within the so-called “functional areas”, and that these locations are different from that of other gliomas (including glioblastomas) [4]. This specific intracerebral distribution of DLGG has now been well demonstrated, using methods based on lobar anatomy as well as voxel-wise methods, or even mathematical probabilistic approaches. Such observation allows two hypotheses regarding the DLGG genesis. First, it is possible that the microenvironment, shaped by environmental demands and specific regional neuron-microenvironment interactions, might influence the risk of tumor development. We will discuss this functional theory in the first part of this chapter. Second, it can be hypothesized that the biological pathways involved in the DLGG genesis may differ according to the tumor location. Biological differences according to the tumor location have been demonstrated, including for example the mutation of the isocitrate dehydrogenase (IDH) gene that is considered as an early event in the DLGG genesis. This hypothesis will be named hereafter the “molecular hypothesis". We will review in this chapter the current knowledge on the cellular and molecular origins of DLGG.

It is also interesting to notice that the geographical distribution of lower-grade gliomas, comprising diffuse grade II and grade III gliomas according to the WHO classification, is also heterogeneous. This has been recently demonstrated in a study by our team in 4790 patients with a newly diagnosed, histologically-proven lower-grade glioma (WHO 2007 classification) in metropolitan France [5]. This observation raises the question of the role of environmental risk(s) factor(s) (“environmental theory”), which will also be addressed in the second part of this chapter.

Finally, we will briefly summarize the current knowledge on genetic susceptibility in gliomas (third part of the chapter).

## 34.2 Functional, Cellular and Molecular Theories

### *34.2.1 DLGG Have Preferential Brain Locations*

It has now been well demonstrated that DLGG have preferential locations within the brain [4, 6, 7]. It is important to note that these locations have been reported using various methods: the classical methods based on the lobar anatomy, but also the voxel-wise methods and probabilistic approaches.

At the lobar level, a first report showed a frequent involvement of so-called "functional" areas, namely the supplementary motor area (27.3%) and insular lobe (25%), with a significant difference when compared with de novo glioblastomas, suggesting a possible different origin between these two kinds of gliomas [4]. This preliminary observation was confirmed by a study demonstrating a higher rate of DLGG in anterior regions of the brain [8], and by a recently published French study on 1097 DLGG [6]. In this series, about 90% of patients had a tumor located in the fronto-temporo-insular regions: 554/1094 frontal, 259/1094 temporal and 177/1094 insular [6]. In a series of 198 DLGG patients from our team, the tumor distribution was as follows: 31.3% frontal tumors, 23.7% temporo-insular tumors, 20.2% fronto-temporo-insular tumors, 12.1% parietal tumors, 9.1% fronto-insular and 3.5% of tumors located at other locations. It is puzzling to note that DLGG scarcely involve the occipital lobe. In a large consecutive series of DLGG recently reported by the UCSF team, only two out of 281 patients (0.71%) had an occipital tumor involving visual regions [9]. The results are almost similar in our consecutive experience with about 400 DLGG, since only six patients (2.0%) had an occipital glioma [10]. In the French Low-Grade Gliomas Consortium series, only 5 out of 1094 (0.46 %) DLGG with known location were occipital [6].

However, in all of these reports, the DLGG spatial classification was based on cerebral lobe or gyri, which lacks accuracy. Two other approaches have thus been used more recently, a voxel-wise method and a probabilistic approach, and have confirmed this data. A recent anatomo-molecular study from our team used for the first time a voxel-wise method to assess the intra-cerebral topography of 198 DLGG patients at diagnosis. As illustrated in Fig. 34.1, the overlap map of all 198 tumors showed a quite homogeneous and symmetrical distribution of the tumors within the fronto-temporo-insular regions, with very little involvement of the posterior regions (unpublished data).

The third approach consists in the construction, by means of a novel probabilistic method, of a graph-based spatial position mapping [7, 11]. We applied this methodology in a consecutive series of 210 DLGG patients at diagnosis, and confirmed the symmetrical distribution of the tumors and the preferential location within frontal (33%), insular (37%) and temporal (18%) areas, with very few tumors located in the occipital and prefrontal lobes (Fig. 34.2).

Whatever the methodology used to assess the preferential locations for DLGG, two main interesting findings should be highlighted.

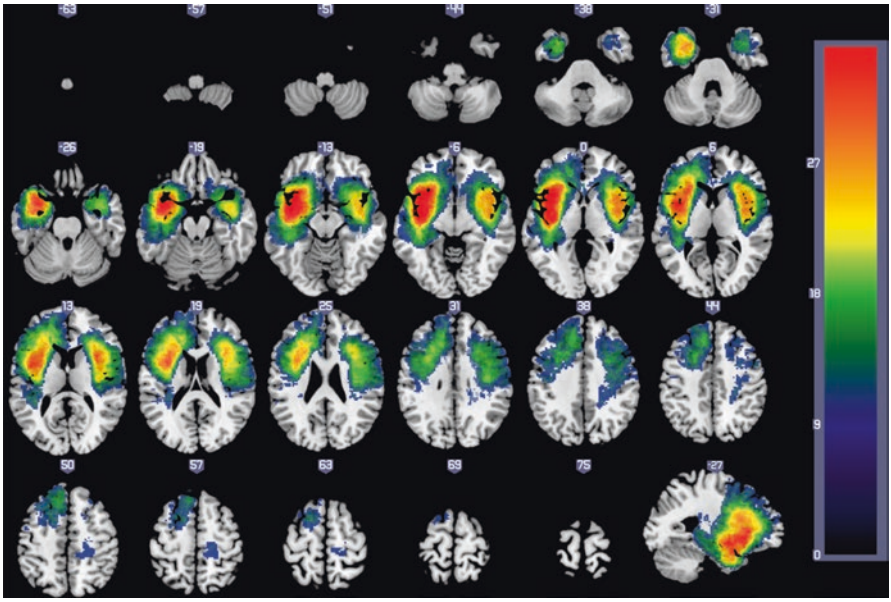

**Fig. 34.1** Tumor overlap map overlaid on a standard Montreal National Institute (MNI) T1 for all 198 patients, presented according to the neurological convention (*left to left* and *right to right*). The color range indicates the number of patients for whom the voxel is lesioned. Each brain section is presented with its z-coordinate in the MNI space

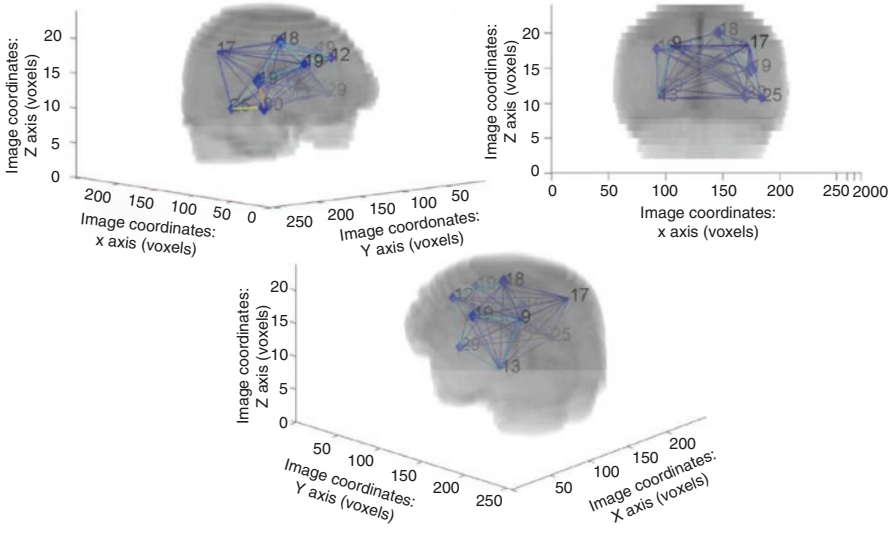


**Fig. 34.2** 3D-representation of the complete clustered graph superimposed to the mean registered image. The numbers of nodes in each cluster are reported

On one hand, there are very few DLGG located in the posterior regions of the brain, including the occipital lobe. This finding was previously reported [6, 10]. It has been further confirmed by the works of our team, and leads to several biological hypotheses regarding DLGG genesis. First, the cytoarchitectony of the visual cortex is not the same, since the insula is constituted by a mesocortex, making a link between the allocortex and the neocortex [4]. Second, differences linked to developmental processes, including the myelination processes, could be involved. Indeed, it is interesting to observe that fronto-temporal areas are among the last myelinated areas during development, the myelination processes occurring until the second decade of life, particularly in the frontal lobe [12, 13]. In the study published by Paus et al. in 111 children and teenagers (4–17 years old), there was an age-dependent increase in white matter density in several areas including the posterior part of the arcuate fasciculus connecting the frontal and temporal areas and involved in language [13]. Interestingly, the myelination processes seem to occur earlier in the posterior regions of the brain (including the occipital lobe), which are only rarely affected by DLGG. It could thus be hypothesized that these temporal differences between regions myelinated at varied periods in the development could participate to the differences in terms of risk of DLGG according to the location. Finally, it seems possible that tumors of different locations could arise from different molecular pathways ("molecular hypothesis"). Indeed, differences in terms of molecular markers, including the mutation of the IDH gene and the 1p19q codeletion, have been reported by several studies [8, 14–22], and further confirmed by a recent work by our team. We will review these data in the present chapter.

On the second hand, DLGG are preferentially located within the so-called "eloquent" areas, including the insula and the supplementary motor area (SMA), which are both functional interfaces between the limbic system (mesiotemporal structure and cingulum) and the temporal pole (for the insula) or the prefrontal cortex (for the SMA). On the contrary, the occipital lobe is not a "transitional" area, and it does not link the limbic system and the neocortex. Moreover, from a functional point of view, both the insula and the SMA play a role in the planning of movements and language [23, 24], while the occipital lobe is not involved in planning. Overall, it can thus be hypothesized that the risk of DLGG is linked, among other factors, to the eloquence of the area involved and that there may be an impact of the microenvironment on DLGG development ("functional theory").

### *34.2.2 The Functional Theory*

The functional theory relates to the impact of the microenvironment or stroma on the tumor development. This hypothesis may be considered to interpret the reasons for the preferential brain locations of DLGG, such as the paralimbic system—in comparison with their non-preferential brain locations, such as the occipital lobe. Indeed, it could be hypothesized that interactions between neurons and glia are different in the SMA and insula compared with those in the occipital lobe. Indeed, glial

cells are known to play a role (1) in neuronal migration, which may explain the existence of migration disorders in some cortical epilepsy, including the extra-temporal epilepsy that often originates from the SMA and insula – but rarely from the occipital region; (2) in the regulation of synaptic transmission; (3) in the control of synapse numbers; and (4) in the energy metabolism of the neuron, explaining the neurovascular and metabolic decoupling in gliomas. Therefore, if we consider that the insula/SMA and the occipital lobe have different structural and functional profiles, repercussions concerning the biology of the local glial cells are likely.

Arguments for the influence of functional parameters and of the subject's activities on the glial cells can be found in the literature on training-induced macroscopic structural changes (of both white and grey matter) in human and animals. A number of neuroimaging studies in healthy volunteers showed that learning could generate a significant increase of gray matter volume in areas specifically involved in tasks extensively repeated [25]. The microscopic mechanisms involved will be discussed farther in this chapter. Interestingly, an implication of the glial cells, either direct (i.e., proliferation of the glial cells [26, 27]) of indirect (i.e., synaptogenesis [28] or myelination [29]) has been suggested. Thus, we might suggest that such modifications in the local glial properties may favor or prevent DLGG development in some specific brain locations.

First, we will shortly review data from the literature regarding training-induced changes in human and animal. Early studies from the 60's have suggested a link between the environmental demands and the brain structure in animals [30, 31]. In the past 15 years, a number of in vivo studies in human have been performed thanks to new imaging techniques, mostly magnetic resonance imaging (MRI) [25]. With these techniques, both the grey ("voxel-based morphometry" or VBM based on a 3D and T1-weighted sequence [32]) and the white matter ("diffusion-tensor imaging » or DTI) were explored. Beyond these morphological parameters, the changes in the functional connectivity induced by training have also been studied using "resting-state" methods, as it can be modulated by the expertise of the subject for a task (see for example the study by Fauvel et al.: modulation of the functional connectivity at rest between several brain areas in 16 musicians compared to 17 matched non-musician controls [33]).

Using these techniques, the macroscopic changes induced by various tasks or activities have been studied in human, from navigation skills in London licensed taxi-drivers [34–36] to cognitive training tasks in students [37] or visuo-spatial tasks with varying complexity (i.e., juggling [25, 38]). These macroscopic changes constitute a powerful phenomenon. They have been reported for a high number of tasks (motor tasks [25, 38–42], pure visual or visuospatial tasks [43], spatial memory and navigation [34, 36], memory tasks [44–46], linguistic tasks [47, 48], calculation [49, 50], reasoning tasks [51], creative and "artistic" tasks [52, 53], and music [54]); from simple tasks [42] or more complex tasks (visuo-motor tasks such a juggling, golf, dance…); on healthy brain (most studies are performed on healthy voluntary subjects) or on damaged brain (i.e., after stroke [55] or in multiple sclerosis patients [56]); in young subjects [25] (including children [57]) or elderly subjects [39, 58]); with controlled tasks or in "ecological" conditions (uncontrolled leisure

activities [58] or cognitive tasks [45]); in the long term (i.e., London licensed taxi drivers [34–36] or in the short term [25, 59–61]); for over-training or for suppression of a task (the withdrawal of the task, even short, is associated with a focal reduction of the grey matter in the corresponding areas [42]); and for both the grey and white matter. However, this phenomenon also seems reversible, with a possible regression of the macroscopic changes after a period of training withdrawal [25], even though a more persistent effect is possible [38, 44]. Therefore, if the hypothesis of an impact of the subject's activities on the genesis of DLGG is true, it can only concern regular activities, such as professional activities, but probably not activities performed punctually. Moreover, it is not completely clear yet whether the morphological changes are linked to a skill itself, or to the fact of learning a new skill. Indeed, correlations between the intensity of the macroscopic changes in MRI and the subject's performance at the task are inconsistently found [25, 43]. Moreover, some studies have reported a regression of the morphological changes without concomitant decrease in the subject's performance at the task [25, 43], suggesting that these macroscopic changes reflect the fact of learning more than the skill itself. This would explain that, in human, there is no significant modification of the brain volume in relation with developing new skills or performing a higher number of activities. However, some discordant data have been reported in animals, among which an increased brain volume and weight in rats placed in an enriched environment [30]. In human, the correlations between the subject's activities (including leisure activities) and brain volume have also been studied in non-demented healthy subjects. In 16 healthy elderly subjects, the grey and white matter volumes were correlated with a composite score considering the education level, activities and leisure [62]. In a larger study in 331 non-demented elderly subjects, a significant association was found between the grey and white matter volumes and education, but not with the activity and leisure score [63]. Finally, if the macroscopic changes visible in MRI are in relation with the learning of a task rather than with the skill/the expertise itself, how could we explain the differences between expert groups and novices in cross-sectional studies? One hypothesis is that expert subjects constantly learn and improve their skills: new streets, new traffic rules etc. for London licensed taxi drivers, new dance steps or choreographies for dancers, for example, which is less true for novice subjects.

To date, the microscopic changes underlying the macroscopic changes induced by training are still uncertain [64]. These changes most probably not only affect one isolated area but rather the whole functional network involved in the task. Microscopically, they probably occur both in the grey and white matter. Microscopic data is lacking and most of it comes from animal studies [26, 64, 65]. Various mechanisms are currently suspected, many of them involving glial cells in a direct or indirect manner: neurogenesis [66, 67], gliogenesis [26, 30, 68], glial hypertrophy (possibly mediated by the interactions between astrocytes and neurons; a recent study on cerebellar cortex in mice suggested that the molecular and functional profiles of astrocytes are regulated by the neurons, through the "sonic hedgehog" pathway [69]) [27, 70, 71], and synaptogenesis (mediated by astrocytes) [70–74] for the grey matter changes and increased glial cells density, increased myelination

(mediated by oligodendrocytes) [26, 75, 76], axonal sprouting (possibly involving NogoA which is mainly expressed by the oligodendrocytes [77]) [65, 67, 78] or vascular modifications for the white matter changes. Thus, glial cells seem involved in training-induced macroscopic changes, either directly (gliogenesis and glial hypertrophy) or indirectly, through the regulation of synapses, axonal sprouting or myelination. It can be hypothesized that these changes could impact DLGG genesis.

As DLGG have preferential locations in "functional" areas, and macroscopic white matter and grey matter changes, possibly mediated by glial cells, can occur after training at a task, it can be hypothesized that an over-solicitation of a functional network by a task or a specific environmental demand may impact DLGG genesis. This hypothesis was named the "functional theory", on the basis of the eloquence of the cerebral regions involved in DLGG. In a recently published study, mice exposed to an enriched environment for over three weeks showed a higher resistance to glioma development after being brain-transplanted with glioma cell lines (glioma development in 73.5% of the transplanted mice in enriched environment group compared to 96.5% in the standard environment group), suggesting a link between glioma development and the amount of brain solicitations [79]. Mice submitted to an enriched environment also showed smaller tumor sizes and reduced proliferation rates in this study. In human, only few studies have investigated the links between the subject's activities and the risk of glioma so far. A small number of studies have reported conflicting results regarding the correlation between the education level and the risk of glioma [80–82]. A Swedish population-based case-control study in 494 glioma patients (and 321 meningioma patients) and 955 controls reported no correlation between the risk of glioma and the education level [81]. In a North-American study, the education level of 600 controls was higher than that of 325 glioma patients (for example, advanced degree in 26% of controls and 18% of cases) [80]. However, a French case-control study including 122 glioma patients (43 DLGG) found that an education level considered as "moderate" was significantly associated with a decreased risk of glioma (OR = 0.35, IC95% 0.16–0.77) compared to subjects with no education [82]. As such association was not found in subjects with a "high" education level, this result must be considered with caution. In the same vein, a recent cohort study found an increased risk of glioma in highly educated people (≥3 years university education) compared to those with primary education [83]. In this study, men and women with an intermediate or high non-manual occupation had a significantly increased risk of glioma. Regarding DLGGs specifically, a hospital-based case-control study in 135 low-grade gliomas (but including gangliogliomas) found no association with education [84]. Finally in a pooled analysis of seven case-control studies including 617 WHO grade II and III oligodendrogliomas and oligoastrocytomas and 1260 controls, 16.2% of cases compared with 17.6% of controls had a higher education level [85].

To date, there is no demonstrated association between professional activities and the risk of DLGG or, more generally, of glioma. A few professions have been inconsistently associated with the risk of brain tumors: health professions [86, 87], electricity workers [88], agriculture workers [89], industrial workers in petrochemical

refineries [90], rubber industries [91], polyvinyl chloride industries [88], chemical industries [87] or nuclear plants; and various other professions such as teachers [92], architects [92, 93], butchers [93], salesmen and waiters [89], servicemen [89]. However these associations are inconstantly found and must be considered with great caution as they could be due to chance only since many of these studies conducted multiple comparisons. Moreover, due to the lack of "functional" classification of the activities, these studies evaluated the professional expositions rather than the neurocognitive functions involved in the profession.

### *34.2.3 The Cellular and Molecular Hypotheses*

It appears increasingly clear that glial tumors emerge from particular initiating cells (cells of origin) transformed by the activation of oncogenic signaling pathways resulting from acquired molecular alterations. This oncogenesis will unfold in a cellular microenvironment, called stroma, itself shaped by loco-regional characteristics that can differ from one brain region to another. The emergence of a tumor in a given area of the brain is then a complex phenomenon in which cellular and molecular phenomena are closely intertwined, so that it is difficult to dissociate the cellular, molecular and functional hypotheses on the origin of gliomas.

Currently available data in the literature on these complex issues present common characteristics: they result from studies conducted in transgenic mice with restricted expression of transgenes in particular cell lineages, and they relate mainly to high-grade gliomas. Understanding of the molecular and cellular events involved in the genesis of low-grade gliomas for now lacks lifelike animal model.

#### 34.2.3.1 Cellular Hypothesis

The oligodendrocyte precursor cells (OPC) and neural stem cells (NSC) have been identified as possible cells of origin of gliomas. OPC represent the major cycle-related population of the adult normal brain, dispersed throughout the gray and white matter. Considering former publications [94–96], OPC seemed particularly involved in the origin of low-grade gliomas. This finding is in good accordance with clinical observations reported by Vergani et al., with a systematic involvement of cortex in a series of 43 DLGG suggesting a centripetal tumor growth [97]. To go further, Galvao et al. showed that OPCs might transform into malignant glial cells by a two-step process. An initial step of malignant transformation through inactivation of TP53 and NF1 genes is followed by a reactivation involving mTOR pathway [98].

Other studies show that, in experimentally raised gliomas, there is interplay between the nature of the cell of origin and the triggered oncogenic signaling pathways. Each of these two elements involved in malignant transformation exerts its influence and the type of glioma thus obtained is the result of their combination.

To find out whether adult lineage-restricted progenitors of central nervous system cells are possible initiating cells of glioblastomas, Alcantara Llaguno et al. induced inactivation of Nf1, Pten and TP53 genes in neural progenitor cells (NPC) and OPC. They obtained two different types of glioblastomas. These tumors were different with regard to their molecular profile, their location in the brain and survival duration of mice developing these tumors. Each type was related to a different cell of origin i.e. NPC or OPC. This work demonstrated that the same oncogenic sequence could give rise to a different tumor type depending on the cell type in which it exerts its action. However experimental tumors thus obtained were histologically classified as glioblastomas, in both cases [99].

On the other hand, in a recent study, Lindberg et al. showed that, depending on the oncogenic pathways activated in the OPCs, a tumor of oligodendroglial or astrocytic type would arise. Overexpression of PDGF-B produced tumors similar to human grade II and grade III oligodendrogliomas while activation of the K-RAS/AKT pathway led to grade III and IV astrocytic tumors. The main finding provided by this work is that the importance of the cells of origin seems inferior to genetic aberrations in determining tumor histopathology [100].

An additional level of complexity is added by the high specialization of the different brain areas. This underlies intrinsic variations, within a given cell type, related to the location, independently to the cell lineage which it belongs. Several studies, once again conducted in mice, showed the diversity linked to the location within a highly compartmentalized organ as the brain. Ko et al. reported distinct gene spatial expression patterns in neurons, astrocytes and oligodendrocytes when analyzed from different brain areas. Gene expression patterns showed strong mirror symmetry between the left and the right hemispheres. Astrocyte and oligodendrocyte-specific transcripts displayed spatially clustered expression patterns less numerous and with less precise boundaries than for neurons [101].

This regional molecular variability in different cell types also affects functionally. First, in normal adult mouse brain, transplanted OPCs differentiated more or less rapidly into myelinating oligodendrocytes depending on whether they were derived from the white-matter or the gray-matter [102]. Second, in an animal model of glioblastoma, the oncogenic induction gives tumors whose growth rate is different depending on the subtype of astrocytes in which oncogenic stimulation was performed. Astrocytes expressing the glutamate aspartate transporter (GLAST) gave rise to more slowly growing tumors than astrocytes expressing glial fibrillary acidic protein (GFAP) [103].

Beyond the nature of the cell of origin and of the oncogenic pathways, the tumor microenvironment, is also involved in tumor development, particularly in the case of DLGG experiencing slow growth. It is the third component in this already complex interactions game. Immune cells represent one of the major components of the tumor microenvironment. Indeed, the immune system is involved in immune tolerance allowing the tumor to settle and then to progress. The immune cells present within the tumor are microglia, resident macrophages of the central nervous system, but also macrophages from peripheral blood that infiltrate secondarily the tumor (tumor associated macrophages TAM). All together, microglia and blood

macrophages represent 30–50 % of the infiltrating cells in gliomas. Accumulating evidence indicates that microglia and TAM promote glioma growth and invasion [104]. At this level too, the diversity encountered between different brain areas is manifested: it has been known for a long time that the distribution and morphology of microglial cells varies from region to region of the brain [105].

There is a link between the immune microenvironment of the tumor and function. Garafolo et al. used the xenograft of glioblastoma cell lines to show that the enriched environment influences tumor development in mice. Indeed, the enriched environment induced the increase of two factors in the tumor microenvironment. The first of them is IL15 that causes accumulation of natural killer (NK) cells in the tumor. NK cells have a direct anti-tumor activity. The second is the important mediator Brain-derived neurotrophic factor (BDNF) that reduced macrophage infiltration and induced a reduction in tumor size [79].

#### 34.2.3.2 Molecular Hypothesis

Once the onset of the tumor is achieved, other molecular events are going to take over and allow tumor development. As a logical consequence of the influences of the original cell, both by its nature and its location, and of the activated oncogenic pathway, molecular profiles determined on resected tumors vary from one region to another.

During the past fifteen years, a number of anatomo-molecular studies showed significant correlations between the location of DLGG and the tumor molecular patterns. First, the IDH mutation, considered as an early key event in the genesis of DLGG, is found with a frequency that varies according to the tumor location. DLGG with IDH mutation are more frequently found in the anterior part of the brain, especially in the frontal lobe in several studies in limited series often mixing DLGG and high-grade gliomas [19–22]. In a recent work from our team (Darlix et al., unpublished data) in a homogeneous and consecutive series of 198 DLGG patients, we confirmed that frontal tumors are more frequently IDH mutant compared to temporo-insular tumors (87.1% vs 57.5%, $p < 0.001$). Second, 1p19q loss, another molecular hallmark of DLGG, has also a different distribution depending on the location. Similarly co-deleted 1p19q gliomas were found more significantly in the anterior part of the brain, especially in the frontal lobe [8, 14–16, 20, 21]. This result has also been confirmed in our recent work, with the presence of a 1p19q codeletion in 45.2% of frontal DLGG compared to 17.0% of temporo-insular DLGG ($p = 0.003$). However, the anatomo-molecular studies published so far have some limitations. Most importantly, their methodology for determining groups of tumors according to their locations often relied on a subjective assessment of lobar anatomy, while it is needed to use different approaches to deal with the question of multi-lobar tumors. In addition, the majority of these studies were conducted on series including gliomas of different grades [8, 20] or a small number of homogeneous tumors [17–19].

The molecular regional differences yet observed in DLGG would have consequences on the outcome of these tumors because prognosis value has been assigned to some of them, especially IDH mutation and 1p19q loss. Therefore, the tumor location could be in itself a prognostic factor.

## 34.3 The Environmental Theory

Beyond their preferential locations within the brain, DLGG also seem to present with a heterogeneous distribution at the geographical level [5]. Indeed, even though the epidemiology of DLGG is poorly known, a few studies have previously suggested such an heterogeneity in the geographical distribution of gliomas, at the worldwide or European level, with a trend towards higher incidence rates in highly-developed countries (http://globocan.iarc.fr/) [106–109]. However these studies have major limits. First, they included gliomas of all grades and even different histological subtypes of primary central nervous system tumors (PCNST). Second, they compared the incidence rates at an international or intercontinental level, resulting in an obvious bias due to differences among continents and European countries in terms of case registrations and access to healthcare. In a study from our team based on data from the French Brain Tumor DataBase [110–112], we analysed the geographical distribution of a homogeneous series of 4790 newly-diagnosed and histologically confirmed diffuse WHO grade II and III gliomas (2099 grade II, 2484 grade III, 38 NOS "not otherwise specified" astrocytomas, 25 NOS oligoastrocytomes and 144 NOS gliomas) in metropolitan France, over a four-year period (2006–2009) [5]. The overall crude rate was $19.4/10^6$. We found that the geographical distribution by region was heterogeneous, with higher incidence rates in Northeast and central parts of France, for all included tumors as well as for grade II and grade III gliomas analysed separately. Since France has a unique healthcare system, access to healthcare is likely to be similar in all regions, especially as the distribution of neurosurgical centers is roughly homogeneous in the metropolitan French territory, with one or more neurosurgical center(s) (depending on the number of inhabitants) in each region (and no region without a neurosurgical center). Therefore, the demonstrated uneven geographical distribution of DLGG raises the question of the role of environmental risk(s) factor(s) (environmental theory).

A possible hypothesis for the uneven DLGG geographical distribution is the impact of environmental factors on DLGG risk. To date, however, there is no demonstrated environmental risk factor of DLGGs. Interestingly, a geographical heterogeneity in the incidence rates was highlighted for other cancers. In France, the incidence rates for all cancers are higher in the North and Northeast regions (data from the National Cancer Institute: http://www.e-cancer.fr/publications/69-epidemiologie/574-la-situation-du-cancer-en-france-en-2011). Especially, the distribution of colorectal cancer (CRC) was comparable to that of WHO grade II and III gliomas in our study, with similar higher incidence rates in the Northeast part of

France. We can thus hypothesize that these two diseases may share some risk factors. Some diets were validated as risk factors in CRC with red and processed meat, alcohol, obesity or abdominal fat being strongly associated with a higher risk of CRC, while the "Mediterranean diet" prevents its occurrence [113, 114]. A working hypothesis could thus be that diet factors, and in particular processed meat, may have an impact on the risk of developing WHO grade II and III gliomas. N-nitroso compounds, mostly found in processed meat, are considered as carcinogenic [115]. Regarding gliomas, an experimental model in rat showed an increased occurrence of glioma after intravenous injections of N-nitroso compounds [116]. In France, the consumption of red and processed meat is higher in the Northeast regions (CREDOC, research center for the study and the observation of living conditions, http://www.credoc.fr/pdf/4p/101.pdf). In epidemiological studies, processed meat has been inconsistently associated with glioma risk [117–121]. Two cohort studies and a large international case-control study found no association between processed meat consumption and the risk of glioma [117–119]. In the case-control study, astrocytomas, oligodendrogliomas and glioblastomas were analyzed both together and separately. Two recent meta-analyses found similar results, with a modest increase of the glioma risk associated with consumption of processed meat in case-control studies but not in cohort studies [120, 121]. So far, no epidemiological study has investigated the association between processed meat and WHO grade II and III glioma risk specifically. Other diet factors have been studied, but none has been associated with DLGG or glioma risk yet. Another interesting observation is the relative similarity between the geographical distribution of WHO grade II and III gliomas [5] and that of multiple sclerosis [122, 123]. As WHO grade II and III gliomas have the same pattern of geographical distribution than multiple sclerosis, these two diseases may share some risk factors. Indeed, there is strong evidence that environmental factors influence the distribution of multiple sclerosis [124]. In particular, sunlight exposure (and, consequently, outdoor activities) is significantly associated with multiple sclerosis prevalence (sunny areas being associated with low prevalence). This association probably involves vitamin D, as a low prevalence of multiple sclerosis has been reported in countries with a poor amount of sunlight but a high consumption of vitamin D (oily fish) [124, 125]. We could thus hypothesize that sunlight and vitamin D intake influence the risk of WHO grade II and III gliomas. Based on the map of the sunlight provided by the Joint Research center of the European Commission (available at: http://re.jrc.ec.europa.eu/pvgis/cmaps/eu_cmsaf_opt/G_opt_FR.png), it seems that regions with low sunlight correlate with those with higher incidence rates of WHO grade II and III gliomas in our study, supporting the hypothesis of an association between sunlight and WHO grade II and III gliomas risk. This hypothesis is also supported by a study that found a reverse association between UVB irradiance and brain tumor risk [126].

The uneven geographical distribution of DLGGs in France [5] also raises the question of the role of genetic risks factors that could be involved in some geographical regions (genetic susceptibility, the genetic predisposition theory).

## 34.4 The Genetic Predisposition Theory

Genetic susceptibility variants could also impact on the risk of DLGG development and have been widely studied in the past years to better understand the origins of this entity. The DLGG molecular epidemiology is extensively reviewed in a previous chapter of the present book ("Molecular Epidemiology of DLGG"); we will only briefly summarize the current knowledge on the subject. Interestingly, about 5% of glioma patients have a familial glioma history [127]. While these aggregations could be in relation with the environment (subjects in a family share environmental exposures), they suggest the existence of a genetic susceptibility. Among susceptibility factors, monogenic genetic syndromes account for 1% of familial cases of glioma [128–130]. Beyond these monogenic syndromes, some non-syndromic genetic factors of susceptibility seem to influence the risk of glioma as well [131].

A familial history of brain tumor is a risk factor of glioma in non-syndromic families [85, 131–133], including for DLGG [131, 132] and oligodendroglial tumors [85]. A pooled analysis of data from two case-control studies found an increased risk of melanomas, sarcomas and PCNST (including DLGG) in first-degree relatives of glioma patients, with no increase in the global cancer risk [131]. In the study published by McCarthy et al., the risk of developing a diffuse WHO grade II and III oligodendroglioma was increased in patients with a familial history of PCNST (odd-ratio = 1.8 CI 95% 1.1–3.1) [85]. In a Swedish study, the standardized incidence was $3.65/10^5$ (CI 95% 2.31–5.47) for first-degree relatives of DLGG patients, and $7.00/10^5$ (CI 95% 3.35–12.87) for siblings, which is significantly higher than the reported incidence in the general population [132]. Various studies have tried to characterize these familial gliomas on a genetic point of view. First, comparative genomic hybridization techniques were used and have suggested that familial gliomas are relatively close to "eneral" gliomas, with only few inconsistently-reported specific alterations [134]. Other studies used linkage analyses to identify candidate genes/genetic variants in familial gliomas. The GLIOGENE project ("Genetic Epidemiology of Glioma International Consortium") was set up in 2006 and includes glioma families treated in 14 institutions and five countries [127]. It allowed the identification of a region of interest located on chromosome 17q [135, 136]. Further analyses of this specific region (17q sequencing) pointed out several candidate genes (Myo19, KIF18B, SPAG9 in particular) [137]. However, none of these genes was found in common for all the described glioma families. Another region of interest located on chromosome 15q23 was reported in several studies [138, 139]. These linkage studies, however, face major difficulties, in particular the fact that, due to the poor survival of many glioma patients, only few families comprise more than two cases alive simultaneously.

More recently, other genetic risk factors for glioma were studied, in particular genetic polymorphisms [140]. These studies found associations between a number of single nucleotide polymorphisms (SNPs) and the risk of the glioma [141–143]. To date, eight SNPs located in seven genes have been associated with an increased

risk of glioma in genome-wide association studies (GWAS) [142]: rare genetic variant in the *TP53* gene (glioblastomas and other gliomas) [144–146]; genetic variants in the *EGFR* gene (gliomas) [147, 148] ; in the *RTEL1* gene ("regulator of telomere elongation helicase") (gliomas) [149–151]; in the *TERT* gene ("telomerase reverse transcriptase") (oligodendrogliomas and astrocytomas, whatever the grade or the IDH status) [149, 151] ; in the *8q24* locus/*CCD26* gene (gliomas, in particular oligodendrogliomas and IDH-mutated tumors, and including DLGG) [152–155] ; in the *PHLDB1* gene (IDH-mutated gliomas, whatever the tumor grade and histological subtype) [151, 155, 156] ; and in the *CDKN2B* gene [149, 150, 157]. These SNPs identified by GWAS studies have been further confirmed in a large case-control study [157], as well as in a meta-analysis [158]. Genetic variants of *TERT*, *RTEL1*, *EGFR* and *TP53* were found associated with an increased risk of glioma, whatever the tumor grade or histological subtype [143]. On the contrary, genetic variants of *PHLDB1* and *CCDC26* (±*CDKN2B)*: conflicting results [155] were shown to be associated with an increased risk limited to specific grades and/or histological subtypes of gliomas. Candidate-gene studies have also identified a number of candidate genes involved in several biological pathways: folate metabolism [159], DNA-repair pathways (XRCC ou "X-ray repair cross complementing group", [160] apoptosis signaling pathway (i.e., CASP8 [161]. However, none of these SNPs has been confirmed in the large case-control study published in 2013 [157].

## 34.5 The Clinical Implications

Such spatiotemporal, functional, and biological considerations may have important implications with regard to the therapeutic strategy and management of DLGG patients. First, the dynamic interactions between DLGG and the brain may vary depending on the eloquence of the areas involved by the tumor. Indeed, it was shown that slow-growing DLGG might induce cerebral plasticity, explaining why most patients showed no or only mild neurological deficit despite voluminous gliomas, even in the so-called "critical" regions [162, 163]. Nonetheless, a recent atlas of DLGG resectability demonstrated that some cerebral areas had low compensatory capabilities [164], constituting a "minimal common brain" among patients [165]. As a consequence, the extent of surgical resection (and thus the median survival [166]) is correlated with the location of the tumor (with regard to the cortex as well as the white matter pathways, therefore the distance from the subventricular zone), that is, with a better tumor removal in "non-eloquent" than in "eloquent" areas and in "compensable" rather "non compensable" structures [9, 167–169]. In addition, a different genetic pattern in temporo-insular DLGG, with a less frequent IDH mutation and 1p19q codeletion compared with frontal DLGG, could also account for the poorer prognosis of these tumors. Indeed, DLGG prognosis was shown to vary according to the tumor location, frontal DLGG being associated with a better intrinsic prognosis compared with

temporal or insular tumors whatever the extent of resection [6]. As a consequence, it might be pertinent to modulate the treatment strategies according to these two subgroups of patients, and discuss a more aggressive strategy for temporo-insular DLGG with, for example, earlier chemotherapy regimens after surgical resection.

The functional, cellular, molecular and environmental parameters discussed in this chapter illustrate very well the close relationships between the pathophysiology of gliomagenesis, the anatomo-functional organization of the brain, and the personalized management of DLGG patients. They will allow a better screening of the population in order to perform an early detection of DLGG—and thus to propose a more precocious and more efficient treatment [170–173]—as well as to improve our knowledge concerning the origin of DLGG.

## 34.6 Conclusions

The origins of DLGG are still unclear, but it seems plausible that an association of genetic susceptibility and biological, functional and environmental factors influence the risk of developing DLGG. Future studies will be needed to investigate these candidate etiologic factors taken together, as interactions between the environment, brain functions and tumor genes are likely. This will allow a better understanding of the origins of DLGG and of the clinical heterogeneity of this entity.

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# Chapter 35
# From Management of Incidental DLGG to Screening of Silent DLGG

**Emmanuel Mandonnet, Luc Taillandier, and Hugues Duffau**

**Abstract** As access to brain MRI is getting wider, it is not uncommon to diagnose incidentally a diffuse low-grade glioma (DLGG) in a neurologically fully asymptomatic patient. Based on the results of maximal safe surgical resection in symptomatic patients—allowing to significantly increase overall survival while preserving quality of life by sparing the cerebral connectome—surgery under local anesthesia with intensive cognitive monitoring and mapping has recently been proposed in incidental DLGG patients. First results showed that, by performing earlier surgery, that is, for smaller tumors, extent of resection was maximized and risk of malignant transformation was minimized, while patients continued to have a normal familial, social and professional life—especially with no epilepsy. As a consequence, it was proposed to set up a policy of screening in the population between 20 and 40 years-old, by offering to healthy volunteers a cerebral MRI. We analyzed the conceptual and practical elements of feasibility, and conclude that benefits would overweight the costs and risks of such a strategy.

**Keywords** Diffuse low-grade glioma • Incidental glioma • Screening • Surgery • Supratotal resection

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## 35.1 Introduction

Recent advances in DLGG management converge to the conclusion that the earlier the treatment (and especially the surgery), the better the survival. Accordingly, a recent review [1] reported that incidentally discovered DLGG should be also early treated, especially when the tumor is accessible to total or, even better supratotal, resection. Up to the point that among other avenues of research, MRI screening in healthy volunteers is currently investigated.

In this chapter, we will first summarize the natural history of DLGG of incidental discovery and present the datas and arguments that plaid in favor of early treatment of incidental DLGG (iDLGG). From there, we will question the rationale of DLGG screening, and address points by points the conceptual and practical issues that could hamper the feasibility of such a project.

## 35.2 Natural History of iDLGG

Incidental gliomas are suspected on an MRI performed for another reason, mainly head trauma, unrelated headaches, participation in a research protocol, or follow-up of another brain pathology. The first issue is to get a high degree of confidence that the lesion at hand is indeed a glioma. In a series of 72 suspected iDLGG [2], it was found that for 15 of them, the diagnosis of glioma was eventually rejected, given a strict radiological stability over a more than 5 years period of time (see also Fig. 35.1). In fact, whereas the diagnosis is quite easy when the morphological (and

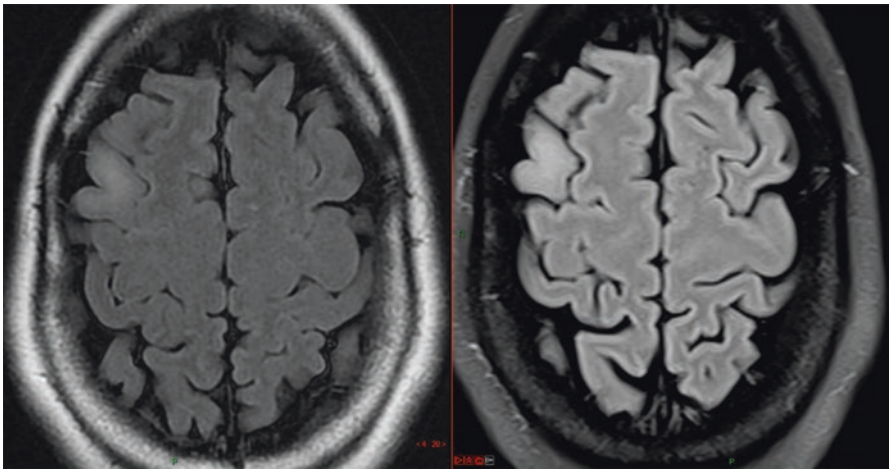

**Fig. 35.1** Suspected DLGG of incidental discovery in a 50-years old lady on axial FLAIR-weighted MRI. No evolution was evidenced over three years of follow-up (*left*: June 2013, *right*: June 2016). Active surveillance was recommended. The patient enjoys a normal life, with no symptoms

spectroscopic) aspect on MRI is typical, the question might be more difficult in other conditions, especially for infracentrimetric lesions (Fig. 35.1). For this reason, an initial radiological follow-up is always warranted, with the aim to evidence by 3D segmentation a quantitative tumor growth of at least 2 mm. Such evolution might be detected over 6 months (growth rate = 4 mm/year) or might need 2 years (growth rate = 1 mm/year). Two series focusing on the natural history of iDLGG [3, 4] reported results in accordance with this policy: the median time between first MRI and oncological treatment was 21 and 10.4 months, respectively.

It is of utmost importance to understand the functional and oncological consequences of the silent growth of iDLGG. First, patients will become symptomatic, after a median delay of 48 months in the French series of iDLGG [3]. Thanks to the great plasticity potential in these slow growing tumors [5], the first symptom is commonly a seizure. But in fact, a biomathematical model suggested that epilepsy onset is the sign that the threshold of compensation has been reached [6]. Accordingly, in patients diagnosed with epilepsy, it has been shown that tumor infiltration along the white matter pathways [7] is correlated with a decrease in verbal semantics [8], in keeping with the low plasticity-potential of long range white matter connectivity [9, 10]. Not surprisingly, it has been found that even in asymptomatic iDLGG patients, a high percentage of patients already exhibits a mild but detectable cognitive dysfunction at diagnosis [11]. In other words, at epilepsy onset, plasticity is already over-passed, meaning that surgical resection will be most likely subtotal, or at best complete, but with little chance to be supracomplete.

From an oncological point of view, the cumulative risk of malignant transformation is progressively increasing during the slow silent growth. It is important to understand that this histological and molecular evolution occurs without detectable clinical sign. It has been shown indeed in a series of patients followed-up for small nonspecific incidental brain lesions, that the first symptom can be a neurological deficit, at a time the tumor is already a grade III [12]. This has been recently confirmed: the malignization of an iDLGG towards a glioblastoma in a patient undergoing active surveillance has been reported, without any symptoms that could have acted as a warning to the clinician [13]. In the same vein, it has been reported that micro-foci of anaplasia are found in 27% of patients operated on for an iDLGG [14] (Fig. 35.2).

## 35.3 A Plea for Early Resection in Patients with a Glioma Incidentally Discovered

Once the diagnosis is considered as certain, the pro and cons of early treatment should be explained to the patient and his/her family.

First, there is strong evidence that surgical resection improves survival in *symptomatic* DLGG patients. Three mains studies indeed reported the survival benefit of

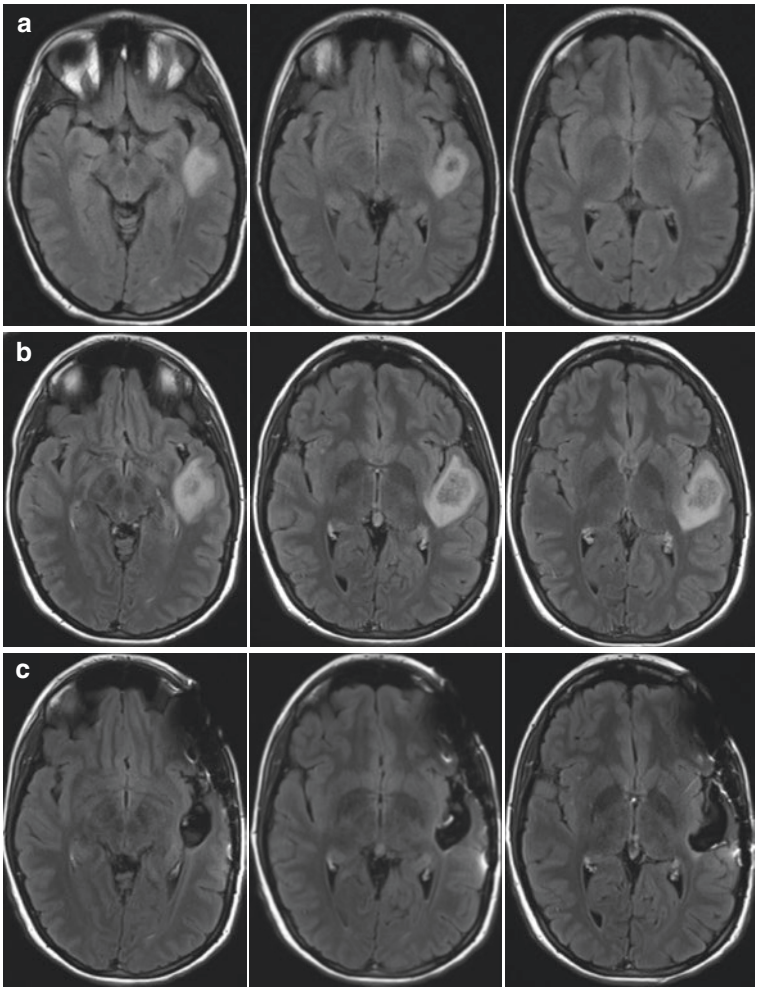


**Fig. 35.2** (**a**) Axial flair MRI of a suspected DLGG of incidental discovery in a 23-years old woman (MRI performed because of migraines). (**b**) With only 6 months of follow-up, the FLAIR abnormality increased, while the patient was still asymptomatic (no seizures, normal neurocognitive assessment, normal life). Of note, the growth rate was about 8 mm of mean diameter/year. As a consequence, awake procedure was proposed, with intraoperative electrical mapping due to the location within the left temporal lobe. Surgery was uneventful, with complete resection verified on postoperative FLAIR-weighted MRI (**c**). Histo-molecular examination revealed an anaplastic glioma, with several foci of mitosis and microvascular proliferation (IDH1 mutated, no 1p deletion, partial loss of 19q). Nonetheless, because a radical resection was achieved, no adjuvant treatment was administrated. With 2 years of follow-up, the MRI is still stable, and the patient enjoys a normal familial, social and professional life (no neuropsychological deficits, no seizures, no antiepileptic drugs, working full-time). This illustration shows that maximal resection can dramatically impact the natural history of the disease, even when the glioma is already anaplastic despite incidental discovery (independently of the molecular profile, since there was no 1p 19q codeletion in her case). This justifies to propose a screening in the general population

complete and subtotal resection on large series of patients [15–17]. More than that, it is believed that supracomplete resection, that would take a margin all around the flair hypersignal area (between 1 and 2 cm, depending on individual functional boundaries), could potentially cure some patients. Hence in a first study [18], it was reported that no malignant transformation was seen in a group of 15 patients with supracomplete resection, compared to 7 out of 29 patients in the control group with complete resection. This result was recently confirmed in a series of 16 patients with supracomplete resection, as no patients experienced malignant transformation, over a median follow-up of more than 11 years [19]. Moreover, in this series of supracomplete resection, long term remission (that is without any recurrence of flair hypersignal), over more than 10 years (and for some patients over almost 20 years) was observed in half of cases.

Unfortunately, in symptomatic patients with long range white matter tracts infiltration, supracomplete resections are rarely possible, in order to preserve the functional status of the patients, in accordance with the philosophy of optimizing the onco-functional balance in DLGG patients [20, 21]. Yet, in the two surgical series of iDLGG previously cited, iDLGG were found smaller than in symptomatic series, meaning that the chances to achieve a supratotal resection are much higher than for symptomatic patients, as recently reported [14, 22]. In summary, there is no doubt that early surgery would improve survival of iDLGG patients.

In fact, those clinicians that plead for "watch and wait" attitude argue that surgery carries a functional risk, and that such a risk is unacceptable in the context of an incidentally discovered lesion. It should be first reminded that since the advent of intraoperative functional mapping in an awake patient, the rate of neurological deficit dropped to a very low level [23, 24], with rates between 0 and 2% in most experienced centers [25–27].

However, in the particular context of iDLGG, one would like to set the bar even higher in terms of functional results, in particular professional activity. There is currently relatively scarce datas in the literature about work resumption rates, as only one study in symptomatic patients reported a 80 % rate of work resumption, in an initial experience of awake surgery [28]. For iDLGG patients, only one study about 11 patients reported such results [14]. In this series, none of the patients experienced long lasting deficits, and the eleven patients resumed their work. Perhaps even more importantly, surgical resection does not seem to induce epilepsy: a recent paper reported no onset of seizures in a series of 21 patients undergoing resection of an iDLGG [22], in keeping with our recent understanding of the physiopathology of glioma epilepsy, allowing to locate the epileptogenic area in the periphery of the glioma [29, 30]. Hence, given that a high percentage of untreated iDLGG patients already exhibits mild cognitive deficits and will present seizure some months/years after initial diagnosis, early surgical resection might contribute to delay these functional impact. In summary, the survival benefit of surgery largely over-weights the functional risk, thus arguing for early resection in incidentally discovered glioma with proven radiological progression (Fig. 35.2).

## 35.4 Rationale for DLGG Screening

Concomitantly to the preliminary successes of the preventive surgery in incidental glioma patients, has emerged the idea of screening [31]. It was based on the intuition that DLGG grow silently for many years before symptoms onset, and that it might be during this silent phase that we missed the action (Fig. 35.2). However, serious issues had to be solved to prove the clinical relevance of this intuition.

First of all, it had to be demonstrated that the risk of overtreatment is low. Indeed, what if the majority of detected cases would have enjoyed a normal life with their silent glioma until dying from another cause? A recent study investigated this question quantitatively, based on available epidemiological datas. It was found that after an initial period of 4 years, the risk of dying from the silent glioma over-weights the risk of dying from another cause [32]. This important result was a prerequisite and laid the foundations for further work in this direction.

Second, one needed to know the rate of people who would be keen to undergo a screening brain MRI if such an MRI was offered in the context of a national health system policy. Whereas attendance rates in national screening programs are very high for other cancers (breast, colorectal, prostate) [33], this could be different for brain tumors: due to the strong symbolic value of the brain, people may be afraid of adverse effects from treatment and could prefer not to be aware of having a silent glioma. A recent survey [34] found that 2/3 of people declared that they would undergo such a screening MRI. We are quite confident with the result of this survey, as exactly the same proportion of subjects effectively completed an MRI in the context of screening in a large cohort of 2176 participants [35]. Although this figure is indeed much lower than attendances rates observed for other cancers, it is sufficiently high to investigate further the feasibility of a screening project.

## 35.5 Elements of Feasibility of Brain MRI Screening

From a medical point of view, the rationale of a screening has been established. However, clinicians still have to overcome several obstacles before launching a large scale screening policy.

One of the main obstacle is the very low prevalence of silent DLGG compared to other brain pathologies that would be also detected on a screening MRI. The prevalence of silent DLGG in the general adult population has been estimated around 4/10, 000 in a meta-analysis of incidental findings on brain MRI [36], which is in fact much smaller than the rate of any other abnormal findings (which approximate 3%) [36]. Indeed, these patients should be seen in clinics by a neurologist or a neurosurgeon to discuss about the different options regarding the discovered abnormality. In particular, a list of potentially fatal pathologies requiring urgent management should be established (such a colloid cysts with hydrocephalus or giant aneurysm). In this perspective, a categorization of incidental findings has been recently proposed [35], and can serve as a starting point. Interestingly, the neuroscientific community has faced over the past years a controversy in the context of incidental discovery

during participation to neuroimaging research. The recent tendency is to move from a non-disclosure attitude to a systematic radiology review and rationalized disclosure system [37, 38]. Hence, if properly anticipated, the discovery of non-glioma abnormalities during screening should not be seen as a real medical problem.

Although our current knowledge of silent DLGG epidemiology is very limited, the time period during which the glioma could be detected is about 15 years [39]. Although this estimation comes from biomathematical modeling of glioma kinetics and relies on some untestable hypothesis, it seems to be a valid one as the same results can be found from a completely different methods, which is only based on epidemiological datas and reasoning [32].

Hence the window of opportunity to detect a silent DLGG is quite large, making this pathology a favorable case for screening (at the difference of high-grade gliomas, for which this period of detectability is much too short).

The next question is to determine the optimal timing of this screening MRI. The distribution of patient ages at the time of radiological onset has been estimated from biomathematical modeling of tumor evolution in a series of 264 patients [40]. This distribution has a Gaussian shape, centered on 30 years of age, with a "width" of 10 years. Based on this datas, we propose to screen at 20, 30 and 40 years of age.

Perhaps it is more problematic to prove that the screening would be economically cost-effective. A rough analysis has shown that the balance would be reached if one can gain 3 years of active life by screening and preventive treatment [32]. It is currently an impossible task to estimate how many years of active life could be gained by an early surgery. But it should be kept in mind that, because about one third of people would not be keen to be screened, a large control group would exist, allowing to evaluate the real efficacy of the screening policy in terms of survival and functional status.

## 35.6 What Are the Equipment and Human Resources Needed to Achieve Brain MRI Screening?

In order to make the screening feasible, we propose to use a single flair sequence on a 3T MRI, with 2–3 mm thickness. If we consider the screening of a class of age in France, 750, 000 people should undergo an MRI. Assuming an attendance rate of 66%, we would expect that 500, 000 people would be effectively screened. Performing 4 cases per hour, 12 h a day, 225 days per year, would allow to screen 10, 800 cases per year per MRI machine. This means that a total of 45 machines should be built to screen a class of age. As the screening would be recommended at three different ages (20, 30 and 40 years of age), about 150 MRI spots would be needed, which would be quite affordable in terms of initial investment.

However, if we want all the MRIs to be reviewed by a neuroradiologist, this would represent 150 full time neuroradiologists. Although such recruitment would be feasible in the future, such human resources are currently not available in France. As a consequence, there is a need to develop computational algorithms to detect automatically abnormal MRIs. Sensitivity should prime over specificity, such that none of abnormal MRIs would be missed. For example, an algorithm with a sensitivity of

100% and specificity of only 10% would detect as abnormal 30% of cases, thus reducing to 50 the required number of neuroradiologists. This would be highly realistic, as this represents only 12.5% of the current number of neuroradiologists in France.

## 35.7 Towards Integrated Highly-Specialized Centers for Management of Screened DLGG

Assuming a screening policy has been developed, the question arises about how the surgical and oncological management of detected cases should be organized. It has to be reminded that, according to the "primum non nocere" doctrine, the surgery should not only avoid any motor or language deficits, but also any impairment of cognitive, emotional or social abilities, in these young people who are fully functional and socio-professionally active. Hence, in the context of screened glioma, the bar has to be set much higher in terms of functional results than in symptomatic or even incidental patients with involuntary discovery of the tumor. In particular, patients should be able to resume their professional activity. Note that this is also a requirement regarding the economical viability of the overall policy. Only ultra-specialized centers, integrating experts in neurosurgery, neuropsychology, neuroradiology and neuro-oncology could pretend to achieve such results with a high level of reliability. How to proceed in order to inform patients about the quality of care of a surgical center in DLGG is a fundamental open question.

## 35.8 Conclusion

DLGG seem to fulfill the essential criteria for screening eligibility. In fact, several small scales studies of brain MRI screening have been undertaken in different European countries, including Netherlands [41], Norway [42] and Germany [35], totalizing 8982 cases. In the Norway study, one silent DLGG has been detected, and it is stated that. "The glioma was resected and re-resected three years later. The operations did not result in postoperative neurological deficits, and the participant is still alive 7 years after the diagnosis". To our knowledge, this is the very first report of a patient operated on for a screened DLGG, and the successful management in this case should encourage the medical community to generalize this policy.

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