Treatment Goals in Low-Grade Gliomas Clinical Management

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The ability of neural circuits to compensate for damage to the central nervous system is called postlesional plasticity. In diffuse low-grade gliomas (LGGs), a crosstalk between the brain and the tumor activates modulations of plasticity, as well as tumor proliferation and migration, by means of paracrine and electrical intercommunications.

brain plasticity neuroplasticity low-grade glioma

1. Introduction

Supratentorial adult low-grade gliomas (LGGs) are a subgroup of histologically and molecularly defined diffuse primary brain neoplasms, including grade 2 IDH-mutant astrocytomas and grade 2 IDH-mutant and 1p19q co-deleted oligodendrogliomas [1]. Early stages of LGG expansion are characterized by a slow invasion of the brain parenchyma (generally, the mean diameter of expansion stands around 2–4 mm per year [2]) with a prominent tropism toward white matter microstructures [3][4]. Such diffusive pattern irremediably leads to an accumulation of genetic and epigenetic alterations that ultimately induce malignant transformation (MT) [5][6][7] and compromise patients' neurological status. In parallel, as glioma cells are physically [8] and electrochemically integrated to the surrounding neural circuits [9][10], a bidirectional relationship exists between the tumor and its host brain: (i) the glioma proliferation is triggered by microstructural electrical [11] and regional functional activities [12], and is further affected by whole-brain network dynamics [13]; (ii) the functional connectivity between gliomas and other brain areas, and in-between remotely situated brain areas, is intensely reshaped to maintain network efficiency and cognitive performances (a compensatory mechanisms also called lesion-induced neuroplasticity, or plasticity) [14] [15]. Such adaptative compensations remain constrained by the intrinsic anatomofunctional architecture of the brain [16][17] and do not have an infinite potential, since it may rapidly be overwhelmed in case of MT, thus affecting patients' cognitive outcomes and clinical course [18][19]. Furthermore, the crosstalk between glioma growth and brain adaptation is perpetually evolving, resulting in significant constraints regarding the efficacy of oncological treatments and their tolerance in terms of cognitive maintenance and quality of life (QOL) preservation [20]. Reciprocally, each therapeutic step may have a decisive impact on short and long-terms plasticity modulations, since treatments may fragilize microcircuits that convey efficient functional remodeling. Therefore, the traditional oncological paradigm whereby the efficacy of one treatment is evaluated at one timepoint without an overall perspective of cumulative medical strategies and ongoing brain-to-glioma interactions can hardly be applied to LGGs. This is the reason why individualized and longitudinal oncological strategies have emerged over the last decade [21][22]: in these models, therapeutic options are considered in a holistic approach and traditional treatments

can be postponed, repeated, or reversed, depending on individual parameters (e.g., tumor volume, effect of the previous line of treatment, functional status) with the ultimate goal of preserving the QOL in the long run. Strikingly, this strategy was shown to be effective, not only to expand the overall survival beyond 16 years in IDH-mutant LGGs, but also to sustain patients' functional status in the long run (the Karnofsky performance status was maintained over 80% during 12.2 years in median in the Nancy experience [23]).

Yet, despite past and recent findings supporting the idea that plasticity is highly impactful on the clinical course of patients harboring LGGs, neuro-oncological guidelines do not currently implement neuroplasticity biomarkers in the decision-making processes that govern treatment strategies [24].

2. Treatment Goals in LGGs Clinical Management

2.1. Functional Goals

LGGs are generally diagnosed in young patients (on average aged from 30 to 40 years) [25][26] who enjoy normal social and professional lives. The overall survival of these patients has considerably evolved over the last two decades, mainly due to the systematization of extensive and early surgical approaches in comparison to "wait and watch" attitudes [27]. However, the natural history of the disease and the cumulative adverse effects of oncological therapies may have a drastic impact on patients' QOL, including individual professional perspectives [28], wellbeing [29], and cognitive functioning, whether at early stages of the disease (and even before the first therapeutical steps [30]) or at the later stages of the oncological management [31]. Consequently, preserving QOL in the long run remains the main objective of the oncological strategies. In parallel to epileptic seizure control, which is the most common symptom in LGG patients [32], health-related QOL highly depends on a combination of social, behavioral, and neuropsychological factors [33]. Two main clinical endpoints have progressively emerged as landmark measures in the recent literature: (i) neurocognitive functioning, which should be evaluated with longitudinal neuropsychological assessments [34][35], and (ii) return to work [36], since the rate of resumption of professional activities reflects the ability of patients to maintain complex, integrated, goal-directed cognitive and behavioral tasks [37], while it also indicates the societal and economic impact of the treatments [38].

2.2. Oncological Goals

The aim of the oncological management of diffuse LGGs is to maintain permanent control over lesion size, in order to reduce the risk of MT. Although most assessments of therapeutic response in glioma trials are based on the response assessment in neuro-oncology (RANO) criteria (which are not directly based on lesion 3D volume but on bidirectional 2D measurements performed on a single slice), the 3D fluid attenuated inversion recovery (FLAIR) volume is by far the most effective radiological measure to assess objective treatment response, with the highest inter-reader agreement [39] and the highest levels of correlation with the risk of MT [40][41][42]. Importantly, both the pre-therapeutic volume [43] and the post-therapeutic volume have been recently revalidated as independent prognostic parameters across all histomolecular subclasses of LGGs [44], with an impact in terms of progression-free survival (postsurgical volume threshold <9.75 mL) and overall survival (postsurgical volume threshold <4.6

mL) [45]. Furthermore, although it is clear that every mL of tumor removed has a long-term impact on the course of the disease, the 10 ± 5 mL volume threshold was consistently established as a strong prognosis factor associated with MT and clinical outcomes [40][41][42][45][46]. Of note, current guidelines and ongoing trials do not account for this volume threshold and keep on employing the historical dichotomy between “low risk” and “high risk” LGG patients [47][48][49], with the age and a less-than-total gross resection as criteria to recommend early adjuvant therapies. Beyond the necessary need to integrate molecular mutations (e.g., IDH mutation, 1p19q codeletion, CDKN2A/B homozygous deletion), the arbitrary cutoff of 40 years and the lack of consideration of recent studies regarding the prognosis impact of the volumetric threshold reduce the scope of this dichotomy [50], and current oncological teams tend to defer adjuvant treatment in subcategories of “high risk” profiles [51], including in selected patients with grade 3/4 foci [52]. The aim of this attitude is to reduce the late adverse effects of oncological treatments (especially radiotherapy, see below).

2.3. Toward an Individual Onco-Functional Balance

Therefore, weighting the value of tumor cytoreduction versus neurological and neurocognitive worsening should be the main purpose when opting for a therapeutic option, not only with short term considerations, but also by anticipating long-term and cumulative adverse effects. The equilibrium between oncological benefits and neurocognitive risks defines the so-called “onco-functional balance” [53], which notably applies to intrasurgical decisions: the surgeon can voluntarily abandon, at that time, a tumor residual within cortical or white matter (WM) areas that subserve critical cognitive functioning to maintain QOL. However, this concept widely surpasses the intrasurgical decision making, since it may encourage sequential and delayed reoperation to optimize the extent of resection without inducing a cognitive deficit, given the fact that plasticity follows an evolving pattern [17]. It can also be applied to radiotherapy strategies, given the negative impact of WM irradiations on neurocognitive functioning [54], or even to chemotherapy, since some patients may not be eligible for sufficient surgical cytoreduction (typically when more than 10 ± 5 mL of tumor infiltrates functional WM tracts). In this setting, patients may benefit from a first line “neoadjuvant” chemotherapy before being reconsidered for a radical surgical (re)treatment [55]. These practical applications of the onco-functional balance urge neuro-oncologists to reconsider individual brain plasticity profiling as a cornerstone of oncological strategies, since brain compensation highly interferes with the benefits and risks of surgery and radiotherapy on neural structures.

In addition, individualized approaches should also integrate each patient’s wishes, professions, and cultural environment [56], which are the epicenters of modern, personalized “à la carte” oncological therapies. For instance, patients with specific professional activities at risk for legal or cultural reasons might benefit from different approaches (e.g., the case of an airplane pilot, free of any seizure, who could never fly again despite ensuring a complete resection after incidental discovery of a LGG was reported [57]). In the same vein, the whole onco-functional balance might be reconsidered in women followed for a LGG who project to have a baby, due to the major impact of pregnancy on tumor growth [58] and the critical effect of preventive total resections on overall survival in this subpopulation [59].

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