

1: IJMS | Special Issue : New Therapeutic Strategies for Gliomas: From the Bench to the Bedside

Low-grade glioma (LGG) (grade 2 or G2G) is a brain infiltrative neoplasia, often invading cortical and subcortical functional structures, while displaying as a rule a somewhat indolent course initially (no patent deficit).

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2: Low-Grade Gliomas in Adults

New Therapeutic Strategies in Gliomas Treatment A potential and futuristic therapeutic approach in gliomas treatment is represented by antisense therapy to block selectively glioma cells.

Advanced Search Abstract Diffuse low-grade glioma grows, migrates along white matter tracts, and progresses to high-grade glioma. Intraoperative mapping, with maximal resection according to functional boundaries, is associated with a longer overall survival OS while minimizing morbidity. However, most studies have investigated the role of only one specific treatment surgery, radiotherapy, chemotherapy without taking a global view of managing the cumulative time while preserving quality of life QoL versus time to anaplastic transformation. Our aim is to switch towards a more holistic concept based upon the anticipation of a personalized and long-term multistage therapeutic approach, with online adaptation of the strategy over the years using feedback from clinical, radiological, and histomolecular monitoring. This dynamic strategy challenges the traditional approach by proposing earlier therapy, by repeating treatments, and by reversing the classical order of therapies eg, neoadjuvant chemotherapy when maximal resection is impossible, no early radiotherapy to improve OS and QoL. New individualized management strategies should deal with the interactions between the course of this chronic disease, reaction brain remapping, and oncofunctional modulation elicited by serial treatments. This philosophy supports a personalized, functional, and preventive neuro-oncology. This controversy is due to several issues, namely i what is the actual natural history of DLGG; ii what is the real impact of treatments on this course; and iii what is the functional risk of therapies? For a long time, most authors have considered DLGG to be a stable and benign brain tumor. The traditional management has been performing only a biopsy to obtain samples for neuropathological examination and then choosing between a single follow-up or a radiotherapy according to the morphological criteria defined by the WHO classification astrocytoma vs oligodendroglioma vs mixed glioma; grade II vs III. The clinical results were usually evaluated using few parameters ie, progression free-survival [PFS], overall survival [OS], and eventually Karnofsky performance score [KPS]. Recent technical and conceptual advances in cognitive neurosciences, imaging, genetics, and treatments have revolutionized our knowledge of DLGG, leading to the seminal principle of personalized management. This aggressive lesion grows continuously, migrates along the white matter pathways, and inevitably progresses to a higher grade of malignancy and leads to neurological disability and ultimately to death. Such a strategy should be adapted to the complex biological course of DLGG at the individual level. Furthermore, when different therapies were nonetheless associated, a classical order of therapies surgery followed by irradiation in incomplete resection, followed by chemotherapy at recurrence was rigidly applied to the group of DLGGs as it was homogeneous, generally without an attempt to tailor the sequence of treatments to the specific patient. Here, our aim is to switch to a more holistic view based on the anticipation of a personalized, long-term multistage therapeutic approach, with online adaptation of the management over the years using feedback provided by clinical, radiological, and histomolecular monitoring at the individual level. This dynamic strategy challenges the traditional attitude with regard to different issues by proposing earlier therapy; repeating treatments, and reversing the classical order of therapies, with the ultimate goal of increasing OS and preserving or even improving QoL. Neuro-oncologists should tailor their management strategy during the follow-up on the basis of real-time oncological control and functional outcome. We propose a new personalized and multistage therapeutic management strategy dealing with the chronic interactions between the natural course of DLGG, the reaction brain remapping, and the oncofunctional modulation elicited by serial treatments. Tumor Progression and Neuroplasticity Pathology and Genetics: Second, some elements are too subjective with regard to grading, such as the notion of anaplasia or cell density. Third, the WHO classification does not distinguish tumoral cells from infiltrated residual brain parenchyma, and it considers the tumor as homogeneous. Nonetheless, heterogeneous foci are frequently found on a background of DLGG that corresponds to foci of increased cell density, possibly with pronounced cytonuclear atypia. Thus, the concept of PFS is meaningless in DLGG before treatment or after incomplete surgical resection because, in essence, all DLGGs are continuously growing, whereas this endpoint would be

unambiguous after a total resection. In this setting, PFS is unambiguous because relapse will be defined as a recurrence of signal abnormality. Indeed, the RANO criteria do not recommend performing objective 3D volumetric assessment of these tumors based upon segmentation on digital imaging and communications in medicine images, in spite of the fact that DLGGs are often irregular. As a consequence, calculation of growth rate is not reliable, which could be a major problem in DLGG with slow kinetics; one might believe that the tumor is stable when it is actually a slow-growing glioma, thus preventing adaptation for optimal management.

Migration These tumors migrate along the white matter tracts. Such a diffusion of glioma cells may induce neurocognitive disorders, probably due, at least partly, to a disconnection syndrome. A low cerebral blood volume correlates with longer OS, while the presence of lactates and lipids on MR spectroscopy is related to more aggressive behavior. Among molecular markers, 1pq codeletion and IDH1 mutation are the most important prognostic factors. After an asymptomatic period that lasts several years as demonstrated in incidental DLGG, seizures are the most common presentation. Many DLGG patients experience disorders of executive functions, attention, concentration, working memory, or emotion. Thus, a systematic assessment of higher functions and health-related QoL is now recommended before oncological treatment

- i to search subtle neuropsychological deficits;
- ii to tailor the therapeutic strategy eg, decision of neoadjuvant chemotherapy rather than surgery first in cases of very diffuse DLGG inducing cognitive disturbances ;
- iii to adapt the surgical methodology eg, to select the optimal tasks that should be administrated during awake surgery ;
- iii to have a pretherapeutic baseline allowing a comparison with the posttherapeutic evaluation;
- and iv to plan specific functional rehabilitation following surgery, which can induce a transient worsening.

Thus, neuro-oncologists should definitely switch from a traditional wait and watch policy to an early therapeutic strategy with the aim of delaying malignant transformation MT and increasing OS while preserving QoL. Due to the invasive feature of DLGG, the residual tumor was doubtlessly underestimated in numerous studies, resulting in erroneous conclusions about the benefit of surgery. When no signal abnormality was visible on control MRI complete resection, patients had a significantly longer OS compared with patients having any residual abnormality. This is due to the fact that surgery delayed histological upgrading because the volume of residual tumor serves as a predictor of AT. 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. To sum up, early and maximal surgical resection is the first therapeutic option to consider in DLGG, as recommended by the European guidelines. A recent series reported that a supratotal resection ie, resection extending beyond the MRI signal abnormalities performed in patients with a DLGG within noneloquent brain regions avoided AT mean follow-up of

The goal of neuropathological examination is to provide the actual grade of the glioma in addition to molecular data. However, there is a high risk of sampling error. Beyond patients who do not want or who are not able to undergo resection for medical reasons, biopsy can be mainly considered for diffuse lesions, such as gliomatosis, when a subtotal resection is not a priori possible.

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