Editorial

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New perspectives: glioma in adult patients

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Abstract

The purpose of this editorial is to consider some of the aspects of the diagnosis and treatment of adult gliomas. These are rare diseases with all their limitations. Innovations in diagnosis and therapy and their constraints are analyzed and compared with the current treatment reality. Aspects affecting these patients' quality of life are highlighted.

Keywords

Glioma, glioblastoma, radiotherapy, immunotherapy, quality of life

Primary neoplasms of the central nervous system are rare and represent a small part of oncology's much larger and more diverse landscape. The latest SEER report shows that the annual incidence of all central nervous system (CNS) tumors, malignant and nonmalignant, was 24.71 per 100,000 population in the US (malignant tumors 7.02 and nonmalignant 17.69).[1]

Although meningioma is the most common nervous system tumor, we focus on glial tumors when we consider brain and spinal tumors, especially in adults.

Glioblastoma is the most frequent glial tumor (14.2% of all glial tumors and 50.1% of all malignant glial tumors), with an annual incidence of 3.5 cases per 100,000 population, sharing with other rare neoplasms the uncertainties and difficulties in treatment planning. From an epidemiological point of view, we do not have any data that would reliably link these neoplasms to toxicity, exposure to radiation, infections, etc. Unlike other cancers, the prognosis has not changed significantly over the past decade, with a discouraging five-year survival rate of approximately 5% for glioblastoma.[1,2]

In recent decades, we have observed exciting advances in surgical approaches and radiological diagnostics. Integrated MRI enriched by advanced techniques such as perfusion and spectroscopy offers an exact understanding of the disease we are dealing with and is a valuable tool in the surgeon's approach. The systematic use of MRI in follow-up allows physicians to follow a patient's disease as it progresses, anticipating disease progression and distinguishing it from treatment side effects. Artificial intelligence promises to make immeasurable progress in the years to come. Applications include the qualitative interpretation of oncological imaging, including temporal volumetric delineation of tumors, extrapolation of tumor genotype, and biological progression from its radiographic phenotype, contributing to the prediction of clinical outcome and evaluation of treatment effects.[3,4] Surgeons using surgical navigation systems housing functional MRI or diffusion tensor imaging datasets, intraoperative MRI ultrasound, and fluorescence-based visualization of tumors have improved the extent of excisions and reduced the incidence of postsurgical sequelae. The use of neurophysiological techniques in awake patients to monitor and preserve language and cognition facilitates resections in eloquent areas.[5,6]

Until 2016, the diagnosis of these neoplasms was only histologically based. Starting with the WHO 2016 classification[7] and more extensively with the WHO 2021 classification, molecular biological data have been integrated with anatomopathological data to provide an integrated diagnosis. A curious novelty of the new classification is the abandonment of the numbering in Roman numerals in

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Table 1. World Health Organization Classification of tumors of the central nervous system, fifth edition: gliomas.

Adult-type diffuse gliomas	Astrocytoma, IDH-mutant
	Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
	Glioblastoma, IDH-wildtype
Pediatric-type diffuse low-grade gliomas	Diffuse astrocytoma, MYB o MYBl1-altered
	Angiocentric Glioma
	Polymorphous low-grade neuroepithelial tumor of the young
	Diffuse Low-grade glioma, MAPK pathway altered
Pediatric-type diffuse high-grade gliomas	Diffuse midline glioma, H3 K27-altered
	Diffuse midline glioma, H3 G34-mutant
	Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
	Infant-type hemispheric glioma
Circumscribed astrocytic gliomas	Pilocytic astrocytoma
	High-grade astrocytoma with piloid features
	Pleomorphic xanthoastrocytoma
	Subependymal giant cell astrocytoma
	Chordoid glioma
	Astroblastoma, *MN1*-altered

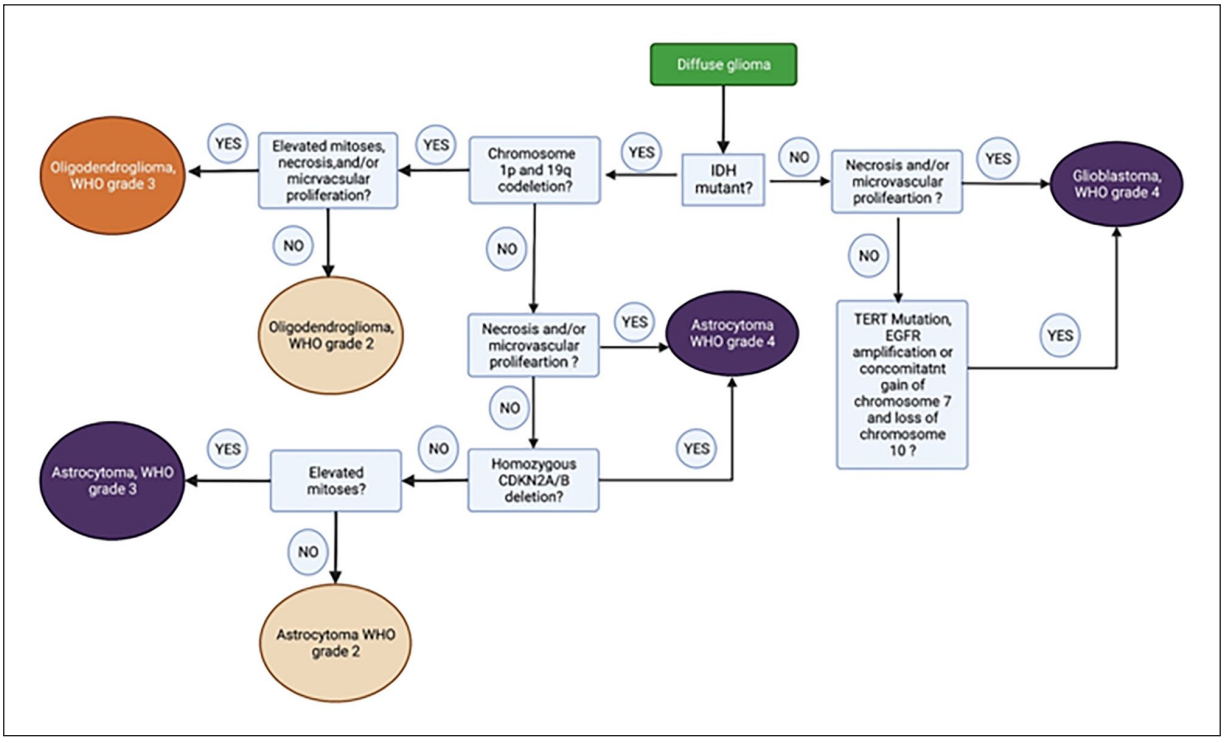

Figure 1. Algorithm for gliomas diagnosis.

favor of Arabic numerals, in line with other tumor classifications.[8]

With the WHO 2021 classification, some entities we previously worked with (e.g., gliomatosis) disappeared and new entities, often very rare, appeared (Table 1).[9]

The cornerstone of the new classification is isocitrate dehydrogenase (IDH) mutation. The identification of this mutation allows the subdivision of glial tumors into IDH mutant and wild-type neoplasms with very different biological and clinical characteristics. A more aggressive clinical course and a worse prognosis characterize wild-type IDH tumors. Glioblastomas were grade 4 IDH1/2 wild-type diffuse gliomas with microvascular proliferation and/or intertumoral necrosis. At the same time, a grade 2-3 IDH1/2-wildtype astrocytic glioma can be classified as glioblastoma if it has at least one of the following molecular features: telomerase reverse transcriptase (TERT) promoter mutation, epidermal growth factor receptor (EGFR) amplification, or concomitant gain of chromosome 7 and loss of chromosome 10 (Figure 1).[8]

The term IDH-mutant glioblastoma has been changed to WHO grade 4 astrocytoma, IDH-mutant in the 2016 WHO classification. Astrocytoma consisted only of IDH-mutant diffuse glioma and was subdivided into three grades (2-4) according to histological findings and CDKN2A/B homozygous deletion status. Following this classification, we understood how a histological grade 2 astrocytoma could have a prognosis similar to a glioblastoma if it had a deletion for the CDK2NA mutation or chromosome 10 deletion or 7 gain.[10]

In IDH-mutated neoplasms, co-deletions on chromosomes 1 and 19 allow oligodendroglial differentiation from astrocytic tumors. Within oligodendroglial tumors, grades 2-3 are maintained; WHO grade 3 (anaplastic) is assigned to an IDH-mutant, 1p/19q co-deleted oligodendroglioma with dense cellularity, microvascular proliferation, necrosis, and "significant" mitotic activity.

Postoperative treatment planning is crucial and should be shared with the various specialists involved in the treatment process on joint boards. Risk factors play a crucial role in treatment planning, particularly the patient's age, performance status, and methylation of the DNA-repair gene O6-methylguanine-DNA methyltransferase (MGMT) promoter activation status. These tumors are more frequent in elderly individuals, making treatment challenging given the frequent coexisting comorbidities.

The treatment of malignant gliomas is based on the widest possible resection, radiotherapy, and chemotherapy with concomitant temozolomide and adjuvant temozolomide for up to six cycles.[11] Supramaximal excision, proposed by some authors in the treatment of diffuse low-grade gliomas, would offer survival benefits, but its association with functional outcomes is still debated.[12] This approach could be theoretically justified from an oncological point of view in malignant gliomas. However, it is rarely possible due to the characteristics of the infiltration, and the possible multifocality observed even in the early stages of the disease. Historically, radiotherapy has been one of the main treatments for brain tumors, and many people with brain tumors will undergo radiotherapy. The timing, total dose, and schedule of radiotherapy are determined by the histology of the disease and integration with analysis of prognostic factors, including age, Karnofsky Performance Status KPS, and residual tumor volume. Radiotherapy should begin within 3-5 weeks of surgery and is commonly administered to glioblastoma patients at 50-60 Gy in daily fractions of 1.8-2 Gy.[13]

Hypofractionated radiotherapy with a single higher dose per fraction and a lower total dose is appropriate in older patients and those with poor prognoses.[14] Regarding newer proton-based techniques, the benefit of proton-based treatments for primary malignant gliomas remains to be seen. However, some authors suggest a lower risk of cognitive decline, which may have significance in the small percentage of long-term survivors. Starting with the Stupp et al. study published in NEJM in 2005,[15] which still sets the benchmark with a survival of approximately 15 months in glioblastoma patients treated with radiochemotherapy with temozolomide, we have not seen any significant improvements in the following years. What is noteworthy in this review is the result of the treatment of glioblastoma patients at first diagnosis with the Optune device's electrical fields, which can improve survival by several months. However, it should be emphasized that the technique still requires considerable patient compliance and is not easily accessible in most European countries due to high costs.[16]

The situation is different for grade 2-3 astrocytomas and oligodendrogliomas, where treatment with alkylating agents and radiotherapy can significantly prolong both period free survival (PFS) and overall survival (OS). Especially in 1p-19q co-deleted oligodendrogliomas, significant survival can be achieved even in tumors with anaplasia findings.[17] Available data suggest that responses may be more frequent and durable with PCV (procarbazine, CCNU, vincristine) combination, and survival may be longer compared to temozolomide mono chemotherapy. Although the results of the treatments should also be considered in light of the toxicities of the agents, temozolomide is better tolerated.[18]

IDH mutation, which is expressed diffusely in cancer cells and not in healthy brain tissue, represents an interesting target for the treatment of these tumors. Some preclinical studies have demonstrated the potential efficacy of IDH inhibitors in blocking the synthesis of D-2-hydroxyglutarate (D-2HG), the end product of IDH mutation, thereby inhibiting glioma cell growth. The question remains whether this effect can be maintained over time and what is the best time to start treatment. Vorasidenib is a first-in-class dual inhibitor of IDH1 and IDH2 mutations designed to enhance blood-brain barrier penetration and shown to be active in an orthotopic model of IDH1-mutant glioma. A recent phase I study reported good tolerability, 18% partial and minor responses and a PFS of 36 months in a cohort of relapsed non-enhancing gliomas. We are now awaiting the results of the phase III INDIGO trial (NCT04164901), which is evaluating vorasidenib in comparison to placebo in patients with non-enhancing grade 2 IDH1 mutant gliomas that have progressed within five years of initial surgery.[19]

Immunotherapy has successfully treated hematological malignancies and a subset of solid tumors. In recent years, immunotherapy has captured the attention of many researchers and the hopes of many patients. Unfortunately, none of the proposed treatments has been shown to be superior to standard treatment with radiotherapy and temozolomide. The recently published results of the CheckMate 548 study confirm these difficulties. A study of 716 patients with newly diagnosed glioblastoma with a methylated or indeterminate MGMT promoter showed that the combination of nivolumab, temozolomide, and radiotherapy (vs. temozolomide plus radiotherapy), although tolerated, did not improve OS.[20]

The possibility of using tumor-infiltrating cells (TILs) and chimeric antigen receptor (CAR) T cells has now become a focus of recent research.[21,22] Achieving efficient effector homing in the nervous system is one of the difficulties in immunotherapy. The fact that gliomas tend to be tumors that do not elicit a robust immune response (cold tumors) and are characterized by a highly immunosuppressive microenvironment also contributes to the poor results.[23,24] Another problem is the widespread use of steroids in these patients and the direct effects of corticosteroids on the activation of the immune system.[25]

An interesting note on vaccination approaches comes from NOA16 (Neurooncology Working Group of the German Cancer Society Study 16). Platten et al. reported the results of a multicenter phase I study in 33 patients with IDH1(R132H) grade 3 and 4 astrocytoma.[26] The patients were treated with a peptide vaccine specific for IDH1(R132H) (IDH1-vac). The study met its primary safety endpoint with vaccine-related adverse events limited to grade 1. Vaccine-induced immune responses were observed in 93.3% of patients. The three-year progression-free and death-free rates were 0.63 and 0.84, respectively. In patients with an immune response, the progression-free rate at two years was 0.82. Of particular interest is the finding of a high incidence of pseudoprogression. This indicates intratumoral inflammatory responses.

In the case of brain tumors, except for a few patients with circumscribed neoplasms (e.g., pilocytic astrocytoma, meningioma), we cannot speak of cured patients. These patients continue to be actively monitored throughout their lives.[27]

Gliomas and related treatments can cause cognitive deficits in approximately 40% of patients. Many glioma patients are aware of their cognitive difficulties. The worst perceived problems were related to neuropsychological deficits.[28] Brain tumors and their treatments therefore have a significant impact on the quality of life of patients. According to data published in 2015 by the Brain Tumor Charity (Losing myself: the reality of life with a brain tumor),[29] 28% of patients will experience personality disorders, and 60% will also experience prolonged fatigue. From a family and social point of view, more than 50% will experience a negative impact on their relationship with their partner, approximately 50% will experience financial problems, 30% will experience severe social isolation and up to 60% will experience a reduction in their social activity.

The survival rate of brain tumor patients is still modest compared to other types of cancer. This makes the fear of dying a key factor in understanding the reality of their lives. This fear often goes beyond the type of tumor, its grade, and the prognosis. The chronic nature of symptoms, which often change abruptly, contributes to a sense of losing control over one's condition and increases the patient's frailty.

The most effective posttreatment follow-up protocol (including duration, frequency, and type of examinations) for glioma patients is not well known.[30] Imaging schedules in glioma follow-up are pragmatic rather than evidence-based. In the guidelines of scientific societies, indications are given for follow-ups that are routinely designed according to tumor grading.[31,32] The prescriptive attitude of the clinician often determines the follow-up. There are no studies to show whether follow-up is necessary and whether this practice impacts the prognosis of patients.

Follow-up can be a time of great stress for the patient. Some patients are very attached to periodic check-ups that they continue to demand and expect throughout the duration of the disease. In contrast, for other patients, every follow-up appointment is destabilizing.

Work is one factor contributing to the health related quality of life (HRQoL) of cancer survivors. Return to work, understood as a return to normalcy, is an outcome parameter also sought in brain tumor patients.[33]

Unfortunately, in glioblastoma, the percentage of patients who can return to work after six months is very low. Patients with glioblastoma who can be considered long-term survivors at five years will continue to have significant symptoms and need to be cared for. In contrast, the situation is better for patients with grade 2 glioma, where approximately 50% of patients return to work. However, the treatment burden has been shown to affect work capacity in the first two years after diagnosis.[34,35,36]

Brain tumors are rare. Therapeutic challenges are related to the limited availability of therapeutic approaches and the peculiarities of the CNS. The nervous system is difficult to target and particularly prone to toxicity.

Another important aspect is that there is a low number of glioma patients enrolled in clinical trials, with enrollment estimates ranging from 8% to 21%. This low enrollment rate is even more pronounced than in other cancer types, where enrollment rates can be as high as 50%.[37]

Given the small number of patients and the complexity of the disease, companies are not very interested in participating in clinical trials and testing new drugs.

How might this daunting therapeutic, diagnostic landscape change in the future?

Next-generation sequencing (NGS) is a technique that can reveal the mutation status of hundreds of genes in a single test. As a result, it is a particularly effective technique for identifying different genomic alterations in gliomas that share the same histological diagnosis.[38] There is growing recognition of the role of both NGS and methylomics in the diagnosis of glioma. To homogenize testing and rationalize resources, it will be necessary to concentrate diagnosis in a few centers in the future. We hope that the availability of more biomolecular information will lead to the identification of disease targets useful for treatment.

At present, however, we must not forget that most brain tumors are not curable, so it is necessary to work on those

aspects that allow patients to enjoy a good quality of life throughout their illness.

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