Significant progress has been made in defining molecular signatures in diffuse gliomas. The clinically significant genetic alterations identified to date probably represent the tip of the iceberg, since new, potentially significant biomarkers are continuously described.

Diffuse gliomas are the most common primary brain tumors. The current World Health Organization (WHO) brain tumor classification (2007) uses exclusively morphological criteria to separate diffuse gliomas into three main subtypes: astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. The WHO defines mixed oligoastrocytomas as tumors with dual glial cellular components (astrocytic and oligodendrogial); however, specific criteria to diagnose these entities are lacking, and the interpretation of tissue specimens is subjective and variable among pathologists.

Grading criteria for diffuse gliomas include the presence of “brisk” mitotic activity, microvascular proliferation, and/or tumor necrosis. Based on these histologic criteria, two WHO grades are described for oligodendroglioma (II, III) and three grades for astrocytoma (II, III, and IV). The morphological features and the WHO grade correlate with survival.[1] The WHO grade is currently the most important classifier for therapeutic decision-making in diffuse gliomas.[2,3] As stated by the authors of the current review, a small amount of tissue is sufficient to establish a diagnosis of glioma. However, grade assignment on the basis of small biopsy samples should be made with caution. A large, nonenhancing, diffusely infiltrating glioma cannot be graded with confidence on the basis of biopsy tissue, since it is possible that higher-grade, mitotically active areas might have been missed during sampling. Communication between surgeon and pathologist, as well as diagnostic expertise on the part of the pathologist, is critical in collecting representative and sufficient tissue for further testing (immunohistochemistry, molecular testing). The clinical, radiological, and pathological characteristics of the tumor will ultimately guide therapeutic decisions.[3]

Recently, extensive progress has been made in our understanding of the molecular alterations and the biology of diffuse gliomas. At the forefront of these advances stand our knowledge of 1p/19q codeletion and of mutations involving the isocitrate dehydrogenase genes (IDH1 and/or IDH2). IDH1/2 mutations are common in young adults with supratentorial diffuse gliomas or secondary glioblastoma. IDH1/2 mutations are acquired early in gliomagenesis, and are followed by acquisition of TP53 mutations or 1p/19q loss—molecular alterations that confer either an astrocytic or an oligodendroglial phenotype, respectively. Recently, Jiao et al showed that ATRX mutations are common and cluster with TP53 mutations in astrocytomas, and that 1p/19q loss clusters with mutations involving CIC in oligodendroglioma. Interestingly, in their series, the majority of mixed astrocytomas had an astrocytic genetic signature (ATRX/TP53 mutations without 1p/19q loss or CIC mutations), evidence against a true “mixed” tumor phenotype.[4] The presence of IDH1/2 mutations confers a significant favorable prognosis in high-grade gliomas (WHO III and IV), and predicts longer progression-free survival irrespective of histology, treatment, and 1p/19q status.[5] The prognostic value of IDH1/2 mutations in low-grade gliomas remains to be defined.[6, 7] Importantly, it has been shown that the IDH mutation status of a tumor is a stronger prognostic value than the WHO grade.[8, 9] There is no compelling evidence to support a predictive role for IDH mutations in diffuse gliomas. Moreover, a subgroup of IDH1-mutated diffuse gliomas (across all WHO grades) have a dismal prognosis. This tumor subcategory lacks ATRX mutations and/or 1p/19q loss.[4] The underlying explanation for the decreased survival in this IDH-mutant subgroup is unknown and remains to be determined. This information has important implications for patient counseling and clinical management. Pertinent questions are: how can we predict which IDH-mutated tumor will behave better and which will not, and how might this information be incorporated into a molecular therapeutic decision–making scheme? The IDH1/2 mutation frequency in diffuse gliomas in nonsupratentorial locations (cerebellum, brainstem, spinal cord) and the prognostic features of these tumors remain to be defined.[10] Combined loss of heterozygosity on 1p and 19q is considered the molecular signature of
oligodendroglioma, and is associated with classic tumor morphology and mutations involving CIC.\[4,11\] Combined 1p/19q loss is a strong prognostic and predictive marker.\[12-14\] An antibody directed against the mutant IDH1-R132H protein is commercially available for formalin-fixed paraffin embedded tissue and accurately detects the presence of the most common IDH1 mutation: R132H.\[15\] It is important to remember that a small proportion of gliomas lacking the IDH1-R132H mutation have noncanonical IDH1 mutations or IDH2 mutations. In such situations, and for accurate molecular classification, DNA sequencing is the best next step. At our institution, we interrogate for noncanonical IDH1 and IDH2 mutations in selected IDH1-R132H-immunonegative/equivocal diffuse gliomas (WHO II and III, and glioblastoma in young adults).

The authors of the current review summarize nicely the most recent advances in the molecular biology of diffuse gliomas, illustrate the clinical application of these advances through clinical case scenarios, and propose a therapeutic decision-making scheme stratified by a combined clinical-radiological, morphological, and molecular approach. The integration of molecular classifiers makes possible a more accurate prediction of response to therapy and of survival compared with tumor morphology alone. This type of personalized approach indeed has the potential to reduce unnecessary therapy-related morbidity and to maximize survival. The integration of molecular biomarkers might also improve the pathological classification of diffuse gliomas by offering more objective and reproducible diagnostic and grading criteria (possibly solving the controversy over mixed oligoastrocytomas briefly outlined above, and better defining criteria for anaplastic gliomas).\[16\]

In light of the current National Comprehensive Cancer Network guidelines, some observations are pertinent for the arm in the authors’ proposed algorithm that concerns the management of IDH1/2-mutant tumors. Could observation with imaging follow-up still be a viable option for completely resected, asymptomatic, IDH1/2-mutant, 1p/19q-intact, low-grade diffuse glioma in younger adults? Should radiation and/or chemotherapy be introduced only in cases of tumor recurrence? These questions become even more challenging in light of the evidence that a subgroup of IDH-mutated diffuse gliomas show dismal prognosis. It is not yet clear how to identify these “atypical” IDH-mutated gliomas, or how molecular information about these tumors should be incorporated into future therapeutic decision-making schemes. Significant progress has been made in defining molecular signatures in diffuse gliomas. The clinically significant genetic alterations identified to date probably represent the tip of the iceberg, since new, potentially significant biomarkers are continuously described. The therapeutic progress in diffuse gliomas is slow, but as these molecular classifiers are integrated into clinical trials and as their role in the clinical management of diffuse gliomas becomes better defined, there is cause for optimism nonetheless.

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