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Current Clinical State of Advanced Magnetic Resonance Imaging for Brain Tumor Diagnosis and Follow Up

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Introduction

Imaging in neuro-oncology has changed substantially in the past decades. The ongoing development of advanced and sophisticated imaging techniques has allowed for evaluation of both the anatomy and physiology of tumors. In addition to structural and phenotypic assessment of a tumor, the use of diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI), perfusion-weighted imaging, magnetic resonance spectroscopy (MRS), and functional magnetic resonance imaging (fMRI) allows for assessment of the cellular, hemodynamic, metabolic, and functional status of the tumor. Such detailed information offers radiologists and clinicians improved avenues for diagnosis, grading of tumors, patient prognostication, and assessment of treatment efficacy. This is especially important as we increasingly learn the effect of biology and genotype on tumor behavior, natural history, and response to therapies. In fact, we now know that a tumor's genetic and molecular profile outweighs its histopathologic phenotypic classification, as reflected in the recently updated 2016 World Health Organization (WHO) classification of central nervous system (CNS) tumors.

This article provides an overview of advanced imaging techniques used in clinical brain tumor imaging today. First, we briefly highlight the important updates and changes in the 2016 WHO classification of brain tumors. Then, we review the clinical applications of advanced imaging techniques for the diagnosis of brain tumors, underscoring the relevance of imaging features to the WHO classification, and for the follow-up of treated tumors while reviewing the current challenges in differentiating treatment effects from active tumor. We also briefly discuss ongoing research efforts to improve our ability to image brain tumors and to extract valuable information about their biology and behavior in both the treatment-naïve and posttreatment settings.

Updates on the WHO Classification of Brain Tumors

Historical classification of brain tumors has largely been based on histopathology, incorporating phenotypic features determined by light microscopy, immunohistochemistry, and ultrastructural characterization. This has been performed chiefly in an effort to define the putative cells of origin or lineage of tumor tissue and their degree of differentiation.[1] For example, in the 2007 WHO classification, all astrocytic tumors were grouped separately from oligodendroglial tumors, independent of the clinical features of the tumor.[2] Recent studies, however, have shown that even tumors with similar microscopic and histologic features that might both be classified as astrocytic tumors, for example, can behave differently depending on their individual genetic and molecular make-up.[3] The importance of the latter in tumorigenesis has paved way for a major revision of the WHO classification (the current 2016 CNS WHO), which now incorporates molecular parameters into its classification scheme. The combination of tumor phenotype and genotype is anticipated to improve accuracy of brain tumor diagnosis and potentially lead to improved patient management and more accurate determinations of prognosis and therapeutic response.[1]

The 2016 CNS WHO provided a major restructuring of diffuse gliomas, incorporating distinct entities defined by genetics. The family of diffuse gliomas now includes all astrocytic (including glioblastoma) and oligodendroglial tumors, which are grouped together and further defined based on their histologic growth pattern, behavior, and shared driver mutations in the isocitrate dehydrogenase genes, *IDH1* and *IDH2*.[1] *IDH1* and *IDH2* mutations are seen in many diffusely

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infiltrating gliomas, particularly low-grade gliomas and secondary high-grade gliomas, and occur early in tumorigenesis.[4] The presence of *IDH1* and *IDH2* mutations, which can be determined with immunohistochemistry or DNA sequencing,[5] predicts better prognosis and a higher rate of tumor response to chemoradiation, in contrast to tumors without the mutations (termed "wildtype").[6] The dual presence of IDH mutation and loss of chromosome arms 1p and 19q (1p/19q codeletion) defines the oligodendroglioma; these genetic alterations correlate with improved tumor response to treatment and longer patient survival.[3,7] Although not required for diagnosis in WHO, *TP53*, and *ATRX* mutations are characteristic of astrocytomas and are additional impactful markers of clinical behavior.[8] Several other genes including *EGFR*, *PTEN*, and *TERT* are altered in gliomas, and while their alterations can also help to elucidate the biology and behavior of a specific tumor (eg, *PTEN* mutation and *EGFR* amplification are characteristic of high-grade tumors such as IDH-wildtype glioblastomas), they are not included in the current WHO.[1] It is worthwhile to note that of the astrocytomas, those that are more circumscribed (pilocytic astrocytoma, pleomorphic xanthoastrocytoma) lack IDH mutations and frequently have *BRAF* alterations, indicating that these tumors behave differently from diffuse astrocytomas.[1,3] In addition, a newly defined WHO entity, the diffuse midline glioma, H3 K27M-mutant, replaces the previous terminology of diffuse intrinsic pontine glioma and indicates a tumor subtype that is predominantly found in the pediatric population; these tumors are further characterized by a midline location (brainstem or thalamus), diffuse growth pattern, and K27M mutations in the histone H3 gene *H3F3A*.[1] In the absence of molecular information (eg, lack of access to molecular diagnostic testing), a designation of NOS (not otherwise specified) is used for certain tumor types; NOS indicates that a lesion cannot be classified any further because of insufficient available information. Other notable changes in the 2016 CNS WHO include the deletion of the term "gliomatosis cerebri" as a distinct entity as it now reflects a growth pattern found frequently in higher-grade gliomas, and the addition of epithelioid glioblastoma as a variant of glioblastoma (in addition to the previously defined variants of giant cell glioblastoma and gliosarcoma).[1] The following summarizes the key points regarding diffuse gliomas presented in this paragraph: WHO grade II diffuse astrocytomas, WHO grade III anaplastic astrocytomas, and WHO grade IV glioblastomas are each further divided into IDH-mutant, IDH-wildtype, and NOS categories, and WHO grade II oligodendrogliomas and WHO grade III anaplastic oligodendrogliomas are divided into IDH-mutant and 1p/19q-codeleted and NOS categories (Table).

The 2016 CNS WHO also restructured the classification scheme of medulloblastomas, other embryonal tumors, and ependymomas, incorporating genetically defined entities. Although there remain histologically defined variants of medulloblastoma (classic, desmoplastic or nodular, extensive nodularity, and large cell or anaplastic), genetic or molecular studies have identified 4 distinct subtypes of medulloblastoma: Wnt-activated, Shh(sonic hedgehog)-activated, group 3, and group 4.[1,9,10] The varying histologic and genetic or molecular subtypes confer different prognoses and are associated with different treatment responses. Incorporation of additional markers such as the presence of *MYC* and *MYCN* amplification and *TP53* mutations can aid in further risk stratification.[10] Embryonal tumors other than medulloblastomas are no longer known as primitive neuroectodermal tumors, but their diagnosis now depends on the presence of C19MC amplification. C19MC-amplified tumors are now named embryonal tumor with multilayered rosettes (ETMR), C19MC-altered. C19MC-nonamplified tumors with histologic features conforming to ETMR are named ETMR, NOS. C19MC-nonamplified tumors with histologic features of medulloepithelioma are named medulloepithelioma.[1] In contrast, there is no available prognostic classification for ependymomas, although 1 genetically defined subtype, which comprises most of the supratentorial tumors in children, has been accepted: ependymoma, *RELA* fusion-positive.[1,11] This entity was included because of the availability of the surrogate antibody L1CAM, which shows an affinity for this particular subtype of ependymoma, for diagnosis.[12]

Major changes to the family of neuronal and mixed neuronal-glial tumors (whose members include ganglioglioma and dysembryoplastic neuroepithelial tumor) are the introduction of diffuse leptomeningeal glioneuronal tumor (characterized by a leptomeningeal tumor that histologically resembles an oligodendroglioma, that may or may not have a parenchymal component, and that has *BRAF* fusion but lacks IDH mutation) as a new entity and multinodular and vacuolated pattern of ganglion cell tumor, which is considered a low-grade or malformative lesion, as a newly recognized pattern.[1] The categories of nerve sheath tumor, meningioma, and mesenchymal, nonmeningoepithelial tumors did not undergo significant revisions in the updated WHO aside from the introduction of brain invasion as a criterion for the diagnosis of atypical meningioma and amalgamation of solitary fibrous tumor and hemangiopericytoma as a single entity.[1]

Diffusion-Weighted Imaging

In brain tumors, DWI has been used to assess tissue cellularity and tumor grade, to differentiate peritumoral edema from nonenhancing, infiltrative tumor, and to differentiate treatment effects from residual or recurrent tumor following surgical resection, chemoradiation, antiangiogenic therapy or any of these. Furthermore, DTI aids in the assessment of white matter tract integrity and is primarily used clinically for presurgical planning and intraoperative guidance.

Glioma studies in the literature using DWI as a metric for tumor grading have primarily focused on its ability to quantify tissue cellularity, which is based on the concept that lower apparent diffusion coefficient (ADC) values correlate with decreased water diffusivity owing to areas of increased cell density.[13-15] Results from the use of DWI/ADC in differentiating low-grade from high-grade gliomas have been mixed.[15-21] The use of mean, minimum, and histogram