UPDATE ON WHO CLASSIFICATION AND TREATMENT OF GLIOMAS

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2016 WHO Classification of Tumors of the Central Nervous System (CNS)

To ensure uniform histopathological diagnostic criteria worldwide, the classification and grading of tumors of the CNS has been based on the consensus of an international working group and published by the World Health Organization (WHO). In 2016, the WHO published an update of the classification of CNS tumors.[1,2] This classification for the first time used molecular parameters in addition to traditional histology to diagnose many CNS tumors, resulting in major restructuring of the classification of many tumors especially gliomas, ependymomas and medulloblastomas.

The current integrated nomenclature is a histopathological diagnosis followed by the genetic features, e.g. *oligodendrogliomas, IDH-mutant and 1p/19q-codeleted*. If molecular testing is not available or the testing is incomplete the diagnostic designation of "not otherwise specified" (NOS) is used. This category also contains the rare tumors for which molecular testing was performed but the tumor does not show diagnostic alterations.[1]

The use of integrated phenotypic and genotypic parameters for the classification of CNS tumors introduces greater objectivity to the diagnosis.[1] In cases where discrepancies arise the genotype trumps the histology. For example, for a tumor that resembles an oligodendrogliomas histologically but has the genotype of an astrocytoma (IDH mutant, 1p/19q intact, *ATRX* and TP53 mutated), the tumor should be diagnosed as an astrocytoma.

Diffuse Gliomas

Diffuse gliomas can be divided into subgroups based on the presence of *IDH* mutations and co-deletion of 1p/19q. For *IDH* testing if immunochemistry for *IDH* R132H is negative, sequencing for *IDH1* codon 132 and *IDH2* codon 172 should be performed. If these are negative, then the tumor is designated IDH-wildtype.

Diffuse astrocytomas (WHO grade II) and anaplastic astrocytoma (WHO grade III)

WHO grade II and III astrocytomas are divided into 3 categories: IDH-mutant, IDH-wildtype and NOS.[1] Most of these tumors are IDH-mutant tumors and have intact 1p/19q. IDH-wildtype astrocytomas are less common and often have the genetic alterations of glioblastoma and a much worse prognosis. If molecular testing is not available or cannot be fully performed the diagnosis will be astrocytoma NOS or anaplastic astrocytoma NOS.

Oligodendrogliomas (WHO grade II) and anaplastic oligodendrogliomas (WHO grade III)

The diagnosis of oligodendrogliomas and anaplastic oligodendrogliomas requires the presence of IDH mutations and combined whole-arm loss of 1p and 19q (1p/19q codeletion). As with astrocytomas, if molecular testing is not possible or is incomplete, the NOS designation is used.

Oligoastrocytomas

The 2016 WHO CNS classification strongly discourages the use of the diagnosis of ***oligoastrocytoma***. Molecular studies suggest that tumors with histologic components of oligodendrogliomas and astrocytoma can almost always be classified as oligodendrogliomas or astrocytoma with molecular testing.[3,4] Oligoastrocytomas and anaplastic oligoastrocytomas are both assigned NOS designations. This indicates that they can only be diagnosed if no molecular testing is available.

Glioblastomas

Glioblastomas are now divided into 1) ***glioblastoma, IDH-wildtype***; ***glioblastoma, IDH-mutated and glioblastoma, NOS***. Glioblastoma, IDH-wildtype account approximately 90% of glioblastomas and correspond to primary glioblastomas the typically present over the age of 55 years of age.[5] Glioblastoma-IDH mutant account for approximately 10% of cases and typically occur in younger patients. They usually correspond to secondary glioblastomas which arise from preexisting lower grade gliomas. The diagnosis for glioblastoma-NOS is reserved for those tumors for which IDH evaluation was not possible.

Variants of IDH-wildtype glioblastoma include giant cell glioblastoma and gliosarcoma. In the 2016 WHO classification a new variant was added: ***epithelioid glioblastoma***. These tumors typically occur in children and young adults and are located in the cerebrum or diencephalon. Histologically they have large epitheliod cells with abundant eosinophilic cytoplasm and frequently have *BRAF*V600E mutations[6,7].

Pediatric diffuse gliomas

Diffuse pediatric gliomas have previously been grouped with their adult counterparts although there is increasing evidence that they have distinct underlying genetic alterations.[8] The 2016 WHO classification introduced a new entity termed ***diffuse midline glioma, H3 K27M-mutant***. This tumor occurs in children and young adults and is characterized by midline location (thalamus, brain stem or spinal cord), and the presence of K27M mutations in the histone *H3F34A* gene.[9,10]

Gliomatosis Cerebri

This entity has been deleted from the 2016 WHO CNS Classification. Previously it was considered a distinct form of glioma characterized by invasive tumor growth involving 3 or more cerebral lobes and often extending to both hemispheres and infratentorial structures and associated with a poor prognosis. However histologically and genetically it does not appear to be a distinct entity and consists of a variety of entities including IDH-wildtype glioblastoma or IDH-mutant astrocytomas or oligodendrogliomas with invasive growth. [11,12]

Medulloblastomas

Medulloblastoma are the most common embryonal tumor of childhood. There has been significant progress in understanding the molecular characteristics of these tumors in recent years.[13,14] By consensus medulloblastomas have been distilled in to 4 main groups: WNT-activated medulloblastomas which have the best prognosis, SHH-activated medulloblastomas, group 3 medulloblastomas which are associated with the worse outcome, and group 4 medulloblastomas.[13,14] The 2016 WHO classification has included major restructuring of the classification of medulloblastoma incorporating a modular and integrated approach to diagnosis that combines histologic and molecular features.

Meningiomas

Meningiomas, the most common primary brain tumor remains divided into 3 histologic grades (WHO grade I, grade II (atypical) and grade III (malignant) which correlate with prognosis. However, the diagnosis of WHO grade II (atypical) meningiomas can now be made by the presence of brain invasion given its association with a worse outcome, in addition to the previous criteria of mitotic counts of 4 or more per 10 high power field, or the presence of 3 out of 5 histologic features (prominent nucleoli, spontaneous necrosis, sheeting (Loss of whirling or fascicular architecture), small cells and high cellularity. The inclusion of brain invasion in the diagnosis of WHO grade II (atypical) meningiomas may require neurosurgeons to collect adjacent normal tissue during the course of surgery, a change from current clinical practice.

Solitary Fibrous Tumor/Hemangiopericytoma

Hemangiopericytomas are rare tumors resembling meningiomas in radiographic appearance that tend to have a high recurrence rates and risk for systemic metastases. For tumors outside the brain, the term hemangiopericytomas has largely been replaced by its incorporation into the family of solitary fibrous tumors as

they are overlapping, if not identical entities. Both solitary fibrous tumors and hemangiopericytomas share inversions at 12q13, fusing the *STAT*6 with the *NAB2* genes.[15] In the 2016 WHO classification the combined term ***solitary fibrous tumor/hemangiopericytomas*** has been introduced for this entity with 3 possible grades.

Clinical implications of the 2016 CNS WHO classification

The 2016 update integrating molecular diagnosis with histologic diagnosis represents important progress and will help improve the diagnosis and classification of brain tumors but has a number of implications impacting clinical practice. Given the importance of IDH mutational status in the diagnosis of gliomas, at a minimum it will be important that most institutions have the capacity stain tumor specimens for *IDH*R132H by immunohistochemistry, and ideally they should have the capacity to sequence those tumors that are negative. A growing number of center are acquiring this capacity but much more work will be necessary to ensure that these tests become widely available in a timely manner. Similarly, the ability to routinely determine 1p/19q codeletion or the presence of ATRX mutations will be important.

Treatment of Gliomas

Newly-diagnosed glioblastoma

Standards therapy for glioblastomas remains maximal safe surgical resection,[16,17] followed by radiation therapy (60Gy over 6 weeks) with concomitant and adjuvant temozolomide.[18,19] Most of the benefit with temozolomide occurs in the 35-40% of patients whose tumors have methylation of the promoter of the O^6-methylguanine DNA methyltransferase (MGMT) gene.[20] A phase III trial of tumor treating fields suggest that that addition of this device to adjuvant temozolomide may prolong progression-free and overall survival by approximately 3 months.[21]

Elderly patients with glioblastoma

Given the median age of glioblastoma of 64 years there are an increasing number of “elderly” patients with glioblastoma who tend to have a worse prognosis and tolerate therapy poorly. Previous studies suggested that a hypofractionated radiation therapy regimen of 40Gy over 3 weeks produced equivalent outcome to 60Gy over 6 weeks.[22] More recent randomized studies suggested that temozolomide was equivalent to 60Gy of radiotherapy (NOA-8 trial) ,[23] and that a hypofractionated radiotherapy regimen was equivalent to temozolomide and superior to 60 Gy of radiotherapy (Nordic trial).[24] In both these studies elderly patients with unmethylated MGMT promoter methylation status appeared not to benefit from temozolomide, leading the European Association of Neuro-Oncology (EANO) to publish guidelines suggested that elderly glioblastoma patients with unmethylated MGMT promoter methylation may be treated with radiotherapy alone.[25] Recently, a phase III trial showed that 40Gy of hypofractionated radiotherapy with temozolomide significantly improved survival compared to hypofractionated radiotherapy alone for patients with both methylated and unmethylated MGMT promoter. As a result, combined radiochemotherapy is suggested for all elderly patients.[26]

Recurrent Glioblastomas

Treatment for recurrent glioblastomas may involve surgery, chemotherapy with lomustine or temozolomide, bevacizumab or tumor treating fields.[25,27-29] Much debate has centered on the value of bevacizumab and whether it prolongs survival. The BELOB study suggested that the combination of bevacizumab with lomustine was superior to either agent alone.[30] Recently, the European Organization For Research and Treatment of Cancer (EORTC) completed a phase III trial comparing bevacizumab and lomustine with lomustine alone. The combination improved progression-free survival and response but unfortunately did not improve overall survival, possibly because a high percentage of patients in the control arm received bevacizumab at progression.[31]

Anaplastic Oligodendroglioma

Two phase III trials show that the addition of PCV chemotherapy (procarbazine, CCNU [lomustine] and vincristine) to radiotherapy for newly diagnosed anaplastic oligodendrogliomas significantly improves survival.[32,33] This is now the standard of care for these tumors, although there is debate regarding whether temozolomide can replace the more toxic PCV regimen.

Anaplastic Astrocytoma

Until recently the value of chemotherapy for these tumors was unclear. Recently, the CATNON trial showed conclusively that the addition of adjuvant temozolomide to radiotherapy significantly improved survival compared to radiotherapy alone.[34] As a result, the current standard of care for these patients is radiotherapy and temozolomide.

Low-Grade Gliomas

For patients with high risk low-grade gliomas ($\geq$ 40 years of age or subtotal resection) the addition of adjuvant PCV chemotherapy to radiotherapy significantly improves survival compared to radiotherapy alone and is the standard of care.[35]

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