Brain Tumor Pathol (2017) 34:139–140
DOI 10.1007/s10014-017-0299-3

EDITORIAL

Updated 2016 WHO classification of tumors of the CNS: turning the corner where molecule meets pathology

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Published online: 24 August 2017

A year has passed since the publication of the updated 2016 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) (2016 WHO) [1]. In Tokyo, the first set of 100 copies, which was released coincidentally on the first day of the 34th Annual Meeting of the Japanese Society of Brain Tumor Pathology, was sold out in 2 h. The positive reception of the work was overwhelming.

This update of the 2016 WHO breaks with the century-old principle of diagnosis based entirely on microscopy by incorporating molecular parameters into the classification of CNS tumor entities for the first time [2]. The aim was to create more homogeneous tumor categories with greater prognostic value [3]. This undoubtedly constitutes a paradigm shift and represents a clear advance in tumor classification. The most emblematic aspect of this paradigm shift was the elimination of the oligoastrocytoma and primitive neuroectodermal tumor (PNET) [4], both of which have caused serious confusion in clinical practice for many years, from the classification. The 2016 WHO requires the evaluation of canonical genetic alterations [5]; hence inconsistent molecular test results have created new diagnostic challenges requiring a more cautious application of molecular testing along with careful weighing of clinical, radiological, and histological data. This editorial is meant briefly to touch upon some important points that have emerged since the publication of the revised WHO classification vis-à-vis these issues. The perspectives I offer below are solely personal and based on my own experience.

The first point I would like to address is the lack of, or restricted access to, genetic technology owing to technological as well as economical barriers, which obtained not only in developing nations but also in advanced nations like Japan in the years preceding the publication of the revised classification. For instance, while IDH (isocitrate dehydrogenase) R132H immunohistochemistry (IHC) is available at many institutions, access to Sanger sequencing for other IDH loci and genetic testing including fluorescence in situ hybridization (FISH) for 1p/19q co-deletion are extremely hard to come by in Asia. In Japan, the cost of genetic testing, including IHC, is not covered by the national health care program due to budgetary constraints. The law also prohibits charging such costs to the patients, with the result that these tests are generally unavailable in daily practice except at research facilities where grant money may be used to cover the costs under the rubric of clinical research. Although the technological barriers may eventually be resolved in the near future, the economic barriers may not. Nonetheless, even in a resource-limited setting, an IHC-based surrogate approach combined with clinical and histological information may provide sufficient information upon which to base clinical decisions.

The second point is the emergence of rare tumors that are not listed in the 2016 WHO classification [6]. Infiltrating gliomas with IDH wildtype but 1p/19q co-deletion are an example of such medical rarities. Some of these may be caused by false positive results of FISH testing, which was designed to detect not only a whole-arm loss of chromosomes but also partial losses often seen in malignant astrocytomas. As well, some of these infiltrating gliomas might be rare examples harboring a true co-deletion but no IDH mutation. Another example is the

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histologically classic oligodendroglioma lacking either the IDH mutation or 1p/19q co-deletion. Possible designations for these tumors include diffuse astrocytoma, IDH-wild-type, diffuse astrocytoma, NOS, or oligodendroglioma, NOS. The 2016 WHO classification provides no clear instructions as to how to deal with such examples. After all, a classification per se is not necessarily meant to cover all exceptions; it is not a diagnostic manual but rather more like a 'concept book.'

The third point touches on the time-lag between the rapid progress of neurology and neuro-oncology and the rather slower pace at which classifications are updated. For example, ATRX-IHC has become a standard stratification factor for the molecular diagnosis of diffuse gliomas in daily neuropathological practice. The European Association for Neuro-Oncology (EANO) guidelines have in fact adopted the combination of IDH1R132H and ATRX-IHC as the first stratification factor for their diagnostic algorithm for diffuse astrocytic and oligodendroglial gliomas. Such an approach was not officially accepted in the 2016 WHO. Rapid progress or changes in the field of brain tumor research and clinical applications have necessitated updating of the classification at shorter intervals, a goal that cannot be achieved within the current WHO framework. To solve this problem, some kind of international effort to achieve real-time consensus regarding the classification and diagnostic processes is required [7].

Last but not least is that the concept and very authenticity of the WHO classification are being challenged due to perceptions of its lack of immediate clinical utility. The WHO classification has long been the accepted international standard by which brain tumors are diagnosed, treated, and investigated. It has been responsive to the needs of a variety of communities or end-users in both developing and developed countries who required a formal classification for their work. However, the users and their needs have diversified, and it has become increasingly difficult to respond adequately to all of their demands with a single classification scheme. Clinicians use classifications to segregate tumors into biologically meaningful categories that represent discrete prognoses [8]. However, genetic data such as the detection of the IDH mutation or 1p/19q status are apparently now thought to correlate better with prognosis than the WHO grading. Molecular assessment allows potential subgrouping of IDH-wildtype glioblastomas, which cannot be done histologically. Researchers who are mainly interested in the results of current genetic science may prefer a purely genetic classification to the WHO scheme. If the next revision of the WHO classification fails to keep pace with the diverse, multidisciplinary input from molecular biologists, neuro-oncologists, radiologists, and other specialists, we may very well see an exodus of users as they abandon the WHO scheme to adopt another classification system [9]. More than 150 entities and tumor variants are listed in the 2016 WHO; however, the extreme limitation of diagnostically relevant genetic signatures means that they are used only for a small number of entities including the adult diffuse glioma and medulloblastoma. For most of the other tumors such as meningiomas, genetic information presently offers little or no advantage either for diagnosis or for the assessment of prognosis. Microscopy still plays a central role in those areas.

A distinctly genetic-first idea could, if allowed to predominate and become fixed, circumvent much of what microscopy can still achieve. Research progresses rapidly but is also often easily overturned. Knowledge, experience, and insight accumulated over nearly a century through microscopy should not be cast aside so carelessly. The core criteria for the diagnosis of brain tumors must rest on a solid, time-tested foundation, at least until the newer methods have achieved a level of reliability comparable to those which have withstood the test of time.

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