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cIMPACT-NOW Update 7: advancing the molecular classification of ependymal tumors

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Running Head: cIMPACT-7 ependymal tumors

Ependymal tumors make up a heterogeneous category of central nervous system (CNS) gliomas with variably expressed morphologic, immunophenotypic, and ultrastructural ependymal features (9). The current WHO classification (2016) lists: subependymoma (WHO grade 1), myxopapillary ependymoma (WHO grade 1), the classic ependymoma with its three histological subtypes – papillary, clear cell, and tanycytic (WHO grade 2), anaplastic ependymoma (WHO grade 3), and one genetically defined type – ependymoma, *RELA* fusion-positive (WHO grade 2 / 3). However, aspects of this scheme are not ideal; for example, in some clinical settings, there is a poor association between tumor grading and outcome (4). In addition, recent studies using DNA methylation profiling to demonstrate molecular groups of ependymoma and genome-wide sequencing to determine the genomic landscape of the disease support the proposition that ependymomas with similar morphologic features from across the neuraxis have distinct origins and oncogenic events of clinicopathologic significance and potential therapeutic utility (12, 14, 15, 17). Seeking to improve the current classification, cIMPACT working committee 2 (WC2) considered a scheme based around molecularly defined types of ependymoma.

Background to the molecular classification of ependymoma

Methylation and gene expression profiling studies have provided evidence for at least nine molecular groups of ependymoma across the three principal anatomic compartments of the CNS: supratentorial (ST), posterior fossa (PF), and spinal cord (SC) (3, 14, 15, 21-23). These molecular

groups have distinct molecular alterations and clinicopathologic characteristics, and their identification has clinical utility.

One molecular group at each anatomic site consists almost entirely of tumors with the morphologic features of subependymoma (15). Of the two remaining ST molecular groups, one is dominated by ependymomas with *C11orf95-RELA* fusion genes, and the other contains tumors with a high frequency of *YAP1-MAMLD1* fusions (1, 17). Occasionally, other fusion genes are present in ST ependymomas; for example, *C11orf95* has been reported to partner with *MAML2* and *YAP1*, and *YAP1* with *FAM118B*. In addition, some ST ependymomas have no detectable fusion gene and rare ependymomas with *C11orf95-RELA* fusions arise in the PF (DWE & KDA – personal observations). Across reported datasets, *C11orf95* and *YAP1* contribute most often to pathogenic fusions in the ST-RELA and ST-YAP1 molecular groups, respectively. These two groups of ST ependymoma are distinguished by their clinical characteristics. However, while a difference in patient outcome was reported for the ST-RELA and ST-YAP1 groups in one retrospective study (15), *RELA* fusion status was not found to be prognostic in another trial-based study (13). The clinical significance of rare genetic fusion events in ST ependymomas remains unclear.

Unlike ST ependymomas, PF ependymomas lack recurrent mutations (12, 17). However, methylation profiling divides them into two main groups, PFA and PFB, which are also distinguished by global levels of histone H3 K27-trimethylation (16). This epigenetic mark is high in PFB ependymomas, but low in PFA tumors. PFA ependymomas occur mainly in infants, while PFB tumors arise mainly in older children and adults. Patient outcome might also be different; most, but not all, studies show that PFA ependymomas have a significantly worse prognosis (13, 15, 16, 21, 23).

Among SC ependymomas are the myxopapillary tumors that predominate in adult patients. These form one methylation group; classic ependymomas form a second, and a rare third group consists of spinal subependymomas. Recently, an aggressive SC ependymoma characterized by early dissemination throughout the neuraxis, an anaplastic morphology, and *MYCN* amplification has been reported (5, 19). Other data indicate that, in adults, classic ependymomas and myxopapillary ependymomas have a similar outcome, suggesting that the latter might be more appropriately assigned to WHO grade 2 (20).

For subependymomas and myxopapillary ependymomas, the relationship between morphology and methylome group is imprecise. Some classic ependymomas without anaplastic features fall into the subependymoma or myxopapillary ependymoma molecular group (22). In addition, the clinical relevance of such findings is unclear; as yet, there is no indication that classification by molecular group provides more clinical utility than the current morphologic classification of these two tumor types.

The above findings have provided impetus to update the classification of ependymomas and, alongside other datasets, have prompted a series of recommendations from cIMPACT WC2:

- Ependymomas should be classified by anatomic site and by molecular group or an associated genetic alteration, so that classification of the disease reflects its underlying biology.
- ST ependymomas should be classified according to the genes, *C11orf95* and *YAP1*, that contribute to most pathogenic gene fusions in each of the two major molecular groups.
- PF ependymomas should be classified according to the two most prevalent molecular groups, PFA and PFB.
- SC ependymomas with *MYCN* amplification should be recognized as a distinctive type of ependymoma with a poor outcome.
- Meaningful data related to the outcome of patients on clinical trials are not yet available for a WHO grade to be assigned to types of ependymoma defined by molecular alterations.
- The rare subependymoma should continue to be identified by morphologic criteria; no clear clinical utility is yet attached to the identification of a subependymoma molecular group at each anatomic site.
- SC myxopapillary ependymomas should continue to be identified by morphologic criteria but designated WHO grade 2, because clinical trial datasets do not support a WHO grade 1 clinical behavior.
- Morphologic subtypes of the classic ependymoma (papillary, clear cell, tanycytic) should be recognized as distinctive patterns in the histopathological description of ependymomas; but, affording no specific clinical utility, they should no longer be included in the classification of the disease.

These recommendations were used to produce a novel classification of ependymal tumors (Table). In this classification, a diagnosis of subependymoma or myxopapillary ependymoma is

made on morphologic criteria. Other ependymomas would be classified according to anatomic site and the results of molecular testing, if available. If molecular testing has been undertaken, yet no result generated to place an ependymoma among the molecularly defined tumor types in the classification, then the histologically defined diagnosis 'ependymoma' is used with the suffix 'NEC' (not elsewhere classified). When molecular testing is unavailable, then 'ependymoma' is used with the suffix 'NOS' (not otherwise specified) (11).

Practical aspects of classifying ependymomas

Longstanding controversy surrounds the clinicopathological utility of grading ependymal tumors (4); though use of WHO grade in the therapeutic stratification of adult patients with ST ependymoma remains established practice (20). Our proposed classification allows only a histologically defined diagnosis of 'ependymoma' to be made at any of the three anatomic sites. However, in the upcoming edition of the WHO classification, several tumor types can be assigned to more than one grade, including ependymal tumors. As currently for the ependymoma, *RELA* fusion-positive, a pathologist will be able to assign either grade 2 or grade 3 to an ependymoma defined by morphologic criteria (Table), and in a change from previous editions of the classification anaplastic ependymoma will not be listed.

A range of diagnostic tests can be used to discover molecular alterations that define the new types of ependymoma. Sequencing might demonstrate the fusion genes of the two types of ST ependymoma, and interphase fluorescence *in situ* hybridization (iFISH) to demonstrate rearrangement of *C11orf95*, *RELA*, or *YAP1* can support the presence of a fusion gene (17). iFISH can also show the defining amplification of the spinal ependymoma, *MYCN*-amplified. Immunohistochemistry to assess the expression of H3 K27-trimethylation can be used to distinguish PFA and PFB ependymomas (16).

DNA methylation profiling is proving to be a powerful tool for the classification of CNS tumors; it works with formalin-fixed paraffin-embedded derivatives and can provide a diagnosis from small tissue samples (2). It is also a powerful adjunct when histopathological features converge on more than one possible diagnosis. For example, the histopathology of ST ependymomas overlaps with several tumor types that were originally identified by methylation profiling, especially the CNS high-grade neuroepithelial tumor with *MN1* alteration (18). Because of its ability to determine whether a ST high-grade neuroepithelial tumor with some ependymal features should not be

classified as an ependymoma or whether a PF ependymoma falls into the PFA or PFB molecular group, WC2 proposes consideration of methylation profiling as a front-line diagnostic test when ependymoma is part of the histopathological differential diagnosis.

WC2 considered chromosome 1q gain as a molecular marker to be used in the classification of PF ependymomas. Gain of 1q is present in 15-20% of PF ependymomas and has been reliably and reproducibly associated with a poor outcome and pattern of progression among patients with these tumors (6-8, 13). However, among nine subtypes of PFA ependymoma discovered by methylation profiling, outcome was highly variable, and subtypes with a poor prognosis could be enriched for 1q gain (subtype PFA-1c) or not (subtype PFA-1e) (14). Considering these data, WC2 proposes that reference to 1q status is placed in the integrated diagnosis among other molecular information (10), rather than used to define a tumor type in the classification.

In conclusion, WC2 proposes a classification of ependymal tumors that extends the principle of defining CNS tumors by characteristic molecular alterations. An integrated and tiered approach to reporting the diagnosis is recommended for capturing information on molecular characteristics alongside histopathological features.

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