Opinion Piece

The "neuroepithelial tumor": Exchanging our trash can for an industrial size dumpster?

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If "a rose by any other name would smell as sweet", then does garbage by any other name smell as foul? Before I argue the affirmative, I must first fully disclose that like every other neuropathologist, I've previously used the term "neuroepithelial tumor" in my own reports and manuscripts. Nevertheless, I've been increasingly concerned that its usage is now pursuing an alarming crescendo with an inversely decreasing specificity.

In the 2015 World Health Organization (WHO) consensus meeting in Heidelberg, a decision was made to abandon the term, "primitive neuroectodermal tumor" or PNET from the subsequent 2016 scheme[1] and this was generally hailed as a major breakthrough, with the promise of enhancing our diagnostic accuracy for central nervous system (CNS) tumor classification. Nonetheless, it was recognized that even with improved definitions, one still encounters occasional "PNET-like" cases that do not conform to currently known entities. As such, it was decided to introduce the term, CNS embryonal tumor, NOS for such cases. Of course, everyone recognized that this was essentially trading in one trash can for another, but with the notion that the new trash can was smaller and with the hope that as additional entities are elucidated over time, eventually this category would disappear altogether. Also, given that in 2013, the soft tissue and bone blue book similarly ditched "peripheral PNET" in favor of Ewing sarcoma[2], this new approach essentially eliminated the diagnosis of "PNET" altogether.

Unfortunately, since the WHO 2016 publication[1], I feel that our trash can is yet again expanding, given that the term "neuroepithelial tumor" (NET) is gaining momentum, both within the literature and in clinical practice. For instance, whereas we previously had only two known NET entities, dysembryoplastic neuroepithelial tumor (DNET) (don't even get me started on "dysembryoplastic") and cribriform neuroepithelial tumor (CRINET), we've since added: 1) high-grade neuroepithelial tumor (HGNET) with *MN1* alteration (HGNET-MN1), 2) HGNET with *BCOR* exon 15 internal tandem duplication (HGNET-BCOR), 3) neuroepithelial tumor with H3 G34 mutation (NET-H3-G34), and 4) polymorphous low-grade neuroepithelial tumor of the young (PLNTY)[3-9]. Additionally, a fifth HGNET or HGNET, not elsewhere classified (HGNET-NEC) is now being used in some clinical reports for malignant CNS neoplasms that don't fit neatly into a well-delineated tumor type, although some of these descriptive diagnoses are eventually replaced by a more specific one with further molecular testing.

The Oxford dictionary definition of neuroepithelium is: "1. A type of epithelium containing sensory nerve endings and found in certain sense organs (e.g. the retina, the inner ear, the nasal membranes, and the taste buds)" or more pertinent to NET, "2. (in embryology) ectoderm that develops into nerve tissue." (https://www.lexico.com/en/definition/neuroepithelium). Other definitions similarly focus on brain development. For instance, according to Wikipedia, "neuroepithelial cells, or neuroectodermal cells, form the wall of the closed neural tube in early embryonic development. The neuroepithelial cells span the thickness of the tube's wall, connecting with the pial surface and with the ventricular or lumenal surface. They are joined at the lumen of the tube by junctional complexes, where they form a pseudostratified layer of epithelium called neuroepithelium. Neuroepithelial cells are the stem cells of the central nervous system, known as neural stem cells, and generate the intermediate progenitor cells known as radial glial cells, that differentiate into neurons and glia in the process of neurogenesis." (https://en.wikipedia.org/wiki/Neuroepithelial_cell). This explains the intended use of neuroepithelial tumor in the original 1988 description of DNET[10], wherein the authors emphasized their view that DNET is likely related to a developmental disorder or malformation, given the frequent histologic findings resembling focal cortical dysplasia in adjacent cortex.

In other circumstances, NET is utilized in a broader fashion to state a belief that a neoplasm is derived from CNS precursor cells. Unfortunately, NET is now often utilized in an even less specific manner, essentially meaning: "I think this is probably a CNS tumor because it's located there, but I wouldn't swear to it under oath in a court of law". As long as the entire oncology team knows that this diagnosis represents our mea culpa of ignorance, then there's no harm in using this term as a placeholder until we know more. However, busy people (including oncologists) often generalize and may assume that given the similar terminology, HGNET, NEC is equivalent to HGNET-MN1 (replacing mostly what was previously diagnosed as astroblastoma, mainly behaving as WHO grade II) or to HGNET-BCOR and NET-H3-G34 (both behaving predominantly as WHO grade IV tumors). In other words, one could falsely assume that all HGNETs are biologically related and should therefore be treated in a similar fashion clinically.

Another major source of confusion comes from very different uses of "NET" by various experts. As already mentioned, in the past, it was an abbreviation for neuroectodermal tumor within both central and peripheral forms of PNET. In neuropathology, it is now being used for neuroepithelial tumor as already discussed, but outside the CNS, NET is currently utilized far more commonly as an abbreviation for neuroendocrine tumor[11]. This newly sanctioned WHO term represents the lower grade or well differentiated subtype of "neuroendocrine neoplasm". In other words, this is the more favorable tumor type, but nevertheless one that occasionally behaves more aggressively; in turn, NET needs to be distinguished from neuroendocrine carcinoma, which is the overtly malignant and high-grade form of disease. Within neuropathology, the most common manifestation of this newly proposed nomenclature is the pituitary neuroendocrine tumor or PitNET, in place of pituitary adenoma[12,13]. Nonetheless, with so many different versions now entering the medical lexicon, no-one should be surprised if one NET subtype is confused for another.

In conclusion, by discarding PNET (i.e., WHO grade IV small blue cell tumor with neuronal features) in favor of NET or HGNET, have we essentially exchanged our trash can for an industrial size dumpster? I occasionally wake up in a sweat from dreaming of a dystopic future wherein the WHO scheme is simply composed of a long list of entities all entitled "neuroepithelial tumor with ___ molecular alteration". Wouldn't it be preferable to go as far as we can with what we know? In other words, if a tumor shows compelling astrocytic features, why not invoke astrocytoma or astrocytic neoplasm in the name? If the tumor has glioneuronal features, why not say so? If indeed, neuroepithelial tumor is the best we can do, then at least, let's make a concerted effort to replace the name once we know more. Of course, this is just one man's opinion and an opinion is only worth the price one pays for it!

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