More new updates on the grading criteria of brain and spinal tumours!

The latest WHO 2021 classification is updated through the identification of new subtypes of brain cancer that is primarily related to the role of molecular diagnostics and other established approaches notably histology and immunochemistry and DNA methylome profiling. The evolution of the classification is continuously progressing with newly recognised entities with the time factor. Histology and immunochemistry facilitate in defining the shape and structure of cancer cells and tissues and how it is distinguishable from normal phenotype/structure. This is referred as morphology. Molecular diagnostics aims to detect molecular biomarkers or mutational analysis of the cancer type.

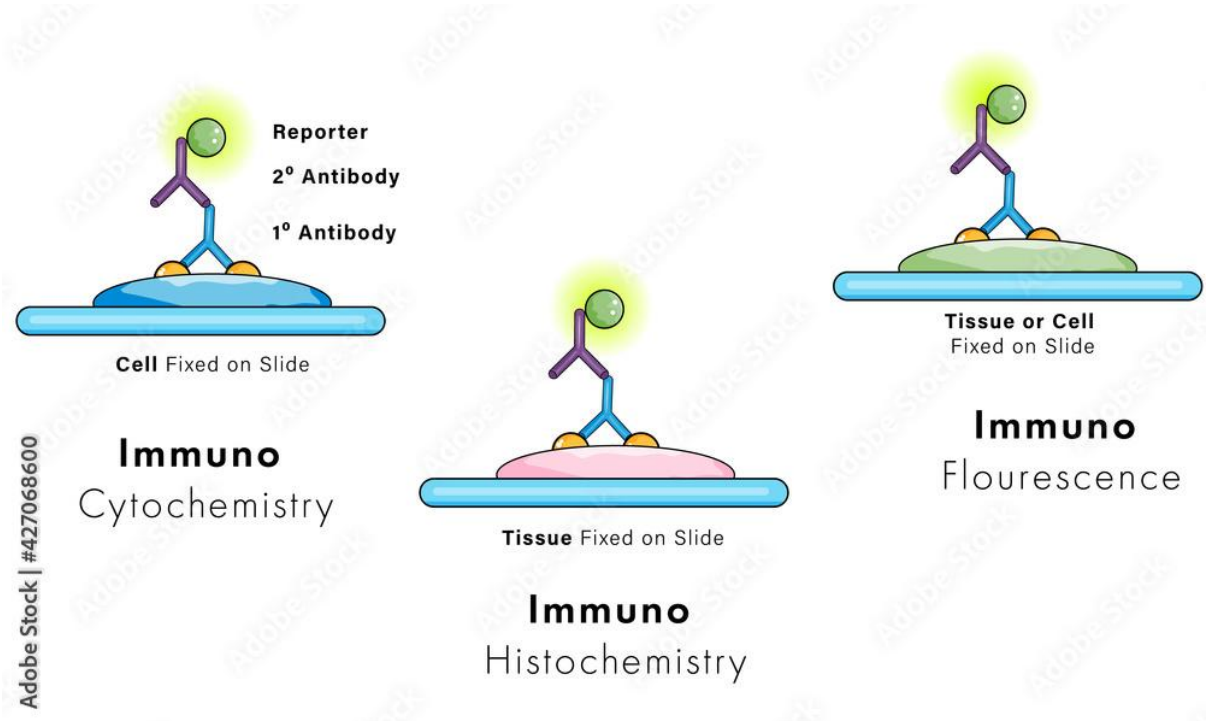

Figure 1: Examples of immunological methods.

Methylome profiling determines the DNA methylation patterns across the genome and regulate transcription in complex and/or rare tumours and small biopsy samples that cannot be examined by alternative conventional methods (Capper *et al*., 2018). It may also be used as a genetic marker but cannot function if the patient is treated with targeted therapy or is participating in

clinical trials where they need to demonstrate specific mutations (Louis *et al*., 2021). An optimised method is yet to develop to limit caveats.

In humans, methyl groups (CH3) are either removed or added by protein enzymes. They can also be recognised by effector proteins that entail protein binding modules (Wigle and Copeland, 2013). Such proteins are part of 344 proteins that are referred as the methylome. 96% of the methylome function in either removing or adding methylation at specific amino acid residues on proteins: lysine and arginine. A minimal amount of proteins function in DNA methylation. They commonly have roles in embryonic development and cellular differentiation. In addition, the process of methylation is considered amongst the small covalent modifications. Small covalent modification of histone proteins helps stabilise the DNA and control local and global gene transcription (Wigle and Copeland, 2013). However, when misregulated of methylation occurs it causes cancer. This preserves it as a potential drug target.

World Health Organisation 2021 classification of central nervous system (CNS) tumours have undergone several changes. The first change is bringing tumour grading closer between CNS tumours and non-CNS neoplasms (Louis *et al*., 2021). This was achieved by the application of Arabic numerals. This alteration was manifested as Arabic numerals for grading was conducted for other organs and there is a risk of typographical error that have clinical consequences (Louis *et al*., 2021). Other applications include to grade neoplasms within types rather across different types of brain tumours (Louis *et al*., 2020). They remain distinctive to other tumour types.

Another change that occurred was a shift of grading criteria. IDH-mutant astrocytoma has previously WHO grade 1 and now in the WHO Classification 2021 it ranges from CNS WHO grade 2 to 4. Meningioma is another example where it was previous graded 4 but now ranges between CNS WHO grade 1 – 3.

The method of reporting grades is presented in the following example:

Integrated diagnosis - Supratentorial ependymoma of the cerebrum, not otherwise specified (NOS)

Histological diagnosis - Ependymoma

CNS WHO grade - 3

Molecular information (listed) - Derivatives extracted from formalin-fixed paraffin-embedded (FFPE) tissue had poor and low quality to undergo molecular sequencing and insufficient remaining tissue to undergo fluorescence in situ hybridization (FISH) studies.

Key points on Integrated diagnosis.

This entails information about the molecular (genes) and histological diagnosis (cell/tissue examination)

Supratentorial ependymoma is an uncommon cancer within the cerebral hemispheres. It is located above the tentorium cerebelli above the cerebrum and may be attached to the ventricles and

NOS – This refers to lack of molecular or histological information for diagnosis or non-diagnostic (negative results due to technical failure or no attempt).

Key points on Molecular information.

FFPE is a long-term preservative method for tissues commonly done in diagnostic surgical pathology. The tissues are fixed with formalin before embedded with Paraffin wax.

FISH is a technique that uses small DNA molecules as probes to Hybridge the target area of the gene. This helps detect if there is inversion, translocation or other structural arrangement or a copy number of a chromosomal area is deleted or duplicated.

There have been approximately 22 new tumors recognized and added to the WHO Classification 2021 for CNS tumors. Amongst the examples is Polymorphous low-grade neuroepithelial tumor of the young (PLNTY). This is a neoplasm of non-nerve cells, specifically the glial cells. It commonly occurs in young people with a history of epilepsy. Under the microscope, calcified areas, diffused growth patterns, and there are similar structures to oligodendroglioma. It is immunoreactive towards CD34. The genetic abnormalities occur in components of the MAPK signalling pathway. They function in multiple cellular events, for instance, tumour proliferation and regulation of the cell cycle (Louis *et al*. 2020).

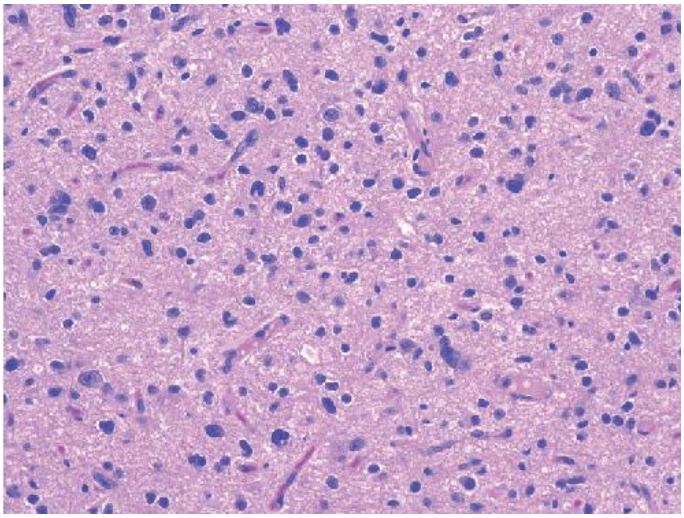

Figure 2: Microscopic image of PLNTY

Another example of a new subtype of tumour is Diffuse hemispheric glioma. It is a malignant form of glioma that affects both the left and right cerebral hemispheres. Amongst the genetic aberrations is the missense mutation in the H3F3A gene. Other contributing mutations are *TP53*, *ATRX* and a substitution of histone H3 G34R/V (Voudouri and Zanazzi, 2023).

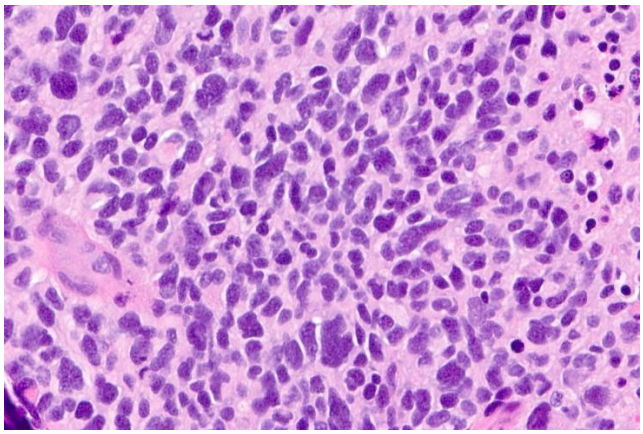

Figure 3: Microscopic image of Diffuse hemispheric glioma

There have been further changes where WHO has classified Gliomas, Glioneuronal Tumours, and Neuronal Tumours into six groups:

1. *Adult-type diffuse gliomas* – This contains most primary brain tumours, particularly IDH-wildtype, and glioblastoma.
2. Pa*ediatric-type diffuse low-grade gliomas* – have a good prognosis.
3. *Paediatric-type diffuse high-grade gliomas* – have a poor prognosis and aggressive behaviour. The division of paediatric tumours into high and low grades helps to prevent overlapping histological features and clear delineation of molecular features.

Note: Diffuse gliomas dichotomized into adult and paediatric brain tumours. This helps to distinguish based on molecular differences and prognosis.

4. Circumscribed astrocytic gliomas – they have a solid growth pattern rather than a diffuse pattern where they are grown in a uniform way as seen in Groups 1 to 3.

5. Glioneuronal and neuronal tumours – they have neuronal differentiation.

6. Ependymomas – they are subdivided by anatomical site, histology, and molecular features.

7. Choroid Plexus Tumors – they have characteristics presented in the epithelium.

However, other cancers, for instance, medulloblastoma, were previously categorized into classic, desmoplastic/nodular, medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic. In the latest WHO Classification, they are now grouped into one *Medulloblastoma, histologically defined*. Changes to morphology have specific clinical associations. Molecular information about medulloblastoma has a distinct association with morphology.

Please read the following article by Louis *et al.*, (2021):

https://pmc.ncbi.nlm.nih.gov/articles/PMC8328013/#CIT0014

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