



Review Article

# Glial and glioneuronal tumors: Navigating the complexity of evolving concepts and new classification

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## Highlights

- Provide unique perspective on the evolving concepts and new classification of glial and glioneuronal tumors.
- Propose a conceptual roadmap to navigate the new WHO classification (5th ed.).
- Highlight common practice tips to aid in diagnosing glial and glioneuronal tumors.

## Abstract

The World Health Organization (WHO) published the 5th edition classification of tumors of central nervous system in 2021, commonly abbreviated as *WHO CNS5*, which became the new standard for brain tumor diagnosis and therapy. This edition dramatically impacted tumor diagnostics. In short it introduced new

tumors, changed the names of previously recognized tumors, and modified the working definition of previously known tumors. The new system appears complex due to the integration of morphological and multiple molecular criteria. The most radical changes occurred in the field of glial and glioneuronal tumors, which constitutes the lengthy first chapter of this new edition. Herein we present an illustrative outline of the evolving concepts of glial and glioneuronal tumors. We also attempt to explain the rationales behind this substantial change in tumor classification and the challenges to update and integrate it into clinical practice. We aim to present a concise and precise roadmap to aid navigation through the intricate conceptual framework of glial and glioneuronal tumors in the context of *WHO CNS5*.

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## Introduction

The scientific research on central nervous system tumors, particularly glial and glioneuronal tumors, has progressed rapidly in the past two decades forcing a substantial shift in the concepts and practice of clinical diagnosis and treatment. In addition to traditional histopathological approaches, the increasing development and utilization of molecular tests have improved the precision of disease characterization. Considering this progress, the World Health Organization (WHO) expert panel has made substantial conceptual changes on tumor classification, as reflected in the most recent (5th) edition of the WHO classification of tumors of the central nervous system, commonly abbreviated as *WHO CNS5*. This new classification provides innovative and updated guidance for providing better patient care worldwide [1]. However, the substantial conceptual change in this new classification poses a significant challenge for clinicians, surgeons, and pathologists to comprehend and adapt to the new guidelines.

The new paradigm has also created challenges in medical education around brain tumors. Some pathologists have presented concise lectures on this topic aimed at educating pathology residents, medical students, as well as colleagues in neurology and neurosurgery. We hope that this article will help clarify the confusing concepts that are challenging many pathologists and clinicians of all experience levels who may not yet be fully aware of these conceptual changes. While *WHO CNS5* made changes to many tumor categories, the major changes are within glial and glioneuronal tumors. This review focuses on this category.

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## Section snippets

### The traditional perspective: How did we think about glial and glioneuronal tumors in the pre- and early molecular era?

The best way to introduce the concept of glial and glioneuronal tumors is to begin with a brief review of normal histology and the theory of histogenesis of normal brain components. The brain is a complex organ; however, the cytological components making up the brain may be simply categorized into neurons and four types of non-neuronal cells known as 'glia.' The originally Greek term 'glia' directly translates to 'glue,' as they were perceived to act as a structural stabilizer for neurons....

### The new molecular age perspective: diverse lineages, age factor, and growth patterns

The glial and glioneuronal tumor classification, as described above, has been based mainly on histomorphological observation, with some revision in 2016 due to emerging molecular evidence. The most recent *WHO CNS5* tumor classification substantially revised the established scheme, and considers the tumor growth pattern, patient age group, and tumor lineage, as well as molecular evidence. The new classification of glial and glioneuronal tumors, described in the first chapter of the 2021 *WHO CNS5*, ...

## How to navigate the roadmap

The final integrated diagnosis encompasses all results acquired from histomorphologic, immunohistochemical, and molecular analyses. This comprehensive work-up required for many brain tumors has impeded the turn-around-time for release of a final diagnosis, and it has created difficulty for pathologists to provide a preliminary diagnosis with confidence— in particular, at the time of intraoperative evaluation. For these reasons, tension builds among pathologists and treating clinicians with...

## Tumor DNA methylation profiling: an emerging powerful tool for aiding in diagnosis and classification of CNS tumors

Tumor DNA methylation profiling is an emerging and powerful tool using epigenetics to assist diagnosis and classification of tumors [21]. The theory behind using tumor methylation profiling for diagnosis and classification is that the methylation pattern of genomic DNA reflects tissue and cell lineage [30]; therefore, the tumor specific DNA methylation profile can be used as a differentiating tool for delineating tumor type and even subtype where applicable [31]. According to the WHO CNS5,...

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## CRediT authorship contribution statement

**Peng Cheng Han:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation, Data curation, Conceptualization. **Tiffany G. Baker:** Writing – review & editing, Conceptualization....

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