# CURRENT PERSPECTIVES ON GLIOMAS

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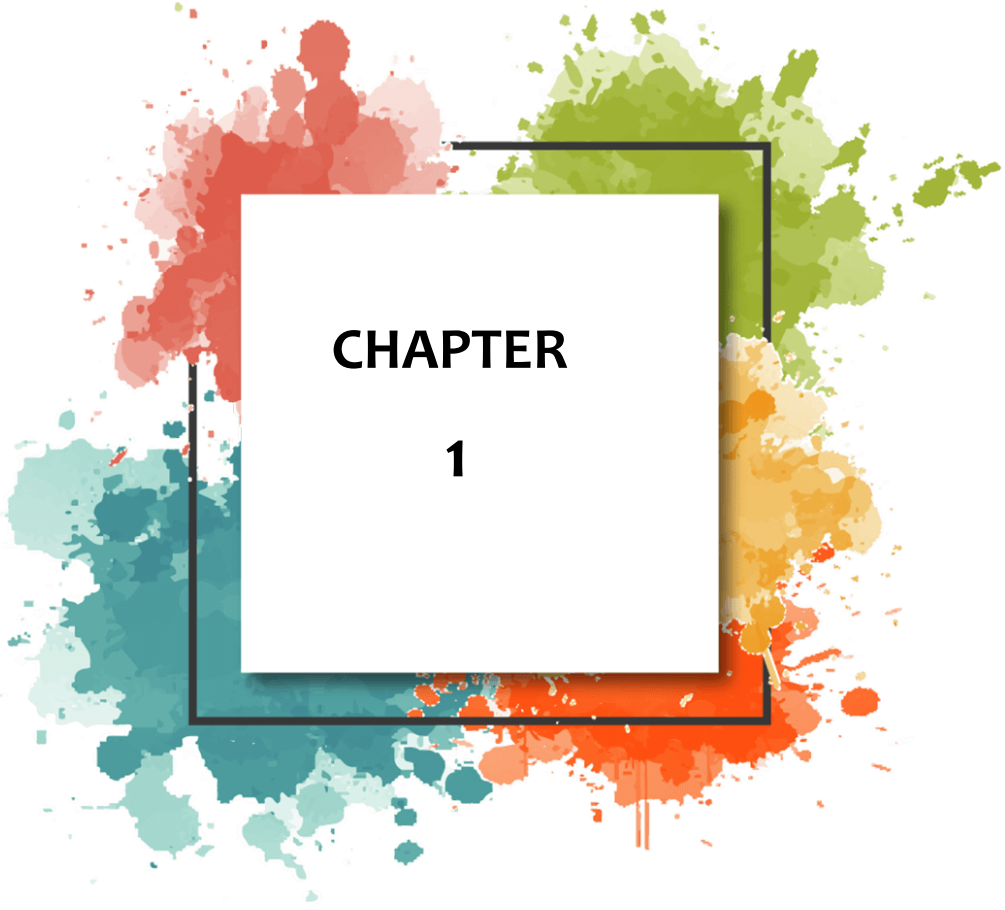
CHAPTER
1

# Current Perspectives on Gliomas

**Tevfik YILMAZ**[1]

**Background**

Accurate classification of the central nervous system is essential for prognosis determination and optimal treatment planning (1). The fifth edition of the World Health Organization Classification of Central Nervous System Tumors (WHO CNS 5), published in 2021, represents the sixth international standard for classifying brain and spinal cord tumors. While histology and immunohistochemistry remain fundamental, this classification emphasizes a more effective integration of advanced molecular diagnostic techniques (2,3).

Molecular biomarkers have gained significant importance, as they provide both supportive and defining information in diagnosis, thereby aiming to enhance clinicopathological utility. Since the first classification of central nervous system tumors was published in 1979, subsequent updates have been released at intervals; however, the most recent edition was issued in a relatively short timeframe (3). Rapid advancements in the understanding of the molecular underpinnings of central nervous system tumors have necessitated this update, as molecular alterations are now recognized to be as critical as histopathological features for accurate diagnosis, prognostic stratification, and therapeutic decision-making (4).

This classification introduces several general changes in terminology. Diagnoses now employ an integrated approach that considers histological features, CNS WHO grade, and molecular findings (1). In this classification, WHO grades have transitioned from Roman to Arabic numerals. Grading is conducted within each tumor type under the integrated diagnostic framework. The term 'anaplasia' has been discontinued, with 'WHO grade 3' now preferred. Additionally, grades are expressed as 'CNS WHO grade …' (5). An additional modification in terminology includes 'not otherwise specified (NOS)' and 'not elsewhere classified (NEC)'. NOS refers to cases where the required molecular tests for CNS lesion classification are lacking, while NEC applies when molecular testing has been conducted but yields insufficient data for more detailed classification (6).

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Based on the classification described in WHO CNS 5, the innovations concerning glial tumors will be summarized. This book will examine the section on glial tumors from the WHO CNS 5 classification under the headings outlined below.

***Gliomas, Glioneuronal Tumors, and Neuronal Tumors***

**Adult-Type Diffuse Gliomas**

- Astrocytoma, IDH-mutant
- Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
- Glioblastoma, IDH-wildtype

**Pediatric-Type Diffuse Low-Grade Gliomas**

- Diffuse astrocytoma, MYB- or MYBL1-altered
- Angiocentric glioma
- Polymorphous low-grade neuroepithelial tumor of the young
- Diffuse low-grade glioma, MAPK pathway-altered

**Pediatric-Type Diffuse High-Grade Gliomas**

- Diffuse midline glioma, H3 K27-altered
- Diffuse hemispheric glioma, H3 G34-mutant
- Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
- Infant-type hemispheric glioma

**Circumscribed Astrocytic Gliomas**

- Pilocytic astrocytoma
- High-grade astrocytoma with piloid features
- Pleomorphic xanthoastrocytoma
- Subependymal giant cell astrocytoma
- Chordoid glioma
- Astroblastoma, MN1-altered

**Euronal and Neuronal Tumors**

- Ganglioglioma
- Desmoplastic infantile ganglioglioma / Desmoplastic infantile astrocytoma
- Dysembryoplastic neuroepithelial tumor
- Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
- Papillary glioneuronal tumor
- Rosette-forming glioneuronal tumor
- Myxoid glioneuronal tumor
- Diffuse leptomeningeal glioneuronal tumor
- Gangliocytoma
- Multinodular and vacuolating neuronal tumor
- Dysplastic cerebellar gangliocytoma (*Lhermitte–Duclos disease*)
- Central neurocytoma
- Extraventricular neurocytoma
- Cerebellar liponeurocytoma

**Ependymal Tumors**

- **Supratentorial Ependymoma**
    - Supratentorial ependymoma, ZFTA fusion-positive
    - Supratentorial ependymoma, YAP1 fusion-positive
- **Posterior Fossa Ependymoma**
    - Posterior fossa ependymoma, group PFA
    - Posterior fossa ependymoma, group PFB
- **Spinal Ependymoma**
    - Spinal ependymoma, MYCN-amplified
- Myxopapillary ependymoma
- Subependymoma

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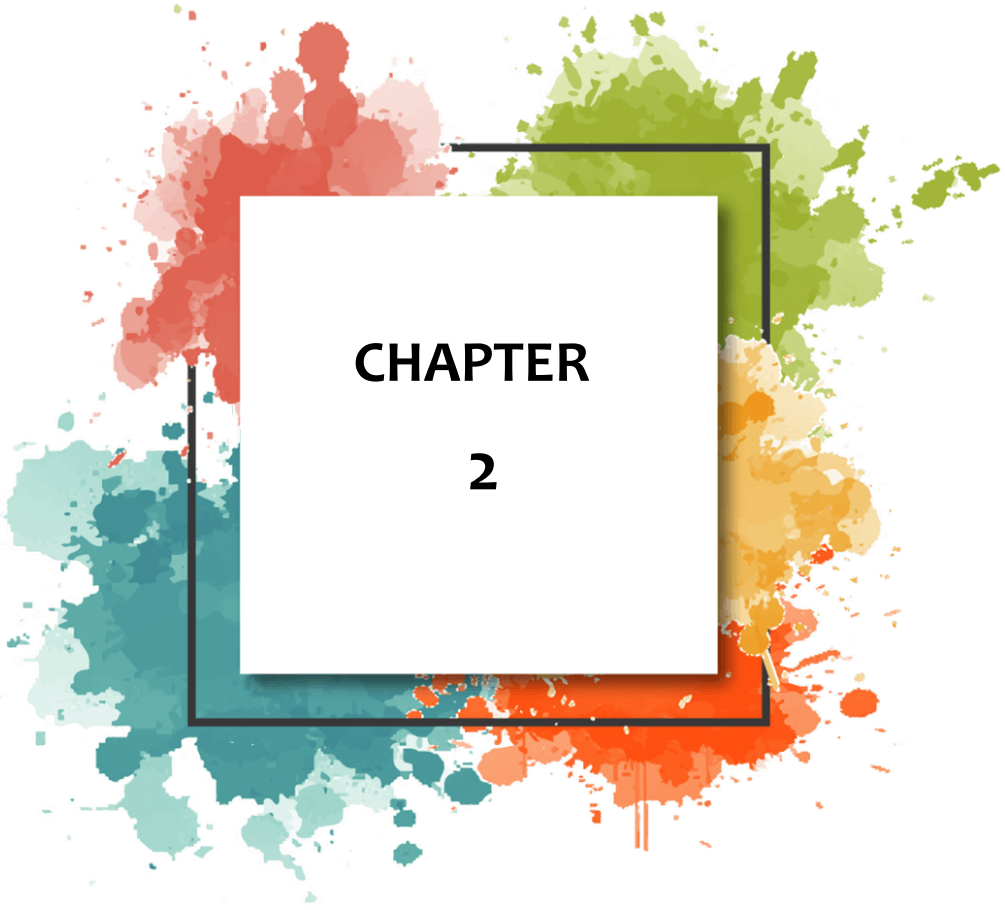
CHAPTER
2

# Adult Type Diffuse Gliomas

**Baris ALTUN**[1]

## Molecular Classification of Adult Diffuse Gliomas

The classification of central nervous system (CNS) tumours has traditionally been based on histopathological features (1). However, this approach often led to variable results between physicians and was insufficient to distinguish tumours with similar morphological features but different biological behaviours (2). This made the standardisation of diagnostic and therapeutic approaches significantly difficult.

The 2016 World Health Organisation (WHO) classification was the first to use specific molecular alterations in the diagnosis of some tumours (1). However, the 2021 WHO classification changed this approach, ushering in a new era in which more than 40 tumour types and subtypes are defined according to their molecular characteristics (3). This radical change reclassified many tumours, including gliomas, under new categories such as "adult-type diffuse gliomas" (3).

The 2021 WHO classification divided adult-type diffuse gliomas into three main categories: isocitrate dehydrogenase (IDH)-mutant astrocytoma; IDH-mutant, 1p/19q-codeleted oligodendroglioma; and IDH-wildtype glioblastoma. In this new classification, "entity" is used instead of "type" and "subtype" is used instead of "variant" (1).

These molecular changes have not only provided a better diagnostic tool but also changed the basis of clinical practice (3). Molecular markers are used to determine the different biological properties of gliomas, malignant character, invasion ability and response to treatment (4). One of the most advanced techniques showing the importance of these molecular data is DNA methylation profiling. This method has started to play a critical role for future classifications by providing high sensitivity in tumour identification (5). As a result, these molecular changes directly affect patient diagnosis and treatment as well as clinical trials (3).

The table below summarises the differences introduced by the 2021 WHO classification for adult diffuse gliomas.

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| Tumour Subtype | Descriptive Molecular Properties | WHO Grade |
|---|---|---|
| IDH-mutant Astrocytoma | IDH mutation, CDKN2A/B homozygous deletion, ATRX and p53 mutations | grade 2, 3, or 4 |
| IDH-mutant, 1p/19q-codeleted Oligodendroglioma | IDH mutation, 1p/19q codeletion | grade 2 or 3 |
| IDH-wildtype Glioblastoma | IDH-wildtype, H3-wildtype, and at least one histological or genetic feature (TERT mutation, EGFR amplification, +7/-10 chromosomal abnormality) | grade 4 |

***Table 1.*** *2021 WHO classification for adult diffuse gliomas*

**IDH-Mutant Astrocytomas**

IDH-mutant astrocytomas are infiltrative central nervous system tumours classified as grade 2, 3 or 4 according to histological features according to the 2021 WHO classification. These tumours usually occur in young and middle-aged adults and have a relatively better prognosis than IDH-wildtype tumours (6). Molecular genetics of these tumours is critical not only for diagnosis but also for determining response to treatment and prognosis (7).

**Epidemiology:**

IDH-mutant astrocytomas are more common in young and middle-aged adults and the mean age at diagnosis is 30-40 years (8). According to a study conducted in Germany, the incidence rate for newly diagnosed IDH-mutant gliomas (including astrocytomas and oligodendrogliomas) is 0.6 per 100,000. Historically, approximately 86% of grade 2 gliomas and 60% of grade 3 gliomas diagnosed before the 2021 WHO classification have IDH mutations (8). A recent study has shown that patients aged 55 years and older have a worse overall survival rate in IDH-mutant astrocytoma compared to younger patients (9).

**Clinical Findings:**

IDH-mutant astrocytomas are generally slow growing lesions with indistinct borders (10). Due to the slow growth rate of these tumours, symptoms may

develop over years (11). Seizures (up to 60%) are frequently among the presenting complaints (10). Other common symptoms include headache, neurocognitive and cognitive problems, hemiparasias, gait and balance disorders.

**Diagnosis:**

IDH-mutant astrocytomas are diagnosed by integration of histopathological evaluation and molecular analyses. The 2021 WHO classification emphasises the importance of molecular findings in the classification of these tumours. Demonstration of the presence of IDH mutation in tumour tissue is a basic criterion for diagnosis. In addition, while histological features such as mitotic activity, microvascular proliferation and necrosis are used in grading, the detection of homozygous deletion of the CDKN2A/B gene is a molecular finding that causes the tumour to be reclassified as grade 4. Radiologically, T2-FLAIR mismatch sign is considered a characteristic finding for these tumours (12).

**Imaging:**

Low-grade (grade 2) tumours show high signal intensity in T2-weighted sequences on MRI, typically do not show contrast enhancement and have low cerebral blood flow (rCBV) values on dynamic perfusion MRI. Although not specific for this tumour type, T2-fluid-attenuated inversion recovery (FLAIR) mismatch sign is a characteristic radiological finding for low-grade IDH-mutant astrocytomas (13). High-grade astrocytomas (grades 3 and 4) may show contrast uptake and high rCBV areas, while grade 4 tumours often show central necrosis areas (14).

**Molecular Markers:**

IDH mutation is the main genetic disorder of these tumours and leads to metabolic production of 2-hydroxyglutarate (2-HG). This process, which causes epigenetic and metabolic changes, also makes these tumours vulnerable to targeted therapies. Mutations in the ATRX and p53 genes are also very common in these tumours. p53 mutations are found in more than 90% of cases and ATRX mutations in more than 70%. Especially R273C hotspot mutation in TP53 gene is associated with faster progression and shorter survival compared to other TP53 mutations. The presence of CDKN2A/B homozygous deletion is one of the most important molecular features leading to classification of the tumour as grade 4 even in the absence of high-grade histological findings such as microvascular proliferation and necrosis (15).

**Treatment:**

The basis of treatment strategies is maximal safe surgical resection. A retrospective analysis shows that each 1 $cm^3$ increase in postoperative tumour volume is associated with worse survival in IDH-mutant astrocytomas (16). Depending on the recurrence risk of the disease, adjuvant treatments such as radiation and chemotherapy (temozolomide) may be applied after surgery. However, studies suggest that adjuvant radiotherapy administered within the first 3 months after diagnosis may be associated with shorter overall survival compared to delayed radiotherapy. IDH inhibitors, especially vorasidenib, one of the new generation targeted therapies, received FDA approval for significantly prolonging progression-free survival in grade 2 IDH-mutant gliomas in the Phase 3 INDIGO trial (17).

**Prognosis:**

IDH-mutant gliomas have a better survival rate than IDH-wildtype gliomas; one-year overall survival rates are 89% and 60%, respectively (18). The grade of the tumour, age of the patient, resection size and molecular markers play a critical role in determining the prognosis (9). While CDKN2A/B homozygous deletion is associated with an aggressive prognosis, it has been reported that patients with ATRX mutation have a better survival rate, while those with p53 R273C hotspot mutation have a worse survival rate (12).

**IDH-Mutant and 1p/19q Coding Oligodendrogliomas**

Oligodendrogliomas are adult-type gliomas with a basic genetic defect involving IDH mutation and 1p/19q codeletion, which is the loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). These tumours are graded as grade 2 or 3 according to their histological features (1). Oligodendrogliomas are rare and slow growing brain tumours and typically occur in the cerebral hemispheres, most commonly in the frontal lobes (19).

**Epidemiology:**

Oligodendrogliomas are rare tumours with an incidence rate of 0.2 per 100,000 and account for approximately 5% of all primary CNS tumours. It is the third most common primary brain neoplasm after glioblastoma and diffuse astrocytoma. It is most common between 35-45 years of age and is more common in males than females. Male/female ratio is 1.1-2. Although these tumours are rare in children, they have been reported more frequently between the ages of 6-12 years (19).

**Clinical Findings:**

The most common clinical finding of oligodendrogliomas is epileptic seizures seen in approximately 60% of patients (15). Other symptoms may include headache, neurocognitive and cognitive problems, side signs and focal neurological deficits depending on the affected cortical region. Due to the slow growth rate of these tumours, symptoms may be ignored by patients for years and tumours may reach large sizes(20).

**Diagnosis:**

The diagnosis of oligodendroglioma is based on the detection of IDH mutation and 1p/19q codeletion in chromosomal arms in addition to histological findings (12). The presence of these two genetic alterations are mandatory molecular markers for the diagnosis of oligodendroglioma. This genetic disorder is seen in 70% to 90% of patients and has diagnostic significance (21). TERT promoter mutations are also frequently found in these tumours (22). Histopathological examination of tumour tissue obtained by biopsy or resection typically has a fried egg appearance, but molecular tests are required for definitive diagnosis.

**Imaging**:

Radiologically, these tumours may resemble astrocytomas as infiltrative and malignant lesions (14). However, the most important radiological feature that distinguishes oligodendrogliomas is the presence of macro calcifications that can frequently be seen on computed tomography. In contrast to astrocytomas, oligodendrogliomas may show small foci of contrast uptake and increased rCBV values in perfusion sequences (23).

**Molecular Markers:**

1p/19q codeletion, which is the main genetic disorder of these tumours, is seen in 70-90% of cases. This genetic alteration is associated with a better prognosis and increased sensitivity to radiotherapy and chemotherapy. Almost all oligodendrogliomas have IDH1 or IDH2 mutations. TERT promoter mutations are also frequently found in these tumours, but TERT-wildtype subgroups may exhibit different characteristics such as younger age and better clinical course (24). CDKN2A/B homozygous deletion is an important poor prognostic marker associated with aggressive behaviour and shorter progression-free survival. Unlike astrocytomas, this does not change the WHO grade of oligodendrogliomas.

**Treatment:**

The first step of treatment is surgery to obtain tissue for diagnosis and to ensure the safest possible removal of the tumour. For high-risk patients, radiotherapy and chemotherapy (temozolomide or procarbazine, lomustine, vincristine -PCV) can be applied after surgery (25). According to the results of the Phase 3 INDIGO trial, vorasidenib, an IDH inhibitor, has become an important treatment option as it prolongs progression-free survival in patients with low risk of recurrence after surgery and has received FDA approval as of August 2024 (17).

**Prognosis:**

The general prognosis of oligodendrogliomas is better than other glioma subtypes with a 5-year relative survival rate of 79.5% (14). IDH mutation and 1p/19q codeletion are important molecular markers associated with a better prognosis (15). Prognosis depends on various factors such as tumour grade, location, extent of resection, age of the patient and genetic findings (14). TERT-wildtype genetic mutation has been shown to be associated with a better progression-free survival (26).

**IDH-Wild-Type Glioblastomas**

Glioblastoma (GBM) is the most common primary malignant brain tumour in adults with high mortality (7). It has a poor prognosis due to its aggressive and rapidly progressive clinical course (13). Glioblastomas are rapidly proliferating tumours originating from neuroglial stem cells (27).

**Epidemiology:**

Glioblastoma accounts for 14.5% of all primary CNS tumours and 48.6% of all malignant primary CNS tumours. The annual incidence rate is 3.23 per 100,000. The mean age at diagnosis is 65 years and the incidence peaks between the ages of 75-85 years, reaching 15.30 per 100,000. It is 1.59 times more common in males than females and 1.99 times more common in Caucasian than in African-American patients (28).

**Clinical Findings:**

Glioblastomas may cause rapidly progressive neurological symptoms due to their aggressive nature. Patients with molecular glioblastoma (mol-GBM), a newly defined subtype of IDH-wildtype glioblastoma, are less likely to develop preoperative motor dysfunction but more likely to develop epilepsy compared to histological glioblastomas (hist-GBM). Common symptoms seen in other glioma

types, such as headache and focal neurological deficits, are also present in glioblastoma (29).

**Diagnosis:**

According to the 2021 WHO classification, GBM is defined as a diffuse and astrocytic glioma and has the characteristics of IDH-wildtype and H3-wildtype. At least one of the histological or genetic features such as microvascular proliferation, necrosis, TERT promoter mutation, EGFR gene amplification and chromosomal +7/-10 abnormalities must be present for the diagnosis to be made (1).

**Imaging:**

Glioblastoma is usually seen as lesions showing contrast enhancement on MRI, but this is not always the case. The newly defined "molecular glioblastoma" (mol-GBM) subtype may contain lower contrast enhancement and intratumoural necrosis compared to histological glioblastomas (hist-GBM). A subset of IDH-wildtype glioblastomas may exhibit low-grade radiological appearance and may not show contrast enhancement (30). These tumours are reported to show different histopathological and molecular features compared to conventional GBM. In one study, 87.5% of newly diagnosed IDH-wildtype glioma patients had tumours with contrast enhancement, while 12.5% had tumours without contrast enhancement. This emphasises that radiological findings alone are not sufficient for diagnosis and molecular profiling is mandatory (29).

**Molecular Markers:**

IDH-wildtype and H3-wildtype mutations are the main diagnostic criteria. Additional molecular features include TERT promoter mutation, EGFR amplification and chromosomal +7/-10 abnormalities. O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is one of the most important biomarkers predicting response to TMZ treatment; methylation suppresses gene expression, making the tumour more sensitive to the drug. PTEN loss and KMT5B alteration have also been reported as important biomarkers for prognosis (31).

**Treatment:**

The standard treatment for glioblastoma is a four-stage approach involving a combination of surgery, radiotherapy and temozolomide (TMZ) chemotherapy. Surgery is the mainstay of treatment to reduce the mass effect and to obtain tissue for molecular testing. However, complete resection is usually not possible due to the diffuse infiltrative nature of glioblastoma (32). After surgery, radiotherapy

and concurrent TMZ chemotherapy are followed by maintenance TMZ treatment (31). Resistance to TMZ is one of the important causes of treatment failure in approximately 50% of patients. This resistance is associated with high expression of MGMT protein (in case the MGMT promoter is not methylated) and overactivation of DNA repair pathways such as MMR (mismatch repair) and BER (base excision repair) (33).

**Prognosis:**

The prognosis of glioblastoma is poor. The mean overall survival is approximately 12.6 to 16 months and the 5-year survival rate is 6.8%. Prognostic factors include age, gender (worse in men), tumour invasion into deep brain structures or functional areas. MGMT promoter methylation is associated with a better prognosis (8). Thenewly defined mol-GBM subtype has a higher survival than hist-GBM, but this difference is not statistically significant (34).

**Targeted Treatment Strategies in Adult Gliomas**

The limited success of conventional therapies has increased the interest in targeted and molecular-based therapies in recent years. One of the most important approaches in this field is inhibitors targeting IDH mutation. IDH mutant cells are highly dependent on the NAD+ recovery pathway because they have altered metabolic pathways (35). This provides a basis for therapies targeting these pathways. Several IDH inhibitors such as Ivosidenib, Olutasidenib, IDH305, TQB3454 and HMPL-306 have been developed and tested in clinical trials. It has been observed that Ivosidenib is effective in grade 2 and 3 IDH-mutant tumours that do not show contrast uptake, but its efficacy is more limited in contrast enhancing tumours (36).

An inhibitor named IDH305 was stopped during a phase I study due to the narrow therapeutic window (26). New generation dual inhibitors such as LY3410738 and HMPL-306 targeting IDH1 and IDH2 simultaneously have been developed (35).

Another promising strategy is Arginine Depletion Therapy (ADT). Glioblastoma cells deficient in ASL, ASS1 or OCT genes cannot synthesise arginine, an essential amino acid, endogenously and become dependent on exogenous arginine (37). ADT reduces arginine levels in the peripheral blood, depriving these tumour cells of nutrients and causing their death. This therapy not only offers metabolic targeting but also affects immune cells in the tumour microenvironment. By promoting the conversion of immunosuppressive microglia to a pro-inflammatory phenotype and the activation of T cells, it

potentiates the glioma-killing effect through a multifaceted mechanism. The safety of ADT has been confirmed in clinical trials. In one phase 1 study, the combination of ADI-PEG20 with cisplatin and pemetrexed in patients with relapsed high-grade glioma resulted in stable disease in 80% of patients. In another phase 1B study, the combination of ADI-PEG20 with TMZ and radiotherapy resulted in a median progression-free survival of 9.5 months. However, the possibility of developing resistance to ADT through re-expression of the ASS1 gene is an issue that requires further investigation (37).

Other emerging targeted therapies for the treatment of glioma include NAMPT inhibitors and CDK9 inhibitors. NAMPT (nicotinamide phosphoribosyltransferase) inhibitors target the NAD+ recovery pathway on which IDH mutant cancer cells are highly dependent (38). In early clinical trials, their efficacy was limited due to dose-limiting toxicities such as bone marrow suppression and retinal toxicity. However, new approaches such as encapsulation with nanoparticles and direct delivery to the brain are promising to increase the therapeutic index. In addition, a phase 1/2 clinical trial investigating the efficacy and safety of the CDK9 inhibitor zotiraciclib as a single agent in patients with relapsed IDH-mutant gliomas is ongoing (39). Preclinical data support that zotiraciclib is effective at lower and less toxic doses in IDH mutant tumours (40).

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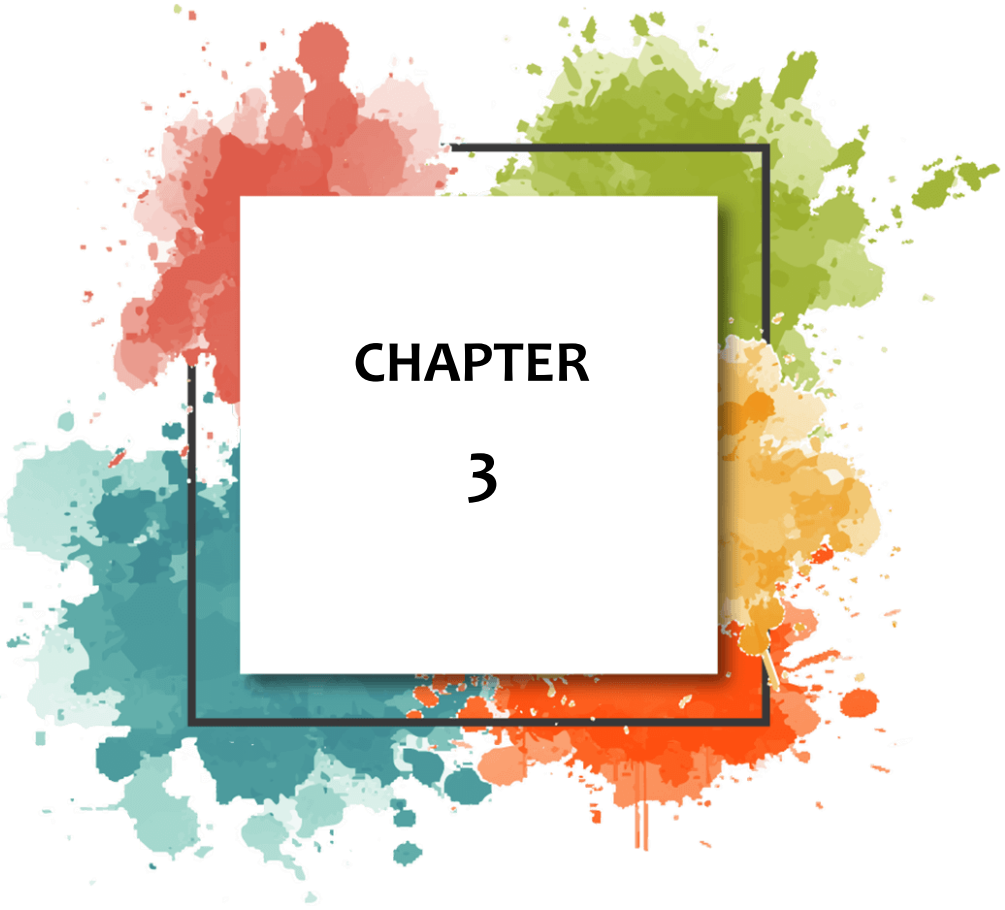
CHAPTER
3

# Pediatric Low-Grade Gliomas

**Kamuran AYDIN**[1]

In children, approximately 35% of tumors are low-grade gliomas, and 60% of supratentorial hemispheric tumors fall into this category. The annual incidence is about 5 cases per million. Low-grade gliomas are classified as World Health Organization (WHO) grade 1 or 2 tumors. The most common clinical manifestation of low-grade glial tumors is seizure, and these tumors are strongly associated with treatment-resistant epilepsy (1). Depending on their location, they may also cause speech impairment, motor weakness, visual disturbances, and memory deficits. Mass effect may lead to headache, nausea, and signs of increased intracranial pressure.

Radiological imaging plays a crucial role in diagnosis, treatment planning, and follow-up. Computed tomography (CT) and magnetic resonance imaging (MRI) are usually sufficient; however, advanced modalities such as functional MRI, MR spectroscopy, perfusion MRI, and positron emission tomography (PET) are increasingly utilized in the evaluation of low-grade gliomas (2,3).

**Clinical Presentation**

The most frequent clinical finding is seizure. Other common manifestations include headache, nausea, and vomiting, with headaches often occurring in the morning. Focal neurological deficits may be present depending on tumor location. Frontal lobe gliomas may cause personality changes and movement disorders; parietal tumors may present with reading difficulties; and temporal lobe gliomas are frequently associated with seizures and speech impairment (2,3).

**WHO Classification of Pediatric Diffuse Low-Grade Gliomas**

In the most recent WHO classification (2021), diffuse gliomas were categorized separately for adults and children. Although histological features appear similar, prognosis and molecular genetics differ significantly between these groups (2).

Pediatric-type diffuse low-grade gliomas are classified into four subtypes:

*Diffuse astrocytoma, MYB- or MYBL1-altered*

*Angiocentric glioma*

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*Polymorphous low-grade neuroepithelial tumor of the young*

*Diffuse low-grade glioma, MAPK pathway-altered*

**Diffuse Astrocytoma, MYB- or MYBL1-Altered**

Diffuse astrocytoma is a newly recognized tumor entity in the 2021 central nervous system (CNS) WHO classification. It is a diffusely infiltrating astrocytic neoplasm with histological features indistinguishable from other astrocytic tumors. It primarily occurs in children, with a median age of 5 years, though cases have been reported up to 26 years of age. No significant sex predilection is noted.

This tumor is strongly associated with treatment-resistant epilepsy and may also cause movement disorders. It most commonly involves the cerebral cortex, followed by cerebral white matter and basal ganglia. Gross total resection is associated with favorable prognosis and high rates of postoperative seizure control, with up to 90% of patients achieving seizure freedom. Diffuse astrocytoma is classified as CNS WHO grade 1. Long-term studies report a 10-year progression-free survival rate of 89.6% and an overall survival rate of 95.2%.

Molecularly, alterations involve MYB or MYBL1, excluding the MYB::QKI fusion. Frequently reported partner genes include PCDHGA1, MMP16, and MAML2. Histologically, mitotic activity is absent or minimal, Ki-67 proliferation index is low, and neither microvascular proliferation nor necrosis is observed. Tumor cells are GFAP-positive (1,2,3,7–9).

***Radiology:***

On MRI, MYB- or MYBL1-altered tumors appear hyperintense or mixed on T2/FLAIR, hypointense on T1, and are typically well-demarcated with mild edema. They usually do not demonstrate restricted diffusion or contrast enhancement. MR spectroscopy shows elevated choline and reduced N-acetylaspartate (1,2,4–7).

***Differential Diagnosis:***

Oligodendroglioma, typically frontal in location with gyriform calcification, and diffuse hemispheric glioma, a higher-grade tumor with cystic, hemorrhagic, and necrotic features and irregular contrast enhancement, should be considered (2).

**Angiocentric Glioma**

Angiocentric glioma is classified as a CNS WHO grade 1 tumor. It predominantly affects patients under 20 years of age, with no significant gender difference. A defining molecular alteration is the MYB::QKI fusion, found in 87% of cases and in 41% of all pediatric low-grade gliomas. It is strongly associated with epilepsy in children and young adults.

Histologically, angiocentric glioma is composed of monomorphous bipolar fusiform cells with a perivascular (angiocentric) growth pattern. These tumors are slow-growing and have a favorable prognosis after complete surgical resection, with low recurrence rates and frequent postoperative seizure improvement. Ki-67 labeling index is typically <5%, with no necrosis or microvascular proliferation. Tumor cells are GFAP-positive, Olig2-negative, and often immunoreactive for epithelial membrane antigen, which is a distinguishing feature (1,2,3,10–12).

***Localization and Imaging:***

Angiocentric gliomas are usually located in the supratentorial cortex and subcortical white matter, most commonly the temporal lobe, followed by the frontal lobe, parietal lobe, brainstem, and thalamus. CT may show low, high, or mixed density, with calcification being rare. MRI typically shows well-defined, T1 iso- to hyperintense, T2 hyperintense lesions, sometimes with cystic changes. Contrast enhancement is uncommon but can occur (>25% of cases). MR spectroscopy demonstrates elevated creatine and choline, reduced N-acetylaspartate, and occasionally lactate peaks. Associations with focal cortical dysplasia have also been described (1,2,4–7).

***Differential Diagnosis:***

Ganglioglioma: typically contains cystic and calcified components, with enhancement in ~50% of cases.

Pleomorphic xanthoastrocytoma: more commonly demonstrates hemorrhage on CT, whereas calcification is rare.

Dysembryoplastic neuroepithelial tumor (DNET): often associated with cortical thickening and typically demonstrates less calcification compared to angiocentric glioma (2).

**Polymorphous Low-Grade Neuroepithelial Tumor of the Young (PLNTY)**

Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is a newly recognized entity in the 2021 WHO classification of central nervous system (CNS) tumors. It predominantly occurs in children and young adults with epilepsy but has also been reported in the fourth and fifth decades of life. A slight female predominance is observed. The most common presenting symptom is seizure, while additional manifestations vary depending on tumor localization. PLNTY is classified as a CNS WHO grade 1 tumor and is typically located in the cortex or subcortical white matter.

Molecularly, PLNTY is characterized by alterations in the MAPK signaling pathway. Immunohistochemically, tumors are strongly positive for GFAP and OLIG2, while negative for IDH1 (R132H), EMA, NeuN, and neuroendocrine markers. Genetic abnormalities most frequently include BRAF V600E mutations (~40%) or FGFR2/3 fusions (~50%). BRAF V600E mutations are more common in older patients, whereas FGFR fusions (e.g., FGFR2-KIAA1598, FGFR2-CTNNA3, FGFR-TACC3) are more frequent in younger patients.

Infiltrative growth with oligodendroglioma-like features may be observed; however, IDH, ATRX, and TP53 mutations are not compatible with the diagnosis of PLNTY. Tumors typically exhibit irregular CD34 staining and a low Ki-67 proliferation index.

Grossly, PLNTY often presents as a well-circumscribed, solid–cystic lesion with peripheral calcified and cystic components. Histologically, the defining features include oligodendroglioma-like components admixed with fibrillary, fusiform, spindle-shaped, or pleomorphic astrocytic cells. Indistinct perivascular pseudorosettes and focal cortical dysplasia in adjacent cortex may be present. Calcification is frequent and often coarse (1,2,3,13–15).

***Radiology:***

On imaging, PLNTY typically appears as a calcified, well-defined supratentorial cortical or subcortical mass, most commonly in the temporal lobe, followed by the occipital, frontal, and parietal lobes, with a right-hemispheric predominance. CT frequently demonstrates granular calcification. On MRI, lesions often have mixed solid–cystic morphology, are hyperintense on T2-weighted imaging, and show no diffusion restriction. A distinctive “salt-and-pepper” sign on T2WI has been described. PLNTY may also occur with cortical dysplasia (1,2,4–6).

***Differential diagnosis:***

Ganglioblastoma: typically isointense to gray matter on T1-weighted imaging, with less frequent calcification and cystic change than PLNTY.

Dysembryoplastic neuroepithelial tumor (DNET): usually exhibits more intratumoral septation and less calcification.

Oligodendroglioma: characterized by gyriform calcification, which is useful in distinguishing it from PLNTY (2).

**Diffuse Low-Grade Glioma, MAPK Pathway-Altered**

Diffuse low-grade glioma, MAPK pathway-altered, is another new diagnostic category introduced in the CNS WHO 2021 classification. It predominantly affects children. Histologically, these tumors resemble other diffuse low-grade gliomas, necessitating molecular confirmation of MAPK pathway alterations for diagnosis.

Tumors are composed of low- to moderately cellular, monomorphic cells with oligodendroglioma-like or astrocytic features that infiltrate the brain parenchyma. Mitotic activity is absent or rare, and microvascular proliferation and necrosis are not observed. Immunohistochemically, GFAP and OLIG2 are positive.

Common molecular alterations include:

*FGFR1 tyrosine kinase domain duplication*

*FGFR1 mutations or fusions*

*BRAF V600E mutation*

*BRAF fusions or insertion mutations*

Tumors with FGFR1 alterations often display oligodendroglioma-like histology. The WHO grading of these tumors remains under debate (1,4,5,16,17).

***Radiology:***

Calcification is frequent in cortical tumors. On MRI, lesions are hypointense on T1 and hyperintense on T2-weighted images. Post-contrast studies usually demonstrate marked and heterogeneous enhancement, though atypical non-enhancing tumors are also reported. Tumors in the diencephalon are generally solid and lobulated, showing strong and homogeneous enhancement without necrosis, edema, or significant mass effect (2).

***Differential diagnosis:***

Ganglioblastoma: typically isointense to gray matter on T1 with minimal calcification and cystic changes.

DNET: characterized by more intratumoral septation and less calcification.

PLNTY: distinguished by its coarse calcification and oligodendroglioma-like components (2).

**Treatment and Prognosis**

Surgical timing depends on radiological findings and the clinical condition of the patient. Emergency surgery is indicated for patients with acute hydrocephalus or uncontrolled seizures. External ventricular drainage may be performed simultaneously in hydrocephalus cases. Elective surgery is recommended for stable patients, with the primary objectives being histological diagnosis and maximal safe resection. Gross total resection is associated with improved survival and seizure control.

Preoperative functional mapping using fMRI, diffusion tensor imaging, somatosensory evoked potentials, and intraoperative electrocorticography (ECoG) can identify eloquent cortical areas and seizure foci, guiding safer and more effective resections (18,19).

When complete surgical resection is not feasible, treatment options include targeted molecular therapies, chemotherapy, and radiotherapy. Radiotherapy is generally avoided in children due to risks of neurocognitive decline and malignant transformation; chemotherapy is preferred. Common regimens include:

Carboplatin monotherapy (monthly administration, reduced infection risk)

Carboplatin + vincristine (CV) (preferred due to lower risk of secondary malignancy/infertility compared to TPCV)

TPCV regimen (thioguanine, procarbazine, CCNU, vincristine)

Vinblastine monotherapy

Stereotactic radiosurgery and brachytherapy are additional options aimed at minimizing damage to normal brain tissue in children.

**Prognosis**

5-year survival after gross total resection: 75–100%

5-year survival after subtotal resection without adjuvant therapy: 50–90%

Chemotherapy regimens in newly diagnosed pediatric low-grade gliomas achieve 3-year progression-free survival of 50–80%, depending on the protocol (2,3,17,18-20).

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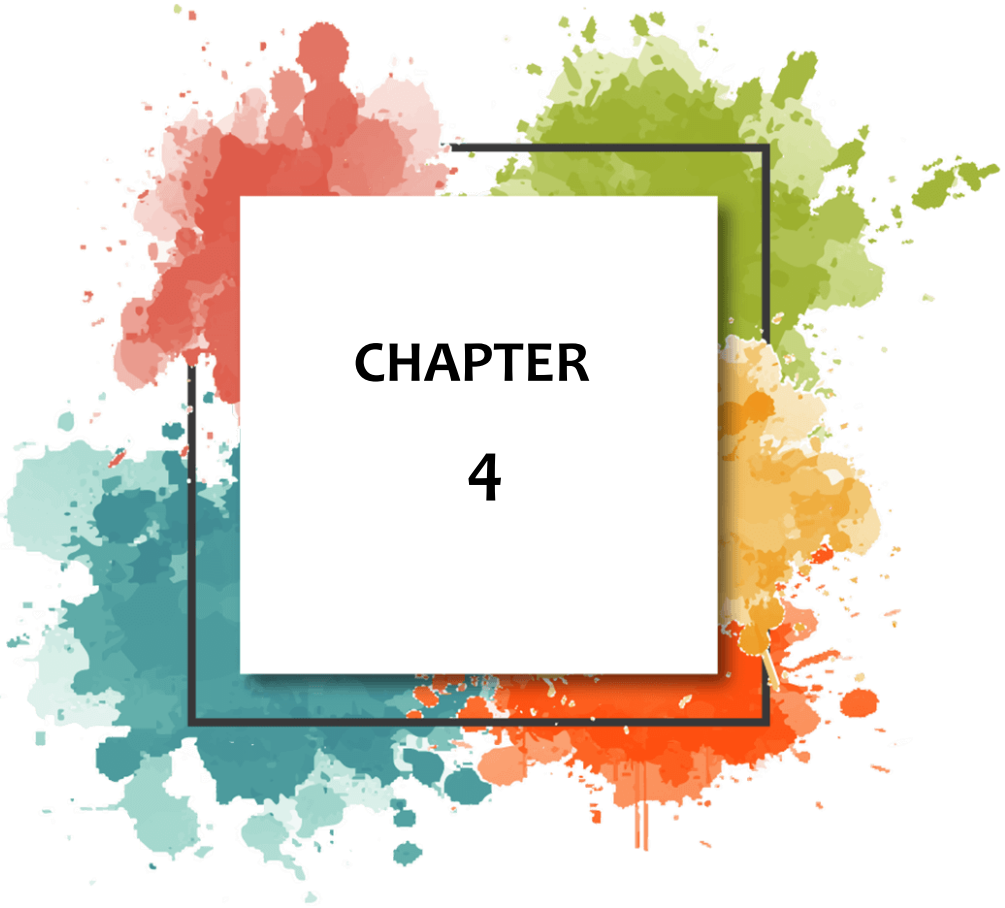
CHAPTER
4

# Pediatric-Type Diffuse High-Grade Gliomas

**Pinar AYDIN OZTURK[1]**

Pediatric-type diffuse high-grade gliomas (PDHGG) rank among the most prevalent malignant brain tumors in the pediatric population and constitute a major cause of cancer-related mortality during childhood (1). PDHGG have an estimated incidence of 1.1 to 1.78 cases per 100,000 pediatric patients and comprise over 40% of mortality among all childhood brain tumors. The reported median overall survival of PDHGG varies from 10 to 73 months (2). Despite its broad age distribution, PDHGG is most frequently diagnosed in patients aged 15 to 19 years (3).

These tumors were previously classified as anaplastic astrocytoma (WHO grade 3) and glioblastoma (WHO grade 4) (2). However, in 2021, the World Health Organization (WHO) published the fifth edition of the Classification of Tumors of the Central Nervous System, which effectively represents the sixth version of the revised classification for brain and spinal cord tumors (4,5). This classification introduced the first distinction between adult and pediatric diffuse gliomas. PDHGG have since been recognized as a separate category, reflecting their unique clinical course and molecular profile compared to adult-type gliomas (5). A key distinguishing characteristic of pediatric gliomas compared to adult gliomas is the elevated frequency of mutations in chromatin-related proteins in pediatric tumors (6).

A major determinant in the classification of PDHGG as a separate glioma subgroup was the identification of mutations involving the histones H3F3A (K27 and G34) and HIST1H3B1 (7). Mutations in histone genes define specific PDHGG subgroups, namely diffuse midline glioma, H3K27-altered, and diffuse hemispheric glioma, H3 G34-mutant. The majority of these histone point mutations are located in the histone variant H3.3, accounting for 83% of K27M mutations and all (100%) G34R/V mutations (8).

Prognosis; Even with aggressive treatment regimens, the five-year survival rate for PDHGG remains below 10% (2). Survival estimates for PDHGG vary according to their anatomical location, such as supratentorial, brainstem, or spinal cord regions. For tumors located in the supratentorial compartment, the five-year overall survival rate is less than 20%, with the majority of patients succumbing

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to the disease within two years of diagnosis (9, 10). In cases of brainstem tumors, the median survival time is less than one year (11).

According to the fifth and latest edition of the WHO Classification, PDHGGs are classified into four distinct subtypes:

1. Diffuse midline glioma, H3 K27-altered
2. Diffuse hemispheric glioma, H3 G34-mutant
3. Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
4. Infant-type hemispheric glioma

### 1. Diffuse midline glioma, H3 K27-altered

Diffuse midline glioma (DMG), H3 K27-altered (trimethylation of lysine 27 on the histone H3 protein), typically involves classic midline structures such as the brainstem, thalamus, cerebellum, gangliocapsular region, cerebellar peduncles, third ventricle, hypothalamus, pineal region, and spinal cord (12)(Figure 1). In the United States, they account for approximately 20% of all pediatric central nervous system tumors (13). Diffuse intrinsic pontine glioma (DIPG) represents about 10–15% of all pediatric brain neoplasms and approximately 75% of all pediatric brainstem neoplasms (14). DMGs are most frequently observed in children between 5 and 10 years of age (15). DIPGs show no gender predilection, with an average age 7 years (16).

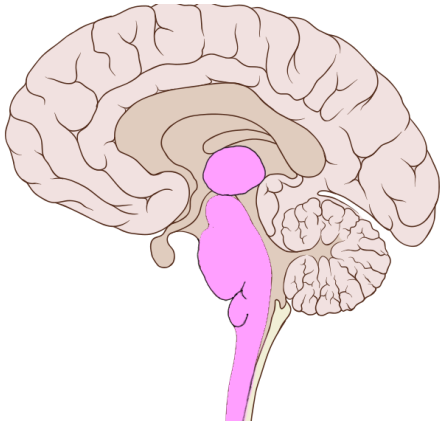

**Fig 1.** Regions affected by DMGs

## Clinical Presentation:

DIPG most often presents with the classic triad of cranial nerve palsy, pyramidal tract involvement, and ataxia (14). Multiple cranial neuropathies, long tract signs (including hyperreflexia, clonus, increased muscle tone, and a positive Babinski sign), and ataxia may also be observed (12).

### Radiogical Findings:

Magnetic resonance imaging (MRI) remains the gold standard for diagnosing DMG, particularly DIPG. Imaging findings of DMG include sharply demarcated or diffuse growth patterns, regions of necrosis and hemorrhage, variable contrast enhancement, and heterogeneous signal intensities on both T1- and T2-weighted sequences (14). Additionally, positron emission tomography may serve as a complementary diagnostic modality in DMG evaluation (17).

DIPG findings commonly consist of T1- and T2-hyperintense lesions affecting over 50% of the pontine region, with associated high perfusion and restricted diffusion. Diagnosis of DIPG is typically made using MRI in conjunction with clinical presentation, without the need for histopathological confirmation (18).

### Histopathology:

The tumor is characterized by a diffuse proliferation of small monomorphic cells and can display polymorphic differentiation including astrocytic, oligodendroglial, epithelioid, piloid, giant cell, or undifferentiated patterns. Areas of microvascular proliferation and necrosis, along with mitotic figures, may be observed. These tumors are considered WHO grade 4 irrespective of necrosis or vascular proliferation. The EGFR subtype is distinguished by prominent mitotic activity (14).

### Immunohistochemistry and Molecular Analysis:

Immunohistochemistry plays a key role in mutation detection, especially for the diagnosis of H3K27M-mutant DMG. The tumor typically exhibits positivity for OLIG2, MAP2, and S100, while the EGFR mutant subtype shows negativity for OLIG2 and positivity for GFAP. Positive nuclear staining for the H3 K27M antibody combined with negative nuclear staining for H3 K27me3 facilitates the detection of dispersed tumor cells in infiltrative regions (14).

Somatic mutations in histone H3 variants encoded by the H3F3A and HIST1H3B genes, specifically the H3K27M (p.Lys27Met) mutation, have been identified in the majority of biopsied DIPGs and broadly across DMGs (19). The H3K27 mutation may be associated with BRAF V600E mutation and, less commonly, with IDH1 mutation (14). Additionally, other molecular alterations,

such as overexpression of the enhancer of zeste homolog inhibitory protein (EZHIP) and alterations in the epidermal growth factor receptor (EGFR), have been demonstrated in pediatric DMG (20).

**Treatment:**

No established curative treatment exists for DMG. Alongside surgical intervention, radiotherapy (commonly delivered as 54–60 Gy in daily fractions of 1.8–2 Gy over six weeks) and chemotherapy, including individualized therapies, are employed. Despite these efforts, prognosis remains unfavorable (21). Reirradiation is the sole effective approach for recurrent disease, functioning as a palliative measure to alleviate symptoms and potentially improve neurological status, rather than offering a cure (22).

Routine biopsy in DIPG continues to be debated and is indicated primarily in the presence of atypical radiological findings (12). The efficacy of temozolomide has been reported in tumors with IDH mutations (23).

**Prognosis:**

While dissemination at diagnosis is uncommon, secondary metastases occur in about 13% of cases and can manifest as intraparenchymal, ventricular, or leptomeningeal disease (24). Prognostic factors include the extent of surgical resection, with gross total or extended resection correlating with increased survival in tumors amenable to surgery (25). In contrast, resection does not appear to improve prognosis in thalamic tumors. Age under three years is associated with longer survival, highlighting its role as a prognostic indicator (12).

**Diffuse hemispheric glioma, H3 G34-mutant**

Diffuse hemispheric glioma (DHG), H3 G34-mutant, is a widely infiltrative WHO grade 4 astrocytoma of the cerebral hemispheres. However, it is recognized as a distinct tumor entity in the 2021 WHO Classification of Central Nervous System Tumors.

Despite its classification as a glioma, transcriptomic and epigenomic analyses indicate a neuronal origin. The average age at presentation is 15 years (26).

**Clinical Findings:**

DHG most commonly involves multiple lobes, with predominant involvement of the frontal and parietal lobes (Figure 2). Clinical manifestations are variable and depend on tumor location, including seizures and motor or sensory impairments (27). Cortical tumors arising in the temporal and parietal lobes represent 16% of cases (28).

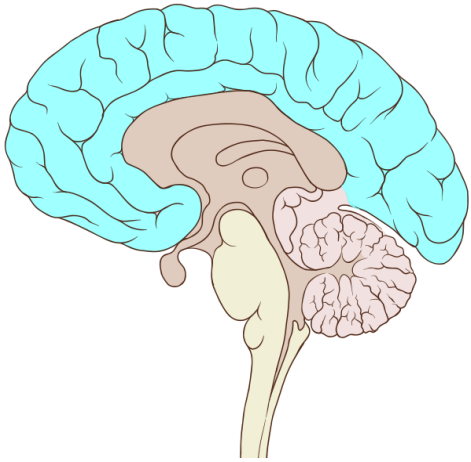

**Fig 2.** Regions affected by DHGs

**Radiological Findings:**

MRI demonstrates findings commonly seen in other gliomas, such as contrast enhancement, necrosis, hemorrhage, and edema, while leptomeningeal and ependymal dissemination may also be observed (29).

**Histopathology:**

These cellular tumors exhibit rapid mitotic activity along with palisading necrosis and microvascular proliferation, resembling glioblastoma. A subset of tumors displays an embryonal (PNET-like) appearance characterized by hyperchromatic nuclei, scant cytoplasm, and structures resembling Homer-Wright rosettes (30).

**Immunohistochemistry and Molecular Analysis:**

These tumors exhibit loss of expression of alpha-thalassemia/mental retardation syndrome X-linked (ATRX), diffuse positivity for p53, and are immunonegative for OLIG2. The Ki-67 proliferation marker shows high labeling. They are designated WHO grade 4 tumors irrespective of microvascular

proliferation or necrosis. Immunohistochemical antibodies for detecting the G34R/V mutation have recently become available (27).

Co-occurring TP53 and ATRX mutations are observed in nearly 90% of cases, with frequent methylation of the MGMT promoter. Among DHGs with H3 G34 mutations, 50–70% carry mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene (26).

A glioblastoma-like morphology correlates with elevated GFAP expression, whereas the embryonal-like pattern is characterized by diffuse synaptophysin positivity and focal GFAP staining. Notably, both patterns show negativity for OLIG2 (31).

**Treatment:**

Attempts at treatment have included surgical gross total or near-total resection, radiotherapy, and chemotherapy with both temozolomide-based and non-temozolomide protocols (32).

The identification of PDGFRA mutations, present in over 50% of cases, may provide novel therapeutic opportunities (31). EGFR amplification is targeted with agents such as Gefitinib, Erlotinib, and Afatinib (23).

**Prognosis:**

The median overall survival for patients with G34-mutant tumors is 22 months. Presence of MGMT promoter methylation is associated with improved prognosis, whereas amplification of oncogenes such as EGFR, CDK4, and MDM2 correlates with poorer outcomes (31).

A more extensive surgical resection and increased patient age correlate with better prognosis. The average time to progression is 10 months, and median survival after progression is approximately 5 months (32).

**2. Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype**

Diffuse pediatric-type high-grade gliomas (DPHGG), characterized by H3-wildtype and IDH-wildtype status, are predominantly supratentorial tumors with poor prognosis (2).

**Clinical Findings:**

DPHGGs, characterized by H3-wildtype and IDH-wildtype status, predominantly localize to the cerebral hemispheres and present with symptoms related to motor or sensory deficits (33)(Figure 3)

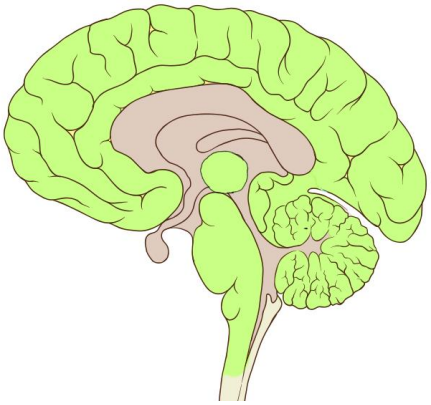

**Fig 3.** Regions affected by DPHGGs

**Radiogical Findings:**

Radiological findings include contrast enhancement, hypointensity on T1-weighted images, hyperintensity on T2/FLAIR sequences, indistinct tumor margins, and peritumoral edema (34).

**Histopathology:**

DPHGG characterized by H3-wildtype and IDH-wildtype profiles may present with glioblastoma-like or embryonal primitive morphologies. The MYCN subtype often shows a biphasic pattern with both a widespread component and nodules limited to surrounding normal brain tissue. Radiation-associated RTK1 subtype tumors may feature prominent myxoid stromal changes (33).

**Immunohistochemistry and Molecular Analysis:**

DPHGGs with H3-wildtype and IDH-wildtype status lack IDH and H3 mutations. These tumors are subclassified into three groups based on DNA methylation profiles: RTK1, associated with platelet-derived growth factor receptor alpha (PDGFRA) amplification; RTK1 also includes tumors arising in Lynch syndrome or mismatch repair (MMR) deficiency syndromes; RTK2, characterized by EGFR amplification and telomerase reverse transcriptase

(TERT) promoter mutations; and the MYCN subtype, defined by MYCN amplification (35).

Focal positivity for GFAP and OLIG2 is observed. The RTK1 subtype may demonstrate loss of MSH2/MSH6 corresponding to germline mutations (33).

**Treatment:**

Management of DPHGG parallels that of other PDHGGs and includes surgical resection, chemoradiotherapy, targeted therapies, and immunotherapeutic approaches. PDGFRA inhibitors, including dasatinib, have demonstrated encouraging outcomes in this subtype (23).

**Prognosis:**

DPHGG that are H3/IDH-wildtype generally have a poor prognosis. The MYCN subtype of DPHGG is associated with the lowest survival rates. Pontine tumors in this subgroup behave more aggressively than their supratentorial counterparts, with median overall survival times of 16.5 months for supratentorial HGG-MYCN and 1.5 months for pontine HGG-MYCN (2).

**3. Infant-type hemispheric glioma**

The primary diagnostic criteria for infant-type hemispheric glioma (INHG) encompass a combination of clinicopathological and molecular features (2).

**Clinical Findings:**

INHG predominantly occurs in early childhood, with most cases presenting within the first year of life. Symptoms are acute and nonspecific, including seizures, lethargy, and irritability. Additionally, congenital cases characterized by macrocephaly and bulging fontanelles have been reported (36).

**Radiogical Findings:**

Radiological evaluation demonstrates a superficially located cerebral hemispheric mass with potential necrotic regions and prominent cystic structures (34)(Figure 4).

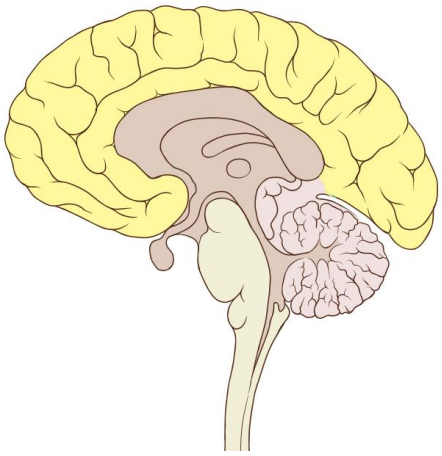

**Fig 4.** Regions affected by INHGs

**Histopathology:**

INHG displays high cellularity, nuclear pleomorphism, elevated mitotic activity, necrosis, and endothelial proliferation consistent with high-grade morphology. Initial diagnoses often include glioblastoma or desmoplastic infantile ganglioglioma/astrocytoma (DIG/DIA). Gemistocytic differentiation is infrequently observed. Tumors harboring anaplastic lymphoma kinase (ALK) fusions may demonstrate ependymal differentiation, a biphasic pattern comprising both low- and high-grade components, or a ganglion cell component (37).

**Immunohistochemistry and Molecular Analysis:**

INHG exhibits rearrangements involving the NTRK1/2/3, ROS1, ALK, or MET genes, resulting in fusion of receptor tyrosine kinases (RTKs) containing intracellular tyrosine kinase domains.

Microdeletions or copy number amplifications on chromosomes result in ALK1 gene fusions with diverse fusion partners. A high Ki-67 proliferation index is often observed (38). ALK fusion-positive tumors demonstrate immunopositivity for GFAP and OLIG2, along with ALK expression (37).

**Treatment:**

Chemoradiotherapy has been utilized alongside surgical resection in INHG; however, standard chemotherapy and radiotherapy yield limited efficacy. It is important to recognize the significant risk of severe neurological sequelae associated with radiation therapy, especially in children younger than 3 years.

Receptor tyrosine kinase gene fusions—including ALK, ROS1, NTRK, and MET—are frequently observed, and preclinical data suggest kinase inhibitors may represent a promising therapeutic strategy for this tumor type (39).

**Prognosis:**

Tumors positive for ALK fusions demonstrate a more favorable prognosis than those harboring ROS1 or NTRK fusions. The application of receptor tyrosine kinase (RTK) inhibitors, including Larotrectinib for NTRK fusions and Alectinib for ALK fusions, holds potential to alter the prognosis of these tumors (36).

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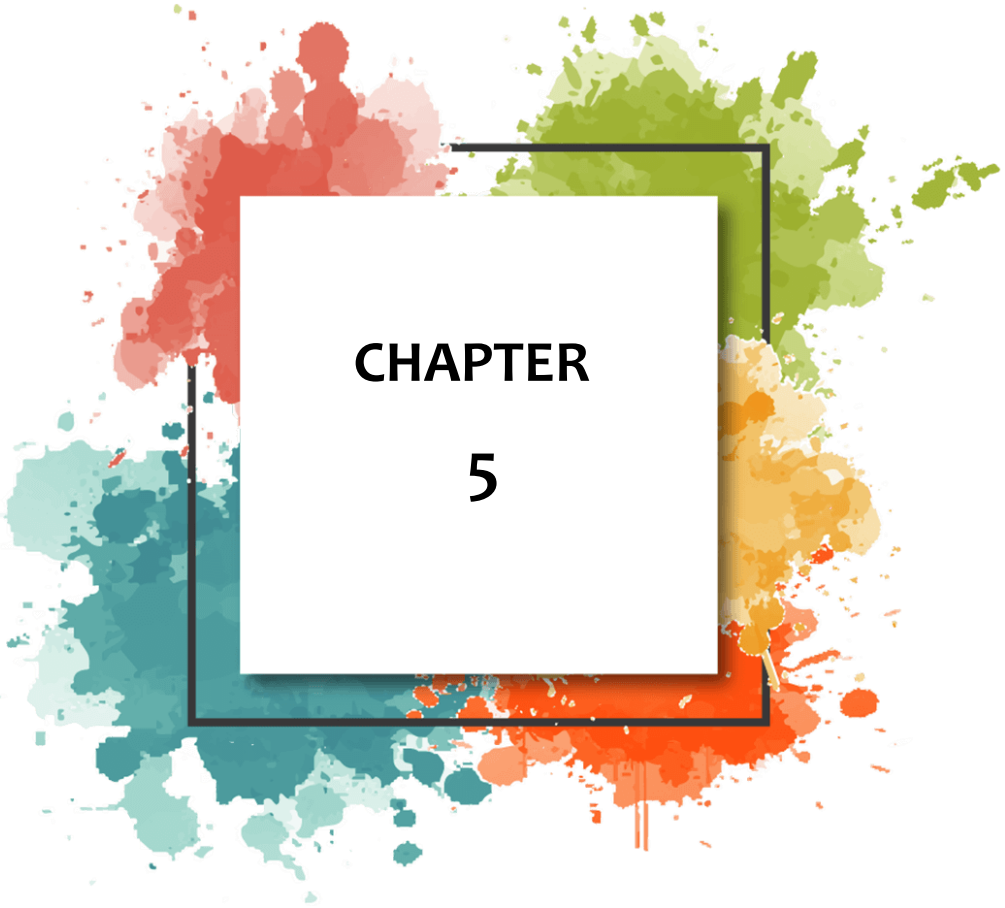
CHAPTER
5

# Circumscribed Astrocytic Gliomas

**Abdurrahman ARPA**[1]

In 2021, the World Health Organization (WHO) introduced the 5th edition of the Classification of Tumors of the Central Nervous System, incorporating substantial revisions that underscore the pivotal role of molecular diagnostics in tumor characterization (1). Significant and novel classifications have been introduced within the glial tumor category, most notably the distinction between adult-type and pediatric-type glial tumors, which have been categorized separately for the first time (2). Additionally, a new category termed "circumscribed astrocytic gliomas" has been established (1).

The tumors included in this category are defined as:

1. Pilocytic astrocytoma
2. Pleomorphic xanthoastrocytoma
3. Subependymal giant cell astrocytoma
4. Chordoid glioma
5. Astroblastoma, MN1-altered
6. High-grade astrocytoma with piloid features

## 1. Pilocytic Astrocytomas

### 1.1 Epidemiology

Pilocytic astrocytoma (PA) represents approximately 5% of all primary brain tumors and predominantly affects children and young adults. There is no recognized gender predilection. The incidence peaks during adolescence, and PA constitutes the most common pediatric glioma, accounting for roughly one-third of all gliomas in this age group (3).

### 1.2 Histopathology and Cytology

Pilocytic astrocytoma is an astrocytic neoplasm containing variable amounts of solid and microcystic components, pilocytic cells, Rosenthal fibers, and eosinophilic granular bodies. It is designated as a WHO grade 1 lesion (3). These tumors are typically circumscribed and display a range of histological patterns

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(4). Rare variants showing oligodendroglioma-like morphology have been linked to FGFR1 mutations (5).

### 1.3 Molecular Genetics and Immunophenotyping

Although most cases are sporadic, pilocytic astrocytoma may also arise in association with neurodevelopmental disorders such as Neurofibromatosis type 1 (NF1) and Noonan syndrome. It represents the most common central nervous system tumor in NF1. The tumor is thought to result from mutations affecting the mitogen-activated protein kinase (MAPK) signaling pathway. In addition, BRAF, FGFR1, and NTRK mutations have also been reported (6).

Immunohistochemical analysis typically demonstrates positive staining for GFAP, OLIG2, ATRX, synaptophysin, and p16 (with loss of p16 expression correlating with poorer prognosis), as well as S100, SOX10, MAP-2, and BRAF V600E. Negative staining is observed for IDH1 R132H, H3 K27M, and p53 (weak, low, or absent). Detection of the BRAF-KIAA1549 fusion by fluorescence in situ hybridization (FISH) is associated with a more favorable clinical outcome (3).

### 1.4 Clinical Presentation:

PA most commonly arises from midline neural structures, with the cerebellum being the predominant site. Other frequent locations include the optic pathway, hypothalamus, basal ganglia, and brainstem; however, they may develop in any region of the CNS. These low-grade, indolent tumors can cause clinical manifestations such as focal neurological deficits or hydrocephalus resulting from ventricular obstruction, contingent on their anatomical site (7).

### 1.5 Radiogical Findings:

PA typically presents as a solid-cystic mass featuring a contrast-enhancing mural nodule and may frequently demonstrate calcifications. On T1-weighted MRI, the solid component is generally isointense or hypointense relative to gray matter, while on T2-weighted sequences it appears hyperintense (8).

### 1.6. Subtypes:

#### 1.6.1. Pilomyxoid Astrocytoma (PMA)

This is a subtype of PA observed in infants and young children, frequently involving the hypothalamic and chiasmatic regions. Unlike classic PA, Rosenthal fibers and eosinophilic granular bodies are typically absent. Their location often precludes complete surgical resection, resulting in a poorer prognosis compared to conventional PA (9).

### 1.6.2. Pilocytic Astrocytoma with Histologic Features of Anaplasia

Malignant transformation in PA is rare; however, it may occur following radiation exposure or in syndromic cases such as NF1. These tumors can exhibit features of anaplasia, including increased infiltration, heightened cellularity, elevated mitotic activity, and enhanced vascularization (10).

### 1.7. Prognosis:

Pilocytic astrocytomas are WHO grade 1 neoplasms with generally excellent clinical outcomes. Prognosis is closely linked to the completeness of surgical excision. Rarely, spontaneous tumor regression can be observed (11). Tumors situated in regions that hinder total resection have a poorer prognosis; in such scenarios, chemotherapy with agents including procarbazine and vincristine may be considered alongside radiotherapy (12). Detection of the BRAF:KIAA1549 fusion correlates with favorable prognosis (3).

## 2. Pleomorphic Xanthoastrocytoma

### 2.1 Epidemiology:

Pleomorphic xanthoastrocytoma (PXA) is a rare, low-grade brain tumor (13). It accounts for less than 0.3% of primary central nervous system neoplasms and typically arises in late childhood or early adulthood, with no apparent sex predilection (3).

### 2.2 Histopathology and Cytology:

Pleomorphic xanthoastrocytoma is defined by the presence of large pleomorphic multinucleated cells, spindle cells, lipid-rich cells, abundant eosinophilic granular bodies, and reticulin accumulation. Molecularly, it often exhibits BRAF V600E mutations or other MAPK pathway gene alterations, alongside homozygous CDKN2A/B deletions. Most PXAs are located supratentorially, showing a particular affinity for the temporal lobe (14).

### 2.3 Molecular Genetics and Immunophenotyping:

The most frequently mutated gene in PXAs is BRAF, which encodes an intracellular component of the MAPK pathway. BRAF is one of the three RAF (rapidly accelerated fibrosarcoma) kinases with the highest oncogenic potential and is the most commonly altered in these tumors (15, 16). This mutation is present in approximately 70% of PXAs. Alterations in p53, p16, and chromosome 10 have also been implicated in PXA pathogenesis. These neoplasms are classified as WHO grade 2 or 3 (17).

Immunohistochemically, PXAs typically demonstrate positive staining for GFAP, vimentin, S100, CD34 (variable), focal synaptophysin, and BRAF V600. Negative staining is observed for IDH1 R132H and p53 (3).

**2.4 Clinical Presentation:**

Pleomorphic xanthoastrocytomas are predominantly supratentorial and show a marked preference for the temporal lobe, with only a minority arising in the cerebellar hemispheres. They generally affect superficial cortical areas (17). Seizures represent the most frequent clinical presentation, whereas symptoms related to raised intracranial pressure—such as headache, nausea, vomiting, and changes in consciousness—may also occur (18). Asymptomatic cases are rare. Complete surgical excision is typically feasible, but tumors situated in deep structures, including the brainstem, may preclude total resection (19).

**2.5 Radiogical Findings:**

Despite their generally favorable prognosis, PXAs may radiologically mimic high-grade gliomas. These lesions are well-circumscribed, superficial, and in contact with the meninges, exhibiting both solid and cystic components. On contrast-enhanced computed tomography (CT), the cystic portion appears hypodense, whereas the solid component is hypo- to isodense. Calcifications may be present within the solid portion, and both components typically demonstrate contrast enhancement. On MRI, the solid component is isointense on T1-weighted images, hyperintense on T2-weighted images, and exhibits heterogeneous post-gadolinium enhancement, with peripheral enhancement of the cystic component. Minimal vasogenic edema may occasionally be observed surrounding the lesion. Leptomeningeal dissemination occurs in a subset of patients. Angiographically, PXAs are hypovascular (17).

**2.6 Prognosis:**

These glial neoplasms generally demonstrate a favorable prognosis. Clinical outcomes are strongly dependent on the completeness of surgical excision and the presence of anaplastic features. Total resection has been associated with long-term remission. The 5-year overall survival rate is reported as approximately 90% for WHO grade II tumors and 57% for grade III lesions. In cases where total resection cannot be achieved, adjuvant treatments—including radiotherapy and chemotherapy—are often recommended due to recurrence risk. Tumors harboring the BRAF V600E mutation may respond favorably to targeted therapy with BRAF inhibitors such as vemurafenib (20).

### 3. Subependymal Giant Cell Astrocytoma

#### 3.1 Epidemiology:

Subependymal giant cell astrocytoma (SEGA) predominantly occurs in children and young adults. It is most frequently observed in patients with tuberous sclerosis complex (TSC), representing the most common central nervous system tumor in this population. These periventricular lesions are composed of large spindle-shaped, ganglion-like astrocytic cells (21).

#### 3.2 Histopathology and Cytology:

SEGAs are well-circumscribed, cellular tumors composed of large gemistocyte-like cells with abundant cytoplasm. The prototypical cell is polygonal with glassy cytoplasm. Tumor cells are typically organized in whorl-like arrangements or broad fascicles. Gemistocyte-like cells exhibit large nuclei with prominent nucleoli and occasional intranuclear inclusions. Accumulations of plasma cells and mast cells may also be present. These neoplasms are classified as WHO Grade I (22).

#### 3.3 Molecular Genetics and Immunophenotyping:

SEGAs are predominantly caused by mutations in the TSC1 or TSC2 genes. Inactivation of either gene results in activation of the mammalian target of rapamycin (mTOR) pathway. Positive immunostaining: GFAP, S100, OLIG2, synaptophysin, NeuN, MAP2, SOX2, and pS6V Negative immunostaining: IDH1 R132H, CD34, HMB45 (3).

#### 3.4 Clinical Presentation:

Subependymal giant cell astrocytomas originate from the subependymal region adjacent to the lateral or third ventricles, commonly near the foramen of Monro. As a result, the majority of patients exhibit clinical signs of elevated intracranial pressure secondary to obstructive hydrocephalus. Instances of spontaneous hemorrhage have also been documented (23).

#### 3.5 Radiogical Findings:

SEGAs usually present as solid intraventricular tumors near the foramen of Monro, often exhibiting punctate calcifications. Enlargement of the ventricles is commonly seen. MRI reveals a solid mass that is hyperintense on T2-weighted sequences, iso- to hypointense on T1-weighted sequences relative to gray matter, with prominent contrast enhancement (24).

### 3.6 Prognosis:

Postoperative results after complete surgical resection are typically very favorable. However, in individuals with tuberous sclerosis complex, concomitant comorbidities can adversely affect outcomes. Tumors that are partially resected or recurrent have been effectively treated using mTOR pathway inhibitors (25, 26).

## 4. Chordoid Glioma

### 4.1 Epidemiology:

Chordoid gliomas (CG) account for less than 0.1% of primary brain tumors. They predominantly affect adults, with a mean age of 45 years, and the female-to-male ratio is approximately 3:1 (27).

### 4.2 Histopathology and Cytology:

Chordoid glioma is a solid, non-infiltrative tumor composed of irregular cords or clusters of epithelioid cells embedded in a variably mucinous stroma, exhibiting chordoma-like features. Tumor cells have abundant eosinophilic cytoplasm and round to oval nuclei with inconspicuous nucleoli. Lymphoplasmacytic infiltration, often accompanied by Russell bodies, is characteristic. Occasionally, chondroid metaplasia or papillary structures may be present, while vascular proliferation and necrosis are absent (28). It is classified as WHO Grade II (1).

### 4.3 Molecular Genetics and Immunophenotyping:

These tumors specifically harbor mutations in the PRKCA gene (29). Immunohistochemistry – positive markers: GFAP, vimentin, CD34, EMA, and cytokeratin.
Immunohistochemistry – negative markers: Brachyury, SSTR2A (3).

### 4.4 Clinical Presentation:

These tumors arise from the anterior portion of the third ventricle. By causing obstructive hydrocephalus, they may lead to headache, nausea, vomiting, and altered consciousness (30). Compression within the third ventricle can also result in endocrine abnormalities, such as diabetes insipidus or panhypopituitarism (31).

### 4.5 Radiogical Findings:

Cranial imaging reveals chordoid gliomas as well-defined, solid, and densely contrast-enhancing masses occupying the third ventricle. They are typically tightly adherent to the ventricular walls. On T1-weighted sequences with contrast,

the lesions show homogeneous enhancement and isointensity relative to gray matter (32).

**4.6 Prognosis:**

Limited data are available regarding the long-term behavior and prognosis of chordoid gliomas. Gross total resection is considered the optimal treatment. Adjuvant radiosurgery may be employed following partial resection. Tumor recurrence has been reported (33).

**5. Astroblastoma, MN1 altered**

**5.1 Epidemiology:**

These tumors can occur from early childhood through the fourth decade of life, with a higher prevalence in females (34).

**5.2 Histopathology and Cytology:**

The histological hallmark is the presence of astroblastic pseudorosettes, characterized by glial cells with broad or slightly tapered processes arranged around a central blood vessel. These tumors exhibit vascular hyalinization and may occasionally display anaplastic features (35). The WHO has not assigned a specific grade.

**5.3 Molecular Genetics and Immunophenotyping:**

Astroblastomas are characterized by structural rearrangements of the MN1 gene. The two most common fusion partners are BEND2 and CXXC5, which result in a gain of function of the MN1 gene. MN1 fusions show a strong correlation with the typical histological features of astroblastoma (34, 36).

Immunohistochemistry demonstrates considerable variability.

**5.4 Clinical Presentation:**

These tumors predominantly localize to the peripheral regions of the cerebral hemispheres. Patients typically present with signs of increased intracranial pressure due to mass effect, seizures, or focal neurological deficits (37).

**5.5 Radiogical Findings:**

Predominantly peripheral supratentorial lesions, these tumors display heterogeneous contrast uptake and minimal surrounding vasogenic edema. They may be solid or cystic, with occasional multiple cysts. The solid portion can appear bubbly, and calcifications are frequently observed. Larger masses often show cystic degeneration and areas of necrosis, while hemorrhage and adjacent

brain infiltration are uncommon (38). On imaging, the solid component appears hypointense on T1-weighted and hyperintense on T2-weighted MRI sequences relative to gray matter, usually enhancing with contrast (39).

**5.6 Prognosis:**

Long-term studies providing insight into prognosis are limited. Gross total resection is theoretically recommended. In cases where surgery is not feasible or total resection cannot be achieved, chemotherapy or radiotherapy may be beneficial.

**6. High-grade Astrocytoma with Piloid Features**

**6.1 Epidemiology:**

This is a rare tumor predominantly seen in middle-aged adults. While most of these tumors arise de novo, a small subset develops from pre-existing pilocytic astrocytomas (40).

**6.2 Histopathology and Cytology:**

Histologically, these tumors exhibit considerable heterogeneity. Necrosis and microvascular proliferation may mimic PXA or glioblastoma, while the presence of eosinophilic granular bodies and Rosenthal fibers is reminiscent of PA. Consequently, supplementary molecular analyses are essential for accurate diagnosis (41, 42). They are assigned a WHO Grade III classification (1).

**6.3 Molecular Genetics and Immunophenotyping:**

Genetic alterations may include changes in MAPK pathway genes (e.g., NF1, FGFR1, or BRAF), homozygous CDKN2A/B deletions, and/or ATRX mutations (43).

**Positive markers:** GFAP, OLIG2, nestin, and p53.

**Negative markers:** IDH1 R132H, ATRX, H3F3A K27M, and p16 (3).

**6.4 Clinical Presentation:**

These tumors can arise anywhere within the central nervous system, with a predilection for the posterior fossa. Clinical manifestations depend on the tumor's anatomical location (44).

**6.5 Radiogical Findings:**

These tumors generally appear well-circumscribed and hyperintense on T2-weighted MRI, containing focal areas of hypointensity, and show hyperintensity on T1-weighted sequences. Diffusion restriction is not present (45, 46).

### 6.6 Prognosis:

Long-term studies providing insights into the prognosis are limited. Gross total resection is theoretically recommended. In cases where surgery is not feasible or total resection cannot be achieved, chemotherapy or radiotherapy may be beneficial.

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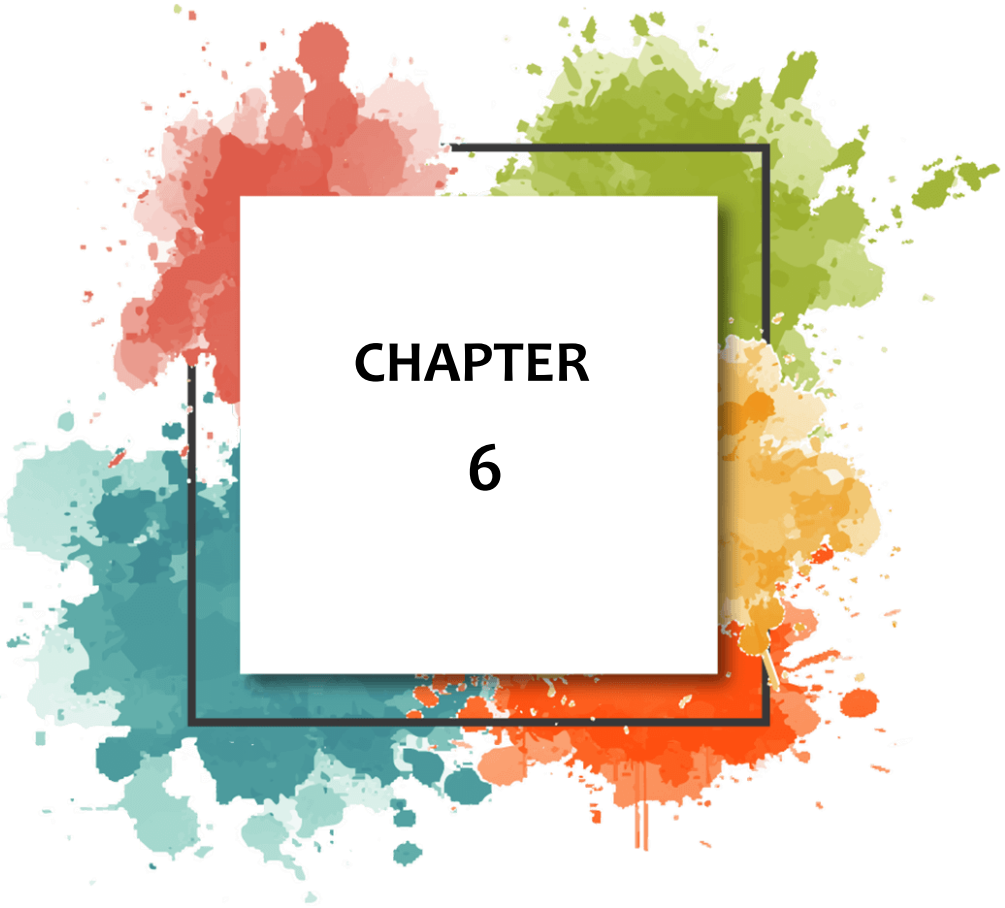
CHAPTER
6

# Neuronal and Mixed Glioneuronal Tumours

**Sezer Onur GUNARA**[1]

Neuronal and mixed glioneuronal neoplasms constitute less than 2% of all central nervous system tumors in the adult population; however, they represent up to 10% of central nervous system neoplasms in pediatric patients. Histopathological evaluation reveals subtypes containing only neuronal cells (dysplastic gangliocytoma, central neurocytoma, extraventricular neurocytoma, etc.) as well as subtypes comprising both neuronal and neuroglial components (ganglioglioma, dysembryoplastic neuroepithelial tumor, diffuse leptomeningeal glioneuronal tumor, etc.) (1,2).

In the 2021 World Health Organization (WHO) classification, all tumors within this group except for dysplastic gangliocytoma can be differentiated based on their DNA methylation profiles. In other words, each of these tumors can be identified at the epigenetic level, allowing treatment planning to be tailored accordingly (3).

According to the 2016 World Health Organization (WHO) grading system, all tumors in this group are classified as low-grade, with the exception of anaplastic ganglioglioma (grade 3). Given their slow-growing nature, the initial clinical manifestation is typically seizures rather than headache or signs of increased intracranial pressure. Headache, nausea, and vomiting may be present in patients with hydrocephalus. Psychiatric manifestations are among the uncommon symptoms, occurring predominantly in patients under the age of 10 years. Patients presenting initially with panic attack diagnoses were later recognized to experience ictal panic, a seizure subtype. Ictal panic manifests as an abrupt, intense fear occurring immediately prior to an epileptic event. EEG studies demonstrated pathological epileptic discharges in the amygdala, hippocampus, and insular regions, substantiating the epileptic origin of these clinical manifestations (4,5).

## 1. Disembryoplastic Neuroepithelial Tumor (DNET)

Tumors classified within this group encompass dysembryoplastic neuroepithelial tumors, gangliogliomas/gangliogliomatosis, desmoplastic infantile astrocytomas/desmoplastic infantile gangliomas, dysplastic gangliogliomatosis of the cerebellum, papillary glioneuronal tumor, rosette-

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forming glioneuronal tumors, diffuse leptomeningeal glioneuronal tumor, cerebellar liponeurocytoma, central neurocytoma, and extraventricular neurocytomas.

Dysembryoplastic neuroepithelial tumors are most frequently encountered in pediatric and young adult populations, with peak prevalence in individuals aged 10 to 25 years. The WHO classifies DNETs as Grade I neoplasms, generally located in the cortex and characterized as mixed glioneuronal tumors. While DNETs can develop throughout the brain, they are observed in the temporal lobe in nearly %66 of cases (6).

The majority of DNET cases approximately %80 are benign, indolent tumors that typically manifest with focal seizure activity upon clinical presentation (7). In patients younger than 20 years, seizures develop in %90 of cases and frequently demonstrate resistance to anticonvulsant therapy (8). Postoperative seizure control improves by approximately 80% within the first year following surgery (6).

On MRI, DNETs typically present as gray, foamy-appearing lesions on T1-weighted sequences localized to the subcortical area, with increased signal intensity on T2-weighted and FLAIR sequences compared to cortical tissue. The characteristic hyperintense rim observed on T2 and FLAIR images around the lesion is considered pathognomonic for DNET and serves to distinguish it from gangliogliomas and focal cortical dysplasia (9). DNETs are generally non-contrast-enhancing lesions, and peritumoral edema is typically absent (10).

Macroscopically, the tumor presents with nodular and cystic formations resulting in cortical thickening. Histologically, it is characterized by specific glial elements and the presence of nodular zones (9).

Although these tumors rarely exhibit aggressive behavior, treatment may be necessary in symptomatic cases, such as those with severe epilepsy. Surgical resection remains the cornerstone of management. Complete surgical resection is associated with improved clinical outcomes; notably, more than 80% of patients who undergo gross total resection and have a shorter duration of epilepsy achieve seizure freedom at one year. Radiotherapy and chemotherapy have no established role in the management of DNET. Malignant transformation is exceedingly rare and has been reported only in cases involving complex-type DNET and extratemporal locations (11,12)

## 2. Ganglioma and Gangliomasitoma

Gangliomas are the most frequently encountered mixed glioneuronal tumors, representing roughly 0.5–1% of central nervous system tumors overall (13). Although gangliomas can occur across all age groups their incidence peaks notably in young adults aged 15 to 20 years (14). Gangliomas, characterized as slow-growing lesions, most commonly present with drug-resistant epilepsy. They are known to induce complex partial seizures (15). Gangliogliomas involving the amygdala may be associated with chronic psychosis in addition to epilepsy. In younger patients with gangliomas located in the temporal lobe or cingulate gyrus, seizures can occasionally present clinically as ictal panic (16,17).

Gangliomas and gangliositomas can present in various anatomical sites such as the brainstem, cerebellum, spinal cord, optic nerve, and amygdala, with the highest incidence in the temporal lobe (~70%) and the frontal lobe (~10%) (18). Gangliomas and gangliomasitomas located in the optic nerve or spinal cord are associated with higher recurrence rates following surgical intervention (19).

On imaging, these tumors typically present as cystic lesions featuring a solid or mural nodule, superficially situated without causing mass effect on CT. Areas of hemorrhage or necrosis are rarely detected, although calcifications may be noted. Adjacent bony erosion secondary to pressure exerted by gangliomas and gangliomasitomas can also be observed (20). On MRI evaluation, these lesions are generally non-contrast-enhancing and show minimal surrounding edema. They present as hypointense on T1-weighted images and hyperintense on T2-weighted images. In nearly half of the cases, the solid tumor mass (21).

Macroscopically, gangliomas present as firm, gray lesions causing cortical expansion. Histologically, they exhibit a combination of atypical ganglion cells and neoplastic glial elements (9). Histopathology reveals ganglionic neuronal tumor cells positive for synaptophysin and/or chromogranin A, which can exhibit binucleation, distinguishing them from normal residual neurons. Glial tumor cells expressing OLIG2 and/or GFAP are also present, demonstrating heterogeneous morphology predominantly of piloid astrocytic type, with occasional oligodendroglial differentiation. The Ki-67 proliferation index is generally below 3%. These tumors frequently exhibit eosinophilic granular bodies, conspicuous lymphocytic infiltration, and CD34-immunoreactive stellate cells (21). Except for anaplastic gangliomas (WHO Grade III), gangliomas are considered benign neoplasms, with gross total resection representing the surgical objective. Subtotal resection correlates with a 5-year survival rate of approximately 62%, compared to 78% in cases with complete tumor removal. Patients who undergo gross total

resection demonstrate superior seizure control outcomes (22). Postoperative radiotherapy is advised after gross total resection for anaplastic gangliomas (23,24).

### 3. Desmoplastic Infantile Astrocytoma and Ganglioma

Desmoplastic infantile astrocytomas (DIA) and desmoplastic infantile gangliomas (DIG) are large cystic benign tumors (WHO Grade 1) presenting during infancy, predominantly involving the parietal and frontal lobes, and typically affecting both the cortex and leptomeninges. DIA are composed exclusively of neuronal cells, whereas DIG contain both neuronal cells and astrocytic components (25). Clinical manifestations of large and aggressive tumors identified radiologically include increased head circumference, fontanelle bulging, and signs of elevated intracranial pressure. The solid tumor component is adherent to the dura mater, whereas the cystic portion lies deeper. On T2-weighted MRI sequences, the solid component appears hypointense. A dural tail sign may be present due to leptomeningeal spread. These tumors are differentiated from infantile ganglioblastomas by the absence of diffusion restriction, except in areas of hemorrhage (26,27).

While complete surgical excision remains the standard treatment, instances of spontaneous tumor regression have been documented following subtotal resection (28).

### 4. Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos Disease)

Dysplastic cerebellar gangliocytomas, also referred to as Lhermitte-Duclos disease, are benign (WHO Grade 1) lesions. This rare pathology results from hypertrophy of the cerebellar folia due to dysplastic ganglion cells, accompanied by disruption of the normal cerebellar cortical architecture. These tumors may be asymptomatic but can also lead to hydrocephalus due to compression of the fourth ventricle. They can occur at any age, although they are most frequently observed in young and middle-aged adults (9).

Dysplastic cerebellar gangliocytomas, which are often solitary lesions, may present as multiple hamartomas in association with Cowden syndrome (29). Characteristic features include cystic enlargement of varying sizes within the cerebellar folia. MRI demonstrates well-circumscribed lesions that are hypointense on T1 and display alternating hypo- and hyperintense layers on T2-weighted images (30). Susceptibility-weighted imaging (SWI) demonstrates dilated veins as hypointense signals adjacent to the thickened cerebellar folia, which exhibit contrast enhancement on post-contrast imaging. Magnetic

resonance spectroscopy shows decreased NAA with preservation of normal choline peaks (31). Although surgical resection is the mainstay of treatment for dysplastic cerebellar gangliocytoma, tumor recurrence has been observed even in cases undergoing gross total resection (32).

### 5. Papillary Glioneuronal Tumor

Papillary glioneuronal tumors, predominantly observed in young adults, are localized, well-circumscribed, low-grade (WHO Grade 1) lesions of the cerebral hemispheres. They comprise both astrocytic and neuronal components. Their histopathological hallmark is the presence of hyalinized vascular pseudopapillae (25).

Papillary glioneuronal tumors may present as cystic, solid, or mural nodular lesions, occasionally demonstrating opacification within the cyst. They are often misinterpreted as gangliogliomas on MRI, with definitive diagnosis typically established through histopathological evaluation. These tumors predominantly involve the frontal and temporal lobes but may also occur in intraventricular locations (23).

These tumors are generally slow-growing, exhibiting an indolent clinical course, and often remain asymptomatic until hydrocephalus-related signs emerge. Surgical resection remains the definitive treatment, with tumor progression and recurrence being exceptionally rare (33).

### 6. Rosette-Forming Glioneuronal Tumors

Rosette-forming glioneuronal tumors are rare benign neoplasms (WHO grade I), predominantly affecting young adults. Although these tumors are most commonly found in the infratentorial area or within the fourth ventricle, they can infrequently present in the supratentorial region, cerebellum, and pineal gland. Clinically, patients typically present with headache and ataxia (34).

Tumor size ranges from 1–2 cm to extensive dimensions, with an absence of surrounding edema. CT scans may reveal surrounding calcifications or bleeding. On MRI, these lesions are characterized by hypointensity on T1-weighted images and hyperintensity on T2-weighted images, often manifesting as multicystic masses exhibiting heterogeneous enhancement after contrast administration (9). Pathologically, these tumors are characterized by astrocytic and neuronal cells forming perivascular pseudorosettes (34). Surgical resection remains the treatment of choice in symptomatic patients (9).

### 7. Diffuse Leptomeningeal Glioneuronal Tumors

Diffuse leptomeningeal glioneuronal tumors, formerly described in the literature as primary leptomeningeal oligodendrogliomatosis, were classified as a distinct entity among central nervous system tumors in the 2016 WHO classification revision. Frequently observed in pediatric patients and males, these tumors exhibit widespread leptomeningeal involvement, regardless of whether a parenchymal component is present. Diffuse leptomeningeal glioneuronal tumors exhibit slow growth, and patients typically present with symptoms related to hydrocephalus secondary to leptomeningeal involvement. The prognosis largely depends on the severity of the resultant hydrocephalus (35).

On MRI, diffuse leptomeningeal glial tumors often present as widespread plaque-like enhancing lesions in the spinal cord, brainstem, and basal cisterns. These lesions are characterized by hyperintense, small cystic or nodular appearances on T2 sequences and primarily involve the spinal cord parenchyma (36). In most cases, cerebrospinal fluid cytological analysis yields negative results, requiring tissue sampling from the meninges to confirm diagnosis. Staging criteria have not been defined by the WHO, and standardized treatment protocols remain lacking (37).

Surgical removal of symptomatic nodules represents the most common operative approach. Adjunctive therapies such as radiotherapy and temozolomide-based chemotherapy have been reported in the literature to enhance survival in pediatric patients (38).

### 8. Cerebellar Liponeurocytomas

Cerebellar liponeuroblastomas, comprising varying proportions of low-proliferative neuronal, astrocytic, and lipomatous cells, typically present clinically with atypical symptoms such as headache. Lesions may present with clinical signs of hydrocephalus if they obstruct cerebrospinal fluid pathways (39).

Although these tumors are classified as low-grade (WHO grade I), recurrence rates of up to 50% have been reported post-surgically without evidence of malignant transformation. Consequently, some authors advocate for their classification as WHO grade II. The primary treatment approach remains surgical resection (40).

### 9. Central and Extraventricular Neurocytomas

Central neurocytomas are predominantly WHO grade II tumors occurring between the ages of 20 and 50, with equal prevalence in males and females. Usually located at the level of the foramen of Monro within the lateral and third

ventricles, these indolent tumors are frequently discovered incidentally and commonly manifest clinically with hydrocephalus secondary to cerebrospinal fluid obstruction (39). Although cases of psychosis and hallucinations have been documented, these manifestations are exceedingly rare (40).

On MRI, the lesions appear hyperintense on T2-weighted sequences, while CT imaging typically demonstrates punctate calcifications. In larger tumors, intralesional hemorrhage may be observed, and fluid–fluid levels can be detected within the cystic component (41).

Surgical resection represents the primary treatment modality for these tumors; however, when complete removal is not feasible, postoperative radiotherapy has been reported to improve survival outcomes (42). Although the role of chemotherapy in the management of these tumors is not yet fully elucidated, it is regarded as a potentially life-saving intervention in cases of recurrence. Chemotherapeutic strategies may include temozolomide as monotherapy or in combination with radiotherapy, lomustine, and etoposide/cisplatin/cyclophosphamide regimens. In general, postoperative and post-radiotherapy recurrences are relatively rare (43).

Extraventricular neurocytomas are WHO grade II lesions that may occur anywhere within the central nervous system and predominantly affect young adults. In approximately 50% of cases, the tumors are located in the frontal and temporal lobes. With 10-year survival rates inferior to those of central neurocytomas, these lesions are regarded as having a relatively more aggressive behavior (44).

MRI findings of extraventricular neurocytomas, appearing as extra-axial masses, often reveal a combination of solid and cystic areas, with peritumoral edema frequently present around the lesion (45).

Management follows the same principles as for central neurocytomas, and recurrence is uncommon except in atypical variants exhibiting necrosis or neovascular proliferation histologically. Radiotherapy is considered an adjunctive option when total tumor removal is not possible.

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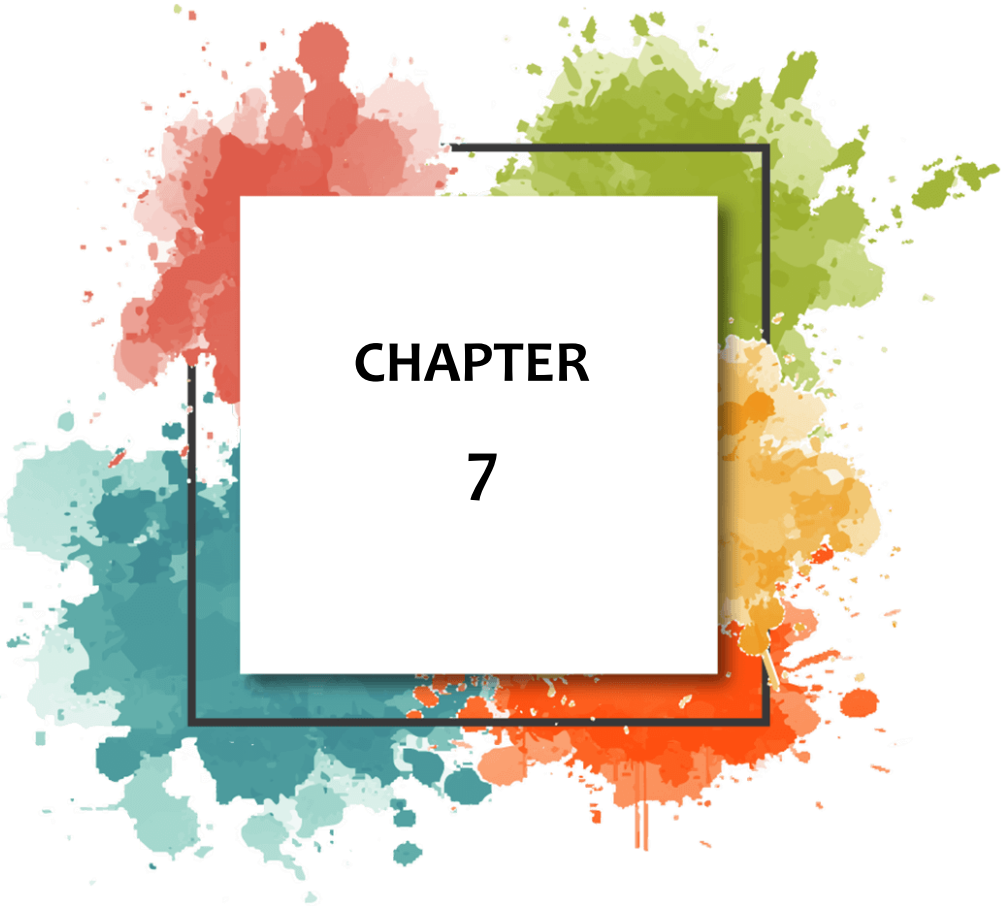
CHAPTER
7

# Ependymomas

**Baris ASLANOGLU**[1]

Ependymomas are tumors originating from ependymal cells lining the cerebral ventricles, forming part of the choroid plexus epithelium and located within the central canal of the spinal cord. Representing approximately 1.6–1.8% of central nervous system (CNS) tumors, ependymomas account for 5.2% of pediatric and about 4% of adult cases (1). According to the Central Brain Tumor Registry of the United States (CBTRUS), the annual incidence of ependymomas ranges from 0.29 to 0.6 per 100,000 population (2). The female-to-male ratio is approximately 1.3:1. While 90% of pediatric ependymomas are intracranial, approximately 65% of adult cases are spinal in location. About 70% of supratentorial ependymomas are found in an extraventricular location (3).

Molecular studies have demonstrated that ependymomas exhibit distinct histopathological characteristics depending on their anatomical localization, patient age group, and tumor grade. These molecular and histopathological differences formed the basis for the definition of ependymoma subgroups in the 2021 World Health Organization (WHO) classification of CNS tumors (4–7).

**WHO 2021 Updated Classification**

The 2021 WHO Classification of CNS Tumors marked a paradigm shift in the diagnosis of ependymomas, moving from a histopathology-based to a molecular subtype-based approach, distinguishing it significantly from previous classifications. Some lesions previously categorized in other brain tumor groups were reclassified as ependymomas following the identification of unique molecular markers, whereas tumors that histologically resembled ependymomas but had distinct molecular profiles were excluded.

In this updated classification, supratentorial ependymomas are characterized by ZFTA, RELA, YAP1, and MAML2 fusions/mutations; posterior fossa ependymomas by H3 K27me3 loss and EZHIP-associated methylation profiles; and spinal ependymomas by MYCN amplification. Histopathologic variants such as “anaplastic ependymoma,” papillary, tanycytic, and clear cell subtypes, which were included in previous classifications, have been removed due to their limited clinical relevance.

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**WHO 2021 Molecular Subtypes of Ependymoma (7)**

Supratentorial Ependymoma

- ZFTA fusion-positive

- YAP1 fusion-positive

Posterior Fossa Ependymoma

- Group PFA

- Group PFB

Spinal Ependymoma

- Classic

- MYCN-amplified

Myxopapillary Ependymoma

Subependymoma

Morphologically, supratentorial and posterior fossa ependymomas are classified as WHO Grade 2 or Grade 3, while myxopapillary ependymomas are classified as WHO Grade 2. ZFTA fusion-positive and YAP1 fusion-positive ependymomas are typically located in the supratentorial compartment. ZFTA fusion-positive tumors are more common, with a median age at diagnosis of approximately 8 years, compared to 1.4 years for YAP1 fusion-positive tumors. YAP1 fusion-positive ependymomas constitute approximately 7% of supratentorial cases.

Ependymomas have a 10-year survival rate of approximately 50%, with a slight predominance reported in female patients (4). Posterior fossa group A (PF-A) and group B (PF-B) ependymomas are localized in the infratentorial region, particularly in the posterior fossa. PF-A ependymomas are more common in boys, with a mean age at diagnosis of 3 years, and typically occur during infancy. These tumors are associated with a poorer prognosis due to high recurrence and metastasis rates, with a 10-year overall survival rate of approximately 56% (8). PF-B ependymomas generally occur in young adults, with a mean age of 30 years and a slight female predominance. This subtype has a 10-year survival rate of around 88% and is associated with a more favorable prognosis (8).

Spinal ependymomas, spinal subependymomas, and MYCN-amplified spinal ependymomas are most frequently located in the cervical and thoracic spinal cord. Spinal ependymomas are the second most common intramedullary tumors

in children and the most common in adults (9), accounting for approximately 30% of pediatric intramedullary tumors. Although spinal ependymomas with MYCN amplification are rare, they demonstrate a more aggressive clinical course, often involving multiple spinal levels and showing leptomeningeal dissemination.

Myxopapillary ependymomas are primarily located in the caudal region of the spinal cord (lumbar and conus medullaris) but have rarely been reported intracranially. In the 2021 WHO classification, myxopapillary ependymomas were upgraded from grade 1 to grade 2 due to high local recurrence rates, despite the lack of clinical utility in molecular subtyping (6). These tumors are most frequently observed in the conus medullaris and filum terminale. In pediatric patients, the risk of cerebrospinal fluid (CSF) dissemination is higher compared to adults (10).

**Clinical Presentation**

The average symptom duration prior to diagnosis ranges from 3 to 6 months. Clinical manifestations vary depending on tumor location. Supratentorial ependymomas most often present with seizures (45.2%), headache (39.7%), and motor weakness (9.6%). Approximately 70% of posterior fossa ependymomas originate from the fourth ventricle and foramen of Luschka, causing fourth ventricle obstruction in about 90% of cases. This results in symptoms of increased intracranial pressure, including headache, nausea, vomiting, papilledema, and lethargy (11,12).

When the cerebellum is involved, patients may exhibit imbalance, truncal and limb ataxia, tremor, dysdiadochokinesia, dysarthria, and nystagmus. Brainstem compression may lead to cranial nerve deficits involving CN VI, VII, and IX–XII, dysphagia, dysarthria, hemiparesis or quadriparesis, and respiratory irregularities (13–15).

The most common initial symptom of spinal ependymomas is localized back or neck pain, depending on the tumor's level (16). Due to the slow and nonspecific progression of symptoms, diagnosis is often delayed. Myxopapillary ependymomas involving the terminal spinal cord regions may affect ascending and descending tracts, producing low back pain as the primary symptom, while bowel and bladder dysfunctions occur in approximately 30% of cases (17,18).

## Radiology

### Brain Computorize Tomography (CT)

Ependymomas often appear as cystic, calcified, and well-circumscribed lesions. They may be isodense or hyperdense relative to brain parenchyma on computed tomography (CT). Calcifications are observed in approximately 50% of cases. Hemorrhage and calcified foci typically appear hyperdense (19).

### Magnetic Resonance Imaging (MRI)

Due to intracellular myxoid accumulation and cyst formation, ependymomas demonstrate low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and intermediate-to-high signal intensity on FLAIR sequences compared to brain parenchyma (20). On contrast-enhanced MRI, these tumors frequently display heterogeneous enhancement, and diffusion-weighted imaging (DWI) may reveal high signal intensity. Increased vascularity often results in low apparent diffusion coefficient (ADC) values. Proton MR spectroscopy typically shows elevated choline levels and reduced N-acetylaspartate (NAA) levels (21). Increased myoinositol levels support the diagnosis of ependymoma over other tumors such as medulloblastoma or hemangioblastoma (22). Spectroscopy is more useful in differentiating radionecrosis from recurrence rather than distinguishing ependymomas from other tumor types (23).

Perfusion MRI is valuable for characterizing ependymomas, monitoring treatment response, and detecting recurrence (24). Spinal ependymomas are usually intramedullary and often associated with syringomyelia (25). They appear isointense or hypointense on T1-weighted images and hyperintense on T2-weighted images. A low T2 signal intensity area known as the “cap sign” may be observed above or below the tumor due to hemosiderin deposition from chronic bleeding (26). Myxopapillary ependymomas typically exhibit isointense signal on T1-weighted and hyperintense signal on T2-weighted images (18). Their location in the conus medullaris with marked contrast enhancement is an important radiologic finding supportive of the diagnosis (25).

Subependymomas appear isointense to hypointense on T1-weighted images and hyperintense on T2-weighted images, but their signal distribution is more homogeneous than ependymomas. They usually show minimal contrast enhancement and no restriction on DWI. Due to low vascularity, relative cerebral blood volume (rCBV) on perfusion MRI is lower than in ependymomas (27,28).

**Differential Diagnosis**

The differential diagnosis of supratentorial ependymomas includes central neurocytoma, microcystic meningioma, astrocytoma, and glioblastoma multiforme. For posterior fossa ependymomas, astrocytoma, medulloblastoma, and cerebral neuroblastoma are primary considerations. The differential diagnosis of spinal ependymomas includes astrocytoma, metastatic tumors, exophytic/extramedullary schwannomas, and filum terminale paragangliomas. Additional differential diagnoses include abscess, encephalitis, arteriovenous malformations, cavernous malformations, and hemorrhage (29).

**Treatment**

Surgery remains the first and most critical step in the standard management of adult intracranial ependymomas.Numerous studies have identified the extent of resection as one of the most important prognostic factors (1,30,31). Gross total resection (GTR)—defined as the absence of residual tumor on post-contrast T1- and T2-weighted MRI obtained three months postoperatively—and infratentorial location are associated with longer survival (32,33). Conversely, incomplete (subtotal) resection is linked to a higher risk of tumor recurrence and cerebrospinal fluid (CSF) dissemination. In posterior fossa lesions, tumor encasement of cranial nerves and brainstem vasculature may limit the feasibility of complete removal (31).

Ependymomas arising in the third or fourth ventricles may cause secondary hydrocephalus by obstructing CSF pathways, while those in the lateral ventricles can obstruct the Foramen of Monro, resulting in ventricular dilatation. Because these tumors often grow slowly, acute symptoms are uncommon. Complete resection typically restores normal CSF flow, thereby resolving obstructive hydrocephalus and obviating the need for additional CSF diversion in most cases. If hydrocephalus persists postoperatively, procedures such as shunting or endoscopic third ventriculostomy may be necessary.

Historically, craniospinal irradiation was widely employed in ependymoma management. However, subsequent evidence has demonstrated that localized radiotherapy provides effective local control with a low risk of spinal dissemination. In adults, there is general agreement that postoperative radiotherapy should be administered in WHO Grade III tumors and in WHO Grade II tumors following incomplete resection (32,33). The role of radiotherapy after GTR in WHO Grade II ependymomas remains controversial (34).

Intracranial subependymomas are rare WHO Grade I tumors. Long-term survival is generally expected after resection; however, ill-defined tumor margins are associated with reduced survival (35).

In pediatric patients, more than half of all ependymomas occur before the age of three (36). Surgery and radiotherapy are the primary treatment modalities, and postoperative radiotherapy improves local control and survival. For children older than three years, a total dose of 59.4 Gy (1.8 Gy/fraction) is recommended. Dose reduction to 54 Gy is advised in patients with impaired neurological status or in those under 18 months of age, with further reductions possible between 12–18 months (37). Nonetheless, recurrence frequently occurs within the irradiated field, even with standard dosing, underscoring the importance of local control (38). For cases of subtotal resection, hypofractionated stereotactic boosts have been proposed in addition to conventional radiotherapy.

Radiotherapy toxicity remains a major concern in young children. Intensity-modulated radiotherapy (IMRT) is preferred to reduce late sequelae. Merchant et al. demonstrated that radiation dose is the most significant predictor of post-treatment intelligence quotient (IQ), with even doses below 20 Gy to the supratentorial region negatively impacting cognitive function (39).

The role of chemotherapy in pediatric ependymomas remains uncertain. In very young children, chemotherapy is often used to delay or avoid radiotherapy due to its long-term adverse effects; in older children, it is generally used as an adjuvant to radiotherapy. Radiotherapy-deferral strategies using chemotherapy have largely been abandoned in patients older than 12 months (40).

In spinal ependymomas, gross tumor resection (GTR) is also a major prognostic determinant. Advances in microsurgical techniques now allow en bloc GTR in most cases, with favorable functional outcomes. Early surgery is recommended. Postoperative local radiotherapy is generally reserved for cases where GTR is not feasible, and subtotal resection(STR) followed by radiotherapy significantly improves progression-free survival (PFS). While the optimal dose is debated, doses exceeding 50 Gy may be beneficial (41,42).

**Prognostic Factors**

1. Extent of Surgical Resection:

The most influential prognostic factor is the completeness of resection. Five-year survival rates range from 67–85% after GTR, compared to 30–50% after subtotal resection. Five-year PFS is 43–64%, and ten-year PFS is 24–53% (21).

2. Tumor Grade:

Histopathological grade strongly impacts prognosis. Five-year survival is approximately 71% for WHO Grade II tumors and 57% for Grade III tumors. Recurrence rates in supratentorial Grade II tumors are around 12%, increasing to 46% in Grade III lesions.

3. Tumor Location:

Supratentorial ependymomas are often of the RELA fusion–positive subtype, which is aggressive and associated with high recurrence. YAP1 fusion tumors have a more favorable prognosis.

Infratentorial ependymomas predominate in children. Complete resection is challenging due to proximity to the brainstem and cranial nerve nuclei, and incomplete removal is linked to worse outcomes. Among molecular subtypes, PF-A tumors have poorer prognosis than PFB, with ten-year survival around 56% (43).

Spinal ependymomas (usually WHO Grade II) are most amenable to total resection and generally require less adjuvant radiotherapy. 10 year survival is approximately 85%.

4. Age:

Adults generally have a more favorable prognosis than children, with ten-year survival rates of ~75% compared to 64% in pediatric patients.

5. Adjuvant Therapy:

Radiotherapy plays a key role in extending disease-free survival, particularly in high-grade or incompletely resected tumors. The role of chemotherapy remains limited and is primarily adjunctive.

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