# High-grade glioma

High-grade gliomas (HGG) are a group of aggressive, fast-growing primary brain tumors that arise from glial cells in the central nervous system (CNS). They are defined by the World Health Organization (WHO) as **grade 3 or grade 4** gliomas, based on histological and molecular features.

## Classification

High-Grade Glioma Classification

## Histological Features

- High mitotic index
- Cellular and nuclear atypia
- Endothelial proliferation
- Tumor necrosis (especially in grade 4)

## Molecular Features

Modern classification incorporates genetic and epigenetic markers:

- **IDH mutation status** (IDH-wildtype = more aggressive)
- **1p/19q codeletion** (defines oligodendrogliomas)
- **ATRX**, **TP53**, **TERT**, **EGFR**, **H3 K27M** mutations
- **Methylation profiling** (used for refined diagnosis)

## Clinical Behavior

- Rapid growth and progression
- Poor response to treatment
- Glioblastoma median survival: **12–18 months** with standard therapy

## Treatment Approaches

- **Surgical resection** (maximal safe)
- **Radiotherapy**
- **Chemotherapy** (e.g., temozolomide)
- **Targeted therapy** and **clinical trials** (guided by molecular profiling)

**Summary**: High-grade gliomas are defined as WHO grade 3 or 4 CNS tumors with aggressive biological behavior, poor prognosis, and increasing reliance on molecular diagnostics for classification and treatment planning.

# Prospective Observational Cohort Studies

In a Prospective Observational Cohort Study 50 adolescent and young adult (AYA) high grade gliomas (HGG) aged 12-29 with newly diagnosed or recurrent HGG and other high risk central nervous system (CNS) tumours were prospectively recruited to the EORTC SPECTA platform study and underwent whole exome sequencing, RNA sequencing and methylation profiling, with central pathological review. Actionable mutations were reported and patients followed up for therapies and outcome.

From 46 locally diagnosed HGGs and 4 other recurrent CNS tumours, molecular and pathology review resulted in histological grade re-classification (n = 10), diagnostic refinement (n = 9), and revised diagnoses (n = 12) in a substantial proportion. Pathogenic constitutional alterations were present in 14 % overall and were largely limited to cases with IDH-wildtype glioblastoma and paediatric-type diffuse HGGs. 91 % of HGGs had potentially actionable alterations affecting RAS/RAF/MAPK (60 %), PI3K/AKT/mTOR (27 %), and cell cycle genes (11 %). High tumour mutational burden (> 10 somatic non-synonymous mutations per Mb of genome targeted) was present in 12 % at diagnosis and 18 % at recurrence, all in histological grade 4 tumours. Ten patients were modified based on molecular profile, of whom 5 remained on treatment at last follow-up.

AYAs HGGs comprise a diverse group of entities; accurate, molecularly-defined diagnosis is critical to direct primary treatment, determine risk of genetic predisposition, and guide molecularly-directed therapy. Current services fail to routinely address diagnosis, personalised molecular profiling, or investigation of therapeutic opportunities for this high-risk, poor-prognosis group of rare cancer patients [1)].

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Its prospective design, multi-institutional collaboration through the EORTC SPECTA platform, and incorporation of cutting-edge molecular profiling (whole exome sequencing, RNA-seq, and methylation analysis) mark substantial methodological strengths. Central pathological review enhances diagnostic accuracy and reproducibility.

Key strengths include:

Comprehensive molecular profiling, enabling nuanced biological understanding.

Central pathology review, allowing detection of misclassification at local centers.

Clinical translation, with a subset of patients receiving molecularly-informed treatment.

Key Findings and Clinical Relevance Reclassification or diagnostic refinement occurred in a striking proportion of cases:

Grade reclassification in 20% (10/50)

Diagnostic refinement in 18%

Revised diagnoses in 24% These numbers underscore the inadequacy of conventional histology alone

in this age group and justify routine molecular characterization.

High rate of actionable mutations (91%) in key oncogenic pathways (RAS/RAF/MAPK, PI3K/AKT/mTOR, and cell cycle genes) highlights the potential for targeted therapies even in historically intractable tumors like HGGs.

Germline pathogenic variants were found in 14%, suggesting a non-negligible hereditary predisposition in this age group and the importance of genetic counseling.

Treatment modification based on molecular results occurred in 10/50 patients (20%), with half maintaining disease control—demonstrating direct translational impact.

Limitations Despite its strengths, several limitations deserve attention:

Small sample size (n = 50), limiting statistical power and generalizability.

Selection bias may exist due to enrollment in specialized centers within the EORTC framework, potentially skewing toward more complex or ambiguous cases.

The diversity of included tumors (not only classic HGGs but also “other high-risk CNS tumors”) may dilute disease-specific insights.

The study lacks a control group or comparator cohort, so the relative utility of molecular profiling versus standard care remains inferential.

Clinical outcomes were modestly explored: only 5 patients showed benefit from targeted therapy, and long-term survival impact remains unclear.

Cost-effectiveness and real-world feasibility of implementing such advanced profiling in routine AYA oncology practice are not addressed.

Implications and Future Directions The SPECTA-AYA study powerfully argues for routine molecular profiling and centralized diagnostic review in AYA HGGs, a group that historically falls into a diagnostic gray zone between pediatric and adult neuro-oncology paradigms. It also reinforces the heterogeneity of AYA gliomas and challenges the reflexive application of adult glioblastoma treatment algorithms to this population.

Future work should aim to:

Expand cohorts to validate findings in broader populations.

Integrate longitudinal outcome tracking to assess the true clinical benefit of molecular-guided interventions.

Define cost-effectiveness thresholds and streamlined diagnostic pathways for implementation in diverse healthcare systems.

Conclusion This study is a significant contribution to the field of neuro-oncology and adolescent medicine. It demonstrates how precision oncology approaches, even in rare and aggressive CNS tumors, can refine diagnosis and occasionally guide effective treatment. However, its findings also expose gaps in access, infrastructure, and long-term data that must be addressed to translate these insights into routine care.

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Morfouace M, Bielle F, Razis E, Estrade F, Rubio A, Bautista F, de Rojas T, Vieito M, Meade S, Sanson M, Marques AC, Preusser M, Hatcher H, Balasubramanian GP, Pineda E, D'Hondt L, Duerinck J, Michotte A, Mawrin C, Ribalta T, Marucci G, Golfinopoulos V, Pfister SM, Jones DT, McCabe MG. Molecular analysis of adolescent and young adult high grade gliomas in the SPECTA-AYA study: Poorly characterised tumours with frequent germline alterations. Eur J Cancer. 2025 May 13;223:115493. doi: 10.1016/j.ejca.2025.115493. Epub ahead of print. PMID: 40393126.