COMPREHENSIVE REVIEW OF ASTROCYTOMA: EPIDEMIOLOGY, MOLECULAR CLASSIFICATION, DIAGNOSIS, SURGICAL MANAGEMENT, ADJUVANT THERAPIES, AND PROGNOSIS

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Abstract

Background: Astrocytomas constitute the most prevalent group of primary brain neoplasms arising from astrocytic glial cells. The 2021 World Health Organization (WHO) Classification of Tumours of the Central Nervous System (CNS) introduced a paradigm shift by integrating molecular diagnostics with histopathology, fundamentally reorganising how astrocytomas are defined, graded, and managed.

Objectives: To provide a comprehensive, evidence-based synthesis of astrocytoma epidemiology, molecular pathogenesis, diagnosis, surgical management, adjuvant therapies, prognosis, and emerging trends, integrating contemporary original research.

Methods: A systematic literature search was conducted across PubMed/MEDLINE, Scopus, and Cochrane Library. Priority was given to high-quality original studies, systematic reviews, and meta-analyses.

Results: Extent of surgical resection (EOR) is the most consistently demonstrated independent prognostic factor across all astrocytoma grades. For anaplastic astrocytoma (grade 3), GTR conferred significantly improved overall survival versus subtotal resection or biopsy in both retrospective and systematic review analyses. Case-based evidence in glioblastoma further reinforces the survival impact of maximal resection.

Conclusion: Astrocytoma management demands individualised, molecularly guided, and surgically aggressive strategies.

Keywords: astrocytoma; extent of resection; glioblastoma; glioma

КОМПЛЕКСНЫЙ ОБЗОР АСТРОЦИТОМЫ: ЭПИДЕМИОЛОГИЯ, МОЛЕКУЛЯРНАЯ КЛАССИФИКАЦИЯ, ДИАГНОСТИКА, ХИРУРГИЧЕСКОЕ ЛЕЧЕНИЕ, АДЪЮВАНТНАЯ ТЕРАПИЯ И ПРОГНОЗ

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Аннотация

Введение: Астроцитомы представляют собой наиболее распространенную группу первичных новообразований головного мозга, возникающих из астроцитарных глиальных клеток. Классификация опухолей центральной нервной системы (ЦНС) Всемирной организации здравоохранения (ВОЗ) 2021 года внесла кардинальные изменения, интегрировав молекулярную диагностику с гистопатологией, что коренным образом изменило подход к определению, классификации и лечению астроцитом.

Цели: Представить всесторонний, основанный на доказательствах анализ эпидемиологии, молекулярного патогенеза, диагностики, хирургического лечения, адъювантной терапии, прогноза и новых тенденций в области астроцитомы, интегрируя современные оригинальные исследования.

Методы: Был проведен систематический поиск литературы в базах данных PubMed/MEDLINE, Scopus и Cochrane Library. Приоритет отдавался высококачественным оригинальным исследованиям, систематическим обзорам и метаанализам.

Результаты: Объем хирургической резекции (ОХР) является наиболее последовательно демонстрируемым независимым прогностическим фактором для всех степеней астроцитомы. Для анапластической астроцитомы (3-я степень) полная резекция (ПТО) обеспечивала значительно улучшенную общую выживаемость по сравнению с субтотальной резекцией или биопсией как в ретроспективном анализе, так и в систематическом обзоре. Данные, полученные на основе клинических случаев глиобластомы, дополнительно подтверждают влияние максимальной резекции на выживаемость.

Заключение: Лечение астроцитомы требует индивидуализированных, молекулярно-ориентированных и хирургически агрессивных стратегий.

Ключевые слова: астроцитома; объем резекции; глиобластома; глиома

1. Introduction

Astrocytomas are the most common primary intrinsic brain neoplasms in adults, encompassing a biological spectrum from the surgically curable pilocytic astrocytoma (WHO grade 1) to the rapidly lethal glioblastoma (WHO grade 4). Despite decades of research, high-grade variants remain among the most therapeutically refractory of all human cancers. The management of astrocytoma has been transformed by two parallel revolutions: the molecular reclassification of gliomas under the 2021 WHO CNS5 framework [12], and the accumulating evidence that maximal safe surgical resection independently prolongs survival across the entire disease spectrum [4, 5, 7].

The diagnosis and management of astrocytoma at every WHO grade — from an umbrella literature review of the disease [1], through dedicated reviews of pilocytic [2] and low-grade diffuse [3] subtypes, to original retrospective and meta-analytic studies examining the prognostic impact of extent of resection in grades 2, 3, and 4 [4–10], and a case study of pilomyxoid astrocytoma [11]. This manuscript synthesises their findings alongside major international evidence to provide a comprehensive, contemporary review.

In the United States, the Central Brain Tumor Registry (CBTRUS) reports that IDH-mutant astrocytoma has an age-adjusted incidence of 0.45 per 100,000, with a median age at diagnosis of 37 years; IDH-wildtype (glioblastoma) is far more common, at 2.66 per 100,000, with a median age of 65 years [13]. Globally, gliomas account for approximately 80% of malignant primary brain tumours; astrocytomas constitute the largest histological subgroup [14]. The five-year survival rate for glioblastoma remains below 10% despite aggressive multimodal therapy, underscoring the continued clinical urgency of this field.

The 2021 WHO CNS5 classification radically reorganised glioma taxonomy by mandating integrated histomolecular diagnosis [12]. IDH mutation status now serves as the primary bifurcation point: IDH-mutant tumours with astrocytic morphology are unified as 'astrocytoma, IDH-mutant' across grades 2–4, while IDH-wildtype infiltrating astrocytomas with high-grade molecular features are reclassified as 'glioblastoma, IDH-wildtype'. The term 'anaplastic astrocytoma' has been retired. These changes have direct clinical implications, as IDH status is the strongest single prognostic determinant in diffuse glioma.

2. Molecular Classification and Pathogenesis

2.1 The 2021 WHO CNS5 Framework

The fifth edition WHO Classification of Tumours of the Central Nervous System (2021) elevated molecular markers to definitional, rather than ancillary, diagnostic criteria for diffuse glioma [12]. As Chaulagain and colleagues outlined in their comprehensive review of low-grade diffuse astrocytoma [3], the core diagnostic markers for astrocytoma, IDH-mutant include IDH1/2 mutation, ATRX loss, and TP53 mutation — a triad that distinguishes IDH-mutant astrocytoma from the 1p/19q-codeleted oligodendroglioma on one hand and IDH-wildtype glioblastoma on the other. Under WHO CNS5, grading is performed within tumour type rather than across all glioma types, and Arabic numerals replace Roman numerals. The key practical change is that IDH-mutant tumours are graded 2, 3, or 4 within the astrocytoma category; histological grade 4 can now be assigned to IDH-mutant tumours based solely on CDKN2A/B homozygous deletion, even without necrosis or microvascular proliferation [12, 15].

2.2 IDH Mutations: Pathobiology and Prognostic Significance

Mutations in isocitrate dehydrogenase 1 or 2 (IDH1/2) are the founding molecular events in low- and intermediate-grade diffuse glioma. The IDH1 R132H substitution accounts for ~90% of IDH mutations in adult glioma; non-canonical IDH1 and IDH2 mutations constitute the remainder. Mutant IDH enzymes produce the oncometabolite D-2-hydroxyglutarate (2-HG), which inhibits alpha-ketoglutarate-dependent dioxygenases including TET2 and histone demethylases, driving a CpG island methylator phenotype (CIMP) and widespread epigenetic reprogramming that underpins gliomagenesis [15].

2.3 ATRX, TP53, and 1p/19q Status

ATRX loss and TP53 mutation characterise IDH-mutant astrocytoma and differentiate it from IDH-mutant oligodendroglioma (which shows 1p/19q codeletion rather than ATRX inactivation). As described in Chaulagain's low-grade diffuse astrocytoma review [3], ATRX loss enables the alternative lengthening of telomeres (ALT) pathway, contributing to chromosomal instability; TP53 mutation further impairs cell cycle checkpoint function, facilitating oncogenic progression. These markers are routinely assessed by immunohistochemistry in neuropathology practice and guide both diagnosis and differential diagnosis.

2.4 CDKN2A/B Deletion and Grade 4 Designation

One of the most clinically significant innovations of WHO CNS5 is the assignment of grade 4 status to IDH-mutant astrocytomas with homozygous CDKN2A/B deletion, even when histological high-grade features (necrosis, microvascular proliferation) are absent [12]. CDKN2A encodes p16INK4A and p14ARF, critical inhibitors of the G1/S cell cycle transition and MDM2-p53 axis, respectively; their loss confers aggressive proliferative capacity equivalent to histologically grade 4 disease [15].

2.5 Glioblastoma, IDH-Wildtype

Glioblastoma, IDH-wildtype, is defined by classic histological features (necrosis, microvascular proliferation) or by specific molecular alterations: TERT promoter mutation, EGFR amplification, or combined +7/−10 chromosomal signature [12]. As Chaulagain and colleagues detail in their glioblastoma literature review [8], GBM accounts for roughly 15% of all brain tumours and is predominantly found in adults over 50 years of age, with males more frequently affected. MGMT promoter methylation — found in approximately 40–45% of GBMs — is the most important predictive biomarker, correlating strongly with benefit from temozolomide chemotherapy. The aggressive tumour microenvironment, intratumoral heterogeneity, and capacity for rapid recurrence contribute to the uniformly poor prognosis despite multimodal therapy [8].

2.6 Pilocytic and Pilomyxoid Astrocytoma

Pilocytic astrocytoma (PA, WHO grade 1) is biologically distinct from diffuse astrocytomas. As Chaulagain's dedicated literature review details [2], it was first described by Harvey Cushing in 1931 based on a series of cerebellar astrocytomas. Its hallmark molecular alteration is the BRAF-KIAA1549 tandem duplication producing constitutive MAP kinase pathway activation; the BRAF V600E point mutation is also found, particularly in extracerebral locations. Pilocytic astrocytoma carries a favourable prognosis — WHO grade 1 by definition — and gross total resection is essentially curative. Pilomyxoid astrocytoma (PMA) is a variant with more aggressive biological features, including a propensity for CSF dissemination and higher recurrence rates after subtotal resection. Chaulagain and colleagues documented an illustrative case of pilomyxoid astrocytoma in which the extent of resection directly influenced surgical outcome, consistent with the broader evidence that maximal removal is the primary therapeutic goal even in this variant [11].

Table 1. WHO CNS5 Classification of Astrocytoma by Grade, Molecular Profile, and Prognosis

WHO Grade	Tumour Type	IDH Status	Key Molecular Markers	Median OS
Grade 1	Pilocytic Astrocytoma	Wild-type	BRAF-KIAA1549 fusion; BRAF V600E	>10 yrs (GTR curative)
Grade 2	Astrocytoma, IDH-mutant	Mutant	IDH1/2 mut; ATRX loss; TP53 mut	~8–12 years
Grade 3	Astrocytoma, IDH-mutant	Mutant	IDH1/2 mut; ATRX loss; mitoses; TP53 mut	~4–6 years
Grade 4 (IDH-mut)	Astrocytoma, IDH-mutant	Mutant	IDH1/2 mut + CDKN2A/B homodeletion, or necrosis/MVP	~2–3 years
Grade 4 (IDH-wt)	Glioblastoma, IDH-wildtype	Wild-type	TERT mut; EGFR amp; +7/−10; PTEN loss	~14–16 months

Abbreviations: GTR, gross total resection; IDH, isocitrate dehydrogenase; mut, mutant; del, deletion; MVP, microvascular proliferation; OS, overall survival; PA, pilocytic astrocytoma; GBM, glioblastoma.

3. Clinical Presentation and Diagnosis

3.1 Symptoms and Clinical Features

The clinical presentation of astrocytoma is strongly conditioned by grade, tumour location, and growth rate. Chaulagain's 2022 umbrella review [1] identified four principal astrocytoma types: pilocytic astrocytoma, grade 2 astrocytoma, anaplastic astrocytoma (now grade 3 IDH-mutant astrocytoma), and glioblastoma multiforme. The clinical appearance and diagnostic approach differ substantially among these subtypes.

Low-grade astrocytomas (WHO 2–3) typically present insidiously with new-onset seizures, which occur in 65–90% of cases and often precede diagnosis by months to years [3]. Progressive focal neurological deficits, headache from raised intracranial pressure, and cognitive changes are common additional features. As Chaulagain's review of anaplastic astrocytoma context describes [7], grade 3 tumours present at a mean age of 41 years with focal or generalised seizures, progressive cognitive deterioration, and headache; blurred vision may also feature depending on tumour location. Glioblastoma typically manifests with a shorter and more dramatic symptom trajectory due to rapid growth; headache, focal deficits, personality change, and features of raised intracranial pressure are cardinal presentations [8]. Pilocytic astrocytoma in children commonly presents with hydrocephalus, ataxia, or visual disturbance depending on location — most frequently the cerebellum in the paediatric population [2].

3.2 Neuroimaging

Magnetic resonance imaging (MRI) remains the gold standard for diagnosis, pre-operative planning, and post-operative surveillance. Low-grade diffuse astrocytomas appear as homogeneous T2/FLAIR hyperintense lesions without contrast enhancement. Glioblastoma classically exhibits heterogeneous ring enhancement, central necrosis, and extensive peritumoral oedema on MRI [8]. Pilocytic astrocytoma appears characteristically as a cystic lesion with an enhancing mural nodule, most commonly in the cerebellum [2].

Advanced MRI sequences — including MR spectroscopy (elevated choline/NAA ratio, 2-HG peak in IDH-mutant tumours), perfusion MRI (elevated rCBV in high-grade areas), and amino acid PET (MET-PET, FET-PET) — further characterise biological tumour volume and grade, and guide biopsy targeting and radiation treatment planning [16].

3.3 Pathological Diagnosis and Molecular Profiling

Histopathological diagnosis, supplemented by comprehensive molecular profiling, is mandatory before definitive treatment. Chaulagain's comprehensive low-grade diffuse astrocytoma review [3] outlines the fundamental role of surgical biopsy or resection in providing tissue for both histological and molecular characterisation. The minimum diagnostic panel under WHO CNS5 includes IDH1 R132H immunohistochemistry (with sequencing for non-canonical mutations if IHC-negative), ATRX and p53 IHC, 1p/19q codeletion testing, TERT promoter sequencing, EGFR amplification and +7/−10 assessment, and CDKN2A/B deletion by FISH or array CGH. For all grades 3 and 4 tumours, MGMT promoter methylation is assessed for therapeutic guidance [12, 15].

4. Surgical Management

4.1 Principles and Goals

Surgery for astrocytoma serves three interlinked purposes: diagnostic tissue acquisition, symptom relief through mass reduction, and — when achievable — survival benefit through maximal tumour removal. As explicitly addressed across Chaulagain's surgical publications

[4–10], the principle of maximal safe resection is now endorsed as the surgical standard for all resectable astrocytomas. The tension between oncological radicality and preservation of neurological function is managed through modern intraoperative technologies and careful pre-operative functional mapping.

4.2 Low-Grade Astrocytoma (WHO Grade 2): Evidence for EOR

The prognostic value of EOR in low-grade astrocytoma has been definitively quantified by Chaulagain and colleagues in a systematic review and meta-analysis analysing five cohort studies [4]. This analysis demonstrated that gross total resection was associated with a statistically significant reduction in mortality risk versus subtotal resection (HR 0.70, 95% CI 0.52–0.94; p=0.02). This finding establishes GTR as an independent prognostic factor at grade 2, independent of adjuvant therapy effects.

Patients undergoing gross total resection achieved median overall survival in the range of 84–120 months — substantially exceeding outcomes with subtotal resection — confirming the meta-analytic HR estimates with direct longitudinal outcome data. These findings are consistent with international landmark trials including EORTC 22845 and RTOG 9802, which established that early surgical intervention and adjuvant chemoradiotherapy significantly delay progression in high-risk low-grade glioma [17].

4.3 Pilocytic Astrocytoma (WHO Grade 1): EOR and Cure

For pilocytic astrocytoma, gross total resection is the primary curative modality. Chaulagain's literature review of pilocytic astrocytoma [2] emphasises that GTR results in long-term progression-free survival exceeding 90% in the majority of patients. Subtotally resected cerebellar tumours may remain stable over extended periods, while those in the optic pathway and hypothalamus carry a higher risk of progression due to the technical impossibility of complete resection in eloquent regions. These observations align with large population-based analyses demonstrating GTR as the dominant prognostic factor for pilocytic astrocytoma across all age groups [22].

4.4 Anaplastic Astrocytoma (WHO Grade 3): EOR Evidence

Anaplastic astrocytoma (now classified as astrocytoma, IDH-mutant, grade 3 under WHO CNS5) represents only 6% of CNS malignancies but carries substantially reduced survival compared to grade 2 disease [7]. In a retrospective single-centre study at Uzhhorod Regional Clinical Center, Chaulagain and colleagues evaluated the relationship between EOR, tumour volume, and overall survival in anaplastic astrocytoma [5]. This study found that both EOR and tumour volume were significant determinants of overall survival, with patients achieving gross total resection experiencing better outcomes than those undergoing subtotal resection or biopsy only.

4.5 Glioblastoma (WHO Grade 4): Maximal Resection Evidence

As Chaulagain's glioblastoma literature review [8] outlines, glioblastoma is the most aggressive primary brain tumour in adults, with rapid recurrence and dismal prognosis despite multimodal treatment. The first [9] documents the impact of gross total resection on survival in an individual patient with glioblastoma, demonstrating through longitudinal follow-up the survival advantage conferred by complete contrast-enhancing tumour removal and providing illustrative clinical context for the meta-analytic data. The second [10] examines the outcome of subtotal resection in glioblastoma, offering a comparative case study perspective that reinforces the importance of maximising resection extent even when GTR is not achievable.

A systematic review and meta-analysis by Brusniak and colleagues, evaluating 14 studies encompassing 6,779 patients, demonstrated that supramaximal resection (removal beyond the contrast-enhancing margin) was associated with significantly improved progression-free survival (HR 0.67; p=0.0007) and overall survival (HR 0.70; p=0.0001) compared to gross total resection of the contrast-enhancing tumour alone [18]. These findings established a new paradigm of oncological radicality for glioblastoma surgery.

4.6 Intraoperative Technologies

The technological toolkit enabling maximal safe resection has expanded substantially. Fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) was validated in a phase III randomised controlled trial (Stummer et al., 2006) as significantly improving rates of complete contrast-enhancing tumour removal in glioblastoma, and is now standard of care in many high-volume neuro-oncology centres [19]. Intraoperative MRI (iMRI) provides real-time residual tumour assessment, reducing residual volumes by 30–40% compared to navigation alone. Awake craniotomy with intraoperative stimulation mapping enables resection to the functional boundary in eloquent cortex, maximising EOR while preserving language and motor function. Diffusion tensor imaging (DTI) tractography facilitates pre-operative white matter tract delineation and integrates with neuronavigation to guide surgical trajectories [16].

Table 2. Summary of Extent of Resection Evidence by Astrocytoma Grade

Grade	Resection	OS Effect	PFS Effect	Source
1 (PA)	GTR vs STR	HR significantly improved	Superior with GTR	Chaulagain et al. [4]; Kim et al. [22]
2	GTR vs STR	HR 0.70 (p=0.02)	Improved	Chaulagain et al. [4] (meta-analysis)
2	GTR (long-term)	Median OS 84–120 mo	~60 months	Chaulagain et al. [6] (retrospective)
3	GTR vs STR/Biopsy	GTR significantly improved	Improved	Chaulagain et al. [5,7] (retrospective/SR)
4 (GBM)	GTR vs STR	Impact demonstrated	Improved	Chaulagain et al. [9,10] (case reports)
4 (GBM)	SMR vs GTR	HR 0.70 (p<0.001)	HR 0.67 (p=0.0007)	Brusniak et al. [18] (meta-analysis, n=6,779)
Pilomyxoid	EOR impact	GTR superior	Reduced recurrence	Chaulagain et al. [11] (case study)

Abbreviations: PA, pilocytic astrocytoma; GTR, gross total resection; STR, subtotal resection; SMR, supramaximal resection; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; SR, systematic review;

5. Adjuvant Therapies

5.1 Radiotherapy

Radiotherapy is central to adjuvant management for grades 3 and 4 astrocytoma. The current standard for glioblastoma remains the Stupp protocol: 60 Gy in 30 fractions over six weeks, delivered concurrently with daily temozolomide, followed by six adjuvant temozolomide cycles [20]. The landmark 2005 EORTC/NCIC trial demonstrated a median OS improvement from 12.1 months (RT alone) to 14.6 months (RT + TMZ), with the two-year survival rate

rising from 10.4% to 26.5%. Updated five-year analysis confirmed 9.8% five-year survival, concentrated in MGMT-methylated patients [20].

For grade 3 IDH-mutant astrocytoma, radiotherapy (54–59.4 Gy) combined with PCV or temozolomide chemotherapy is recommended. The CATNON trial (EORTC 26053-22054) established a significant overall survival benefit from adjuvant temozolomide in grade 3 non-codeleted glioma (HR 0.64; p=0.0014), providing the strongest randomised evidence base for this patient population [21]. The role of radiotherapy in pilocytic astrocytoma is generally limited, reserved for subtotally resected or progressive tumours, particularly in the optic pathway and brainstem [2].

5.2 Temozolomide Chemotherapy

Temozolomide (TMZ) is an oral alkylating agent that methylates the O6 position of guanine, inducing mismatch repair-mediated cell death. As Chaulagain's glioblastoma review [8] describes, TMZ's efficacy is profoundly modulated by MGMT promoter methylation status. Methylated tumours silence MGMT expression, impairing DNA repair and increasing TMZ cytotoxicity — resulting in a median OS of 21.7 months versus 12.7 months in unmethylated GBM [20]. The Stupp protocol (concurrent and adjuvant TMZ) prolongs median survival by 2.5 months compared to RT alone (14.6 vs. 12.1 months), with the 2-year OS rate increasing from 10.4% to 26.5% [20].

5.3 Tumour Treating Fields

Tumour Treating Fields (TTFields; Optune, Novocure) deliver intermediate-frequency alternating electric fields via transducer arrays applied to the scalp. The EF-14 phase 3 randomised trial demonstrated that addition of TTFields to adjuvant TMZ improved median PFS (6.7 vs. 4.0 months) and OS (20.9 vs. 16.0 months) compared to TMZ alone, with HR 0.63 for both endpoints [23]. These technological advances, combined with the continued surgical emphasis on maximal resection documented across Chaulagain's work [5, 7, 9, 10], illustrate the multimodal nature of contemporary glioblastoma management.

5.4 Targeted Therapies and Immunotherapy

Vorasidenib (an IDH1/2 inhibitor) demonstrated a significant improvement in progression-free survival (HR 0.39; p<0.001) versus placebo in grade 2 IDH-mutant glioma in the INDIGO trial, marking the first positive randomised trial for low-grade glioma in decades [24]. This development is directly relevant to the patient populations studied in Chaulagain's grade 2 and low-grade reviews [C3, C4, C6], offering a new systemic treatment option for IDH-mutant astrocytomas following surgery. For BRAF V600E-mutant pilocytic and related astrocytomas — as described in Chaulagain's pilocytic review [2] — BRAF/MEK inhibitor combinations (dabrafenib + trametinib) have shown robust response rates in paediatric and young adult patients.

6. Prognosis and Outcomes

Prognosis in astrocytoma is determined by a convergence of molecular, clinical, and surgical factors. The dominant prognostic hierarchy is: (1) IDH mutation status, (2) WHO grade, (3) MGMT promoter methylation (for grades 3–4), (4) extent of surgical resection, (5) patient age and performance status, and (6) tumour location. Molecular data and EOR evidence from Chaulagain's published works provide a directly applicable framework for understanding the prognosis of patients managed at regional neurosurgical centres.

Glioblastoma carries a median overall survival of approximately 14.6–21.9 months with the Stupp protocol [20], with MGMT methylation conferring a near-doubling of survival (21.7 vs. 12.7 months). One-year relative survival for IDH-wildtype astrocytoma/glioblastoma combined is approximately 48.7%, while IDH-mutant 1p/19q-codeleted oligodendroglioma achieves 96.5% one-year relative survival [13], reflecting the profound biological and prognostic differences between these molecularly defined entities.

7. Emerging Trends and Future Directions

7.1 Liquid Biopsy and Molecular Monitoring

Circulating tumour DNA (ctDNA) from cerebrospinal fluid or peripheral blood offers the prospect of non-invasive, dynamic molecular monitoring. CSF ctDNA can detect IDH mutations, EGFR amplification, and MGMT methylation status with high sensitivity in high-grade astrocytoma. Longitudinal ctDNA monitoring may enable earlier detection of progression and emergence of resistance mutations, potentially guiding adaptive therapeutic decisions.

7.2 Artificial Intelligence in Imaging and Surgery

Machine learning algorithms applied to pre-operative MRI are advancing non-invasive IDH genotyping, MGMT methylation prediction, and CDKN2A deletion detection from conventional imaging sequences. In the surgical domain, AI-assisted intraoperative image analysis combined with hyperspectral imaging may enable automated tumour margin delineation at cellular resolution.

7.3 Novel Therapeutic Targets

Beyond IDH and BRAF inhibition, the FGFR1 mutation and NTRK fusion sub-populations of astrocytoma respond to kinase inhibitors (larotrectinib for NTRK; futibatinib for FGFR1). Oncolytic viral therapy, convection-enhanced delivery of targeted toxins, and CAR-T cell approaches targeting GD2 and IL13Rα2 are in early clinical development. Metabolic targeting strategies exploiting the glutamine dependency of IDH-mutant tumours and the altered lipid metabolism of glioblastoma are mechanistically novel avenues distinct from conventional cytotoxic therapy.

7.4 Personalised and Adaptive Trial Design

The growing understanding of astrocytoma molecular heterogeneity demands personalised therapeutic strategies. Platform trials (GBM AGILE, INSIGhT) using adaptive Bayesian designs allocate treatment based on molecular target rather than histological classification, enabling efficient identification of efficacious agents in molecularly selected sub-populations. The INDIGO trial of vorasidenib in grade 2 IDH-mutant glioma [24] exemplifies this biomarker-driven approach and is directly applicable to the patient populations characterised in Chaulagain's low-grade astrocytoma studies [3, 4, 6].

Conclusion

Astrocytoma encompasses a biologically diverse spectrum of primary brain neoplasms, now best understood through the integrated histomolecular lens of the 2021 WHO CNS5 classification. IDH mutation remains the single most important prognostic determinant, distinguishing a relatively favourable IDH-mutant lineage (grades 2–4) from the rapidly lethal IDH-wildtype glioblastoma.

Adjuvant therapy continues to evolve: the Stupp protocol remains standard for glioblastoma, augmented by Tumour Treating Fields; vorasidenib has transformed the treatment landscape

for grade 2 IDH-mutant astrocytoma; and BRAF/MEK inhibitor combinations offer new options for BRAF-altered pilocytic astrocytomas. Immunotherapy has not yet achieved its potential in glioblastoma, but molecular subtyping and novel delivery strategies continue to be explored. The integration of liquid biopsy, AI-assisted imaging, and adaptive trial platforms promises increasingly precise tumour characterisation and treatment monitoring.

References:

1. Chaulagain D, Smolanka V, Smolanka A. Diagnosis and Management of Astrocytoma: A Literature Review. International Neurological Journal. 2022;18(1):23-29. doi:10.22141/2224-0713.18.1.2022.925
2. Chaulagain D, Smolanka V, Smolanka A. Pilocytic Astrocytoma: A Literature Review. International Neurological Journal. 2022;18(3):39-45. doi:10.22141/2224-0713.18.3.2022.942
3. Chaulagain D, Smolanka V, Smolanka A. A Comprehensive Review of Low-Grade Diffuse Astrocytoma: Characteristics, Molecular Classification and Surgical Treatment. International Neurological Journal. 2022;18(4):39-45. doi:10.22141/2224-0713.18.4.2022.957
4. Chaulagain D, Smolanka V, Smolanka A, Munakomi S, Havryliv T. The Role of Extent of Resection on the Prognosis of Low-Grade Astrocytoma: A Systematic Review and Meta-Analysis. Egyptian Journal of Neurosurgery. 2022;37:19. doi:10.1186/s41984-022-00161-1
5. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. Do Extent of Resection and Tumor Volume Affect the Overall Survival of Anaplastic Astrocytoma? A Retrospective Study from a Single Center. Open Access Macedonian Journal of Medical Sciences. 2022;10(B):2060-2064. doi:10.3889/oamjms.2022.10697
6. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. The Impact of Extent of Resection on the Long-Term Surgical Outcome of Grade II Diffuse Astrocytoma: A Retrospective Study. International Neurological Journal. 2023;19(1). doi:10.22141/2224-0713.19.1.2023
7. Chaulagain D, Smolanka V, Smolanka A, Munakomi S. Impact of Gross-Total Resection Versus Other Extent of Resections for the Overall Survival of Anaplastic Astrocytoma: A Systematic Literature Review. Romanian Neurosurgery. 2023;37(3):333-339. doi:10.33962/roneuro-2023-060
8. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. Glioblastoma: A Literature Review. International Neurological Journal. 2023;19(2). [Uzhhorod National University, Ukraine]
9. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. Case Report: Impact of Gross Total Resection on Survival in Glioblastoma. F1000Research. 2024;13:487. doi:10.12688/f1000research.150065.1
10. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. Exploring the Effect of Subtotal Resection on Survival Outcome in Glioblastoma: A Case Study. [Regional Clinical Center of Neurosurgery and Neurology, Uzhhorod National University, Ukraine, 2025]
11. Chaulagain D, Smolanka V, Smolanka A, Havryliv T. The Impact of Extent of Resection in Surgical Outcome of Pilomyxoid Astrocytoma: A Case Study. Ukrainian Neurosurgical Journal. 2021;27(4):43-48. doi:10.25305/unj.242926
12. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A Summary. Neuro Oncol. 2021;23(8):1231-1251. doi:10.1093/neuonc/noab106
13. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: Primary Brain and Other CNS Tumors Diagnosed in the United States in 2016–2020. Neuro Oncol. 2023;25(Suppl 4):iv1-iv99. doi:10.1093/neuonc/noad149
14. Ostrom QT, Gittleman H, Farah P, et al. CBTRUS Statistical Report: Primary Brain and Other CNS Tumors Diagnosed in the United States in 2017–2021. Neuro Oncol. 2024;26(Suppl 6):vi1-vi55.
15. Brat DJ, Aldape K, Colman H, et al. Grading of Adult Diffuse Gliomas According to the 2021 WHO Classification of Tumors of the Central Nervous System. Laboratory Investigation. 2022;102(2):127-135. doi:10.1038/s41374-021-00681-4
16. Park YW, Ahn SS, Kim EH, et al. Advanced MRI for the Diagnosis and Management of Diffuse Gliomas. Front Oncol. 2023;13:1079965. doi:10.3389/fonc.2023.1079965
17. van den Bent MJ, Afra D, de Witte O, et al. Long-term Efficacy of Early Versus Delayed Radiotherapy for Low-Grade Astrocytoma and Oligodendroglioma in Adults: EORTC 22845 Randomised Trial. Lancet. 2005;366(9490):985-990. doi:10.1016/S0140-6736(05)67070-5
18. Brusniak K, Tomczyk M, Kaczmarek A, et al. Supramaximal versus Gross Total Resection in Glioblastoma IDH-Wildtype and Astrocytoma IDH-Mutant Grade 4: Systematic Review and Meta-Analysis. World Neurosurgery. 2023;179:e46-e55. doi:10.1016/j.wneu.2023.07.124

19. Stummer W, Pichlmeier U, Meinel T, et al. Fluorescence-Guided Surgery with 5-Aminolevulinic Acid for Resection of Malignant Glioma: A Randomised Controlled Multicentre Phase III Trial. Lancet Oncol. 2006;7(5):392-401. doi:10.1016/S1470-2045(06)70665-9
20. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med. 2005;352(10):987-996. doi:10.1056/NEJMoa043330
21. van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and Concurrent Temozolomide for 1p/19q Non-Co-Deleted Anaplastic Glioma (CATNON): Second Interim Analysis. Lancet Oncol. 2021;22(6):813-823. doi:10.1016/S1470-2045(21)00090-5
22. Kim IK, Gittleman H, Ostrom QT, et al. Efficacy of Various Extent of Resection on Survival Rates of Patients with Pilocytic Astrocytoma: Based on a Large Population. Scientific Reports. 2024;14:24812. doi:10.1038/s41598-024-75751-0
23. Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients with Glioblastoma: EF-14 Trial. JAMA. 2017;318(23):2306-2316. doi:10.1001/jama.2017.18718
24. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma (INDIGO Trial). N Engl J Med. 2023;389(7):589-601. doi:10.1056/NEJMoa2304194
25. Weller M, van den Bent M, Preusser M, et al. EANO Guidelines on the Diagnosis and Treatment of Diffuse Gliomas of Adulthood. Nat Rev Clin Oncol. 2021;18(3):170-186. doi:10.1038/s41571-020-00447-z

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