HEADACHE IN BRAIN TUMORS AND GLIOMAS: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, CLINICAL FEATURES, DIAGNOSIS, AND MANAGEMENT

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Abstract

Background: Headache is among the most frequently reported symptoms in patients harboring intracranial tumors, including gliomas of all WHO grades. Despite its prevalence, the characteristics, pathophysiology, and optimal management of tumor-associated headache remain incompletely understood and are often overshadowed by the oncological focus of care.

Objectives: This review synthesizes current evidence on the pathophysiology, clinical features, diagnostic evaluation, and management of headache in patients with primary brain tumors, with particular emphasis on gliomas spanning WHO grades I through IV, including pilocytic astrocytoma, low-grade diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma (GBM).

Methods: A narrative review of peer-reviewed literature was conducted using PubMed, MEDLINE, Scopus, and the Cochrane Database. Publications from 1990 to 2024 were considered, with priority given to prospective cohort studies, systematic reviews, and authoritative guidelines including ICHD-3 and the 2021 WHO CNS tumor classification.

Results: Headache occurs in approximately 36–60% of brain tumor patients, with the highest prevalence and severity in GBM and posterior fossa tumors. The classic early-morning headache is present in fewer than one-third of patients; most tumor-associated headaches resemble tension-type or non-specific headache. Pathophysiological mechanisms include raised intracranial pressure, meningeal traction, vasogenic peritumoral edema, and neuroinflammatory sensitization. Headache characteristics differ meaningfully across tumor types as documented in literature reviews of GBM, astrocytomas, and pilocytic astrocytoma. Management requires integration of corticosteroids, analgesics, neurosurgical resection, and palliative care; extent of resection independently influences headache outcomes and survival.

Conclusion: Tumor-associated headache requires systematic evaluation with neuroimaging and an individualized, multidisciplinary management strategy encompassing the full disease trajectory.

Keywords: brain tumor; glioma; headache; intracranial hypertension; glioblastoma; astrocytoma

ГОЛОВНАЯ БОЛЬ ПРИ ОПУХОЛЯХ ГОЛОВНОГО МОЗГА И ГЛИОМАХ: ВСЕСТОРОННИЙ ОБЗОР ПАТОФИЗИОЛОГИИ, КЛИНИЧЕСКИХ ОСОБЕННОСТЕЙ, ДИАГНОСТИКИ И ЛЕЧЕНИЯ

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Аннотация

Введение: Головная боль является одним из наиболее часто встречающихся симптомов у пациентов с внутричерепными опухолями, включая глиомы всех степеней злокачественности по классификации ВОЗ. Несмотря на ее распространенность, характеристики, патофизиология и оптимальное лечение головной боли, связанной с опухолью, остаются недостаточно изученными и часто отходят на второй план из-за онкологической направленности лечения.

Цели: В данном обзоре обобщены современные данные о патофизиологии, клинических особенностях, диагностической оценке и лечении головной боли у пациентов с первичными опухолями головного мозга, с особым акцентом на глиомы от I до IV степени злокачественности по классификации ВОЗ, включая пилоцитарную астроцитому, низкодифференцированную диффузную астроцитому, анапластическую астроцитому и глиобластому (ГБМ).

Методы: Был проведен обзор рецензируемой литературы с использованием баз данных PubMed, MEDLINE, Scopus и Cochrane Database. Рассматривались публикации с 1990 по 2024 год, при этом приоритет отдавался проспективным когортным исследованиям, систематическим обзорам и авторитетным руководствам, включая ICHD-3 и классификацию опухолей ЦНС ВОЗ 2021 года.

Результаты: Головная боль встречается примерно у 36–60% пациентов с опухолями головного мозга, при этом наибольшая распространенность и тяжесть наблюдаются при глиобластоме и опухолях задней черепной ямки. Классическая утренняя головная боль присутствует менее чем у одной трети пациентов; большинство головных болей, связанных с опухолями, напоминают головную боль напряжения или неспецифическую головную боль. Патофизиологические механизмы включают повышенное внутричерепное давление, менингеальное натяжение, вазогенный перитуморальный отек и нейровоспалительную сенсибилизацию. Характеристики головной боли значительно различаются в зависимости от типа опухоли, как это задокументировано в обзорах литературы по глиобластоме, астроцитомам и пилоцитарной астроцитоме. Лечение требует интеграции кортикостероидов, анальгетиков, нейрохирургической резекции и паллиативной помощи; объем резекции независимо влияет на исходы головной боли и выживаемость.

Вывод: Головная боль, связанная с опухолью, требует систематической оценки с помощью нейровизуализации и индивидуализированной, междисциплинарной стратегии лечения, охватывающей всю траекторию заболевания.

Ключевые слова: опухоль головного мозга; глиома; головная боль; внутричерепная гипертензия; глиобластома; астроцитома

1. Introduction

Brain tumors encompass a heterogeneous group of neoplasms arising from the cellular constituents of the central nervous system (CNS) or from metastatic spread of systemic cancers. According to the Central Brain Tumor Registry of the United States (CBTRUS),

approximately 87,000 primary CNS tumors are diagnosed annually in the United States, with gliomas constituting the largest proportion of malignant primary brain tumors [1]. As Chaulagain et al. documented in their overview of intracranial tumors, almost every type of brain tumor can create symptoms based on the part of the brain affected, and headache ranks among the most universally reported presenting complaints across histological subtypes [37].

The 2021 WHO Classification of Tumors of the Central Nervous System integrates molecular and genomic parameters alongside histological features, defining tumor entities including IDH-mutant astrocytomas, IDH-mutant and 1p/19q-codeleted oligodendrogliomas, and glioblastoma as a WHO grade 4 IDH-wildtype astrocytoma [3]. Chaulagain et al. have published a series of literature reviews covering the principal glioma entities — glioblastoma [38], astrocytoma [39], low-grade diffuse astrocytoma [40], pilocytic astrocytoma [41], and broader intracranial tumor classifications [37] — collectively providing granular clinical descriptions of headache as a presenting and prognostic symptom across the glioma spectrum.

Headache is one of the most common neurological complaints in clinical practice and simultaneously one of the most frequently reported initial symptoms of an intracranial neoplasm. Epidemiological studies have consistently reported headache prevalence rates of 36–60% among brain tumor patients at diagnosis or during the disease course [4,5,6]. In a seminal prospective study by Forsyth and Posner involving 111 patients with intracranial tumors, headache was identified as the presenting complaint in approximately 48% of cases [4].

Despite its frequency, tumor-associated headache is frequently mischaracterized or attributed to pre-existing primary headache disorders. The overlap in phenomenology between tumor-related headache and common primary headaches — including tension-type headache (TTH) and migraine — poses a substantial diagnostic challenge in both primary and secondary care settings. Missing the diagnosis of an underlying brain tumor in a patient presenting with new or changed headache carries profound clinical consequences, including delayed neurosurgical intervention and poorer prognosis.

This review provides a comprehensive synthesis of current evidence pertaining to headache in the context of primary brain tumors and gliomas. It addresses mechanisms underlying headache generation, clinical and semiological features distinguishing tumor-related headache from primary headache disorders, diagnostic workup including neuroimaging, and current principles of medical and surgical management. The review also examines quality-of-life implications and emerging therapeutic directions.

2. Pathophysiology of Headache in Brain Tumors

2.1 Raised Intracranial Pressure

The most widely recognized mechanism of tumor-associated headache is elevation of intracranial pressure (ICP). The Monro-Kellie doctrine stipulates that the intracranial compartment — bounded by the rigid calvarium — maintains a fixed total volume comprising brain parenchyma, CSF, and intravascular blood. Intracranial neoplasms increase total volume and, once compensatory mechanisms are exhausted, produce progressive ICP elevation. This triggers traction on pain-sensitive intracranial structures — particularly the meninges, venous sinuses, and perivascular adventitia — densely innervated by trigeminal nociceptive fibers [7,8].

As described in the literature review by Chaulagain et al. on intracranial tumors, symptoms attributable to ICP elevation — including headache, nausea, and vomiting — arise when the growing tumor mass exceeds the limited compliance of the cranial vault [37]. Supratentorial tumors must achieve considerable mass before significantly elevating ICP, whereas posterior fossa tumors rapidly obstruct CSF outflow through the fourth ventricle and aqueduct, producing hydrocephalus even when relatively small [8].

2.2 Meningeal Traction and Nociceptive Activation

Pain-sensitive structures within the cranial vault include the dural venous sinuses, dural arteries, the falx cerebri, the tentorium cerebelli, and proximal large cerebral arteries.9 The trigeminal nerve (CN V) serves as the principal afferent for supratentorial structures, while the glossopharyngeal (CN IX), vagal (CN X), and upper cervical (C1–C3) nerves innervate the posterior fossa. Supratentorial tumors therefore tend to produce frontally or vertex-referred headache, while posterior fossa lesions produce occipital or cervical pain — a pattern consistently identified in clinical descriptions of pilocytic astrocytoma, which predominantly arises in the posterior fossa [41].

2.3 Peritumoral Vasogenic Edema

Vasogenic edema, resulting from disruption of the blood-brain barrier (BBB) by tumor-derived angiogenic factors including VEGF, amplifies mass effect disproportionately to tumor volume alone. Glioblastoma, in particular, generates extensive peritumoral edema that can exceed the neoplasm itself in volume [10,38]. Chaulagain et al.'s review of GBM notes that headaches, nausea, vomiting, and changes in vision are common symptoms of glioblastoma, and that the tumor's aggressive vascular biology contributes substantially to the peritumoral edematous burden responsible for these symptoms [38]. The rapid and dramatic relief of tumor-associated headache with dexamethasone provides indirect but compelling evidence for edema's mechanistic role [11].

2.4 Vascular, Inflammatory, and Tumor-Grade-Specific Mechanisms

Gliomas induce a complex neuroinflammatory microenvironment characterized by microglial activation, cytokine release (IL-1β, TNF-α, prostaglandins), and aberrant neovascularization [12]. These mediators sensitize peripheral and central trigeminal nociceptors, lowering the threshold for pain generation. Higher-grade tumors, by virtue of greater mitotic activity, necrosis, hemorrhage, and BBB disruption, generate more severe neuroinflammatory stimuli — consistent with the clinical observation that headache is more frequent and more severe in WHO grade 3–4 gliomas compared to grade 1–2 tumors, as reflected across Chaulagain et al.'s comparative reviews of astrocytoma grades [38-41].

3. Clinical Features and Presentation

3.1 Characteristics of Tumor-Associated Headache

A persistent clinical misconception holds that tumor-associated headache reliably manifests as a severe early-morning headache with nausea and vomiting — the so-called "classic brain tumor headache." Empirical data do not support this characterization as a reliable diagnostic criterion. Forsyth and Posner found this classic pattern in fewer than 17% of their cohort of 111 brain tumor patients [4]. In the prospective study by Schankin et al. of 85 patients, the most common headache phenotype was tension-type (77%) [14].

The typical tumor-associated headache is bifrontal or bilateral, dull or pressure-like in quality, and gradually progressive over days to weeks. It is aggravated by Valsalva maneuver, bending forward, or recumbency — features attributable to transient ICP increases. Nocturnal or early-morning exacerbation reflects the physiological nadir of venous drainage and CSF absorption during recumbency. Headache severity correlates only modestly with tumor grade, though GBM-associated headaches are more frequently severe and accompanied by rapid-onset neurological deficits [38].

3.2 Red-Flag Features

Certain headache characteristics constitute neurological "red flags" mandating urgent neuroimaging. The SNOOP4 framework captures principal warning signs:

- Systemic symptoms or signs (fever, weight loss, immunosuppression, history of malignancy)
- Neurological symptoms or signs (focal deficits, seizures, altered consciousness, papilledema)
- Onset: sudden, thunderclap, or first/worst headache of life
- Older age: new headache onset after age 50
- Prior headache history: change in pattern, frequency, or severity
- Positional aggravation or Valsalva provocation
- Progressive headache over days to weeks
- Papilledema on fundoscopy

Valentinis et al. confirmed in a prospective cohort of 504 patients that progressive headache associated with neurological signs was the most powerful predictor of underlying intracranial neoplasm [15]. Christiaans et al. similarly demonstrated that a new headache in a patient with known systemic malignancy warrants immediate brain imaging [32].

3.3 Headache by Tumor Type and Grade

Glioblastoma (GBM), the most aggressive primary brain malignancy and classified as a WHO grade 4 IDH-wildtype astrocytoma, is associated with headache in 50–60% of patients at diagnosis [16,38]. Chaulagain et al.'s literature review of GBM documents headache as one of the cardinal presenting symptoms alongside focal neurological deficits, cognitive change, and seizures, and attributes its severity to the tumor's rapid growth, extensive peritumoral edema, and propensity for midline shift [38]. Astrocytomas spanning grades I–III present with headache at varying rates depending on growth rate and edema burden. Chaulagain et al.'s review of astrocytoma diagnosis and management describes headache as a prominent symptom across pilocytic astrocytoma (grade I), diffuse astrocytoma (grade II), anaplastic astrocytoma (grade III), and GBM (grade IV), noting that higher-grade tumors are more likely to produce ICP-related headache while lower-grade lesions more commonly present with seizures as the dominant feature [39]. Low-grade diffuse astrocytoma (WHO grade II), characterized by high cellular differentiation, slow growth, and extensive infiltration of neighboring brain areas, produces headache in 30–45% of patients. Chaulagain et al.'s comprehensive review of this entity highlights its predominance in young adults and the indolent, often chronic, nature of associated headache that may be present for months or years before diagnosis [40].

Pilocytic astrocytoma (PA), a WHO grade I glioma and the most common pediatric brain tumor, has a strong predilection for the cerebellum, optic pathways, and hypothalamus. Chaulagain et al.'s literature review of pilocytic astrocytoma documents cranial nerve deficits, ataxia, and evidence of elevated intracranial pressure — including headache — as characteristic

presenting features, with the high headache prevalence in cerebellar PA directly attributable to obstructive hydrocephalus from fourth ventricular compression [41].

Table 1. Headache Characteristics by Primary Brain Tumor Type

Tumor Type (WHO Grade)	Headache Prevalence	Typical Quality	Key Mechanism	Key Reference
GBM (Grade IV)	50–60%	Dull, progressive, severe	Vasogenic edema, ↑ICP, midline shift	Chaulagain et al., 2022 [38]
Anaplastic Astrocytoma (Grade III)	40–55%	Progressive, ICP-type	Mass effect, edema, infiltration	Chaulagain et al., 2022 [39,42]
Diffuse Astrocytoma / LGG (Grade II)	30–45%	Chronic, tension-type	Gradual mass effect, mild edema	Chaulagain et al., 2022 [40]
Pilocytic Astrocytoma (Grade I)	40–70%*	Occipital, severe	Obstructive hydrocephalus (4th ventricle)	Chaulagain et al., 2022 [41]
Meningioma	36–40%	Dull, bilateral	Dural traction, venous sinus compression	Moliterno et al., 2019 [13]
Brain Metastases	40–60%	Progressive, bilateral	Multiple lesions, edema, ↑ICP	Christiaans et al., 2002 [32]
Primary CNS Lymphoma	Variable	Diffuse, progressive	Periventricular infiltration, ↑ICP	Omuro & DeAngelis, 2013 [12]

* Higher prevalence reflects predominantly posterior fossa location with resultant obstructive hydrocephalus. GBM = glioblastoma multiforme; LGG = low-grade glioma; ICP = intracranial pressure.

4. Diagnosis and Evaluation

4.1 Clinical History and Neurological Examination

A systematic clinical history remains the cornerstone of diagnostic evaluation. The clinician must characterize headache onset (acute vs. subacute vs. chronic), progression, quality, severity using a validated numerical rating scale, temporal pattern, and modifying factors. Critical associating features include nausea, vomiting, visual disturbance, diplopia, focal weakness, speech disturbance, cognitive change, and seizures — all of which feature prominently in clinical descriptions of intracranial tumors [37,38,39]. Neurological examination must comprehensively assess for papilledema (a marker of ICP elevation), cranial nerve palsies, visual field defects, motor or sensory asymmetry, coordination, and gait abnormalities. The presence of any abnormality on neurological examination in a headache patient constitutes a compelling indication for neuroimaging. Chaulagain et al.'s review of astrocytoma notes that neurological examination findings depend on tumor location and grade, with posterior fossa tumors classically producing ataxia and cranial nerve palsies alongside headache [39,41].

4.2 Neuroimaging

Magnetic resonance imaging (MRI) with gadolinium contrast is the gold-standard neuroimaging modality for suspected intracranial neoplasia. Standard sequences include T1-

weighted pre- and post-contrast, T2-weighted, FLAIR, diffusion-weighted imaging (DWI), and susceptibility-weighted imaging (SWI) [17]. Contrast enhancement reflects BBB disruption and is characteristic of high-grade tumors, metastases, and several other pathologies. Chaulagain et al.'s review of GBM describes the imaging characteristics of glioblastoma, including ring enhancement with central necrosis and surrounding FLAIR signal abnormality representing infiltrative tumor and edema [38].

Advanced MRI sequences complement standard imaging. MR spectroscopy (MRS) provides metabolic characterization, with elevated choline and reduced N-acetylaspartate (NAA) typifying glioma tissue. As documented in the review of low-grade diffuse astrocytoma, imaging features of grade II gliomas include hyperintensity on T2/FLAIR sequences without enhancement, and volumetric assessment correlates with clinical symptom burden including headache [40]. Diffusion tensor imaging (DTI) and functional MRI (fMRI) inform neurosurgical planning in eloquent cortex regions.

CT of the brain with and without contrast remains the first-line modality in emergency settings owing to wide availability and high sensitivity for hemorrhage and significant mass effect. However, CT is inferior to MRI for detecting small tumors, low-grade infiltrative lesions, and posterior fossa pathology. Patients with a normal CT and persistent neurological headache should proceed to MRI [19].

4.3 Differential Diagnosis

The differential diagnosis includes pre-existing primary headache disorders, treatment-related headaches, infectious complications, and coagulopathy-related hemorrhage. The International Classification of Headache Disorders, 3rd edition (ICHD-3), provides operational diagnostic criteria for "headache attributed to intracranial neoplasm" (code 7.4), defined as headache caused by the tumor and resolving or significantly improving after effective tumor treatment [18]. Pseudotumor cerebri, cerebral venous sinus thrombosis, and leptomeningeal carcinomatosis may produce headache phenotypes overlapping with primary tumor-associated headache and require dedicated neuroimaging and CSF evaluation for exclusion.

5. Management of Headache in Brain Tumor Patients

5.1 General Principles

Effective management requires an individualized, multidisciplinary approach addressing the underlying tumor, ICP dynamics, peritumoral edema, and the patient's overall functional status. Treatment of the underlying neoplasm — through surgery, radiotherapy, and chemotherapy — remains the most definitive means of alleviating tumor-associated headache when successful [19].

5.2 Corticosteroids

Dexamethasone is the most commonly employed agent for acute management of tumor-associated headache mediated by peritumoral vasogenic edema. It acts by downregulating VEGF expression, reducing BBB permeability and edema accumulation. Standard initial dosing is 4–8 mg twice daily, with higher doses (up to 16–24 mg/day) for severe deficits or impending herniation [20]. Symptomatic improvement typically occurs within 24–72 hours. In GBM patients — where vasogenic edema is a dominant contributor to headache — corticosteroids are a routine component of initial management, as reflected in the management discussions of Chaulagain et al.'s GBM review [38].

5.3 Analgesic Pharmacotherapy

Analgesic selection follows the WHO analgesic ladder. Paracetamol and NSAIDs provide first-line relief for mild to moderate tumor-associated headache. NSAIDs should be used with caution in patients receiving anticoagulation or with chemotherapy-related thrombocytopenia. Opioid analgesics may be required for severe refractory headache, particularly in palliative contexts [21]. Adjunct agents including tricyclic antidepressants and gabapentinoids are useful when neuropathic pain components or co-existing headache disorders are present.

5.4 Management of Raised ICP and Hydrocephalus

When headache is attributable to CSF obstruction and hydrocephalus — as frequently occurs in pilocytic astrocytoma of the posterior fossa [41] — CSF diversion is indicated. External ventricular drainage (EVD) provides rapid relief and real-time ICP monitoring in acute presentations. Endoscopic third ventriculostomy (ETV) or ventriculoperitoneal shunting (VPS) is appropriate for sustained obstructive hydrocephalus. Osmotherapy with hypertonic saline or mannitol provides transient ICP reduction and is reserved for acute herniation syndromes.

5.5 Neurosurgical Intervention

Surgical resection remains the most effective single intervention for addressing the primary pathological driver of tumor-associated headache. Maximal safe resection reduces tumor volume, relieves mass effect, and reduces the edematous burden. In GBM, extent of resection (EOR) is independently associated with improved overall survival and quality-of-life outcomes [22]. Chaulagain et al.'s retrospective study of anaplastic astrocytoma patients at a single center demonstrated that extent of resection and tumor volume significantly affect overall survival in WHO grade III gliomas, underscoring the principle that greater surgical removal translates to improved clinical outcomes including headache relief [42].

5.6 Radiotherapy and Chemotherapy

Standard-of-care treatment for GBM — concurrent radiotherapy with temozolomide followed by adjuvant temozolomide — can produce both headache relief through tumor reduction and transient exacerbation through radiation-related edema [24]. Prophylactic dexamethasone is routinely administered during radiotherapy to mitigate edema-related symptom exacerbation. For low-grade gliomas, Buckner et al. demonstrated that radiotherapy with PCV chemotherapy significantly improved survival compared to radiotherapy alone, with concomitant improvement in symptom burden [27].

5.7 Palliative and Supportive Care

For patients with high-grade gliomas in the palliative phase, headache management is a primary therapeutic goal. The EANO guidelines for palliative care in glioma patients emphasize proactive symptom assessment using validated instruments such as the MDASI-BT, enabling early adjustment of analgesic regimens and psychological support to patients and caregivers [21,25].

Table 2. Summary of Management Strategies for Headache in Brain Tumor Patients

Category	Intervention	Primary Indication	Notes / Caveats
Pharmacological	Dexamethasone 4–16 mg/day	Peritumoral vasogenic edema (esp. GBM [38])	Taper as soon as feasible; multiple AEs with prolonged use
Pharmacological	Paracetamol / NSAIDs	Mild–moderate headache	NSAIDs: caution with anticoagulants/thrombocytopenia
Pharmacological	Opioid analgesics	Severe / refractory headache; palliative phase	Titrate carefully; monitor sedation/constipation
Pharmacological	Mannitol / hypertonic saline	Acute ICP crisis / herniation	Temporizing; requires ICP monitoring
Surgical	Maximal safe resection	Tumor-related mass effect (GBM, anaplastic AA [42])	EOR correlates with symptom relief and survival
Surgical	CSF diversion (VPS / ETV)	Obstructive hydrocephalus (esp. pilocytic AA [41])	Urgent in symptomatic hydrocephalus
Radiation / SRS	Stereotactic radiosurgery	Focal tumors / metastases	High local control; monitor for radiation necrosis
Targeted / Biological	Bevacizumab (anti-VEGF)	Steroid-refractory edema	Off-label for edema; may reduce corticosteroid need
Palliative / Supportive	MDASI-BT; palliative care integration	High-grade glioma (recurrent / end-stage)	EANO guidelines recommend early integration [21]

AA = astrocytoma; AEs = adverse events; EOR = extent of resection; GBM = glioblastoma; ICP = intracranial pressure; NSAIDs = non-steroidal anti-inflammatory drugs; VPS = ventriculoperitoneal shunt; ETV = endoscopic third ventriculostomy; SRS = stereotactic radiosurgery; MDASI-BT = MD Anderson Symptom Inventory Brain Tumor module.

6. Prognostic Implications and Quality of Life

Headache exerts a multidimensional impact on quality of life (QoL) in brain tumor patients. The symptom burden — in conjunction with fatigue, cognitive impairment, seizures, and neurological deficits — contributes substantially to functional disability and psychological distress. Armstrong et al. validated the MDASI-BT as a reliable and sensitive instrument for capturing symptom burden in brain tumor patients, demonstrating that headache consistently ranks among the most impactful symptoms on daily functioning [25].

The relationship between headache and tumor progression is bidirectional. Worsening headache, particularly when accompanied by new neurological deficits or altered consciousness, is a reliable clinical indicator of tumor progression, radiation necrosis, or hemorrhage within the tumor. In the retrospective study by Chaulagain et al. examining the impact of extent of resection and tumor volume on overall survival in anaplastic astrocytoma, greater surgical resection was associated with improved survival outcomes, supporting the principle that effective surgical debulking — through reduction of mass effect and edema — confers meaningful headache relief alongside survival benefit [42].

In GBM, Sanai et al. demonstrated that an EOR threshold of ⩾78% was independently associated with improved overall survival [22]. Quality-of-life studies in high-grade glioma consistently identify headache as one of the most burdensome symptoms, particularly in the post-progression and palliative phases. Sizoo et al. found headache in over 60% of patients in the final weeks of life [28]. These findings underscore the importance of proactive palliative headache management throughout the disease trajectory. For low-grade gliomas, Buckner et al. demonstrated in the RTOG 9802 trial that early chemoradiotherapy significantly improved both progression-free and overall survival, with concomitant symptomatic benefit [27]. As Chaulagain et al. noted in the review of low-grade diffuse astrocytoma, these tumors predominantly affect young adults, and headache-related functional impairment over a protracted disease course has significant implications for vocational and social quality of life [40].

7. Emerging Trends and Future Directions

7.1 Advanced Neuroimaging for Headache Prediction

MR-based intracranial pressure assessment using phase-contrast MRI to measure CSF pulsatility, and optic nerve sheath diameter ultrasonography, offer non-invasive ICP estimation. Functional connectivity MRI has identified headache-associated alterations in thalamocortical and descending pain modulation networks, suggesting that central sensitization mechanisms operative in chronic primary headache disorders may also contribute to tumor-associated headache chronification [30].

7.2 Molecular Biomarkers and Personalized Management

The 2021 WHO CNS tumor classification's integration of molecular markers — IDH mutation status, MGMT promoter methylation, TERT promoter mutation, and 1p/19q codeletion — has transformed glioma prognostication and treatment selection [3]. IDH-mutant gliomas carry significantly more favorable prognoses and generate less severe headache burden owing to their slower growth and lesser angiogenic activity compared to IDH-wildtype GBM. MGMT promoter methylation predicts response to temozolomide [36] and is associated with improved tumor control, indirectly correlating with better headache outcomes. The clinical implications of these molecular distinctions for headache management are discussed in Chaulagain et al.'s reviews of astrocytoma and low-grade diffuse astrocytoma [39,40].

7.3 Immunotherapy and Tumor Treating Fields

Immune checkpoint inhibitors have not yet demonstrated efficacy in unselected GBM populations, though trials in molecularly selected patients continue. Tumor treating fields (TTFields), delivering low-intensity alternating electric fields via scalp transducer arrays, represent an approved adjunctive treatment for newly diagnosed and recurrent GBM following the EF-14 trial [31]. Scalp irritation at transducer sites may produce localized headache, manageable with topical agents and array rotation protocols.

7.4 Digital Health and Patient-Reported Outcomes

Integration of electronic patient-reported outcome measures (ePROMs) into neuro-oncology practice enables continuous real-world symptom monitoring between clinic visits. Digital platforms allowing patients to report headache severity, character, and impact daily — with automated alerts when thresholds are exceeded — hold promise for earlier intervention and reduced emergency healthcare utilization. Such systems align with the multidisciplinary, patient-centered approach advocated in EANO palliative care guidelines [21].

8. Conclusion

Headache is a clinically significant, highly prevalent, and diagnostically pivotal symptom in patients harboring primary brain tumors and gliomas. Its pathophysiology is multifactorial, encompassing raised intracranial pressure, meningeal traction, peritumoral edema, neuroinflammatory sensitization, and tumor-site-specific mechanisms. The "classic" early-morning brain tumor headache is present in a minority of patients; the more common phenotype overlaps substantially with benign primary headache disorders, rendering clinical differentiation challenging. Systematic application of red-flag criteria, prompt MRI neuroimaging, and integration of molecular pathological findings are essential to timely diagnosis. Management must integrate corticosteroids, analgesic pharmacotherapy, neurosurgical resection, oncological treatment, and palliative care across the disease trajectory. Closer collaboration between headache specialists, neuro-oncologists, neurosurgeons, and palliative care clinicians is strongly recommended, alongside prospective longitudinal research mapping headache trajectory, molecular correlates of headache burden, and randomized trials of headache-specific interventions in brain tumor patients.

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