Discover Oncology

Review

Unlocking new horizons: advances in treating IDH-mutant, 1p/19q-codeleted oligodendrogliomas

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Abstract
Oligodendrogliomas are a distinct subtype of diffuse gliomas characterized by IDH mutations and 1p/19q codeletion, classified as grade 2 or 3 based on histological features. This review examines current advancements in the diagnosis, treatment, and prognosis of oligodendrogliomas, with an emphasis on personalized approaches driven by molecular insights. Surgery remains the cornerstone of treatment, aiming for maximal safe resection to obtain tissue for diagnosis and alleviate symptoms. For grade 2 tumors with residual disease but no symptomatic progression, the IDH inhibitor vorasidenib has emerged as a promising option to delay the need for radiation therapy (RT) and chemotherapy. For grade III oligodendrogliomas, postoperative combined-modality therapy with RT and chemotherapy, such as the PCV regimen, demonstrates significant survival benefits, while temozolomide is an alternative due to its ease of administration and reduced toxicity. Recurrent oligodendrogliomas present therapeutic challenges, necessitating tailored strategies based on prior treatments and the interval since initial therapy. Options include repeat surgery, reirradiation, or novel targeted therapies. Advances in molecular diagnostics, such as homozygous CDKN2A/B deletion as a prognostic marker, have refined risk stratification and informed treatment decisions. Despite these strides, further research is needed to optimize long-term outcomes and address resistance mechanisms. This review underscores the importance of integrating molecular diagnostics with clinical management to achieve personalized, evidence-based care for patients with oligodendrogliomas.

Keywords IDH-mutant oligodendrogliomas · 1p/19q codeletion · Molecular diagnostics · Personalized therapy · Prognostic markers

1 Introduction

Oligodendroglial tumors constitute about 5–10% of all glial tumors and typically emerge in individuals aged 30–60, with low-grade tumors appearing at younger ages than their anaplastic counterparts. Though often characterized by a protracted clinical course, these tumors remain almost invariably fatal.

Historically, treatment decisions for oligodendroglial tumors relied primarily on tumor grade (2 vs. 3) and drew from studies involving both astrocytic and oligodendroglial tumors. These early investigations preceded the identification of oligodendroglial tumors' unique molecular and prognostic profiles distinct from other glial neoplasms. Later, retrospective analysis of 1p/19q status in some studies refined treatment recommendations to align with the current World Health Organization (WHO) classification system [1].

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Per the WHO classification of central nervous system tumors, a definitive diagnosis of oligodendroglioma hinges on the co-occurrence of an isocitrate dehydrogenase (IDH) mutation and combined 1p/19q chromosomal loss (algorithm 1) [2]. Tumors are then classified as grade 2 (low-grade) or grade 3 (anaplastic) based on histopathologic characteristics. Yet, with advances in molecular glioma diagnostics, the biological and prognostic differences between grade 2 and grade 3 oligodendrogliomas—when treated with radiotherapy and chemotherapy—have diminished.

The classification and diagnosis of diffuse gliomas have evolved markedly with the advent of molecular diagnostics. The flowchart below delineates the systematic process for classifying gliomas, integrating histology, IDH mutation status, and other molecular markers, in accordance with the latest WHO guidelines (Fig. 1).

This review focuses on the treatment strategies and prognosis for grade 2 and grade 3 IDH-mutant, 1p/19q-codeleted oligodendrogliomas.

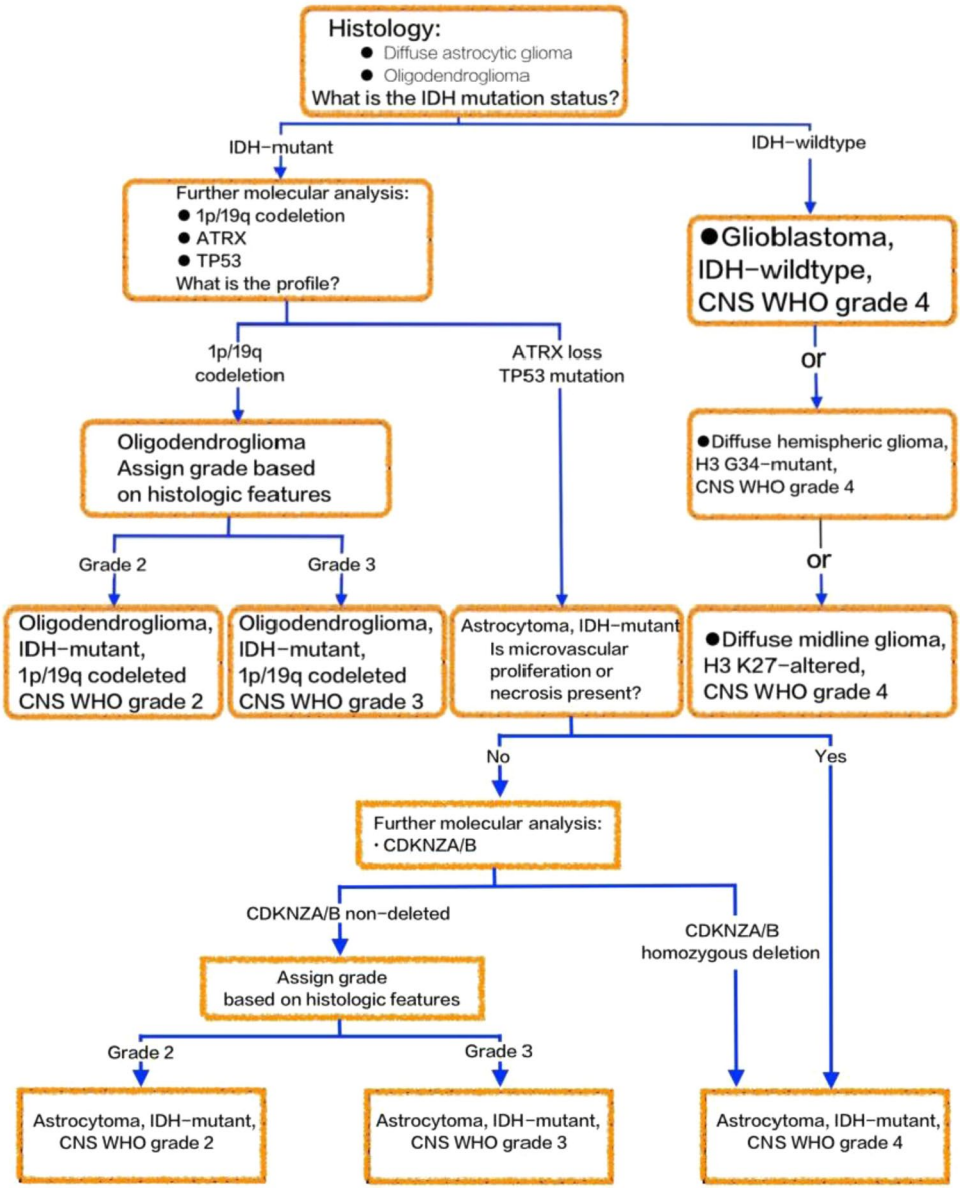

Fig. 1 Algorithm for the classification and diagnosis of diffuse gliomas in adults

2 Surgical strategies for oligodendrogliomas

Surgical intervention holds a central role in the management of suspected diffuse gliomas, particularly by providing the tissue necessary for definitive histopathological and molecular diagnosis, as well as alleviating symptoms caused by mass effect. For oligodendrogliomas, as with other glioma subtypes, achieving maximal safe resection remains a cornerstone of treatment. The extent of resection, however, is often dictated by the tumor's location and its proximity to critical neurological structures. In cases where the tumor resides in eloquent brain regions, partial resection or diagnostic biopsy may be the only feasible options to preserve neurological function.

The advent of modern microsurgical techniques, coupled with advanced preoperative imaging modalities and intraoperative navigation tools, has revolutionized the surgical management of gliomas. These innovations enable more precise delineation of tumor boundaries, allowing surgeons to achieve maximal resection while minimizing the risk of neurologic deficits. Nonetheless, when the objectives of extensive tumor resection conflict with the need to preserve neurological integrity, the priority is to prevent new, permanent deficits. This underscores the delicate balance required in surgical decision-making for these patients [3].

Although randomized controlled trials comparing maximal surgical resection with limited resection for gliomas are unavailable—and unlikely to be conducted due to ethical and logistical challenges—evidence from observational studies and secondary analyses of clinical trials supports the survival benefits of greater tumor resection in oligodendrogliomas. For grade 3 oligodendrogliomas, studies demonstrate a clear correlation between extensive resection and improved survival outcomes [4]. For grade 2 oligodendrogliomas, the evidence has been less conclusive due to their favorable prognosis and prolonged clinical course, necessitating long follow-up periods and large cohorts. A systematic review by the Congress of Neurological Surgeons found insufficient evidence to confirm that greater extent of resection improves overall survival in WHO grade 2, 1p/19q-codeleted oligodendrogliomas [5]. However, a recent study with a median follow-up of 11.7 years reported significantly longer median overall survival after gross total resection (not reached, 95% CI 18.3 to NA) compared to non-gross total resection (22.2 years, 95% CI 19.9 to NA; $P = 0.04$) in 190 grade 2 oligodendrogliomas, providing robust evidence for the prognostic significance of minimizing residual disease in this subgroup [6]. These findings highlight the importance of maximal safe resection, tailored to tumor grade and patient-specific factors, to optimize outcomes [4, 5, 7].

3 Approaches to postoperative management

Table 1 offers a concise overview of postoperative management strategies for oligodendrogliomas, summarizing recommended treatment options based on tumor grade and patient-specific clinical factors.

The flowchart below guides clinicians through the postoperative management of IDH-mutant, 1p/19q-codeleted oligodendrogliomas, outlining optimal treatment pathways based on tumor grade and residual disease, as detailed in Table 1.

This algorithm delineates a stepwise approach to postoperative management, focusing on tumor grade and residual disease. For WHO grade 2 tumors, observation or vorasidenib-targeted therapy is favored, while grade 3 tumors generally necessitate combined radiotherapy and chemotherapy (Fig. 2). By integrating clinical and molecular features, this process seeks to optimize treatment outcomes.

Although surgery is a vital initial step in managing oligodendrogliomas, it seldom achieves a cure. These inherently infiltrative tumors often defy complete resection due to their diffuse spread and closeness to critical

Table 1 Treatment strategies for grade 2 and grade 3 oligodendrogliomas

Tumor grade	Primary therapy	Secondary options	Targeted therapy
Grade 2	Watchful waiting or vorasidenib	Radiotherapy (RT) + chemotherapy (PCV/temozolomide)	Vorasidenib
Grade 3	Radiotherapy + PCV/temozolomide	Repeat resection (if feasible) or alternative chemotherapies	Vorasidenib

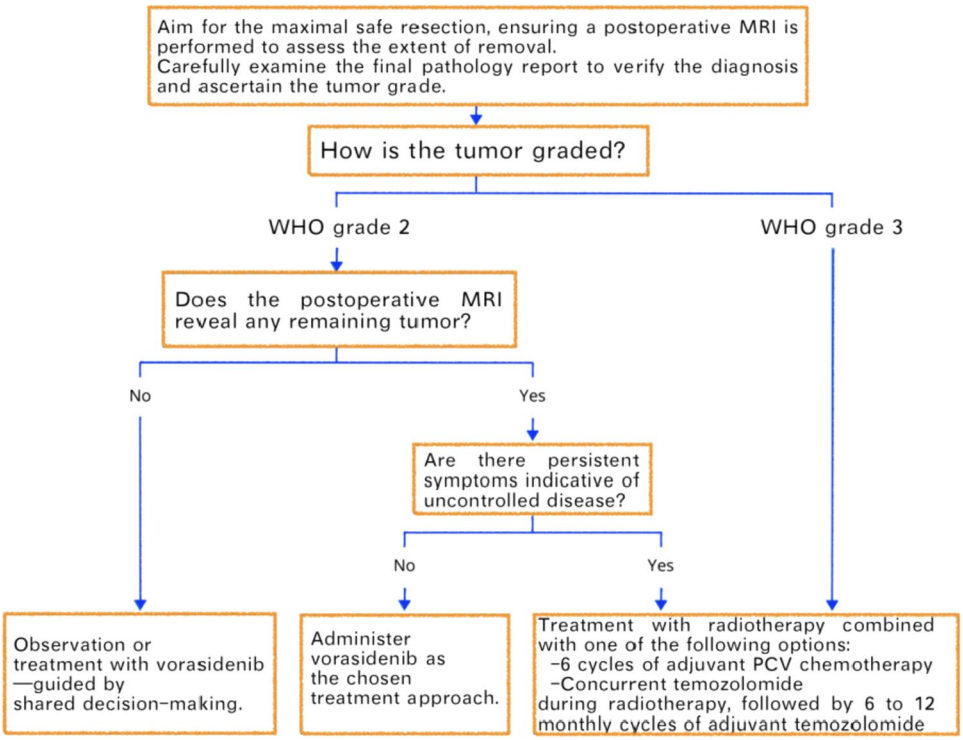

Fig. 2 Initial treatment strategy for IDH-mutant, 1p/19q-codeleted oligodendrogliomas

neurological structures. As a result, nearly all patients need additional anticancer therapies to manage residual or recurrent disease and enhance long-term outcomes.

The standard of care for oligodendrogliomas has advanced significantly over recent decades. Landmark randomized trials from the 1990s established that combined-modality therapy—radiotherapy (RT) paired with chemotherapy—markedly outperforms RT alone in survival outcomes. Long-term follow-up from these seminal studies has cemented this approach as the cornerstone of modern management for both grade 2 and grade 3 oligodendrogliomas. Furthermore, breakthroughs in molecular profiling, particularly the discovery of isocitrate dehydrogenase (IDH) mutations and the advent of IDH-targeted therapies, have launched an era of personalized medicine, refining therapeutic precision and efficacy.

Despite these advances, postoperative management retains complexities that fuel ongoing research. A key debate centers on the optimal timing of adjuvant therapy post-surgery. For patients with low-risk disease—marked by minimal residual tumor, favorable molecular profiles, and no high-risk features—deciding to start adjuvant therapy demands careful consideration. Clinicians must weigh the benefits of early intervention, like enhanced disease control, against the risks of treatment toxicities and potential progression during observation.

As insights into the molecular and clinical diversity of oligodendrogliomas grow, ongoing research promises to hone therapeutic strategies. This evolution seeks to maximize survival while safeguarding quality of life, delivering tailored, evidence-based care to every patient.

3.1 Grade 2 tumors

For patients newly diagnosed with grade 2 oligodendroglioma, three main postoperative management options are available outside clinical trials: watchful waiting, combined radiation therapy (RT) and chemotherapy, or IDH-targeted therapy. The use of an IDH inhibitor, such as vorasidenib—an IDH1/2 inhibitor—is informed by the INDIGO trial findings. In August 2024, the U.S. Food and Drug Administration (FDA) approved vorasidenib for treating grade 2 oligodendroglioma and grade 2 IDH-mutant astrocytoma [8].

3.1.1 Risk stratification

Effective management of IDH-mutant, 1p/19q-codeleted oligodendrogliomas hinges on precise risk stratification to tailor postoperative therapy. Historically, clinical factors such as age (>40 years), tumor grade, tumor size (>4–5 cm), and extent of resection guided treatment decisions, often prioritizing radiotherapy (RT) and chemotherapy for high-risk patients. However, advances in molecular diagnostics, particularly following the WHO 2016 and 2021 classifications, have revealed limitations in relying solely on these traditional markers, which may oversimplify the biological complexity of individual cases [1, 9].

A refined risk stratification framework now integrates molecular and clinical features to optimize therapeutic decisions. Key high-risk features include persistent or uncontrolled neurological symptoms, contrast enhancement on MRI, significant postoperative residual tumor (>1 cm), rapid tumor growth, and homozygous CDKN2A/B deletion. Notably, homozygous CDKN2A/B deletion, identified as a critical adverse prognostic marker primarily in grade 3 oligodendrogliomas, is associated with aggressive behavior and shorter progression-free survival [2, 10]. Unlike IDH-mutant astrocytomas, where CDKN2A/B deletion upgrades histologically lower-grade tumors to WHO grade 4, this molecular marker does not currently alter the WHO grading of oligodendrogliomas but significantly informs risk assessment and treatment intensity [11, 12]. For instance, grade 3 oligodendrogliomas with CDKN2A/B deletion often warrant immediate RT and chemotherapy, while those lacking this marker in younger patients with gross total resection may justify observation [9, 13].

Low-risk patients—characterized by minimal residual disease, non-enhancing tumors, stable symptoms, and absence of CDKN2A/B deletion—may benefit from watchful waiting or IDH-targeted therapies like vorasidenib. The phase 3 INDIGO trial demonstrated that vorasidenib, an IDH1/2 inhibitor, significantly extended progression-free survival (27.7 vs. 11.1 months; HR 0.39, 95% CI 0.27–0.56) in grade 2 IDH-mutant gliomas with residual disease, leading to its FDA approval in August 2024 for grade 2 oligodendrogliomas and astrocytomas [14]. These findings support vorasidenib's role in low- to intermediate-risk cases, though its utility in CDKN2A/B-deleted tumors remains unestablished, highlighting the need for further research [9, 14]. However, as insights into glioma molecular biology deepen, the clinical relevance of distinguishing grade 2 from grade 3 tumors may diminish. This field remains under active study and is poised to evolve with emerging data [9, 15].

By integrating clinical factors with molecular diagnostics, such as IDH mutation status, 1p/19q codeletion, and CDKN2A/B deletion, clinicians can personalize treatment strategies—balancing disease control with quality of life. Ongoing trials, such as CODEL (NCT00887146), are further refining risk stratification by comparing RT-plus-PCV with RT-plus-temozolomide, promising to enhance precision in managing this molecularly distinct glioma subtype [16].

3.1.2 Patients with gross total resection

For patients with grade 2 oligodendroglioma after gross total resection, watchful waiting remains a key postoperative strategy. This approach rests on their typically favorable prognosis, with low risk of early progression and years of asymptomatic stability without further therapy. By delaying treatment, it reduces the risk of toxicities, preserving quality of life as long as feasible.

The emergence of isocitrate dehydrogenase (IDH)-targeted therapies, notably vorasidenib, offers a groundbreaking option for select patients. The INDIGO trial highlights vorasidenib, an IDH1/2 inhibitor, as effective in delaying progression in those with measurable residual disease. Yet, its relevance for patients without detectable disease remains unclear, given their exclusion from the trial. Moreover, while early-phase trial safety data for vorasidenib are promising, they stem from a limited cohort, and the long-term effects on safety and tolerability warrant further study.

Given these nuances, postoperative management calls for a tailored approach. For those considering IDH-targeted therapy, the promise of extended progression-free survival must be balanced against uncertainties about long-term safety and tolerability. Here, shared decision-making between clinicians and patients becomes essential to weigh treatment benefits against potential risks.

For patients choosing watchful waiting, management relies on structured surveillance to track disease progression. The sections below detail the evidence behind this strategy, surveillance protocols, and approaches to managing recurrence or progression.

3.1.2.1 Rationale for observation Grade 2 oligodendrogliomas with IDH mutations and 1p/19q codeletion grow significantly slower than their astrocytic IDH-mutant low-grade glioma counterparts. This leisurely progression often allows patients to delay additional therapy for years, supporting observation as a viable initial strategy after gross total resec-

tion [17]. Though not curative, surgery typically stabilizes these tumors for an extended period before progression necessitates further intervention.

A key debate in clinical management centers on how patient age and neurologic deficits shape postoperative treatment timing. Advanced age (e.g., >40 years) and neurologic deficits are often flagged as triggers for early therapy. Yet, these are prognostic—not predictive—factors, unvalidated by prospective trials to pinpoint which patients in a genetically uniform tumor group benefit from immediate action. For instance, the RTOG 9802 trial, assessing RT with or without procarbazine, lomustine, and vincristine (PCV) in high-risk low-grade gliomas, set age > 40 as an entry threshold [18]. This cutoff has since been adopted by some experts, including the NCCN guidelines, to guide immediate postoperative therapy [19].

Understanding the natural course of untreated, fully resected grade 2 oligodendrogliomas relies heavily on older studies blending oligodendroglial and astrocytic tumors, often lacking molecular profiling. One prospective series of 111 patients under 40 with low-grade gliomas post-gross total resection reported survival rates of 99% at 2 years and 93% at 5 years [20].

More precisely, patients with pure oligodendrogliomas, minimal residual disease (<1 cm), and preoperative tumors under 4 cm achieved progression-free survival rates of 100% at 2 years and 70% at 5 years. Smaller retrospective studies of molecularly defined IDH-mutant, 1p/19q-codeleted grade 2 oligodendrogliomas reinforce these results, bolstering the case for watchful waiting post-gross total resection [21].

Choosing watchful waiting requires a personalized approach, weighing these tumors' indolent nature against the risks of delayed treatment. As insights into molecular and clinical risk factors deepen, ongoing research will sharpen observation criteria and enhance outcomes for this distinct patient group.

3.1.2.2 Surveillance interval for oligodendrogliomas Active surveillance for oligodendroglioma patients typically entails contrast-enhanced MRI every 3–4 months initially [22]. If imaging remains stable for one to two years, follow-up intervals may extend to 6–9 months. This shift aligns with their often prolonged progression-free survival, balancing thorough monitoring with reduced unnecessary scans.

Oligodendrogliomas typically recur locally near resection cavity margins. Yet, interpreting subtle imaging changes over time poses distinct challenges. Slight shifts in nonenhancing T2 or FLAIR signals might indicate recurrence, postoperative effects, or benign variations, complicating differentiation. For greater accuracy, new MRI scans should be routinely compared to the earliest postoperative images—the most reliable baseline for detecting meaningful changes.

Years of consistent follow-up are often needed to distinguish nonspecific imaging fluctuations from true progression with confidence. Not every subtle change demands immediate action; for slow-growing lesions, timing further treatment hinges on careful clinical judgment. This underscores the value of a tailored approach, blending the patient's clinical status with a nuanced grasp of imaging patterns to guide prudent, informed decisions.

3.1.2.3 Management at the time of tumor progression Managing recurrent or progressive tumors in patients under observation after initial resection requires a personalized and carefully tailored approach. Treatment decisions hinge on multiple factors: the tumor's growth rate across serial MRI scans, total tumor volume, location within the brain, feasibility of safe resection, patient preferences for additional surgery, presence of contrast enhancement, and, when available, the histopathologic grade of the progressing tumor.

Several common scenarios and their management strategies include:

- Safe and extensive re-resection

For patients with recurrent tumors amenable to safe, extensive, or gross total re-resection, surgery remains a strong option. If re-resection results in minimal or no residual tumor and pathology confirms a grade 2 tumor, a renewed watch-and-wait approach may be suitable. This strategy balances ongoing surveillance with avoiding overtreatment in cases of slow-growing, low-grade disease.

- Small-volume or nonenhancing tumor

For patients with small-volume, nonenhancing recurrent tumors—or those ineligible for or opposed to further surgery—vorasidenib offers a reasonable next-line therapy. This mirrors its role in newly diagnosed patients with residual disease, providing a noninvasive option to delay more aggressive interventions.

- Rapid progression or significant tumor burden

In cases of rapid progression or substantial tumor burden, re-resection is often advised. Surgery serves dual purposes here: debulking to relieve mass effects and obtaining updated pathology to confirm the diagnosis and reassess tumor grade. Postoperative management depends on the extent of resection and pathology findings, with subsequent treatments aligned to protocols for newly diagnosed patients, ensuring a comprehensive, individualized approach.

3.1.3 Management of patients with residual disease and stable symptoms

For patients with residual disease after surgery but no uncontrolled symptoms, IDH-targeted therapy with vorasidenib is typically preferred over radiotherapy (RT) plus chemotherapy or watchful waiting. This approach harnesses vorasidenib's ability to delay disease progression while minimizing the immediate side effects of RT and chemotherapy.

Although the INDIGO trial excluded patients with enhancing disease, this is not an absolute contraindication to vorasidenib in stable patients without uncontrolled symptoms, particularly those with low risk of under-graded tumors (e.g., due to small biopsies or grade-clinical discrepancies), as most newly diagnosed grade 2 oligodendrogliomas are nonenhancing or minimally enhancing; while other IDH inhibitor trials suggest lower response rates in enhancing vs. nonenhancing tumors, these findings stem from recurrent/progressive cases, not new grade 2 diagnoses [14]. No consensus exists on residual tumor size as a treatment criterion, emphasizing clinical judgment and multidisciplinary discussion to select vorasidenib candidates, especially those deferring RT plus chemotherapy. The phase 3 INDIGO trial enrolled 331 patients aged ≥ 12 with residual/recurrent grade 2 IDH-mutant gliomas post-surgery only, with measurable nonenhancing disease (≥1 cm, bidimensional), Karnofsky score ≥ 80, no glucocorticoids, and suitability for watchful waiting [14]; randomized to vorasidenib (40 mg daily) or placebo, median age was ~40 (16–71), with >80% having residual tumors > 2 cm, meeting NCCN "high-risk" criteria [19]. After a median follow-up of months, vorasidenib significantly extended progression-free survival (27.7 vs. 11.1 months; HR 0.39, 95% CI 0.27–0.56) and reduced subsequent treatment needs (intervention-free rates: 85.6 vs. 47.4% at 18 months, 83.4 vs. 27.0% at 24 months) [14]. Vorasidenib's safety profile is favorable, with serious adverse events <2% and discontinuation <4% in both groups, though seizure control, quality of life, and overall survival data are pending; its main grade ≥ 3 adverse event is elevated alanine aminotransferase (9.6%). Other FDA-approved IDH inhibitors—ivosidenib, olutasidenib, safusidenib (mutant-IDH1), and enasidenib (mutant-IDH2)—are under study, awaiting robust trials to confirm efficacy.

3.1.4 Management of patients with uncontrolled symptoms or progression on vorasidenib

For patients with uncontrolled disease-related symptoms or progression despite initial vorasidenib treatment, postoperative therapy combining radiotherapy (RT) and chemotherapy is generally recommended. In select cases, repeat surgery may be considered beforehand if deemed safe and likely to yield significant clinical benefit.

The combination of RT and chemotherapy has shown substantial survival benefits in low-grade oligodendrogliomas. Among the strongest evidence is the RTOG 9802 trial, which studied 251 patients with supratentorial low-grade gliomas randomized to postoperative RT (54 Gy in 30 fractions) alone or with six cycles of adjuvant PCV chemotherapy (procarbazine, lomustine, vincristine) [23].

Eligible patients included those aged 18–39 with subtotal resection or biopsy, and those 40 or older regardless of resection extent. The cohort was histologically diverse: diffuse astrocytoma (26%), oligodendroglioma (42%), and mixed astrocytoma/oligodendroglioma (32%). Randomization was stratified by age, contrast enhancement, and histology (astrocytic vs. oligodendroglial predominant).

After a median follow-up of 11.9 years, adding PCV to RT significantly extended median overall survival (13.3 vs. 7.8 years; hazard ratio [HR] 0.59, $p = 0.03$) [18]. However, this benefit came with increased hematologic toxicity: grade 3 and 4 events occurred in 8 and 3% of the RT-alone group, respectively, vs. 51 and 15% in the RT-plus-PCV group. No treatment-related deaths or secondary leukemias were reported [23].

The survival advantage of PCV was consistent across histologic subtypes, with the greatest effect in oligodendrogliomas (n = 101; HR 0.43, 95% CI 0.23–0.82) [18]. Post hoc molecular analysis of 42% of cases revealed an even stronger benefit in IDH-mutant, 1p/19q-codeleted oligodendrogliomas (HR 0.21, $p = 0.029$) [24], underscoring the value of molecular profiling in treatment planning.

Preliminary data from the ECOG-ACRIN E3F05 trial, presented in abstract form, further endorse RT with concurrent and adjuvant temozolomide for low-grade gliomas, including 1p/19q-codeleted oligodendrogliomas [25].

Both PCV and temozolomide are effective against oligodendrogliomas and other diffuse gliomas, but their relative efficacy remains unclear without head-to-head trials. The ongoing CODEL trial seeks to resolve this by comparing RT-plus-PCV with RT-plus-temozolomide in 1p/19q-codeleted tumors.

Temozolomide offers practical advantages over PCV, including easier administration, better tolerability, and wider availability in some regions. However, its long-term survival benefit compared to PCV, especially in molecularly defined oligodendrogliomas, remains under evaluation.

3.2 Management of grade 3 oligodendrogliomas

3.2.1 Timing and selection of therapy

For most patients with newly diagnosed grade 3 oligodendrogliomas, IDH-mutant, and 1p/19q-codeleted, the standard of care is immediate postoperative radiotherapy (RT) paired with adjuvant chemotherapy, irrespective of resection extent or other clinical risk factors (Fig. 2). The choice between PCV (procarbazine, lomustine, vincristine) or temozolomide should be tailored to the patient's clinical profile, factoring in age, comorbidities, and treatment tolerability. An exception to immediate therapy may apply to younger patients with gross total resection of a grade 3 tumor lacking homozygous CDKN2A/B deletion. Here, uncertainty about the prognostic value and consistency of grade 2 versus grade 3 classifications in molecularly defined oligodendrogliomas may justify a conservative stance. For these patients—often with a favorable prognosis—a watch-and-wait approach, akin to that for resected grade 2 oligodendrogliomas, may be suitable [3, 10, 13, 26].

Currently, no clinical evidence supports using IDH inhibitors like vorasidenib for grade 3 IDH-mutant, 1p/19q-codeleted gliomas, and these therapies lack approval for this indication. However, as insights into glioma molecular biology deepen, the clinical relevance of distinguishing grade 2 from grade 3 tumors may diminish. This field remains under active study and is poised to evolve with emerging data [9].

3.2.2 The role of RT plus chemotherapy in grade 3 tumors

Robust evidence from two landmark phase III trials supports combining radiotherapy (RT) and chemotherapy for grade 3 oligodendrogliomas, IDH-mutant, and 1p/19q-codeleted. With extensive follow-up and molecular analyses, these studies confirm that postoperative RT with PCV (procarbazine, lomustine, vincristine) chemotherapy significantly boosts long-term survival compared to RT alone [27–29]. Together, they cement the combined-modality approach as a cornerstone of treatment, optimizing outcomes for patients with grade 3 oligodendrogliomas.

3.2.3 Landmark trials supporting RT plus PCV in grade 3 oligodendrogliomas

3.2.3.1 EORTC 26951 The EORTC 26951 trial, conducted by the European Organisation for Research and Treatment of Cancer, delivered pivotal evidence for RT paired with PCV in grade 3 oligodendrogliomas and oligoastrocytomas (per pre-2016 WHO terminology). It randomized 368 patients to either RT alone or RT followed by six cycles of PCV [27, 29, 30]. Both arms received 59.4 Gy of RT, with additional therapy allowed upon progression. In the RT-plus-PCV group, 53% required subsequent chemotherapy (mostly temozolomide) compared to 88% in the RT-alone arm, underscoring the durability of combined therapy. After a median follow-up of 19 years, RT-plus-PCV patients showed improved overall survival (median 3.5 vs. 2.6 years; HR 0.78, 95% CI 0.63–0.98), with the greatest benefit in 1p/19q-codeleted tumors [29]. Of 316 patients analyzed molecularly, 80 had 1p/19q codeletion. In this subgroup, progression-free survival (PFS) was markedly longer with RT plus PCV (median 13.1 vs. 4.2 years; HR 0.49, 95% CI 0.29–0.83), alongside a trend toward better overall survival (median 14.2 vs. 9.3 years; HR 0.60, 95% CI 0.35–1.03). At 20 years, 37% of 1p/19q-codeleted patients in the RT-plus-PCV arm were alive, compared to 14% with RT alone. Methylation profiling of 115 tumors showed that MGMT methylation and CpG island hypermethylated phenotype (CIMP) predicted PCV benefit [31]. For MGMT-methylated tumors, median overall survival with RT plus PCV was 8.65 vs. 1.98 years with RT alone. CIMP-positive tumors similarly gained substantial survival (median 9.51 vs. 3.27 years).

3.2.3.2 RTOG 9402 The RTOG 9402 trial reinforced the value of integrating PCV with RT for grade 3 oligodendrogliomas. It enrolled 291 patients, randomized to either four cycles of intensified PCV followed by RT or RT alone, both at 59.4 Gy [28]. After over 17 years of follow-up, patients with 1p/19q-codeleted tumors (n = 125) showed significantly

longer overall survival with PCV plus RT (median 13.2 vs. 7.3 years; HR 0.61, 95% CI 0.40–0.94) [29]. Long-term data underscored this durability: 37% of the PCV-plus-RT group survived to 20 years, compared to 15% with RT alone. These results highlight PCV's transformative impact on 1p/19q-codeleted grade 3 oligodendrogliomas.

The complementary findings of EORTC 26951 and RTOG 9402 provide compelling support for RT combined with PCV in grade 3 oligodendrogliomas, especially in the 1p/19q-codeleted subgroup. This combined-modality approach stands as a treatment cornerstone, offering substantial survival gains for these aggressive tumors.

3.2.4 Choice between PCV and temozolomide

Both PCV (procarbazine, lomustine, vincristine) and temozolomide are established adjunctive therapies alongside radiotherapy (RT) for oligodendrogliomas, yet expert consensus on the preferred regimen remains elusive. The choice hinges on patient-specific factors like tolerability, logistics, and personal preferences. PCV's efficacy is robustly supported by three landmark trials: RTOG 9802 (focused on grade 2 oligodendrogliomas) and two pivotal studies on grade 3 oligodendrogliomas—EORTC 26951 and RTOG 9402 [18, 27, 28]. These trials showed that adding PCV to RT significantly extends progression-free survival (PFS) and overall survival (OS) compared to RT alone, with the most pronounced benefits in 1p/19q-codeleted tumors. Further evidence emerges from a German subset analysis of anaplastic gliomas and a retrospective survey of 1000 patients with grade 3 oligodendrogliomas, suggesting superior survival with PCV over temozolomide in 1p/19q-codeleted cases, though these were not prospective head-to-head comparisons with RT, warranting cautious interpretation [32, 33]. Temozolomide offers practical advantages: simpler administration, better tolerability, and proven survival benefits in other malignant gliomas [34–36]. A small trial in grade 2 glioma patients further bolsters its efficacy [25]. For those valuing convenience, reduced short-term toxicity, or struggling with PCV's side effects, temozolomide is an appealing alternative. For grade 3 tumors, the optimal timing and sequencing of temozolomide with RT remain unclear. Whether concurrent administration during RT outperforms sequential delivery is uncertain, and concerns about delayed toxicities with concurrent use highlight the need for further study. The ongoing CODEL trial—comparing RT-plus-PCV with RT-plus-concurrent and adjuvant temozolomide in 1p/19q-codeleted tumors—promises to shed light on these questions, refining treatment strategies and clarifying regimen efficacy [16]. The sequencing of RT and chemotherapy in combined approaches remains under investigation, with key trials adopting different strategies:

- EORTC 26951: PCV followed RT completion.
- RTOG 9402: Four cycles of intensified PCV preceded RT.
- NCCN guidelines favor standard PCV after RT, as in EORTC 26951, citing lower tolerability with the intensified pre-RT PCV regimen from RTOG 9402 [19]. Similarly, temozolomide is typically sequenced post-RT, aligning with clinical practice to balance efficacy and patient comfort while minimizing adverse effects.

3.3 Diffuse tumors requiring large RT fields

While combined-modality therapy with radiotherapy (RT) and chemotherapy is standard for grade 2 and 3 diffuse gliomas, certain scenarios may favor initial chemotherapy alone. For instance, patients with oligodendrogliomas presenting as diffuse, multilobar, or bihemispheric tumors—requiring extensive RT fields that might span the entire brain—face a heightened risk of delayed neurocognitive toxicity from large-field or whole-brain radiation. In such cases, this risk may outweigh the benefits of combined therapy, positioning chemotherapy as a suitable first-line option.

However, this approach lacks robust validation from prospective studies focused solely on oligodendroglial tumors. Data, often from molecularly defined grade 2 and 3 gliomas, suggest that single-modality chemotherapy typically yields inferior overall survival compared to combined-modality trials, emphasizing the need for careful patient selection and tailored planning.

3.3.1 Evidence supporting chemotherapy alone

The EORTC 22033-26033 trial offers the strongest evidence for single-modality chemotherapy in grade 2 oligodendrogliomas. It enrolled 477 patients with high-risk low-grade gliomas—defined by age > 40, progressive disease,

tumor size > 5 cm, midline crossing, or neurologic symptoms—randomizing them to either 12 cycles of postoperative dose-intense temozolomide (75 mg/m^2 daily for 21 days per 28-day cycle) or RT (50.4 Gy) [37].

In the IDH-mutant, 1p/19q-codeleted oligodendroglioma subgroup, progression-free survival (PFS) was similar: 55 months with temozolomide vs. 62 months with RT. Yet, with only four years of median follow-up, mature overall survival data are pending. These findings indicate temozolomide as a viable option for select patients, especially where RT risks significant neurocognitive harm.

3.3.2 Limitations of chemotherapy alone in grade 3 tumors

The initial phase of the CODEL trial underscores challenges with chemotherapy-only regimens in grade 3 oligodendrogliomas. In this truncated randomized study of 36 patients, the temozolomide-only arm showed worse outcomes than RT-based arms (with or without temozolomide). Notably, three of 12 tumors in the temozolomide-only group were IDH-wildtype, likely skewing results.

After 6.6 years of median follow-up, 83% (10/12) of the temozolomide-only group experienced tumor progression, compared to 37.5% in RT arms (HR 3.12, 95% CI 1.26–7.69) [38]. Adjusted overall survival trended worse, though not significantly (HR 2.78, 95% CI 0.58–13.2). No notable neurocognitive decline differences emerged at three months, highlighting the need for longer-term data.

The NOA-4 trial compared single-modality chemotherapy to RT in grade 3 gliomas, including anaplastic oligodendrogliomas. In a 1p/19q-codeleted subset, longer-term follow-up showed PCV outperforming temozolomide in PFS (9.4 vs. 4.5 months), though initial chemotherapy vs. RT showed no outcome difference [39].

While chemotherapy alone may suit patients with diffuse oligodendrogliomas needing large RT fields, it carries limitations, including potentially reduced survival compared to combined therapy. Treatment must be individualized, weighing tumor traits, patient factors, and neurocognitive risks. Ongoing studies like CODEL should clarify optimal sequencing and combinations, refining strategies for these complex cases.

3.4 Ongoing randomized trials in diffuse glioma management

The management of diffuse gliomas is a dynamic field, propelled by molecular diagnostics that have reshaped tumor classification and treatment approaches. A standout ongoing study in oligodendroglial tumors is the phase III Alliance for Clinical Trials in Oncology/EORTC intergroup trial ("CODEL"). This trial targets patients with 1p/19q-codeleted anaplastic or low-grade gliomas, randomizing them to:

(1) Radiation therapy (RT) followed by PCV (procarbazine, lomustine, vincristine), or
(2) RT with concurrent and adjuvant temozolomide, as in the clinical trial NCT00887146 (registered on April 23, 2009).

The ongoing CODEL trial—comparing RT plus PCV with RT plus concurrent and adjuvant temozolomide in 1p/19q-codeleted tumors—promises to shed light on these questions, refining treatment strategies and clarifying regimen efficacy. The CODEL trial was registered on April 23, 2009 (ClinicalTrials.gov identifier: NCT00887146).

Its findings are expected to clarify the comparative efficacy and long-term outcomes—particularly survival and disease progression—of these strategies.

Another key study, the POLCA trial in France, compares PCV chemotherapy alone to RT followed by PCV, uniquely prioritizing cognitive function as its primary endpoint. By focusing on cognition, POLCA seeks to illuminate the neurocognitive impact of these treatments, addressing a vital quality-of-life factor for glioma patients.

4 Delivery of treatment

4.1 Vorasidenib

Vorasidenib, an oral IDH1/2 inhibitor, gained regulatory approval in August 2024 for adults and children aged ≥ 12 with IDH-mutant grade 2 astrocytoma or oligodendroglioma [8]. This breakthrough therapy represents a major step forward in the targeted treatment of these molecularly defined gliomas.

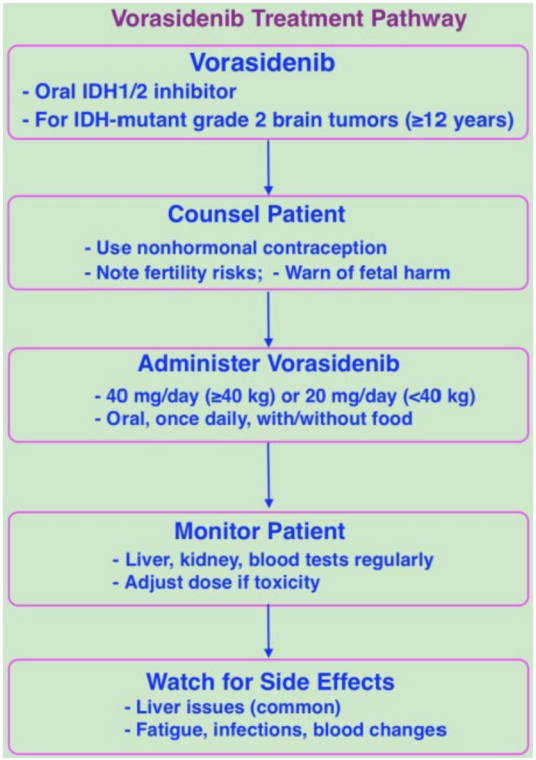

Fig. 3 Vorasidenib treatment pathway

The Vorasidenib Treatment Pathway provides a structured, step-by-step guide for clinicians treating patients with IDH-mutant brain tumors. It includes counseling on risks, dosing instructions, monitoring requirements, and common side effects, ensuring a standardized approach to patient care (Fig. 3).

4.1.1 Pretreatment counseling

Thorough counseling is essential before starting vorasidenib to address key risks:

- *Fetal harm*: Preclinical studies indicate fetal harm, though human data are lacking to rule out similar risks. Patients should use effective nonhormonal contraception during treatment and for three months post-discontinuation, as vorasidenib may impair hormonal contraceptive efficacy, risking failure or breakthrough bleeding.
- *Fertility considerations*: Preclinical evidence suggests potential fertility impairment in both sexes. Patients planning future fertility should be informed of these uncertainties.

4.1.2 Dosing and administration

Recommended dosing for vorasidenib is:

- Adults and children ≥ 40 kg: 40 mg orally once daily.
- Children < 40 kg: 20 mg orally once daily.

It can be taken any time of day, with or without food, offering administration flexibility. Tablets must remain whole—do not split, crush, or chew—to maintain integrity. Routine antiemetic prophylaxis is typically unnecessary.

- *Drug interactions*: Vorasidenib is primarily metabolized by CYP1A2. Concomitant use of CYP1A2 inhibitors (e.g., ciprofloxacin) or inducers (e.g., phenytoin) is contraindicated, as they may significantly alter plasma levels, potentially reducing efficacy or increasing toxicity.

4.1.3 Monitoring parameters

Regular monitoring is critical to ensure safety and catch adverse events early:

- *Liver function tests*: Baseline ALT, AST, GGT, total bilirubin, and alkaline phosphatase assessments are required, followed by checks every two weeks for the first 2 months, monthly for the next two years, and as clinically needed thereafter.
- *Renal and hematologic monitoring*: Baseline kidney function, electrolytes, and complete blood count (CBC) evaluations are advised, with monthly follow-ups during treatment.
- *Toxicity management*: Adjust doses per prescribing guidelines to manage toxicity.

4.1.4 Adverse effects

Hepatotoxicity is the primary concern, necessitating consistent monitoring:

- *Liver enzyme elevations*: In the INDIGO trial, ALT and AST elevations occurred in 59 and 46% of patients, respectively, with grade 3/4 events in 10 and 5% [8, 14]. Median time to first elevation was 57 days. Other increases included GGT (34%), alkaline phosphatase (9%), and bilirubin (5%). Rare cases of autoimmune hepatitis and hepatic failure were reported.

Hematologic effects included:

- Increased Hemoglobin: 13%, no grade 3/4 events.
- Lymphopenia: 11%, with 1.8% grade 3/4.
- Neutropenia: 14%, with 2.4% grade 3/4.
- Thrombocytopenia: 12%, no grade 3/4.

Other common adverse effects (≥ 15%), mostly low-grade and comparable to placebo, were:

- Fatigue
- COVID-19 infection
- Seizures
- Musculoskeletal pain
- Diarrhea

Vorasidenib's integration into practice marks a promising advance for IDH-mutant gliomas. While its benefits are significant, optimizing outcomes demands diligent monitoring, adherence to dosing protocols, and ongoing safety and efficacy assessments. Further clinical experience should deepen understanding of its role in disease management and quality of life.

4.2 Involved-field radiation therapy (RT) in diffuse gliomas

Radiation therapy (RT) is pivotal in managing diffuse gliomas, targeting local tumor control while minimizing neurotoxicity [3]. Its timing, dosage, and schedule are customized based on the tumor's histologic subtype and prognostic factors, as detailed earlier.

4.2.1 Dose and schedule

When RT is indicated, the dose and fractionation schedule are carefully calibrated to optimize efficacy and limit toxicity. Postoperative RT typically starts three to five weeks after surgery.

- Grade 2 oligodendroglioma

For grade 2 oligodendrogliomas and other low-grade gliomas, a total dose of 45–54 Gy is standard, delivered in 1.8 Gy fractions [19]. The clinical target volume (CTV) extends a 1 cm margin around the MRI-defined gross tumor volume (GTV). This range balances therapeutic benefit with long-term safety, as higher doses have not shown superior outcomes in historical studies [40–42].

- Grade 3 oligodendroglioma

For grade 3 oligodendrogliomas and other high-grade gliomas, a total of 59.4–60 Gy is typical, given in 1.8–2 Gy fractions [19].

- Alternative RT modalities

Techniques like hyperfractionated RT [43], proton therapy [44, 45], and fractionated stereotactic radiotherapy [46] have been explored for infiltrative gliomas, but they lack clear therapeutic advantages over conventional RT.

4.2.2 Side effects of radiation therapy

Radiotherapy (RT) is generally well-tolerated but may cause acute toxicities (e.g., fatigue, cerebral edema exacerbating neurological symptoms) and long-term risks, including neurocognitive decline and rare secondary neoplasms [3, 19]. Toxicities vary by radiation field and patient factors, requiring careful monitoring to balance efficacy and safety.

RT remains a cornerstone of diffuse glioma management, with dosing and scheduling tailored to tumor grade and patient profile. While well-tolerated, it demands vigilant monitoring for acute and long-term side effects. Advances in RT techniques and supportive care continue to enhance outcomes and reduce risks.

4.3 Procarbazine, lomustine, and vincristine (PCV) regimen

The PCV regimen—a cornerstone chemotherapy protocol for oligodendrogliomas—is delivered in six cycles, with each spanning six or eight weeks based on tumor grade:

- *Grade 2 tumors*: Eight-week cycles, per the RTOG 9802 trial [17].
- *Grade 3 tumors*: Six-week cycles, as in the EORTC 26951 trial [23].

Dosing schedule per cycle [3]:

- *Lomustine*: 110 mg/m^2 orally on day 1 (max: 200 mg).
- *Procarbazine*: 60 mg/m^2 orally on days 8–21.
- *Vincristine*: 1.4 mg/m^2 IV on days 8 and 29 (max: 2 mg).

Vincristine's inclusion is debated due to its limited penetration of an intact blood–brain barrier, questioning its contribution. However, no studies directly compare full PCV to a lomustine-procarbazine duo.

4.3.1 Baseline and laboratory monitoring

Effective PCV administration demands rigorous monitoring:

- *Baseline and day 1 of each cycle*: assess complete blood count (CBC) with differential, serum creatinine, ALT, AST, and total bilirubin [47].
- *Weekly CBCs*: Begin at week 4 to track hematologic recovery.

4.3.2 Premedication and supportive care

- *Antiemetics*: Lomustine and procarbazine are moderately emetic—premedicate with a 5-HT3 antagonist (e.g., ondansetron, 8 mg orally). Vincristine, minimally emetic, requires no prophylaxis.
- *Bowel management*: Counter vincristine- or antiemetic-induced constipation proactively with docusate sodium or senna.

4.3.3 Drug-specific considerations

The PCV regimen carries significant toxicities requiring careful monitoring [48, 49]. Lomustine and procarbazine cause frequent hematologic toxicity (e.g., lymphopenia, thrombocytopenia in 25–40% of patients) and hepatotoxicity (ALT/AST elevations in >50%) [49]. Procarbazine may induce hypersensitivity rashes (25–50%) or rare hypertensive crises with tyramine-rich foods or MAO inhibitors, necessitating dietary restrictions [48, 50]. Vincristine is associated with sensory neuropathy, often requiring discontinuation if symptoms emerge [47]. Dose adjustments and supportive care (e.g., antiemetics, bowel management) are critical to manage these effects.

Discontinuation is typically advised at initial signs, given limited evidence of its added benefit here.

The PCV regimen remains a vital strategy for oligodendrogliomas, driving significant gains in progression-free and overall survival. Its use demands meticulous monitoring and tailored dose adjustments to manage toxicities effectively. Despite its challenges, PCV endures as a cornerstone for well-selected patients, reinforcing its key role in tumor management.

5 Monitoring and supportive care

Your text is already very clear, detailed, and well-structured—excellent work! It provides a thorough guide to monitoring and follow-up for diffuse gliomas with a strong clinical foundation. That said, I can still offer a subtle polish to enhance readability, streamline phrasing, and refine the flow while keeping all technical details intact. Here's the revised version:

5.1 Treatment monitoring and follow-up

Managing diffuse gliomas demands ongoing evaluation of treatment response and vigilant tracking of disease progression. This integrates contrast-enhanced brain MRI—assessing both enhancing and nonenhancing tumor volumes—with clinical evaluations.

Follow-up imaging frequency is tailored to patient-specific factors, including molecular subtype, clinical status, tumor grade, prior treatments, and therapeutic goals [22]:

- *Observation after surgery*: Surveillance for untreated tumors follows guidelines outlined earlier.
- *During Vorasidenib therapy*: Start with a baseline contrast-enhanced brain MRI, then image every three months for the first three years. For stable disease beyond three years with no new symptoms, extend to every six months.
- *During RT plus chemotherapy*: Perform MRI 2–6 weeks post-RT to set a baseline before adjunctive chemotherapy. For grade 2 or 3 oligodendrogliomas, delaying the first MRI to ~ four months post-RT minimizes pseudoprogression misinterpretation. Imaging during chemotherapy varies:
    - *PCV*: Every two to three cycles.
    - *Monthly Temozolomide*: Every two to four cycles.
    - *Posttreatment*: After RT and chemotherapy, image every six to nine months indefinitely for grade 2 and 3 tumors. For RT or chemotherapy alone, more frequent imaging (every three to four months or semiannually) is recommended until progression. New symptoms—like seizures or neurological decline—prompt earlier scans.
    - *After first progression*: MRI frequency typically rises due to heightened risk of further tumor growth.

Table 2 Treatment monitoring and follow-up

Scenario	Monitoring frequency	Additional notes
Observation after surgery	Follow outlined surveillance recommendations	Tailor imaging schedule based on tumor grade, location, and patient factors
During vorasidenib therapy	- *Baseline MRI*: An MRI is required before starting therapy - *First 3 years*: Imaging every 3 months - *Beyond 3 years*: Every 6 months if stable	Extend intervals only if disease is stable and no new symptoms are present
During RT plus chemotherapy	- *Baseline MRI*: Conducted 2–6 weeks post-RT - *Grade 2/3 tumors*: Delay baseline MRI to ~ 4 months post-RT to minimize pseudoprogression misinterpretation	Establishes a reliable baseline for adjunctive chemotherapy evaluation
Imaging during chemotherapy	- *PCV regimen*:Imaging every 2–3 cycles - *Monthly temozolomide*: Imaging every 2–4 cycles	Adjust intervals based on clinical response and treatment tolerability
Post first-stage treatment	- *RT+ chemotherapy*: Imaging every 6–9 months indefinitely for grade 2/3 tumors - *RT or chemotherapy alone*: Every 3–4 months initially, then semiannually	Earlier imaging recommended if new symptoms (eg,seizures,neurological decline)emerge
When new symptoms occur	- Immediate imaging recommended if seizures, new neurological deficits, or unexplained symptoms arise	Early detection can help identify pseudo-progression, recurrence, or treatment complications
After first progression	MRI frequency increases due to heightened risk of tumor growth	Individualize intervals based on clinical progression and patient condition

The table below summarizes recommended monitoring and follow-up strategies for diffuse gliomas, based on treatment modalities and disease progression (Table 2).

5.2 Tumor-associated epilepsy

Seizures are a major morbidity factor in supratentorial oligodendrogliomas [51]. For refractory epilepsy, surgical tumor resection is recommended, as complete or near-complete removal strongly correlates with better seizure control [52].

While some advocate seizure-specific surgeries using intraoperative recordings to target foci, evidence doesn't clearly favor these over standard resections [53, 54]. RT and chemotherapy also improve seizure control in many cases, even without radiographic tumor response [55].

5.3 Reproductive health

Reproductive health is a critical consideration for patients with oligodendrogliomas and other IDH-mutant diffuse gliomas, which often strike those of childbearing age. Before treatment begins, discussing fertility risks is vital to empower informed reproductive choices [56].

5.3.1 Fertility preservation strategies

- *Males*: Sperm banking is advised for those seeking future paternity.
- *Females*: Consult reproductive specialists to explore options like embryo or oocyte cryopreservation [57]. These should ideally occur before chemotherapy or vorasidenib to minimize genetic risks to gametes.

5.3.2 Fertility risks by treatment agent

- *Chemotherapy drugs*: Procarbazine is associated with a high risk of infertility. As an alkylating agent, temozolomide also has the potential to impact reproductive function. Changes in semen parameters have been observed in males with gliomas following temozolomide exposure [58]. However, the clinical significance of these changes and the rates of infertility associated with temozolomide are not well studied in either males or females. Fetal harm and adverse developmental outcomes associated with temozolomide exposure have been reported in both pregnant patients and pregnant partners of male patients, as well as in animal studies [59].
- *Vorasidenib*: Preclinical data suggest potential irreversible fertility impairment, seen in animal models [8].

Incorporating thorough counseling on these risks into treatment planning is essential. Proactive discussion equips patients to balance care complexities with long-term goals.

5.4 Cognitive function

Neurocognitive dysfunction is prevalent in primary brain tumor patients, stemming from the tumor, surgery, epilepsy, medication side effects, and long-term chemotherapy or radiation therapy (RT) impacts. This impairment can profoundly affect quality of life, demanding proactive management.

Baseline neurocognitive testing is key to pinpointing deficits and validating patient concerns, offering a detailed view of cognitive strengths and weaknesses for tailored care. Cognitive rehabilitation programs have proven effective for those with difficulties, reducing impairments and boosting function [60].

6 Recurrent disease

The management of recurrent oligodendroglial tumors hinges on prior therapies [3]. Both the PCV regimen (procarbazine, lomustine, vincristine) and temozolomide are effective for recurrence, though response rates and disease control duration are typically lower than in first-line settings or post-radiation therapy (RT). Repeat surgical resection or reirradiation may also be viable in select cases.

7 Temozolomide

For recurrent oligodendrogliomas, temozolomide and PCV are effective second-line options, though response rates are lower than in first-line settings [61–63]. Temozolomide achieves objective response rates of 25–44%, with median progression-free survival (PFS) of 7–10 months [61, 62]. PCV yields a 17% response rate post-temozolomide, with 50% progression-free at 6 months [63]. Monitoring includes regular complete blood counts and liver function tests to manage hematologic and hepatic toxicities [59].

To ensure safe administration, temozolomide dosing requires adjustment based on hematologic parameters. The initial dose is typically 150 or 200 mg/m^2 per day for 5 consecutive days per cycle. On days 22 and 29 of each cycle, ANC and platelet levels are assessed to determine the lowest observed values, guiding subsequent dosing decisions. If ANC falls below 1000/μL or platelets below 50,000/μL, treatment is deferred until ANC exceeds 1500/μL and platelets exceed 100,000/μL, with the dose reduced by 50 mg/m^2 per day in the next cycle. If ANC is between 1000/μL and 1500/μL and platelets between 50,000/μL and 100,000/μL, treatment is delayed until recovery, maintaining the initial dose. If ANC exceeds 1500/μL and platelets exceed 100,000/μL, the dose may be increased or maintained at 200 mg/m^2 per day for 5 days. This dose modification schedule is detailed in Fig. 4, providing a structured approach for clinicians to manage temozolomide therapy effectively.

7.1 PCV regimen

Data on PCV's efficacy post-temozolomide progression are sparse but suggest viability for some patients [63]. A retrospective analysis of 24 patients showed a 17% objective response rate, with 50% progression-free at 6 months and 21% at 12 months. While encouraging, further studies are needed to clarify PCV's role here.

7.2 Bevacizumab

Bevacizumab, a VEGF-targeting monoclonal antibody, aids symptomatic edema in glioblastomas but has a limited, unclear role in recurrent oligodendroglial tumors [64–66].

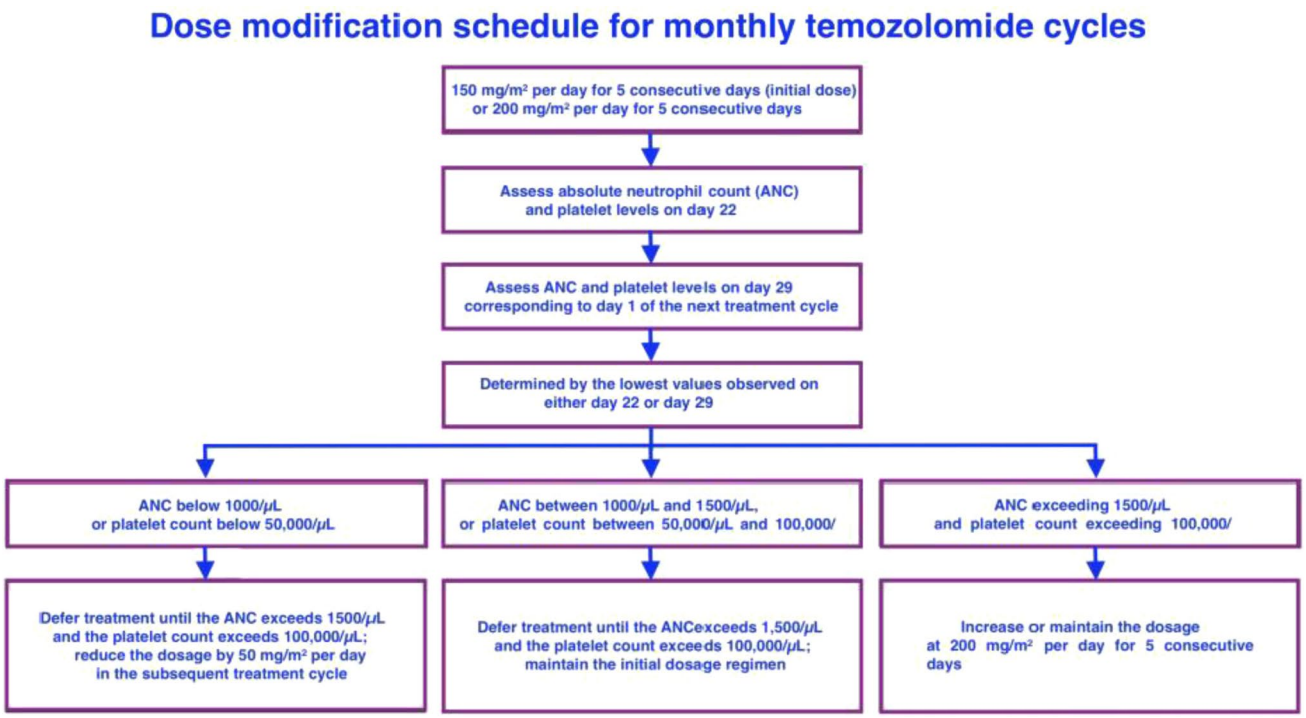

Fig. 4 Dose modification schedule for monthly temozolomide cycles

In a retrospective study of 22 patients with alkylator-refractory recurrent anaplastic oligodendrogliomas, bevacizumab yielded a 68% partial response rate, yet median PFS was 6.8 months and OS was 8.5 months. A study combining bevacizumab with irinotecan reported a 72% response rate, but median PFS was just 140 days. The TAVAREC trial, testing bevacizumab plus temozolomide in IDH-mutant gliomas, showed no significant benefit, reinforcing its limited routine utility.

7.3 Alternative cytotoxic agents

For progression after temozolomide or PCV, options like paclitaxel, irinotecan, carboplatin, and etoposide-cisplatin combinations are largely experimental [67–77]. These show limited activity in oligodendroglial tumors, with response rates typically <15% and progression within 12 months for most patients. Their modest efficacy highlights the need for more effective alternatives.

7.4 Experimental IDH-targeting treatments

IDH-targeted therapies are opening new paths for IDH-mutant gliomas, including oligodendroglial tumors, with promising agents under investigation:

- *Ivosidenib*: An IDH1 inhibitor approved for acute myeloid leukemia, it showed promise in a phase I trial of 66 patients with advanced IDH1-mutant gliomas—3 partial responses, 86% stable disease, and a median PFS of 13.5 months [78].
- *Olutasidenib and Safusidenib*: These IDH1 inhibitors excelled in nonenhancing tumors in phase I/II trials, suggesting potential for disease control in select cases [79, 80]. Safusidenib, now in phase II, offers preliminary efficacy worth exploring further.

Managing recurrent oligodendroglial tumors remains challenging. While alternative cytotoxic agents yield modest results, IDH-targeted therapies promise to extend PFS. Ongoing development of novel agents and personalized strategies is vital to improve outcomes in this complex population.

8 Prognosis

Oligodendroglial tumors, though often tied to a prolonged clinical course, are ultimately life-limiting due to progression and therapy resistance. This underscores the urgent need for ongoing research and innovation in their management.

Historical data pegged median overall survival at 10–15 years for low-grade oligodendrogliomas and 5–9 years for anaplastic cases [33, 81, 82]. These estimates, predating the 2016 WHO shift to histopathologic-molecular classification, encompassed a broader tumor spectrum—many lacking the favorable prognosis of IDH-mutant, 1p/19q-codeleted oligodendrogliomas.

Newer evidence points to improved outcomes for molecularly defined oligodendrogliomas. Long-term follow-up from multicenter randomized trials shows median survival nearing 20 years for grade 2 tumors and 14 years for grade 3 tumors treated with radiation therapy (RT) and PCV (procarbazine, lomustine, vincristine) [18, 27–29].

Traditional poor prognostic factors in gliomas also apply to oligodendroglial tumors, including:

- Advanced age
- Male gender
- Poor functional status or pre-existing neurological deficits
- Tumor location beyond frontal or parietal lobes
- Tumor size > 4–5 cm
- Absence of seizures at presentation.

Their relevance in the molecularly defined, post-IDH era remains uncertain and merits further study [83–85].

Tumor grade retains prognostic weight. Historically, WHO grade 3 oligodendrogliomas trailed grade 2 by a median of ~5 years in survival. Yet, among IDH-mutant, 1p/19q-codeleted tumors, this gap may narrow, requiring extended studies to confirm [86, 87].

Homozygous CDKN2A/B deletion stands out as a key adverse marker, nearly exclusive to grade 3 oligodendrogliomas [10]. Other negative histopathologic features—microvascular proliferation, necrosis, high mitotic activity, and elevated Ki-67 indices—also correlate with worse outcomes in anaplastic IDH-mutant, 1p/19q-codeleted cases [88]. These markers enhance risk stratification and guide treatment planning.

Advanced molecular diagnostics have reshaped our grasp of prognostic factors in oligodendroglial tumors. Still, continued research, long-term follow-up, and innovative therapies are vital to further boost outcomes for this unique glioma subset.

9 Conclusion

Oligodendrogliomas, a unique subset of diffuse gliomas, are defined molecularly by IDH mutations and 1p/19q codeletion and graded as WHO 2 or 3 based on histology. Maximal safe surgical resection is the treatment cornerstone, though complete removal is often constrained by tumor location and extent. For grade 2 tumors with residual disease but no symptomatic progression, the IDH inhibitor vorasidenib is recommended to delay radiation and chemotherapy. Conversely, symptomatic progression calls for combined radiotherapy and chemotherapy.

Grade 3 oligodendrogliomas typically require postoperative combined-modality therapy, which outperforms radiotherapy alone in survival outcomes. Chemotherapy options include the PCV regimen—valued for its survival gains—and temozolomide, preferred for its simpler administration and reduced toxicity.

For recurrence, management is tailored to prior treatments, surgical feasibility, and time since last radiation. This personalized strategy optimizes disease control while accounting for patient-specific factors and therapeutic history, improving outcomes across this varied population.

Acknowledgements In this review, we comprehensively discuss current treatment paradigms, including the role of maximal safe resection, the impact of IDH-targeted therapies such as vorasidenib, and the ongoing debate regarding the optimal timing of radiation and chemotherapy. Furthermore, we explore emerging molecular biomarkers, such as homozygous CDKN2A/B deletion, and their implications for risk stratification and personalized therapy. Our analysis integrates findings from recent clinical trials and translational research, providing a framework for refining treatment decisions in this evolving landscape.

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Declarations

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Competing interests The authors declare no competing interests.

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