Research Article

Clinical Utility and Prognostic Value of IDH Mutation in Gliomas Patients in Kurdistan Region: A Retrospective Comparative Analysis With Wild-Type Variants

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Abstract

Background:
Isocitrate dehydrogenase (IDH) mutation has emerged as a key molecular biomarker in gliomas, with significant implications for diagnosis, classification, and prognosis under the WHO CNS5 framework. However, regional data from the Kurdistan Region of Iraq remain limited, particularly regarding its real-world clinical utility.
Objective:
To evaluate the clinical and prognostic significance of IDH mutation status among glioma patients in the Kurdistan Region through a retrospective comparative analysis.
Methods:
This retrospective, multicenter observational study included 150 histopathologically confirmed glioma patients treated between October 2023 and January 2026 across major oncology centers in Erbil, Duhok, and Sulaymaniyah. Patients were stratified into IDH-mutant and IDH wild-type groups. Clinicodemographic, histopathological, treatment, and survival data were analyzed. Survival outcomes were assessed using Kaplan–Meier analysis and Cox proportional hazards models.
Results:
IDH mutation was identified in 24.0% of patients. IDH-mutant patients were significantly younger at diagnosis compared to wild-type patients (43.1 ± 14.2 vs. 49.8 ± 12.8 years, $p < 0.05$). IDH-mutant tumors were associated with lower WHO grades and higher prevalence of astrocytoma and oligodendroglioma subtypes ($p < 0.001$). Disease progression was significantly lower in the IDH-mutant group (44.4% vs. 70.2%, $p = 0.002$), with longer time to progression (28.3 vs. 12.6 months, $p < 0.001$). Overall survival was significantly improved in IDH-mutant patients (34.2 vs. 18.4 months; HR = 0.42, 95% CI: 0.28–0.64, $p < 0.001$). Multivariable analysis confirmed IDH mutation as an independent predictor of improved survival (HR = 0.45, $p < 0.001$).
Conclusion:
IDH mutation status is a strong independent prognostic marker in glioma patients in the Kurdistan Region, associated with significantly improved survival outcomes. These findings support routine implementation of molecular diagnostics and highlight the importance of integrating IDH status into clinical decision-making and regional neuro-oncology practice.

Key words: Glioma, Isocitrate Dehydrogenase (IDH) Mutation, Wild-Type Variants, Survival Analysis, Kurdistan Region (Iraq)

Key Points

- IDH-mutant gliomas showed significantly longer overall survival.
- IDH mutation independently predicted better prognosis.
- Routine IDH testing supports WHO CNS5-based glioma management.

Importance of the Study
IDH mutation is a well-established molecular biomarker in diffuse gliomas, yet evidence from the Kurdistan Region of Iraq has been limited. This study provides one of the largest regional comparative analyses evaluating the prognostic impact of IDH mutation in routine clinical practice. We demonstrate that IDH-mutant gliomas are associated with significantly longer overall and progression-free survival and remain an independent predictor of favorable outcome after adjustment for major clinical factors. These findings support routine implementation of molecular diagnostics and reinforce the importance of integrating WHO CNS5 molecular classification into glioma management in resource-limited settings.

Introduction

Gliomas represent a spectrum of primary central nervous system (CNS) tumors that range from indolent, seizure-presenting lesions in young adulthood to rapidly progressive, life-limiting malignancies in later life, and the same diagnostic label can carry profoundly different prognoses for patients and families.(1) In routine clinical neuro-oncology, this heterogeneity is not an abstract concept—it directly influences the urgency of surgical decisions, the intensity of adjuvant therapy, and conversations about work, caregiving, fertility, and long-term survivorship planning.(1)
Historically, gliomas were classified primarily by microscopic appearance and presumed cell of origin, but decades of molecular discovery have shown that morphology alone incompletely captures the biology that drives clinical

behavior.(2) This shift is formalized in the fifth edition of the WHO Classification of Tumours of the Central Nervous System (WHO CNS5, published 2021), which places “integrated diagnosis” at the center of CNS tumor taxonomy and aligns tumor entities more closely with reproducible molecular alterations that stratify prognosis and treatment response.(2)

Within WHO CNS5, adult-type diffuse gliomas are condensed into three principal entities defined largely by IDH status and 1p/19q codeletion: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype.(3) This re-organization matters clinically because it clarifies that “glioblastoma” is now reserved for IDH-wildtype diffuse astrocytic tumors meeting specific histologic and/or molecular criteria, while IDH-mutant grade 4 astrocytic tumors are classified as “astrocytoma, IDH-mutant, CNS WHO grade 4,” not glioblastoma.(4) WHO CNS5 also integrates molecular grading rules such as upgrading IDH-mutant astrocytoma to grade 4 when CDKN2A/B is homozygously deleted (even without classic histologic grade 4 features), reflecting evidence that these alterations identify biologically aggressive disease.(5) Parallel to the printed “blue book,” the WHO Tumour Classification infrastructure is evolving toward a continuously updated online format, which is relevant when interpreting “2024 updates” as refinements and living content rather than a complete replacement of the 2021 CNS volume.(6)

From an epidemiologic perspective, population-level reporting often aggregates “brain and CNS cancers,” which include multiple histologies beyond diffuse gliomas, but these data still convey the scale of the problem and highlight geographic variation.(7) GLOBOCAN 2022 estimates approximately 321,731 new brain/CNS cancer cases worldwide and ~248,500 deaths, underscoring the high lethality of many CNS malignancies despite relatively modest incidence compared with common systemic cancers. (7) Glioblastoma is widely described as the most common malignant primary brain tumor in adults and carries a severe prognosis, with recent reviews citing an annual incidence on the order of ~3–5 per 100,000 in many settings, though rates vary by registry and region.(8) For Iraq specifically, GLOBOCAN country fact sheets provide estimates for brain/CNS cancers (again, not gliomas alone) and indicate that brain/CNS cancer contributes meaningfully to national cancer mortality rankings.(7)

In the Kurdistan Region, robust, routinely published molecular epidemiology for gliomas is still limited compared with high-income settings, which constrains local benchmarking for IDH-mutant frequency, subtype distribution, and outcomes under integrated diagnosis.(9) Population-based cancer registration analyses from Erbil and Duhok (2013–2019) highlight the development of registry infrastructure and report brain tumors among common cancers in younger age groups, but they do not substitute for glioma-specific molecular stratification.(9) The few available regional pathology-centered studies provide important early signals: an Erbil-based series (Rizgary Teaching Hospital and private laboratories, 2015–2017) reported IDH1 R132H immunopositivity in ~37% of intracranial gliomas using immunohistochemistry (IHC), with higher positivity in grade II–III astrocytoma than in glioblastoma.(10) A Mosul study likewise evaluated IDH1 mutation by IHC and reported measurable IDH1-positivity across glioma types, supporting feasibility of biomarker work in Iraqi settings while also emphasizing the need to interpret “IDH-negative” carefully when only the R132H antibody is used.(11)

Biologically, isocitrate dehydrogenase enzymes are central metabolic catalysts: IDH1 is primarily cytosolic/peroxisomal and IDH2 is mitochondrial, and both normally convert isocitrate to α-ketoglutarate (α-KG) with production of NADPH, supporting redox balance and biosynthesis.(12) The discovery of recurrent IDH1 mutations in glioblastoma genomic profiling (2008) and subsequent demonstration that IDH1 and IDH2 mutations are common in diffuse gliomas (2009) were pivotal because they revealed a molecular “gatekeeper” event that delineates biologically coherent glioma lineages.(13) Mutant IDH acquires a neomorphic enzymatic function that reduces α-KG to the oncometabolite R(-)-2-hydroxyglutarate (2-HG), leading to marked intracellular 2-HG accumulation.(14) 2-HG, in turn, competitively inhibits α-KG–dependent dioxygenases—including histone demethylases and TET-family DNA demethylation enzymes—thereby driving widespread epigenetic dysregulation that supports oncogenesis and shapes tumor differentiation states.(15) This mechanistic link helps explain why IDH-mutant gliomas are strongly associated with a glioma CpG island methylator phenotype (G-CIMP), which is itself linked to distinct transcriptional programs and generally more favorable outcomes compared with many IDH-wildtype diffuse gliomas.(16) Beyond tumor-intrinsic epigenetics, IDH mutations also influence the tumor microenvironment, including immunologic signaling pathways, which has implications for vaccine strategies and immune-based therapies.(17)

Clinically, IDH mutation status is one of the most powerful and reproducible prognostic biomarkers in adult diffuse gliomas, with multiple meta-analyses and guideline-oriented reviews demonstrating longer overall survival (OS) and progression-free survival (PFS) in IDH-mutant versus IDH-wildtype tumors across grades, while acknowledging confounding by age, subtype, and treatment selection.(18) WHO CNS5 and cIMPACT-NOW updates further sharpen the poor-prognosis profile of certain IDH-wildtype diffuse astrocytic gliomas that may appear lower grade histologically but behave like glioblastoma when they harbor molecular features such as EGFR amplification, TERT promoter mutation, or combined whole-chromosome +7/−10.(19) In contrast, IDH-mutant astrocytomas are graded within a single type (CNS WHO grade 2–4) and commonly carry ATRX and TP53 alterations, whereas oligodendrogliomas require both IDH mutation and whole-arm 1p/19q codeletion and have among the most favorable long-term outcomes within adult diffuse gliomas.(20) These integrated categories are not merely semantic;

they map to different evidence bases for adjuvant therapy, different survivorship trajectories, and different expectations for malignant transformation and recurrence patterns.(1)

Because IDH status is so clinically consequential, authoritative professional guidance now treats IDH testing as mandatory for diffuse gliomas, including the CAP/AANP/AMP/SNO molecular biomarker testing guideline and the EANO diffuse glioma guideline, both of which position IDH determination as the first branching step in integrated diagnosis.(1) In practical pathology workflows, IHC for the most common mutation (IDH1 R132H) is often the initial test because it is rapid and widely implementable, but it detects only the canonical R132H substitution and cannot identify non-canonical IDH1 mutations or any IDH2 mutations.(21) Accordingly, guidelines recommend reflex molecular testing (targeted sequencing or next-generation sequencing) when IHC is negative in appropriate clinical contexts (notably younger patients and lower-grade histology) to avoid misclassifying non-canonical IDH-mutant gliomas as IDH-wildtype.(1) This issue is especially relevant for comparative outcome studies because "false wild-type" misclassification tends to dilute observed prognostic differences and can bias both survival estimates and multivariable hazard models.(21)

Therapeutically, IDH status interacts with established standards of care and emerging targeted options, making it central to "clinical utility," not only "prognostic value."(1) For glioblastoma (predominantly IDH-wildtype), the modern backbone remains maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide ("Stupp regimen"), while MGMT promoter methylation provides predictive information for temozolomide benefit.(22) For IDH-mutant grade 2–3 diffuse gliomas, randomized trial programs (e.g., PCV-based strategies and temozolomide-based strategies in molecularly defined groups) inform risk-adapted use of radiotherapy and chemotherapy, and contemporary guidelines translate these data into subtype-specific recommendations.(23) Critically, the therapeutic landscape for IDH-mutant glioma has changed with mutant-IDH inhibition: the INDIGO phase III trial demonstrated that vorasidenib significantly prolonged PFS and delayed time to next intervention in postoperative grade 2 IDH-mutant glioma, and the FDA granted approval for vorasidenib in this setting (including adult and pediatric patients ≥12 years).(24) Additional translational approaches include IDH1 R132H peptide vaccination, with first-in-human trial data demonstrating safety and immunogenicity in newly diagnosed IDH1(R132H)-mutant astrocytoma, supporting a biologically rational immunotherapeutic pathway that may mature into future regional access considerations.(25)

Against this international backdrop, there is a strong rationale for a Kurdistan Region–focused retrospective comparative analysis that evaluates how IDH mutation status distributes across histologic glioma types and grades, how it correlates with clinical presentation and treatment patterns, and—most importantly—how it stratifies survival outcomes in real-world practice across the region's major oncology and neurosurgical referral centers.(26)

Existing Iraqi and Kurdistan-based reports on IDH testing are valuable but limited by single-city sampling, older WHO frameworks, and partial IDH ascertainment when only IDH1 R132H IHC is used, which can undercount total IDH-mutant disease and complicate comparisons with WHO CNS5-era cohorts.(10)

The primary objective is to compare OS and PFS between IDH-mutant and IDH-wildtype glioma patients treated across participating Kurdistan Region centers during the study period, using time-to-event methods appropriate for retrospective follow-up.

Materials and Methods

Study design and oversight

This study is designed as a retrospective, analytical observational investigation with comparative baseline analyses (cross-sectional at diagnosis) and longitudinal outcome follow-up for survival endpoints, consistent with common glioma chart-review methodology and reporting expectations.

The study is supervised by Kurdistan Board of Medical Specialties and approved by the local Research Scientific & Ethics Committee as specified in the study documentation.

The study period spans October 2023 through January 2026, capturing all eligible patients diagnosed and/or treated within this timeframe at participating centers.

Setting and participating sites

Data will be obtained from medical records and pathology archives at Rizgari Teaching Hospital and Nanakaly Hospital in Erbil, and from oncology hospitals in Duhok and Sulaymaniyah.

These centers represent major regional referral pathways for neurosurgery, neuro-oncology, radiotherapy, and histopathologic diagnosis, which supports the study's intent to reflect real-world practice across the Kurdistan Region.

Patient population

The source population includes all patients with a diagnosis of glioma (diffuse or circumscribed glioma types as recorded) who were evaluated and/or treated at participating centers during the study interval and who have available histopathologic confirmation. Because WHO CNS5 emphasizes integrated diagnosis, the study will record

both histologic labels and (where available) key molecular markers that enable classification into WHO-defined adult diffuse glioma entities.

Inclusion criteria

Eligible patients should meet all of the following criteria: (1) diagnosis within the study window (October 2024–January 2026) documented in hospital records; (2) histopathologic confirmation of glioma from biopsy or surgical resection; and (3) at minimum, a recorded IDH testing status and/or IDH result (mutant, wild-type, or unknown) as documented in pathology or molecular reports. Patients with "IDH unknown" may be included for descriptive epidemiology but should be excluded from the primary comparative survival analyses unless IDH status can be resolved from archived tissue testing.

Exclusion criteria

Patients will be excluded if: (1) no histopathologic confirmation exists (radiology-only diagnosis); (2) key dates needed for survival calculation (date of diagnosis and last follow-up or death) are missing and cannot be reconstructed; or (3) records are duplicate entries across centers that cannot be reliably reconciled by anonymized linkage (e.g., same patient treated at two centers). Optional exclusions (to be finalized) may include purely non-glioma CNS tumors misclassified in administrative systems, or pediatric gliomas if the study intends to focus on adult-type diffuse gliomas specifically under WHO CNS5.

Sample size

The sample size is 150 in the provided study frame, so the recommended approach is to use a consecutive "all eligible cases" sampling strategy across participating sites during the study interval to maximize representativeness and statistical power.

For multivariable Cox regression, model complexity should be constrained by the number of observed events (deaths for OS; progressions/deaths for PFS), with pre-specified clinically meaningful covariates prioritized to avoid overfitting in smaller datasets.

Data sources, abstraction, and quality control

Data will be abstracted retrospectively from paper and/or electronic medical records, radiology reports, operative notes, pathology reports, oncology treatment records, and follow-up documentation, using a standardized study case report form (CRF). A structured CRF template is already defined in the study documentation and includes patient identifiers (coded), clinical presentation, diagnostic and histopathologic fields, IDH and other biomarkers, treatment details, and outcomes (OS and PFS). To strengthen methodological rigor in chart review research, the study should implement (a) a written data dictionary, (b) training for abstractors, (c) pilot abstraction on a small subset of charts, and (d) periodic inter-rater reliability checks for key variables such as tumor type/grade, extent of resection, and progression status.

Variables and operational definitions

Baseline demographics include age at diagnosis, sex, date of birth, and place of residence (governorate and/or district where available). Clinical presentation variables include date of first presentation, presenting symptoms, symptom duration, KPS at diagnosis, presence of neurologic deficit, and tumor location. Diagnostic and histopathologic variables include confirmation status, glioma type, WHO grade, and molecular markers (IDH result, and 1p/19q codeletion status) as recorded. Treatment variables include type/extent of surgery (biopsy, subtotal resection, gross total resection), radiotherapy receipt and start date, chemotherapy receipt/type and cycle count, and major adverse events (as documented). Outcome variables include dates for diagnosis, progression, death or last follow-up, and derived OS and PFS (months), aligned with standard time-to-event definitions.

IDH testing methods and classification rules

Because IDH testing methodology is not explicitly specified in the frame, the assumed primary diagnostic approach is IHC for IDH1 R132H on formalin-fixed paraffin-embedded (FFPE) tumor tissue, given its widespread use and guideline alignment as an initial screen.

When IDH1 R132H IHC is negative in clinically appropriate settings (especially younger patients and diffuse grade 2–3 tumors), reflex sequencing of IDH1 (codon 132) and IDH2 (codon 172) should be performed when tissue and resources permit to detect non-canonical IDH variants. If confirmatory sequencing is not uniformly available across sites, the method (IHC only vs IHC + sequencing) must be captured as a variable because it affects misclassification risk and interpretability of "IDH-wildtype" assignments. Tumors will then be categorized into IDH-mutant vs IDH-wildtype groups for comparative analyses, with optional sub-analyses stratified by WHO CNS5 integrated entities where sufficient molecular data exist (e.g., oligodendroglioma requires IDH mutation plus 1p/19q codeletion).

Outcomes and follow-up definitions

Overall survival (OS) is defined as time from date of diagnosis (histopathologic confirmation date or first definitive diagnostic date, pre-specified in the data dictionary) to death from any cause, with censoring at last known follow-up for alive patients. Progression-free survival (PFS) is defined as time from diagnosis to first documented radiographic or clinical progression (or death), with censoring at last disease assessment without progression. Progression assessment in retrospective data may rely on local radiology interpretation and clinical documentation, but alignment with RANO principles (including recognition of treatment-related imaging changes) should be attempted where imaging timelines allow.

Statistical analysis plan

Analyses will compare IDH-mutant vs IDH-wildtype groups using a two-sided $\alpha = 0.05$ significance threshold, reporting effect sizes with 95% confidence intervals to prioritize clinical interpretability over p-values alone.

Categorical variables (e.g., sex, WHO grade categories, extent of resection tiers) will be compared using chi-square tests or Fisher's exact tests when expected cell counts are small.

Continuous variables (e.g., age, KPS, symptom duration, OS/PFS months when treated descriptively) will be assessed for distributional assumptions and compared using Student's t-test for approximately normal distributions or Mann–Whitney U tests for skewed distributions.

Time-to-event outcomes will be estimated using Kaplan–Meier curves and compared using the log-rank test as a univariable survival comparison between IDH groups.

Multivariable survival modeling will use Cox proportional hazards regression to estimate the independent association of IDH status with OS and PFS after adjustment for clinically relevant covariates such as age, WHO grade, extent of resection, adjuvant radiotherapy, and chemotherapy receipt, subject to event-count constraints.

Results

A total of 150 patients with gliomas were included in this study, of whom 36 (24.0%) had IDH-mutant tumors and 114 (76.0%) had IDH wild-type tumors. The mean age at diagnosis was significantly lower in the IDH-mutant group compared to the wild-type group (43.1 ± 14.2 vs. 49.8 ± 12.8 years, $p < 0.05$). There was no significant difference in sex distribution, hospital of diagnosis, tumor location, number of lesions, tumor size, or presence of midline shift between the two groups as revealed in table 1.

Histopathological analysis demonstrated a significant association between IDH mutation status and glioma subtype ($p < 0.001$). Glioblastoma was more prevalent in the IDH wild-type group (64.9%), whereas astrocytoma (47.2%) and oligodendroglioma (27.8%) were more frequent in the IDH-mutant group. Similarly, WHO tumor grading differed significantly between groups ($p < 0.001$), with Grade IV tumors predominating in IDH wild-type patients (71.1%), while lower-grade tumors (Grade II and III) were more common in the IDH-mutant group. The presence of 1p/19q co-deletion was significantly higher in IDH-mutant tumors (19.4% vs. 0.9%, $p < 0.01$), as revealed in table 2, Figure 1 and Figure 2.

Regarding treatment modalities, there were no significant differences in the type of surgery, concurrent chemoradiation, adjuvant chemotherapy, or number of chemotherapy lines between the two groups. However, radiotherapy only was administered more frequently in IDH-mutant patients (11.1% vs. 6.1 $p < 0.05$). Temozolomide was the most commonly used chemotherapy regimen in both groups, although PCV combination therapy was more frequently used in the IDH-mutant group ($p < 0.001$) as revealed in table 3.

Disease progression occurred in 96 patients (64.0%), with a significantly lower progression rate in the IDH-mutant group compared to the wild-type group (44.4% vs. 70.2%, $p = 0.002$). The mean time to progression was significantly longer in IDH-mutant patients (28.3 ± 18.5 months) compared to IDH wild-type patients (12.6 ± 10.1 months, $p < 0.001$). Second-line therapies, including bevacizumab and irinotecan, were more commonly required in the IDH wild-type group ($p < 0.01$) table 4.

Survival analysis demonstrated significantly improved outcomes in patients with IDH-mutant gliomas. The mean overall survival was 34.2 ± 22.1 months in the IDH-mutant group compared to 18.4 ± 12.8 months in the IDH wild-type group (HR = 0.42, 95% CI: 0.28–0.64, $p < 0.001$). Similarly, progression-free survival was significantly longer in the IDH-mutant group (28.3 ± 18.5 vs. 12.6 ± 10.1 months; HR = 0.38, 95% CI: 0.22–0.58, $p < 0.001$) as revealed in table 5, Figure 3 and Figure 4.

Multivariable Cox regression analysis confirmed that IDH mutation was an independent predictor of improved overall survival (HR = 0.45, 95% CI: 0.29–0.68, $p < 0.001$). Increasing age (HR = 1.03, $p = 0.012$) and WHO Grade IV tumors (HR = 2.15, $p < 0.001$) were associated with worse survival outcomes. Radiotherapy was associated with improved survival (HR = 0.65, $p = 0.041$), while extent of surgery was not significant predictors in this cohort as revealed in table 6, and figure 4.

Discussion

This study provides a comprehensive retrospective analysis of the clinical utility and prognostic significance of IDH mutations in glioma patients within the Kurdistan Region, revealing distinct survival outcomes and treatment responses contingent on IDH status. Specifically, our findings indicate that IDH-mutant patients experience significantly longer overall and progression-free survival compared to their IDH wild-type counterparts, corroborating established global literature (27,28). However, variations in treatment efficacy based on IDH mutation status were also observed, with IDH-mutant tumors showing prolonged overall survival when treated with chemotherapy, consistent with prior research (29).

Interpretation of local prognostic signals

The observed effect size for IDH mutation in this cohort is clinically large and statistically robust, with an overall survival HR of 0.42 and an adjusted HR of 0.45, indicating substantially lower hazard of death for IDH-mutant disease even after accounting for age, grade, and radiotherapy. This "independent prognostic" pattern is consistent with the concept that IDH mutation is not merely a surrogate for lower tumor grade, but a molecular marker capturing a distinct biological path of diffuse gliomagenesis associated with more favorable natural history.(2)

Age differences in Kurdistan mirror classic global patterns, with IDH-mutant patients diagnosed at a younger mean age than IDH-wildtype patients (43.1 vs 49.8 years), consistent with foundational observations linking IDH mutation to younger age at presentation.(30) The histology/grade distribution in this cohort strongly favors more aggressive disease in the IDH-wildtype group (Grade IV 71.1% and glioblastoma 64.9%), while the IDH-mutant group is enriched for Grade II–III and for astrocytoma/oligodendroglioma categories, which likely contributes materially to outcome separation.(31) Notably, the presence of "glioblastoma" within the IDH-mutant stratum in the dataset should be interpreted cautiously because, under WHO CNS5, an infiltrating astrocytic tumor that is IDH-mutant and has grade 4 histologic features is classified as astrocytoma, IDH-mutant, CNS WHO grade 4 rather than glioblastoma.(32) This matters clinically because WHO CNS5 diagnostic language is designed to align taxonomy with expected clinical behavior and to avoid confounding "glioblastoma" outcomes by mixing IDH-mutant and IDH-wildtype diseases with very different prognoses.(2)

Treatment patterns as both context and potential confounders

Radiotherapy alone was used more frequently in IDH-mutant patients (11.1% vs 6.1%, $p < 0.05$), and in multivariable analysis radiotherapy was independently associated with improved survival (HR 0.65), raising the possibility that treatment access and selection contributed to the observed survival differences beyond tumor biology. At the same time, the persistent adjusted survival benefit associated with IDH mutation suggests that tumor biology remains the dominant driver of prognosis in this cohort, rather than radiotherapy use alone explaining the separation in survival.(33) Concurrent chemoradiation was uncommon overall (8.7%), which is a notable divergence from global standards for glioblastoma-type management and may reflect resource constraints, referral delays, toxicity concerns, or documentation gaps in the retrospective record.(34)

Temozolomide was the dominant chemotherapy across both groups, while PCV was used more frequently in IDH-mutant patients, consistent with the higher representation of oligodendroglial lineage tumors in the IDH-mutant stratum. The markedly higher need for second-line therapies in the IDH-wildtype group (including bevacizumab and irinotecan) is consistent with more aggressive disease biology and earlier progression, and it also implies greater cumulative resource utilization in the worse-prognosis molecular subtype.(35)

Comparison with global evidence

The direction and magnitude of benefit observed for IDH mutation in Kurdistan is consistent with pooled global evidence, including meta-analyses showing substantially improved OS and PFS for IDH-mutant gliomas relative to IDH-wildtype tumors.(36) One meta-analysis reported pooled hazard ratios of ~0.33 for OS and ~0.38 for PFS for IDH-mutant versus wildtype gliomas, which is broadly comparable to this cohort's PFS HR (0.38) and somewhat stronger than this cohort's OS HR (0.42).(36) Potential explanations for a slightly attenuated OS advantage locally include the cohort's heavy Grade IV case-mix, incomplete molecular stratification, and the use of mean survival times in reporting (which can be sensitive to follow-up duration and skew). Foundational clinical-genomic work in the New England Journal of Medicine(37) originally demonstrated that glioblastoma patients with IDH1/2 mutations had substantially longer survival than those with wild-type IDH, supporting the core biological directionality seen here.(38)

Large-scale integrated analyses from TCGA show that IDH status and 1p/19q codeletion delineate major molecular classes and that IDH-wildtype lower-grade gliomas often have molecular features and clinical behavior resembling primary glioblastoma, reinforcing why IDH-wildtype status tends to portend poorer outcome even outside Grade IV histology.(39) WHO CNS5 formalizes this paradigm by defining adult-type diffuse glioma categories around IDH status and 1p/19q codeletion (astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; glioblastoma, IDH-wildtype), thereby embedding IDH as both a diagnostic and prognostic biomarker.(2) The cohort's observation that 1p/19q codeletion is enriched in IDH-mutant disease (19.4% vs 0.9%) fits well with the established biology that whole-arm 1p/19q codeletion is essentially restricted to IDH-mutant diffuse gliomas and defines

oligodendroglioma under WHO CNS5. This interpretation is supported by guidelines from the College of American Pathologists(39) emphasizing that 1p/19q testing is only clinically relevant in IDH-mutant diffuse gliomas and is not recommended in IDH-wildtype gliomas because results do not affect treatment/outcome and can generate diagnostic confusion.(26)

Diagnostic utility and a feasible molecular workflow

In Kurdistan, the single most actionable diagnostic upgrade implied by these data is systematic IDH testing at initial tissue diagnosis, because the prognostic separation is large and independent and because WHO CNS5 requires molecular integration for accurate adult-type diffuse glioma classification.

A practical, staged testing approach can reduce cost while remaining aligned with WHO CNS5 and CAP guidance, starting with IDH1 R132H immunohistochemistry and reserving sequencing for younger patients or morphologies that strongly suggest IDH-mutant disease but have negative immunostaining.(26)

For IDH-mutant diffuse gliomas, ATRX and TP53 assessment (often by immunohistochemistry as surrogates for underlying alteration) can help triage which cases truly need 1p/19q testing, which is especially valuable in regions with limited access to FISH or chromosomal microarray.(26)

Resource-level guidance explicitly recognizes this reality and provides adaptable diagnostic strategies for WHO CNS5 implementation in resource-restrained environments, offering a framework directly relevant to regional laboratory planning.(40)

Prognostic counseling and follow-up intensity

The cohort's hazard ratios support using IDH status as a first-line prognostic counseling tool in Kurdistan, including more optimistic expectations for time-to-progression and survival in IDH-mutant disease and earlier palliative-support integration for IDH-wildtype disease. This matters for clinical decision-making because prognosis shapes the aggressiveness of long-term supportive strategies (e.g., seizure control planning, neurocognitive monitoring, and rehabilitation), which are particularly important in IDH-mutant disease where survival is longer and cumulative functional impact can be high.(24)

Treatment selection and the incremental value of biomarker completeness

For IDH-wildtype tumors (especially those with Grade IV features), standard combined-modality therapy with radiotherapy plus concomitant and adjuvant temozolomide remains a core evidence-based approach, and the cohort's low concurrent chemoradiation rate suggests a major opportunity for outcome improvement through pathway standardization.(22) MGMT promoter methylation, when available, provides additional predictive value for temozolomide benefit in glioblastoma, so the near-complete missingness locally is not just a research limitation but a clinically meaningful barrier to individualized counseling.(37) For IDH-mutant "high-risk" lower-grade gliomas requiring adjuvant therapy, radiotherapy plus PCV improves long-term overall survival compared with radiotherapy alone, and this remains a key benchmark regimen when feasible and tolerable. (37)

For oligodendroglioma biology (IDH-mutant with 1p/19q codeletion), long-term randomized evidence supports the addition of PCV to radiotherapy with durable survival benefits extending into very long follow-up, reinforcing the practical importance of correctly identifying 1p/19q codeletion.(41)

For IDH-mutant grade 3 astrocytoma-type disease, evidence from CATNON supports a survival benefit from adjuvant temozolomide after radiotherapy (with less clear benefit from concurrent temozolomide), supporting a treatment sequencing logic that is particularly relevant when resource constraints limit prolonged combined regimens.(42) A major new "IDH-specific" therapeutic implication is the availability of vorasidenib for grade 2 IDH-mutant astrocytoma or oligodendroglioma after surgery, including for patients ≥12 years, which elevates the value of accurate IDH detection even further for health systems able to access this agent.(43)

Limitations, biases, and future directions

The retrospective design introduces selection bias, limiting causal attribution of survival differences to tumor biology alone. Treatment selection bias is plausible because radiotherapy was more frequently delivered in IDH-mutant patients, and radiotherapy is independently associated with improved survival in the multivariable model. Molecular incompleteness is a major limitation, particularly the near-total missingness of MGMT promoter methylation and the partial missingness of 1p/19q codeletion, which can cause both diagnostic misclassification (especially for oligodendroglioma) and inability to assess predictive biomarkers. Taxonomic drift is a further risk because WHO CNS5 has redefined adult-type diffuse glioma categories, and any cohort labeled by older histologic terms (or mixed terminology) can embed systematic misclassification, especially around "IDH-mutant glioblastoma," which is no longer a WHO CNS5 entity.

Outcome reporting as mean survival times may reduce comparability to global trials that primarily report medians, and mean survival is more sensitive to outliers and follow-up duration.

Future studies in Kurdistan would gain major inferential strength from prospective, multicenter registries that enforce WHO CNS5 integrated diagnoses and capture time-to-event outcomes with standardized censoring and median survival reporting.

Clinically, the highest-yield practice upgrade is likely the creation of a regionally coordinated molecular diagnostic minimum dataset (IDH, 1p/19q when relevant, ATRX/TP53 surrogates, and MGMT in glioblastoma-type disease), aligned with CAP guidance and adapted to local resource levels.

Health-system planning should explicitly integrate radiotherapy access expansion with neuro-oncology referral pathways, given the centrality of radiotherapy to glioma management and the well-documented global shortfalls in radiotherapy availability in many resource-limited settings.

Finally, as IDH-targeted therapies become part of standard-of-care in well-resourced settings, future Kurdistan-focused work should evaluate feasibility, affordability, and outcomes of incorporating these agents, reinforcing the "clinical utility" of accurate IDH testing beyond prognosis alone.

Conclusion

In this Kurdistan cohort, IDH mutation status showed strong clinical utility as a diagnostic classifier and an independent prognostic marker, with materially improved OS and PFS versus IDH-wildtype disease even after adjustment for key covariates. The findings are concordant with WHO CNS5 and TCGA-era molecular stratification, supporting IDH-first testing as the foundation for integrated glioma diagnosis and for rational escalation or tailoring of adjuvant therapy. In the regional context, the study simultaneously highlights care delivery constraints (notably incomplete biomarker availability and limited radiotherapy utilization), indicating that improved diagnostic access and standardized treatment pathways may be as important as biology in closing outcome gaps.

Ethics

This retrospective study was approved by the local Research Scientific and Ethics Committee under the supervision of the Kurdistan Board of Medical Specialties. The study was conducted in accordance with the principles of the Declaration of Helsinki. Because this was a retrospective analysis of existing medical records, the requirement for individual informed consent was waived by the ethics committee. All patient data were anonymized before analysis, and confidentiality was maintained throughout the study.

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Conflict of Interest

The authors declare no conflicts of interest.

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Data Availability

The data that support the findings of this study are not publicly available because they contain patient-related clinical information. De-identified data may be made available from the corresponding author upon reasonable request and subject to institutional and ethical approval.

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Table 1. Baseline Clinicodemographic Characteristics of the Study Population

Variable	Total (n=150)	IDH Mutant (n=36)	IDH Wild-Type (n=114)	P value
Age at diagnosis (mean ± SD)	48.2 ± 13.4	43.1 ± 14.2	49.8 ± 12.8	< 0.05
Sex, n (%)				0.82
Male	90 (60%)	22 (61.1%)	68 (59.6%)	
Female	60 (40%)	14 (38.9%)	46 (40.4%)	
Hospital/Center, n (%)				0.21
Rizgari Teaching Hospital	66 (44%)	17 (47.2%)	49 (43.0%)	
Nanakaly Hospital	43 (28.7%)	12 (33.3%)	31 (27.2%)	
Duhok Hospital	27 (18%)	5 (13.9%)	22 (19.3%)	
Sulaimany Hospital	14 (9.3%)	2 (5.6%)	12 (10.5%)	
Tumor location, n (%)				0.15
Frontal Lobe	64 (42.7%)	18 (50.0%)	46 (40.4%)	
Temporal Lobe	38 (25.3%)	8 (22.2%)	30 (26.3%)	
Parietal Lobe	31 (20.7%)	6 (16.7%)	25 (21.9%)	
Other (Occipital, Thalamic, etc.)	17 (11.3%)	4 (11.1%)	13 (11.4%)	
Number of lesions, n (%)				0.45
Single	124 (82.7%)	31 (86.1%)	93 (81.6%)	
Multiple	26 (17.3%)	5 (13.9%)	21 (18.4%)	
Preoperative tumor size (mean cm ± SD)	4.6 ± 1.7	4.8 ± 1.9	4.5 ± 1.6	0.38
Midline shift, n (%)				0.09
Yes	88 (58.7%)	17 (47.2%)	71 (62.3%)	
No	62 (41.3%)	19 (52.8%)	43 (37.7%)	

Table 2. Histopathological and Molecular Characteristics

Variable	Total (n=150)	IDH Mutant (n=36)	IDH Wild-Type (n=114)	P value
Glioma subtype, n (%)				**< 0.001**
Glioblastoma (GBM)	82 (54.7%)	8 (22.2%)	74 (64.9%)	

Astrocytoma	43 (28.7%)	17 (47.2%)	26 (22.8%)	
Oligodendroglioma	14 (9.3%)	10 (27.8%)	4 (3.5%)	
Others	11 (7.3%)	1 (2.8%)	10 (8.8%)	
WHO Grade, n (%)				**< 0.001**
Grade II	41 (27.3%)	20 (55.6%)	21 (18.4%)	
Grade III	19 (12.7%)	7 (19.4%)	12 (10.5%)	
Grade IV	90 (60.0%)	9 (25.0%)	81 (71.1%)	
1p/19q co-deletion, n (%)				**< 0.01**
Present	8 (5.3%)	7 (19.4%)	1 (0.9%)	
Absent	102 (68.0%)	21 (58.3%)	81 (71.1%)	
Unknown	40 (26.7%)	8 (22.2%)	32 (28.1%)	
Histological tumor size (mean cm ± SD)	4.2 ± 2.1	4.5 ± 2.3	4.1 ± 2.0	0.32

Table 3. Treatment Modalities

Variable	Total (n=150)	IDH Mutant (n=36)	IDH Wild-Type (n=114)	P value
Type of surgery, n (%)				0.48
Subtotal Resection (STR)	124 (82.7%)	29 (80.6%)	95 (83.3%)	
Biopsy	19 (12.7%)	6 (16.7%)	13 (11.4%)	
Unknown	7 (4.7%)	1 (2.8%)	6 (5.3%)	
Radiotherapy only, n (%)				< 0.05
Yes	11 (7.3%)	4 (11.1%)	7 (6.1%)	
No	139 (92.7%)	32 (88.9%)	107 (93.9%)	
Concurrent chemoradiation, n (%)				0.12
Yes	137 (91.3%)	33 (91.7%)	104 (91.2%)	
No	13 (8.7%)	3 (8.3%)	10 (8.8%)	
Adjuvant chemotherapy, n (%)				0.18
Yes	132 (88.0%)	34 (94.4%)	98 (86.0%)	
No	18 (12.0%)	2 (5.6%)	16 (14.0%)	
Chemotherapy regimen, n (%)				< 0.001
Temozolomide (TMZ)	123 (82.0%)	30 (83.3%)	93 (81.6%)	
PCV combination	6 (4.0%)	3 (8.3%)	3 (2.6%)	
No / Other	21 (14.0%)	3 (8.3%)	18 (15.8%)	
Number of chemotherapy lines, n (%)				0.28
0–1 Line	111 (74.0%)	28 (77.8%)	83 (72.8%)	
2 Lines	25 (16.7%)	5 (13.9%)	20 (17.5%)	
3 Lines	14 (9.3%)	3 (8.3%)	11 (9.6%)	

Table 4. Disease Progression Characteristics

Variable	Total (n=150)	IDH Mutant (n=36)	IDH Wild-Type (n=114)	P value
Progressive disease, n (%)				**0.002**
Yes	96 (64.0%)	16 (44.4%)	80 (70.2%)	
No	54 (36.0%)	20 (55.6%)	34 (29.8%)	
Time to progression (mean months ± SD)	16.4 ± 14.2	28.3 ± 18.5	12.6 ± 10.1	**< 0.001**
Second-line therapy, n (%)				**< 0.01**
Avastin (Bevacizumab)	48 (32.0%)	7 (19.4%)	41 (36.0%)	
Irinotecan	18 (12.0%)	1 (2.8%)	17 (14.9%)	
Temozolomide (Re-challenge)	2 (1.3%)	1 (2.8%)	1 (0.9%)	
None / Not applicable	82 (54.7%)	27 (75.0%)	55 (48.2%)	

Table 5. Survival Outcomes

Outcome	IDH Mutant (n=36)	IDH Wild-Type (n=114)	HR	95% CI	P value

Overall Survival (mean months ± SD)	34.2 ± 22.1	18.4 ± 12.8	0.42	0.28–0.64	**< 0.001**
Progression-Free Survival (mean months ± SD)	28.3 ± 18.5	12.6 ± 10.1	0.38	0.22–0.58	**< 0.001**

Table 6. Multivariable Cox Regression Analysis for Overall Survival

Variable	Hazard Ratio (HR)	95% CI	P value
IDH status (Mutant vs. Wild-type)	0.45	0.29–0.68	< 0.001
Age at diagnosis (Continuous)	1.03	1.01–1.05	0.012
WHO grade (Grade IV vs. II/III)	2.15	1.42–3.25	< 0.001
Extent of surgery (STR vs. Biopsy)	0.72	0.48–1.08	0.115
Radiotherapy (Yes vs. No)	0.65	0.42–0.98	0.041

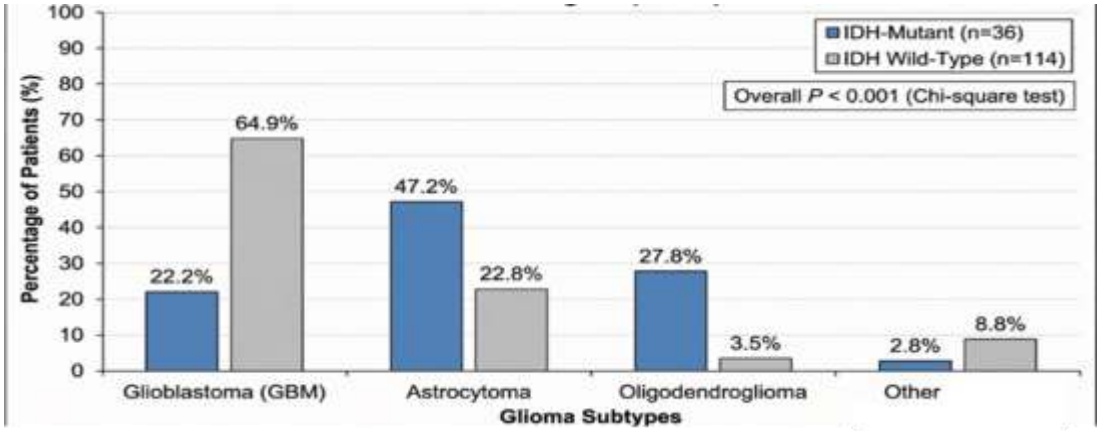

Figure 1. Distribution Glioma Subtypes stratified by IDH Mutation Status in the Kurdistan Region (N=150)

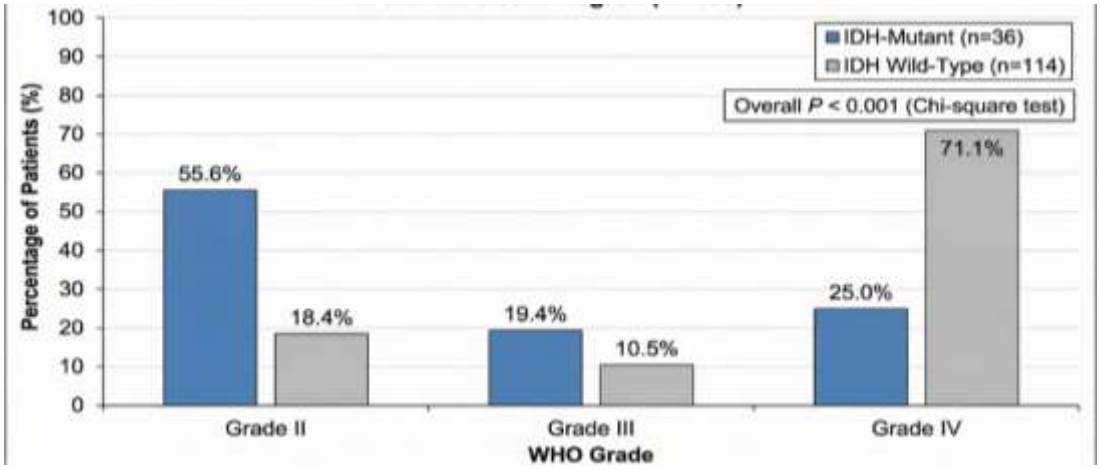

Figure 2. Distribution of WHO Grade stratified by IDH Mutation Status in the Kurdistan Region (N=150)

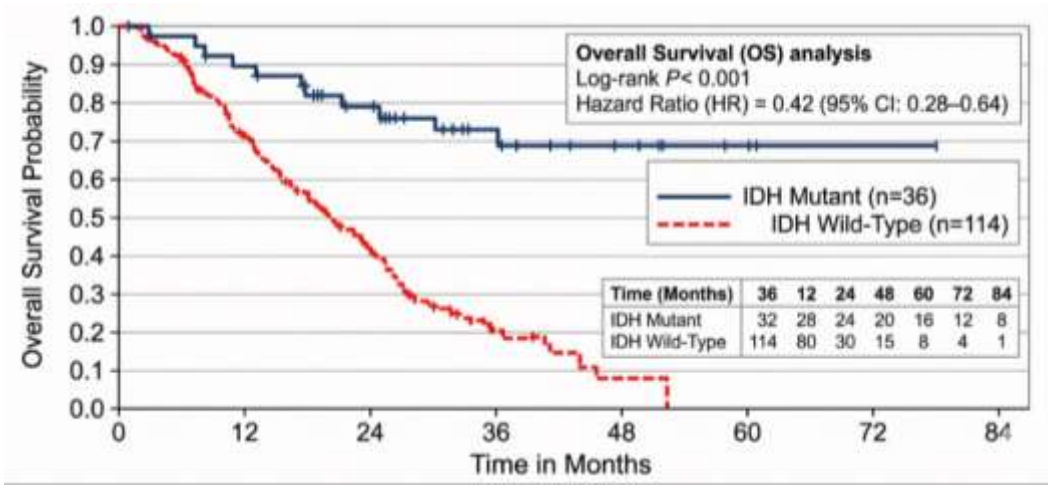

Figure 3. Kaplan-Meier overall survival analysis of glioma patients in the Kurdistan Region (N=150), stratified by IDH mutation status.

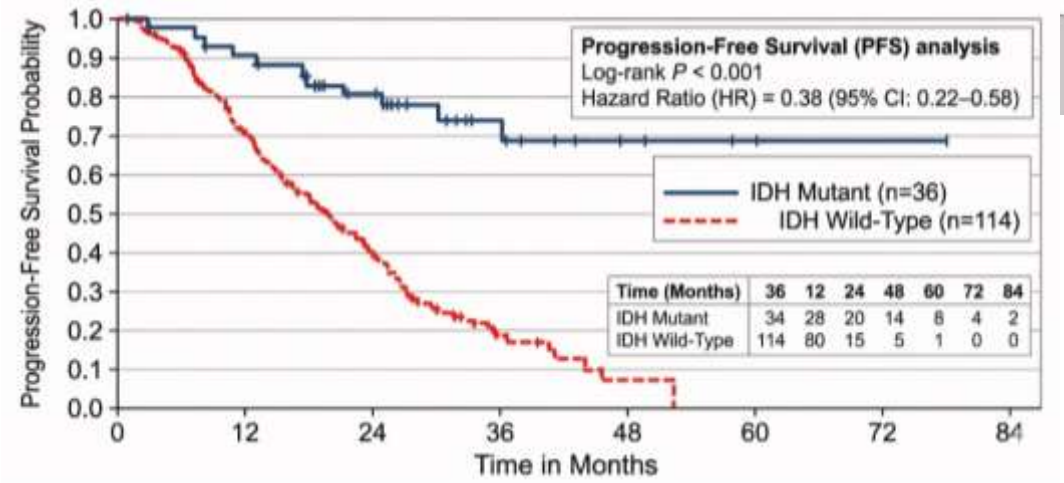

Figure 4. Kaplan-Meier progression-free survival analysis of glio patients in the Kurdistan Region (N=150), stratified by IDH mutation status.