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RESEARCH

Long-term outcomes in IDH-wildtype (IDH-wt) gliomas with historical WHO grade 2 and 3 histology

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Abstract

Purpose IDH-wt diffuse gliomas with histologic grade 2–3 features and distinct molecular characteristics are now classified as molecular glioblastoma, yet outcomes and optimal management remain incompletely defined in a contemporary cohort.

Methods Adults with histologic grade 2–3 IDH-wt gliomas diagnosed from 1996 to 2019 were retrospectively identified. Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan-Meier methods, with Cox regression used to assess prognostic factors. To account for noncanonical IDH mutations, subgroup analyses were performed in those age > 55 or with next generation sequence (NGS) IDH testing.

Results A total of 134 patients were included, with a median follow-up of 29.8 months. Median OS was 35 months (95% CI: 28.8–43), and median PFS was 20.9 months (95% CI: 14.5–27.4). Grade 2 tumors demonstrated significantly improved outcomes compared to grade 3 tumors (median OS 94.5 vs. 29.8 months; median PFS 50.6 vs. 15.3 months). Among grade 3 tumors, sequential radiation and chemotherapy yielded a median OS of 29.8 months versus 29.8 months with concurrent chemoradiation followed by chemotherapy ($p = 0.17$); median PFS was 22.2 months versus.

Conclusion IDH-wt gliomas with grade 2-3 histology have heterogeneous outcomes. Grade 3 tumors show survival comparable to molecular glioblastoma, while a subset of grade 2 tumors exhibit prolonged survival. Concurrent chemoradiation did not confer a survival advantage over sequential therapy in grade 3 tumors, supporting reevaluation of treatment intensity in selected patients.

Keywords Molecular glioblastoma · Concurrent chemoradiation · Sequential radiation and chemotherapy · IDH wildtype glioma radiotherapy management · Molecular grade 4 glioma management · Molecular grade 4 glioblastoma · Chemotherapy · Radiotherapy · Sequential

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Introduction

Many gliomas with histologically lower grade appearing features but an absence of an isocitrate dehydrogenase (IDH) mutation are considered IDH-wildtype (IDH-wt) diffuse gliomas and currently reclassified as WHO grade 4 under the 2021 WHO criteria [1]. This reclassification was prompted by analyses demonstrating survival outcomes comparable to WHO grade 4 glioblastoma (GBM). Among some of the molecular features identified as hallmarks for aggressive behavior consistent with molecular GBM include TERT promoter mutations, EGFR amplification, and chromosome 7 gain/10 loss. [2] However, these distinctions may not encompass all the potential features for the now historical grade 2 or grade 3 gliomas that are IDH-wt and reclassified as grade 4. Clinical trial data have demonstrated notable heterogeneity in the population's molecular profile and outcomes. [3] Separately, germline predisposition syndromes including POT1, Li-Fraumeni syndrome, NF1, and Lynch syndrome can give rise to IDH-wt gliomas that may behave distinctly or be newly classified in pediatric type-gliomas, underscoring that reclassification as WHO grade 4 is not universal across all IDH-wt tumors. Hence there is an unmet need to better define the historical outcomes of the population of specifically IDH-wt lower grade histologically appearing tumors that accounts for the treatment received to provide context for future therapeutic outcomes. Secondly, emerging data demonstrate that these forms of IDH-wt lower histological grade diffuse gliomas and molecular GBM may not benefit from the same chemoradiation therapy clinical practice regimens defined by classic histological grade 4 GBM. In fact, unplanned subset analyses of grade 3 IDH-wt gliomas enrolled in CATNON have questioned the role of concurrent therapy, although the study was not initially designed to directly compare concurrent followed by adjuvant chemotherapy versus sequential RT followed by adjuvant chemotherapy [4].

Despite this updated classification, IDH-wt lower-grade gliomas (LGGs) remain under characterized. Prior studies demonstrate poor outcomes among these tumors frequently mirroring those of histologic GBM with reported median OS between 15 and 30 months [2,5,6]. However, these data are often derived from mixed populations or smaller cohorts, limiting the ability to account for treatment heterogeneity or incorporate longitudinal follow-up. Moreover, recent studies have suggested the existence of clinically meaningful heterogeneity within IDH-wt LGGs, including subsets of patients with unexpectedly prolonged survival [7,8].

In this context, we sought to characterize long-term outcomes in a contemporary real-world cohort of patients with IDH-wt gliomas with WHO grade 2 and 3 histological features. By accounting for treatment paradigms prior to 2021, this study adds real-world evidence to the limited literature on IDH-wt LGGs and provides a framework for identifying subsets of patients who may benefit from risk-adapted therapeutic strategies.

Methods

Patient identification

Patients > 18 years old diagnosed between 1996 and 2019 with histologic WHO grade 2 or 3 gliomas and confirmed IDH-wt status were identified using natural language processing (NLP) within pathology reports of "astrocytoma," "anaplastic astrocytoma". Tumors designated as WHO grade 1 or WHO grade 4, specifically with histologic features of GBM microvascular proliferation and/or pseudopalisading necrosis were excluded. Also excluded were those with known IDH mutations based on immunohistochemistry (IHC) or next generation sequencing (NGS). Histologic grade was assigned based on the designation in the original pathology report at first diagnosis and corresponded to the contemporaneous WHO classification at the time of diagnosis. Because case identification relied on pathology reports specifically diagnosed as astrocytoma or anaplastic astrocytoma, tumor entities with distinct diagnostic labels such as glioneuronal tumors would be excluded. However, beyond the exclusion of tumors with known IDH mutation and H3K27M alteration, formal molecular or DNA methylation-based reclassification according to WHO 2021 criteria was not performed for this historical cohort.

IDH status determination

IDH mutation status was ascertained using data from pathology reports, IHC, and NGS. IHC was used to detect the IDH1-R132H mutation. In patients without NGS, IDH-wt status was based on negative IHC. An additional subgroup analysis was conducted in patients with IDH-wt status confirmed specifically by NGS, providing a high molecular certainty cohort for sensitivity analysis when compared to the total cohort. Secondly, because non-canonical IDH mutations are less common in those > 55 years, a subgroup analysis was performed in patients over the age of 55 with IDH-wt status determined by IHC alone combined with those with NGS testing for additional sensitivity analysis. NGS testing was performed using the MD Anderson Mutation Analysis Precision Panel (MAPP), a targeted panel of approximately 700 genes sequenced on the NovaSeq 6000 platform, or the Oncomine Comprehensive Assay; both platforms include coverage of IDH1/2, TERT promoter, EGFR, CDKN2A, ATRX, and TP53, among other genes. Available molecular

features including chromosome 7 gain/10 loss, TERT promoter alteration, and EGFR amplification were abstracted where reported; however, complete molecular profiling data were available in only a small subset of patients, precluding formal incorporation into multivariable analyses. Additionally, tumors with H3K27M alterations were excluded, as these represent a distinct molecular entity under current WHO classification.

Clinical and treatment variables

Collected demographic and clinical data included age at diagnosis, sex, race/ethnicity, tumor size and location, and pre-operative Karnofsky Performance Status (KPS). Tumor size was assessed based on maximum tumor dimension from radiology reports or individual review of the images when available with T2/FLAIR used for non-enhancing tumors and T1c used for enhancing tumors. In our analysis with stratification by size, we a priori selected less than vs. greater than 5 cm as a potentially clinically meaningful threshold for historical high-risk features based on EORTC 22033–26033, recognizing that some cases of the population could have been classified as high-risk lower grade gliomas in the past. Surgical intervention was categorized based on operative and imaging documentation as gross total resection (GTR), subtotal resection (STR), or biopsy only. Adjuvant therapy was classified into five treatment groups: (1) concurrent chemoradiation followed by chemotherapy (CRT+chemotherapy), (2) radiation followed by chemotherapy (RT+chemotherapy), (3) RT alone, (4) chemotherapy alone, and (5) no adjuvant therapy. Chemotherapy regimens included temozolomide (TMZ) or PCV. RT dose and fractionation were abstracted from treatment plans where available.

Statistical analysis

Descriptive statistics were used to summarize patient, tumor, and treatment characteristics. OS and PFS were estimated using the Kaplan-Meier method, with time measured from diagnosis to death for OS and to progression or death for PFS. Radiographic progression was determined based on the radiologist's interpretation of serial surveillance MRI and confirmatory clinical documentation in the chart; given the retrospective nature of this cohort spanning nearly two decades, formal application of a single standardized progression framework such as RANO or RANO 2.0 could not be verified for all cases, representing an inherent limitation of retrospective real-world data. Survival curves were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were constructed to evaluate factors associated with OS and PFS. Covariates considered in multivariable models included age at diagnosis, tumor size ($\geq$5 cm vs. $<$5 cm), histologic grade (grade 3 vs. grade 2), post-operative Karnofsky Performance Status ($\geq$80 vs. 50–70), extent of resection (gross total resection vs. subtotal resection/biopsy), and treatment strategy (RT alone, concurrent CRT, or sequential RT followed by chemotherapy), with appropriate reference categories specified a priori. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.

Prespecified subgroup and sensitivity analyses were performed to assess the robustness of treatment effects and prognostic associations in molecularly relevant cohorts. These included analyses restricted to grade 3 tumors, as well as a biologically enriched subgroup with IDH status confirmed by NGS or by IHC only in patients aged $>$55 years. Additional sensitivity analyses evaluated survival outcomes stratified by treatment sequencing (concurrent vs. sequential) within these subgroups. All survival analyses used endpoint-specific time and event variables, and patients with indeterminate event coding were excluded from the corresponding analyses. All statistical tests were two-sided, and p-values $<$0.05 were considered statistically significant. Analyses were performed using SPSS Statistics, version 29.0 (IBM Corp, Armonk, NY).

To reduce treatment-selection bias in the grade 3 cohort comparison of CRT+chemotherapy versus RT+chemotherapy, a propensity score matched analysis was performed using nearest-neighbor matching based on age, postoperative Karnofsky Performance Status, extent of resection, and tumor size. Balance was assessed across matched cohorts prior to survival comparison. Propensity-matched survival was analyzed using Kaplan-Meier methods and log-rank testing (Supplementary Figure B3).

Results

Patient demographic and clinical characteristics

A total of 134 adult patients diagnosed with IDH-wt historical histological grade 2 or 3 diffuse gliomas between 1996 and 2019 were included (Table 1). Patients with multifocal disease or brainstem disease were excluded as these would impact both treatment and survival independently. The median age at diagnosis was 51 years (range 16–74), with a slight male predominance (55.2%). Most patients were white (88.2%), and frontal or temporal lobes were the most common tumor locations. Histologically, 78.4% had grade 3 tumors, and 21.6% had grade 2 tumors. The predominant histologic subtype was anaplastic astrocytoma (76.9%). Gross total resection (GTR) was achieved in 22.3%, subtotal resection (STR) in 31.3%, and biopsy alone in 44.0%. Of

Table 1 Total cohort patient characteristics of grade 2 and 3 IDH wildtype diffuse gliomas

Characteristic		Total $N=134$	%
Age, years (median, range)		51 (16–74)	
Female		60	44.8
Male		74	55.2
Tumor Location			
Right		69	51.4
Left		60	44.7
Bilateral		4	2.9
Midline		1	0.7
Tumor Lobe			
Frontal		42	31.3
Temporal		60	44.7
Parietal		19	14.1
Occipital		2	1.5
Cerebellum		3	2.2
Basal ganglia		7	5.2
Tumor lobe Unknown		1	0.7
KPS pre-operative (median, range)		90 (50–100)	
KPS pre-operative 50–70		6	4.5
KPS pre-operative 80–100		110	82.0
KPS preoperative, Unknown		18	13.4
Extent of Resection			
GTR		30	22.3
STR		42	31.3
Biopsy		59	44.0
Extent of resection unknown		3	2.2
KPS post-operative (median, range)		90 (50–100)	
KPS post-operative 50–70		14	10.4
KPS post-operative 80–100		119	88.8
KPS post -operative, Unknown		1	0.7
Tumor size (median, range)	3.65 cm (0.6–8.6)		
Tumor size > 5 cm		22	16.4
Tumor size, Unknown		49	36.6
Grade			
Grade 2		29	21.6
Grade 3		105	78.4
Tumor Histology*			
Anaplastic Astrocytoma,		103	76.9
Low grade glioma		27	20.1
Oligoastrocytoma		4	2.9
IDH Determination			
IDH determined by IHC		79	59.0
IDH determined by NGS		55	41.0

those with known measured tumor size, the median tumor size was 3.65 cm, with 16.4% measuring > 5 cm. Median preoperative KPS and postoperative KPS scores were similar at 90, with a KPS of ≥ 80 in 82% preop and 88.8% postop.

Treatment characteristics

Most patients received adjuvant RT (88.8%) and chemotherapy (73%), with TMZ being the primary agent (Table 2). The most common treatment sequence for the entire cohort was CRT+chemotherapy (42.5%), followed by RT+chemotherapy (23.1%).

Among patients with grade 3 tumors ($n=105$), the majority received CRT+chemotherapy (48.6%), followed by RT+chemotherapy (22.9%), while smaller proportions received RT alone (9.5%), CRT alone (6.7%), or had unknown treatment (12.4%). No patients in this group received chemotherapy alone. In contrast, among patients with grade 2 tumors ($n=29$), treatment was more heterogeneous, with 34.5% receiving RT alone,

Table 1b Treatment patterns of patients receiving therapy on study

		N = 134	%
Adjuvant Therapy			
Adjuvant RT		119	88.8
Adjuvant Chemotherapy		98	73.0
Radiation Dose (*N* = 119)			
Radiation median, range	57 Gy (52.2–60)		
Radiation 57 Gy/30		43	36.1
Radiation 54 Gy/30		18	15.1
Radiation 60 Gy/30		22	18.4
Radiation 50.4 Gy/28		6	5
Radiation 59.4 Gy/33		5	4.2
Radiation 52.2 Gy/29		1	0.8
Radiation Dose, Unknown		24	20.1
Adjuvant treatment sequence			
Concurrent chemoradiotherapy followed by adjuvant chemotherapy		57	42.5
Radiotherapy alone		20	14.9
Concurrent Chemoradiotherapy alone		8	5.9
Radiotherapy followed by chemotherapy (sequential therapy)		31	23.1
Chemotherapy alone		1	0.7
Sequence Unknown		17	12.6

24.1% receiving RT+chemotherapy, and 20.7% receiving CRT+chemotherapy. Smaller proportions received CRT alone (3.4%) or chemotherapy alone (3.4%), while 13.8% had unknown treatment data (Supplemental Table A1/A2). Of patients receiving adjuvant chemotherapy, the large majority received TMZ, while only 1 patient received PCV-based therapy; given this limited sample, a formal outcome comparison between chemotherapy regimens could not be performed.

Molecular characteristics

Among patients with available molecular data, TERT promoter mutation was present in 8 of 26 evaluable patients (30.8%), EGFR amplification in 19 of 40 (47.5%), CDKN2A deletion in 17 of 40 (42.5%), TP53 mutation in 31 of 71 (43.7%), ATRX loss in 8 of 46 (17.4%), and combined chromosome 7 gain/chromosome 10 loss in 1 of 18 (5.6%) evaluable patients. Complete molecular profiling was not available for the majority of the cohort, consistent with the retrospective, multi-decade nature of this dataset.

Survival outcomes

The median follow-up was 29.8 months (2.3–217 months). For the total cohort, median OS was 35 months (95% CI: 28.8–43) (Fig. 1A), and median PFS was 20.9 months (95% CI: 14.5–27.4). In a subgroup of 87 patients with either NGS-confirmed IDH-wt status or IHC-only testing and age > 55, similar outcomes were observed, with a median OS of 30.9 months and median PFS of 14.4 months (Supplemental Figure A1/A2).

When stratified by tumor grade (Fig. 1B), patients with grade 2 tumors had a median OS of 94.5 months (95% CI: 17.3-171.7) and median PFS of 50.6 months (95% CI: 35.6–65.7). In contrast, grade 3 tumors had a median OS of 29.8 months (95% CI: 25.8–37.7) and median PFS of 15.3 months (95% CI: 8.5–22.1). On subgroup analysis (Supplemental Figure B1), patients with grade 2 tumors had a median OS of 50 months (95% CI: 0-137.5) and median PFS of 32.1 months (95% CI: 3.6–60.6), whereas grade 3 tumors had a median OS of 27 months (95% CI: 21.6–32.5) and median PFS of 12.1 months (95% CI: 8.8–15.5).

Treatment outcomes by modality and subgroup

Among patients with grade 3 tumors, we compared outcomes between those treated with CRT+chemotherapy ($n = 51$) and those treated with sequential RT+chemotherapy ($n = 24$). Median OS was 29.8 months (95% CI: 17.1–42.5) for CRT+ chemotherapy and 29.8 months (95% CI: 22.7–36.8) for RT+chemotherapy ($p = 0.17$) (Fig. 2A). Median PFS was 22.2 months (95% CI: 11.5–32.8) for sequential therapy versus 11.0 months (95% CI: 9-13.1) for concurrent therapy ($p = 0.16$) (Fig. 2B). Baseline characteristics were well balanced between these two groups, including age (median 52 vs. 49.5 years, $p = 0.91$), postoperative KPS ≥ 80 (84% vs. 96%, $p = 0.26$), extent of resection (GTR 26% vs. 25%, $p = 1.00$), and tumor size ≥ 5 cm (31% vs. 29%, $p = 1.00$), suggesting the absence of a significant

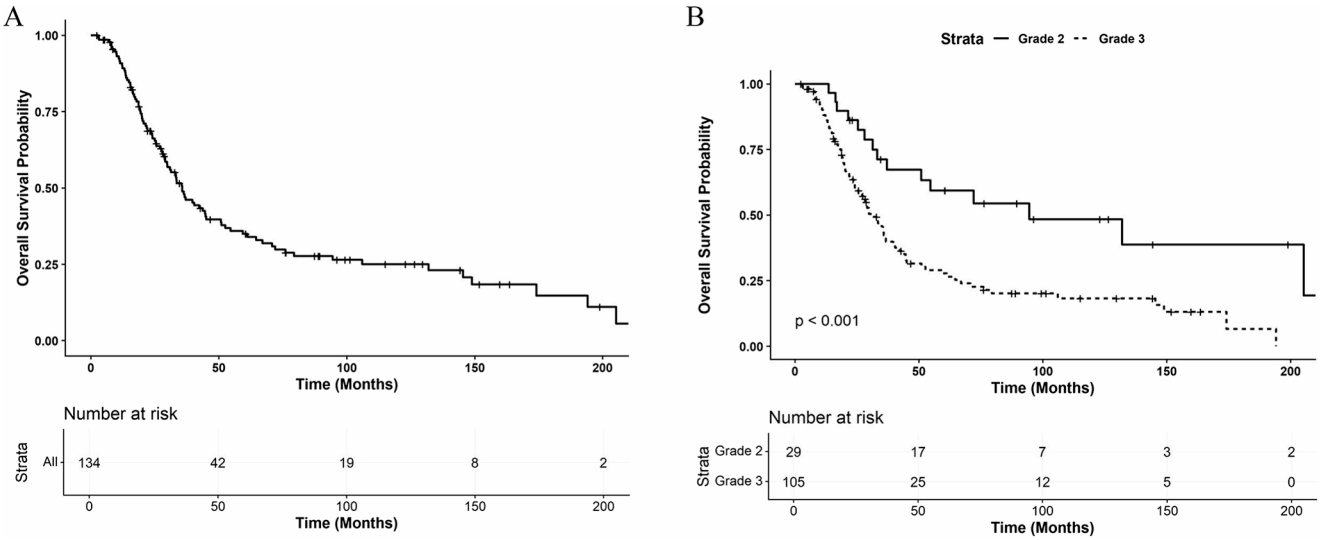

Fig. 1 Overall survival outcomes for (**A**) total cohort of patients and (**B**) stratified by grade

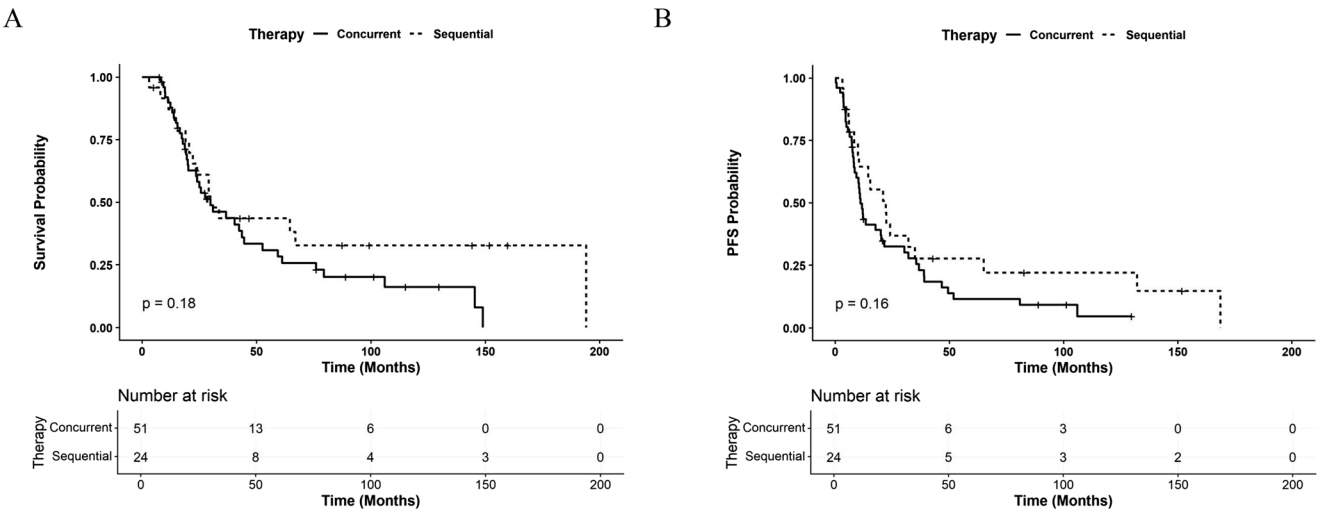

Fig. 2 (**A**) Overall survival and (**B**) progression-free survival outcomes for patients with IDH-wt WHO grade 3 gliomas treated with either concurrent CRT+chemotherapy vs. sequential RT+chemotherapy

survival difference was not attributable to baseline imbalance between treatment groups.

Subgroup analysis showed similar results. Among the 72 patients with grade 3 tumors in this subgroup, CRT+chemotherapy ($n=34$) yielded a median OS of 28.8 months (95% CI: 23.6–45.8), while RT+chemotherapy ($n=17$) resulted in a median OS of 35.6 months (95% CI: 18.2–49.6) (Supplemental Figure B1). Median PFS was 18.5 months (95% CI: 12.1–26.7) for CRT+ chemotherapy and 16.6 months (95% CI: 8.4–31.9) for RT+chemotherapy (Supplemental Figure B2).

In propensity score matched analysis (11 sequential and 19 concurrent pairs matched by age, postoperative KPS, extent of resection, and tumor size), no significant OS difference remained between sequential RT+chemotherapy and CRT+chemotherapy (log-rank $p=0.69$), supporting the robustness of the primary analysis (Supplementary Figure B3).

Multivariable Cox regression analyses showed that grade 3 histology, biopsy/STR, and postoperative KPS. <80 were significantly associated with worse OS and PFS (Table 3, Supplementary Tables B-F). Notably, treatment modality (CRT+chemotherapy vs. RT+chemotherapy) was not associated with a statistically significant difference in outcomes in any subgroup.

Table 2 Univariable and multivariable cox proportional hazard model of overall survival of patients on study

Variable	*N*-134	Univariable HR (95% CI)	*p*	Multivariable HR (95% CI)	*P* value
Age ≤ 40 (*reference*)	32	—	—	—	—
Age > 40	102	1.42 (0.85–2.39)	0.16	1.58 (0.74–3.39)	0.23
Male (*reference*)	74	—	—	—	—
Female	60	1.4 (0.92–2.1)	0.1	1.73 (0.86–3.49)	0.12
Tumor size < 5 cm (reference)	63	—	—	—	—
Tumor size ≥ 5 cm	22	1.16 (0.65–2.08)	0.61	1.11 (0.57–2.18)	0.74
Grade 2 (*reference*)	29	—	—	—	—
Grade 3	105	2.61 (1.47–4.65)	< 0.001	3.27 (1.32–8.09)	0.01
Post-op KPS < 80 (*reference*)	14	—	—	—	—
Post-op KPS ≥ 80	119	0.42 (0.23–0.78)	0.006	0.37 (0.16–0.83)	0.018
GTR (*reference*)	30	—	—	—	—
STR/biopsy	101	2.43 (1.37–4.32)	0.002	1.87 (0.9–3.89)	0.093
By treatment					
Radiotherapy followed by chemotherapy (sequential therapy) (*reference*)	31	—	—	—	—
Concurrent chemoradiotherapy followed by adjuvant chemotherapy	57	1.30 (0.71–2.4)	0.38	0.82 (0.37–1.83)	0.64
Concurrent chemoradiotherapy alone	8	1.28 (0.49–3.35)	0.26	0.97 (0.3–3.14)	0.97
Radiotherapy alone	20	1.36 (0.67–2.74)	0.38	1.52 (0.57–4.01)	0.39

Discussion

Our study contributes to the evolving understanding of IDH-wt diffuse gliomas with historically grade 2 and 3 histologic features by demonstrating that, while many of these tumors exhibit aggressive clinical behavior, outcomes are heterogeneous. The OS for the cohort (median OS 35 months) aligns with prior reports suggesting poor prognosis in IDH-wt gliomas. Notably, grade 3 tumors demonstrated outcomes comparable to those reported in molecular GBM with a median OS of 29.8 months and a 5-year OS of 27.2%, whereas a subset of grade 2 tumors showed substantially prolonged survival and 5-year OS of 59.3%. These findings suggest that histologic grade retains prognostic relevance even within IDH-wt tumors and may reflect underlying biological diversity not fully captured by current molecular classification.

A key focus of this study was evaluating treatment patterns and their association with survival, particularly the impact of concurrent CRT. In grade 3 tumors, no statistically significant survival benefit was observed for CRT+chemotherapy over RT+chemotherapy, with 5-year OS rates of 27.7% and 43.6%, respectively. This lack of observed benefit persisted in subgroup analyses limited to patients with NGS-confirmed IDH-wt tumors and those over 55 with IHC-only testing, suggesting it was not driven by molecular misclassification.

These findings may challenge conventional treatment paradigms extrapolated from Stupp for histological GBM [9]. The final publication of the CATNON trial similarly found no benefit of concurrent CRT over adjuvant TMZ alone in grade 3 gliomas [4]. In a post-hoc analysis restricted to IDH-wt grade 3 patients on CATNON, median OS was 19.2 months with concurrent TMZ versus 21.6 months without. However, CATNON enrolled predominantly IDH-mutant patients, limiting its direct applicability to our cohort.

Our grade 3 cohort demonstrated somewhat longer survival than the IDH-wt subset reported in CATNON. However, important differences in study design limit direct comparison, as all patients in our cohort received adjuvant TMZ, whereas earlier CATNON arms permitted RT or CRT alone. Thus, CATNON primarily evaluated the role of concurrent TMZ rather than directly comparing sequential RT followed by chemotherapy versus concurrent CRT followed by chemotherapy, as performed in our study. Taken together, our cohort most closely mirrors the subset of CATNON patients who received adjuvant therapy, and demonstrates comparably or modestly improved survival within that context.

In our analysis, the absence of an observable advantage with concurrent CRT in this cohort raises the possibility that certain patients with IDH-wt grade 3 gliomas may not benefit from aggressive multimodal therapy. This is clinically significant because, in the absence of prospective trial data specific to molecular GBM, treatment paradigms for these patients have largely been extrapolated from other higher-grade gliomas and commonly favor concurrent CRT+chemotherapy. Importantly, prior studies have demonstrated that combined CRT is associated with increased treatment-related toxicity, including higher

rates of hematologic adverse events, fatigue, and potential impacts on neurocognitive function and quality of life [10–12]. While it remains possible that patient selection factors or comorbidities contributed to treatment assignment and survival differences, our findings suggest that treatment intensity should be re-evaluated in molecularly defined subgroups, particularly when potential toxicity may outweigh clinical benefit.

Moreover, the relatively favorable outcomes seen in the grade 2 subgroup, although limited by small sample size, further highlight the biological heterogeneity within IDH-wt gliomas and suggest the need to further stratify patients with IDH-wt gliomas using both histologic and molecular features. This heterogeneity has important implications for both prognostication and treatment selection, particularly in avoiding potential overtreatment in patients with more indolent disease biology. The diversity in survival outcomes within this population likely reflects underlying biology not fully captured by histology or current molecular classification alone, and our institutions clinical trial data suggest that epigenetic/methylation profiling may further improve risk stratification to better inform treatment decisions [3]. Together, these findings support the hypothesis that IDH-wt tumors encompass a spectrum of clinical behavior, and that a uniform treatment approach may not be appropriate across all patients in this category [13]. This is further supported by emerging evidence from cIMPACT-NOW, which has highlighted that TERT promoter alterations in isolation may be less prognostic in the absence of other additional molecular markers and that more techniques such as methylation/epigenetic profiling may better sub-define these tumor entities [15,16]. Hence it underscores the limitations of applying uniform reclassification and treatment strategies without comprehensive molecular profiling.

Limitations and future directions

This study is limited by its retrospective design, heterogeneity in molecular testing methodologies, and potential confounding factors influencing treatment selection. In particular, comprehensive molecular reclassification according to WHO 2021 criteria, including DNA methylation-based profiling, was not performed for the majority of this historical cohort, as such testing was not routinely available for much of the 1996–2019 study period; while tumors with known IDH mutation, H3K27M alteration, and histologic features of glioblastoma were excluded, we cannot fully exclude the possibility that a rare number of newly reclassified ‘pediatric-type’ high grade gliomas in an adult population remained unrecognized within this cohort. However, this can be taken in the same context of trials that enrolled similar populations based primarily on histological grade and IDH status (when available) such as CATNON [17]. A valuable consideration is that studies such as ours with long term follow up accounting for the differences in therapy patterns are only feasible in large observational databases given that the WHO classification updated only recently in 2021. Next, the lack of full NGS data in all patients particularly prior to its routine existence introduces the possibility that some tumors with non-canonical IDH mutations were misclassified among those with only IHC testing. Our study attempted to mitigate this by restricting subgroup analyses to patients over 55 years old or with NGS confirmation for additional validation and sensitivity analysis. Lastly, therapy was at the discretion of the treating physician, and it is possible that decision of concurrent or sequential therapy for grade 3 patients were made on nuanced factors not captured in this dataset. Our dataset attempted to capture in detail several factors including pre- and postoperative KPS, tumor location and size as best as possible to address measurable factors. Due to limitations in reports of tumor size for non-enhancing tumors compared to contrast-enhancing tumor on MRI, there may be heterogeneity in tumor measurement reporting. Despite these limitations, our consistent findings across subgroup strengthened the observations. Importantly, propensity score matched analysis yielded similar findings, suggesting the absence of benefit with concurrent therapy was not fully explained by measured treatment-selection bias.

Future studies should aim to further elucidate which patients with IDH-wt grade 2 or 3 tumors derive benefit from intensified therapy and which may be appropriate candidates for treatment de-escalation. Prospective trials incorporating comprehensive molecular profiling and standardized treatment protocols will be essential to refine management strategies and avoid overtreatment in patients to minimize toxicity exposure.

Conclusion

In this contemporary cohort of IDH-wt diffuse gliomas with grade 2 and 3 histologic features, outcomes were divergent even after adjusting for historical treatment patterns and emphasizes the importance of histological grade among the population. This highlights the diversity within the potential cohort of newly defined molecular GBMs and recognizes that while a subset has outcomes modeling high grade gliomas, there are also subsets with longer survival outcomes. Next, in patients with grade 3 histological features survival was not improved by the addition of concurrent CRT followed by chemotherapy compared to sequential RT followed by chemotherapy. These findings suggest the role of uniform concurrent CRT for molecular GBM warrants

further prospective evaluation to better define groups that may benefit, which is an element not completely addressed by the important recent CATNON publication. Our findings underscore the importance of future stratification in informing treatment decisions and suggest that therapeutic de-intensification may be appropriate for select patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-026-05712-2.

Author contributions P.C., O.H. and D.N.Y wrote the main manuscript text and statistical analysis, and K.A. prepared Figures in R software. All authors reviewed the manuscript.

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Data availability Restrictions apply to the availability of these data and may not be publicly available.

Declarations

Ethical approval This retrospective study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of The University of Texas MD Anderson Cancer Center (IRB approval number #2023−0812; approved October 24, 2023). Given the retrospective nature of the study, the requirement for individual informed consent was waived by the IRB.

Consent to participate This study was a retrospective review of existing medical records. The requirement for individual informed consent to participate was waived by the Institutional Review Board of The University of Texas MD Anderson Cancer Center in accordance with applicable regulations.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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