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Original Article

Construction and external validation of a prognostic model for high-grade glioma based on IDH1 mutation status: implications for concurrent chemoradiotherapy efficacy

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Abstract: This retrospective cohort study investigated the impact of isocitrate dehydrogenase 1 (IDH1) mutations on the efficacy and prognosis of concurrent chemoradiotherapy in high-grade gliomas (HGGs) and constructed a validated overall survival (OS) nomogram model. A total of 242 patients were included in the training cohort (2019-2021) and 182 patients in the time validation cohort (2022-2023). All patients received standard concurrent chemoradiotherapy. The median progression-free survival (PFS) in the 72 IDH1-mutant patients was 27.0 months, significantly longer than the 12.0 months in the 170 wild-type patients (hazard ratio =1.79; P<0.001). OS was also longer in IDH1-mutant patients (this endpoint has not yet been met), while the OS in wild-type patients was 20.0 months (HR=2.55; P<0.001). Furthermore, the objective response rate (ORR) in IDH1-mutant patients was 58.3%, significantly higher than the 37.6% in wildtype patients (P=0.005); the disease control rate was 88.9%, also higher than the 76.5% in wildtype patients (P=0.041). Cox regression analysis identified five independent prognostic factors associated with OS: IDH1 wildtype (HR=1.638), Karnofsky Performance Status (KPS) score <70 (HR=1.396), WHO grade 4 (HR=2.273), O^6-methylguanine-DNA methyltransferase (MGMT) demethylation (HR=2.054), and <6 cycles of adjuvant chemotherapy (HR=1.977). The nomogram model constructed in this study showed good calibration, with a C-index of 0.721 in the training cohort and 0.640 in the time-validation cohort, demonstrating a positive net clinical benefit in both cohorts. IDH1 status showed significant interactions with adjuvant chemotherapy cycles (P=0.007) and MGMT methylation status (P=0.040), respectively. In conclusion, IDH1 mutation is an independent predictor of good treatment response and improved prognosis in patients with HGGs receiving concurrent chemoradiotherapy, and the validated nomogram can serve as a practical tool for individualized clinical decision-making.

Keywords: High-grade glioma, isocitrate dehydrogenase 1, concurrent chemoradiotherapy, prognosis, nomogram, external validation

Introduction

High-grade gliomas (HGGs) are the most common primary malignant tumors of the adult central nervous system (CNS), including World Health Organization (WHO) grade 3 anaplastic gliomas and WHO grade 4 glioblastomas (GBMs). These tumors are highly aggressive and have a remarkably poor prognosis [1]. According to the 2023 report from the U.S. Central Brain Tumor Registry, glioblastomas account for 48% of all malignant brain tumors, with an annual incidence of approximately 3.21 cases per 100,000 people, a median overall survival (OS) of approximately 12-15 months, and a 5-year survival rate of less than 10% [2, 3]. The standard treatment for HGGs is maximally safe surgical resection, followed by concurrent chemoradiotherapy (CCRT) and adjuvant chemotherapy [4]. Even so, patients receiving the same standard treatment regimen still show significant individual differences in treatment response and outcome. The chemical biological characteristics of the tumor have a significant impact on treatment efficacy and survival outcomes.

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Isocitrate dehydrogenase (IDH) gene mutations are one of the most critical molecular markers in gliomas. According to the 2021 WHO Classification of Tumors of the Central Nervous System, IDH status is a core molecular marker of glioma [5]. IDH gene mutations can alter the function of enzymes, leading to the production of 2-hydroxyglutaric acid. Analysis shows that this process triggers widespread epigenetic changes and metabolic reprogramming, affecting tumor proliferation, invasion, and treatment sensitivity [6]. Multiple studies have demonstrated that patients with IDH wild-type HGGs have a worse prognosis than those with IDH mutations, and IDH status is an independent good prognostic predictor [7, 8]. In August 2024, the U.S. saw a significant breakthrough: the U.S. Food and Drug Administration approved vorasisidenib as the first drug targeting IDH mutations for the treatment of patients aged 12 years and under with surgically treated grade 2 IDH1/2 mutant astrocytomas or oligodendrogliomas, marking the arrival of the era of precision medicine [9]. The prognostic value of IDH mutations is widely recognized, but their impact on the efficacy of concurrent chemoradiotherapy and their interaction with other clinical and pathological factors remain unclear. Previous studies have largely focused on the impact of IDH mutations on OS, while studies assessing the impact of IDH mutation status on short-term responses to concurrent chemoradiotherapy (such as objective response rate (ORR) and disease control rate (DCR)) are less common [7]. Furthermore, IDH mutations often coexist with other molecular markers such as O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. Multiple studies in 2023 confirmed that MGMT promoter methylation is an important prognostic factor for patients with IDH wildtype glioblastoma and a predictor of their response to temozolomide (TMZ) treatment [7, 8]. Some studies suggest [10, 11] that patients with the molecular subtype of IDH mutation combined with MGMT methylation have better prognoses and better responses to chemotherapy. However, whether these factors have synergistic or antagonistic effects, and the combined effect of both on treatment regimen selection, remains to be further elucidated.

Accurate prognostic assessment is the foundation of precision medicine. In recent years, various prognostic models for HGGs have been developed to assist clinical decision-making. Studies in 2023 and 2024 established nomogram prediction models integrating clinical and pathological features [12-14]. However, most of these models lack the inclusion of molecular markers or do not have independent time-validation cohorts, a deficiency that casts doubt on their universality and clinical application value. Furthermore, most existing models only assess patient survival and do not involve treatment response assessment, further limiting their application in clinical decision-making.

This study conducted a retrospective cohort study of 424 patients with HGGs undergoing concurrent chemoradiotherapy to systematically evaluate the association between isocitrate dehydrogenase 1 (IDH1) mutation status and treatment efficacy and survival prognosis. Univariate and multivariate Cox regression analyses were used to screen for independent prognostic factors such as IDH1 status; subgroup analysis and interaction tests were used to explore the heterogeneity of the prognostic value of IDH1 mutation; sensitivity analysis was also conducted to consider the impact of perpetual time bias and improve the reliability of the results. Based on this, this study constructed a nomogram prognostic prediction model that includes IDH1 status, Karnofsky Performance Status (KPS) score, WHO classification, MGMT promoter methylation status, and adjuvant chemotherapy cycles. The model's discriminative and calibrated properties were validated through an independent time-validation cohort of 182 patients. This model is expected to become a practical prognostic tool that guides clinicians in developing individualized treatment plans based on molecular characteristics.

Methods and materials

Sample size calculation

The sample size estimation was mainly based on previously reported effect sizes of the impact of IDH mutation status on glioma prognosis. A meta-analysis conducted by Xia et al., which included 9487 patients [15], reported that the OS combined hazard ratio (HR) for IDH mutant patients compared to wildtype patients was 0.39 (95% CI: 0.34-0.45).

This study used IDH1 wildtype as the reference category, and therefore used its reciprocal (HR≈2.56) to represent the expected relative risk of death for wildtype patients compared to mutant patients. This method followed the standard procedure of converting published effect sizes into Cox proportional hazards model sample size calculations. The Schoenfeld formula for survival analysis was $d = (Z_\alpha/2 + Z_\beta)^2/P(1-P)[\ln(HR)]^2$, where the two-sided test $\alpha=0.05$, test power 80%, IDH1 mutation rate 30%, HR=2.5, and the estimated number of events required was approximately 88. To ensure sufficient statistical power for multivariate Cox regression analysis, this study also adhered to the event-to-variable principle. The final model included five candidate predictors (IDH1 status, KPS score, WHO classification, MGMT promoter methylation status, and number of adjuvant chemotherapy cycles). Following the recommendation of at least 10-15 events per variable, a minimum of 50-75 events was required. In this study, the estimated incidence of HGGs events was approximately 70%, and the inclusion of 424 patients generated approximately 296 events. This resulted in an event-to-variable ratio of approximately 59 (296 events/5 variables), significantly higher than the recommended minimum, thus improving model stability and reducing the risk of overfitting. Furthermore, to meet the requirements for training and validation cohort division, and considering missing data (approximately 10%) and loss to follow-up (approximately 5%), the maximum sample size was further increased.

Considering all these factors, it was determined that the training and validation cohorts should include at least 350 patients. This study included a total of 424 patients (242 in the training cohort and 182 in the validation cohort), which met the sample size requirement and can provide sufficient statistical power for univariate and multivariate Cox regression analysis and prognostic model construction.

Study subjects

Study design and general information

This retrospective training set-external validation cohort study was approved by the Medical Ethics Committee of Shanxi Cancer Hospital, and informed consent was waived. The training cohort included 242 HGG patients treated at Shanxi Cancer Hospital from January 2019 to December 2021; the time-validation cohort independently enrolled 182 patients meeting the same criteria from January 2022 to December 2023. All patients were followed up until June 2024.

Inclusion criteria: (1) Adult patients aged ≥18 years; (2) Postoperative tumor pathological diagnosis of WHO grade 3 or 4 glioma [5]; (3) Patients receiving standard concurrent chemoradiotherapy, i.e., surgical resection combined with radiotherapy combined with temozolomide chemotherapy; (4) Confirmed test results for IDH1 mutation status and MGMT promoter methylation status; (5) Complete clinical data and follow-up information; (6) Expected survival of more than 3 months; (7) No history of other malignant tumors.

Exclusion criteria: (1) Severe failure of vital organs such as heart, liver, and kidney; (2) Comorbid severe infection or immune system disease; (3) Inability to complete standard treatment regimen for other reasons; (4) Incomplete clinical data or withdrawal from the study during the trial.

Clinical data collection

The following clinical data was collected from all enrolled patients: (1) Baseline demographic characteristics: age (≥50 years/<50 years), sex (male/female); (2) Tumor-related indicators: tumor location (frontal lobe/non-frontal lobe), maximum diameter (<4 cm/≥4 cm), WHO pathological grade (grade 3/4), among which IDH1 mutation status can reflect the molecular subtyping characteristics of glioma [18]; (3) Treatment-related factors: degree of surgical resection (gross total resection (GTR)/subtotal resection (STR)), radiotherapy dose (54-60 Gy/<54 Gy); (4) Adjuvant therapy: number of adjuvant chemotherapy cycles (≥6 cycles/<6 cycles), application of tumor treating fields (TTFields) (yes/no), and combination therapy with bevacizumab (yes/no); (5) Functional status assessment: Karnofsky Performance Status (KPS) score (≥70 points/<70 points); (6) Efficacy evaluation indicators: based on the short-term efficacy assessment results after the completion of concurrent chemoradiotherapy, divided into complete remission (CR), partial remission (PR), stable disease (SD), and dis-

ease progression (PD); (7) Patient prognostic outcomes: progression-free survival (PFS), OS.

Measurement methods

Histopathological examination

Postoperatively, tumor specimens were fixed in formalin, embedded in paraffin, and routinely stained with hematoxylin and eosin (H&E). Pathological diagnosis and grading were performed by two senior pathologists according to the 2021 World Health Organization Classification of Tumors of the Central Nervous System. In case of disagreement, a consensus diagnosis was reached through discussion.

Molecular pathological detection

The R132 mutation status of the IDH1 gene was detected using polymerase chain reaction (PCR)-Sanger sequencing [16]. DNA was extracted from formalin-fixed paraffin-embedded tissue using a Qiager kit, and PCR amplification of the IDH1 gene exon 4 fragment was performed using specific primers. After purification, the amplified product was bidirectionally sequenced using Sanger sequencing technology, with sequencing performed by Shanghai Sangon Biotech Co., Ltd. The sequencing results were analyzed using Chromas software: detection of the R132 mutation indicated an IDH1 mutant type, while absence indicated a wildtype.

The methylation status of the MGMT gene promoter region was detected using methylation-specific PCR. DNA was treated using a bisulfite conversion kit (Zymo Research), and PCR amplification was performed with methylated and unmethylated primers, respectively. After 2% agarose gel electrophoresis, the methylation status of each PCR product was determined based on the presence and type of amplified bands: methylation was indicated by the presence of an amplified band only with methylated primers; demethylation was indicated by the presence of an amplified band only with unmethylated primers; and partial methylation was indicated by the presence of amplified bands with both methylated and unmethylated primers. In this study, partial methylation was grouped into the methylation group for statistical analysis.

Imaging examination

All patients underwent regular brain magnetic resonance imaging (MRI) examinations before surgery and during follow-up (equipment: Siemens Magnetom Skyra 3.0T or GE Discovery MR750 3.0T). Scanning sequences included T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), liquid-attenuated inversion recovery sequence (FLAIR), and enhanced T1WI (gadopentetate dimeglumine intravenously, dose 0.1 mmol/kg). The maximum diameter of the tumor was measured on enhanced T1WI sequences, and the maximum value among the maximum diameters of the tumor enhancement areas in axial, coronal, and sagittal views was taken. The extent of surgical resection was assessed by MRI within 48-72 hours postoperatively: residual enhancing tumor volume <1 cm^3 was defined as GTR, and ≥ 1 cm^3 was defined as STR [17]. Imaging assessments were independently performed by two radiologists with more than 5 years of experience in neuroimaging diagnosis, and consensus was reached through discussion when opinions differed.

Functional status assessment

The KPS score was used to assess the patients' preoperative general condition. The KPS score ranges from 0-100 points, with higher scores indicating better functional status. In this study, patients were divided into KPS≥70 and KPS<70 groups [14], and the assessments were performed by trained neurosurgeons.

Treatment protocol and efficacy evaluation

Treatment protocol

All patients received standard Stupp protocol treatment: (1) Surgical treatment: Maximum safe tumor resection. (2) Concurrent chemoradiotherapy: Concurrent chemoradiotherapy was initiated 2-4 weeks post-surgery. 3D conformal radiotherapy or intensity-modulated radiotherapy was used. The planned target volume dose was 54-60 Gy/30 fractions/6 weeks (conventionally fractionated 2 Gy/fraction), concurrently with oral temozolomide 75 mg/m^2/day, taken daily during radiotherapy. (3) Adjuvant chemotherapy: Adjuvant chemotherapy was initiated 4 weeks after the completion of concurrent chemoradiotherapy. Temozolomide

150-200 mg/m^2/day (150 mg/m^2 in the first cycle, increasing to 200 mg/m^2 in subsequent cycles if well tolerated), taken for 5 consecutive days, with each cycle lasting 28 days, for a planned total of 6 cycles. Some patients, based on their condition, physical status, and economic circumstances, selectively received TTFields treatment (Optune system, 200 kHz alternating electric field, worn for ≥18 hours daily) or combined with bevacizumab (5 mg/kg, intravenous infusion, once every 2 weeks).

Efficacy evaluation

Primary endpoint: PFS was defined as the time interval from the date of diagnosis (pathological diagnosis date) to the date of first radiographic progression of the disease, death from any cause, or the date of last follow-up, whichever occurs first.

Secondary endpoints: (1) OS was defined as the time interval from the date of diagnosis to the date of death from any cause or the date of last follow-up. (2) ORR referred to the proportion of patients achieving CR or PR, ORR = (CR + PR)/total number of cases × 100%. (3) DCR was determined as the proportion of patients achieving CR, PR, or SD. DCR = (CR + PR + SD)/total number of cases × 100%.

Short-term efficacy evaluation criteria: 4 weeks after the completion of concurrent chemoradiotherapy (28±7 days after radiotherapy), short-term efficacy was assessed according to Response Assessment in Neuro-Oncology (RANO) criteria: (1) CR: Complete disappearance of all measurable and non-measurable lesions, no new lesions, stable or decreased corticosteroid dosage, stable or improved clinical symptoms, and these outcomes maintained for at least 4 weeks. (2) PR: A reduction of ≥50% in the sum of the products of the maximum perpendicular diameters of all measurable lesions compared to baseline, no new lesions, stable or decreased corticosteroid dosage, stable or improved clinical symptoms, and these outcomes maintained for at least 4 weeks. (3) SD: Failure to meet the criteria for CR, PR, or PD. (4) PD: The sum of the products of maximum perpendicular diameters of all measurable lesions increased by ≥25% compared to the minimum value after treatment, or new lesions appear, or clinical symptoms significantly worsen. Efficacy evaluation was jointly completed by neurosurgeons and radiologists.

Follow-up: All patients were followed up regularly through outpatient, inpatient, or telephone follow-up until June 30, 2024. Follow-up content includes: (1) Survival status (survival/death); (2) Tumor recurrence or progression; (3) Treatment-related adverse events; (4) Subsequent treatment (reoperation, salvage chemotherapy, radiotherapy, etc.).

Follow-up frequency: Every 3 months in the first year after treatment, every 6 months in the second year, and annually thereafter. Enhanced brain MRI was routinely performed during follow-up to assess tumor status. Loss to follow-up was defined as being unable to be contacted for two consecutive follow-up visits.

Statistical analysis

Statistical analysis was performed using R software version 4.5.1 (Vienna, Austria, R Foundation for Statistical Computation) and SPSS software version 27.0 (Armonke, New York, USA, IBM). For intergroup comparisons, normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x}\pm$sd) and compared using independent samples t-tests; non-normally distributed continuous data were expressed as median (interquartile range) [M (Q_1, Q_3)] and compared using the Mann-Whitney U test. Categorical data were expressed as number of cases and percentages [n (%)] and compared using the χ^2 test or Fisher's exact test. Besides, the χ^2 test was used to compare the differences in clinical characteristics between IDH1 mutant and wild-type patients.

Kaplan-Meier survival curves were plotted, and log-rank test to compare survival differences between groups. Univariate Cox proportional hazards regression models were used to analyze potential prognostic factors influencing PFS and OS. Variables with *p*-values <0.05 in the univariate analysis were included in the multivariate Cox regression analysis. Results were expressed as hazard ratio (HR) and 95% confidence interval (CI). Collinearity was then assessed in the multivariate model using variance inflation factor (VIF) analysis and Spearman correlation analysis. Based on the independent prognostic factors identified in the

multivariate Cox regression analysis, an OS nomogram model was constructed using the "rms" package in R software. The model's discriminative power was assessed using the concordance index (C-index) and the area under the time-dependent receiver operating characteristic (ROC) curve (AUC). A C-index and AUC value closer to 1.0 indicated better model discriminative power. The model's calibration was assessed using calibration curves, Brier score, and the Hosmer-Lemeshow test. A lower Brier score indicated better consistency between the model's predictions and actual observations, with a Hosmer-Lemeshow *P* value >0.05 indicating acceptable model calibration. A Brier score close to 0 indicated good calibration, with a Hosmer-Lemeshow P>0.05 indicating good model fit. Decision curve analysis (DCA) was used to assess the net benefit of the model's clinical application; a higher net benefit curve indicated better clinical application value.

Based on the risk scores calculated from the nomogram, patients were divided into low-risk, intermediate-risk, and high-risk groups using the ternary percentile of the training cohort as the cutoff value. This method provides an objective, data-driven strategy for risk stratification, achieving a balanced distribution of patients across groups. Survival curves were plotted using the Kaplan-Meier method and analyzed in parallel. The log-rank test was used to compare survival differences among the three groups; and Cox regression analysis was used to calculate the HR of each group relative to the low-risk group. The same risk score cutoff value was used to validate the model over time in a validation cohort.

Forest plots were used to present the subgroup analysis results, clarifying the impact of IDH1 mutation status on OS in different clinical subgroups (age, sex, KPS score, WHO classification, MGMT methylation status, degree of surgical resection, radiotherapy dose, adjuvant chemotherapy cycles, TTFields application, and combination therapy with bevacizumab). Cox regression models with interaction terms were used to assess the interaction effects, with P<0.05 considered statistically significant.

Subgroup analysis was conducted on patients who received chemotherapy within one year prior to the start of the study in February 2017, using the same Cox regression analysis method as for the correlation between previous adjuvant chemotherapy cycles and OS. Time-dependent covariate Cox model: Adjuvant chemotherapy cycles were considered time-dependent covariates; early deaths were excluded (cases that died within 6 months of diagnosis were excluded and re-analyzed). Milestone analyses were performed at 3 months, 6 months, and 9 months to observe the HR trends at each time point.

All statistical tests were two-tailed, with P<0.05 considered statistically significant.

Results

Patient baseline characteristics

There were no statistically significant differences between the two groups in terms of IDH1 mutation status (P=0.408), age (P=0.584), sex (P=0.593), KPS score (P=0.168), tumor location (P=0.587), maximum tumor diameter (P=0.447), WHO classification (P=0.747), MGMT promoter methylation status (P=0.340), extent of surgical resection (P=0.286), radiotherapy dose (P=0.767), number of adjuvant chemotherapy cycles (P=0.056), TTFields (P=0.751), or combination therapy with bevacizumab (P=0.895), indicating that the baseline characteristics of the two groups were balanced and highly comparable (**Table 1**).

Comparison of clinical characteristics between IDH1 mutant and wildtype patients

In the training cohort, compared with wildtype patients, mutant patients had a higher proportion of patients <50 years of age (54.17% vs. 33.53%, P=0.003), a higher proportion of females (54.17% vs. 39.41%, P=0.034), and a higher proportion of patients with KPS scores ≥70 (77.78% vs. 64.71%, P=0.045). Besides, mutant patients had a higher proportion of WHO grade 3 tumors (55.56% vs. 30.59%, P<0.001), and a significantly higher rates of MGMT promoter methylation than wildtype patients (61.11% vs. 41.76%, P=0.006). Furthermore, GTR was significantly higher in patients with mutant tumors than in those with wildtype tumors (65.28% vs. 49.41%, P=0.024). There were no significant differences between the two groups in tumor location (P=

Table 1. Comparison of baseline characteristics between training and validation cohorts

Variable	Total (n=424)	Training cohort (n=242)	Validation cohort (n=182)	Test statistic	*P*-value
IDH1 mutation status				0.684	0.408
Mutant	133 (31.37%)	72 (29.75%)	61 (33.52%)		
Wildtype	291 (68.63%)	170 (70.25%)	121 (66.48%)		
Age (years)				0.299	0.584
<50	173 (40.80%)	96 (39.67%)	77 (42.31%)		
≥50	251 (59.20%)	146 (60.33%)	105 (57.69%)		
Sex				0.285	0.593
Female	181 (42.69%)	106 (43.80%)	75 (41.21%)		
Male	243 (57.31%)	136 (56.20%)	107 (58.79%)		
KPS score				1.905	0.168
≥70	302 (71.23%)	166 (68.60%)	136 (74.73%)		
<70	122 (28.77%)	76 (31.40%)	46 (25.27%)		
Tumor location				0.295	0.587
Frontal lobe	143 (33.73%)	79 (32.64%)	64 (35.16%)		
Non-frontal	281 (66.27%)	163 (67.36%)	118 (64.84%)		
Maximum tumor diameter (cm)				0.578	0.447
<4	159 (37.50%)	87 (35.95%)	72 (39.56%)		
≥4	265 (62.50%)	155 (64.05%)	110 (60.44%)		
WHO grade				0.104	0.747
Grade 3	164 (38.68%)	92 (38.02%)	72 (39.56%)		
Grade 4	260 (61.32%)	150 (61.98%)	110 (60.44%)		
MGMT promoter methylation				0.911	0.34
Methylated	193 (45.52%)	115 (47.52%)	78 (42.86%)		
Unmethylated	231 (54.48%)	127 (52.48%)	104 (57.14%)		
Extent of resection				1.139	0.286
GTR	220 (51.89%)	131 (54.13%)	89 (48.90%)		
STR	204 (48.11%)	111 (45.87%)	93 (51.10%)		
Radiation dose				0.088	0.767
54-60 Gy	400 (94.34%)	229 (94.63%)	171 (93.96%)		
<54 Gy	24 (5.66%)	13 (5.37%)	11 (6.04%)		
Adjuvant chemotherapy cycles				3.653	0.056
≥6 cycles	279 (65.80%)	150 (61.98%)	129 (70.88%)		
<6 cycles	145 (34.20%)	92 (38.02%)	53 (29.12%)		
TTFields				0.101	0.751
Yes	68 (16.04%)	40 (16.53%)	28 (15.38%)		
No	356 (83.96%)	202 (83.47%)	154 (84.62%)		
Bevacizumab combination				0.017	0.895
Yes	78 (18.40%)	44 (18.18%)	34 (18.68%)		
No	346 (81.60%)	198 (81.82%)	148 (81.32%)		

Note: IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields.

0.178), maximum tumor diameter (P=0.973), radiotherapy dose (P=0.536), number of adjuvant chemotherapy cycles (P=0.205), TTFields (P=0.140), and combination therapy with bevacizumab (P=0.446) (**Table 2**).

Relationship between IDH1 mutation status and survival prognosis

Survival analysis revealed that IDH1 mutation status was closely related to the prognosis of

Table 2. Comparison of clinical characteristics between IDH1-mutant and IDH1-wildtype patients in the training cohort

Variable	Total (n=242)	Mutant (n=72)	Wildtype (n=170)	Test statistic	*P*-value
Age (years)				9.001	0.003
<50	96 (39.67%)	39 (54.17%)	57 (33.53%)		
≥50	146 (60.33%)	33 (45.83%)	113 (66.47%)		
Sex				4.473	0.034
Female	106 (43.80%)	39 (54.17%)	67 (39.41%)		
Male	136 (56.20%)	33 (45.83%)	103 (60.59%)		
KPS score				4.012	0.045
≥70	166 (68.60%)	56 (77.78%)	110 (64.71%)		
<70	76 (31.40%)	16 (22.22%)	60 (35.29%)		
Tumor location				1.818	0.178
Frontal lobe	79 (32.64%)	28 (38.89%)	51 (30.00%)		
Non-frontal	163 (67.36%)	44 (61.11%)	119 (70.00%)		
Maximum tumor diameter (cm)				0.001	0.973
<4	87 (35.95%)	26 (36.11%)	61 (35.88%)		
≥4	155 (64.05%)	46 (63.89%)	109 (64.12%)		
WHO grade				13.38	<0.001
Grade 3	92 (38.02%)	40 (55.56%)	52 (30.59%)		
Grade 4	150 (61.98%)	32 (44.44%)	118 (69.41%)		
MGMT promoter methylation				7.591	0.006
Methylated	115 (47.52%)	44 (61.11%)	71 (41.76%)		
Unmethylated	127 (52.48%)	28 (38.89%)	99 (58.24%)		
Extent of resection				5.128	0.024
GTR	131 (54.13%)	47 (65.28%)	84 (49.41%)		
STR	111 (45.87%)	25 (34.72%)	86 (50.59%)		
Radiation dose				-	0.536
54-60 Gy	229 (94.63%)	67 (93.06%)	162 (95.29%)		
<54 Gy	13 (5.37%)	5 (6.94%)	8 (4.71%)		
Adjuvant chemotherapy cycles				1.604	0.205
≥6 cycles	150 (61.98%)	49 (68.06%)	101 (59.41%)		
<6 cycles	92 (38.02%)	23 (31.94%)	69 (40.59%)		
TTFields				2.181	0.14
Yes	40 (16.53%)	8 (11.11%)	32 (18.82%)		
No	202 (83.47%)	64 (88.89%)	138 (81.18%)		
Bevacizumab combination				0.581	0.446
Yes	44 (18.18%)	11 (15.28%)	33 (19.41%)		
No	198 (81.82%)	61 (84.72%)	137 (80.59%)		

Note: IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields.

HGG patients. The median PFS for mutant patients was 27.0 months (95% CI: 18.0-30.0), significantly better than the 12.0 months (95% CI: 9.0-16.0) for wildtype patients. Compared with mutant patients, wildtype patients had a significantly higher risk of disease progression or death (HR=1.79, 95% CI: 1.30-2.48, P<0.001). The 1-year, 2-year, and 3-year PFS rates for mutant patients were 68.1%, 53.9%, and 23.8%, respectively, all significantly higher than the 46.5%, 22.0%, and 11.0% for wildtype patients (all P<0.001).

Regarding OS, the median OS for mutant patients had not yet been reached (95% CI: 30.0 - not reached), while the median OS for

Table 3. Comparison of survival outcomes between IDH1-mutant and IDH1-wildtype patients in the training cohort

Outcome	IDH1-mutant (n=72)	IDH1-wildtype (n=170)	HR (95% CI)*	*P*-value
PFS				
Median PFS (months, 95% CI)	27.0 (18.0-30.0)	12.0 (9.0-16.0)	1.79 (1.30-2.48)	<0.001
1-year PFS rate	0.681	0.465	-	<0.001
2-year PFS rate	0.539	0.22	-	<0.001
3-year PFS rate	0.238	0.11	-	<0.001
OS				
Median OS (months, 95% CI)	NR (30.0-NR)	20.0 (18.0-23.0)	2.55 (1.74-3.74)	<0.001
1-year OS rate	0.875	0.7	-	<0.001
2-year OS rate	0.663	0.363	-	<0.001
3-year OS rate	0.52	0.174	-	<0.001

Note: IDH1: Isocitrate Dehydrogenase 1, PFS: Progression-Free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, NR: Not Reached. *HR>1 indicates a higher risk of progression or death in the IDH1-wildtype group compared to the IDH1-mutant group.

wildtype patients was 20.0 months (95% CI: 18.0-23.0). Compared with mutant patients, wildtype patients had a significantly higher risk of death (HR=2.55, 95% CI: 1.74-3.74, P< 0.001). The 1-year, 2-year, and 3-year OS rates for mutant patients were 87.5%, 66.3%, and 52.0%, respectively, all significantly higher than those for wildtype patients (70.0%, 36.3%, and 17.4%, respectively) (all P<0.001) (**Table 3**).

Univariate and multivariate cox regression analysis of PFS

Univariate Cox regression analysis showed that IDH1 wildtype (vs. mutant) was significantly associated with poorer PFS (HR=1.794, 95% CI: 1.300-2.476, P<0.001). Additionally, KPS score <70 (vs. ≥70) (HR=1.836, 95% CI: 1.365-2.470, P<0.001), WHO grade 4 (vs. grade 3) (HR= 1.842, 95% CI: 1.364-2.486, P<0.001), and MGMT promoter demethylation (vs. methylation) (HR=2.348, 95% CI: 1.754-3.143, P< 0.001), STR (vs. GTR) (HR=1.718, 95% CI: 1.295-2.279, P<0.001), and <6 cycles of adjuvant chemotherapy (vs. ≥6 cycles) (HR=2.322, 95% CI: 1.745-3.089, P<0.001) were also significantly associated with PFS.

Age (≥50 years vs. <50 years, P=0.091), sex (male vs. female, P=0.282), tumor location (non-frontal lobe vs. frontal lobe, P=0.773), maximum tumor diameter (≥4 cm vs. <4 cm, P=0.201), radiotherapy dose (<54 Gy vs. 54-60 Gy, P=0.225), TTFields (not used vs. used, P=0.350), and combination therapy with bevacizumab (not combined vs. combined, P=0.410) were not significantly associated with PFS (all P>0.05).

After including variables with P<0.05 in the univariate analysis into the multivariate Cox regression analysis, the results showed that KPS score <70 (HR=1.566, 95% CI: 1.148-2.135, P=0.005), WHO grade 4 (HR=1.955, 95% CI: 1.428-2.677, P<0.001), MGMT promoter demethylation (HR=2.143, 95% CI: 1.579-2.910, P<0.001), and <6 cycles of adjuvant chemotherapy (HR=2.141, 95% CI: 1.580-2.902, P<0.001) were independent risk factors for PFS.

However, IDH1 wildtype (vs. mutant) (HR= 1.120, 95% CI: 0.800-1.569, P=0.509) and STR (vs. GTR) (HR=1.237, 95% CI: 0.919-1.666, P=0.161) were no longer statistically significant after adjusting for other factors (**Figure 1**).

Univariate and multivariate cox regression analysis of OS

Univariate Cox regression analysis showed that IDH1 wildtype (vs. mutant) was significantly associated with worse OS (HR=2.551, 95% CI: 1.740-3.742, P<0.001). Additionally, KPS score <70 (vs. ≥70) (HR=1.784, 95% CI: 1.303-2.443, P<0.001), WHO grade 4 (vs. grade 3) (HR= 2.359, 95% CI: 1.672-3.328, P<0.001), and MGMT promoter demethylation (vs. methylation) (HR=2.457, 95% CI: 1.783-3.384, P< 0.001), STR (vs. GTR) (HR=1.640, 95% CI: 1.208-2.226, P=0.002), and <6 cycles of adjuvant chemotherapy (vs. ≥6 cycles) (HR=2.218,

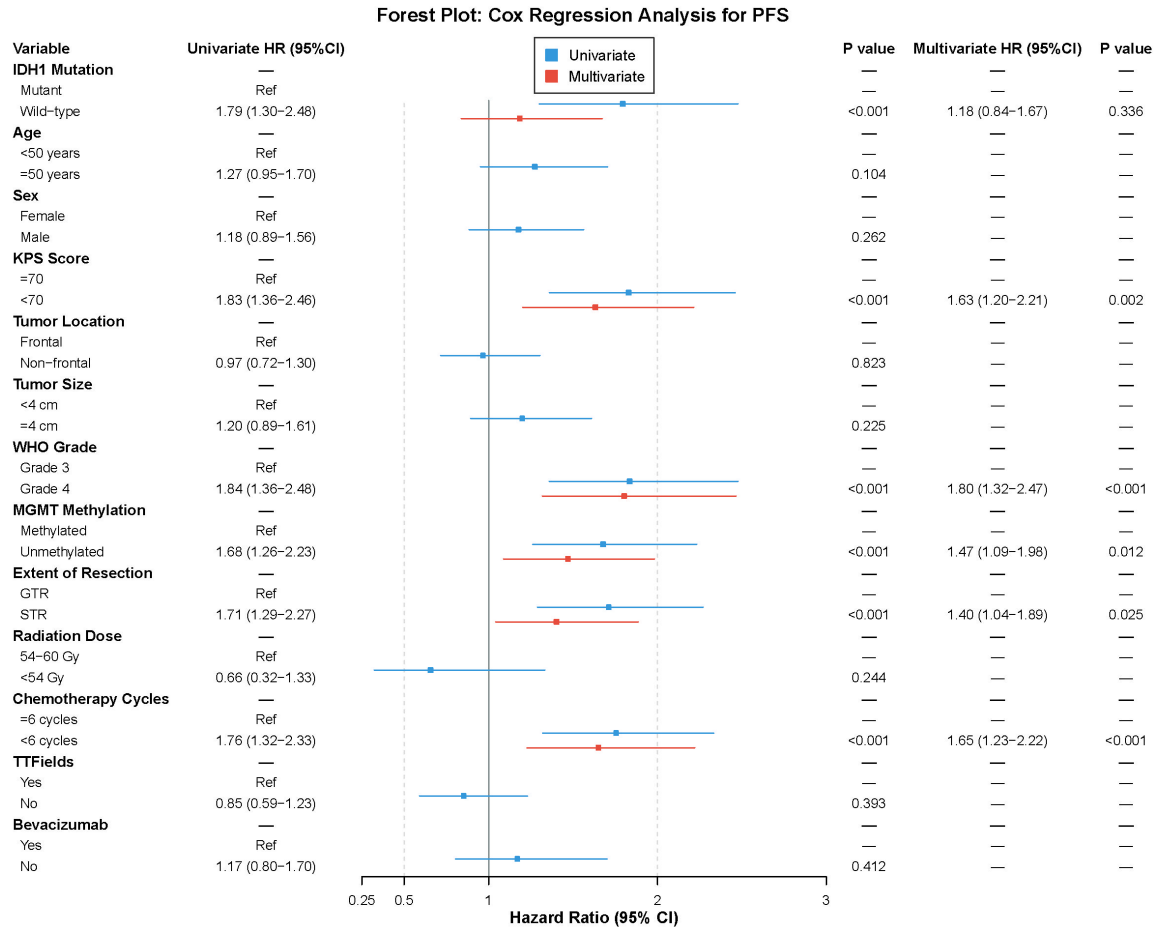

Figure 1. Forest plot of univariate and multivariate Cox regression analysis for progression-free survival. Note: PFS: Progression-Free Survival, HR: Hazard Ratio, CI: Confidence Interval, IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields.

95% CI: 1.633-3.014, P<0.001) were significantly associated with OS.

Age (≥50 years vs. <50 years, P=0.118), sex (male vs. female, P=0.106), tumor location (non-frontal lobe vs. frontal lobe, P=0.949), maximum tumor diameter (≥4 cm vs. <4 cm, P=0.105), radiotherapy dose (<54 Gy vs. 54-60 Gy, P=0.252), TTFields (not used vs. used, P=0.675), and combination therapy with bevacizumab (not combined vs. combined, P=0.746) were not significantly associated with OS (all P>0.05).

Multivariate Cox regression analysis showed that IDH1 wildtype (vs. mutant) (HR=1.638, 95% CI: 1.104-2.430, P=0.014), KPS score <70 (HR=1.396, 95% CI: 1.007-1.935, P=0.045), WHO grade 4 (HR=2.273, 95% CI: 1.594-3.241, P<0.001), MGMT promoter demethylation (HR=2.054, 95% CI: 1.476-2.859, P<0.001), and <6 cycles of adjuvant chemotherapy (HR=1.977, 95% CI: 1.430-2.734, P<0.001) were independent risk factors for OS. STR (vs. GTR) was no longer statistically significant after adjusting for other factors (HR=1.128, 95% CI: 0.818-1.555, P=0.464) (**Figure 2**).

Collinearity was diagnosed for variables included in the multivariate Cox regression model after univariate screening. The results, as shown in Tables S1, S2, S3, indicate that the VIF values for all variables were close to 1.0, and no strong pairwise correlations were observed among the included variables. These findings suggest that multicollinearity is extremely low and unlikely to have a substantial impact on the stability of the multivariate model.

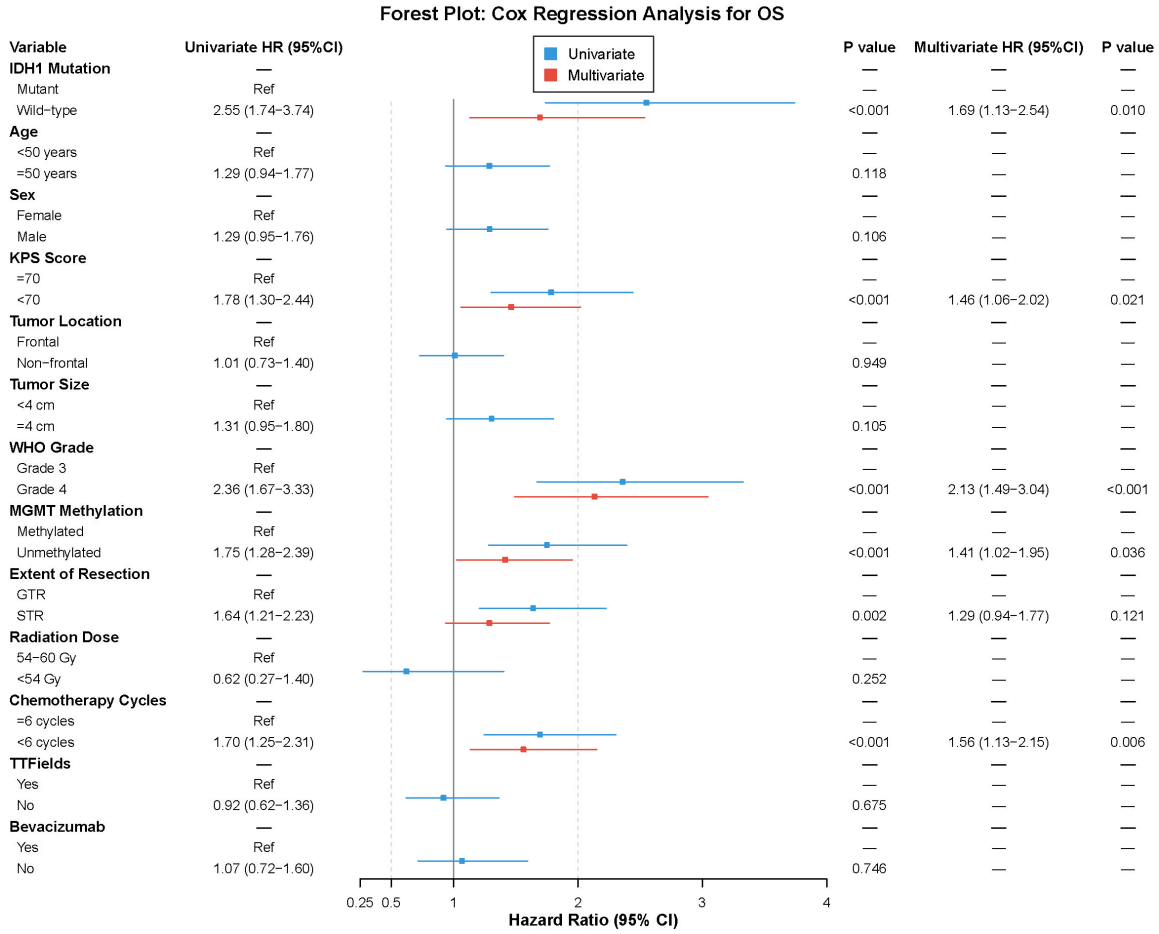

Figure 2. Forest plot of univariate and multivariate Cox regression analysis for overall survival. Note: OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields.

Relationship between IDH1 mutation status and short-term efficacy of concurrent chemoradiotherapy

An assessment of the short-term efficacy of concurrent chemoradiotherapy in the training cohort revealed a significant correlation between IDH1 mutation status and treatment response. The ORR was 58.3% in IDH1-mutant patients, significantly higher than the 37.6% in wildtype patients (P=0.005). Similarly, the DCR was 88.9% in IDH1-mutant patients, also significantly higher than the 76.5% in wildtype patients (P=0.041). These results suggest that patients with IDH1-mutant HGGs have a better treatment response to concurrent chemoradiotherapy (**Table 4**).

Subgroup analysis of the impact of IDH1 mutation status on disease control rate

To further explore whether the impact of IDH1 mutation status on the efficacy of concurrent chemoradiotherapy varies with different clinical characteristics, this study conducted a subgroup analysis. The results showed that the benefit of IDH1 mutation on DCR was mainly reflected in specific subgroups. In the MGMT promoter methylation subgroup, DCR of IDH1-mutant patients was 97.7%, significantly higher than the 78.9% of wildtype patients (OR=11.52, 95% CI: 1.46-90.63, P=0.004). Similarly, in the GTR subgroup, DCR of IDH1 mutant patients was 95.7%, also significantly higher than the 77.4% of wildtype patients (OR=6.58, 95% CI: 1.46-29.65, P=0.006).

Table 4. Comparison of treatment response to concurrent chemoradiotherapy between IDH1-mutant and IDH1-wildtype patients in the training cohort

Response assessment	Overall (n=242)	IDH1-mutant (n=72)	IDH1-wildtype (n=170)	χ^2	*P*-value
CR	27 (11.2%)	13 (18.1%)	14 (8.2%)		
PR	79 (32.6%)	29 (40.3%)	50 (29.4%)		
SD	88 (36.4%)	22 (30.6%)	66 (38.8%)		
PD	48 (19.8%)	8 (11.1%)	40 (23.5%)		
ORR (CR + PR)	106 (43.8%)	42 (58.3%)	64 (37.6%)	7.972	0.005
DCR (CR + PR + SD)	194 (80.2%)	64 (88.9%)	130 (76.5%)	4.156	0.041

Note: IDH1: Isocitrate Dehydrogenase 1, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease, ORR: Objective Response Rate, DCR: Disease Control Rate.

Table 5. Subgroup analysis of the effect of IDH1 mutation status on disease control rate

Subgroup	IDH1-mutant DCR	IDH1-wildtype DCR	OR (95% CI)	*P*-value
KPS score				
≥70	92.9% (52/56)	80.9% (89/110)	3.07 (1.00-9.43)	0.064
<70	75.0% (12/16)	68.3% (41/60)	1.39 (0.40-4.88)	0.763
WHO grade				
Grade 3	90.0% (36/40)	86.5% (45/52)	1.40 (0.38-5.16)	0.751
Grade 4	87.5% (28/32)	72.0% (85/118)	2.72 (0.88-8.35)	0.104
MGMT status				
Methylated	97.7% (43/44)	78.9% (56/71)	11.52 (1.46-90.63)	0.004
Unmethylated	75.0% (21/28)	74.7% (74/99)	1.01 (0.38-2.67)	1
Extent of resection				
GTR	95.7% (45/47)	77.4% (65/84)	6.58 (1.46-29.65)	0.006
STR	76.0% (19/25)	75.6% (65/86)	1.02 (0.36-2.90)	1
Adjuvant chemotherapy cycles				
≥6 cycles	95.9% (47/49)	85.1% (86/101)	4.10 (0.90-18.70)	0.058
<6 cycles	73.9% (17/23)	63.8% (44/69)	1.61 (0.56-4.61)	0.451

Note: IDH1: Isocitrate Dehydrogenase 1, DCR: Disease Control Rate, OR: Odds Ratio, CI: Confidence Interval, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection.

In the subgroups of patients with KPS score ≥70 (P=0.064), <70 (P=0.763), WHO grade 3 (P=0.751), WHO grade 4 (P=0.104), MGMT promoter demethylation (P=1.000), STR (P= 1.000), ≥6 cycles of adjuvant chemotherapy (P=0.058), and <6 cycles of adjuvant chemotherapy (P=0.451), there were no significant differences in DCR between IDH1 mutant and wildtype patients (all P>0.05). These results suggest that the benefit of IDH1 mutation on the efficacy of concurrent chemoradiotherapy is more significant in patients with MGMT promoter methylation and those undergoing GTR (**Table 5**).

Construction of the OS prediction model

Based on multivariate Cox regression analysis, this model included five independent prognostic factors: IDH1 mutation status, KPS score, WHO grade, MGMT promoter methylation status, and adjuvant chemotherapy cycles. A nomogram was constructed to predict OS in HGG patients. The risk score was calculated as follows:

Risk Score = 0.512 × IDH1 + 0.345 × KPS + 0.816 × WHO + 0.740 × MGMT + 0.701 × Chemotherapy Cycles

Where, IDH1 (wildtype =1, mutant =0), KPS (<70=1, ≥70=0), WHO (grade 4=1, grade 3=0), MGMT (unmethylated =1, methylated =0); chemotherapy cycles (<6 cycles =1, ≥6 cycles =0).

When using this nomogram, first obtain the corresponding score on the corresponding scale based on the specific values of each variable,

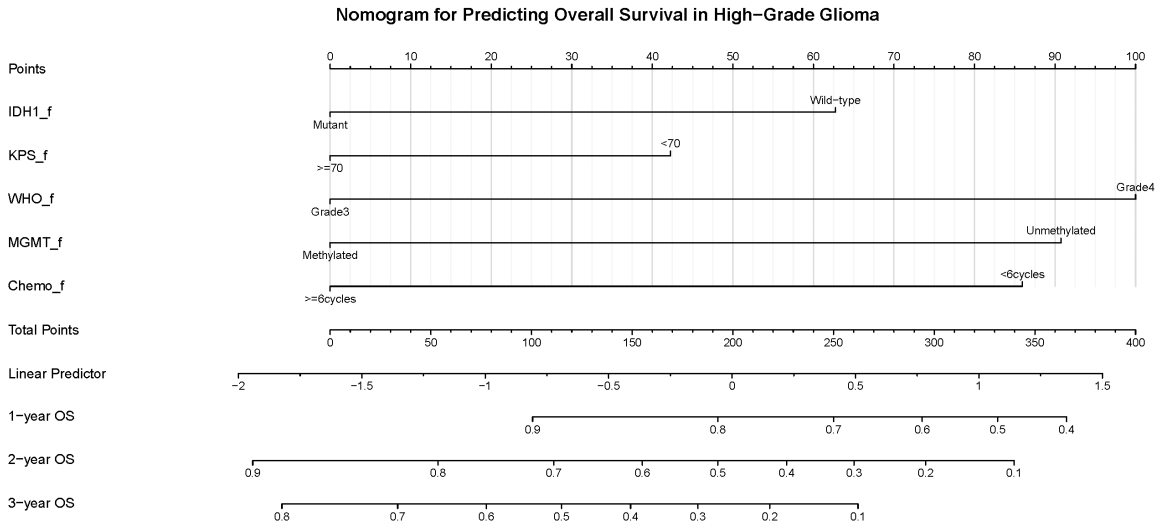

Figure 3. Nomogram for predicting overall survival in patients with high-grade glioma. Note: IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, OS: Overall Survival.

then add up all the variable scores to obtain the total score, and finally read the predicted 1-year, 2-year, and 3-year survival probabilities from the bottom scale using the total score (**Figure 3**).

Validation of the predictive model in the training cohort

The constructed OS prediction model was internally validated in the training cohort. Time-dependent ROC curve analysis showed that the AUC for predicting 1-year, 2-year, and 3-year OS was 0.822 (95% CI: 0.755-0.889), 0.778 (95% CI: 0.718-0.839), and 0.866 (95% CI: 0.814-0.919), respectively, indicating good model discrimination. The model's C-index was 0.721 (95% CI: 0.681-0.761), further confirming its discriminative ability.

The calibration curve showed good agreement between the model's predicted 3-year OS probability and actual observations in the training cohort. Quantitative analysis showed a Brier score of 0.1504; the Hosmer-Lemeshow goodness-of-fit test showed no significant underfit (χ^2=8.11, df=8, P=0.4229), indicating ideal calibration. Decision curve analysis showed that within the threshold probability range of 0.01-0.80, the model's net benefit was higher than that of the "all treatment" and "no treatment" strategies, with a maximum net benefit of 0.675.

Based on the ternary risk score, patients were divided into low-risk (score ≤1.328), intermediate-risk (1.328< score ≤2.068), and high-risk (score >2.068) groups. Kaplan-Meier survival analysis showed a statistically significant difference in OS among the three groups (log-rank test, P<0.001). This tri-stratified risk classification demonstrated a clear risk differentiation effect, with the risk of death increasing stepwise from the low-risk to the high-risk group. Compared with the low-risk group, the intermediate-risk group had a 1.64-fold increased risk of death (HR=2.64, 95% CI: 1.77-3.93), and the high-risk group had a 5.27-fold increased risk of death (HR=6.27, 95% CI: 4.21-9.34) (**Figure 4** and **Table 6**).

Validation of the predictive model in the validation cohort

The predictive model built from the training cohort was applied to the validation cohort for external validation. Time-dependent ROC curve analysis showed that the model's AUCs for predicting 1-year, 2-year, and 3-year OS were 0.701 (95% CI: 0.605-0.796), 0.647 (95% CI: 0.565-0.729), and 0.766 (95% CI: 0.670-0.863), respectively. The model's C-index was 0.640, indicating that the model maintained good discriminative power in the external validation population.

In the validation cohort, the calibration curves also demonstrated acceptable agreement

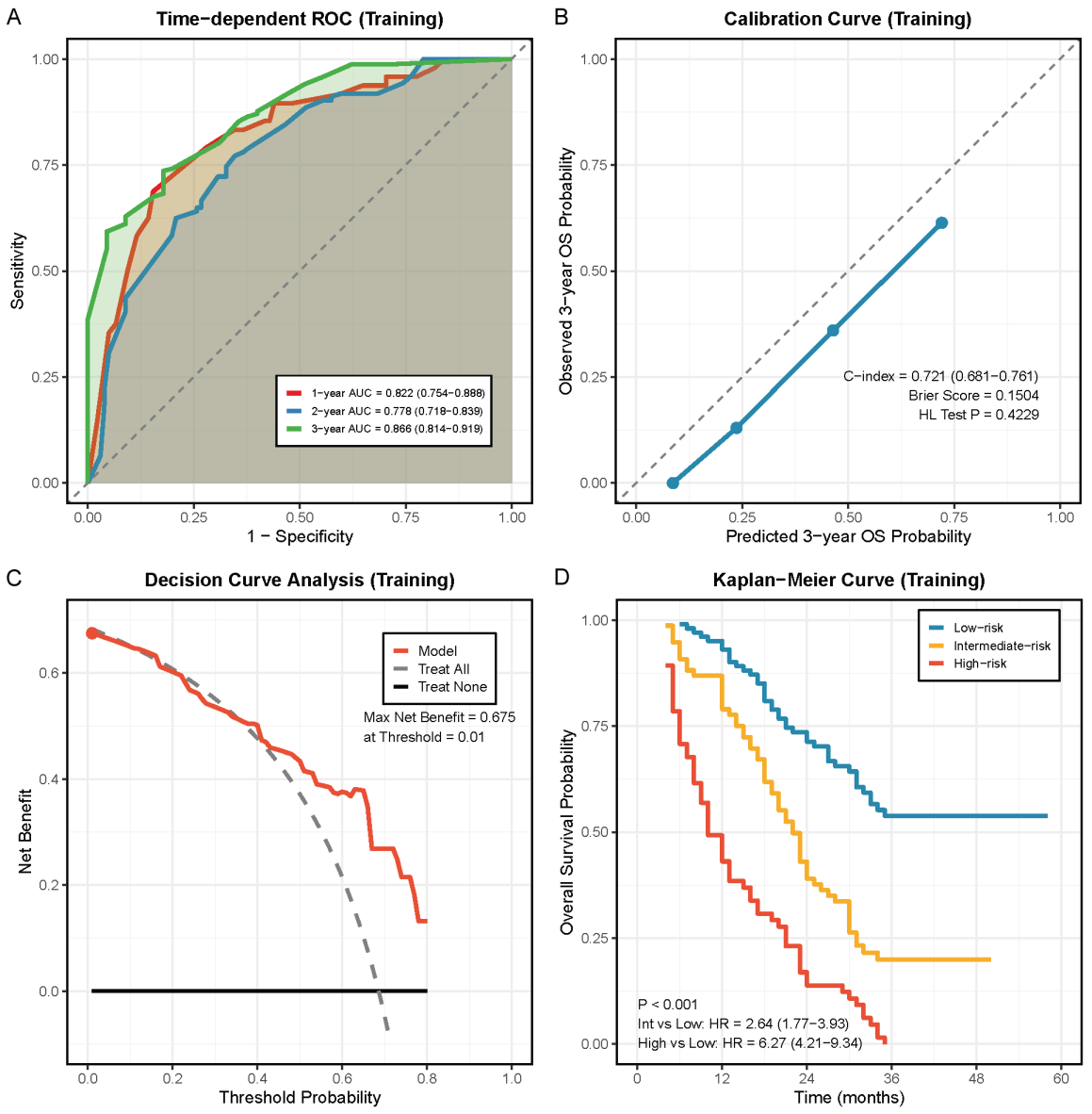

Figure 4. Validation of the prognostic model in the training cohort. A. Time-dependent ROC curve, demonstrating the model's discriminative ability in predicting 1-year, 2-year, and 3-year overall survival; B. Calibration curve, showing the consistency between the model-predicted 3-year survival probability and observed values; C. Decision curve analysis, illustrating the clinical net benefit of the model at different threshold probabilities; D. Kaplan-Meier survival curve, demonstrating the difference in overall survival across different risk stratification groups. Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval, OS: Overall Survival, HL: Hosmer-Lemeshow, HR: Hazard Ratio.

between the model's predicted 3-year OS probability and actual observations. The Brier score was 0.1682; the Hosmer-Lemeshow goodness-of-fit test showed no significant bias (χ^2=8.92, df=7, P=0.2587), suggesting good calibration of the model in the external validation set. Decision curve analysis showed that the model had a positive net benefit within the threshold probability range of 0.01-0.80, with a maximum net benefit of 0.685.

Applying the risk stratification cutoff values determined in the training cohort to the validation cohort, Kaplan-Meier survival analysis showed that the differences in OS among the three groups remained statistically significant (log-rank test, P<0.001). Compared with the low-risk group, the intermediate-risk group had a 0.77-fold increased risk of death (HR=1.77, 95% CI: 1.17-2.68), and the high-risk group had a 1.75-fold increased risk of death (HR=2.75,

Table 6. Validation results of the prognostic model in training and validation cohorts

Metric	Training cohort	Validation cohort
C-index (95% CI)	0.721 (0.681-0.761)	0.64
1-year AUC (95% CI)	0.822 (0.755-0.889)	0.701 (0.605-0.796)
2-year AUC (95% CI)	0.778 (0.718-0.839)	0.647 (0.565-0.729)
3-year AUC (95% CI)	0.866 (0.814-0.919)	0.766 (0.670-0.863)
Brier score	0.1504	0.1682
HL test *P*-value	0.4249	0.2587
Log-rank P	<0.001	<0.001
HR: intermediate vs. low risk	2.64 (1.77-3.93)	1.77 (1.17-2.68)
HR: high vs. low risk	6.27 (4.21-9.34)	2.75 (1.79-4.23)

Note: C-index: Concordance Index, AUC: Area Under the Curve, CI: Confidence Interval, HL: Hosmer-Lemeshow, HR: Hazard Ratio.

95% CI: 1.79-4.23). External validation results confirmed that the predictive model has good generalization ability and clinical application value (see **Figure 5** and **Table 6**).

Subgroup analysis and interactions of IDH1 mutation status on overall survival

To explore whether the impact of IDH1 mutation status on OS varies across different clinical subgroups, we conducted subgroup analysis and examined interactions. In the overall population, IDH1 wildtype patients had a higher risk of death compared to mutant patients (HR=2.55, 95% CI: 1.74-3.74, P<0.001).

Interaction analysis found significant interactions between IDH1 mutation status and the number of cycles of adjuvant chemotherapy (interaction P=0.007) as well as MGMT promoter methylation status (interaction P=0.040). Specifically, in the subgroup with <6 cycles of adjuvant chemotherapy, the risk of death was significantly increased in patients with IDH1 wildtype (HR=3.90, 95% CI: 2.23-6.83, P< 0.001); while in the subgroup with ≥6 cycles of adjuvant chemotherapy, IDH1 mutation status was not significantly associated with the risk of death (HR=1.29, 95% CI: 0.76-2.19, P=0.340). Similarly, in the subgroup with unmethylated MGMT promoter, the risk of death was significantly increased in patients with IDH1 wildtype (HR=3.50, 95% CI: 1.89-6.51, P<0.001); while in the subgroup with methylated MGMT promoter, the association between IDH1 mutation status and the risk of death was not statistically significant (HR=1.49, 95% CI: 0.92-2.43, P=0.108).

In subgroups of WHO grade (interaction P=0.368), age (interaction P=0.774), sex (interaction P=0.427), KPS score (interaction P=0.930), extent of surgical resection (interaction P=0.200), radiotherapy dose (interaction P=0.367), TTFields (interaction P=0.969), and combined bevacizumab therapy (interaction P=0.793), no significant difference was found in the prognostic impact of IDH1 mutation status (all interaction P>0.05) (see **Figure 6**).

Sensitivity analysis: relationship between adjuvant chemotherapy cycles and OS

To evaluate the robustness of the association between the number of adjuvant chemotherapy cycles and OS and to explore the impact of potential immortality bias, we used various sensitivity analysis methods to validate the results (**Figure 7A** and **7B**).

As shown in **Figure 7A**, in the original multivariate Cox regression analysis, patients receiving <6 cycles of adjuvant chemotherapy had a significantly higher risk of death than those receiving ≥6 cycles (HR=2.02, 95% CI: 1.47-2.77, P<0.001). After a 6-month landmark analysis, this association attenuated but remained statistically significant (HR=1.64, 95% CI: 1.15-2.34, P=0.006). Further analysis using a time-dependent covariate Cox model showed that <6 cycles of adjuvant chemotherapy remained significantly associated with worse OS (HR= 1.60, 95% CI: 1.12-2.27, P=0.009). Additionally, in the analysis excluding deaths within 6 months, <6 cycles of chemotherapy remained a risk factor for poor prognosis (HR=1.64, 95% CI: 1.15-2.34, P=0.006).

Figure 7B illustrates the impact of the number of adjuvant chemotherapy cycles on OS at different landmark time points (3-9 months). It can be seen that the number of patients included in the analysis gradually decreased at each time point, but the HR for the group with <6 cycles of chemotherapy remained greater than 1. The overall HR value showed a trend of initially decreasing slightly and then stabilizing, without any change in direction. These results

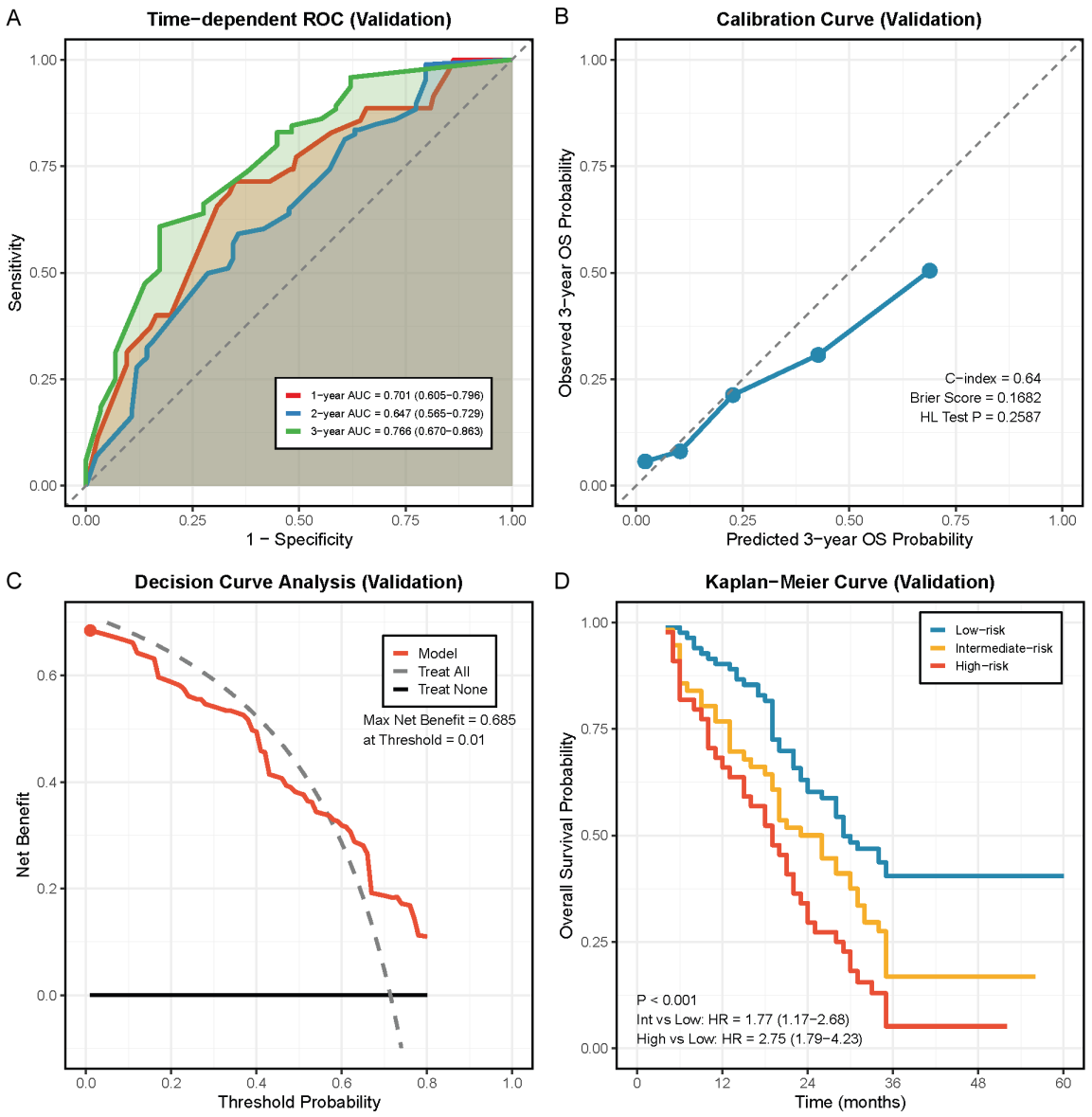

Figure 5. External validation of the prognostic model in the validation cohort. A. Time-dependent ROC curve, demonstrating the model's discriminative ability in predicting 1-year, 2-year, and 3-year overall survival; B. Calibration curve, illustrating the consistency between the model-predicted 3-year survival probability and observed values; C. Decision curve analysis, showing the clinical net benefit of the model at different threshold probabilities; D. Kaplan-Meier survival curve, demonstrating the difference in overall survival across different risk stratification groups. Note: ROC: Receiver Operating Characteristic, AUC: Area Under the Curve, CI: Confidence Interval, OS: Overall Survival, HL: Hosmer-Lemeshow, HR: Hazard Ratio.

suggest that although effect sizes differed at different landmark time points and under different analytical methods, insufficient adjuvant chemotherapy cycles were consistently associated with worse OS.

Discussion

A retrospective cohort study of 424 HGG patients undergoing concurrent chemoradiotherapy found that IDH1 mutations were associated with improved treatment response and prolonged survival. Compared to patients with wildtype tumors, those with IDH1-mutant tumors had significantly higher ORR and DCR. The median OS in the mutant group was not yet reached, while it was 20.0 months in the wildtype group. Furthermore, this study constructed a nomogram model incorporating IDH1 status, KPS score, WHO classification, MGMT

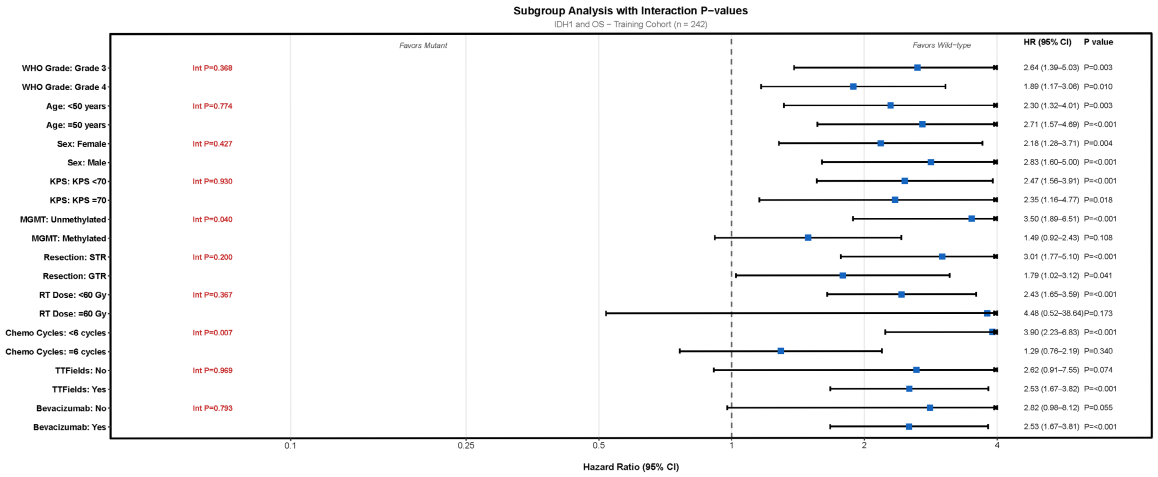

Figure 6. Forest plot of subgroup analysis for the effect of IDH1 mutation status on overall survival. Note: IDH1: Isocitrate Dehydrogenase 1, OS: Overall Survival, HR: Hazard Ratio, CI: Confidence Interval, WHO: World Health Organization, KPS: Karnofsky Performance Status, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, RT: Radiotherapy, Gy: Gray, TTFields: Tumor Treating Fields, Int P: Interaction *P*-value.

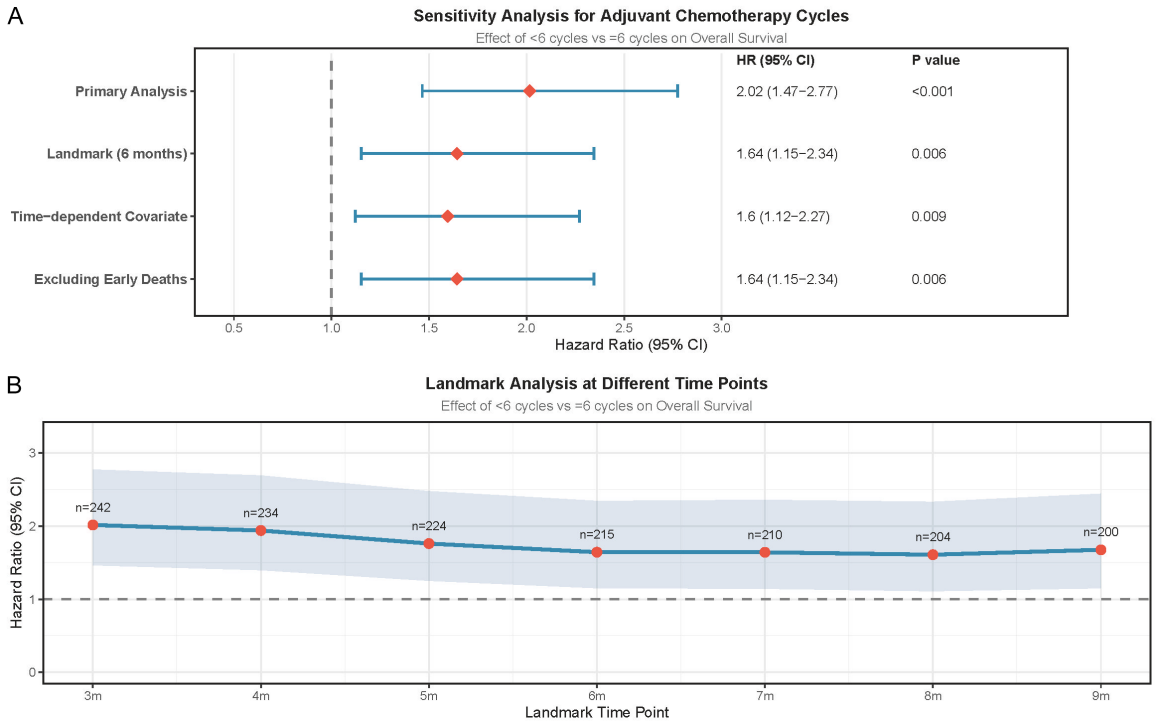

Figure 7. Sensitivity analysis for the association between adjuvant chemotherapy cycles and overall survival. A. Forest plot of hazard ratios (HRs) and 95% confidence intervals (CIs) for OS across different analytical approaches, including the primary analysis, 6-month landmark analysis, time-dependent covariate model, and analysis excluding early deaths. B. Landmark analyses at different time points (3-9 months) showing the effect of adjuvant chemotherapy cycles (<6 vs. ≥6) on OS. Shaded areas represent 95% CIs, and numbers indicate patients included at each landmark time point. Note: HR, hazard ratio; CI, confidence interval; OS, overall survival. HR>1 indicates an increased risk of death associated with <6 cycles of adjuvant chemotherapy.

promoter methylation status, and adjuvant chemotherapy cycles. Preliminary validation showed that the model had acceptable discrimination and calibration. Overall, these find-

ings support the clinical application of IDH1 as a biomarker for predicting treatment efficacy and assessing prognosis in HGG patients undergoing concurrent chemoradiotherapy.

A major advantage of this study is that it extends the role of IDH1 from long-term prognosis to short-term treatment efficacy. Previous studies have largely focused on the association between IDH mutations and patient survival outcomes [7, 8], while evidence regarding the association between IDH mutations and response to concurrent chemoradiotherapy is relatively scarce. Our findings suggest that IDH1 mutation may help identify patients who can benefit from standard chemoradiotherapy regimens. This benefit is biologically plausible: 2-hydroxyglutarate (2-HG) accumulated in IDH-mutant tumors can inhibit α-ketoglutarate-dependent dioxygenase and alter DNA damage repair pathways [19]. Previous studies have reported that IDH mutations increase tumor sensitivity to alkylating agents such as temozolomide by weakening poly (ADP-ribose) polymerase 1-mediated repair and homologous recombination repair capabilities [20]. Similarly, 2-HG can further affect gene expression related to treatment sensitivity by inhibiting histone and DNA demethylase-induced hypermethylation [21]. IDH mutations may also alter nicotinamide adenine dinucleotide phosphate and glutathione metabolism, reducing antioxidant capacity and thus increasing tumor sensitivity to radiotherapy-induced oxidative stress [22]. The above mechanism explains the superior ORR and DCR in patients with IDH1 mutations [23].

Subgroup analysis revealed that the effect of IDH1 mutations is context-dependent. Its positive effect on disease control was more significant in patients with MGMT promoter methylation and those who underwent total tumor resection, suggesting a potential interaction between molecular and clinical factors. This result has important clinical implications: MGMT methylation reduces DNA repair capacity and can synergistically enhance tumor sensitivity to temozolomide in conjunction with IDH mutations [6, 10]. Similarly, GTR minimizes residual tumor burden, which, combined with the relatively slow progression of IDH-mutant tumors, contributes to better disease control. These results suggest that a more comprehensive understanding of biomarkers is needed for their clinical application, rather than focusing solely on IDH1 status.

Consistent with previous studies, OS was significantly better in IDH1-mutant patients than in wild-type patients in this study [25]. Unexpectedly, this study found that IDH1 status had no significant impact on PFS in univariate analysis, but it remained an independent predictor of OS. The reason for this difference may be that PFS focuses more on initial treatment failure and early disease progression, while OS reflects a more comprehensive disease progression, including recurrence patterns, salvage therapy failure, and tumor progression characteristics. In this study cohort, IDH1 mutations were associated with more favorable clinicopathological features, such as lower WHO grade and higher incidence of MGMT methylation, and their direct impact on PFS may be mediated by these associated features. Conversely, the persistent association between IDH1 mutations and OS suggests a more systematic impact on tumor biological behavior and long-term clinical outcomes [26].

Interaction analysis further enriched the prognostic value of IDH1. The study observed a significant interaction between IDH1 status and adjuvant chemotherapy cycles and MGMT promoter methylation. In patients with fewer than 6 cycles of adjuvant chemotherapy, IDH1 wild-type was associated with a markedly higher risk of death, but this difference was weakened in patients with ≥6 cycles of chemotherapy. Similarly, the adverse prognostic impact of IDH1 wildtype was more pronounced in the MGMT demethylated subgroup [24]. The above results indicate that adequate adjuvant chemotherapy can partially offset the adverse prognosis associated with IDH1 wild-type, while MGMT methylation can, to some extent, mask the prognostic differences caused by IDH1 status. Combined with clinical research findings, this study supports a risk-adaptive treatment strategy: for IDH1 wild-type patients, especially those with demethylated MGMT, enhanced monitoring is necessary, and intensive or experimental treatment regimens should be considered [27].

Based on independent prognostic factors identified through multivariate analysis, this study

constructed a nomogram model for individualized prediction of OS. Compared to previous glioma prognostic models [12, 28, 29], this model has several practical advantages: the study subjects were limited to HGGs patients receiving concurrent chemoradiotherapy, and the major molecular marker IDH1, as defined in the 2021 WHO classification, was included [5]; the model specifically incorporates MGMT promoter methylation status [10, 11] and adjuvant chemotherapy cycles, encompassing both tumor biological characteristics and treatment implementation. The model was subsequently validated in an independent time cohort, showing good performance [30]. Clinical studies suggest that this nomogram can be used for risk stratification, patient communication, and clinical trial design. High-risk patients identified by the model may be considered for more aggressive treatment regimens or additional interventions such as TTFields (at appropriate times); while low-risk patients can adopt individualized treatment strategies that focus more on quality of life. The model can also intuitively predict 1-year, 2-year, and 3-year survival probabilities, facilitating communication between doctors, patients, and families [31].

Fundamentally, the perpetual time bias present in retrospective studies of adjuvant chemotherapy cycles prompted this study to conduct a series of sensitivity analyses to evaluate the robustness of this association. Milestone analysis, exclusion of early deaths, and time-dependent Cox model analysis all yielded consistent conclusions: fewer than 6 chemotherapy cycles were associated with worse OS. Perpetual time bias is a recognized methodological problem in observational treatment studies. Results are more reliable if they remain robust across various analytical methods. These findings support maintaining standard temozolomide adjuvant therapy regimens in clinical practice as much as possible, avoiding premature discontinuation of medication through active supportive care and treatment regimen adjustments [4].

This study also has certain limitations. First, the retrospective, single-center design inherently carries the risk of selection bias, and the inclusion criteria requiring patients to have an expected survival of more than 3 months may lead to an overestimation of patients with better baseline prognoses in the cohort. Although time-validation was achieved, this model has not yet undergone truly geographically external validation, and future multicenter prospective studies are needed to confirm the generalizability of the results. Second, the molecular testing was not comprehensive enough, only assessing IDH1 R132 mutations and not systematically detecting IDH2 and other related biomarkers. Furthermore, this study used methylation-specific PCR to assess MGMT promoter methylation, a clinically common method that cannot achieve quantitative detection. Although the overall treatment regimen was uniform, heterogeneity in adjuvant therapy and other treatment regimens may still affect the study outcomes. Additionally, the follow-up period was insufficient to fully elucidate the long-term survival of the IDH1-mutant subgroup.

Future research needs to further explore its biological and clinical significance: more mechanistic studies are needed to clarify the interaction between IDH mutations and the tumor immune microenvironment; current evidence suggests that 2-HG can regulate T cell function and the tumor immune microenvironment. The nomogram constructed in this study requires prospective, multicenter clinical validation and can be further integrated with molecular and radiomics features to improve predictive accuracy. With the approval of IDH inhibitors such as voracidis for the treatment of IDH-mutant gliomas, evaluating whether IDH-targeted therapy can be included in the treatment regimen for HGGs, and its optimal combination with concurrent chemoradiotherapy, is of significant clinical importance.

Conclusion

This large-sample retrospective cohort study confirms that IDH1 mutation is an important predictor of treatment efficacy and prognosis in HGG receiving concurrent chemoradiotherapy. Compared with wildtype patients, IDH1-mutant patients have significantly prolonged OS and better short-term response to concurrent chemoradiotherapy. Interaction analysis shows that standard adjuvant chemotherapy can partially compensate for prognostic differences caused by IDH1 status. This study constructed a nomogram model based on IDH1

status, KPS score, WHO classification, MGMT methylation status, and chemotherapy cycles. After independent external validation, it showed good calibration and discrimination, and can serve as an effective tool for clinical risk stratification and individualized treatment decisions. The findings provide evidence-based medical support for precision medicine practices based on molecular characteristics and lay the foundation for future exploration of IDH-targeted therapy in HGGs.

Disclosure of conflict of interest

None.

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Table S1. Variance inflation factor analysis of variables included in the multivariable Cox regression model in the training cohort

Variable	VIF
IDH1 mutation status	NA*
KPS score	1.053
WHO grade	1.025
MGMT promoter methylation status	1.056
Extent of resection	1.068
Adjuvant chemotherapy cycles	1.081

Note: IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields. *IDH1 mutation status was used as the temporary dependent variable for VIF calculation.

Table S2. Spearman correlation coefficients among variables included in the multivariable Cox regression model in the training cohort

Variable	IDH1 mutation	KPS score	WHO grade	MGMT methylation	Extent of resection	Chemotherapy cycles
IDH1 mutation	1	0.129	0.235	0.177	0.146	0.081
KPS score	0.129	1	0.071	0.002	0.128	0.185
WHO grade	0.235	0.071	1	0.124	0.055	-0.018
MGMT methylation	0.177	0.002	0.124	1	0.162	0.132
Extent of resection	0.146	0.128	0.055	0.162	1	0.185
Chemotherapy cycles	0.081	0.185	-0.018	0.132	0.185	1

Note: IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields.

Table S3. *P* values for Spearman correlation analysis among variables included in the multivariable Cox regression model in the training cohort

Variable	IDH1 mutation	KPS score	WHO grade	MGMT methylation	Extent of resection	Chemotherapy cycles
IDH1 mutation	-	0.045	<0.001	0.006	0.024	0.207
KPS score	0.045	-	0.269	0.975	0.047	0.004
WHO grade	<0.001	0.269	-	0.054	0.397	0.781
MGMT methylation	0.006	0.975	0.054	-	0.012	0.041
Extent of resection	0.024	0.047	0.397	0.012	-	0.004
Chemotherapy cycles	0.207	0.004	0.781	0.041	0.004	-

Note: IDH1: Isocitrate Dehydrogenase 1, KPS: Karnofsky Performance Status, WHO: World Health Organization, MGMT: O6-methylguanine-DNA methyltransferase, GTR: Gross Total Resection, STR: Subtotal Resection, Gy: Gray, TTFields: Tumor Treating Fields.