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Clinical characteristics and outcomes of adult IDH-mutant brainstem gliomas: Institutional case series and systematic review

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Abstract

Background. Adult IDH-mutant brainstem gliomas (BSGs) are rare and appear molecularly distinct from H3K27-altered diffuse midline gliomas. We aimed to provide a comprehensive characterization by integrating an institutional cohort with a pooled individual-patient analysis.

Methods. Adults with IDH-mutant BSGs diagnosed at our institution were identified. A PRISMA-guided search of PubMed and Scopus captured additional cases. Individual-level demographic, radiographic, molecular, treatment, and outcome data were abstracted. Kaplan-Meier and log-rank testing evaluated survival associations with age, sex, WHO grade, surgery, chemoradiation, IDH variant, MGMT methylation, ATRX status, and location.

Results. Eighty-four patients were analyzed (n=7 institutional, n=77 literature-derived). Mean age was 37.8 years; 68.6% male. Most tumors involved the pons/medulla (90.4% astrocytomas; 68.7% WHO grade 2). Among evaluable cases, MGMT methylation was present in 47.5%, ATRX loss in 53.2%, and TP53 mutation in 84.3%. Non-canonical IDH variants accounted for 45.3% of cases. Median overall survival (OS) was 77.3 months. In multivariate analysis, non-canonical IDH variants independently predicted improved OS (HR=0.37, P=.012), while surgical resection showed a strong clinical trend toward improved OS (HR=0.48, P=.073). Chi-squared analysis confirmed no significant difference in high-grade tumor distribution between resection and biopsy groups (P=.52), suggesting the trend was not driven by selection bias.

Conclusions. Adult IDH-mutant BSGs represent a clinically meaningful subgroup with outcomes more favorable than H3K27-altered gliomas but shorter than supratentorial IDH-mutant gliomas. Their recurrent molecular features, including frequent non-canonical IDH variants, warrant study in larger cohorts to clarify biological significance, refine prognostication, and inform the potential role of IDH-targeted therapies.

Key Points

- Adult IDH-mutant brainstem gliomas show a distinct molecular phenotype.
- Non-canonical IDH variants predict improved survival.
- Nearly half lack R132H and require sequencing for diagnosis.

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Importance of the Study

Adult IDH-mutant brainstem gliomas (BSGs) are exceptionally rare, with most existing literature limited to isolated cases. By integrating an institutional cohort with a patient-level systematic review, this study provides the largest and most detailed characterization of this population to date. Our findings establish that these tumors possess a distinct molecular profile, frequently enriched for non-canonical IDH variants, and demonstrate markedly better survival than H3K27-altered diffuse midline gliomas (DMGs). Critically, we identify prognostic associations not previously recognized in the brainstem, including an independent survival advantage for non-R132H IDH mutations and a strong clinical trend favoring surgical resection. These insights refine clinical expectations and underscore the necessity of comprehensive molecular sequencing, as nearly half of these cases harbor variants undetectable by standard immunohistochemistry. By defining this unique clinical and biological entity, our study provides a framework for more personalized management and supports the investigation of IDH-targeted therapies in this underserved population.

Diffuse gliomas in the infratentorial region—including the brainstem, cerebellum, and spinal cord constitute about <5% of all gliomas.[1,2] Of these, brainstem gliomas (BSGs) comprise a highly heterogeneous group and represent one of the most challenging entities in neuro-oncology due to their deep-seated location, heterogeneous biology, and limited therapeutic options.[1–3]

Isocitrate dehydrogenase (IDH)-mutated BSGs remain rare and poorly understood partly due to historical reluctance to perform biopsies in this area, the common assumption of tumor grade based solely on imaging features, and the relatively recent changes that advanced the role of molecular diagnostics in CNS tumor classification.[4] They are found both in pediatric and adult populations, but their clinical behavior, molecular landscape, and prognosis differ between the age groups.[5,6]

Historically, adult BSGs were presumed to behave uniformly as aggressive diffuse midline gliomas (DMGs) harboring H3K27M alterations.[7,8] However, the integration of molecular diagnostics into the World Health Organization (WHO) classification has revealed a distinct subset characterized by isocitrate dehydrogenase (IDH) mutations, biologically and clinically divergent from H3K27M-mutant tumors, and typically associated with more favorable outcomes.[9]

While IDH mutations are common in supratentorial diffuse gliomas, their occurrence within the brainstem is exceedingly rare, estimated at 5%-15% of adult BSGs.[4,10] These infratentorial IDH-mutant gliomas predominantly affect young adults, displaying radiographic and histopathologic features akin to their supratentorial counterparts.[3,11] Clinically, they often follow a more indolent course, underscoring the prognostic and therapeutic value of precise molecular characterization.[3,11]

Despite growing recognition, the current understanding of IDH-mutant BSGs remains fragmented, limited by small sample sizes and isolated institutional reports. Comprehensive data synthesis is essential to define their clinicopathologic spectrum, molecular profiles, and treatment outcomes more accurately.

To address this gap, we present seven institutional cases of adult IDH-mutant BSGs, integrated with a systematic review and pooled individual-patient analysis of all published cases. This study provides the most detailed characterization to date of the clinical, histological, molecular, and prognostic features of IDH-mutant BSGs in adults.

Institutional Case Series

Methods

Adult patients with histologically confirmed IDH-mutant BSG diagnosed at our institution between 2014 and 2025 were retrospectively identified from the neuropathology and neuro-oncology databases. Clinical, radiologic, pathology including immunohistochemistry and next-generation sequencing (NGS), treatment information and outcomes were abstracted from the electronic medical record and institutional molecular diagnostics reports. The study was approved by the University of Pittsburgh Institutional Review Board and conducted with appropriate ethical oversight.

Case Series Summary

We identified a series of seven patients diagnosed with IDH-mutant BSG (Table 1). The median age at diagnosis was 40 years (range: 22-56), and five of the seven patients were male.

At diagnosis, presenting neurological deficits in the institutional cohort (n=7) included dysarthria (Pts 1, 2, 4, 7), hemiparesis/limb weakness (Pts 2, 6, 7; with left grip weakness in Pt 4), dysphagia (Pts 2, 4), and diplopia/CN VI palsy (Pts 2, 6, 7; diplopia also in Pt 4). Additional features included Valsalva-induced headache (Pts 3, 5), vertigo/dizziness (Pts 4, 6), paresthesias/numbness (Pt 4), gait ataxia/foot drop/imbalance (Pt 6), facial droop and hypogeusia (Pt 7), and pseudobulbar affect (Pt 7). No patients presented with seizures. KPS at diagnosis ranged from 60 to 100, and steroid use at presentation was common (documented in Pts 2, 3, 4, 6, 7).

Radiologically, tumor involvement was most frequently observed in the pons, which was affected in five of the seven patients. Among these, two patients demonstrated direct extension from the pons into the medulla, while another showed spread from the left brachium pontis to the medulla.

Table 1. Institutional case series of non-pediatric IDH-mutant BSGs: clinical, radiographic, histologic and molecular data, treatment, and long-term outcomes

Patient	Sex	Age at Dx	Date of Dx	Clinical features at Dx	Location	Radiology features	Initial biopsy pathology	Molecular findings	Initial treatment	Progression (date)	Subsequent therapies	2nd biopsy pathology	Tx after progression	Survival status	Last follow-up
1	M	52	7/31/25	Dysarthria (1 mo) KPS = 90 Steroids (–) Seizure (–)	Lower pons & medulla	T2/FLAIR matched; Equivocal enhancement; Infiltrative. Initial impression: Glioma	Not done (high risk); cfDNA → malignant glioma	NGS (2025): IDH1 R132H; EGFR PG719C; MGMT-	Planned RT → TMZ (date: to be determined)	–	–	–	–	Alive	9/26/25
2	F	22	4/6/12	Hemiparesis (R), dysarthria, dysphagia, diplopia, headaches (3 mo) KPS = 80 Steroids (+) Seizure (–)	Pons, midbrain, cerebellum	T2/FLAIR matched; Faint enhancement; Infiltrative. Initial impression: Glioma	Infiltrating astrocytoma, WHO II	NGS (2016): IDH1 R132C, TP53+, NF1 loss, MGMT -, ATRX WT, 1p/19q not deleted	IMRT + Avastin → Avastin mono	11/4/15 progression	TMZ (1 cycle, intolerable), Avastin + PCV (PC only after rash)	12/13/17: Anaplastic astrocytoma, IDH+, TP53+, NF1+, MGMT-	Nivolumab + Avastin + TMZ	Deceased 9/22/18	9/22/18
3	M	27	4/1/10	Intermittent Valsalva-induced headaches KPS = 100 Seizure (–) Steroids (+)	Pons	T2/FLAIR matched; No enhancement; Infiltrative. Initial impression: Glioma	Anaplastic astrocytoma, WHO III	NGS (2018): IDH1 R132C TP53+, ATRX, PTEN, CDKN2A, CAC copy number loss, MGMT-	RT 54 Gy + TMZ + targeted agents (Vorinostat, Sorafenib, Herceptin, Avastin)	Multiple: 2015, 2016, 2017	TMZ x9, Re-RT 2016, Avastin+Nivo, Gamma knife, PCV, BAY1436032, Ivosidenib	3/21/18: Recurrent anaplastic astrocytoma	Avastin + Ivosidenib	Deceased 2/27/19	2/27/19
4	M	32	5/29/20	Diplopia, vertigo, paresthesia (hands), dysphagia, dysarthria, L grip weakness KPS = 60 Seizure (–) Steroids (+)	Pons	T2/FLAIR matched; No enhancement; Infiltrative. Initial impression: Glioma	Non-diagnostic	-	IMRT 60 Gy + 3 cycles TMZ	9/7/23, 4/3/24 progression	Re-RT (30 Gy/12Fx), adjuvant TMZ x5, Dordaviprone trial	2024 resection: NGS showing Astrocytoma, IDH1 R132H, WHO IV, IGF1, TP53+, MYCN amplified FGFR2 mutation and PDGFRA/KIT	Resection	Deceased 7/2/24	7/2/24
5	M	42	3/28/19	Valsalva-induced headache, near-syncope, lightheadedness, transient blurred vision KPS = 90 Steroids (–) Seizure (–)	Brainstem	T2/FLAIR matched; Equivocal enhancement; Infiltrative. Initial impression: Glioma	Diffuse astrocytoma, WHO II	NGS (2019): IDH1 R132S, TP53+, ATRX loss	CRT (RT + TMZ 2019) → 1 yr adjuvant TMZ	Stable since 2020	–	—	–	Alive	8/6/25
6	F	40	4/6/21	Hemiparesis (L), gait ataxia (foot drop), diplopia (CN VI palsy), base of neck pain, vertigo KPS = 70% Steroids (+) Seizure (–)	R pons → medulla	T2/FLAIR matched; No enhancement; Infiltrative. Initial impression: Glioma	Diffuse astrocytoma, WHO II	NGS (2021): IDH1 R132H, TP53+, ATRX, MGMT-	RT 54 Gy + PC x6 cycles	1/27/25 possible radionecrosis	Boswelia (2025), surveillance	–	–	Alive	9/2/25
7	M	56	10/11/18	Facial droop (R), hemiparesis (R), dysarthria, hypogeusia, diplopia, pseudobulbar affect KPS = 100 Steroids (+) Seizure (–)	L brachium pontis → medulla	T2/FLAIR matched; No enhancement; Infiltrative. Initial impression: Glioma	Diffuse astrocytoma, WHO II	NGS (2018): IDH2 R172K, TP53+, CTNNB1 loss, MGMT+, Ki67 15%	RT 30Fx (2018) + PCV (no V, 2 cycles)	Stable since 2019	–	–	–	Unknown	9/29/23

Broader brainstem involvement was noted in 1 patient, while midbrain and cerebellar regions were each affected in 1 case. All tumors were hyperintense on T2/FLAIR without evidence of mismatch. Contrast enhancement was absent in most cases; only one patient showed faint linear enhancement, while two had equivocal findings. Tumors predominantly exhibited an infiltrative growth pattern. Histopathologic diagnoses included diffuse astrocytoma confirmed through molecular profiling. 4 patients had low grade (WHO II) at initial diagnosis, 2 high grade (III and IV), 1 patient still pending histologic grade.

Molecular characterization using targeted next-generation sequencing was available for all patients. IDH1 mutations were detected in six of the seven patients (including three R132H, two R132C, one R132S), and one patient had an IDH2 R172K mutation. Other notable molecular alterations included TP53 mutations (6/6), MGMT methylation (1/5), ATRX retention/loss (reported in 3/5), MYCN, FGFR2, KIT, and NF1 copy number loss in one case.

One patient (case 4) ultimately underwent resection at malignant transformation. Overall, 6/7 received focal radiation (typically IMRT 54-60 Gy) and 5/7 received temozolomide. Alkylator backbones beyond TMZ were common: PC/PCV (Procarbazine, lomustine/vincristine) in 4/7. Bevacizumab was used in 2/7 (including one with maintenance monotherapy), and immune checkpoint therapy (nivolumab) in 2/7. Targeted/novel agents included IDH inhibition in 1/7 (ivosidenib ± BAY-1436032), dordaviprone in 1/7, and in one case, vorinostat, sorafenib, and trastuzumab. Salvage approaches included re-irradiation in 2/7 and stereotactic radiosurgery in 1/7.

Outcomes were variable: three patients remain alive and stable at last follow-up, one patient's outcome is unknown, and three patients had died by the data cutoff. One long-term survivor (case 5) had a stable disease course for over 5 years after diagnosis, and another survived nearly 9 years despite having high grade astrocytoma at diagnosis (case 3) (Figure 1). Two patients experienced prolonged progression-free intervals following combined modality treatment. The median PFS for the series was 51.5 months, and the median OS was 77.5 months (Figure 2A and B).

Systematic Review and Pooled Individual-Patient Analysis

Methods

Search methods

A systematic literature search of PubMed and Scopus was performed from inception through September 2025 following PRISMA 2020 guidelines, using combinations of keywords: (*brainstem/brain stem glioma, astrocytoma, or glioblastoma*), *including* (*diffuse intrinsic pontine glioma [DIPG]*), (*midline glioma*), (*pontine/pons astrocytoma or glioma*), (*midbrain astrocytoma or glioma*), (*medulla/medullary astrocytoma or glioma*), *and* (*infratentorial astrocytoma or glioma*)*; combined with* (*isocitrate dehydrogenase [IDH], IDH1, IDH2, IDH mutation, IDH-mutant, or IDH-mutated*). A formal study protocol was not prepared for this systematic review, and the study was not registered in any public database (e.g. PROSPERO).

Selection process

Two independent reviewers (M.T.G. and N.N.G.) screened the titles and abstracts of all identified articles using the Rayyan tool. The same reviewers then independently assessed the full-text articles for eligibility according to the predefined inclusion criteria. Any discrepancies encountered during the screening or selection process were resolved through discussion and consensus between the two reviewers.

Studies were eligible for inclusion if they met the following criteria:

1. Primary observational design (retrospective, prospective, or case-control).
2. Case series or single case reports.
3. Histopathologic confirmation of a glioma (e.g., astrocytoma, oligodendroglioma).
4. Primarily located in the brainstem (pons, medulla, or midbrain).

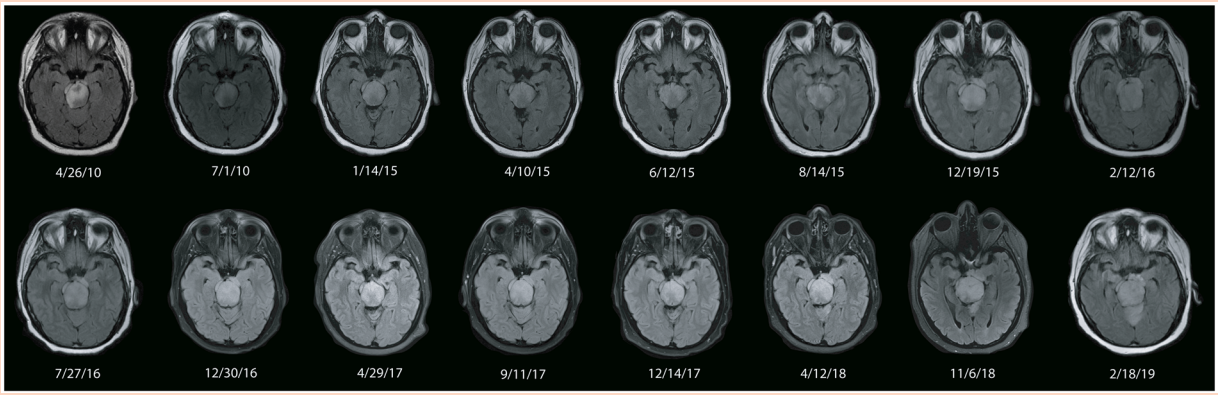

Figure 1. Serial axial T2 MRI of an IDH-mutant grade 3 brainstem astrocytoma (Case 3), showing slow radiographic progression over nearly a decade of follow-up.

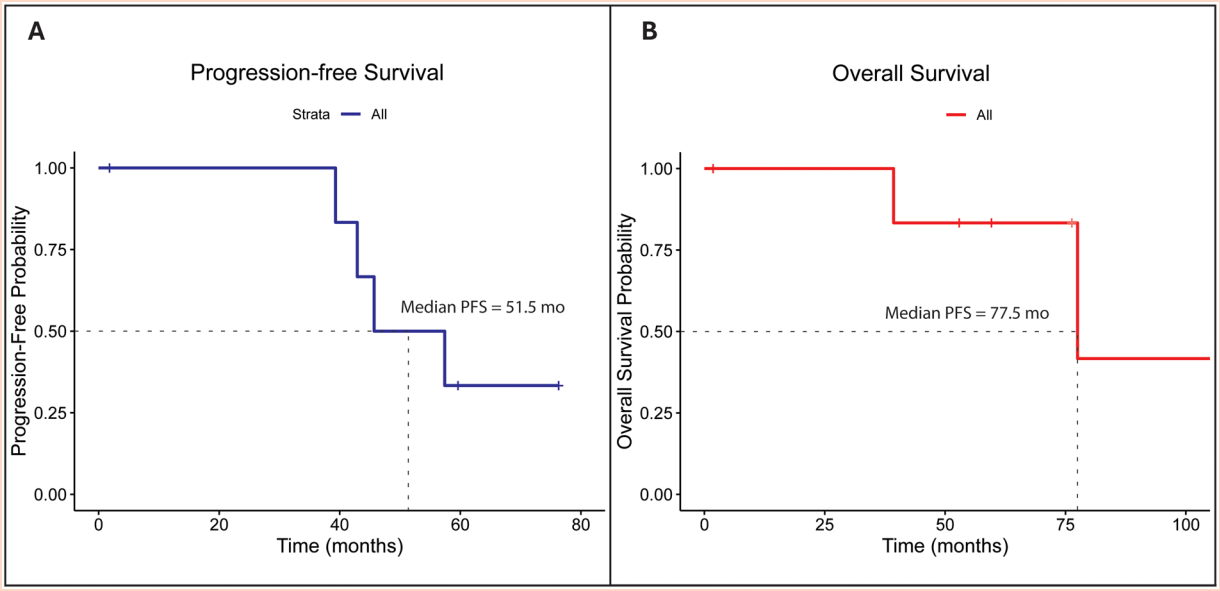

Figure 2. Kaplan-Meier progression-free survival (A) and overall survival (B) analyses for the case series of 7 adult IDH-mutant brainstem gliomas.

5. Molecular verification of an *IDH1* or *IDH2* mutation (see Supplementary Table S2).
6. Availability of individual-level clinicopathologic and outcome data.
7. Non-pediatric patients (age >17 years).
8. Full-text publication available in English.

Studies were excluded if they met any of the following conditions:

1. Histology other than glioma.
2. Pediatric (age ≤ 17 years).
3. Gliomas not primarily located within the brainstem (eg thalamic, cerebellar, or hemispheric tumors).
4. Studies lacking molecular confirmation of *IDH1* or *IDH2* mutation status.
5. Review articles, conference abstracts, editorials, letters, or commentaries without original patient data.
6. Duplicate reports or overlapping cohorts from the same institution (the most comprehensive or recent dataset was retained).
7. Insufficient clinical, pathological, or survival data for individual patient extraction.
8. Non-English language publications or inaccessible full texts.

Data extraction and variable definition. — Individual-patient clinical data were retrospectively compiled into a structured dataset incorporating demographic, histopathological, molecular, treatment, and outcome variables. Extracted variables included patient age at diagnosis, sex, tumor histology, and WHO CNS grade. Molecular characteristics were recorded where available and included MGMT promoter methylation status, IDH mutation, TP53 and ATRX expression. Treatment information was also recorded, including whether patients underwent surgery versus biopsy only, and whether they received radiotherapy, chemotherapy, or a combination. For anatomical location analysis, tumors were grouped as involving a single brainstem region (eg pons, midbrain, or medulla alone) versus those extending across multiple regions (eg pons+medulla, pons+midbrain), to assess the prognostic impact of focal versus diffuse anatomical involvement.

Risk of bias/quality assessment. — Because the literature component consisted primarily of case reports and small case series, methodological quality was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists for Case Reports and Case Series, as appropriate to study design. Two reviewers (M.T.G. and K.M.) independently assessed each included study. Discrepancies were resolved through discussion and, when needed, adjudication by a senior reviewer (K.G.A.). Given the descriptive nature of the included evidence, this assessment was used to characterize reporting quality and potential sources of bias rather than to generate weighted exclusion criteria (see Supplementary Material, Table S3).

Outcomes of the Study

The primary outcome of interest was OS, defined as the time from diagnosis to death or last clinical follow-up. Patients who were alive at their last follow-up visit were censored at that time point. The secondary outcome was PFS, defined as the time from diagnosis to disease progression, death, or last follow-up. Patients with missing PFS data were excluded from PFS time-to-event analysis. Event status was determined using the "Current Status" field, standardized

through case-insensitive keyword matching to identify events (eg "died," "dead," or "dropped"). All survival durations were converted to numeric values (in months), and binary censoring variables were defined accordingly for use in survival modeling.

Survival Analysis

Kaplan-Meier (KM) survival curves were generated for key clinical and molecular subgroups, restricted to astrocytoma histologies only. Group differences were assessed using the log-rank test, and median survival times with corresponding *P*value were reported.

Analyses were conducted for:

- Age groups (≤39 vs ≥40)
- Sex
- Tumor grade (Grade 2 vs 3 vs 4)
- Surgical intervention (surgery vs biopsy only)
- Adjuvant therapy (RT only vs RT + chemotherapy)
- Molecular markers (MGMT methylation, ATRX, IDH1 R132H mutation, TP53, PDGFRA)
- Tumor location (single vs multiple brainstem regions).
- Enhancing vs non-enhancing on MRI

Assessment of Histological Selection Bias

To evaluate potential selection bias regarding surgical intervention, the distribution of histological grades (WHO Grade 2 vs. WHO Grades 3 and 4) between the resection and biopsy cohorts was compared using Pearson's chi-squared test with Yates' continuity correction. This analysis was performed to determine if surgical resection was disproportionately favored for lower-grade tumors, which could confound survival outcomes.

Multivariate Modeling and Covariate Selection

Multivariate Cox proportional hazards regression was performed to identify independent predictors of OS. To maintain statistical power and ensure model stability, WHO grades were dichotomized into low-grade (Grade 2) and high-grade (Grades 3 and 4) groups. The final multivariate model included surgical intervention, IDH mutation subtype (canonical R132H vs. non-canonical variants), WHO grade group, and age as covariates. Model performance was evaluated using Harrell's Concordance Index (C-index). A complete-case analysis approach was adopted for multivariate modeling; patients with missing data for any included covariate were excluded from the final regression. To address potential selection bias regarding surgical intervention, a Pearson's chi-squared test with Yates' continuity correction was used to compare the distribution of histological grades between the resection and biopsy cohorts. Variables with high rates of missingness (eg MGMT and ATRX) were analyzed in separate subset models to preserve the primary cohort's power.

Software

All analyses were conducted using R version 4.5.0 with the survival, survminer, and dplyr packages.

Results

Systematic Review

The initial search yielded a total of 2,153 articles. After removal of 433 duplicates, 1,720 records remained for title and abstract screening. Of these, 151 were selected for full-text review, and 131 were excluded for not meeting eligibility criteria. A total of 20 studies,[3,7,10,12–28] encompassing 77 were included in the final analysis (see Supplementary Table S1). The screening process is illustrated in Figure 3 using the PRISMA 2020 flow diagram.

Patient Demographics

A total of 84 patients with IDH-mutant BSGs were included in the analysis, comprising 77 patients identified across 21 published studies and 7 additional patients from our institutional case series (Table 2) (see Supplementary Table S1). Because several variables were incompletely reported across published cases, proportions for selected clinical, radiographic, and molecular features were calculated using the number of evaluable cases for each variable. Age at diagnosis was available for 76 patients, with a mean age of 37.8 ± 10.8 years (range, 17-66). Among 70 patients with reported sex, 48/70 (68.6%) were male and 22/70 (31.4%) were female; sex was unavailable for 14/84 patients (16.7%).

Clinical and Radiologic Characteristics

Tumor location was specified in 67/84 cases, while 17/84 (20.2%) were reported only as involving the brainstem without further anatomic detail. Among the 67 cases with specified location, the most common sites were pons+medulla (23/67, 34.3%), pons (22/67, 32.8%), and medulla (12/67, 17.9%), followed by pons+MCP (5/67, 7.5%), pons+midbrain (3/67, 4.5%), pons+medulla+MCP (1/67, 1.5%), and pons+midbrain+MCP (1/67, 1.5%).

Contrast enhancement status was available in 26/84 cases (31.0%); among evaluable cases, 19/26 (73.1%) were non-enhancing and 7/26 (26.9%) were enhancing. Enhancement status was not reported in 58/84 cases (69.0%) (Table 2).

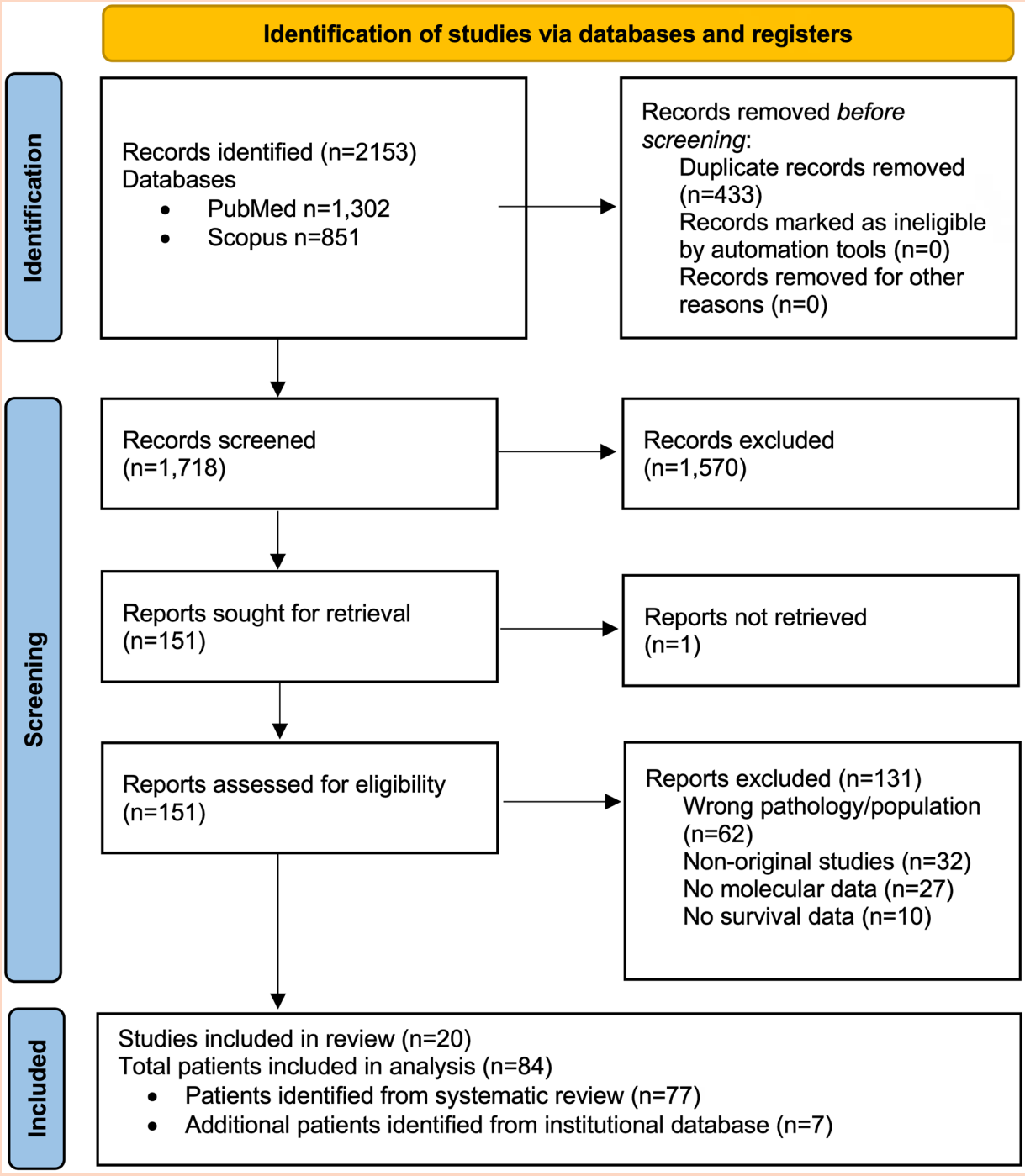

Figure 3. PRISMA flowchart (From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n7).

Histologic and Molecular Features

Histologic classification was available in 83/84 cases. Among these, 75/83 (90.4%) were astrocytomas and 8/83 (9.6%) were oligodendrogliomas; histology was not specified in 1/84 cases (1.2%). WHO grade was available in 83/84 cases, of which 57/83 (68.7%) were grade 2, 20/83 (24.1%) were grade 3, and 6/83 (7.2%) were grade 4; WHO grade was not reported in 1/84 cases (1.2%).

MGMT promoter status was available in 40/84 cases (47.6%); among these, 19/40 (47.5%) were methylated and 21/40 (52.5%) were unmethylated. The specific IDH variant was reported in 64/84 cases (76.2%). Among cases with specified variants, IDH1 R132H was the most common

Table 2. Clinicopathologic and radiographic characteristics of non-pediatric IDH-BSGs in the combined cohort ($n=84$)

Variable	Level	Result
Demographics	Mean age (years)	37.8 ± 10.8 ($n=76$; range: 17-66)
	Sex	
	Male	48/70 (68.6%)
	Female	22/70 (31.4%)
	NA	14/84 (16.7%)
Clinical characteristics	Tumor location	
	Pons + Medulla	23/67 (34.3%)
	Pons	22/67 (32.8%)
	Medulla	12/67 (17.9%)
	Pons + MCP	5/67 (7.5%)
	Pons + Midbrain	3/67 (4.5%)
	Pons + Medulla + MCP	1/67 (1.5%)
	Pons + Midbrain + MCP	1/67 (1.5%)
	Brainstem, NOS	17/84 (20.2%)
	% Enhancement	
	Non-enhancing	19/26 (73.1%)
	Enhancing	7/26 (26.9%)
	NA	58/84 (69.0%)
	WHO Grade	
	Grade 2	57/83 (68.7%)
	Grade 3	20/83 (24.1%)
	Grade 4	6/83 (7.2%)
	NA	1/84 (1.2%)
	Histology	
	Astrocytoma	75/83 (90.4%)
	Oligodendroglioma	8/83 (9.6%)
	NA	1/84 (1.2%)
Molecular features	MGMT promoter status	
	Methylated	19/40 (47.5%)
	Unmethylated	21/40 (52.5%)
	NA	44/84 (52.4%)
	IDH variant	
	IDH1 R132H	35/64 (54.7%)
	IDH1 R132G	12/64 (18.8%)
	IDH1 R132C	7/64 (10.9%)
	IDH1 R132S	6/64 (9.4%)
	IDH1 R132L	1/64 (1.6%)
	IDH2 R172G	1/64 (1.6%)
	IDH2 R172K	1/64 (1.6%)
	IDH2 R172S	1/64 (1.6%)
	IDH2 R132S	1/64 (1.6%)
	NA/Not specified	19/84 (22.6%)
	ATRX	
	Loss	33/62 (53.2%)
	WT	29/62 (46.8%)
	NA	22/84 (26.2%)
	TP53	
	Mutated	59/70 (84.3%)
	WT	11/70 (15.7%)
	NA	14/84 (16.7%)
	PDGFRA	
	Mutated	4/41 (9.8%)
	WT	37/41 (90.2%)
	NA	43/84 (51.2%)

(*continued*)

Table 2. Continued

Variable	Level	Result
Treatment pattern	Biopsy only	
	Yes	40/68 (58.8%)
	No	28/68 (41.2%)
	NA	16/84 (19.0%)
	Surgery (resection)	
	Yes	27/68 (39.7%)
	No	41/68 (60.3%)
	NA	16/84 (19.0%)
	Radiation	
	Yes	60/70 (85.7%)
	No	10/70 (14.3%)
	NA	14/84 (16.7%)
	Chemotherapy	
	Yes	44/71 (62.0%)
	No	27/71 (38.0%)
	NA	13/84 (15.5%)
Outcomes	Survival status	
	Dead	45/84 (53.6%)
	Alive	32/84 (38.1%)
	Censored/Lost	7/84 (8.3%)
	Median OS (Astrocytoma)	77.3 months (95% CI 61-117.2)
	Median PFS (Astrocytoma)	63.0 months (95% CI 56-111.7)

Abbreviations: MGMT, O6-methylguanine-DNA methyltransferase; ATRX, alpha-thalassemia/mental retardation X-linked; PDGFRA, platelet-derived growth factor receptor-alpha; IDH, isocitrate dehydrogenase; MCP, middle cerebellar peduncle; OS, overall survival; PFS, progression-free survival; NA, not available; WT, wild type; TP53, tumor protein p53.

(35/64, 54.7%), followed by IDH1 R132G (12/64, 18.8%), IDH1 R132C (7/64, 10.9%), IDH1 R132S (6/64, 9.4%), IDH1 R132L (1/64, 1.6%), and noncanonical IDH2 variants (4/64, 6.3%). The specific variant was not reported in 20/84 cases (23.8%).

ATRX status was available in 62/84 cases (73.8%); among these, 33/62 (53.2%) showed ATRX loss and 29/62 (46.8%) were wild-type/retained. TP53 status was available in 70/84 cases (83.3%); among these, 59/70 (84.3%) harbored TP53 mutations and 11/70 (15.7%) were wild-type. PDGFRA status was available in 41/84 cases (48.8%); among these, 4/41 (9.8%) harbored PDGFRA alterations and 37/41 (90.2%) were wild-type (Table 2).

Treatment Patterns

Biopsy-only status was available in 68/84 cases (81.0%); among these, 40/68 (58.8%) underwent biopsy only and 28/68 (41.2%) did not. Surgical resection status was available in 68/84 cases (81.0%); among these, 27/68 (39.7%) underwent resection and 41/68 (60.3%) did not. Radiation data were available in 70/84 cases (83.3%); of these, 60/70 (85.7%) received radiation and 10/70 (14.3%) did not. Adjuvant chemotherapy data were available in 71/84 cases (84.5%); of these, 44/71 (62.0%) received chemotherapy and 27/71 (38.0%) did not (Table 2).

Survival Status

At last follow-up, 45/84 patients (53.6%) were deceased, 32/84 (38.1%) were alive, and 7/84 (8.3%) were lost to follow-up (Table 2).

Survival Analysis and Prognostic Factors in Astrocytoma Histologies

Median OS for the pooled cohort (n = 73) was 77.3 months, while median PFS (substituted when unavailable), was 66.0 months (see Supplementary Figure S1). Neither age group (<40 vs ≥40 years) nor sex significantly influenced survival ($P = .6$ and 0.45, respectively) (see Supplementary Figure S1). Similarly, tumor location (Figure 4A) involving multiple regions had no impact ($P = .091$). When stratified by WHO grade (Figure 4B), there was a stepwise decrease in survival with increasing grade, with median OS of 83.0 months for grade 2, 62.4 months for grade 3, and 39.3 months for grade 4; median PFS showed a similar pattern (73.0 vs 66.63 vs 39.3 months). This difference was borderline for OS (log-rank $P = .0529$) non-significant for PFS (log-rank $P = .49$) (see Supplementary Figure S1). Notably, IDH1 non-R132H variants (Figure 4C) were associated with significantly longer median OS compared with R132H-mutant cases (111.7 vs 61 months; $P = .01$). MGMT

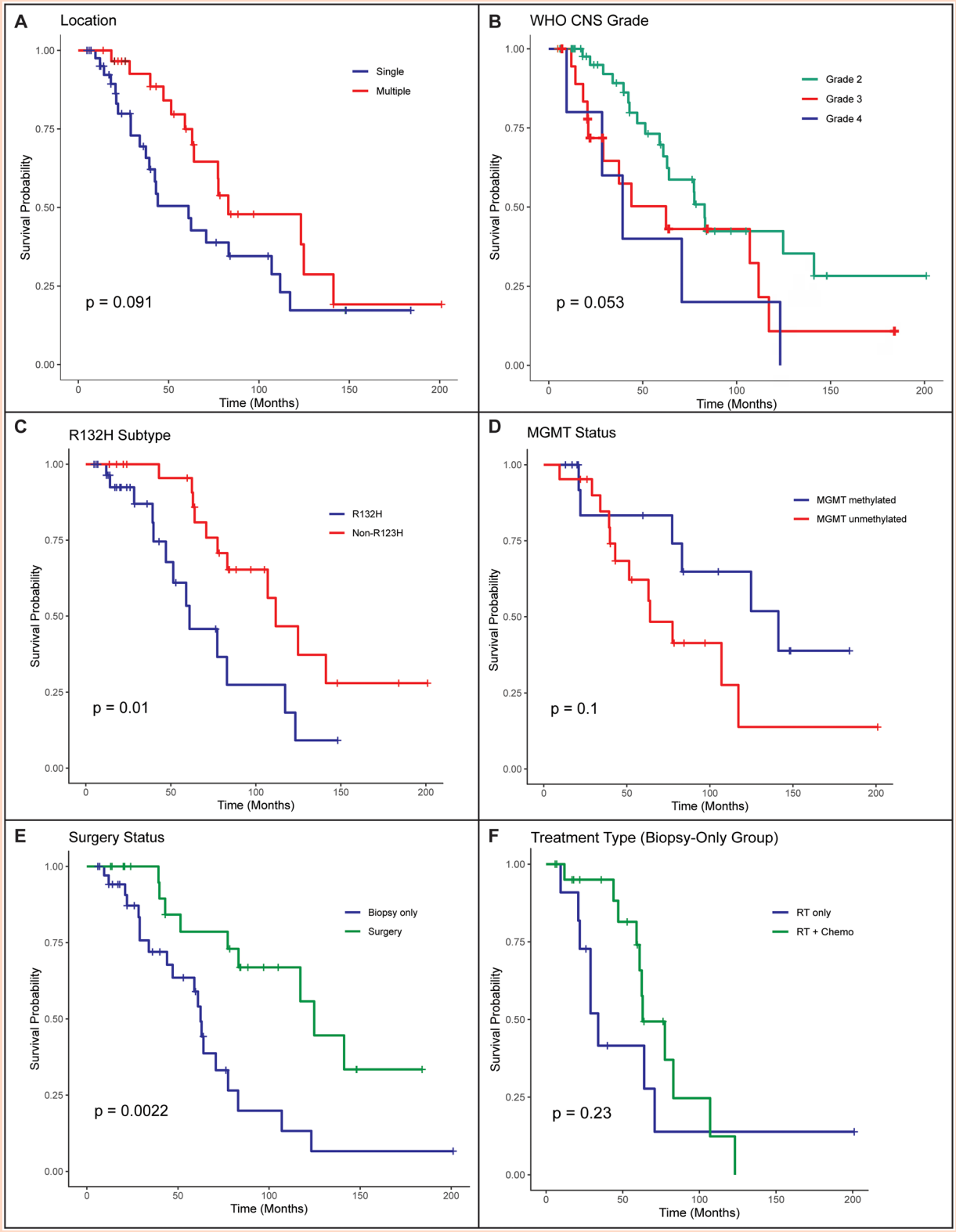

Figure 4. (A-F) Kaplan-Meier overall survival analyses for the pooled cohort of adult IDH-mutant brainstem gliomas with survival data. (A) Tumor involvement of single versus multiple brainstem regions (n=73)—(B) WHO CNS grade (grade 2 vs 3 vs 4) (n=72)—(C) IDH1 R132H vs non-R132H—(D) MGMT promoter methylation status (n=37)—(E) Surgical intervention (biopsy only vs resection) (n=61)—(F) Treatment (among biopsy-only patients, RT alone versus RT plus chemotherapy) (n=33). Log-rank P values are displayed on each panel.

Table 3. Multivariate survival predictors and histological distribution in IDH-mutant brainstem gliomas

Analysis type	Variable	Category	Value/result	Statistical metric
Multivariate Cox Model (n = 67, events = 29)	Surgical resection	Biopsy only	1.00 (Reference)	–
		Resection	0.48 (0.22-1.07)	$P = .073$
	IDH mutation type	Canonical (R132H)	1.00 (Reference)	–
		Non-canonical	0.37 (0.17-0.80)	$P = .012$[1]
	WHO Grade Group	Low-Grade (G2)	1.00 (Reference)	–
		High-Grade (G3/4)	1.32 (0.60-2.91)	$P = .492$
	Age	Continuous	0.99 (0.94-1.03)	$P = .582$
Model performance	C-index	–	0.707	se = 0.053
Chi-square analysis (Selection Bias Test)	Histology vs. surgery	Biopsy ($n = 40$)	32.5% HGG	–
		Resection ($n = 27$)	22.2% HGG	–
	Comparison	–	$X^2 = 0.408$	$P = .523$

[1]statistical significance (P < 0.05)

methylation ($P = .44$) (Figure 4D) and ATRX loss ($P = .83$) (see Supplementary Figure S1) were not associated with significant survival differences. Patients undergoing resection (Figure 4E) demonstrated significantly longer median OS (124.8 vs 62.4 months, log-rank $P = .0022$) and PFS (99.9 vs 56.7 months, log-rank $P = .0965$) compared with biopsy-only patients. In contrast, radiation plus chemotherapy vs radiation alone (63 vs 34 months; $P = .23$) (Figure 4F) and the presence of enhancement of MRI (see Supplementary Figure S1) showed no significant difference.

An analysis of histological distribution across surgical groups was conducted to identify potential selection bias ($n = 67$). In the biopsy-only group, 32.5% of tumors were classified as high-grade (WHO Grade 3 or 4), compared to 22.2% in the surgical resection group. Pearson's chi-squared test confirmed no statistically significant difference in the distribution of high-grade pathologies between the two cohorts ($X^2 = 0.408$, $P = .523$) (Table 3).

In a multivariate Cox model adjusting for age and tumor grade, IDH mutation subtype was an independent prognostic factor, with non-canonical variants exhibiting a significantly lower hazard of death (HR = 0.37, $P = .012$) (Table 3). Surgical resection was associated with a 52% reduction in the risk of mortality, representing a strong clinical trend toward improved OS (HR = 0.48, 95% CI: 0.22-1.07, $P = .073$). To assess for selection bias, a Chi-squared test was performed, confirming that the distribution of high-grade tumors did not differ significantly between the resection (22.2%) and biopsy (32.5%) groups ($P = .52$) (Table 3).

Discussion

Our comprehensive analysis establishes that adult IDH-mutant BSGs represent a distinct and more indolent subset of brainstem tumors. While earlier studies reported only a handful of such cases, our pooled analysis synthesizes data from 84 adult patients. These tumors differ from the more aggressive H3K27-altered diffuse midline gliomas (DMGs) in both molecular characteristics and clinical behavior.[29–31]

Clinical, Pathologic, and Molecular Features

In our cohort, IDH-mutant BSGs predominantly affected younger adults (mean age ~38 years) with a male predominance (~68%). Most tumors were in the pons, often with medullary extension, and were overwhelmingly astrocytomas (.90.4%). For comparison, supratentorial IDH-mutant gliomas also peak in young to middle-aged adults (ages 35-44) but show a more balanced sex ratio (1.3:1 M:F) and typically occur in the frontal lobes.[32–34]

We observed that 91% of patients had gliomas WHO grades 2 and 3, with only ~8% demonstrating WHO grade 4. This proportion of low-grade lesions is higher than in supratentorial IDH-mutant astrocytomas, where grade 4 cases are more frequent.[33,35,36] Additionally, ATRX loss (53.2%) and MGMT promoter methylation (47.5%) were identified in known evaluable cases; these rates are markedly lower than the >85%-90% prevalence reported in supratentorial cases, further distinguishing the brainstem phenotype.[11]

A striking finding is the distribution of IDH mutation variants. While IDH1 R132H accounts for ~90% of supratentorial cases, it represented only ~55% of our cohort.[37,38] Non-canonical mutations appear to be the predominant form in infratentorial gliomas, reaching a prevalence of 59% to 80% in recent studies.[11,26] Because these variants are not detectable by standard R132H IHC, comprehensive sequencing is essential in suspected cases.[39] Although the WHO 2021 classification groups these as a single tumor type regardless of location,[39] methylation-based analyses show that infratentorial cases cluster separately.[11,40] Our findings regarding variant distribution support the possibility of a distinct epigenetic subgroup, though larger cohorts with genome-wide methylation data are required to confirm this within the WHO framework.[41]

Radiographic and Diagnostic Considerations

Radiologically, IDH-mutant BSGs often exhibit features of low-grade tumors, such as diffuse T2/FLAIR hyperintensity and minimal contrast enhancement (~27% in our review).[26,42]

However, enhancement is not a reliable discriminator, as it may occur upon progression,[43] while H3K27-altered gliomas can appear deceptively indolent on imaging.[44] Given this overlap, histologic and molecular confirmation via biopsy is critical when safely feasible.[7,45] Distinguishing IDH-mutant from H3K27M-altered tumors has profound prognostic and therapeutic implications.[46,47] In cases where biopsy poses a high risk, advanced MR spectroscopy for 2-hydroxyglutarate[48,49] or CSF liquid biopsy for tumor DNA[50,51] may serve as valuable investigational tools for diagnosis.

Outcomes and Prognosis

Adult IDH-mutant BSGs demonstrate significantly better outcomes than pediatric DMGs, which have a median survival of ~12 months. In contrast, our adult cohort showed a median overall survival (OS) of ~77 months, with prior studies reporting similar or longer durations.[18,26] While favorable compared to DMGs,[11] this survival is lower than that of supratentorial IDH-mutant astrocytomas, where median survival often exceeds a decade.[52] This discrepancy likely reflects the brainstem's surgical inaccessibility, the predominance of biopsy-only procedures, and distinct molecular features like lower MGMT methylation.

Resection was associated with significantly longer survival, and non-R132H variants similarly conferred a survival advantage. However, in our multivariate analysis, the surgical benefit shifted to a clinical trend, likely reflecting reduced statistical power in the molecularly defined cohort. These findings should be interpreted cautiously due to small subgroup sizes and potential selection bias, despite our chi-square analysis showing no significant histological disparity between surgical groups.

Notably, patients with non-canonical IDH mutations had a significantly longer median OS (~112 months) compared to the canonical R132H variant (~61 months), a finding that remained significant in our multivariate model. This aligns with supratentorial data suggesting non-R132H variants exhibit more favorable prognostic methylation classes.[53] However, given the small sample size, it remains unclear if this reflects true biological variation or residual confounding factors like tumor localization. In supratentorial diffuse gliomas, MGMT promoter methylation is a recognized favorable prognostic marker, whereas its impact in IDH-mutant, non-codeleted astrocytomas is more variable.[54,55] Finally, the lack of correlation between age, sex, and prognosis aligns with modern risk-stratification models where molecular markers supersede demographic factors.

Therapeutic Implications

Management typically mirrors protocols for IDH-mutant gliomas in other regions. Since meaningful resection is often unfeasible, patients usually receive definitive therapy with radiation followed by alkylating chemotherapy. While chemoradiation showed a median OS advantage over radiation alone in our cohort, the difference was not statistically significant. Targeted IDH inhibitors, such as vorasidenib, also offer a promising precision medicine approach,[38] as illustrated by one patient in our series who responded after CSF-based molecular confirmation.[51]

Limitations

Despite being the largest dataset to date, our study has several limitations. First, cases with atypical molecular features, novel therapeutic responses, or unusually prolonged survival are more likely to be reported, which may lead to overestimation of survival outcomes in pooled analyses. Accordingly, the median overall survival reported here should not be interpreted as a population-level benchmark but rather as a synthesis of selectively reported cases.

Second, data heterogeneity across institutions, including variations in imaging, molecular testing, and clinical documentation, may affect the reliability of pooled variables. Second, treatment comparisons are limited by selection bias. Patients undergoing resection versus biopsy, or receiving chemoradiation versus radiation alone, likely differed in baseline characteristics such as tumor size, location, and overall health. These confounders may obscure true treatment effects.

Third, subgroup analyses, such as those based on tumor grade, or IDH variant, were constrained by small sample sizes, limiting statistical power. Although resection and IDH variant were statistically associated with improved outcomes, these subgroup signals should be interpreted cautiously given small event counts and risk of residual confounding. Furthermore, the technical heterogeneity of molecular testing across studies, ranging from IHC for the R132H variant to comprehensive next-generation sequencing, introduces potential classification bias. In cases confirmed via IHC alone, non-canonical IDH variants may have been under-detected, potentially influencing the reported survival differences between molecular subtypes.

Finally, outcome data were inconsistently reported. In many cases, overall survival was used as a surrogate for progression-free survival due to limited follow-up or missing progression data. Short follow-up durations in some reports may have led to overestimation of survival. Although we attempted to mitigate lead-time bias by excluding cases with <5 months of follow-up, residual bias may persist.

Conclusion

Adult IDH-mutant BSGs appear to represent a rare and potentially clinically meaningful subgroup within the spectrum of BSGs. In contrast to the uniformly poor prognosis typically associated with H3K27-altered diffuse midline gliomas, pooled adult cases in our series suggest comparatively longer survival, with median overall survival approaching 6 to 7 years in pooled adult cases, although still lower than survival typically reported for supratentorial IDH-mutant astrocytomas. These tumors predominantly occur in young adults, frequently harbor noncanonical IDH variants, and demonstrate lower rates of ATRX loss and MGMT promoter methylation compared with supratentorial counterparts. Taken together, our findings suggest that IDH-mutant BSGs may differ in clinically relevant ways from

other adult BSGs, but further study is needed to define the extent of their biological distinctiveness.

From a clinical standpoint, identifying an IDH mutation in BSGs has direct prognostic and therapeutic relevance. Given the limitations of R132H-specific immunohistochemistry, comprehensive molecular profiling, via tissue biopsy or emerging non-invasive approaches such as CSF liquid biopsy, is essential. Accurate molecular diagnosis enables risk-stratification and opens the door to targeted therapy.

As an orphan disease, IDH-mutant BSGs warrant particular attention. Unfortunately, patients with brainstem involvement were excluded from the INDIGO study and from more recent trials (CTR20242581), representing a missed opportunity. Given their favorable biology and the emerging efficacy of IDH inhibitors in supratentorial disease, extending these therapies to infratentorial tumors is both rational and necessary. Prospective studies and molecularly stratified trials are needed to define optimal treatment strategies, including the role of resection, sequencing of IDH-targeted agents, and management at recurrence.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

brainstem glioma | diffuse astrocytoma | IDH mutation | outcomes | prognostic factors

Author Contributions

Kalil G. Abdullah, Jan Drappatz, and Maged T. Ghoche conceived and designed the study—Data were acquired by Maged T. Ghoche, Neslihan Nisa Gecici, and Kenji Miki—Fanen Yuan, Maged T. Ghoche, Kenji Miki, Michal Nisnboym Ziv, Pascal O. Zinn, Jan Drappatz, and Kalil G. Abdullah contributed to data analysis and interpretation—The manuscript was drafted by Kalil G. Abdullah, Jan Drappatz and Maged T. Ghoche—All authors, including Ghoche, Abdullah, Drappatz, Gecici, Miki, Yuan, Mantica, Marker, Pearce, Ziv, and Zinn, critically revised the manuscript and reviewed the submitted version. Maged T. Ghoche, Kalil G. Abdullah, and Jan Drappatz approved the final version on behalf of all authors. Statistical analysis was performed by Maged T. Ghoche. Administrative, technical, and material support were provided by Kalil G. Abdullah, Jan Drappatz, Pascal O. Zinn, and Maged T. Ghoche. Study supervision was jointly provided by Kalil G. Abdullah and Jan Drappatz.

Conflict of Interest Statement

Dr. Jan Drappatz reports research support and consulting fees from Servier. The remaining authors declare no conflicts of interest.

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Ethics Statement

This study involved analysis of published data and an institutional cohort approved by the local IRB.

Data Availability

Data are available in the Supplementary Material.

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