RESEARCH ARTICLE OPEN ACCESS

Characteristics and Outcomes of Patients With IDH-Mutant Grade 2 and 3 Gliomas After Deferred or Adjuvant Radiotherapy

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Neurology® 2025;105:e213797. doi:10.1212/WNL.0000000000213797

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Abstract

Background and Objectives

Current treatment guidelines for patients with isocitrate dehydrogenase (IDH)–mutant (IDHm) glioma recommend radiation (XRT) and chemotherapy after surgery in most cases based on studies in which XRT was compared with XRT plus chemotherapy. Although XRT has been shown to improve time to tumor progression, there has never been a controlled study in this population in which adjuvant XRT (aXRT) demonstrated superior overall survival (OS) over initial observation. The aim of this study was to evaluate the effect of timing of XRT on survival in IDHm-glioma.

Methods

We performed a retrospective observational cohort study, comprising a cohort of adult patients with grade 2 or 3 IDHm-gliomas seen at 2 academic centers (University of Washington and Stanford University) between 2007 and 2022 (identified through research data registries). The main comparison of interest was patients who received XRT within 3 months of diagnosis and before progression, that is, as adjuvant treatment (aXRT), versus those who did not have aXRT (deferred XRT, dXRT). The primary outcome measures were median progression-free survival and OS. Survival analysis was performed through multivariable Cox proportional hazard modeling, propensity matching, and subset analysis.

Results

A total of 450 eligible patients were identified (mean age 39.7 years; 41% female). The median survival of the combined cohort was 19.1 years (25th–75th percentiles 9.75–27.8 years). 47.1% of patients received aXRT. Patients with aXRT demonstrated similar time to next intervention (hazard ratio [HR] 0.83, 95% CI 0.65–1.07) but showed a markedly diminished OS compared with the dXRT cohort (HR of death 2.90, 95% CI 1.9–4.42, $p < 0.001$). This shorter OS with aXRT was appreciated in all assessed subgroups, including patients considered high risk by grade, age, and extent of resection. This shorter OS was also consistent in multivariable analysis and in propensity-matched cohorts.

Discussion

Although retrospective, the marked OS difference between aXRT and dXRT groups suggests that aXRT may be not be as beneficial as what was once thought, especially regarding long-term survival. These results also offer justification for the use of a dXRT group in studies assessing adjuvant treatments, as well as a reconsideration of the current treatment paradigm for these patients, especially given the recent introduction of IDH inhibitors.

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The Article Processing Charge was funded by the authors.

Glossary

aXRT = adjuvant XRT; **dXRT** = deferred XRT; **EHR** = electronic health record; **EOR** = extent of resection; **FDA** = Food and Drug Administration; **HR** = hazard ratio; **IDH** = isocitrate dehydrogenase; **IDHm** = IDH-mutant; **IRB** = institutional review board; **KPS** = Karnofsky Performance Status; **OS** = overall survival; **PFS** = progression-free survival; **SMD** = standardized mean difference; **STR** = subtotal resection; **TNI** = time to next intervention; **UW** = University of Washington; **WHO** = World Health Organization; **XRT** = radiation therapy.

Introduction

Historically, gliomas have been divided into low grade, grade 1 (G1) and grade 2 (G2), and high grade, grade 3 (G3) and grade 4 (G4), based on histologic features alone. While the clinical trials that inform current treatment guidelines enrolled patients in the era of these histologic classification schemas, molecular diagnosis and grading of glioma is now the standard approach. Within diffuse gliomas, the presence or absence of the isocitrate dehydrogenase (IDH) mutation is disease defining for both astrocytomas and oligodendrogliomas. Patients with G2 and G3 IDH-mutant (IDHm)-gliomas are responsive to chemotherapy and have median overall survival (OS) that exceeds a decade, leading some to classify these together as "lower grade glioma."[1] Although G2/G3 IDHm-gliomas are chemosensitive, radiation therapy (XRT) has become the first-line treatment for patients with these tumors, despite lack of evidence of survival benefit and known long-term neurotoxicity with XRT.

Three prospective clinical trials have evaluated the timing of XRT, and none found a survival benefit with postoperative XRT (EORTC 22845,[2] NOA-04,[3] EORTC22033-26033[4]). For instance, in NOA-04, 51% of patients with glioma had confirmed IDH mutation and within this cohort, no significant difference was found in OS or progression-free survival (PFS) based on whether patients received adjuvant postoperative XRT; this finding was consistent in both IDHm astrocytoma and IDHm oligodendroglioma.[3] Modern interpretation of these and other prospective clinical trials in patients with G2/G3 gliomas is challenging because of the mismatch between the diagnosis used at the time of enrollment and the redefined molecular diagnosis when outcome data ultimately become available. Evaluation of IDHm-glioma relies on post hoc analysis of a limited number of patients in whom IDH status was confirmed. This retrospective study was designed to evaluate survival impact of adjuvant treatment on patients with G2/G3 IDHm-gliomas in the real-world setting outside the strict confines of clinical trials.

As the diagnosis of gliomas has evolved over the past 15 years, so has the preferred first-line treatment. The preference for deferring surgery and watchful waiting has shifted to a tendency for early adjuvant XRT (aXRT) and chemotherapy[5-7] (Table 1) despite a lack of prospective data demonstrating OS benefit from aXRT. For a variety of clinical reasons, including deleterious effects of radiation (including neurocognitive effects, secondary malignancies, and secondary vasculopathies), some patients with both G2 and G3 IDHm-gliomas elect to defer radiation.[8-10] Vorasidenib, a novel IDH1/2 inhibitor, was recently shown to significantly delay disease progression in a landmark trial of G2 IDHm-gliomas leading to recent Food and Drug Administration (FDA) approval, thus adding a promising new option for these patients.[11] It is, therefore, necessary to critically evaluate the impact of aXRT in the modern classification era of gliomas. With this in mind, this study reports patient/tumor characteristics and survival outcomes of patients who underwent XRT within 3 months of diagnosis (aXRT), compared with patients who did not (deferred or dXRT).

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This project was reviewed by independent Institutional Review Boards (IRBs) at Stanford University and University of Washington (UW). Both IRBs determined the study to be minimal risk and exempt from the need for informed consent.

Patient Population

Patients were retrospectively identified from electronic health records (EHRs) through clinical research data registries at Stanford University and UW. Inclusion criteria for this cohort were patients who were seen at either Stanford University or UW adult neuro-oncology clinics between 2007 and 2022 with a diagnosis of glioma (confirmed by biopsy or resection), the presence of IDH mutation, World Health Organization (WHO) 2021 classification grading of G2 or G3 at diagnosis, and information on at least the initial treatment available. Patient records were individually reviewed, and data were collected for patient demographics (i.e., institution, age, sex), tumor characteristics (including molecular/genetic data), treatment modalities (i.e., extent of resection [EOR], initiation of systemic treatments [e.g., TMZ or PCV], XRT), and clinical course (i.e., dates of diagnosis, treatment initiation with chemotherapy/XRT, treatment at progression, and death or censorship). Patients with missing data on treatment modalities were not included. Tumors were classified using the 2021 WHO Classification of CNS Tumors when applicable (e.g., if a glioma had originally been histologically classified as an astrocytoma but had 1p19q co-deletion, it was re-coded as an oligodendroglioma; if an astrocytoma had CDKN2A/B homozygous deletion on initial pathology, it was

Table 1 Recent Guidelines on the Management of Patients With IDHm-Glioma

Diagnosis	ASTRO 2022	ASCO-SNO 2021	EANO guidelines	NCCN 2023
Grade 2 IDH mutated astrocytoma				
dXRT	<4–6 cm tumor And Gross total resection (defined as <1 cm residual tumor on MRI) And Age younger than 40 y	"Initial therapy may be deferred until radiographic or symptomatic progression in some people with positive prognostic factors or concerns about short-term and long-term toxicity given the natural history of the disease"	Observation in younger patients (pragmatic cutoff ~40–45 y of age) after gross total resection who are asymptomatic or with seizures only, can be managed through observation alone	40 y old And Gross total resection Or In highly select patients
aXRT	Subtotal resection And/or Age 40 y or older And/or Tumor size ≥4–6 cm And/or Tumor crosses midline refractory seizures, presurgical neurologic symptoms from tumor	All patients should be offered	"If further treatment beyond surgery is deemed necessary"	Older than 40 y Or Subtotal resection Or Consideration of tumor size and neurologic deficits
Grade 3 IDH mutated astrocytoma				
aXRT	All patients	All patients	All patients	All patients
Grade 2 oligodendroglioma				
dXRT	<4–6 cm tumor And Gross total resection (defined as <1 cm residual tumor on MRI) And Age <40 y	"Initial therapy may be deferred until radiographic or symptomatic progression in some people with positive prognostic factors or concerns about short-term and long-term toxicity given the natural history of the disease"	Observation in younger patients (pragmatic cutoff ~40–45 y of age) after gross total resection who are asymptomatic or with seizures only, can be managed through observation alone	Observation if younger than 40 y old And Gross total resection Or In highly select patients
aXRT	Subtotal resection Age 40 y or older Tumor size ≥4–6 cm Tumor crosses midline refractory seizures, presurgical neurologic symptoms from tumor	All patients should be offered	"If further treatment beyond surgery is deemed necessary"	40 y old Or Subtotal resection Consideration of tumor size and neurologic deficits
Grade 3 oligodendroglioma				
dXRT	Not recommended	Not recommended	Without homozygous *CDKN2A/B* deletion And Gross total resection And In the absence of neurologic deficits for younger patients (<40 y of age)	Not recommended
aXRT	All patients	All patients	Most patients	All patients

Abbreviations: ASCO = American Society of Clinical Oncology; ASTRO = American Society for Radiation Oncology; aXRT = adjuvant radiation therapy; dXRT = deferred radiation therapy (no adjuvant radiation therapy); EANO = European Association of Neuro-Oncology; NCCN = National Comprehensive Cancer Network; SNO = Society of Neuro-Oncology.

considered grade 4 and thus excluded from this study). Extent of resection was determined based on interpretation of the radiologist and treating clinician. XRT within 3 months of diagnosis and before progression was considered aXRT, whereas not receiving XRT within the first 3 months was considered dXRT. The 3-month cutoff for XRT was chosen based on precedent from clinical trials in this population[12]; because this is a retrospective nonrandomized observational

study, the reason for decision for aXRT vs dXRT was not always reflected in the medical record. Where it was documented, decision was made based on the judgment of the treating clinicians and patient preference and typically also from a multidisciplinary tumor board. Patients in the dXRT cohort either never received XRT during the period of analysis of this study or received it at time of disease recurrence/progression.

The definition of high-risk and low-risk glioma has fluctuated over the past 20 years, but general consensus uses a combination of EORTC-defined and RTOG-defined factors.[4,13,14] The current National Comprehensive Cancer Network guidelines (Table 1) define high-risk features as either (1) having a grade 3–4 tumor, (2) having residual disease after surgery, or (3) being older than 40 years. Having any of these 3 features automatically confers high-grade designation, and based on the guidelines, these patients are recommended to proceed with aXRT.[15] To investigate the impact of XRT timing in high-risk patients, we created a subset of patients in our study with these high-risk features (i.e., patients who possessed any of the high-risk features listed above).

Statistical Analysis

OS was calculated from date of pathologic diagnosis to date of death or last note in EHR confirming that the patient was still alive. Time to next intervention (TNI, a metric used in recent trials[11]) was calculated from date of diagnosis to date when therapy was changed/added. Patients lost to follow-up were right-censored. Survival analysis was performed using Kaplan-Meier analyses and compared using log-rank tests comparing aXRT vs dXRT in the entire cohort, in propensity-matched (a statistical technique used in observational studies to estimate causal effects with reduced potential bias from confounding variables) cohorts described further, in a subset of patients with high-risk disease, and in a subset of patients with residual disease after surgery. To further explore whether a specific subset of patients with glioma derives OS benefit from aXRT, we performed univariate analysis using subsets of all variables listed in the demographics and characteristics table. Univariate and multivariable analyses of the covariates were performed using the Cox proportional hazard model, and Schoenfeld residuals were used to confirm the proportional hazard model. Multivariable OS and TNI models were created using a set of predefined covariates that have been shown to affect survival or used in clinical guidelines[16]—grade, histology, age, extent of resection, initial systemic therapy after surgery, and XRT timing (aXRT vs dXRT). Because age of 40 years is traditionally used to differentiate patients into high vs low risk in multiple guidelines (Table 1), this cutoff was used in this study.[15,17,18] Hazard ratios (HRs) in this study describe the HR of death (for OS) or time to next intervention (for TNI). Cohorts with aXRT vs dXRT were matched accounting for the aforementioned covariates according to nearest-neighbor 1:1 propensity matching and a caliper width of 0.25. A 2-sided p value of <0.05 was considered statistically significant. Statistical analysis was performed using R software, version 4.2.2.

Data Availability

The data that support the findings of this study are available from the corresponding author, L.R., on reasonable request.

Results

Clinical Characteristics

A total of 450 patients were included in this study (eFigure 1). Patient demographics, clinical characteristics, and tumor classification are summarized in Table 2. There were 124 patients with G2 and 92 with G3 astrocytomas, in addition to 150 patients with G2 and 84 with G3 oligodendrogliomas, respectively. The median OS was 270 (25th–75th percentile 217–334) months for G2 oligodendroglioma, 216 months (25th–75th percentile 130–not reached) for G2 astrocytoma, 164 months (25th–75th percentile 49–199) for G3 oligodendroglioma, and 166 months (25th–75th percentile 71–263) for G3 astrocytoma. Regarding extent of resection, 177 patients had gross total resection, 212 had subtotal resection (STR), and 47 had biopsy alone. The median year of diagnosis was 2015 (25th–75th percentile 2012–2018, min/max 1988–2022). The median Karnofsky Performance Status (KPS) was 90 in both the aXRT and dXRT cohorts; in particular, 65% of patients in the aXRT group had KPS of at least 90 and 67% in the dXRT group had KPS of at least 90. Among those who received XRT, the median time from diagnosis to initiation of XRT was 1.4 months in the aXRT group and 3.3 years in the dXRT group. The median follow-up time for the entire cohort was 5.4 years (25th–75th percentiles 2.9–9.4 years)

Time to Next Intervention

During the period of follow-up, 103 TNI events (48.5%) occurred in the aXRT group and 166 (69.7%) occurred in the dXRT group. However, a significant difference was not detected in TNI between aXRT and dXRT groups (Figure 1). In univariate analysis (Table 3), factors associated with unfavorable TNI were G3 tumor (HR 1.41, 95% CI 1.09–1.82, p = 0.009) and residual disease (STR [HR 1.46, 95% CI 1.12–1.90, p = 0.005] and biopsy [HR 1.64, 95% CI 1.09–2.46, p = 0.017]). There were no significant differences in TNI detected based on age, 1p19q status, initial systemic therapy, and XRT timing. In multivariable analysis (Table 3), initial systemic therapy and aXRT showed significantly improved TNI compared with no initial systemic therapy (HR 0.73, 95% CI 0.54–0.99, p = 0.045) and dXRT (HR 0.63, 95% CI 0.47–0.84, p = 0.002), respectively. The other variables remained significant/nonsignificant and in the same directions as the univariate model.

Overall Survival

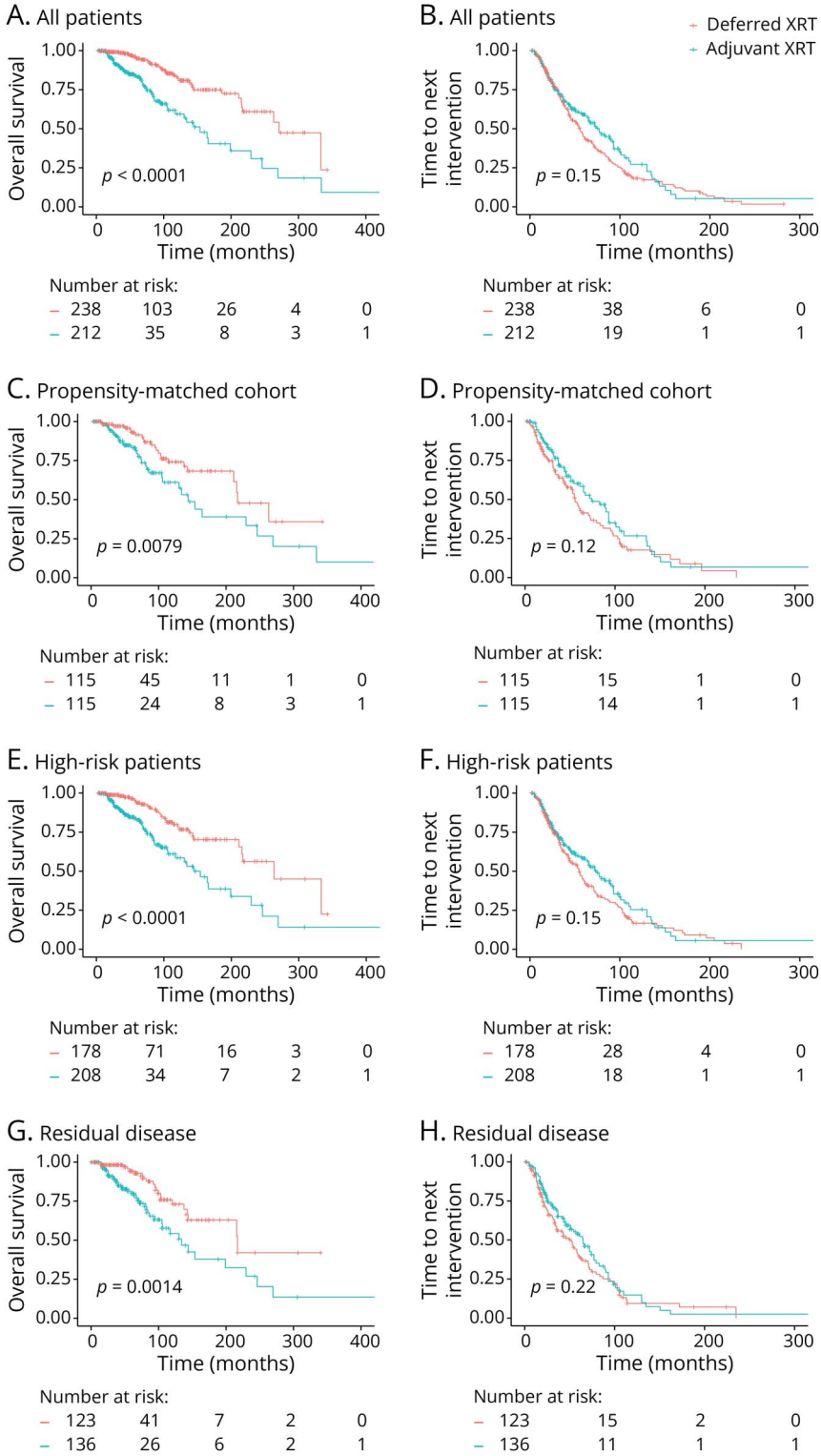
During the period of follow-up, 57 deaths (26.9%) occurred in the aXRT group and 37 (13.5%) occurred in the dXRT group. In univariate analysis of the entire cohort of patients with G2/G3 IDHm-gliomas (Table 3), aXRT was associated with significantly shorter OS (HR 2.90, 95% CI 1.9–4.42, p <

Table 2 Demographics for All Patients

Characteristic	Overall (N = 450)[a]	Deferred XRT (N = 238)[a]	Adjuvant XRT (N = 212)[a]
Institution			
Stanford University	195 (43)	130 (55)	65 (31)
University of Washington	255 (57)	108 (45)	147 (69)
Sex			
Male	267 (59)	139 (58)	128 (60)
Female	183 (41)	99 (42)	84 (40)
Age			
<40	255 (57)	140 (59)	115 (54)
≥40	195 (43)	98 (41)	97 (46)
Pathology and grade			
Grade 2 oligodendroglioma	150 (33)	108 (45)	42 (20)
Grade 2 astrocytoma	124 (28)	89 (37)	35 (17)
Grade 3 oligodendroglioma	84 (19)	28 (12)	56 (26)
Grade 3 astrocytoma	92 (20)	13 (5.5)	79 (37)
Extent of resection			
Resection	14 (3.1)	9 (3.8)	5 (2.4)
Biopsy	47 (10)	25 (11)	22 (10)
STR	212 (47)	98 (41)	114 (54)
GTR	177 (39)	106 (45)	71 (33)
Initial systemic treatment			
No initial systemic treatment	208 (46)	166 (70)	42 (20)
Initial systemic treatment	242 (54)	72 (30)	170 (80)
KPS (median)	90	90	90
Laterality			
Left	225 (50)	112 (47)	113 (53)
Right	221 (49)	124 (52)	97 (46)
Bilateral/midline	4 (0.9)	2 (0.8)	2 (0.9)
Location			
Frontal	261 (58)	144 (61)	117 (55)
Parietal	40 (8.9)	18 (7.6)	22 (10)
Temporal	77 (17)	43 (18)	34 (16)
Other	72 (16)	33 (14)	39 (18)
MGMT status			
Unmethylated	44 (31)	20 (28)	24 (34)
Methylated	99 (69)	52 (72)	47 (66)

[a] n (%); median.
[b]Oligodendroglioma is molecularly defined by both 1p19q co-deletion and IDH mutation.
[c]Data were missing for 176 patients.

Figure 1 Kaplan-Meier Curves for OS and TNI



Kaplan-Meier curves comparing aXRT and dXRT for (A) OS in all patients, (B) TNI in all patients, (C) OS in a propensity-matched cohort, (D) TNI in a propensity-matched cohort, (E) OS in a cohort of high-risk patients, (F) TNI in a cohort of high-risk patients, (G) OS in a cohort of patients with residual disease after surgery, and (H) TNI in a cohort of patients with residual disease after surgery. In all curves, a hazard ratio of death is provided using log-rank tests. The lines represent the Kaplan-Meier curves, and the shaded regions represent the lower and upper limits of the 95% CIs for survival estimates. aXRT = adjuvant radiation therapy; dXRT = deferred radiation therapy (no adjuvant radiation therapy); high-risk = patients with either grade 3 tumors, grade 2 tumors with residual disease after surgery, or grade 2 tumors with gross total resection but older than 40 years; OS = overall survival; TNI = time to next intervention.

0.001) as was G3 (HR 3.50, 95% CI 2.28–5.36, $p < 0.001$), residual disease (STR [HR 1.93, 95% CI 1.21–3.08, $p = 0.006$] or biopsy [HR 2.04, 95% CI 1.04–4.03, $p = 0.039$]), age 40 or older (HR 1.51, 95% CI 1.00–2.28, $p = 0.0048$), and treatment with initial systemic therapy (HR 2.47, 95% CI 1.61–3.79, $p < 0.001$). In particular, the median OS was 271 months (22.6 years) (25th–75th percentiles 144–333 months) for patients with dXRT compared with 154 months (12.8 years) (25th–75th percentiles 75–246) for those with aXRT (Figure 1A, $p < 0.0001$). A significant difference was

Table 3 Univariate and Multivariable Models for OS and TNI

	Univariate			Multivariable		
	Hazard ratio	95% CI	*p* Value	Hazard ratio	95% CI	*p* Value
TNI survival analysis						
Grade						
Grade 2	Reference			Reference		
Grade 3	1.41	1.09–1.82	0.009	2.08	1.52–2.85	<0.001
1p19q status						
Oligodendroglioma	Reference			Reference		
Astrocytoma	1.12	0.88–1.43	0.347	1.10	0.85–1.41	0.472
Age						
<40	Reference			Reference		
≥40	0.90	0.71–1.15	0.409	0.95	0.73–1.24	0.710
Extent of resection						
Gross total resection	Reference			Reference		
Subtotal resection	1.46	1.12–1.90	0.005	1.64	1.25–2.17	<0.001
Biopsy	1.64	1.09–2.46	0.017	2.03	1.33–3.08	0.001
Initial systemic therapy						
No initial systemic therapy	Reference			Reference		
Initial systemic therapy	0.92	0.72–1.19	0.543	0.73	0.54–0.99	0.045
XRT						
Deferred XRT	Reference			Reference		
Adjuvant XRT	0.83	0.65–1.07	0.150	0.63	0.47–0.84	0.002
OS analysis						
Grade						
Grade 2	Reference			Reference		
Grade 3	3.50	2.28–5.36	<0.001	2.94	1.74–4.50	<0.001
1p19q status						
Oligodendroglioma	Reference			Reference		
Astrocytoma	1.19	0.79–1.79	0.395	1.26	0.81–1.950	0.306
Age						
<40	Reference			Reference		
≥40	1.51	1.00–2.28	0.048	1.84	1.18–2.88	0.007
Extent of resection						
Gross total resection	Reference			Reference		
Subtotal resection	1.93	1.21–3.08	0.006	1.94	1.17–3.20	0.010
Biopsy	2.04	1.04–4.03	0.039	2.66	1.30–5.43	0.007
Initial systemic therapy						
No initial systemic therapy	Reference			Reference		
Initial systemic therapy	2.47	1.61–3.79	<0.001	1.34	0.81–2.22	0.260

Continued

Table 3 Univariate and Multivariable Models for OS and TNI *(continued)*

	Univariate			Multivariable		
	Hazard ratio	**95% CI**	***p* Value**	**Hazard ratio**	**95% CI**	***p* Value**
XRT						
Deferred XRT	Reference			Reference		
Adjuvant XRT	2.90	1.9–4.42	<0.001	1.69	1.04–2.77	0.036

Abbreviations: OS = overall survival; TNI = time to next intervention.
p Values were considered significant if <0.05.

not observed in MGMT-methylated patients compared with unmethylated patients regarding OS or PFS (HR 0.64, 95% CI 0.31–1.34, $p = 0.24$; HR 0.89, 95% CI 0.57–1.39, $p = 0.60$, respectively). In a multivariable model of OS (Table 3), aXRT, G3, age 40 or older, and residual disease remained significantly unfavorable while the group with initial systemic therapy was no longer significantly different from those without initial systemic therapy.

Given the impact of residual disease on survival, aXRT was evaluated specifically in patients who only underwent biopsy or STR (Figure 1, G and H). In this group, patients with dXRT had longer OS compared with patients who had aXRT (mOS 217 months [25th–75th percentiles 120–not reached] vs 134 months [25th–75th percentiles 74–246], $p = 0.0014$) and did not have significantly different TNI (median 52 months [25th–75th percentiles 20–95] vs 65 months [25th–75th percentiles 26–93], $p = 0.22$). Furthermore, because guidelines currently recommend that patients considered high risk (based on age, grade, and EOR as detailed above[4,13,14]) undergo aXRT, a subgroup analysis was performed on high-risk patients based on these criteria (Figure 1, E and F). Similarly, patients with dXRT had significantly prolonged OS (median 263 months [25th–75th percentiles 138–333] vs 144 months [25th–75th percentiles 75–246], $p < 0.001$) and no significant difference was detected in TNI (median 55 months [25th–75th percentiles 26–103] vs 74 months [25th–75th percentiles 27–130], $p = 0.15$).

Propensity Matching

Propensity score matching was used to adjust for imbalance in potentially confounding covariates (age, grade, 1p19q status, EOR, and initial systemic therapy) between patients with aXRT and those with dXRT. Two well-balanced cohorts were created (Figure 1, C and D). Other than 1p19q status that had standardized mean difference (SMD) <0.2, all remaining variables had SMD <0.1 (eTable 1). Using this model, the dXRT group again demonstrated significantly improved OS compared with the aXRT group (217 months [25th–75th percentiles 144–not reached] vs 144 months [25th–75th percentiles 75–270], $p = 0.0079$) and did not demonstrate significantly different TNI (55 months [25th–75th percentiles 26–103] vs 74 months [25th–75th percentiles 37–135], $p = 0.14$). To account for the fact that 1p19q status had SMD >0.1, dXRT vs aXRT was analyzed in the propensity-matched cohort, adjusting for 1p19q status as a covariate. This analysis showed that OS was significantly longer in the dXRT group compared with the aXRT group (HR 2.05, 95% CI 1.19–3.52, $p < 0.01$) and TNI was not significantly different in the dXRT group compared with the aXRT group (HR 0.77, 95% CI 0.54–1.09, $p = 0.14$). Because these results were consistent with the original propensity-matched analysis, this suggests that the conclusions are robust and not driven by potential imbalance in 1p19q status.

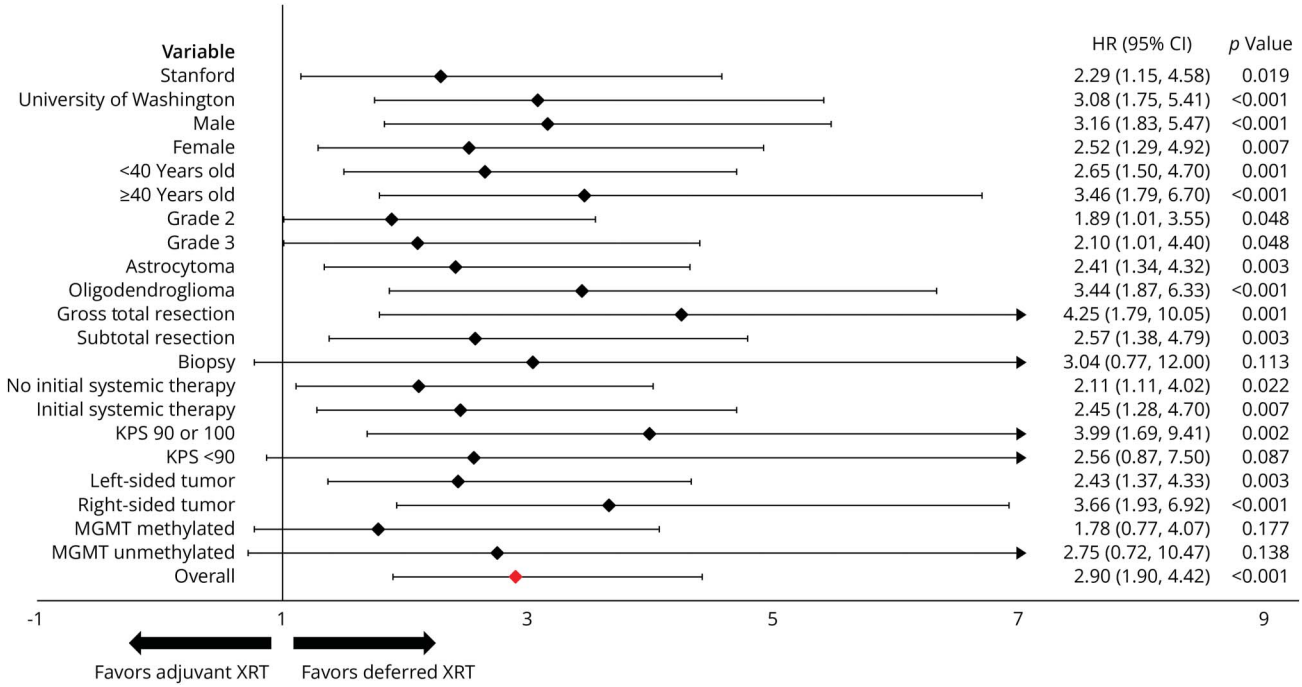
Subset Analysis

In this analysis evaluating all clinical and demographic factors listed in Table 2, no subset of patients was associated with improved OS with aXRT (Figure 2). With the exceptions of biopsy, KPS <90, and MGMT status where patients had nonsignificantly improved OS with dXRT, all other subsets demonstrated statistically significant improved OS with dXRT compared with aXRT.

Discussion

G2/G3 IDHm-gliomas are recognized as a distinct subtype of diffuse gliomas that, although incurable, are more responsive to chemotherapy, and patients with these tumors have median survival surpassing a decade. Maximal safe resection has been repeatedly shown to improve survival in this population and continues to represent the core pillar of management.[19] Post hoc analysis of patients with G2/G3 IDHm-gliomas demonstrated prolonged OS with the addition of chemotherapy to XRT compared with XRT alone. However, a benefit of aXRT has never been demonstrated in this population compared with deferring XRT until disease progression. This is an important question, as many reports describe both cognitive and structural changes after XRT in patients with IDHm-gliomas,[20-22] leading us to evaluate survival in patients who defer radiation. This study of 450 patients with G2/G3 IDHm-gliomas was undertaken to evaluate the impact of adjuvant treatment on OS and TNI. Contrary to our initial hypothesis, we found that patients treated with aXRT actually had significantly shorter OS compared with patients with dXRT, despite longer TNI in multivariable analysis with aXRT.

Figure 2 Overall Survival Univariate Subset Analysis Comparing Adjuvant vs Deferred XRT



This figure demonstrates univariate analysis for each subset cohort of patients listed on the left as well as for the overall population. Each hazard ratio of death (for adjuvant XRT relative to deferred XRT) and its corresponding 95% CI are shown, with corresponding values listed on the right. XRT = radiation therapy.

Mismatch between TNI and OS has been reported in multiple gliomas studies including the EORTC 22845 "Non-Believers Trial," which demonstrated that aXRT prolonged time to disease progression but did not affect OS.[2] Furthermore, clinical trials of bevacizumab in glioblastoma demonstrated radiographic and clinical improvement without improving survival.[23] With these examples in mind, it is, therefore, not unreasonable to expect a discrepancy between aXRT and dXRT in our patient population.

In addition to XRT timing, we evaluated other pertinent factors in this cohort. MGMT promotor methylation status has been demonstrated to be a reliably predictive and prognostic biomarker in glioblastoma[24] although its value as a biomarker in IDHm-glioma is less clear, with mixed results in the literature.[25,26] In our cohort, MGMT promotor methylation status did not have a significant impact on PFS or OS. In a multivariable model of OS, patients with grade 3 tumors had significantly worse OS than those with grade 2, and while astrocytoma demonstrated worse OS compared with oligodendroglioma, this difference did not meet the threshold for significance. In the literature, oligodendroglioma has been shown to demonstrate improved OS compared with astrocytoma while grade (2 vs 3) is less clear, with mixed results reported.[6] Age older than 40 years in our cohort was also found to demonstrate significantly worse OS. Age-based differences in IDHm-glioma have been reported in the literature although others have not reported a difference.[27,28] Finally, reported gross total resection was found to demonstrate significantly improved OS relative to biopsy and STR, consistent with most other reports.[28,29]

The main limitation of this study is its retrospective and nonrandomized nature, which evokes the possibility of selection bias. We, therefore, introduced several measures to minimize such biases. To create balanced cohorts for grade, 1p19q status, age, extent of resection, and initial systemic therapy, propensity-matched analysis generated well-matched cohorts and aXRT was still associated with shorter OS (Figure 1C). Although it is possible that other variables not available for this analysis (e.g., tumor size) might have affected the decision of aXRT vs dXRT, shortened survival with aXRT was notably seen in patients with high-risk features such as residual disease, grade 3 tumors, and age older than 40 (Figure 1E). These findings seem to challenge multiple guidelines recommending aXRT for patients with G2/G3 IDHm-gliomas.[6,13,15] Notably, patients in both aXRT and dXRT cohorts had the same median KPS of 90 at time of diagnosis, suggesting that the patients in the aXRT cohort were not more functionally impaired than patients with dXRT at initial diagnosis. We acknowledge that practice patterns (including decisions of XRT timing and type/extent of XRT) might have changed over the years that patients included in this study were diagnosed, although the interquartile range for the year of diagnosis was 6 years. We also realize that patients in this study were treated at academic centers with access to

a tumor board, which might not be as applicable to some community sites.

By assessing hundreds of patients with G2/G3 IDHm-gliomas, collected from 2 independent academic centers, and having the benefit of long-term follow-up, this work provides unique insights that are not seen in studies that include a mixture of patients with IDHm-gliomas and IDHwt-gliomas. Of interest, despite a trend in national guidelines recommending aXRT, our study demonstrated that at both centers, rates of dXRT (53%) were higher than what would be expected from these guidelines. A separate recent study investigating rates of initial postsurgical observation in patients with IDHm-glioma found this rate to be 44%–53%,[30] corroborating our findings.

The surprising finding of shorter OS with aXRT led to further review of previous studies of IDHm-glioma that included data regarding timing of radiation and survival. In a multicenter retrospective study of 392 patients with G2 IDHm-gliomas, the dXRT group had longer OS with HR 0.32 (95% CI 0.20–0.053).[31] Similarly, in a multicenter pathology study of patients with 373 G2/3 IDHm-gliomas, the 234 patients treated with aXRT had a mOS of 11.6 years compared with 14.4 years in the 139 who had deferred radiation (HR 1.725 [95% CI 1.228–2.422]).[32] In a study segmenting patients with IDHm-glioma by age category, patients with upfront treatment with a combination of chemotherapy and XRT had lower OS compared with those with surgery alone ($p < 0.01$).[27] Furthermore, the final results from the large prospective trial, EORTC 22033–26033, showed that upfront TMZ alone demonstrated comparable PFS and OS with upfront XRT.[33]

While this study supports clinical judgment to consider deferring XRT rather than simply following current clinical guidelines that incorporate "high-risk" categories, understandably there is concern that without treatment, IDHm-gliomas will grow. Volumetric analysis of IDHm-gliomas demonstrates that untreated tumors have variable growth rates with periods of both faster and slower growth before treatment.[34] There is also a prevailing assumption that growing tumor is worse for neurologic function than the potential for radiation-related neurologic injury. We also acknowledge that recent advances in XRT delivery have allowed for more targeted fields with potentially less toxicity.[35] However, a recent evaluation of data from 5,539 patients enrolled in multiple prospective studies of diffuse glioma, over 95% of whom were treated with aXRT, found that after treatment, during the progression-free interval, there was clinically significant decline in quality of life.[36] This study suggests that even if tumor is not progressing, effects of XRT may significantly affect quality of life. A recent study similarly found that radiation use was significantly associated with worse health-related quality of life and cognitive outcomes among patients with oligodendroglioma.[37]

Given its limitations, our results should be interpreted cautiously. While our retrospective study alone would not be expected to change treatment patterns, it supports the notion that prospective studies include arms without aXRT. This is especially clinically relevant as our study occurs contemporaneously with the approval of vorasidenib as an effective and minimally toxic treatment for IDHm-gliomas.[11] The results of this study combined with our analysis suggest a re-evaluation of the current treatment paradigm for patients with high-risk and low-risk IDHm-glioma.

This large retrospective study of patients with molecularly defined G2/G3 IDHm-gliomas evaluated the impact of timing of radiation treatment on survival. Treatment guidelines for patients with IDHm-gliomas have trended toward immediate postsurgical chemoradiation based on studies that predated incorporation of IDH mutation and instead contained a mixture of what are currently known as glioblastomas and IDHm-gliomas (they also predate the FDA approval of vorasidenib). This study and others highlight the higher-than-expected percentage of patients with G2/G3 IDHm-gliomas who defer XRT. We found that aXRT was associated with shorter survival in patients with IDHm-gliomas. With the demonstration that IDH1/2 inhibition can provide a relatively safe alternative treatment option, we stand at an important crossroad in the quest to optimize the standard recommendation of chemoradiation.

Author Contributions

T. Lanman: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. I. Densmore: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Nagpal: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. L. Recht: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. T. McGranahan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

No targeted funding reported.

Disclosure

T. Lanman, I. Densmore, and L. Recht report no disclosures relevant to the manuscript. S. Nagpal has served on the advisory board for Servier and has received research support from Stanford University: NCT04164901 - Servier. T. McGranahan has served on the advisory board and speaker's bureau for Servier and has received research support from University of Washington: NCT04164901 - Servier, NCT02655601 - Biomimetix, NCT03970447 - Denovo, Biohaven, Vigeo, NCT04471844 - Novocure, NCT05580562 - Chimerix. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology*® January 21, 2025. Accepted in final form April 10, 2025. Submitted and externally peer reviewed. The handling editor was Associate Editor Rebecca Burch, MD.

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