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RAPID COMMUNICATION



Impact of radiation fractionation on pseudoprogression in older patients with glioblastoma: a retrospective cohort study

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ABSTRACT

Aims: We aimed to investigate a potential association between hypofractionated radiotherapy (HFRT) vs. conventional radiotherapy (CRT) and development of pseudoprogression in patients over the age of 65 treated for glioblastoma (GBM).

Materials & methods: Seventy-nine patients with glioblastoma (29 who received HFRT and 50 who received CRT) were included in this retrospective cohort study from a single institution. Demographic, clinical, and radiation information, including development of pseudoprogression and standard prognostic factors like Karnofsky Performance Status (KPS) and extent of surgical resection, were collected.

Results: Radiation regimen alone was not associated with development of pseudoprogression. Patients who had lower KPS at the time of diagnosis and received HFRT had lower rates of pseudoprogression. There was no association between radiation regimen, pseudoprogression, and any other clinical factors.

Conclusion: Older patients with glioblastoma who receive HFRT are not more likely to develop pseudoprogression than those who receive CRT. Patients with lower functional status receiving HFRT may be less likely to mount an inflammatory response leading to pseudoprogression. Prospective investigation is warranted to validate these results and evaluate other factors leading to treatment complications in older patients with glioblastoma in order to optimize outcomes and minimize toxicity.

PLAIN LANGUAGE SUMMARY

Patients with glioblastoma, a type of brain cancer, often receive radiation therapy. Conventional radiotherapy (CRT) involves daily doses over 30 days. Patients over the age of 65 with glioblastoma can receive a higher-dose radiation schedule over 15 days called hypofractionated radiation (HFRT) with the same lifespan increase as in CRT. We thought HFRT, with more radiation per dose, could increase the chance of developing pseudoprogression, which is the brain's post-radiation immune response appearing as if the tumor is growing back. Using patient records over 5 years, we determined whether having received CRT or HFRT affected the chances of developing pseudoprogression. While we found no direct link, we discovered patients who received HFRT and had a lower Karnofsky Performance Status (KPS) score – a scale measuring a patient's ability to carry out day-to-day activities, with a high score indicating a high ability – had lower rates of pseudoprogression. A possible explanation is patients with lower KPS scores could be considered biologically older and therefore have weaker immune systems, suppressing the immune response caused by high radiation doses. More research is needed to confirm these findings and help tailor treatment plans for older patients with glioblastoma to improve their outcomes.

ARTICLE HIGHLIGHTS

- Patients with glioblastoma (GBM) over the age of 65 often receive either conventional radiotherapy (CRT), involving 60 Gy over 30 days, or hypofractionated radiotherapy (HFRT), involving 40.05 Gy over 15 days.
- Because of the higher radiation dose per fraction, it is possible that patients with GBM receiving HFRT could be more likely to develop pseudoprogression, a neuroinflammatory response that mimics tumor recurrence on post-treatment MRI scans.

ARTICLE HISTORY

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Glioblastoma; pseudoprogression; radiation therapy; hypofractionated; Karnofsky Performance Status

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- We conducted a retrospective cohort analysis of patients ≥ 65 years old with GBM seen at the University of Rochester Medical Center from 2017–2022 to determine the effect radiation fractionation has on the likelihood of developing pseudoprogression.
- Patients with GBM over the age of 65 who received HFRT are not more likely to develop pseudoprogression than those who receive CRT.
- Patients with glioblastoma over the age of 65 who have a lower Karnofsky Performance Status (KPS) score at the time of diagnosis and receive HFRT may have a decreased likelihood of developing pseudoprogression.

2. Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor in adults and is associated with a poor prognosis [1–3]. A current standard of care for GBM in patients under the age of 70, denoted conventional radiotherapy (CRT), includes maximally safe surgical resection followed by 60 Gy of radiation therapy delivered in 30 fractions with concurrent and adjuvant temozolomide [4]. However, there is no standard of care for patients with GBM over the age of 70, who comprise approximately 40% of the GBM population [5–7]. Recent studies have highlighted that certain prognostic factors, such as Karnofsky Performance Status (KPS), extent of surgical resection, and MGMT methylation status, have a significant influence on overall survival (OS) in very elderly patients with GBM over the age of 75, with KPS being found to be especially predictive of OS in patients with GBM over the age of 80 [8–10]. Further understanding of prognostic factors and how to appropriately select treatment plans for older patients with GBM is critical to ensuring adequate care for this population.

In two multi-center randomized clinical trials, hypofractionated radiotherapy (HFRT) – which typically involves 40 Gy delivered in 15 fractions – was found to be non-inferior to the conventional course of radiotherapy for older patients with GBM over the age of 65, and one suggested improved tolerance of HFRT [11,12]. In theory, HFRT also reduces time toxicity, the time patients spend in medical care [13], and is an accepted treatment option for older patients with GBM per international guidelines [14]. Furthermore, the role of TMZ for patients with poor functional status and an unmethylated O⁶-methylguanine-DNA methyltransferase (MGMT) promoter is unclear, and therefore TMZ is occasionally withheld for these patients [15].

HFRT involves larger doses of radiation per fraction compared to CRT (2.67 Gy vs. 2 Gy). While the biologically effective dose (BED) – the true biological dose of radiation the patient receives over the course of treatment – for 40.05 Gy in 15 fractions remains lower than

60 Gy in 30 fractions, giving larger doses per fraction may cause vascular damage and substantially impact the neuroimmune microenvironment surrounding the tumor, increasing inflammation [16,17]. Of particular concern in clinical neuro-oncology practice is pseudoprogression, a neuroinflammatory response that presents as progression on post-treatment magnetic resonance imaging (MRI) of the brain but resolves on its own [18–23]. Pseudoprogression is defined as increased contrast enhancement in the first two post-treatment MRI scans at 1 and 3 months following radiation, eventually subsiding without changes to adjuvant therapy [18,24,25]. Pseudoprogression may present with accompanying focal neurologic symptoms – such as headaches, hemiparesis, or altered mental status – and may require clinical management [18,20,23,26–28]. Pseudoprogression can be misdiagnosed as true progression, leading to potential patient harm through discontinued adjuvant chemotherapy or improper candidate selection for clinical trials targeting recurrent GBM [24]. Discerning pseudoprogression from true progression is critical to proper clinical care for patients with GBM and identifying factors associated with pseudoprogression may help improve care for patients who develop this complication.

Since patients receiving HFRT receive a higher dose per fraction, we hypothesized that this population may experience higher rates of pseudoprogression than patients receiving CRT do through an increased neuroinflammatory response. We sought to describe the association between pseudoprogression and treatment regimen for a retrospective cohort of older patients with GBM who received neuro-oncology care at our institution.

3. Material & methods

3.1. Study design

We conducted a retrospective cohort study of all patients age ≥ 65 years who underwent radiation therapy for primary and histopathologically confirmed GBM based on WHO 2021 criteria and who received

their primary neuro-oncology care at the University of Rochester Medical Center (URMC) from January 1st, 2017 to December 31st, 2022 [29]. We obtained approval from our Institutional Research Study Review Board (RSRB00008544) and a waiver of informed consent to examine electronic health records in URMC's neuro-oncology database. This manuscript was prepared according to the STROBE guidelines.

3.2. Selection of patients

An initial study population was first comprised of patients whose electronic medical records obtained from the neuro-oncology database indicated an age of 65 years or older at the time of initial GBM diagnosis. Patients who were diagnosed prior to the revised WHO 2021 criteria and had IDH-mutant histopathology were retroactively determined to have grade 4 astrocytoma, IDH-mutant and were excluded from the study. Patients who had confounding variables, such as enrollment in an immunotherapy clinical trial or missing treatment information, were excluded. One patient had brain metastases concomitant with a diagnosis of GBM and was also excluded. We further excluded patients in whom an evaluation of pseudoprogression was not possible due to death during radiation or within 3 months of chemoradiation completion, incomplete chemoradiation treatment, lack of post-treatment MRIs at 1 and 3 months after radiation completion, or clear tumor progression within 3 months following chemoradiation.

3.3. Data extraction

Demographic factors, including age at diagnosis, date of diagnosis, date of first disease progression, and date of death, were collected. OS was calculated as time between date of diagnosis and date of death, while progression free survival (PFS) was calculated as time between date of diagnosis and date of first progression as determined by Response Assessment in Neuro-Oncology (RANO) criteria [24]. Clinical variables such as tumor histopathology, extent of surgical resection, KPS at diagnosis, and MGMT promoter methylation status were also collected.

Radiation treatment information, including total dose, dose per fraction, and number of fractions were collected. BED was calculated from the collected data using an online tool (<http://eqd2.com/>). Treatment protocols involving a 60 Gy dose in 30 fractions were designated as CRT [4]. Treatment protocols involving a 40 Gy dose in 15 fractions were designated as HFRT [11,12]. While most subjects received a dose per

fraction of either 2 Gy (CRT) or 2.67 Gy (HFRT), several underwent a treatment protocol that deviated from these groups. Treatment protocols that included a dose per fraction of 2.2 Gy or under most resembled CRT in total dosage and BED, while protocols with a dose per fraction of over 2.2 Gy most resembled HFRT in total dosage and BED. Therefore, treatment protocols that deviated from either of these groups were classified as CRT for a dose per fraction of under 2.2 Gy and HFRT for a dose per fraction of greater than 2.2 Gy. Receipt of concurrent and/or adjuvant temozolomide (TMZ) chemotherapy and tumor-treating fields were documented. Additional information on complications such as number of hospitalizations post-diagnosis and fall history were also collected but are not reported.

Pseudoprogression was defined as new or enlarging contrast enhancement on MRIs taken within 3 months of completion of chemoradiation treatment that resolved without targeted intervention [18,24,25]. Incidence and date of onset of pseudoprogression was recorded from the medical record according to RANO criteria [18]. Specifically, patient records were first queried for equivalent phrases such as "pseudoprogression," "pseudo progression," "treatment response," "treatment effect," "radiation response," and "radiation effect." Patients were then marked as having developed pseudoprogression based on clinical documentation indicating a new, enlarging, and self-resolving area of contrast enhancement on MRI within 3 months of completing radiotherapy. The remaining record was then examined to determine if the presumed pseudoprogression had progressed or resolved at the next visit. If the enhancement progressed on subsequent imaging, the patient was retroactively noted to have tumor progression on the date of presumed pseudoprogression. If pseudoprogression was first noted beyond 3 months post radiation, this was not considered true pseudoprogression given the definition of the phenomenon. If the clinical documentation regarding pseudoprogression was unclear, MRIs were reviewed by an attending neuro-oncologist (authors LEH or NAM) to clarify the discrepancy. Patients for whom radiographic discernment of pseudoprogression vs. true progression remained indeterminate after review were excluded from the study.

3.4. Statistical methods

Patients were grouped according to their radiation cohort and their pseudoprogression status. Nominal variables were described in absolute counts and percentages for each group. Clinical variables were

systematically compared to pseudoprogression status, with radiation cohort treated as a confounding variable that could affect the tested relationship. Therefore, both marginal and conditional associations were tested, and each statistical test was performed threefold, once for the entire study population and twice by conditioning on radiation cohort.

A significance level of $\leq 5\%$ was used for all tests. The log-rank test was used to compare Kaplan-Meier survival functions for the pseudoprogression and non-pseudoprogression cohorts. For tests involving other quantitative clinical variables, specifically age at diagnosis and BED, the Wilcoxon rank-sum test without continuity correction was employed. For tests involving nominal clinical variables, Pearson's chi-square test without continuity correction was employed if expected values for each subgroup totaled 5 or more. If this condition was not met both marginally and conditionally, Fisher's exact test was employed instead. Patients with missing data in a categorical clinical variable, such as KPS, were excluded from analysis within that particular statistical test. It cannot be verified whether this approach would introduce bias; however, exclusions for the purposes of statistical analysis were modest. Statistically significant results for tests involving categorical variables were followed by odds ratio analysis. If the categorical variable was ordinal with more than 2 categories, Goodman-Kruskal's gamma was employed to identify potential concordant or discordant trends. All statistical evaluations were performed in and all figures were created with R v4.3.3.

4. Results

4.1. Patient demographics

From our central neuro-oncology database, we initially identified 125 patients who were diagnosed with GBM at the age of 65 or older. From this population, 79 matched our inclusion criteria (Figure 1). Our study population included 51 males and 28 females. 97.5% of subjects identified as Caucasian and 96.2% had non-Hispanic ethnicity. Median age at diagnosis was 71.4 years (range: 65-85.7 years). 28 patients had a methylated MGMT promoter (35.4%), 41 had an unmethylated MGMT promoter (51.9%), and 10 patients had indeterminate or unknown MGMT methylation status (12.7%). Respectively, 26 (32.9%) had biopsy only, 8 (10.1%) partial resection, and 45 (57.0%) gross total resection of tumor prior to chemoradiation. 29 patients underwent HFRT (36.7%) with 22 of these receiving concurrent TMZ (75.9%). Of the remaining 50 patients who underwent CRT (63.3%), 48 received concurrent TMZ (96.0%). Demographic information is summarized in Table 1. 16 of the 29 patients receiving HFRT and 22 of the 50 patients receiving CRT developed pseudoprogression (Table 2).

4.2. Age at diagnosis analysis

Older patients were more likely to receive HFRT than CRT (Figure 2(A); $p < 0.0001$). However, there was no statistically significant difference in age at diagnosis between patients who developed or did not develop

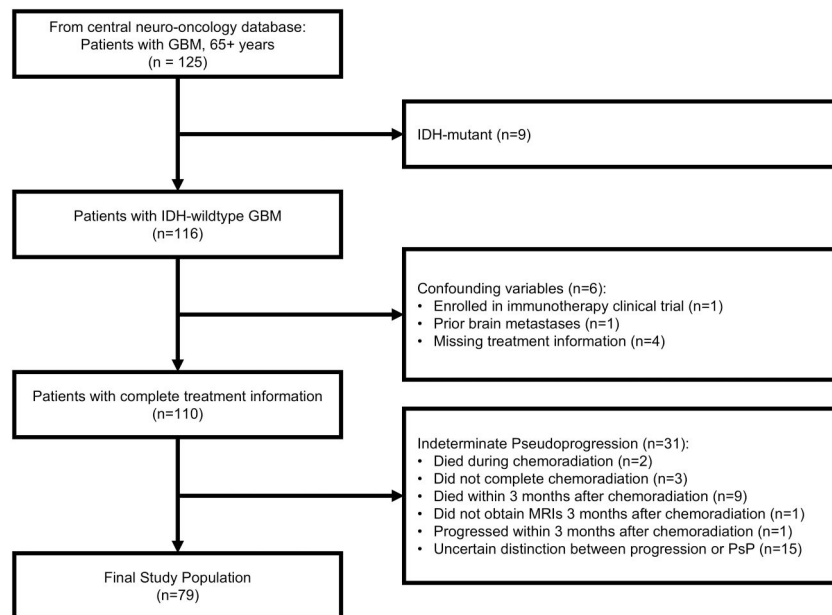


Figure 1. Exclusion flowchart detailing final study population. Patients were identified from a central database containing electronic medical records of patients who received neuro-oncology care at the University of Rochester Medical Center.

Table 1. Patient characteristics.

Patients (n = 79)		
Sex	No.	%
Female	28	35.4
Male	51	64.6
Median Age at Diagnosis	71.4 (65–85.7)	
Age at Diagnosis	No.	%
65–70	35	44.3
71–75	24	30.4
76–80	18	22.8
81+	2	2.5
Patients with KPS < 70	18	22.8
MGMT Status	No.	%
MGMT methylated	28	35.4
MGMT unmethylated	41	51.9
MGMT indeterminate or unknown	10	12.7
Extent of Surgical Resection	No.	%
Biopsy	26	32.9
Subtotal	8	10.1
Gross total	45	57.0
Median Overall Survival (months)	14.1	
Treatment Regimen	No.	%
<i>Hypofractionated radiation</i>	29	36.7
With chemotherapy	22	75.9
Without chemotherapy	7	24.1
<i>Conventional radiation</i>	50	63.3
With chemotherapy	48	96.0
Without chemotherapy	2	4.0
Radiation Dose	Median	
<i>Hypofractionated radiation</i>		
Dose per fraction	2.67 Gy	
BED	75.57 Gy	
<i>Conventional Radiation</i>		
Dose per fraction	2 Gy	
BED	99.41 Gy	
Death	No.	%
	70	88.6

*KPS: Karnofsky Performance status; MGMT: O⁶-methylguanine-methyltransferase; BED: biologically effective dose.

Table 2. Pseudoprogression characteristics of older patients with GBM by radiation cohort.

Patients (n = 79)		
	No.	%
Pseudoprogression present		
<i>Hypofractionated radiation</i>	29	–
Yes	16	55.2
No	13	44.8
<i>Conventional radiation</i>	50	–
Yes	22	44.0
No	28	56.0

pseudoprogression; this was observed in the full study population, within patients who underwent HFRT, and within patients who underwent CRT (Figure 2(B–D)). There similarly was no difference in distribution of age at diagnosis for patients who did or did not develop pseudoprogression (Figure 2(E–F)).

4.3. Survival analysis

Median overall survival was 14.1 months for all patients (95% CI: 12.5–16.9), 13.2 months for patients who underwent HFRT (95% CI: 11.6–16.7), and 16.6 months for patients who underwent CRT (95% CI: 12.8–20.3). There was no statistically significant

difference in overall survival based on pseudoprogression status (Figure 3).

4.4. Radiation cohort analysis

Median BED for patients who received HFRT and CRT respectively were 75.57 Gy and 99.41 Gy, and BED for patients who received CRT was found to be significantly larger than for those who received HFRT ($p < 10^{-15}$). Radiation cohort did not predict development of pseudoprogression (Figure 4(A); $X^2 = 0.918$, $p = 0.338$). Receipt of concurrent TMZ, extent of surgical resection, and MGMT methylation status were not significantly associated with pseudoprogression status (Figure 4(B–D)). Dichotomizing extent of surgical resection by combining cohorts of patients who received biopsies or partial resections did not yield a statistically significant result upon repeat chi-square analysis. Dichotomizing MGMT methylation status by excluding patients with an indeterminate or unknown methylation status also did not yield a statistically significant result.

Approximately half of patients had a KPS ≤ 80 (Figure 5(A)). Therefore, we dichotomized KPS into a categorical variable by splitting patients with a KPS > 80 vs. those with KPS ≤ 80 , excluding two subjects with no KPS marked in their records from the analysis. Patients who received HFRT and had a KPS ≤ 80 were less likely to develop pseudoprogression ($X^2 = 3.88$, OR: 5.00, 95% CI: 2.151–11.620, $p = 0.049$). There was no difference in rate of pseudoprogression for those with higher or lower KPS in the full study population and CRT cohort (Figure 5(B)). Goodman-Kruskal analysis of pseudoprogression status dependent on KPS without dichotomization for HFRT patients did not yield a statistically significant concordant or discordant trend (Figure 5(C); $\gamma = 0.363$, 95% CI: -0.129 – 0.855).

Finally, in patients who developed pseudoprogression, those who received HFRT were more likely to need a clinical intervention to manage neurological symptoms, such as a change in dexamethasone dose or treatment with bevacizumab; however, this trend was not statistically significant ($X^2 = 1.895$, $p = 0.169$).

5. Discussion

This study examines potential clinical correlations between radiotherapy regimen and development of pseudoprogression for older patients with GBM, for whom there is no standard of care and thus have treatment decisions made based on their functional status and preferences. While this study was motivated by our anecdotal observations in the clinic that

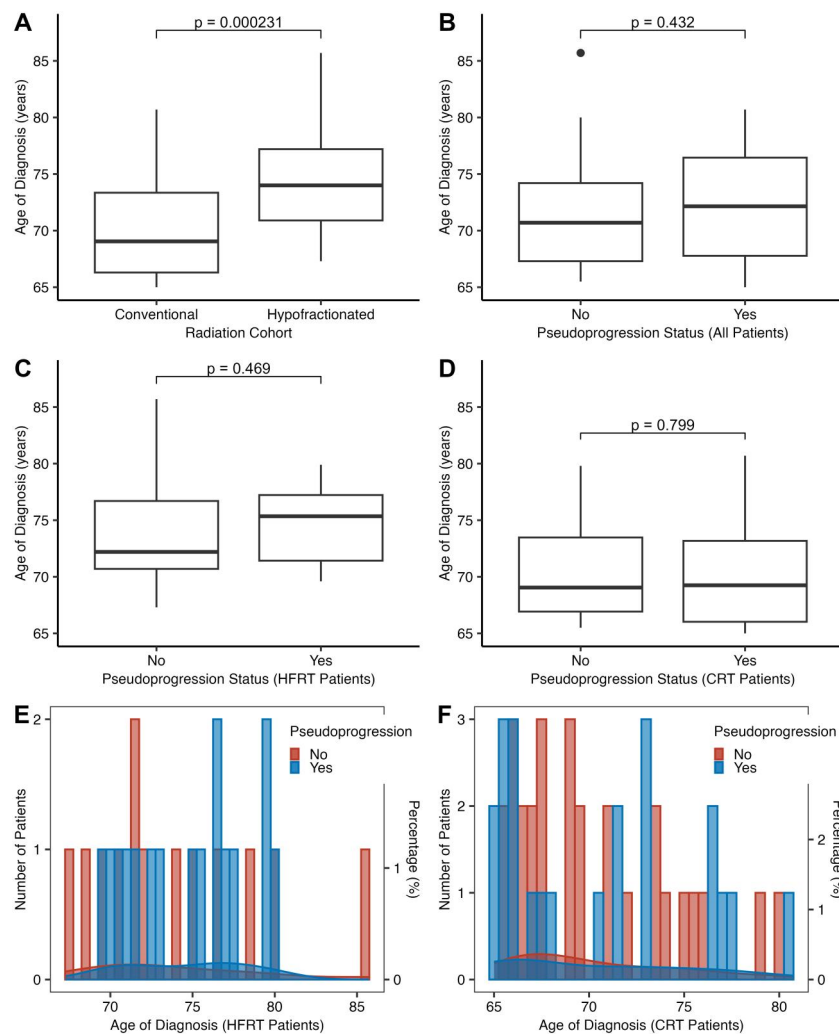


Figure 2. Age at diagnosis by radiation cohort. (A) Age at diagnosis for conventional radiotherapy (CRT) and hypofractionated radiotherapy (HFRT) patient cohorts. (B) Age at diagnosis for patients who developed pseudoprogression vs. patients who did not develop pseudoprogression. (C) Age at diagnosis in the HFRT cohort for patients who developed pseudoprogression vs. patients who did not develop pseudoprogression. (D) Age at diagnosis in the CRT cohort for patients who developed pseudoprogression vs. patients who did not develop pseudoprogression. (E) Histogram (by count, left y-axis) and kernel density estimator (by percentage, right y-axis) depicting the distribution of ages at diagnosis in the HFRT cohort. (F) Histogram (by count, left y-axis) and kernel density estimator (by percentage, right y-axis) depicting the distribution of ages at diagnosis in the CRT cohort.

patients who received HFRT seemed to develop pseudoprogression at a higher rate than those who received CRT, we did not see this result within our statistical analysis. Interestingly, average BED for patients who received HFRT was lower than for those who received CRT; therefore, it may be possible that the lack of a significant difference in rates of pseudoprogression between the two groups was impacted by the discrepancy in BED. It would thus be of interest to examine rates of pseudoprogression in patients treated with hypofractionated radiation protocols that involve a higher BED, a practice that is occurring at some institutions.

Furthermore, the majority of our analyses did not show any significant correlation between traditionally

prognostic clinical variables in neuro-oncology practice and pseudoprogression after factoring in type of radiotherapy received. One interesting though non-significant trend we discovered was that patients were more likely to need clinical intervention to address pseudoprogression if they received HFRT rather than CRT. If this is the case, it may suggest that HFRT increases the severity of post-treatment neuroinflammatory response; further studies should evaluate this hypothesis.

In our study, MGMT methylation status was not significantly associated with development of pseudoprogression, which differs from what has been previously reported in the literature [30]. However, a recent study employing RANO 2.0 guidelines for diagnosis of

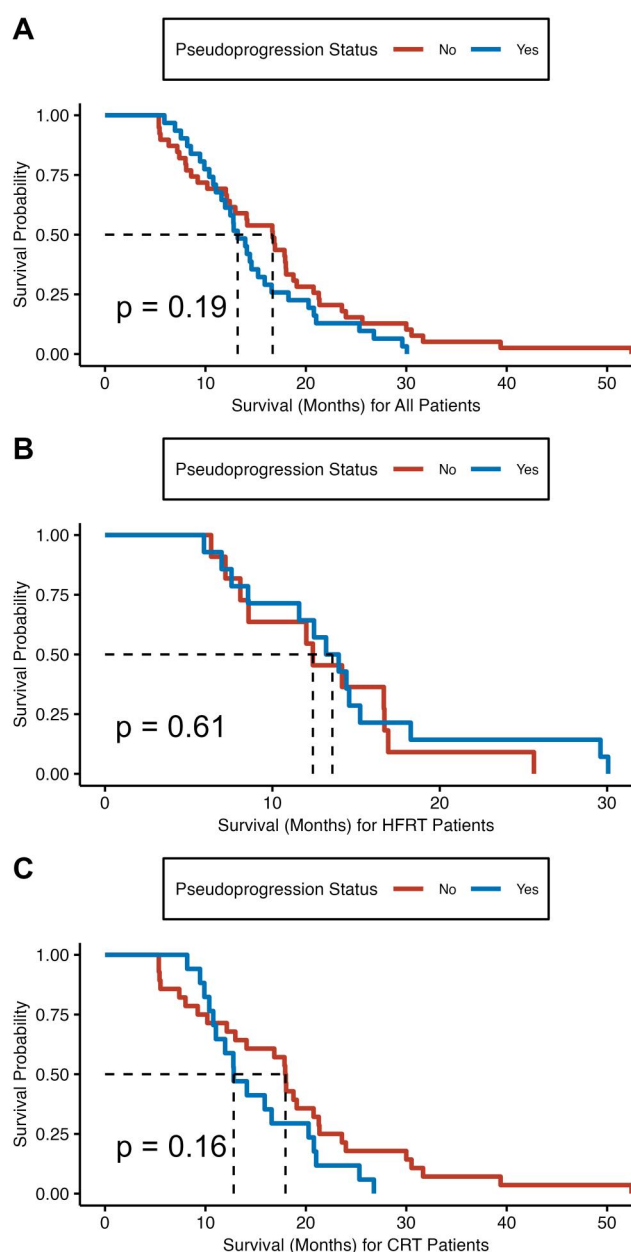


Figure 3. Kaplan-Meier survival curves depicting overall survival for each radiation cohort. Overall survival was defined as starting from first histopathological diagnosis until date of death. (A) Kaplan-Meier survival curve for all patients. (B) Kaplan-Meier survival curve for patients who received hypofractionated radiotherapy (HFRT). (C) Kaplan-Meier survival curve for patients who received conventional radiotherapy (CRT).

pseudoprogression found lower incidences in patients with methylated MGMT promoters than previously described, suggesting that the new criteria for pseudoprogression may be more stringent and thus affect the relationship between MGMT methylation status and pseudoprogression [31]. Notably, the incidence of pseudoprogression in our cohort for patients with MGMT promoter methylation is high compared to

rates reported in the literature, which may be attributed to our study population including only older patients with GBM. Furthermore, the lack of association between MGMT methylation status and development of pseudoprogression could be attributed to our study having a small sample size and containing patients with inconclusive or unknown MGMT promoter methylation status.

The single statistically significant result of importance that we obtained from our analyses was the association between KPS and development of pseudoprogression for patients who received HFRT, but not for patients who received CRT. Our result suggested that patients who received HFRT with lower KPS at diagnosis (≤ 80) were less likely to develop pseudoprogression than patients with higher KPS (> 80). We ventured that low KPS, while a crude measure, could be a surrogate to suggest effective biological age. It is commonly known that the immune system weakens with age, particularly with older adults, in a phenomenon known as immunosenescence, a process in which T cell function becomes defective and the innate immune response chronically activates low-grade inflammation [32–35]. As pseudoprogression is primarily an inflammatory response actuated by immune cells within the brain [20,26–28], a patient with an immunosenescence-compromised immune response may not have adequate capacity to demonstrate radiographically detectable neuroinflammation upon receipt of chemoradiation treatment.

However, this hypothesis is limited in several respects. First, the KPS cutoff in this study at a score of 80 was selected for dichotomization purposes and adequate statistical comparison given our small sample size. However, we recognize that a KPS score of 80 is still considered to indicate good performance status [36], raising the question of if we should be measuring performance status differently in older patients. Regardless, our tests only reveal KPS (≤ 80) as a potential factor influencing the likelihood of developing pseudoprogression. Second, the p-value corresponding to the chi-square analysis was very close to the significance level of $\leq 5\%$, meaning that the result should be accepted with caution. Third, two patients had missing KPS scores within their charts, one of whom received HFRT and could have affected the results of the test if their KPS was not missing given the small size of the HFRT cohort. Finally, performing Goodman-Kruskal analysis with KPS in relation to pseudoprogression did not reveal a statistically significant concordant or discordant trend, which calls to question why a

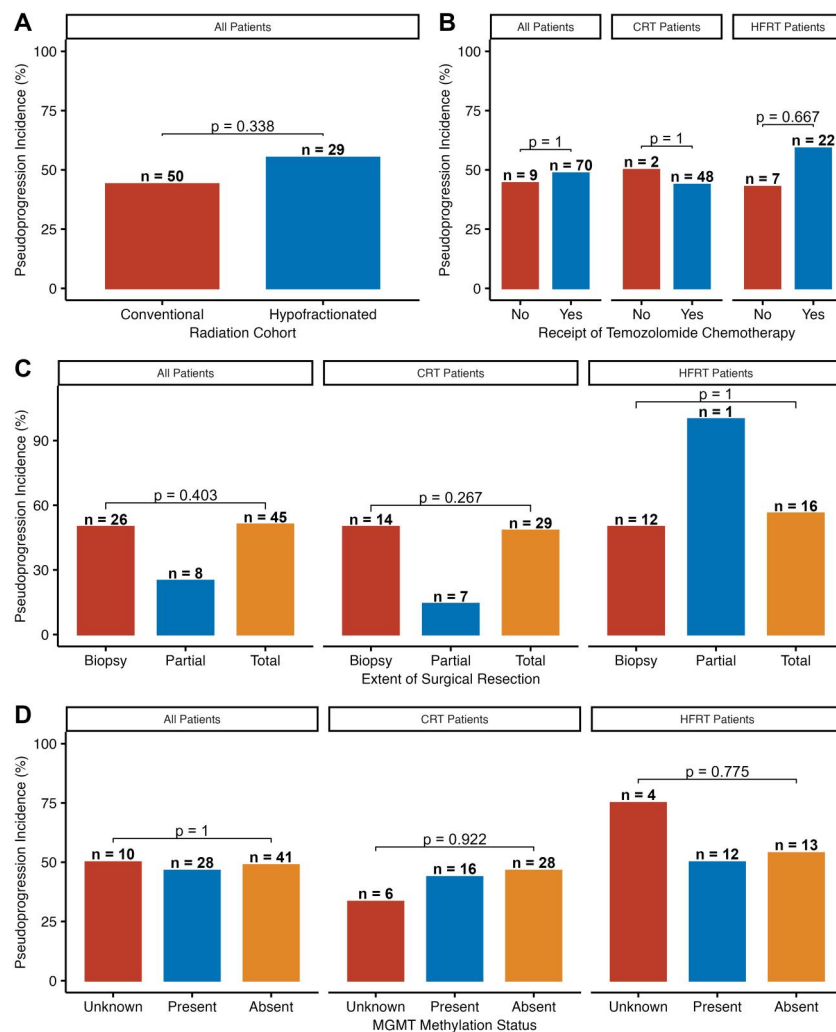


Figure 4. Statistical analyses for variables associated with pseudoprogression status and radiation cohort. In all tests, Pearson's chi-square test was employed if expected values for each subgroup totaled 5 or more for each cohort, and Fisher's exact test otherwise. (A) Association between pseudoprogression status and radiation cohort (Pearson's chi-square test). (B) Association between pseudoprogression status and receipt of temozolomide chemotherapy, conditioned on radiation cohort (Fisher's exact test). (C) Association between pseudoprogression status and extent of surgical resection, conditioned on radiation cohort (Fisher's exact test). (D) Association between pseudoprogression status and MGMT methylation status, conditioned on radiation cohort (Fisher's exact test). *HFRT: hypofractionated radiotherapy; CRT: conventional radiotherapy; MGMT: O⁶-methylguanine-methyltransferase.

statistically significant result was only found when dichotomizing KPS as a categorical variable.

This study has several general limitations. First, the retrospective and single-institution nature of our investigations introduces results that may not be fully generalizable. There were instances where clinical information in the electronic medical record was not consistently available, such as in the case where a subject received a significant amount of care at another institution. Second, our exclusion criteria may introduce selection bias as they select for patients who were healthy enough to survive for three months post-treatment despite the generally short prognosis in GBM, while patients who undergo HFRT tend to be

older, be perceived to be frailer, and have shorter expected OS [37]. However, we reasoned that this exclusion criteria would minimize overall study bias to prevent inclusion of patients who might disproportionately be allocated to either the pseudoprogression or non-pseudoprogression cohorts due to inadequate post-treatment evaluation.

Third, RANO criteria and molecular classification of brain tumors were revised during the timeframe we extracted our study cohort [18,24,29]. For example, patients who were diagnosed with GBM but had IDH-mutant status had to be excluded from our study. Lack of standardized records was most salient when trying to ascertain subjects' pseudoprogression

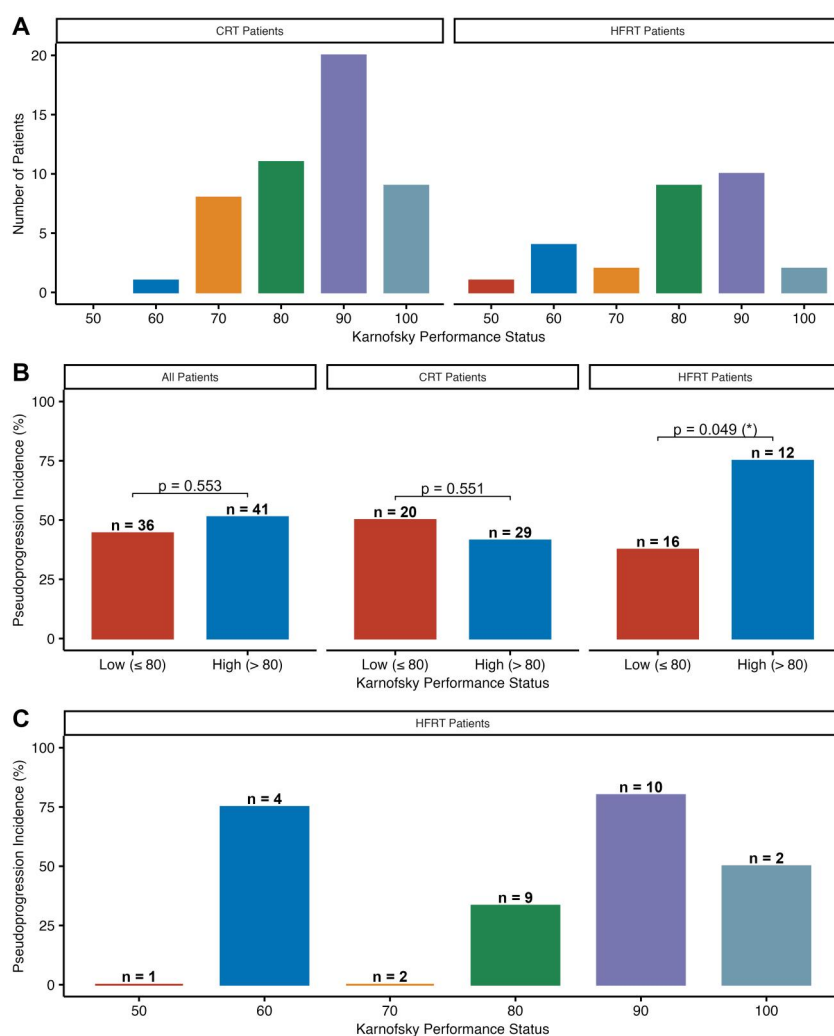


Figure 5. Statistical analysis of Karnofsky Performance Status (KPS) in association with pseudoprogression and radiation cohort. (A) Distribution of KPS scores in both conventional radiotherapy (CRT) and hypofractionated radiotherapy (HFRT) cohorts. **(B)** Association between pseudoprogression status and KPS, conditioned on radiation cohort (Pearson's chi-square test). **(C)** Distribution of pseudoprogression and KPS in the HFRT cohort.

statuses and time of onset. Advanced imaging techniques recommended by the RANO 2.0 Working Group, such as diffusion MRI, perfusion MRI, or amino acid positron emission tomography imaging were not yet employed as standard of care to aid in determining for pseudoprogression vs. true progression in our cohort. Therefore, many patients who were noted to have developed pseudoprogression had to instead be retroactively recategorized or even excluded from the study [18]. For example, patients who developed pseudoprogression six months after completing radiotherapy did not fit the RANO criteria [18,24]. Patients who presented with true progression a month after having pseudoprogression also had to have their pseudoprogression status revised by an attending neuro-oncologist. Our decision to minimize selection bias and maximize consistency by excluding patients who did not fit the RANO criteria and 2021 WHO Classification

of CNS Tumors led to a smaller population than initially screened [18,24,29] and thus lower than ideal power for our statistical tests.

A final caveat is how patients are selected for CRT or HFRT. As seen in Figure 2(A), a patient who received HFRT is more likely to be older than a patient who received CRT. Within our practice, HFRT is often offered to patients who have shorter life expectancy, are less robust, or are presumed to have higher risk of treatment toxicity in an attempt to improve quality-of-life for patients while still improving OS [11,12]. As previously discussed in the context of KPS, these factors may be associated with a patient's ability to mount a post-treatment neuroinflammatory response and thus may serve as confounders to the statistical analyses we conducted. We cannot retrospectively ascertain how clinicians made decisions to select particular patients for CRT and HFRT without changing

the way in which we prescribe HFRT to a more random and experimental approach. This major limitation is inherent to an observational study investigating the correlation between radiotherapy regimen and likelihood of developing pseudoprogression. A future prospective study with careful documentation of why a particular radiotherapy fractionation is selected is warranted to confirm the hypotheses generated in the current study.

Our negative results are reassuring for current neuro-oncology practice, as discovering that HFRT increases the likelihood of developing pseudoprogression – which may lead to a false diagnosis for recurrent GBM or be accompanied with adverse clinical symptoms such as increased cerebral edema – could introduce additional clinical complexity when deciding on radiotherapy recommendations. Our one statistically significant result noting a decreased likelihood of developing pseudoprogression in patients with lower KPS who received HFRT is intriguing and may add a layer of potential nuance in clinical care. A future prospective cohort study – enrolling more patients than included in this retrospective analysis and using advanced imaging techniques to assess for pseudoprogression – in the era of WHO 2021 diagnostic criteria and RANO 2.0 is warranted to better understand how and when older patients develop pseudoprogression after radiotherapy as well as what impact this, or other treatment toxicities, has on their overall outcomes and quality of life. We have recently begun to use a comprehensive Geriatric Assessment (CGA) and calculate deficit accumulation frailty index (DAFI) to more precisely assess frailty rather than simply using age and KPS [38–43]. We previously found that DAFI score-calculated frailty was a better prognostic marker than a combination of KPS, MGMT methylation, and age [42]. We believe that measures such as geriatric assessment and DAFI may be superior to KPS in understanding a patient's frailty and help to guide better treatment decisions in older patients with GBM. Prospective incorporation of frailty measures will be critical in future studies to understand this relationship.

6. Conclusion

There was no increased rate of developing pseudoprogression or need for clinical intervention to manage pseudoprogression in older patients with GBM who received HFRT compared to those who received CRT. However, patients who received HFRT and had lower KPS were less likely to develop pseudoprogression, potentially suggesting that patients who were

perceived to have lower functional status are less likely to develop an immune inflammatory response to treatment even with a higher radiation dose per fraction. Therefore, clinicians may take into account measures of functional status and frailty when considering the impact of treatment decisions on toxicity risk, including the development of pseudoprogression.

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Author contributions

Derek L. Chien collected data, performed statistical analyses and wrote the manuscript. Sara J. Hardy assisted with statistical analyses and provided expertise in radiation and neuro-oncology. Jennifer N. Serventi collected some data and provided valuable feedback on the manuscript. Jacqueline M. Behr collected some data and provided valuable feedback on the manuscript. Nimish A. Mohile provided expertise in neuro-oncology, assisted with data collection and exclusion, performed imaging analysis, guided the primary author throughout the process, and provided valuable feedback on the manuscript. Lauryn E. Hemminger generated the idea for the study, provided expertise in neuro-oncology, assisted with data collection and exclusion, performed imaging analysis, guided the primary author throughout the process, and provided valuable feedback on the manuscript.

Ethical approval

To conduct the research outlined in this manuscript, we first obtained a waiver of informed consent to retrospectively collect data from URM's electronic medical record database of neuro-oncology patients. We received this waiver and the approval to perform the study from URM's Institutional Research Study Review Board (RSRB00008544).

Disclosure statement

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The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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