Hypofractionated Proton Reirradiation for Recurrent Glioblastoma: Clinical and Dosimetric Outcomes from a Large Single Institution Series

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Abstract

Introduction: Management of recurrent glioblastoma remains a major challenge, with no treatment shown to meaningfully prolong survival. Reirradiation may offer local control but is often constrained by concerns regarding dose to critical normal tissues. We evaluated clinical outcomes, toxicity, and cumulative dosimetric parameters in patients with recurrent glioblastoma treated with hypofractionated proton reirradiation.

Materials and Methods: We retrospectively identified patients with recurrent glioblastoma treated with hypofractionated reirradiation courses of 35 Gy in 10 fractions. Cumulative composite dosimetry was calculated using EQD2 ($\alpha/\beta = 2$) for organs at risk (OARs). Overall survival (OS) was estimated using Kaplan Meier methods. Cox proportional hazards modeling was performed to identify factors associated with OS. A contemporaneous cohort treated with hypofractionated photon reirradiation was identified for comparison.

Results: A total of 89 patients were treated with hypofractionated proton reirradiation for recurrent glioblastoma between 2015 and 2025 with median follow up of 7.2 months. Median age was 58 years (IQR 48–68), and 48% underwent reresection prior to reirradiation. Composite dosimetry demonstrated that the initial radiation course accounted for the majority of cumulative OAR dose, with proton reirradiation contributing limited additional exposure. Median OS from reirradiation in the proton cohort was 8.3 months (95% CI 6.27–9.47), with 6 and 12 month OS of 62.6% and 24.9%, respectively. On multivariable analysis, increasing age was independently associated with worse OS. A comparator cohort of 49 patients treated with photon reirradiation was identified. OS did not differ between proton and photon reirradiation cohorts. 8 (5.8%) patients experienced Grade 3 or 4 radiation necrosis. No Grade > 4 toxicities were observed.

Conclusions: Hypofractionated proton reirradiation was feasible and associated with favorable toxicity outcomes, supporting its use as a retreatment option. Prospective studies are needed to further define optimal patient selection.

Introduction

Glioblastoma (GBM) is the most common malignant brain tumor in adults and is uniformly fatal. The standard of care treatment consists of resection followed by adjuvant radiation with concurrent temozolomide followed by adjuvant temozolomide and the option of tumor treating fields.[1] Despite intensive multimodality treatment, more than 90% of patients have disease recurrence within two years.[2] Management of recurrent GBM is challenging and heterogeneous, often involving a combination of surgery, systemic therapy, and reirradiation.

Reirradiation is an important salvage option, supported by data suggesting that focal high dose radiotherapy can provide benefit in selected patients.[3] A major limitation of reirradiation for GBM is the cumulative dose to critical central nervous system structures. Prior radiation often brings tissues such as the brainstem, optic nerves, and optic chiasm close to or beyond tolerance thresholds, constraining the ability to deliver a second therapeutic course of radiation while minimizing the risk of toxicity.[4] Proton therapy has the potential to overcome some of these limitations by exploiting the physical dose deposition properties of the Bragg peak to reduce exit dose and spare uninvolved normal tissues including critical intracranial structures.[5]

Hypofractionated proton reirradiation is of interest in the setting of recurrent GBM due to its ability to deliver high biologically effective doses to the recurrent tumor while limiting dose to

previously irradiated normal structures. Photon radiation has been demonstrated to prolong progression free survival in combination with bevacizumab.[3] However, clinical data supporting proton reirradiation remain limited to small retrospective series with heterogeneous dose and fractionation schemes without dosimetric analyses or correlation between cumulative dose and observed toxicity.[6,7]

Given the limited and heterogeneous data supporting proton reirradiation for recurrent glioblastoma, we assembled a cohort of patients treated with hypofractionated proton reirradiation to evaluate (1) technical feasibility, (2) safety, and (3) clinical outcomes. We performed dosimetric analyses to assess cumulative dose to critical structures and evaluated toxicity. Survival outcomes were evaluated and compared with an internal cohort of patients treated with photon reirradiation. This analysis seeks to address critical knowledge gaps regarding the safety and potential clinical benefit of hypofractionated proton reirradiation among patients with recurrent glioblastoma.

Materials and Methods

Study Design

Under Institutional Review Board (IRB) approval, patients who completed standard of care treatment for GBM followed by retreatment for recurrence between January 2010 and February 2025 were retrospectively reviewed. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies (**Supplementary Figure 1, Supplementary Table 1**).[8] Eligible patients were >18 years old at time of pathologically confirmed diagnosis of GBM and prescribed 35 Gy in 10 fractions as their reirradiation course. Reirradiation was defined per the ESTRO consensus guidelines.[9] Criteria for pathologic diagnosis were histologic features consistent with grade 4

glioma or molecular diagnosis of GBM per WHO 2021 criteria.[10] Patients were excluded if they were <18 years of age, received alternative fractionation schemes, IDH-mutant astrocytoma or other pathology inconsistent with GBM, had transformed from a low grade glioma to a high grade glioma, or were a histologic variant (gliosarcoma).

We reviewed surgical and biopsy reports to extract IDH status and MGMT promoter methylation status. Patients were categorized as MGMT promoter methylated or unmethylated. Patient medical records were reviewed to assess dose, fractionation, and modality (proton versus photon). Modality was decided by the treating radiation oncologist. We reviewed whether patients underwent reresection at time of progression prior to reirradiation. Performance status at the time of reirradiation was recorded. Dosimetric analysis using 2 Gy per fraction equivalent dose (EQD2) was recorded for critical organs at risk (OARs) using an α/β ratio of 2. Plan summations were available for 131 patients, and patients without plan summations were excluded from dosimetric analyses. Toxicity was classified according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5) for Grade 3 or greater acute or late toxicity consistent with reporting in major trials in this patient population.[3,11] Radiation necrosis was recorded if Grade 3 or higher according to CTCAE v5 (severe symptoms, medical intervention beyond steroids or surgery required). Radiation necrosis was differentiated from progression on the basis of multi-disciplinary tumor board review Including imaging, pathological, and clinical assessments. Our institutional practice includes MRI assessment with post-contrast T1-weighted imaging, T2-weighted and FLAIR sequences, diffusion weighted imaging with ADC mapping, susceptibility weighted imaging, and perfusion imaging, most commonly dynamic susceptibility contrast perfusion MRI with evaluation of relative cerebral blood volume (rCBV). Elevated perfusion/rCBV, progressive nodular enhancement, increasing mass effect, and concordant clinical decline were considered more suggestive of tumor recurrence, whereas low perfusion, stable or decreasing enhancement over time, central necrosis, and fluctuating or

transient imaging changes within the expected treatment window favored treatment effect or pseudoprogression. Furthermore, lesion were followed with serial imaging to assess interval evolution, and pathologic confirmation was incorporated when surgical resection or biopsy was performed. Consistent with standard neuro-oncology practice, the final determination of recurrence versus treatment effect was based on the integrated clinical, radiographic, and pathologic assessment (when available) over time. Reirradiation was defined as in-field when more than 80% of re-irradiation volume was within the 95% isodose line of the first course of radiation. Systemic therapy was considered concurrent if received during radiation.

Simulation and Treatment

All patients underwent simulation with computed tomography (CT) and with MRI scans with T1 post contrast and T2 FLAIR sequences. Images were transferred to Eclipse treatment planning system (Varian Medical Systems). CT and MRI were coregistered for contouring. Contouring was completed per institutional standard with gross tumor volume (GTV) defined as progressive enhancing disease with clinical target volume (CTV) expansion at the discretion of the treating clinician generally between 0 and 5 mm. Treatment planning was completed with Eclipse treatment planning systems (Varian Medical Systems) and delivered with IBA pencil-beam scanning techniques. Field selection was based on maximal sparing of organs at risk and previously irradiated brain tissue. All volumes and plans were peer-reviewed per institutional standard. The following plan sum constraints were utilized for hypofractionated proton or photon reirradiation: brainstem EQD2 D0.03 cc < 80 Gy, optic chiasm/optic nerves EQD2 D0.03 cc < 70 Gy. $\alpha/\beta = 2$ was utilized. Consraints could be exceeding at the discretion of the treating clinician. All radiation plans underwent peer review per institutional standards. Following completion of reirradiation, patients were followed with repeat MRIs with advanced imaging metrics per institutional standard.

Statistical Analysis

Baseline characteristics were summarized by treatment group using descriptive statistics. Group comparisons used the Wilcoxon rank sum test or t test for continuous variables and chi squared or Fisher's exact tests for categorical variables. OS was defined as the time from the end of reirradiation to death from any cause, with patients censored at the date of last known follow up. Survival distributions were estimated using the Kaplan Meier method and compared using the log rank test. Median follow up was calculated using the reverse Kaplan Meier method.

Multivariable Cox proportional hazards regression was used to evaluate factors associated with OS from reirradiation. Covariates were selected a priori based on clinical relevance and included age at diagnosis (modeled as a continuous variable) and performance status at the time of reRT (categorized as Karnofsky Performance Status [KPS] 90–100, 70–80, and ≤60).

Time from completion of initial radiotherapy to re-irradiation was evaluated as a continuous variable. To assess whether a linear functional form was appropriate, time to reRT was first modeled as a linear term in the Cox model. To allow for potential non-linear associations, time to reirradiation was subsequently modeled using restricted cubic splines with three knots placed at default quantiles.

Model fit between the linear and spline models was compared using a likelihood ratio test. The overall association of time to reRT with survival and the presence of non-linearity were further evaluated using Wald tests for the spline terms. Adjusted hazard ratios across the continuous range of time to reRT were estimated from the spline model and visualized with 95% confidence

intervals. All models were adjusted for age at diagnosis and performance status at reRT. Two-sided p-values <0.05 were considered statistically significant.

Results

Baseline and Treatment Characteristics

We identified a total of 89 patients treated with hypofractionated proton reirradiation for recurrent glioblastoma between 2015 and 2025. The patient and treatment characteristics are summarized in **Table 1**. A representative example of proton reirradiation is included in **Figure 1**. Median age was 58 years at the time of reirradiation (IQR 48 - 68). 61% of patients were male. The majority of patients had a KPS between 70 - 80 (57%) and had MGMT unmethylated tumors (62%). A total of 76% of patients who received proton reirradiation had an initial course of radiation of 60 Gy in 30 fractions, while 13% of patients had a hypofractionated initial course of radiation of 40 Gy in 15 fractions, and remaining patients had other fractionations. Patients received both photon (51%) and proton (36%) radiation during the initial course, some patients had mixed plans (13%). Approximately half (57%) of patients were treated with tumor treating fields (TTF). Median time between the end of initial course to the beginning of reirradiation was 15.5 months (range 4-92). Approximately half (48%) of patients underwent reresection prior to proton reirradiation, and the majority of patients (65%) received concurrent bevacizumab or temozolomide (32%) with reirradiation.

All patients received 35 Gy in 10 fractions (**Table 1**). Dosimetric outcomes for critical organs at risk (brainstem, optic chiasm, and optic nerves) among patients treated with proton reirradiation are summarized in **Figure 2**. Initial radiation accounted for the majority of cumulative exposure to OARs, whereas proton reirradiation (gray points) contributed limited additional dose. Photon

reirradiation dosimetric data is presented for comparison within the figure by the blue points. Median composite D0.03 cc EQD2 values are included. Reirradiation dose to critical organs at risk was modulated according to prior radiation exposure, with lower D0.03 cc values at low to moderate original doses and greater variability at higher prior doses, reflecting anatomic constraints (**Figure 2**).

We identified an additional 49 patients treated with hypofractionated photon reirradiation during the same time frame. Patient characteristics are also included **Supplementary Table 2**. Compared to patients treated with proton reirradiation, patients treated with photon radiation were more likely to have undergone reresection and have received a first course of photon therapy.

Toxicity

One patient ended treatment early due to global decline in performance status in the setting of disease progression. All other patients completed the full treatment course. In total, 8 (5.8%) patients in the entire cohort developed radiation necrosis including 5 (5.6%) patients treated with proton reirradiation and 3 (6.1%) patients treated with photon reirradiation. All patients who developed radiation necrosis had in-field reirradiation. No patients developed optic neuropathy or necrosis involving the brainstem.

Outcomes

Median follow up from the beginning of reirradiation for the proton cohort was 7.2 months. The median overall survival was 8.3 months (95% CI 6.3-9.5) with 6 and 12 month overall survival of 62.6% and 24.9%, respectively (**Figure 3A**). The median overall survival for the photon cohort

was 7.2 months (95% CI 4.7-9.5) with 6 and 12 month OS of 53.1% and 22.4%, respectively. Median OS from time of reirradiation was not significantly different between proton and photon cohorts (**Figure 3B**).

Table 2 summarizes univariable and multivariable Cox proportional hazards analyses for overall survival in the proton reirradiation cohort. On univariable analysis, inferior overall survival was associated with increasing age (HR per year 1.03, 95% CI, 1.01–1.06; p = 0.003) and receipt of an initial radiation course dose of 40 Gy in 15 fractions (HR 2.29, 95% CI, 1.18–4.43; p = 0.015). MGMT promoter methylation (HR 0.59, 95% CI, 0.34–1.01; p = 0.055) and KPS ≤60 at reirradiation (HR 2.23, 95% CI, 0.99–5.03; p = 0.053) demonstrated borderline associations with overall survival on univariable analysis. On multivariable analysis, increasing age remained independently associated with inferior overall survival (HR per year, 1.02; 95% CI, 1.00–1.05; p = 0.045). Initial radiation course dose of 40 Gy in 15 fractions was no longer independently associated with overall survival (HR 1.84, 95% CI, 0.89–3.78; p = 0.099). KPS ≤60 at reirradiation remained borderline associated with inferior overall survival on multivariable analysis (HR 2.26, 95% CI, 0.98–5.17; p = 0.055). Initial radiation modality was not associated with overall survival on either univariable or multivariable analyses. We performed a sensitivity analysis incorporating TTG as a covariate into the primary multivariable model. TTF was not independently associated with OS from reRT (HR 0.95, 95% CI 0.62-1.46, p=0.8). The estimates for other included covariates were materially unchanged from the primary model, supporting the robustness of the primary analysis.

When modeled as a linear covariate, time from completion of initial course of radiation to reirradiation was not significantly associated with OS (HR per 6 month increase 0.96, 95% CI 0.89–1.03; p = 0.30). In contrast, restricted cubic spline modeling demonstrated a significant overall association between time to re-irradiation and survival (p = 0.038), with evidence of a

non-linear relationship (p for non-linearity = 0.020). Comparison of the spline model with the corresponding linear model using a likelihood ratio test confirmed improved model fit with the non-linear specification. Spline analysis revealed a steeply elevated hazard of death among patients undergoing early reirradiation, followed by a rapid decline in hazard with increasing time to reirradiation, and subsequent plateauing beyond approximately 15–18 months (**Figure 4**). These findings suggest that the prognostic impact of time to reirradiation is concentrated in earlier intervals and is not adequately captured by a linear modeling assumption.

Discussion

In this single institution retrospective study, we evaluated the feasibility, safety, and clinical outcomes of proton reirradiation among patients with recurrent glioblastoma who were previously treated with high dose brain radiation therapy. This represents the largest reported experience with hypofractionated proton reirradiation in glioblastoma to date and first to include an internal photon comparator. We found that proton reirradiation was feasible and associated with favorable toxicity outcomes despite substantial cumulative radiation exposure. Despite the aggressive biology of recurrent glioblastoma and absence of salvage therapy proven to prolong survival, we demonstrated that proton reirradiation is an important modality when retreatment is considered, particularly when cumulative dose to critical structures is limiting with photons. Modality for re-treatment is chosen at the discretion of the treating radiation oncologist. Based on the retrospective nature of this study it is difficult to say why a treatment modality was selected for each individual patient. However, proton therapy is employed when it is thought that it will make a measurable difference in sparing of critical OARs compared to a photon plan. External factors, such as insurance approval, proximity to OAR, and patient toleranace for treatment time also play a role in decision making. This determination ultimately is made by the

treating radiation oncologist and can be both direct photon-proton plan comparison or for the various other factors reviewed.

The main rationale for proton therapy in the setting of brain reirradiation is a reduction of dose to critical structures including the optic apparatus and brainstem and uninvolved normal brain tissue while maintaining adequate target coverage. This is particularly critical among patients with glioblastoma who receive initial high dose courses of radiation, including standard fractionation to 60 Gy[12] or hypofractionated courses of 40 Gy.[13] Univariable analysis suggests that dose given during course 1 is an important factor influencing survival. Based on the data by Roa et al. the patients who are treated with a this hypofractionated regimen were often older or had poor baseline performance status.[13]It was ultimately at the discretion of the treating physician to decide if a patient was fit enough to receive standard fractionation to a total of 60Gy. Given the median of 8 months between initial treatment and recurrence, the second course of radiation often occurs within one year of the first course.[8] In this context, we observed that the interval between initial radiotherapy and re-irradiation was non-linearly associated with overall survival. The observed association between early re-irradiation and inferior survival likely reflects underlying tumor biology, as patients requiring early retreatment may harbor more aggressive or treatment-resistant disease rather than experiencing inferior outcomes due to re-irradiation itself. This short time interval between the first and second course of radiation limits opportunity for normal tissue recovery. These theoretical advantages are reflected in the low observed rates of high-grade toxicity in our cohort despite substantial cumulative dose exposure. Importantly, this study is the first to provide detailed cumulative dosimetric analyses of critical structures in the setting of hypofractionated proton reirradiation for glioblastoma, allowing direct correlation of normal tissue dose with observed toxicity outcomes.

Two retrospective analyses of proton therapy for recurrent glioblastoma have been previously reported. A pooled analysis of 45 patients enrolled in the Proton Collaborative Group study 01 009 (NCT01255748) reported a median survival of 14 months following reirradiation.[6] A second single institution retrospective analysis of 13 patients reported median survival of 8 months following reirradiation.[7] Both studies used a variety of dose and fractionation schemes with limited reporting of doses to critical organs at risk. In contrast, the present study enriches the existing literature by examining a substantially larger cohort of patients treated with a homogeneous hypofractionated proton reirradiation approach and by providing detailed dosimetric analyses for target volumes and OARs across both radiation courses. This comprehensive characterization enables a more robust assessment of clinical outcomes and treatment-related safety associated with proton-based reirradiation.

The addition of hypofractionated radiation therapy prolongs disease control among patients with recurrent glioblastoma compared to systemic therapy alone. The randomized phase II RTOG 1205 trial compared bevacizumab alone with bevacizumab plus hypofractionated photon reirradiation.[3] Patients were treated with 35 Gy in 10 fractions at least six months from the first course of radiation. While the addition of reirradiation did not improve OS (median 10.1 vs. 9.7 months), it was associated with a significant improvement in progression free survival (7.1 months vs 3.8 months, HR 0.73). Furthermore, reirradiation was delivered with minimal acute toxicity and no delayed grade 3 or greater toxicity, supporting the safety and clinical activity of reirradiation in appropriately selected patients. In the present study, approximately two-thirds of patients received concurrent bevacizumab at the time of reirradiation, mirroring the experimental arm of RTOG 1205, and demonstrated a comparable median OS of 8.3 months (Figure 3).[14] Notably, only 2.3% of patients enrolled in RTOG 1205 were treated with proton therapy, whereas our cohort provides substantially greater representation of proton-based reirradiation, thereby extending the available safety and feasibility data for this modality.[14] The ongoing

randomized LEGATO study is evaluating benefit of adding hypofractionated reirradiation to lomustine among patients with recurrent glioblastoma.[15] Importantly, neither trial addresses whether advanced radiation modalities such as proton therapy are capable of further reducing normal tissue dose and improving the therapeutic ratio.

Survival outcomes following reirradiation for recurrent GBM remain modest and heterogeneous, reflecting differences in patient selection, radiation modality, and dose fractionation. A range of dose and fractionations have been utilized including conventionally fractionation[16,17], moderately hypofractionated regimens such as 35 Gy in 10 fractions[3,18] and 39 Gy in 13 fractions[19] as well as hypofractionated approaches with stereotactic radiosurgery (SRS)[20,21] generally reporting survival between 8 and 12 months following reirradiation and influenced by patient selection. While reirradiation has not consistently improved survival, proton-based approaches may expand candidacy for retreatment and support durable local control in selected patients. While our data are not powered to detect predictive or prognostic factors that influence survival in this cohort, certain patient factors like good performance status, younger age, longer time between courses, and small re-treatment volume are favorable considerations for reirradiation with proton therapy. Other factors, such as, dose contribution to critical OARs from initial course and volume overlap between initial course and re-treatment are case-based considerations. These patients benefit from multidisciplinary discussion.

Target delineation is based on contrast enhanced MRI[3] which is difficult to distinguish from treatment effects in the setting of previously treated glioblastoma.[22] Other strategies have included the use amino acid PET, including of O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) PET for improved target delineation.[22,23] However, a recent randomized study of FET PET versus standard target delineation in the setting of recurrent glioblastoma did not show improved

outcomes with FET PET based delineation.[19] Therefore, standard MRI based delineation remains the standard practice for treatment of reirradiation in the setting of glioblastoma.[9]

This study has several limitations, including its retrospective design and potential selection bias favoring patients eligible for proton therapy. Upfront treatment heterogeneity and the absence of systematic neurocognitive or quality of life assessments further limit interpretation. Given overall limited prognosis following reirradiation for glioblastoma, patients may not survive long enough to experience late toxicities, limiting extrapolation of these data to other diseases with improved prognosis. Furthermore, this study was not designed to compare clinical outcomes or toxicity between proton and photon re-irradiation approaches, and the data do not establish reduced toxicity or improved efficacy with proton therapy despite theoretical advantages. Given the resource intensive nature of proton therapy, further studies are required to neurocognitive outcomes, quality of life, and cost effectiveness in this setting. Despite these limitations, it is the largest series of proton reirradiation for glioblastoma in the literature and the first to offer a direct comparison to a photon arm.

Conclusion

Hypofractionated proton reirradiation for recurrent glioblastoma was feasible and well tolerated in this single institution retrospective analysis. To our knowledge, this study represents the largest reported experience of hypofractionated proton reirradiation for recurrent glioblastoma and is the first to incorporate detailed dosimetric analyses alongside an internal photon comparator. Although survival outcomes remain limited by the aggressive biology of recurrent glioblastoma, proton therapy may expand candidacy for reirradiation by reducing normal tissue

dose while achieving therapeutic doses to recurrent disease. Further prospective evaluation is needed to refine treatment selection and optimize retreatment strategies.

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Figure Captions

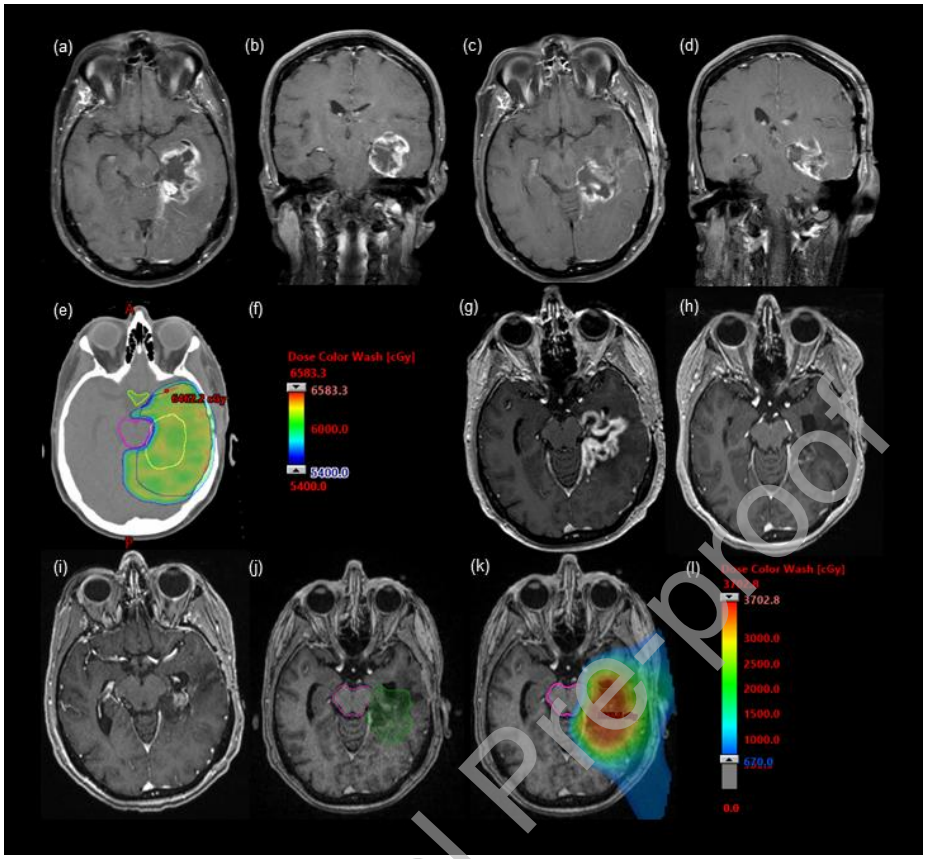
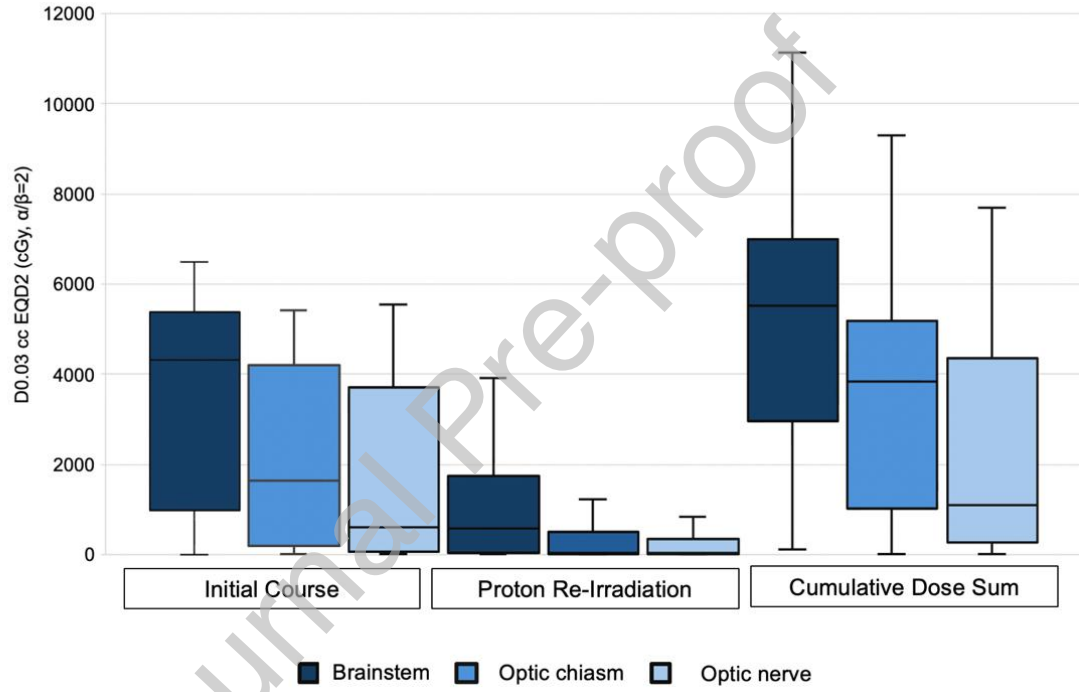


Figure 1. A representative example of proton reirradiation. A 68-year-old female was diagnosed with an IDH wildtype, MGMT unmethylated left temporal glioblastoma (a, b) for which she underwent maximal safe resection (c, d). The patient received adjuvant radiation therapy (60 Gy in 30 fractions) with concurrent temozolomide. Shown in (e) is gross tumor volume, based on contrast enhancing disease at the time of simulation (yellow); clinical target volume based on the T2 flair sequence (blue); isodose line set at 54 Gy (f), the tolerance of the nearby critical organs at risk (brainstem (pink), optic chiasm (green). The brainstem D0.03cc (EQD2, $\alpha/\beta = 2$ Gy) was 5166 cGy. Two months after completion of radiation, she had progression on MRI (g). She continued adjuvant temozolomide and initiated bevacizumab with excellent response (h) which she remained on for 9 months prior to further progression on MRI (i). Her case was discussed at multidisciplinary tumor board, and consensus recommendation was for

reirradiation. She received 35 Gy in 10 fractions of proton radiation with bevacizumab (j-l). Shown in (j) is planning target volume (green), nearby critical organs at risk (brainstem (pink) with T1 post contrast MRI fused. Dose carving around the brainstem (k), accomplished with proton therapy, allowed for a low contribution from course 2 (l); (EQD2, α/β = 2 Gy) D0.03 cc of 2180 cGy. Cumulative dose (EQD2, α/β = 2 Gy) to the brainstem across both courses was 8790 cGy. The patient did not develop any Grade 3 or greater toxicities from treatment.

A



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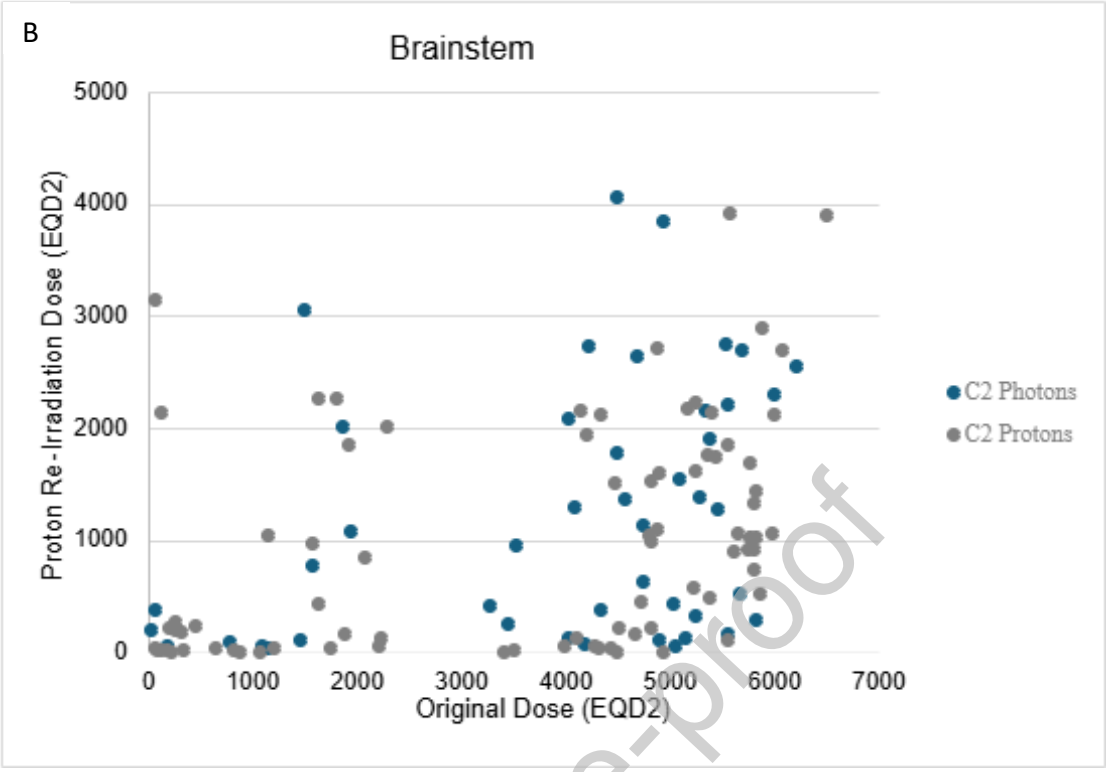

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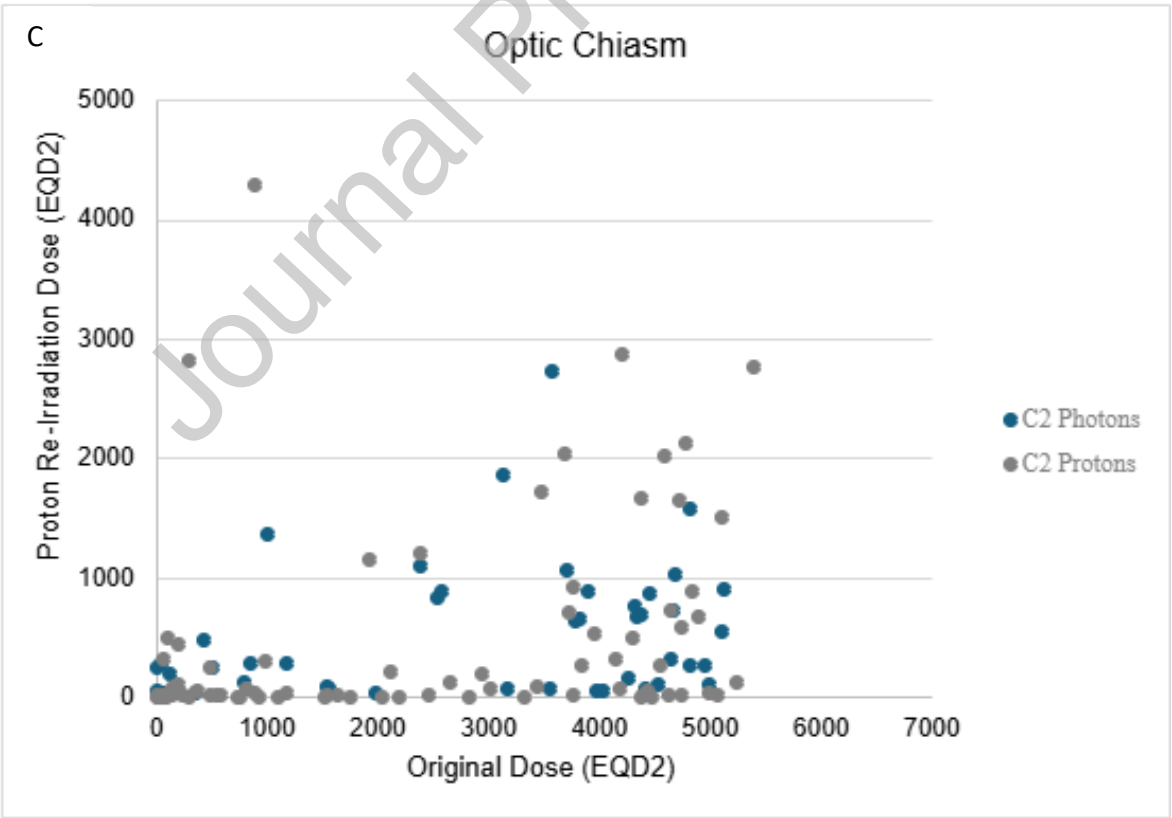


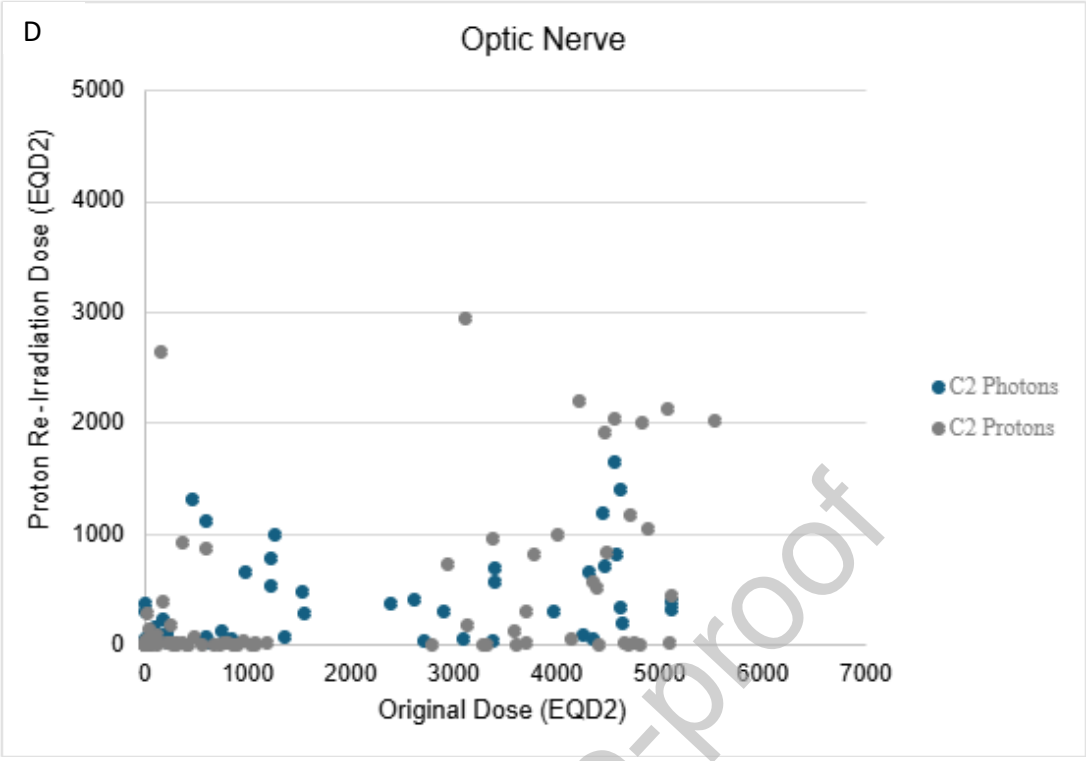


Figure 2. (A) D0.03 cc EQD2 doses to critical organs at risk for initial course of radiation, proton reirradiation, and composite plan sums. Boxes represent the interquartile range with the median indicated by the horizontal line. Whiskers denote the range. While proton reirradiation contributes modest additional dose, composite median EQD2 values remain within conventionally accepted tolerance ranges across structures. Scatter plots depict maximum dose to 0.03 cc (D0.03cc) to critical organs at risk including the brainstem (B), optic chiasm (C), and optic nerve (D) during reirradiation as a function of original treatment dose. Photon dosimetric data are represented by the blue points, while proton data are represented in gray. All doses are reported as equivalent dose in 2 Gy fractions (EQD2; α/β = 2 Gy, cGy).

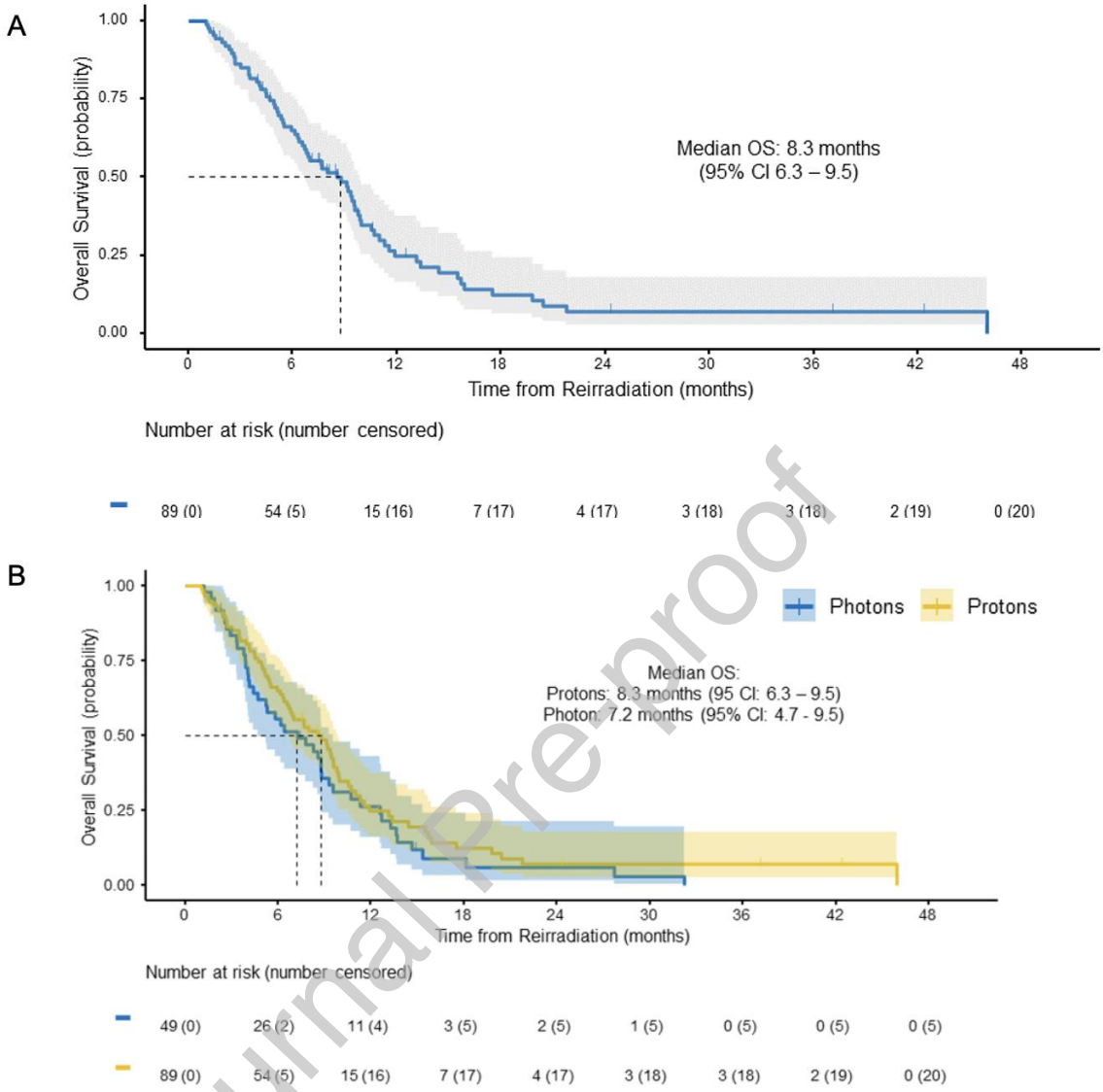
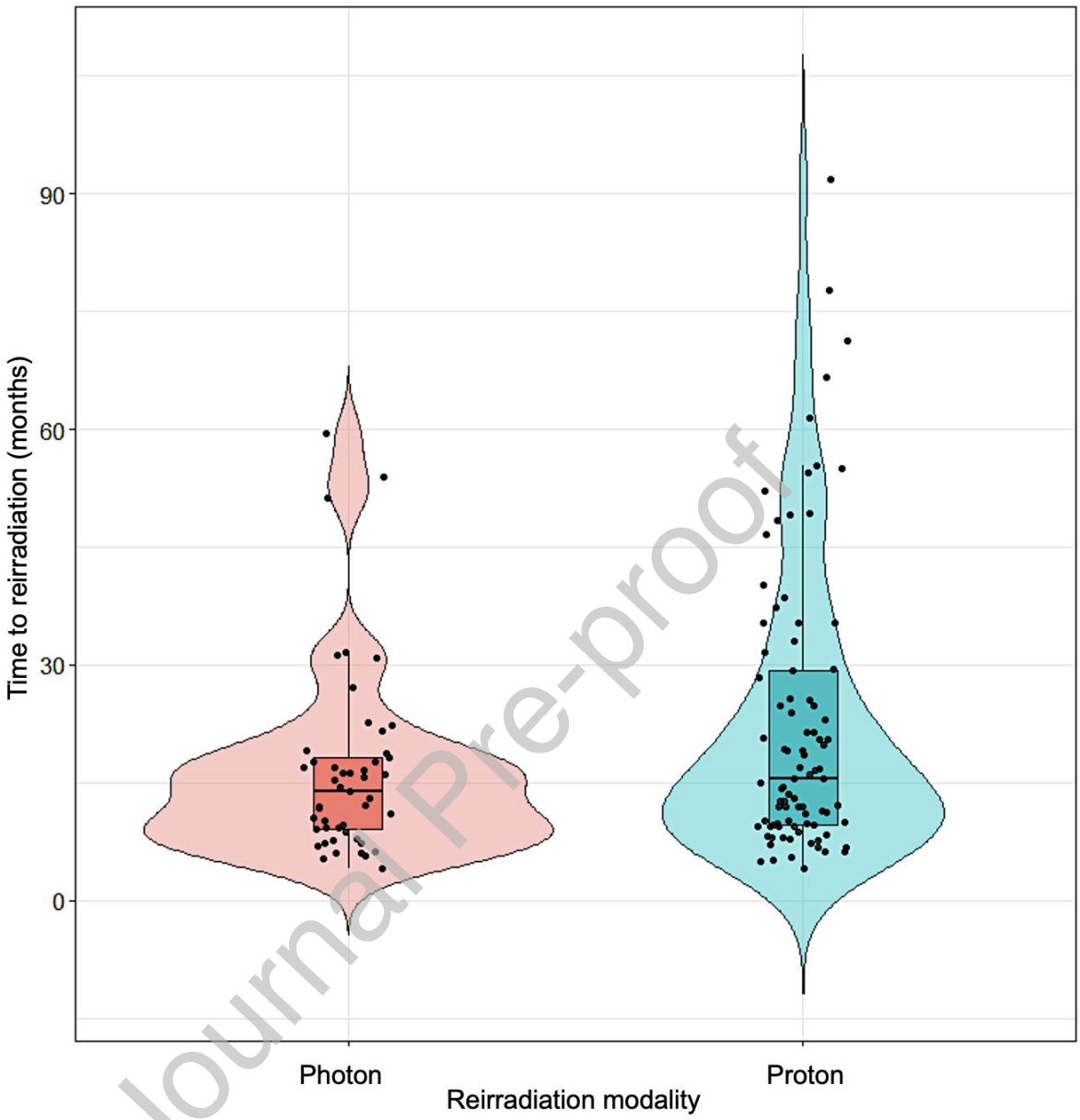


Figure 3. A) Overall Survival after proton reirradiation. B) Overall survival after proton versus photon reirradiation. The tick marks represent censored events. The tables below each graph represent the number at risk at each time point.

4A



4B

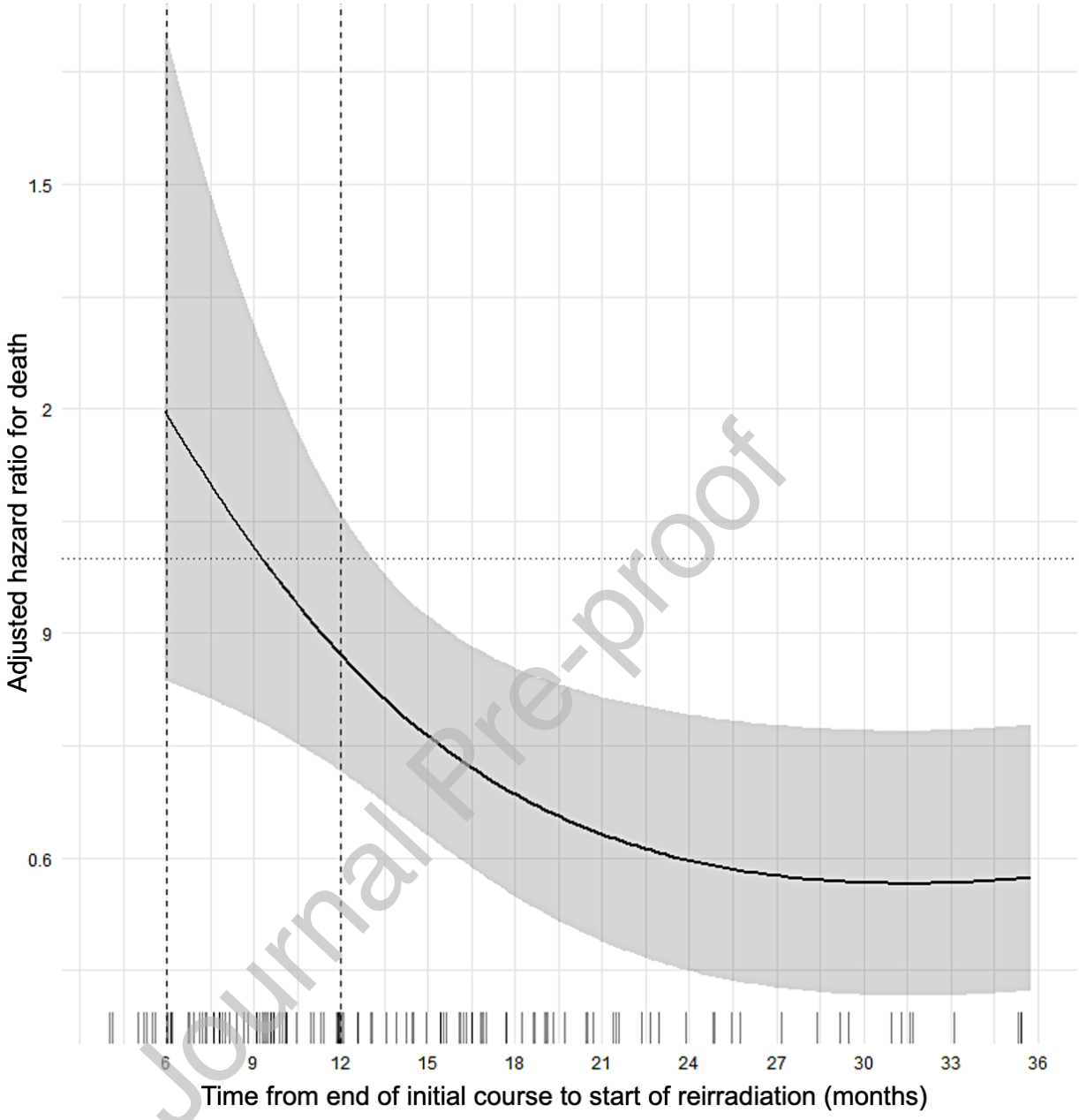


Figure 4. A) Violin plot for the time to reirradiation stratified by treatment modality. The median and interquartile range are represented by the dox and whisker plot. Individual patients are represented as jitter dots on the graph. Density of jitter plots are correlated with the width of each violin. Outliers are those beyond the whisker plots. B) Adjusted restricted cubic spline. The dashed line represents 12 months as a cut off between early reirradiation (before 12 months)

compared with after 12 months. The gray bar represents the 95% confidence interval. The p-value for non-linearity = 0.020.

Supplemental Figure 1. Diagram depicting study population per STROBE guidelines.

Table 1. Baseline Patient and Treatment Characteristics

Variable	N=89[1]
Patient Characteristics	
Median age (years, range)	58 (48-68)
Sex	
Male	54 (61%)
Female	35 (39%)
KPS	
90-100	10 (11%)
70-80	51 (57%)
≤60	28 (31%)
Tumor Characteristics	
Tissue Diagnosis	
MSR	83 (93%)
Biopsy	6 (7%)
IDH Status	
Wildtype	89 (100%)
Mutant	0 (0%)
MGMT	
Unmethylated	55 (62%)
Methylated	28 (31%)
Unknown	6 (7%)
Treatment Characteristics	
Initial Radiation Course: Dose	
60Gy/30 fx	68 (76%)
40Gy/15 fx	12 (13%)
Initial Radiation Course: Modality	
Photon	33 (37%)
Proton	32 (35%)
Mixed	12 (14%)
TTF	
Yes	51 (57%)

No	38 (43%)
Reirradiation Characteristics	
Reresection	43 (48%)
Concurrent Systemic	72 (81%)
Bevicazumab	47 (65%)
Temozolamide	23 (32%)
Pembrolizumab	9 (13%)
Reirradiation Definition	
ESTRO Type 1	85 (96%)
ESTRO Type 2	4 (4%)

[1]Median (IQR) or Frequency (%)
Abbreviations: KPS = Karnofsky Performance Status, MSR = Maximal Safe Resection, IDH = Isocitrate Dehydrogenase, MGMT = O^6-methylguanine DNA methyltransferase, Gy= Gray, Fx= fraction, ESTRO= European Society for Radiotherapy and Oncology. ESTRO Type 1= direct overlap of initial and re-treatment volume. ESTRO Type 2= no direct overlap of initial volume and re-treatment volume.

Table 2. Univariable and Multivariable Cox Regression Analysis for Overall Survival

	Univariable		Multivariable	
Variable	HR[1] (95% CI[2])	P-value	HR (95% CI)	P-value
Age (continuous, per year)	**1.03 (1.01-1.06)**	**0.003**	**1.02 (1.00-1.05)**	**0.045**
Sex (ref: Male)			-	-
Female	0.81 (0.50-1.32)	0.406	-	-
Concurrent TMZ (ref: No)			-	-
Yes	1.01 (0.4-2.5)	0.988	-	-
Original Tissue Diagnosis (ref: resection)				
Biopsy	1.49 (0.64-3.49)	0.353	-	-
MGMT (ref: unmethylated)				
Methylated	0.59 (0.34-1.01)	0.055	-	-
Unknown	0.84 (0.30-2.37)	0.742	-	-
C1 Dose				
60Gy/ 30 fx	0.88 (0.41-1.88)	0.741		
40Gy/ 15 fx	**2.29 (1.18-4.43)**	**0.015**	1.84 (0.89-3.78)	0.099
C1 Modality				
Photon	1.23 (0.74-2.07)	0.427		
Proton	1.22 (0.58-2.56)	0.595		

KPS at reRT (ref: 90-100)				
KPS 70-80	0.79 (0.37-1.71)	0.555	-	-
KPS ≤60	2.23 (0.99-5.03)	0.053	2.26 (0.98-5.17)	0.055
Reresection (ref: no)			-	-
Yes	0.75 (0.46-1.21)	0.241		
C2 GTV less than median GTV (ccs)	0.88 (0.54-1.44)	0.614		

[1] HR = Hazard Ratio, [2]CI= Confidence Interval. Abbreviations: Ref = reference group, TMZ= temozolomide, MGMT = O^6-methylguanine DNA methyltransferase, C1= Course 1, ReRT = Reirradiation, KPS = Karnofsky Performance Status, C2= Course 2, GTV= Gross tumor volume. Bolded values are significant ($p<0.05$).