

High-dose Salvage Re-irradiation in Recurrent/progressive Adult Diffuse High-Grade Glioma: Development of a Novel Prognostic Scoring System

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Abstract

Purpose: Over the past two decades, high-dose salvage re-irradiation (re-RT) has been used increasingly in the multimodality management of adults with recurrent/progressive high-grade glioma (HGG). Several factors that determine outcomes following re-RT have been incorporated into prognostic models to guide patient selection. We aimed to develop a novel four-tiered prognostic model incorporating relevant molecular markers from our single-institutional cohort of patients treated with high-dose salvage re-RT for recurrent/progressive HGG.

Methods: Various patient, disease, and treatment-related factors impacting upon survival following salvage re-RT were identified through univariate analysis. Each of these prognostic factors was further subdivided and assigned scores of 0 (good-risk), 1 (intermediate-risk), or 2 (high-risk) to create a composite prognostic scoring system. Scores from individual prognostic factors were added to derive the cumulative score (ranging from 0 to 16), with increasing scores indicating worsening prognosis.

Results: A total of 111 patients with recurrent/progressive HGG treated with salvage high-dose re-RT constituted the study dataset. We could assign patients into four prognostic subgroups (A=15 patients, score 0-3); (B=50 patients, score 4-7); (C=33 patients, score 8-10); and (D=13 patients, score 11-16) with completely non-overlapping survival curves suggesting the good discriminatory ability of the proposed prognostic scoring system. Post-re-RT survival was significantly higher in Group A compared to groups B, C, and D, respectively (stratified log-rank p-value <0.0001).

Conclusion: A novel four-tiered prognostic scoring system incorporating traditional factors as well as relevant molecular markers is proposed for selecting patients appropriately for high-dose salvage re-RT.

Introduction

Diffuse gliomas constitute the most common malignant primary tumors of the brain and central nervous system (CNS) in adults [1]. Traditionally, adult diffuse gliomas were classified morphologically by the World Health Organization (WHO) into astrocytoma, oligodendroglioma, or mixed oligoastrocytoma and histologically into Grades II, III or IV [2]. Lower histological grade (WHO grade II-III) and oligodendroglial morphology are typically associated with indolent behaviour compared to glioblastoma (WHO grade IV), which runs an aggressive clinical course with a median survival of 15–18 months [3, 4]. Newer biological insights have changed our fundamental understanding of the etiopathogenesis of adult diffuse gliomas leading to their revised histo-molecular classification based on isocitrate dehydrogenase (IDH) mutation and 1p/19q co-deletion in the 2016 update of the WHO classification of CNS tumors [5]. Epigenetic silencing of methyl-guanine-DNA-methyl transferase (MGMT) gene promoter by methylation has shown to be a predictive biomarker of response to temozolomide (TMZ)-based chemotherapy as well as an independent prognostic factor in patients with newly-diagnosed glioblastoma [3, 6]. The contemporary standard of care for adult diffuse gliomas is maximal safe surgical resection followed by fractionated external beam radiotherapy (RT) with concurrent and/or adjuvant TMZ chemotherapy [7, 8] depending on

histology and molecular markers. Despite aggressive multimodality therapy at initial diagnosis, almost all patients with diffuse gliomas recur and progress over time with transformation from lower grade to a higher grade and increasing biological aggressiveness. Local recurrence remains the predominant pattern of failure, with over 80% of patients relapsing in and around the index tumor-bed [9].

Currently, there is no defined 'standard-of-care therapy for recurrent/progressive adult diffuse high-grade glioma (HGG), which continues to be managed empirically based on personal, institutional, and physician biases and preferences [10, 11]. Salvage therapy at relapse is generally individualised and ranges from best supportive care, surgical re-excision, re-irradiation (re-RT) with or without systemic therapies (chemotherapy and/or targeted therapy) either alone or in combination to participation in prospective clinical trials of investigational new agents [12]. Over the past two decades, highly conformal salvage re-RT of the recurrent planning target volume (PTV) avoiding spillage into adjacent organs-at-risk (OARs) by integrating modern high-precision techniques with fundamental radiobiological principles has provided encouraging survival outcomes with an acceptable quality of life (QOL) in recurrent/progressive HGG [13–15]. Clinical outcomes of salvage therapy in recurrent/progressive HGG can be quite heterogeneous based on patient, disease, and treatment-related characteristics. Several factors that determine outcomes following re-RT have been identified and incorporated into prognostic models or indices to guide case selection in the salvage setting [16–21]. Some of these factors like age, Karnofsky performance status (KPS), histological grade, and disease-free interval (DFI) are common to many indices, while re-excision, dose and volume of re-RT have been proposed as additional factors. In contemporary neuro-oncology practice, the biology of adult diffuse glioma is increasingly defined by the molecular landscape [22, 23]. However, till date, none of the prognostic indices have incorporated molecular markers such as IDH mutation, 1p/19q co-deletion, and/or MGMT methylation for prognostication in recurrent/progressive HGG. We have recently reported encouraging survival outcomes in our single-institutional cohort [24] of patients treated with high-dose salvage re-RT as part of aggressive multimodality management for recurrent/progressive HGG. Herein, we present a novel four-tiered prognostic model incorporating various patient, disease, and treatment-related factors, including relevant molecular markers from the same dataset.

Materials And Methods

The present study cohort comprised of adults with diffuse glioma that had documented recurrent/progressive disease after adequate upfront treatment at initial diagnosis and were treated with conventionally fractionated high-dose salvage re-RT (Fig. 1) at an academic neuro-oncology unit of a comprehensive tertiary-care cancer centre. Details regarding patient selection, salvage therapy, response assessment and prognostic factors for survival have been published previously [24]. DFI was defined as the time interval between the starting of the initial course of RT (RT1) and the date of first documented clinico-radiological evidence of recurrence/progression. The linear quadratic (LQ) model was used to provide estimates of biologically effective dose (BED) of irradiation using an α/β value of 2 for nervous tissues [25]. This was converted into an equivalent dose in 2Gy fractions (EQD2) for each course of RT, which were summated to derive cumulative BED and EQD2, without correcting for assumed recovery

during the interval between the two courses of RT. Efficacy of re-RT was assessed in terms of progression-free survival (PFS) and overall survival (OS) after re-RT. Post-re-RT PFS was defined as the time interval from initiation of re-RT till further documented clinico-radiological progression, death, or last follow-up, while post-re-RT OS was calculated from the start of re-RT till death from any cause or last follow-up. All time-to-event outcomes were analyzed using the product-limit method of Kaplan-Meier, expressed as 1-year estimates and median survival with 95% confidence intervals (CI), and compared using the log-rank test. Any p-value < 0.05 considered as statistically significant. All key prognostic factors (patient, disease, and treatment-related) identified on univariate analysis as above were further subdivided and assigned scores of 0 (good-risk), 1 (intermediate-risk), or 2 (high-risk) to create a prognostic scoring system (Table 1). These factors included age and KPS at re-RT, histological subtype, grade at initial diagnosis, time interval between two courses of RT, disease biology (IDH-mutation and MGMT gene promoter methylation), re-excision, histological grade at recurrence/progression, dose at re-RT and use of salvage systemic therapy. Scores from individual prognostic factors were added to derive the cumulative score (ranging from 0 to 16), with increasing scores indicating worsening prognosis. Due to retrospective nature of our study with less than minimal risk to participants, our Institutional Ethics Committee (IEC) granted waiver of consent.

Table 1
Prognostic Glioma Re-irradiation Scoring System

| <i>Prognostic factor(s)</i> | <i>Category</i> | <i>Points</i> |
|--------------------------------------------------|----------------------------------------------|----------------------|
| Age at re-RT | > 50 years | 2 |
| | 40–50 years | 1 |
| | < 40 years | 0 |
| KPS at re-RT | ≤ 70 | 1 |
| | ≥ 80 | 0 |
| Histological/morphological subtype | Astrocytoma | 1 |
| | Oligodendroglioma | 0 |
| WHO histological grade at initial diagnosis | Grade IV | 2 |
| | Grade III | 1 |
| | Grade II | 0 |
| Time interval between both courses of RT | < 3 years | 2 |
| | 3–6 years | 1 |
| | > 6 years | 0 |
| Molecular markers | Both IDH-wild type and unmethylated MGMT | 2 |
| | | 1 |
| | Anything in between including unknown status | 0 |
| | Both IDH-mutant and methylated MGMT | |
| Re-excision | None | 2 |
| | STR | 1 |
| | NTR/GTR | 0 |
| WHO histological grade at recurrence/progression | Grade IV | 1 |
| | Grade III | 0 |

Cumulative scores range from 0–16 (higher scores indicate worse prognosis)

re-RT = re-irradiation, KPS = Karnofsky performance status, WHO = World Health Organization, RT = radiotherapy, IDH = isocitrate dehydrogenase, MGMT = O⁶methylguanine DNA methyl transferase, STR = subtotal resection, NTR = near total resection, GTR = gross total resection, EQD2 = equivalent dose in 2Gy fractions

| <i>Prognostic factor(s)</i> | <i>Category</i> | <i>Points</i> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------|
| Dose at re-RT | EQD2 < 50Gy | 1 |
| | EQD2 ≥ 50Gy | 0 |
| Salvage systemic therapy | None | 2 |
| | Pre-re-RT | 1 |
| | Post-re-RT | 0 |
| <i>Cumulative scores range from 0–16 (higher scores indicate worse prognosis)</i> | | |
| <i>re-RT = re-irradiation, KPS = Karnofsky performance status, WHO = World Health Organization, RT = radiotherapy, IDH = isocitrate dehydrogenase, MGMT = O⁶ methylguanine DNA methyl transferase, STR = subtotal resection, NTR = near total resection, GTR = gross total resection, EQD2 = equivalent dose in 2Gy fractions</i> | | |

Results

Between 2010 till 2019, a total of 111 patients with recurrent/progressive HGG were treated at our institute with salvage high-dose re-RT and constitute the present study cohort. Patient, disease, and treatment characteristics at initial diagnosis and at recurrence/progression have been described in detail previously [24]. Briefly, the median age of the study cohort at initial diagnosis and recurrence/progression was 36 years (range 18–56 years) and 40 years (range 21–60 years), respectively. All patients had undergone debulking surgery at index diagnosis, followed by adjuvant RT (median EQD2 of 56.4Gy). Fifty-six (48%) patients had also received chemotherapy either concurrently with RT or as adjuvant after RT or both. The vast majority (91%) of patients underwent salvage surgery at recurrence/progression, and almost half of them received systemic chemotherapy prior to re-RT. The median time to recurrence/progression was 4.3 years with an inter-quartile range (IQR) of 2.3–7.4 years, while the median time to re-RT was 4.8 years (IQR = 3.6–7.9 years). Re-RT was delivered using intensity-modulated radiation therapy (IMRT) to a dose range of 45-59.4Gy at 1.8Gy per fraction over 5-6.5 weeks for a cumulative median EQD2 of 104.3Gy (IQR = 102.6-109.4Gy). Concurrent chemotherapy, most commonly TMZ, was administered in two-thirds of patients. At a post-re-RT median follow-up of 14 months (IQR = 8–20 months), the 1-year Kaplan-Meier estimates of PFS and OS following re-RT were 42.8% (95%CI: 33.4–52.2%) and 61.8% (95%CI: 52.6–71.0%) respectively, yielding a median post-re-RT PFS of 10.9 months (95%CI: 9.8–12.1 months) and median post-re-RT OS of 14.4 months (95%CI: 12.9–16.2 months) respectively.

Prognostic scoring system: We could assign patients into four prognostic subgroups (A = 15 patients, score 0–3); (B = 50 patients, score 4–7); (C = 33 patients, score 8–10); and (D = 13 patients, score 11–16) respectively with completely non-overlapping survival curves from our dataset suggesting the good discriminatory ability of the proposed prognostic scoring system (Fig. 2). Median post-re-RT PFS was significantly higher (stratified log-rank p-value < 0.0001) in Group A (20.4 months, 95%CI: 9.9–30.9

months) compared to Group B (12.7 months, 95%CI: 9.1–16.2 months); Group C (9.4 months, 95%CI: 6.6–12.2 months); and Group D (4.2 months, 95%CI: 2.9–5.6 months) respectively (Table 2). Similarly, median post-re-RT OS was significantly higher (stratified log-rank p-value < 0.0001) for patients in Group A (23.1 months, 95%CI: 20.2–25.2 months) compared to Group B (17.5 months, 95%CI: 14.1–20.9 months); Group C (11.8 months, 95%CI: 9.4–14.1 months) and Group D (6.3 months, 95%CI: 3.9–8.8 months) respectively (Table 2). Based on the above findings, patients in subgroup D may not derive significant benefit from high-dose re-RT and could be considered as candidates suitable for systemic salvage therapy or best supportive care alone.

Table 2
Post-re-irradiation survival outcomes in the entire study cohort (N = 111)

| Prognostic group* (Cumulative score) | No. of patients | Median post-re-RT PFS (95%CI) in months | Median post-re-RT OS (95%CI) in months |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------------------------------|-----------------------------------------------|
| A (0–3 points) | 15 | 20.4 (9.9–30.9) months | 23.1 (20.2–25.2) months |
| B (4–7 points) | 50 | 12.7 (9.1–16.2) months | 17.5 (14.1–20.9) months |
| C (8–10 points) | 33 | 9.4 (6.6–12.2) months | 11.8 (9.4–14.1) months |
| D (11–16 points) | 13 | 4.2 (2.9–5.6) months | 6.3 (3.9–8.8) months |
| <i>No = number, re-RT = re-irradiation, PFS = progression-free survival, CI = confidence interval, OS = overall survival</i> | | | |
| <i>*Stratified log-rank p-value was statistically significant (p < 0.0001) across the four prognostic subgroups (A to D) both for post-re-RT PFS as well as post-re-RT OS</i> | | | |

Discussion

The lack of a universally acceptable ‘standard-of-care’ makes salvage therapy difficult and challenging in recurrent/progressive HGG. Any benefit of salvage therapies must be carefully balanced against potential treatment-related toxicity and harmful impact on health-related QOL. Despite significant advances, outcomes after aggressive salvage multimodality therapy in recurrent/progressive HGG remain dismal, with median survivals ranging around 9–12 months only [13, 14]. Selection of local treatment for recurrent/progressive HGG, particularly glioblastoma, largely depends upon remaining life expectancy, patterns of failure, assessment of prognostic factors, and anticipated toxicity [26, 27]. The narrow therapeutic index of CNS re-RT is often influenced by multiple factors such as age, RT parameters (dose per fraction, dose, and volume of each course), cumulative total dose, and time-interval between both courses [25]. However, clinical outcomes following re-RT vary significantly, suggesting the need for careful and judicious case selection.

Over the years, researchers have combined several known prognostic factors in recurrent/progressive HGG to devise various prognostic models and indices [28]. Younger age, good performance status, oligodendroglial morphology, and lower histologic grade (WHO grade III) of glioma at recurrence/progression are accepted favorable prognostic factors. Other factors such as volume of recurrent disease, re-excision, the time interval between two courses RT, and use of systemic therapy have been studied somewhat inconsistently. In a single-institution cohort of 233 adult patients of recurrent/progressive diffuse glioma treated between 1990 and 2010 with fractionated salvage re-RT (median dose of 36Gy, 2Gy per fraction) at Heidelberg [16], age, histological grade, and DFI were combined into a scoring system to assign patients into four prognostic classes clearly separating them with excellent (0 point, n = 62); good (1 point, n = 51); moderate (2 points, n = 41); and poor (3–4 points, n = 89) survival after re-RT. Muller et al. [17] adapted an existing recursive partitioning analysis (RPA) classification in recurrent HGG using age (< 50 versus \geq 50 years), WHO histologic grade (III vs IV), and KPS (\geq 70 versus < 70 or \geq 90 versus < 90) to construct their prognostic model in 117 patients of recurrent/progressive HGG treated with re-operation and dendritic cell vaccination and classified them into three classes as I (good prognosis), II (intermediate prognosis), and III (poor prognosis) respectively. They further validated this model in 165 patients of recurrent/progressive HGG treated with re-operation and re-RT, suggesting its applicability independent of the applied therapeutic strategy. The Heidelberg or Combs score was validated in an independent dataset of 209 patients treated at another centre in Germany and modified subsequently to include re-excision, KPS, and tumor volume at recurrence. This new Combs prognostic score [18] could range from 0–7 and classified patients into four prognostic subgroups as a = 0–1 points; b = 2–3 points; c = 4–5 points; and d = 6–7 points (higher scores indicating worse prognosis) with non-overlapping survival. Both the original Combs score and its modification were further validated in an independent multi-centre cohort [21, 29], confirming their prognostic utility in clinical practice. Researchers in Germany further pooled data in a multivariable model from 353 patients of recurrent/progressive HGG treated with salvage re-RT at various institutions to develop a novel re-irradiation risk score (RRRS) based on a linear combination of initial histology, clinical performance status, and age into three prognostic groups which successfully predicted post-re-RT survival outcomes [20] and later found validation in another independent multicenter cohort [30]. In parallel, researchers from the National Institutes of Health developed a prognostic scoring system [19] in their small cohort of 31 patients with recurrent/progressive HGG treated with re-RT using three sub-scores defined as independent factors (age, KPS, WHO grade, presence of symptoms); target control (tumor size, tumor location, presence of diffuse disease); and anticipated risk of toxicity risk (OAR location, OAR dose distribution, DFI). A score of 1–3 per variable was assigned in each category, and each of the three sub-scores were calculated by adding all relevant factors in that category. Patients were assigned to good, intermediate, or poor-risk groups within each of three sub-scores (Score 1, Score 2, and Score 3, respectively), with a higher cumulative score indicating a better prognosis. Furthermore, scores from independent factors (Score 1) and target control (Score 2) were combined to classify patients into two prognostic classes as poor prognosis (Score 1 + Score 2 \leq 15 points) and good prognosis, respectively (Score 1 + Score 2 > 15 points) respectively. The most recent prognostic score was developed by researchers from the University of California San Francisco in their single-institution cohort [21] of 116

patients of recurrent/progressive HGG treated between 2008 to 2016 with salvage stereotactic radiosurgery (SRS) delivering $\geq 12\text{Gy}$ in a single-fraction, fractionated SRS (5-8Gy x 3–5 fractions), hypofractionation (2.25-4Gy per fraction) or standard fractionation (1.8-2Gy per fraction). Three factors, i.e., KPS ≤ 80 (2 points), time to initial progression ≤ 16 months (2 points), and BED < 40 for SRS and < 45 for non-SRS (3 points), were combined into a scoring system that classified patients into three prognostic classes (A = 0 point; B = 2–4 points; and C = 5–7 points) predicting freedom from progression accurately. A similar analysis for survival combined age ≥ 55 years (1 point), time to initial progression ≤ 12 months (1 point), and PTV $> 6\text{cc}$ for SRS and $> 130\text{cc}$ for non-SRS (2 points) into a scoring system classifying patients into three prognostic classes (A = 0 point; B = 1–2 points; and C = 3–4 points) with non-overlapping survival.

Two desirable attributes to judge the performance of any prognostic model include discrimination and calibration. Discrimination reflects the ability of a model to characterize and segregate subsets of patients with differing prognoses. Calibration refers to the predictive ability of a prognostic model when tested in another cohort. Our prognostic scoring system demonstrates good discriminatory ability as reflected in the non-overlapping survival curves between Groups A to D (with highly significant p-values) that can help in selecting patients for salvage re-RT at recurrence/progression after adequate upfront treatment in adults with diffuse glioma. We will test its calibration in a subsequent validation study in a non-overlapping cohort of patients with recurrent/progressive HGG. To the best of our knowledge, this is the first prognostic model incorporating molecular biology of adult diffuse glioma along with other traditionally used prognostic factors to guide case selection.

Strength And Limitations

We present the first prognostic scoring system that includes relevant molecular markers done routinely on resected tumor tissues in adult diffuse glioma in contemporary neuro-oncologic practice, which should be considered a major strength of our study. This scoring system is based on a single institutional cohort of patients with recurrent/progressive HGG treated fairly uniformly with high-dose salvage re-RT as part of aggressive multimodality therapy at relapse. Apart from the relevant molecular markers, other key clinicopathological factors were also included in our scoring system leading to more statistical granularity and methodologic robustness. Despite the aforesaid strengths, few caveats and limitations remain. The retrospective design of our study makes it susceptible to inherent biases that could confound the analysis and interpretation of results. There was a clear imbalance in the number of patients in each prognostic subgroup (lesser representation in the best and worst subgroups - A and D respectively) which could be a potential source of bias during survival analysis. Our scoring system includes 10 key prognostic factors, some of which may not be readily available, posing difficulties in universal adoption. We could not include the volume of recurrent tumor (PTV at re-irradiation) in our scoring system due to the lack of availability of such information in many patients; it is likely that patients with lower disease burden at relapse would fare better than large volume recurrences. We combined IDH-mutation and MGMT methylation into a single parameter to reflect disease biology; in lower grade (grades II-III) gliomas, there is substantial collinearity between IDH-mutation and MGMT methylation, which could

confound statistical analysis and interpretation. Although we characterized gliomas by morphology (oligodendroglial vs astrocytic), we did not include 1p/19q co-deletion as one of the molecular markers associated with favorable outcomes in our score. Finally, we did not attempt any validation of the proposed prognostic scoring system in an independent, non-overlapping cohort.

Conclusions

Patients with recurrent/progressive HGG continue to be treated with aggressive salvage multimodality therapy based on personal, physician, and institutional biases and preferences. A novel four-tiered prognostic scoring system incorporating traditional factors as well as relevant molecular markers is proposed for selecting patients appropriately for high-dose salvage re-RT that needs calibration and validation testing in an independent non-overlapping cohort.

Declarations

Compliance with Ethical Standards:

Funding: No funding support was involved in the study.

Conflict of Interest: None of the authors have any conflicts of interest to declare.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Ethics Committee (IEC) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Given the retrospective nature of the study with less than minimal risk to participants, IEC granted waiver of consent.

Data availability: Data from this analysis can be made available on reasonable request.

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Author contributions:

Tejpal Gupta: Conceptualization, design, methodology, study conduct, and final manuscript Madan Maitre: Data extraction, analysis, and writing - original draft Priyamvada Maitre: Data extraction and analysis Abhishek Chatterji: Statistical analysis and literature review Archya Dasgupta: Literature review and editing of draft manuscript Aliasgar Moiyadi: Study conduct Prakash Shetty: Study conduct Sridhar Epari: Study conduct and editing of draft manuscript Ayushi Sahay: Study conduct Vijay Patil: Study conduct and literature review Jayant Sastri Goda1: Study conduct and data extraction Rakesh Jalali: Study design, conduct, and editing of draft manuscript

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Figures

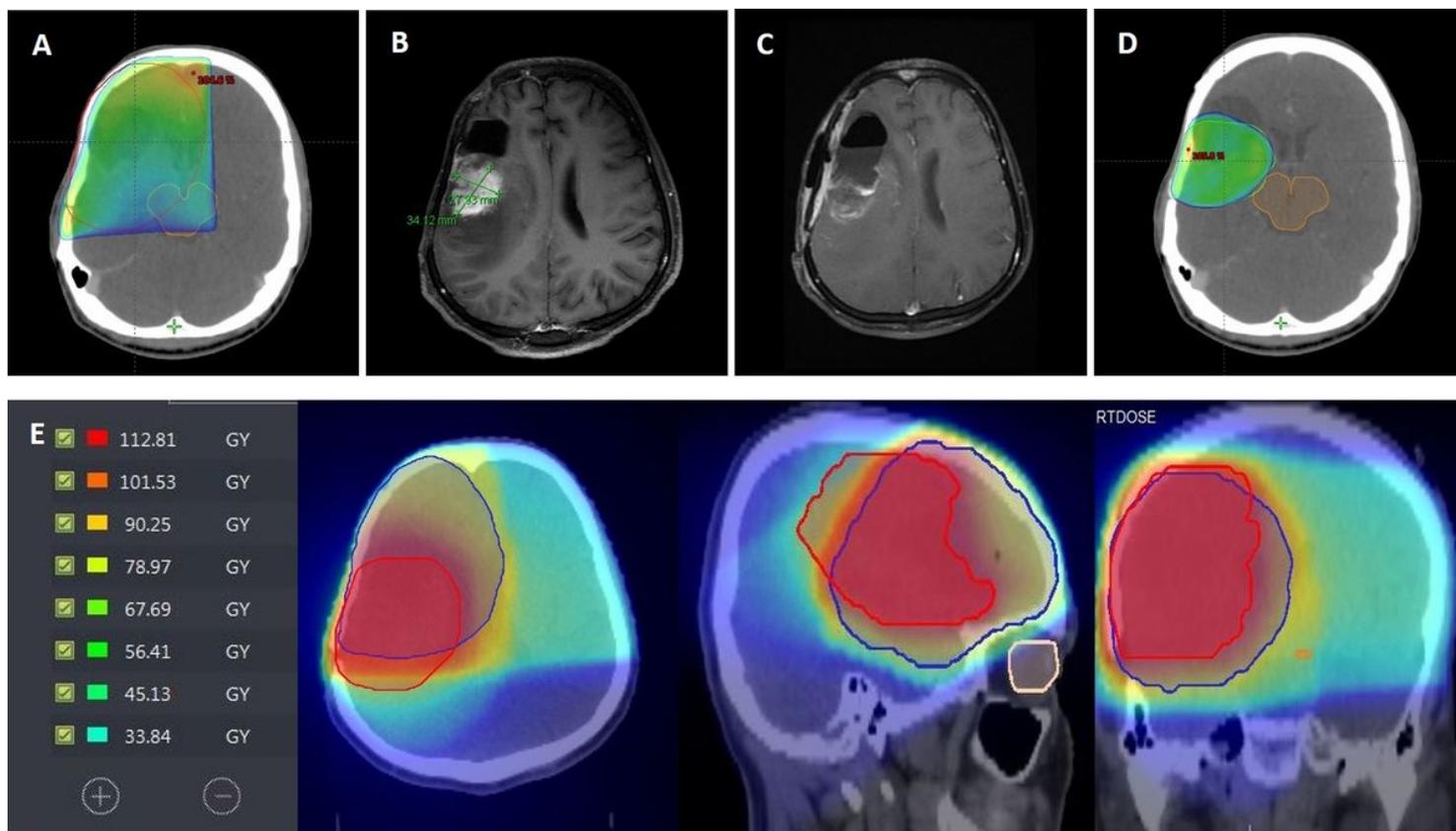


Figure 1

Axial planning computed tomography scans of a patient with right frontal anaplastic astrocytoma treated using three-dimensional conformal radiotherapy plus concurrent and adjuvant temozolomide chemotherapy at initial diagnosis. Note good coverage of the index tumor-bed by 95% dose-wash of the prescribed dose of 59.4Gy in 33 fractions (A). Three years later, the patient developed local recurrence just posterior to the resection cavity as seen on axial post-contrast T1-weighted magnetic resonance imaging (B) for which he underwent near total re-excision (C) proven to be glioblastoma on biopsy. Patient underwent salvage re-irradiation using intensity modulated radiation therapy (IMRT) to a dose of 50.4Gy/28 fractions with 95% dose-wash covering the recurrent tumor-bed (D). Composite dose-wash after summing both plans showing absolute total dose (in Gy) to the different regions of the brain in axial, sagittal, and coronal planes (E). Note cumulative doses of 100-112Gy to the recurrent tumor-bed

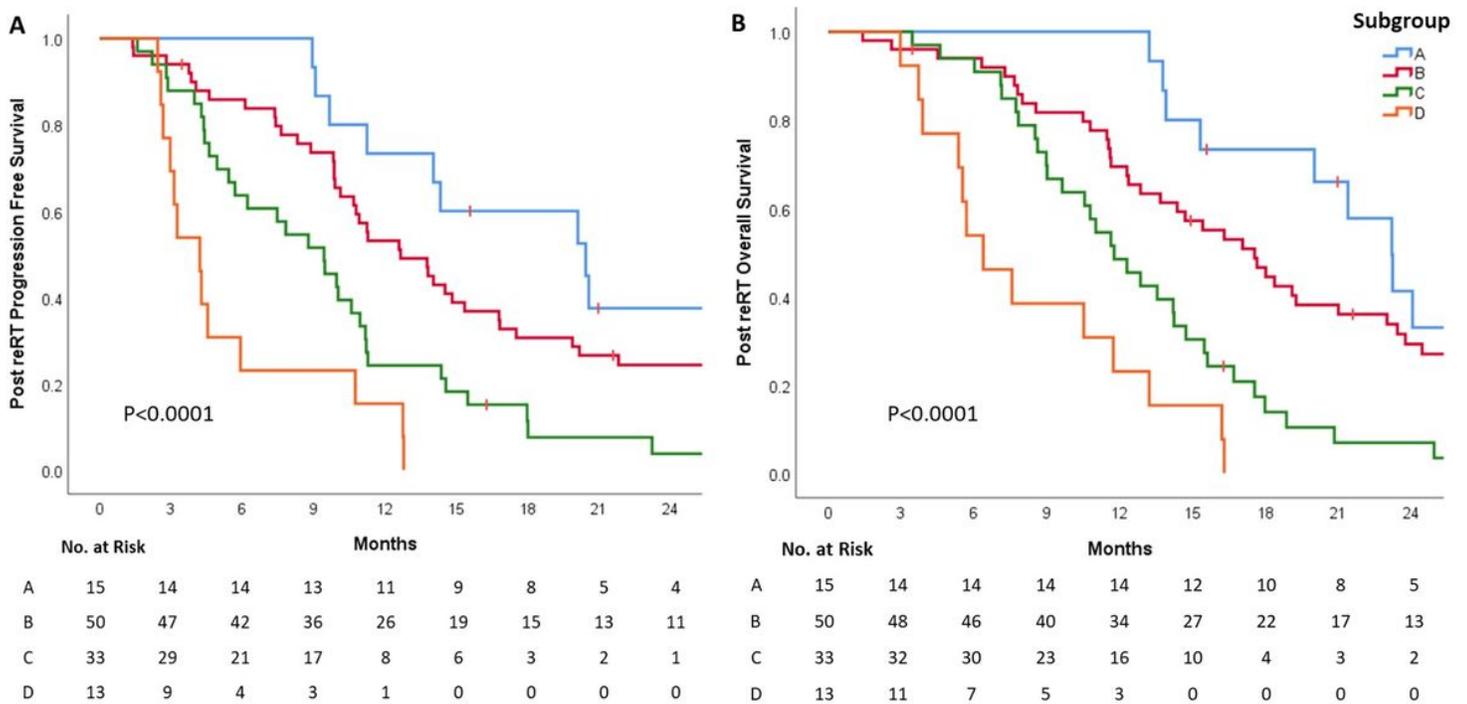


Figure 2

Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) stratified by the novel four-tiered prognostic scoring system. Note the completely non-overlapping survival curves suggesting good discriminatory ability of the proposed model