Title

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Journal

Neuro-oncology practice, 6(5)

ISSN

2054-2577

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Publication Date

2019-09-01

DOI

10.1093/nop/npz017

Peer reviewed

Neuro-Oncology Practice
6(5), 364–374, 2019 | doi:10.1093/nop/npz017 | Advance Access date 12 April 2019

Reirradiation of recurrent high-grade glioma and development of prognostic scores for progression and survival

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Abstract

Background. Optimal techniques and patient selection for salvage reirradiation of high-grade glioma (HGG) are unclear. In this study, we identify prognostic factors for freedom from progression (FFP) and overall survival (OS) after reirradiation, risk factors for high-grade toxicity, and validate clinical prognostic scores.

Methods. A total of 116 patients evaluated between 2000 and 2018 received reirradiation for HGG (99 WHO grade IV, 17 WHO grade III). Median time to first progression after initial therapy was 10.6 months. Salvage therapies before reirradiation included surgery (31%) and systemic therapy (41%). Sixty-five patients (56%) received single-fraction stereotactic radiosurgery (SRS) as reirradiation. The median biologically effective dose (BED) was 47.25 Gy, and the median planning target volume (PTV) was 4.8 cc for SRS and 95.0 cc for non-SRS treatments. Systemic therapy was given concurrently to 52% and adjuvantly to 74% of patients.

Results. Median FFP was 4.9 months, and median OS was 11.0 months. Significant multivariable prognostic factors for FFP were performance status, time to initial progression, and BED; for OS they were age, time to initial progression, and PTV volume at recurrence. High-grade toxicity was correlated to PTV size at recurrence. Three-level prognostic scores were generated for FFP and OS, with cross-validated receiver operating characteristic area under the curve (AUC) of 0.640 and 0.687, respectively.

Conclusions. Clinical variables at the time of reirradiation for HGG can be used to prognosticate FFP and OS.

Keywords

glioblastoma | glioma | prognosis | recurrence | reirradiation

High-grade gliomas (HGGs) are the most common primary malignancy of the brain in adults.[1] The standard of care initial therapy is surgery followed by fractionated radiation therapy with concurrent and adjuvant temozolomide. Despite this, approximately 40% of WHO grade III gliomas and 90% of WHO grade IV gliomas (glioblastomas) will progress within 2 years.[2–4] The management of HGG after initial recurrence is less well defined. Options include surgery, radiation therapy, systemic therapy, or some combination thereof.[5] Multiple studies have suggested reirradiation combined with bevacizumab may have a survival advantage over bevacizumab alone.[6,7]

This hypothesis is currently being tested in the randomized phase II trial RTOG 1205 (NCT01730950). Reirradiation can be performed using fractionated radiation therapy,[8] hypofractionated radiation,[9] high dose-per-fraction stereotactic radiation,[10] or single-fraction stereotactic radiosurgery (SRS).[11] Larger tumors are typically treated with more fractionated regimens, but whether any specific dose, technique, or fractionation improves disease outcomes is unclear. Expert consensus supports reirradiation for patients with good performance status, small tumors, and a long period from prior radiation.[12] However, no prospective evidence definitively supports reirradiation in any subgroup.[13]

In this situation, retrospective studies and prognostic scores can assist with patient selection. The most notable prognostic scoring system, the "Combs Score" and its modified version, the "New Combs Score," were derived to predict overall survival (OS) after reirradiation; these scores include tumor grade, age at reirradiation, time from initial therapy, KPS, tumor volume, and surgery before radiation.[8,14] Other reported prognostic features include reirradiation dose,[15,16] use of salvage chemotherapy,[16,17] extent of resection,[17,18] methylguanine-DNA methyltransferase (MGMT) promoter methylation status,[19] and radiographic response.[20–22] There is inconsistency about which features are prognostic for survival and how to quantify them. Few series examine prognostic factors for time to progression, which may be equally important for treatment decisions.[19–23] Toxicity is also a consideration, and some series have reported higher toxicity rates with larger target volumes and higher doses.[24,25]

The goal of the current study was to assess prognostic factors in a large independent cohort of HGG patients reirradiated using a variety of doses and techniques. We use these results to generate prognostic scores for freedom from progression (FFP) and OS after reirradiation. Our results may aid patient selection for reirradiation and stratification for prospective studies.

Materials and Methods

Eligibility and Data Collection

A retrospective institutional database was searched between 2000 and 2018 for patients with an initial diagnosis of HGG (WHO grade III or IV), who received radiation therapy with initial treatment and received at least 1 additional course of radiation therapy after progression. Use of retrospectively collected data for research was approved by the institutional IRB. Demographic, pathologic, and clinical data were collected including sex, age, KPS, initial tumor grade, initial tumor location and diameter, isocitrate dehydrogenase (*IDH*) mutation status, and MGMT promoter methylation status. Anaplastic glioma subtype (astrocytoma vs oligodendroglioma) was not examined because of the change in WHO classification in 2016; however, the tumor grading system was unchanged. Data collected on initial therapy included extent of resection, radiation therapy technique/dose/fractionation, and concurrent and/or adjuvant systemic therapies.

Time to initial progression was defined as the interval between completing postoperative radiation therapy and MRI showing tumor progression. MRIs were obtained regularly for surveillance, typically every 2-3 months or as clinically indicated. As a retrospective study there was no uniform definition of progressive disease, although the MacDonald criteria and the updated RANO (Response Assessment in Neuro-Oncology) criteria were used during this period.[26,27] For the purposes of this study, progression was indicated by consensus from the treating physicians, initiation of new tumor-directed therapy, and/or pathologic confirmation of progressive disease.

Data collected about progression and reirradiation included salvage surgeries and systemic therapies, time from initial radiation to reirradiation, age and KPS at reirradiation, reirradiation technique/dose/fractionation, reirradiation target volume, and concurrent and/or adjuvant systemic therapies. Biologically effective dose (BED) of reirradiation was calculated using $\alpha/\beta = 10$ for tumor effects (BED10) and $\alpha/\beta = 3$ for late effects (BED3).

Reirradiation Techniques

Reirradiation was performed using a variety of techniques. Gamma Knife radiosurgery (GK; Elekta) used a stereotactic frame and MRI-guided treatment planning with no planning target volume (PTV) margin from the lesion defined by contrast-enhanced T1-weighted MRI. The CyberKnife system (Accuray) was also used for either single or multifraction radiosurgery. Fractionated reirradiation was performed using linear accelerators with fixed-angle, arcs, or helical techniques, using a 2-5 mm PTV margin. Fractionated treatments variably targeted the contrast-enhancing lesion only or included the larger T2–fluid-attenuated inversion recovery signal abnormality. Reirradiation dose/fractionations were organized into 4 groups for this study: "stereotactic radiosurgery (SRS)" (single fraction, ≥12 Gy); "fractionated SRS (FSRS)" (5 to 8 Gy per fraction); "hypofractionation" (2.25 to 4 Gy per fraction); and "standard fractionation" (1.8 to 2 Gy per fraction).

Study Endpoints

Primary endpoints were FFP and OS from the completion of reirradiation. FFP was defined as lacking radiographic progression on MRI, censored at last MRI without evidence of progression. Patient records were cross-referenced to the University of California San Francisco (UCSF) Cancer Registry. FFP (progression is an event but not death) was chosen rather than the combined endpoint progression-free survival (PFS; progression and death are events). In our data, OS follow-up from the cancer registry was more complete than progression follow-up from clinical records, thus PFS would overestimate the time to progression but not contribute any information about survival. Toxicity was graded using Common Toxicity Criteria (v4). Given the uncertainties in identifying lower-grade toxicities retrospectively, only toxicities of grade 3 or higher (grade 3+) were recorded. Toxicities were defined as acute (≤90 days from end of reirradiation) or late (>90 days).

Table 1 Clinical and Treatment Features at Reirradiation With Univariable Regression Results

Characteristic	Number (Percentage) or Median (Minimum, IQR, Maximum)	Univariate Cox Analysis: FFP		Univariate Cox Analysis: OS	
		Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Pathologic Grade					
Grade 4	99 (85%)	Ref		Ref	
Grade 3	17 (15%)	0.54 (0.28-1.03)	.06	0.62 (0.35-1.13)	.12
IDH Mutation					
No	39 (91%)	Ref		Ref	
Yes	4 (9%)	0.90 (0.31-2.59)	.84	1.45 (0.50-4.18)	.49
Data not available	73	–	–	–	–
MGMT Promoter Methylation					
No	14 (50%)	Ref		Ref	
Yes	14 (50%)	0.79 (0.33-1.87)	.59	0.88 (0.38-2.03)	.76
Data not available	88	–	–	–	–
Months to Initial Progression	10.6 (0.2, 5.1-22.5, 150.6)	0.99 (0.98-1.0)	.05	0.99 (0.97-1.0)	.02
Months From First Progression to Reirradiation	1.9 (0.0, 0.7-5.6, 83.1)	1.0 (0.98-1.02)	.98	1.01 (0.99-1.02)	.39
Months from Initial Radiation to Reirradiation	14.4 (0.7, 8.7-31.5, 152.3)	0.99 (0.98-1.00)	.09	0.99 (0.98-1.00)	.08
Salvage Surgery before Reirradiation					
Any	44 (38%)	1.06 (0.68-1.65)	.81	1.28 (0.85-1.92)	.24
Number if Any	1 (1, 1-1, 3)	1.16 (0.67-1.96)	.58	0.69 (0.41-1.17)	.17
Salvage Systemic Therapy Before Reirradiation					
Any	47 (41%)	1.33 (0.86-2.06)	.20	1.17 (0.85-1.75)	.43
Number if Any	1 (1, 1-2, 4)	0.80 (0.41-1.58)	.50	1.73 (1.07-2.82)	.03
Age at Reirradiation	51 (21, 43-61, 77)	1.00 (0.98-1.02)	.99	1.01 (0.99-1.03)	.08
KPS at Reirradiation	80 (40, 70-90, 100)	0.98 (0.96-1.00)	.04	0.98 (0.96-0.99)	.01
Data not available	10	–	–	–	–
Reirradiation Fractionation Group					
Standard Fractionation	8 (7%)	1.19 (0.51-2.81)	.68	1.36 (0.62-3.00)	.44
Hypofractionation	33 (28%)	0.83 (0.51-1.36)	.47	1.29 (0.82-2.03)	.27
FSRS	10 (9%)	0.82 (0.38-1.74)	.61	0.83 (0.41-1.68)	.61
SRS	65 (56%)	Ref	Ref	Ref	Ref
Reirradiation Prescription Dose (Gy, BED10)					
Non-SRS	47.25 (15.00, 42.12-51.0, 123.80)	1.00 (0.98-1.01)	.09	1.00 (0.99-1.02)	.64
SRS	48.12 (26.40, 41.60-50.40, 60.0)	0.94 (0.90-0.99)	.03	0.96 (0.93-1.01)	.10
Reirradiation Prescription Dose (Gy, BED3)					
Non-SRS	75.83 (26.67, 63.0-90.0, 169.20)	1.00 (0.99-1.01)	.86	1.00 (0.99-1.01)	.99
SRS	119.60 (60.0, 101.33-126.0, 153.30)	0.98 (0.96-1.00)	.03	0.99 (0.97-1.00)	.09
Reirradiation PTV Volume (cc)					
Non-SRS	95.0 (0.9, 43.3-250.9, 783.6)	1.00 (0.99-1.00)	.21	1.003 (1.0-1.004)	.01
SRS	4.8 (0.3, 2.7-7.8, 17.1)	1.05 (0.98-1.12)	.15	1.08 (1.01-1.15)	.03
Data not available	42	–	–	–	–

Table 1 Continued

Characteristic	Number (Percentage) or Median (Minimum, IQR, Maximum)	Univariate Cox Analysis: FFP		Univariate Cox Analysis: OS	
		Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Reirradiation Maximum Dose (Percentage of Prescription)					
Non-SRS	108% (103%, 105%-118%, 200%)	2.11 (0.54-8.28)	.29	1.58 (0.36-6.89)	.54
SRS	200% (164%, 200%-200%, 228%)	2.61 (0.01-13.0)	.59	2.04 (0.07-57.2)	.68
Data not available	37	–	–	–	–
Reirradiation Target Number	1 (1, 1-1, 5)	1.46 (0.94-2.27)	.10	1.28 (0.92-1.79)	.15
Concurrent Systemic Agents With Reirradiation[a]					
Any	58 (52%)	1.03 (0.67-1.58)	.91	1.13 (0.75-1.68)	.56
Temozolomide/Lomustine	38 (35%)	0.79 (0.50-1.27)	.34	0.96 (0.63-1.47)	.86
Bevacizumab	18 (17%)	1.21 (0.69-2.12)	.51	1.47 (0.86-2.49)	.16
Data not available	7	–	–	–	–
Adjuvant Systemic Agents With Reirradiation[a]					
Any	80 (78%)	0.93 (0.53-1.64)	.79	0.92 (0.56-1.51)	.73
Temozolomide/Lomustine	49 (48%)	0.70 (0.45-1.10)	.12	0.81 (0.54-1.23)	.33
Bevacizumab	31 (30%)	1.07 (0.67-1.72)	.78	1.33 (0.85-2.10)	.21
Data not available	13	–	–	–	–

Abbreviations: BED, biologically effective dose; FFP, freedom from progression; FSRS, fractionated stereotactic radiosurgery; Gy, gray, radiation dose; IQR, interquartile range; MGMT, methylguanine-DNA methyltransferase; OS, overall survival; PTV, planning target volume; SRS, stereotactic radiosurgery.
Percentages reflect proportion of patients with available information.
[a]Sum greater than 100% because of classification overlap.

Statistical Analysis

FFP and OS were estimated using the Kaplan–Meier method. Potential prognostic variables (Table 1) were evaluated using univariable Cox regression analysis. Because radiation dose and PTV are prescribed differently for SRS treatments, these variables were analyzed separately for SRS/non-SRS treatments. Variables with Cox regression P value < .1 were analyzed for covariance with respect to each other using Kruskal–Wallis, Spearman, and Fisher exact tests, and 1 of each pair of highly covariant variables (P < .001) were selected for exclusion. Continuous variables were then dichotomized using receiver operating characteristic (ROC) analysis around thresholds best determining the lowest quartile of FFP or OS. Multivariable regression was then performed with backward selection using the Akaike Information Criterion or until each variable was significant at P < .05. Separate multivariable models were developed for FFP and OS. Final thresholds and models were assessed using ten-fold cross-validation over 10 000 random samples. New thresholds and models were constructed for every training set and applied to the test set to obtain ROC area under the curve (AUC) integrated from 0 to 60 months at 1-month intervals.[28] Prognostic scores were created using significant multivariable factors, weighted by rounded hazard ratios and combining scores with hazard ratios within 95% confidence interval (95% CI) into classes. Patients with missing data for the significant multivariable factors were excluded from the creation of the corresponding prognostic scores; the groups used for the prognostic score creation were compared to the full group to check for selection bias. Other survival scores were tested on our data for comparison using ten-fold cross-validation.[8,14] Proportional hazard assumptions for prognostic scores were tested using Schoenfeld residuals. Statistical analyses were performed in R using RStudio v.1.1 (RStudio, Inc).

Results

Patient Characteristics and Initial Therapy

Clinical features of the 116 eligible patients are summarized in Table 2. Ninety-nine patients (85%) had glioblastoma (grade IV) with initial diagnosis; the remainder had anaplastic glioma (grade III). Using the WHO classification in effect at the time of treatment, 10 were described as anaplastic astrocytoma and 7 as anaplastic oligoastrocytoma. Ninety-six patients (83%) had their diagnosis confirmed by internal pathology review. For initial radiation, 72 patients (62%) received 60 Gy in 30 daily fractions, and 109 patients (94%) received 58-62 Gy in 1.8-2.0 Gy fractions. For initial

Table 2 Initial Therapy Clinical and Treatment Features

Characteristic	Number (Percentage) or Median (Min, IQR, Max)
Sex	
Female	50 (43%)
Male	66 (57%)
Age at Initial Diagnosis	49 (20, 38-60, 77)
Initial Tumor Laterality	
Left	50 (47%)
Right	52 (49%)
Bilateral	3 (3%)
Unpaired structure	2 (2%)
Data not available	9
Initial Tumor Location(s)[a]	
Frontal	47 (44%)
Temporal	38 (36%)
Parietal	20 (19%)
Occipital	9 (9%)
Thalamus	5 (5%)
Cerebellum	4 (4%)
Brainstem	3 (3%)
Data not available	10
Initial Tumor Diameter (cm)	4.2 (1.8, 3.2-5.8, 7.5)
Data not available	49
KPS at Diagnosis	
100%	4 (4%)
90%	38 (37%)
80%	47 (45%)
70%	12 (12%)
≤60%	3 (3%)
Data not available	12
Initial Surgery Extent of Resection	
Gross total resection	45 (41%)
Near total resection	13 (12%)
Subtotal resection	42 (38%)
Biopsy	11 (10%)
Data not available	5
Initial Radiation Dose (Gy, BED10)	72 (57.5, 72-72, 130.3)
Data not available	11
Concurrent Systemic Agents With Initial Radiation[a]	
Temozolomide	103 (94%)
Bevacizumab	3 (3%)
Clinical trial agent	19 (17%)
Carmustine	1 (1%)
None	4 (4%)
Data not available	6
Adjuvant Systemic Agents With Initial Radiation[a]	
Temozolomide	101 (92%)
Bevacizumab	11 (10%)
Clinical trial agent	33 (30%)
None	6 (5%)
Data not available	6

Abbreviations: BED, biologically effective dose; Gy, gray, radiation dose; IQR, interquartile range; Max, maximum; Min, minimum. Percentages reflect proportion of patients with available information.
[a]Sum greater than 100% because of classification overlap.

systemic therapy, 109 patients (94%) received concurrent temozolomide and 107 patients (92%) received adjuvant temozolomide.

First Progression and Salvage Therapy

The median time to first progression after initial therapy was 10.6 months (interquartile range [IQR] 5.1-22.6) (Table 1). After first progression, 62 patients (53%) had at least 1 other salvage therapy (surgery or systemic therapy) before reirradiation. The median time from first progression to reirradiation was 1.9 months (IQR 0.7-5.6), and the median time from the end of initial radiation to beginning of reirradiation was 14.4 months (IQR 8.7-31.5). Various radiation dose/fractionations were prescribed for reirradiation, but the most common were 60 Gy in 30 fractions for standard fractionation (4/8 patients), 35 Gy in 10 fractions for hypofractionation (16/33 patients), 30 Gy in 5 fractions for FSRS (5/10 patients), and 18 Gy single fraction for SRS (20/65 patients). Review of the 8 patients in the standard fractionation group indicated that at least 5 were recurrences out of the previously irradiated field, allowing for higher reirradiation doses.

Toxicity of Reirradiation

Of 116 patients, 115 completed the prescribed reirradiation, with 1 patient stopping by choice without toxicity. For 97 patients with toxicity data before 90 days, 4 had grade 3+ acute toxicity: 2 cases of cerebral edema requiring steroids, and 2 cases of hydrocephalus requiring shunting. For 55 patients with toxicity data after 90 days, 5 had grade 3+ late toxicity: 1 case of status epilepticus at 5 months, 3 cases of symptomatic radiation necrosis at 6.7 to 8.9 months, and 1 case of severe cognitive decline at 11 months, all without evidence of glioma progression. There were no grade 5 toxicity events. Cumulative incidence of any grade 3+ toxicity was 3% at 3 months, 6% at 6 months, and 18% at 12 months from reirradiation. Cumulative incidence of symptomatic radiation necrosis was 7% at 12 months. Grade 3+ toxicity was significantly correlated with larger

reirradiation PTV volumes, with 12 months' cumulative incidence of 6% for patients with PTV volume less than median (10 cc), and 30% for patients with PTV greater than 10 cc ($P = .02$, hazard ratio 7.04). There were no associations seen between toxicity and reirradiation BED3, cumulative BED3, dose/fractionation group, time from initial radiation to reirradiation, KPS at reirradiation, or use of any concurrent/adjuvant systemic therapy. After first reirradiation, 23 patients had at least 1 additional course of reirradiation. Thirteen patients had salvage surgery after reirradiation, and 51 had additional systemic therapy after reirradiation.

FFP After Reirradiation and Prognostic Score

Median FFP after reirradiation was 4.9 months (95% CI 4.2-7.0), with 6-months FFP 46%, 12-months FFP 20%, and 24-months FFP 7% (Fig. 1). By univariable regression, FFP was significantly associated with grade, KPS at reirradiation, time to initial progression, and reirradiation BED10 (Table 1). Time from initial radiation to reirradiation met criteria for multivariable model inclusion; however, this was excluded for being covariant with time to initial progression ($P = 2E–16$). ROC analysis identified KPS ≤ 80%, time to initial progression ≤16 months, and BED10 < 40 Gy for SRS and BED10 < 45 Gy for non-SRS treatments as thresholds (Table 3). Multivariable model backward selection excluded grade before all remaining variables were significant. The final multivariable model included data from 94 patients with 80 events, with overall likelihood ratio of 28.8 ($P = .001$). Twenty-two patients were omitted from the full group because of missing KPS and progression follow-up data; however, there were no significant differences between the subset used for the prognostic score and the full group on any considered variable (Supplemental Table S1). Variables from the final model were combined into a progression prognostic score, summed with 2 points for KPS ≤ 80%, 2 points for time to initial progression ≤16 months, and 3 points for BED10 < 40 Gy for SRS or <45 Gy for non-SRS treatments (Table 4). Progression Class A included 12 patients with 0 points, Class B included 63 patients with 2-4 points, and Class C included 19 patients with 5-7 points. With Class A as a reference, hazard ratio for Class B was 2.34 (95% CI 1.10-5.00, $P = .028$) and Class C was 7.29 (95% CI 3.05-17.39, $P < .001$). Median FFP for Class A was 13.3 months (95% CI 4.9-NA), for Class B was 6.1 months (95% CI 4.7-7.4), and for Class C was 2.1 months (95% CI 1.3-3.5) (Fig. 2).

OS After Reirradiation and Prognostic Score

Median OS after reirradiation was 11.0 months (95% CI 7.9-13.2), with 6-month OS 73%, 12-month OS 45%, and 24-month OS 19% (Fig. 1). By univariable regression using continuous variables, OS was significantly correlated with KPS at reirradiation, time to initial progression, and PTV volume (Table 1). Also meeting criteria for multivariable model inclusion were age at time of reirradiation and number of systemic therapies received before reirradiation. Number of systemic therapies was excluded for being positively covariant with PTV volume ($P = .0004$). ROC analysis identified KPS ≤ 80%, age at reirradiation ≥55 years, time to initial progression ≤12 months, and PTV volume > 6.4 cc for SRS and >131 cc for non-SRS treatments as thresholds (Table 3). Multivariable model backward selection excluded KPS before all remaining variables were significant. The final multivariable model included data from 74 patients with 64 events with overall likelihood ratio of 29.8 ($P = .001$). Forty-two patients were omitted from the full group because of missing PTV volume data; however, there were no significant differences between the subset used for the prognostic score and the full group on any considered variable (Supplemental Table S1). Variables from the final model were combined into a survival prognostic score, summed with 1 point for age at reirradiation ≥55 years, 1 point for time to initial progression ≤12 months, and 2 points for PTV > 6.4 cc for SRS or

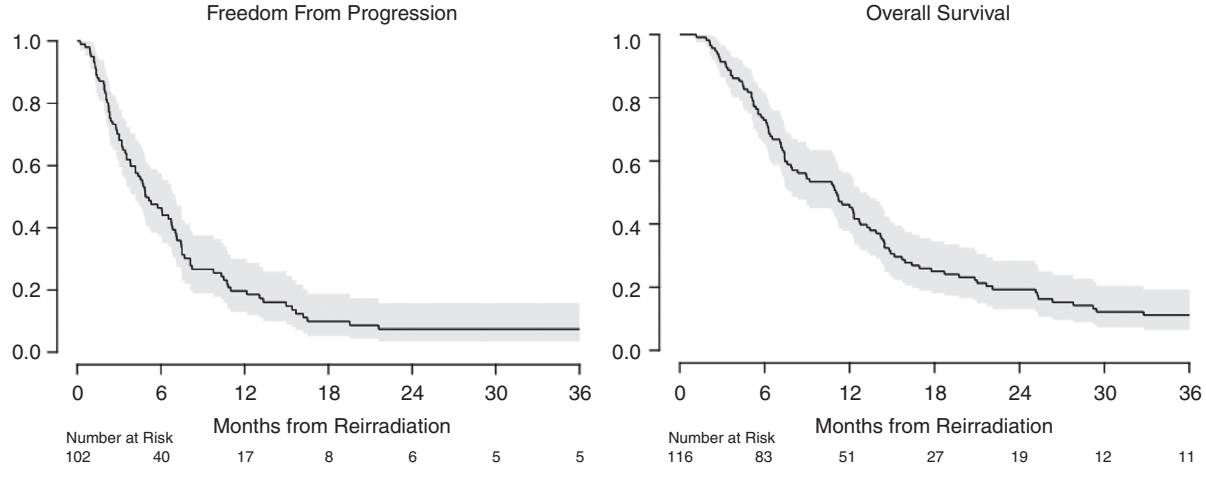

Fig. 1 Kaplan–Meier curves for freedom from progression and overall survival for all patients. Shaded bands are 95% confidence intervals.

Table 3 Dichotomized Variables for Prognostic Models With Outcomes and Univariable and Multivariable Cox Regression Results

		Univariate Regression		Multivariable Regression	
Variable (n)	Median Months (95% CI)	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Freedom From Progression					
All Patients (116)	4.9 (4.2-7.0)				
KPS at Reirradiation (106)					
90%-100% (39)	6.7 (4.7-13.3)	Ref		Ref	
≤80% (67)	4.2 (3.2-6.1)	1.95 (1.21-3.15)	.0065	1.77 (1.09-2.89)	.022
Time to Initial Progression (116)					
>16 months (36)	7.5 (6.5-15.7)	Ref		Ref	
≤16 months (80)	3.8 (3.0-6.1)	2.17 (1.34-3.53)	.0017	1.93 (1.14-3.27)	.014
Reirradiation Dose (BED10) (116)					
≥40 Gy (SRS) or ≥45 Gy (non-SRS) (91)	6.1 (4.9-7.7)	Ref		Ref	
<40 Gy (SRS) or <45 Gy (non-SRS) (25)	2.2 (1.4-3.5)	3.30 (1.98-5.49)	<.0001	2.96 (1.75-4.99)	<.0001
Overall Survival					
All patients (116)	11.0 (7.9-13.2)				
Age at Reirradiation (116)					
<55 (69)	12.3 (9.2-14.4)	Ref		Ref	
≥55 (47)	7.9 (6.1-12.3)	1.67 (1.12-2.49)	.012	1.73 (1.04-2.89)	.036
Time to Initial Progression (116)					
>12 months	13.4 (11.5-20.8)	Ref		Ref	
≤12 months	7.4 (6.2-11.2)	1.68 (1.13-2.49)	.0098	2.33 (1.37-3.97)	.0020
Reirradiation PTV Volume (74)					
≤6.4 cc (SRS) or ≤131 cc (non-SRS)	14.2 (11.2-17.8)	Ref		Ref	
>6.4 cc (SRS) or >131 cc (non-SRS)	6.2 (4.8-8.3)	2.89 (1.71-4.91)	<.0001	3.85 (2.19-6.75)	<.0001

Abbreviations: BED, biologically effective dose; Gy, gray, radiation dose; PTV, planning target volume; SRS, stereotactic radiosurgery.

>131 cc for non-SRS treatments (Table 4). Survival Class A included 12 patients with 0 points, Class B included 37 patients with 1-2 points, and Class C included 20 patients with 3-4 points. With Class A as a reference, hazard ratio for Class B was 2.89 (95% CI 1.27-6.58, $P = .012$) and Class C was 10.99 (4.32-27.99, $P < .001$). Median OS for Class A was 25.1 months (95% CI 12.0-NA), for Class B was 13.4 months (95% CI 11.0-15.9), and for Class C was 5.1 months (95% CI 3.6-7.2) (Fig. 2). There was significant correlation between FFP prognostic score and OS prognostic score classification ($P = .002$), with 89% of patients in OS Class A also in FFP Class A, 46% of patients in OS Class B also in FFP Class B, and 48% of patients in OS Class C also in FFP Class C.

Prognostic Scores for Progression and Survival After Reirradiation

The Combs prognostic scores were also tested on our data. The original Combs score for OS is based on WHO grade, time from initial radiation to reirradiation, and age.[8] Class A included 8 patients with 1 point, Class B included 34 patients with 2 points, and Class C included 74 patients with 3-4 points (Table 4). A regression model based on the Combs score was significant with overall likelihood ratio of 7.2 ($P = .03$). With Class A as a reference, hazard ratio for Class B was 1.85 (95% CI 0.76-4.49, $P = .17$) and Class C was 2.60 (95% CI 1.11-6.10, $P = .03$) (Fig. 2). Median survival for Class A was 20.7 months (95% CI 7.9-NA), for Class B was 11.5 months (95% CI 8.3-21.0), and for Class C was 9.0 months (95% CI 7.2-13.2). We also tested the New Combs score, which adds re-resection, KPS, and tumor volume.[14] This score divides patients into 4 classes, although the lowest risk class (Class A, 0-1 points) represented only 1 patient in our series and was censored. The remaining 3 classes included 18 patients in Class B with 2-3 points, 45 patients in Class C with 4-5 points, and 7 patients in Class D with 6-7 points. A regression model based on the New Combs score was significant with overall likelihood ratio 9.4 ($P = .002$). With Class B as a reference, hazard ratio for Class C was 2.40 (95% CI 1.24-4.61, $P = .009$) and Class D was 3.62 (95% CI 1.40-9.39, $P = .008$). Median survival for Class B was 14.8 months (95% CI 12.3-NA), for Class C was 9.2 months (95% CI 7.4-14.2), and for Class D was 6.2 months (95% CI 5.5-NA) (Fig. 2).

Prognostic accuracy of the scores was assessed using ten-fold cross-validated AUC. The mean AUC of the progression score was 0.640 (95% CI 0.604-0.676) and of the

Table 4 Prognostic Scores

UCSF Progression Score	UCSF Survival Score	Combs Survival Score	New Combs Survival Score
KPS ≤ 80% = +2 points	Age ≥ 55 = +1 point	WHO Grade III = 1 point	Combs Survival Score plus:
Time to Initial Progression ≤ 16	Time to Initial Progression ≤ 12	WHO Grade IV = 2 points	No re-resection = +1 point
Months = +2 points	months = +1 point	Age ≥ 50 = +1 point	KPS < 80% = +1 point
BED10 < 40 Gy (SRS) or BED10 < 45 Gy (non-SRS) = +3 points	PTV > 6 cc (SRS) or PTV > 130 cc (non-SRS) = +2 points	Time from initial radiation to reirradiation ≤ 12 months = +1 point	PTV > 47 cc = +1 point
Class A = 0 points (13%)	Class A = 0 points (17%)	Class A = 1 point (7%)	Class A = 0-1 points (1%)
Class B = 2-4 points (67%)	Class B = 1-2 points (53%)	Class B = 2 points (29%)	Class B = 2-3 points (26%)
Class C = 5-7 points (20%)	Class C = 3-4 points (29%)	Class C = 3-4 points (64%)	Class C = 4-5 points (64%)
			Class D = 6-7 points (10%)
Class A: mFFP 13.3 months	Class A: 17%, mOS 25.1 months	Class A: mOS 20.7 months	Class A: mOS NA
Class B: mFFP 6.1 months	Class B: 53%, mOS 13.4 months	Class B: mOS 11.5 months	Class B: mOS 14.8 months
Class C: mFFP 2.1 months	Class C: 29%, mOS 5.1 months	Class C: mOS 9.0 months	Class C: mOS 7.4 months
			Class D: mOS 6.2 months

Abbreviations: BED, biologically effective dose; Gy, gray, radiation dose; mFFP, median freedom from progression; mOS, median overall survival; PTV, planning target volume; SRS, stereotactic radiosurgery; UCSF, University of California San Francisco.
Percentages are proportion of patients with available data assigned to classification group.

survival score was 0.687 (95% CI 0.633-0.719). Against our data, the AUC of the original Combs score was 0.552 (95% CI 0.514-0.601) and of the New Combs score was 0.578 (95% CI 0.500-0.651). For all prognostic scores, the proportional hazard assumption was maintained with no significant deviation from linear by the Schoenfeld residuals (Fig. S1).

Discussion

Patient selection remains one of the primary challenges for reirradiation of HGGs. Current American Society of Clinical Oncology guidelines suggest that young patients with good performance status may be offered focal reirradiation; however, the absence of prospective evidence is recognized.[13] Optimal patient selection depends on several questions, including: (a) Who will progress quickly after reirradiation, thus favoring alternative therapies or supportive care alone? (b) Who will have significant toxicity after reirradiation, thus favoring changes in treatment technique or other alternatives? and (c) Who will live the longest after reirradiation, thus benefiting from local therapy, but with increased risk of late toxicity? To help answer these questions, this study details our institutional experience from a large group of patients receiving reirradiation for HGG. Our series is reflective of the temozolomide era, with nearly all patients receiving initial therapy similar to the Stupp regimen.[2] A variety of radiation techniques and systemic therapies were used at the time of reirradiation, allowing for informative comparisons within this group.

We identified patient age, KPS, and tumor size as major prognostic factors. Age may be a proxy for tumor biology, with *IDH* mutations more common among young patients and telomerase reverse transcriptase (*TERT*)-mutated and triple-negative gliomas more common among older patients.[29] The median age at initial diagnosis in our series was 49 years vs a median of 65 years nationally,[1] possibly indicating an existing selection bias toward younger patients for reirradiation. In our study, KPS ≤ 80 was an optimal threshold predicting disease progression, which is similar to the NIH prognostic scale after glioblastoma re-resection.[30] KPS and age both reflect underlying patient frailty and sensitivity to tumor progression and treatment toxicity. As for tumor size, a strong inverse association was identified between tumor volume and survival, which is again consistent with other reirradiation series and utilized in prognostic scores for repeat surgery.[9,15,21,23,30–34] Our results also revealed a positive correlation between number of salvage systemic therapies before reirradiation and PTV volume. This likely reflects clinical decisions to defer reirradiation in patients with larger tumors. While our findings with respect to age, KPS, and tumor size are not new, they support the notion that our patient population is consistent with those of other studies.[8,9,11,15,17,19,23,24,31–33,35]

While our results support the natural conclusion that tumor grade was prognostic for FFP, the hazard ratio was interestingly lower as compared with other features. Time from initial radiation to progression was identified as a strong prognostic factor and thus was incorporated into scores both for OS and progression. In the setting of reirradiation (with or without chemotherapy), time to initial progression may represent the "chemo/radiation responsiveness" of the tumor better than histological grade alone. Other series have variably reported either time to initial progression or time between initial radiation and reirradiation.[8–10,16–18,21,23,35,36] These 2 time periods are overlapping and highly covariant, yet distinct. Our results also revealed that time from initial progression to reirradiation (during which other salvage therapies might be given) showed no correlation to outcomes. These results suggest

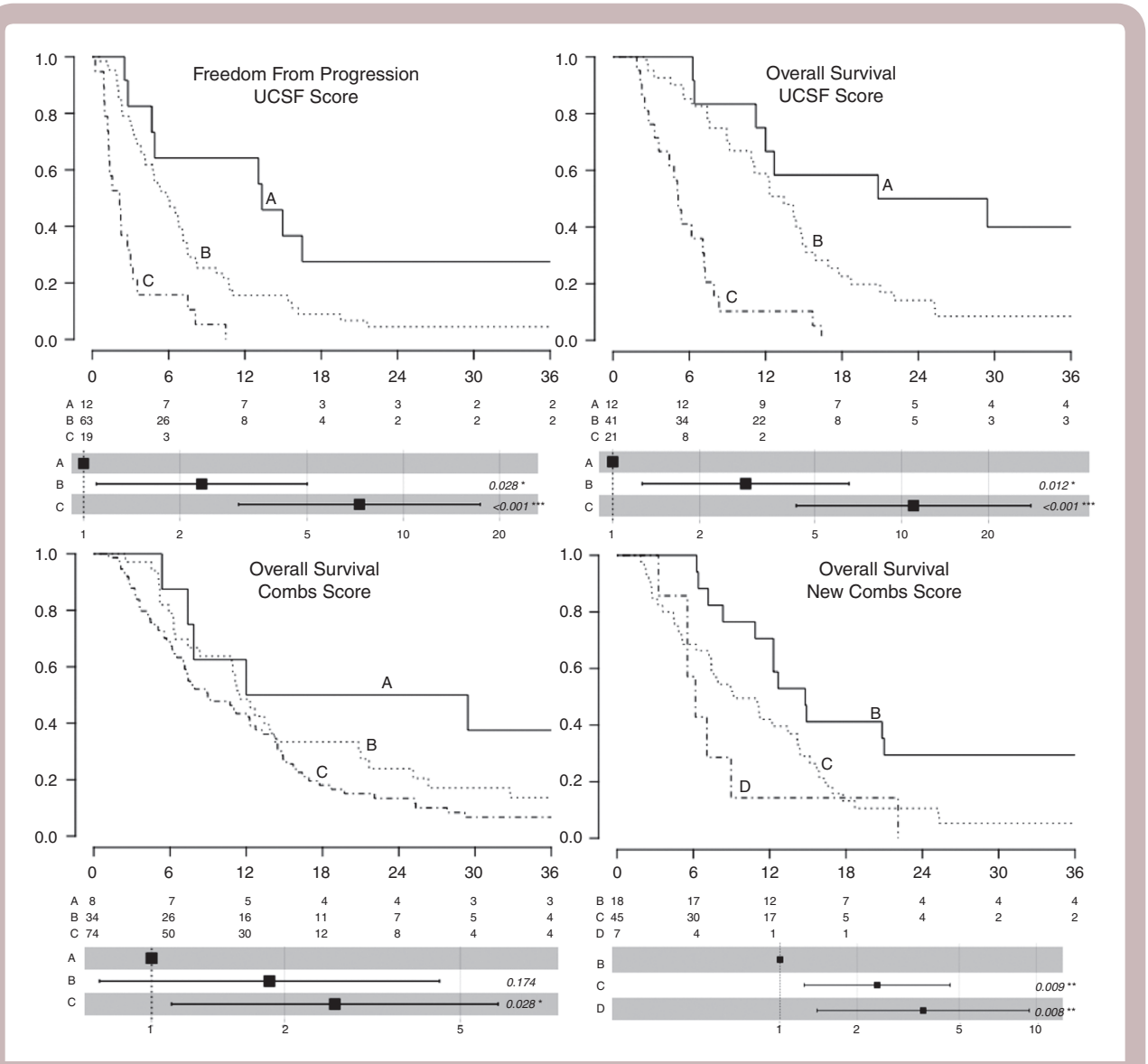

Fig. 2 Outcomes by prognostic score classes. Timeline is in months from reirradiation. Numbers below timeline represent number at risk. Forest plots are log-rank hazard ratios and *P* values by prognostic score class. UCSF indicates University of California San Francisco.

that time to progression may have greater prognostic value. Although in most cases they will be similar, there is an important distinction. For example, consider Patient A, who progresses soon after initial radiation, but is salvaged with multiple surgeries and systemic therapies before reirradiation. Patient B does not progress until later, then has reirradiation at the same time as Patient A. While Patients A and B have the same time between radiation courses, our data would predict worse outcomes after reirradiation for Patient A because of the rapid initial recurrence.

We identified a significant dose threshold for reirradiation. The dose for non-SRS treatments was considered separately from SRS treatments since SRS is typically delivered with a maximum dose much higher than the prescription dose (median 200% vs 108% in our series; Table 1). Our identified thresholds were 40 Gy BED10 for SRS (16 Gy in 1 fraction) and 45 Gy BED10 for non-SRS treatments (approximately 30 Gy in 5 fractions, 35 Gy in 10 fractions, or 40 Gy in 20 fractions). Similar dose thresholds have been identified in other reirradiation series.[9,16,36,37] The possibility remains that patients were selected to receive lower radiation doses because of confounding factors such as patient frailty or tumor proximity to radiation-sensitive structures. However, in our series no significant covariance was seen between BED10, PTV volume, or KPS, supporting the conclusion that there is indeed a significant dose threshold to achieve with reirradiation. Moreover, we found no evidence that any particular dose/fractionation or technique (SRS vs non-SRS) affects survival or progression as long as threshold BED10 was met. Because our progression score includes radiation dose, which is determined by the treating radiation oncologist, in practice it is also a predictive score and provides a dose goal to achieve if feasible. PTV volume is also technically determined by the radiation oncologist,

but we consider this a proxy for tumor recurrence volume and could be estimated before treatment planning.

We saw no evidence that any concurrent or adjuvant systemic therapies with reirradiation influenced disease progression or survival. This is in contrast to other studies suggesting survival advantage with the addition of systemic therapy, particular bevacizumab.[16,33,35,38,39] We also did not see any prognostic effect by *IDH* mutation or MGMT promoter methylation, although molecular marker data were available for only a minority of patients. MGMT status has been reported as a prognostic factor in reirradiation for glioma, albeit with continuous temozolomide.[19] Related to this, we did not examine anaplastic glioma subtypes (astrocytoma vs oligodendroglioma) because of the change in WHO classification over the study period; however, only a minority of the patients had anaplastic gliomas (15%), and these subtypes would now be classified using molecular markers in the 2016 WHO classification system. Future studies should integrate molecular markers with current prognostic factors.

Nearly all patients completed prescribed reirradiation. There were low rates of acute high-grade toxicity, although cumulative incidence of high-grade toxicity rose to 18% by 12 months after reirradiation. Some toxicity may be misattributed to radiation in this retrospective study; examining radiation necrosis only, the cumulative incidence at 12 months was only 7%. This is similar to other reirradiation series in which symptomatic radiation necrosis rates are typically less than 10%.[20,23,24,36] There was an association between PTV volume and high-grade toxicity, which is expected given the necessity to irradiate larger volumes of normal brain. No association was seen with prescription dose or cumulative dose, although true dose overlap was not examined in this study because of lack of detailed treatment plans for most patients. Conclusions about toxicity are limited by the small number of events, although the rising incidence up to 12 months suggests that low toxicity with large-volume hypofractionated reirradiation is dependent on low long-term survival. For patients expected to survive beyond 12 months, further fractionation may be recommended to reduce late toxicity, especially for large-volume disease.

We constructed multivariable prognostic scores for FFP and OS, with significant differences in outcomes between each class. We also validated the original Combs score and New Combs score on our dataset,[8,14] showing that both were significantly correlated with outcomes and that the New Combs score slightly improved accuracy by cross-validated AUC. The New Combs score incorporates 6 factors, including re-resection, which we did not identify as an independent prognostic factor. By comparison, our survival score uses 3 factors and had higher AUC, although not greater than the commonly accepted threshold of 0.7. Although ten-fold cross-validation uses separate subsets for model building and validation, the higher AUC for our model may still be attributable to use of the same dataset and independent external validation is needed. To our knowledge, cross-validated AUCs have not previously been published for these scores.

Other limitations of this study are due to the retrospective design. There are missing data, and potential inconsistencies in data recording over time. Two variables included in the prognostic scores (KPS and PTV at reirradiation) were not available, primarily from older records. These limited the patients available for development of the prognostic scores. Toxicity data are also likely incomplete and the absence of documented toxicity does not necessarily mean toxicity did not occur. Although patients without available data were not considered at risk for calculation of cumulative incidences, some selection bias is possible. These limitations further emphasize the need for external validation of the prognostic scores. There is also heterogeneity among patients since there were no predefined selection criteria for reirradiation. However, the study population matches what is seen in clinical practice and allows for informative comparisons between risk factors.

In conclusion, our study supports that a subset of patients with recurrent HGGs can experience prolonged FFP and survival after reirradiation, particularly young patients with good performance status, longer time from initial radiation to first progression, small recurrence volume, and an adequate reirradiation dose. Prognostic scores can be used as guidelines for clinical decisions, but need to be validated on independent data. Reirradiation technique and fractionation did not change disease outcomes as long as minimum effective dose was met, suggesting these can be chosen to minimize toxicity risk, primarily related to tumor volume. This series of mostly high-dose per fraction reirradiation had few acute high-grade toxicities, although high rates of toxicity with longer follow-up require further investigation. We saw no prognostic impact of concurrent/adjuvant systemic therapy with reirradiation, although the repertoire of systemic therapies is constantly changing and this question should be reexamined. Prospective studies are needed to better define treatment options in this population, and prognostic scores may be useful for patient stratification.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (http://neuro-oncology.oxfordjournals.org/).

Funding

This study was supported in part by the Alpha Omega Alpha Carolyn L. Kuckein Student Research Fellowship (J.H.H.).

Acknowledgments

The authors would like to acknowledge Ann Griffin, PhD, and the UCSF Cancer Registry.

Conflict of interest statement. None declared.

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