Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Details and Cohorts

Risk modeling was performed in the development cohort from University of California, San Francisco (UCSF) and tested in the validation cohort from the Ohio Brain Tumor Study (OBTS) and Mayo Clinic.

UCSF Cohort - Treatment

The Stupp protocol of chemoradiation included Temozolomide given combined with 54 Gy fractioned irradiation for 6 weeks followed by cyclic temozolomide for 6-12 months. This protocol was published and widely used in clinical practice after 2005 therefore subgroup analysis of patient survival in the post 2005 era in this dataset includes patients treated between 2005-2018 (Stupp R 2005).

UCSF Cohort - Pathology

Immunohistochemistry for IDH1 R132H mutation was performed using mouse monoclonal anti-IDH1 p.R132H (DIA H09) (Dianova, Hamburg, Germany) (Capper D 2009). Per the guidelines of the European Association for Neuro-Oncology (EANO) (Weller M 2014), negative immunostaining for IDH1 R132H mutation was followed by sequencing for alternate mutations in IDH1 or IDH2 in patients who were 55 years of age or younger at diagnosis or had a history of pre-existing lower grade glioma (Watanabe T 2009). MGMT (06-Methylguanine-DNA methyltransferase) gene promoter methylation was either determined by quantitative bisulfite sequencing or by methylation-specific PCR using formalin-fixed, paraffin-embedded (FFPE) tissue.

UCSF Cohort - Measurement of tumor volumes and calculation of volumetric extent of resection

Pre-operative and post-operative tumor volumes were quantified by using BrainLab Smartbrush software (Brainlab, Munich, Germany). Pre-operative MRI scans were obtained within 24 hours prior to resection, and post-operative scans were all obtained within 72 hours post-resection. Total contrast-enhancing (CE) and non-enhancing (NE) tumor volumes were measured at both pre-operative and post-operative time points. The total CE tumor volume was measured on T1-weighted post-contrast images, and the non- enhancing tumor volume was measured on T2 or FLAIR sequences. Manual segmentation was performed with region-of-interest analysis “painting” inclusion regions based on fluid-attenuated inversion-recovery (FLAIR) sequences from pre- and post-operative MRI scans to quantify tumor volume. Extent of Resection (EOR) was calculated as: (pre-operative tumor volume - post-operative tumor volume)/pre-operative tumor volume x 100%. Multifocal or multicentric disease was defined as noncontiguous areas of disease based on T1-weighted post contrast images or FLAIR sequences. All multifocal lesions were measured separately and summed together for a single volumetric measurement. Manual segmentations were performed by co-authors RM, JY, SJH, ML and YL with tumor volumetrics verified for accuracy after an initial training period. Volumetric measurements were made blinded to patients’ clinical outcomes. All patients in the cohort had available preoperative and postoperative MRI scans for analysis. To ensure that post-operative FLAIR signal was not surgically induced edema or ischemia, FLAIR pre- and post-operative MRIs were carefully compared alongside DWI sequences prior to including each region in the volume segmentation.

External Validation Cohort

The Ohio Brain Tumor Study (OBTS) is an ongoing prospective IRB-approved protocol, which has served as multi-institution tissue source site network for the TCGA GBM and LGG studies and Gliogene Studies (Brennan CW 2013), (Melin BS 2017), (Daniel J. Brat 2015), (Ceccarelli M 2016). From each newly diagnosed glioblastoma patient the following is obtained after written informed consent: pre-treatment blood sample, formalin-fixed paraffin-embedded (FFPE) tumor tissue, medical history, imaging, medical chart review/clinical data, and active yearly follow-up for clinical outcomes.

The Mayo Clinic glioma case-control study has been described previously [Eckel-Passow 2015],[Melin BS 2017], [Wrench M 2009],[Jenkins RB 2010]. This study was approved by the Mayo Clinic Office for Human Research Protection, and informed written consent was obtained from all participants. Cases were identified at diagnosis (at

Mayo Clinic) or at the time of pathologic confirmation (diagnosed elsewhere and treated at Mayo Clinic); patients were at least 18 years of age and had a surgical resection or biopsy between 2004 and 2014. One patient was diagnosed in 2004 and the rest were post-2005. Patient clinical data were extracted from the electronic medical record. Following consent, a blood sample and tissue sample was obtained.

eMethods 2. Statistical Details

Overall survival (OS), the censored data outcome, was recorded as the time from first surgery to time of death for those patients who died of any cause and time of last follow-up or end of study (December 9, 2018) for those patients who were alive (censored). Initially, clinical, imaging and surgery variables were assessed for inclusion in univariate Cox proportional hazards survival models (Supplementary eTable 2). Multiple approaches were attempted to accommodate violation of the linearity and proportional hazards assumptions. In univariate models, when tumor volume and percent resected (as the variables of interest) violated the proportional hazards assumption splines were employed (for example, see Supplementary eFigure 1), while other variables that violated the assumption (e.g., temozolomide treatment) were included as strata factors. Nonetheless, splines and strata lead to complex models with difficult interpretations.

Therefore, to determine clinically interpretable and relevant risk groups in a multivariate setting including interactions, we employed recursive partitioning survival trees, via the partDSA algorithm (Molinaro, Lostritto, and Laan 2010), (Lostritto, Strawderman, and Molinaro 2012). Such methods are non-parametric and, therefore, do not require the proportional hazards assumption. Clinical, surgical, and imaging variables found to be independently significant by Cox proportional hazard models were included as potential splits in the trees. MGMT was not included due to the large number of missing and unstable imputation values (see Missing Values below). For analyses within molecular subgroups (Post-2005/IDH-known, MGMT-only, and IDH-WT), only patients within the specific subtype were included. The tree that minimized the five-fold cross-validated integrated Brier error was selected for each. Leaves of the resulting trees defined the final risk groups from which the corresponding Kaplan-Meier curves were generated. Hazard ratios and 95% confidence intervals for the risk groups were calculated via the Cox proportional hazards model as a univariable and after adjusting for MGMT status.

After the final models were selected from the development cohort, we assessed the models with the external validation set. The corresponding Kaplan-Meier curves were generated and hazard ratios and 95% confidence intervals for the test set were calculated via the Cox proportional hazards model. For the IDH-wildtype survival tree (Supplementary eFigure 3), we included the IDH-missing patients as part of the validation via repeated imputation of IDH status (Molinaro, Simon, and Pfeiffer 2005)(Kerlikowske, et al. 2010). Imputation was done stratified by age group where those younger than 55 were imputed as IDH-mutant with a binomial proportion of 0.15 (as seen in the unimputed data) and those over 55 with a binomial proportion of 0.03 (as seen in the unimputed data). One thousand imputed samples of the IDH-missing subgroup (n=247) were constructed and those deemed IDH-wildtype were combined with the Mayo Clinic and OBTS cohorts to form validation sets. The Kaplan-Meier median, curves, and Cox proportional hazards coefficients were averaged over the 1,000 validation sets and reported in Supplementary eFigure 3 (Molinaro, Simon, and Pfeiffer 2005)(Kerlikowske, et al. 2010)(Moons KG 2012).

Missing values: Univariate and multivariate Cox proportional hazard survival models were based only on those patients with data for the specific variable(s) tested. For multivariate models, partDSA performs an imputation "on the fly" at each split. Thus, at each split, the non-missing observations for a given variable are used to find the best split, and the missing observations are imputed based on the mean or mode (depending on whether the variable is continuous or categorical) of the non-missing observations in that node. Once the node assignment of the missing observations is determined using the imputed values, the imputed values are returned to their missing state. For missing values in the external validation set, the grand mean or mode from the corresponding variables in the development set are used (Molinaro, Lostritto, and Laan 2010)(Kim 2001). Given the percentage of **missing with MGMT methylation**, we attempted imputation via partDSA as well as via multivariate imputation by chained equations (*mice* package in R)(van Buuren and Groothuis-Oudshoorn 2011); however, different models arose from the two different imputation techniques. Thus, we determined imputation was not stable for MGMT methylation and restricted the MGMT methylation analysis to only those patients with MGMT methylation measured.

All analyses were conducted using the statistical software R (http://www.r-project.org/).

eTable 1. Demographic Table for UCSF Cohort and Mayo and OBTS Validation Cohort

Statistical comparison and summary characteristics for newly diagnosed glioblastoma patients between the UCSF cohort and Mayo/OBTS-External validation cohorts using linear model ANOVA and Pearson's Chi-squared test.

	UCSF-Cohort (N=761)	Mayo-Cohort (N=107)	OBTS-Cohort (N=99)	p value
Age at Initial Diagnosis				0.002[1]
(0,30]	9 (1.2%)	5 (4.7%)	0 (0.0%)	
(30,50]	150 (19.7%)	19 (17.8%)	12 (12.1%)	
(50,60]	223 (29.3%)	28 (26.2%)	23 (23.2%)	
(60,70]	235 (30.9%)	39 (36.4%)	32 (32.3%)	
(70,100]	144 (18.9%)	16 (15.0%)	32 (32.3%)	
Survival status				< 0.001[1]
ALIVE	50 (6.6%)	21 (19.6%)	2 (2.0%)	
DEAD	711 (93.4%)	86 (80.4%)	97 (98.0%)	
IDH status				0.11[1]
N-Miss	247	0	62	
Wildtype	478 (93.0%)	96 (89.7%)	37 (100.0%)	
Mutant	36 (7.0%)	11 (10.3%)	0 (0.0%)	
Temozolomide Treatment				< 0.001[1]
N-Miss	47	2	1	
Yes	628 (88.0%)	86 (81.9%)	64 (65.3%)	
No	86 (12.0%)	4 (3.8%)	34 (34.7%)	
Other	0 (0.0%)	15 (14.3%)	0 (0.0%)	
Preoperative contrast-enhancing postgadolinium enhancement				0.34[2]
Mean (SD)	32.6 (28.2)	35.2 (27.8)	36.5 (27.3)	
median	24.8	30.5	28.7	
Q1, Q3	10.7, 46.9	13.9, 49.9	14.2, 52.8	
Range	0.1 - 173.8	1.1 - 125.2	2.9 - 112.8	
Preoperative non-enhancing hyperintensity				0.32[2]
Mean (SD)	85.3 (55.7)	83.0 (52.4)	94.8 (58.3)	
median	75.0	80.9	102.3	
Q1, Q3	40.3, 121.2	39.4, 120.2	39.2, 130.5	
Range	1.2 - 274.8	3.9 - 214.6	7.3 - 269.1	
Postoperative contrast-enhancing postgadolinium enhancement				0.73[2]
Mean (SD)	3.2 (6.9)	3.0 (6.0)	3.8 (5.8)	
median	0.6	0.6	1.3	
Q1, Q3	0.0, 3.1	0.0, 3.0	0.0, 5.1	

Range	0.0 - 57.6	0.0 - 34.9	0.0 - 39.0	
Postoperative non-enhancing hyperintensity				< 0.001[2]
Mean (SD)	40.2 (33.4)	32.6 (30.4)	64.4 (40.8)	
median	33.8	30.1	59.2	
Q1, Q3	13.5, 56.8	7.5, 44.9	29.9, 90.9	
Range	0.0 - 200.3	0.1 - 163.0	5.8 - 180.3	
Contrast-enhancing extent of resection, % by volume				0.23[2]
Mean (SD)	89.6 (17.2)	91.6 (15.9)	87.1 (17.4)	
median	97.0	98.5	94.0	
Q1, Q3	87.0, 100.0	90.8, 100.0	81.2, 100.0	
Range	10.0 - 100.0	6.0 - 100.0	14.0 - 100.0	
Non-enhancing extent of resection, % by volume				< 0.001[2]
Mean (SD)	53.7 (23.3)	59.5 (23.9)	29.1 (18.9)	
median	54.0	62.0	22.0	
Q1, Q3	39.0, 70.0	46.5, 75.5	14.0, 40.5	
Range	0.0 - 100.0	-6.0 - 99.0	1.0 - 81.0	

1. Pearson's Chi-squared test
2. Linear Model ANOVA

eTable 2. Univariable Survival Analysis for UCSF Cohort

Univariate Cox proportional hazards model for newly diagnosed glioblastoma patients from UCSF cohort.

Variables		Hazard Ratio (univariable)
Sex	Female	-
	Male	1.01 (0.87-1.18, p=0.85)
Age at Diagnosis	Continuous	1.42 (1.33-1.52, p<0.001)
Diagnosis Year 2005	Post 2005	-
	Pre 2005	0.89 (0.73-1.09, p=0.25)
KPS Preoperative Cat	<=70	-
	70-80	0.80 (0.62-1.03, p=0.09)
	90-100	0.60 (0.47-0.76, p<0.001)
Tumor Location By Lobe	Frontal	-
	Brainstem, insular, basal ganglia, or thalamus	0.90 (0.51-1.61, p=0.73)
	Cerebellum	4.29 (1.06-17.37, p=0.04)
	Occipital	1.20 (0.87-1.66, p=0.26)
	Parietal	1.08 (0.87-1.34, p=0.47)
	Temporal	1.08 (0.90-1.30, p=0.41)
Tumor Location By Hemisphere	Left	-
	Bilateral	2.10 (0.99-4.45, p=0.05)

	Right	1.17 (1.00-1.36, p=0.05)
IDH status	Wildtype	-
	Mutant	0.26 (0.17-0.41, p<0.001)
MGMT Status	Methylated	-
	Unmethylated	1.55 (1.14-2.10, p=0.005)
Adjuvant XRT TMZ	Both	-
	Neither	5.10 (3.98-6.54, p<0.001)
	Radiation Only	3.13 (2.30-4.25, p<0.001)
	Temozolomide Only	1.36 (1.01-1.82, p=0.04)
Preoperative contrast-enhancing postgadolinium enhancement	Continuous	1.00 (1.00-1.00, p=0.05)
Postoperative contrast-enhancing postgadolinium enhancement	Continuous	1.04 (1.03-1.05, p<0.001)
Preoperative non-enhancing hyperintensity	Continuous	1.00 (1.00-1.00, p=0.438)
Postoperative non-enhancing hyperintensity	Continuous	1.01 (1.00-1.01, p<0.001)
Contrast-enhancing extent of resection, % by volume	Continuous	0.99 (0.98-0.99, p<0.001)
Non-enhancing extent of resection, % by volume	Continuous	0.99 (0.99-0.99, p<0.001)

eTable 3. Multivariate Cox Regression Analyses for UCSF Cohort

For IDH-mutant GBM patients (n=36), in Cox proportional hazards models, percent of resection of contrast-enhancing tumor was statistically significant when adjusting for age, KPS, and temozolomide treatment (below, Model 1: IDH-MT contrast-enhancing EOR). When the non-statistically significant variables are removed, the percent extent of resection remains significant (Model 2: IDH-MT contrast-enhancing EOR). The same holds true for percent resection of non-enhancing tumor (IDH-MT non-enhancing EOR Models 3 and 4). In model 4, we stratified by temozolomide treatment due to the violation of the proportional hazards' assumption. Only 7 of 36 IDH-mutant patients had MGMT methylation measured, so this variable was not evaluated. For both enhancing and non-enhancing percent resected, the assumption of linearity was not met (one of the assumptions of the Cox model).

Model 1: IDH-MT contrast-enhancing EOR. Multivariate Cox model with contrast-enhancing EOR, Age, KPS, and Postoperative Temozolomide for IDH-Mutant cohort (n=22, 14 observations deleted due to KPS missingness).

Variables	Hazard Ratio	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value	Assumption of proportional hazards met	Linearity
Age at Initial Diagnosis	1.00	0.96	1.05	0.86	□	
Contrast-enhancing Extent of resection	**0.95**	**0.91**	**0.99**	**0.02**	□	×
KPS >70 vs. KPS <=70	0.68	0.08	6.13	0.73	□	
Postoperative Temozolomide Yes vs. No	0.62	0.09	4.30	0.63	□	

Model 2: IDH-MT contrast-enhancing EOR. Multivariate Cox model with contrast-enhancing EOR and stratified Postoperative Temozolomide for IDH-Mutant cohort (n=36).						
Contrast-enhancing Extent of resection	**0.96**	**0.94**	**0.98**	**0.00**	□	×
Model 3: IDH-MT non-enhancing EOR. Multivariate Cox model with non-enhancing EOR, Age, KPS, and Postoperative Temozolomide for IDH-Mutant cohort (n=22, 14 observations deleted due to KPS missingness).						
Age at Initial Diagnosis	0.97	0.92	1.02	0.23	□	
Non-enhancing Extent of resection	**0.96**	**0.93**	**0.99**	**0.02**	□	×
KPS >70 vs. KPS <=70	1.19	0.21	6.66	0.85	□	
Postoperative Temozolomide Yes vs. No	0.34	0.06	2.00	0.23	□	
Model 4: IDH-MT non-enhancing EOR. Multivariate Cox model with non-enhancing EOR and stratified by Postoperative Temozolomide for IDH-Mutant cohort (n=36).						
Non-enhancing Extent of resection	**0.97**	**0.96**	**0.99**	**0.002**	□	×
Model 5: IDH WT contrast-enhancing EOR. Multivariate Cox model with contrast-enhancing EOR, Age, KPS, and Postoperative Temozolomide for IDH-Wildtype cohort (n=269, 197 observations deleted due to KPS missingness, 12 observations deleted due to Postoperative XRT missingness).						
Age at Initial Diagnosis	**1.04**	**1.03**	**1.06**	**0.00**	□	
Contrast-enhancing Extent of resection	**0.99**	**0.98**	**0.99**	**0.00**	×	×
KPS >70 vs. KPS <=70	**2.22**	**1.45**	**3.39**	**0.00**	□	
Postoperative Temozolomide Yes vs. No	**0.38**	**0.24**	**0.61**	**0.00**	×	
Postoperative XRT Yes vs. No	**0.13**	**0.06**	**0.27**	**0.00**	□	
Model 6: IDH WT contrast-enhancing EOR. Multivariate Cox model with contrast-enhancing EOR, Age, KPS, Postoperative XRT, MGMT status stratified by Postoperative Temozolomide for IDH-wildtype cohort (n=114, 197 observations deleted due to KPS missingness, 12 observations deleted due to Postoperative XRT missingness, and 155 observations deleted due to MGMT status missingness).						
Age at Initial Diagnosis	**1.04**	**1.01**	**1.06**	**0.002**	□	
Contrast-enhancing Extent of resection	**0.98**	**0.97**	**0.99**	**0.00**	×	×
KPS >70 vs. KPS <=70	1.98	0.94	4.17	0.07	□	
Postoperative XRT Yes vs. No	**0.09**	**0.03**	**0.32**	**0.00**	□	

MGMT Status Unmethylated vs. Methylated	**1.89**	**1.23**	**2.91**	**0.004**		
Model 7: IDH WT non-enhancing EOR. Multivariate Cox model with non-enhancing EOR, Age, KPS, and stratified Postoperative Temozolomide for IDH-wildtype cohort (n=267, 2 observations deleted due to non-enhancing missingness, 197 observations deleted due to KPS missingness, and 12 observations deleted due to Postoperative XRT missingness).						
Age at Initial Diagnosis	**1.04**	**1.03**	**1.05**	**0.00**		
Non-enhancing Extent of resection	**0.99**	**0.99**	**1.00**	**0.004**		×
KPS >70 vs. KPS <=70	**2.21**	**1.43**	**3.40**	**0.00**		
Postoperative XRT Yes vs. No	**0.22**	**0.10**	**0.47**	**0.00**		
Model 8: IDH WT non-enhancing EOR. Multivariate Cox model with non-enhancing EOR, Age, KPS, and MGMT status stratified by Postoperative Temozolomide treatment for IDH-wildtype cohort (n=113, 2 observations deleted due to non-enhancing missingness, 197 observations deleted due to KPS missingness, 12 observations deleted due to Postoperative XRT missingness, and 154 observations deleted due to MGMT status missingness).						
Age at Initial Diagnosis	**1.03**	**1.01**	**1.05**	**0.02**		
Non-enhancing Extent of resection	**0.99**	**0.98**	**1.00**	**0.02**		×
KPS >70 vs. KPS <=70	**2.89**	**1.42**	**5.91**	**0.004**		
Postoperative XRT Yes vs. No	**0.13**	**0.04**	**0.44**	**0.001**		
MGMT Status Unmethylated vs. Methylated	**1.85**	**1.21**	**2.85**	**0.005**		

eTable 4. Demographic Table for 4 Risk Groups for UCSF Subset Newly Diagnosed After 2005 and Known Tumor *IDH* Status

Recursive partitioning analysis (RPA) and survival curves for Post-2005/IDH known patients (n=434) found four risk groups based on adjuvant temozolomide-treatment (TMZ Post-op), IDH status, age at diagnosis and residual non-enhancing tumor (NE Post-op). Groups are denoted by number in Manuscript Figure 2. Group 1 are the patients who did not receive temozolomide. Group 2 are the temozolomide-treated patients with IDH-wildtype tumors older than 65. Group 3 are the temozolomide-treated patients with IDH-wildtype tumors under 65 with >5.4mL of non-enhancing residual tumor. Group 4 is the combination of two sub-groups: temozolomide-treated patients with IDH-mutant tumors and temozolomide-treated patients with IDH-wildtype tumors under 65 with <=5.4mL of non-enhancing residual tumor. Group 1 had the worst survival, Group 2 had the next worse survival, Group 3 had intermediate survival and Group 4 had the best survival.

	Group 1 (N=38)	Group 2 (N=122)	Group 3 (N=212)	Group 4 (N=62)	Total (N=434)
Sex					
Female	11 (28.9%)	43 (35.2%)	92 (43.4%)	17 (27.4%)	163 (37.6%)
Male	27 (71.1%)	79 (64.8%)	120 (56.6%)	45 (72.6%)	271 (62.4%)
Age at Initial Diagnosis					
Mean (SD)	68.4 (10.7)	70.8 (4.6)	54.1 (7.8)	51.1 (11.9)	59.6 (11.5)
median	67.6	69.9	55.1	52.4	60.5
Q1, Q3	61.1, 76.8	67.1, 73.6	49.0, 60.1	43.1, 60.5	52.2, 67.4
Range	49.5 - 89.0	65.1 - 84.5	26.9 - 65.0	21.3 - 74.1	21.3 - 89.0
Diagnosis Year 2005					
Post 2005	38 (100.0%)	122 (100.0%)	212 (100.0%)	62 (100.0%)	434 (100.0%)
KPS Preoperative cat					
N-Miss	7	51	109	26	193
<60	8 (25.8%)	5 (7.0%)	4 (3.9%)	2 (5.6%)	19 (7.9%)
60	0 (0.0%)	4 (5.6%)	5 (4.9%)	1 (2.8%)	10 (4.1%)
70	4 (12.9%)	16 (22.5%)	13 (12.6%)	1 (2.8%)	34 (14.1%)
80	14 (45.2%)	25 (35.2%)	24 (23.3%)	9 (25.0%)	72 (29.9%)
90	4 (12.9%)	18 (25.4%)	51 (49.5%)	19 (52.8%)	92 (38.2%)
100	1 (3.2%)	3 (4.2%)	6 (5.8%)	4 (11.1%)	14 (5.8%)
Tumor Location By Lobe					
N-Miss	0	5	13	2	20
Frontal	10 (26.3%)	40 (34.2%)	79 (39.7%)	24 (40.0%)	153 (37.0%)
Brainstem, insular, basal ganglia, or thalamus	2 (5.3%)	3 (2.6%)	3 (1.5%)	3 (5.0%)	11 (2.7%)
Cerebellum	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Occipital	5 (13.2%)	8 (6.8%)	12 (6.0%)	4 (6.7%)	29 (7.0%)
Parietal	6 (15.8%)	24 (20.5%)	36 (18.1%)	8 (13.3%)	74 (17.9%)
Temporal	15 (39.5%)	41 (35.0%)	69 (34.7%)	21 (35.0%)	146 (35.3%)
Tumor Location By Hemisphere					

N-Miss	0	5	13	2	20
Bilateral	0 (0.0%)	0 (0.0%)	3 (1.5%)	1 (1.7%)	4 (1.0%)
Left	21 (55.3%)	52 (44.4%)	99 (49.7%)	33 (55.0%)	205 (49.5%)
Right	17 (44.7%)	65 (55.6%)	97 (48.7%)	26 (43.3%)	205 (49.5%)
IDH status					
Mutant	3 (7.9%)	0 (0.0%)	0 (0.0%)	28 (45.2%)	31 (7.1%)
Wildtype	35 (92.1%)	122 (100.0%)	212 (100.0%)	34 (54.8%)	403 (92.9%)
MGMT Status					
N-Miss	21	61	121	34	237
Methylated	8 (47.1%)	27 (44.3%)	39 (42.9%)	15 (53.6%)	89 (45.2%)
Unmethylated	9 (52.9%)	34 (55.7%)	52 (57.1%)	13 (46.4%)	108 (54.8%)
Adjuvant XRT TMZ					
N-Miss	0	4	5	0	9
Both	0 (0.0%)	114 (96.6%)	205 (99.0%)	61 (98.4%)	380 (89.4%)
Neither	20 (52.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	20 (4.7%)
Radiation Only	18 (47.4%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	19 (4.5%)
Temozolomide Only	0 (0.0%)	3 (2.5%)	2 (1.0%)	1 (1.6%)	6 (1.4%)
Preoperative contrast-enhancing postgadolinium enhancement					
Mean (SD)	33.7 (27.9)	31.3 (26.4)	32.5 (25.6)	25.5 (36.9)	31.3 (27.9)
median	24.0	21.9	26.6	10.8	22.9
Q1, Q3	10.9, 50.2	12.6, 46.9	12.9, 43.9	2.4, 25.9	11.0, 44.4
Range	2.1 - 116.7	0.4 - 118.6	0.1 - 172.1	0.2 - 160.9	0.1 - 172.1
Preoperative non-enhancing hyperintensity					
Mean (SD)	93.8 (55.8)	81.1 (55.2)	86.4 (51.1)	65.6 (62.1)	82.6 (54.7)
median	80.1	71.2	79.5	43.1	73.3
Q1, Q3	60.7, 131.5	37.0, 120.6	43.1, 122.4	17.9, 103.8	37.7, 121.1
Range	4.0 - 217.1	1.2 - 266.3	10.2 - 255.1	5.0 - 217.6	1.2 - 266.3
Postoperative contrast-enhancing postgadolinium enhancement					
Mean (SD)	6.5 (13.7)	2.8 (5.0)	3.4 (7.3)	0.7 (1.6)	3.1 (7.1)
median	1.5	0.6	0.7	0.0	0.5
Q1, Q3	0.3, 4.6	0.1, 2.8	0.0, 3.1	0.0, 0.5	0.0, 2.8
Range	0.0 - 55.8	0.0 - 25.3	0.0 - 57.6	0.0 - 8.3	0.0 - 57.6
Postoperative non-enhancing hyperintensity					
Mean (SD)	45.5 (36.9)	37.4 (32.5)	41.1 (30.7)	15.2 (28.1)	36.7 (32.6)

median	32.1	30.9	35.1	3.7	29.8
Q1, Q3	21.8, 62.8	11.0, 53.3	18.2, 53.8	1.6, 9.5	10.8, 51.7
Range	1.9 - 154.7	0.7 - 144.3	5.4 - 200.3	0.0 - 146.1	0.0 - 200.3
Contrast-enhancing extent of resection, % by volume					
Mean (SD)	81.7 (23.2)	90.5 (14.1)	89.9 (17.4)	94.5 (14.1)	90.0 (16.9)
median	86.6	96.8	97.1	100.0	97.5
Q1, Q3	78.2, 98.6	86.3, 99.6	90.2, 100.0	96.8, 100.0	88.4, 100.0
Range	17.5 - 100.0	12.9 - 100.0	9.9 - 100.0	31.6 - 100.0	9.9 - 100.0
Non-enhancing extent of resection, % by volume					
Mean (SD)	52.4 (26.5)	54.4 (23.5)	52.5 (18.8)	78.2 (23.8)	56.7 (23.3)
median	60.0	55.0	53.0	90.0	58.0
Q1, Q3	30.0, 74.0	39.5, 72.0	43.0, 67.0	67.0, 95.0	43.0, 73.0
Range	1.0 - 92.0	0.0 - 97.0	0.0 - 88.0	0.0 - 100.0	0.0 - 100.0

eTable 5. Temozolomide-Treated Tumors for UCSF Subset Newly Diagnosed After 2005 by Known Tumor *IDH* Status

Summary characteristics for two subgroups in Group 4 in Supplementary eTable 4 and Manuscript Figure 3B in UCSF cohort: temozolomide-treated/IDH-wildtype tumors/<=65 years of age/<=5.4mL of non-enhancing residual tumor and temozolomide-treated/IDH-mutant tumors for UCSF subset of newly diagnosed glioblastoma patients after 2005 with known tumor IDH status.

	Group 4A:IDH-wildtype (N=34)	Group 4B:IDH-mutant (N=28)	Total (N=62)
Sex			
Female	10 (29.4%)	7 (25.0%)	17 (27.4%)
Male	24 (70.6%)	21 (75.0%)	45 (72.6%)
Age at Initial Diagnosis			
Mean (SD)	55.6 (7.2)	45.6 (14.1)	51.1 (11.9)
median	57.3	42.6	52.4
Q1, Q3	51.6, 60.9	36.8, 55.0	43.1, 60.5
Range	30.5 - 64.8	21.3 - 74.1	21.3 - 74.1
Diagnosis Year 2005			
Post 2005	34 (100.0%)	28 (100.0%)	62 (100.0%)
KPS Preop cat			
N-Miss	13	13	26
<60	0 (0.0%)	2 (13.3%)	2 (5.6%)
60	0 (0.0%)	1 (6.7%)	1 (2.8%)
70	1 (4.8%)	0 (0.0%)	1 (2.8%)
80	8 (38.1%)	1 (6.7%)	9 (25.0%)
90	10 (47.6%)	9 (60.0%)	19 (52.8%)
100	2 (9.5%)	2 (13.3%)	4 (11.1%)
Tumor Location By Lobe			
N-Miss	0	2	2
Frontal	13 (38.2%)	11 (42.3%)	24 (40.0%)
Brainstem, insular, basal ganglia, or thalamus	1 (2.9%)	2 (7.7%)	3 (5.0%)
Cerebellum	0 (0.0%)	0 (0.0%)	0 (0.0%)
Occipital	3 (8.8%)	1 (3.8%)	4 (6.7%)
Parietal	3 (8.8%)	5 (19.2%)	8 (13.3%)
Temporal	14 (41.2%)	7 (26.9%)	21 (35.0%)
Tumor Location By Hemisphere			
N-Miss	0	2	2
Bilateral	1 (2.9%)	0 (0.0%)	1 (1.7%)
Left	21 (61.8%)	12 (46.2%)	33 (55.0%)
Right	12 (35.3%)	14 (53.8%)	26 (43.3%)
IDH status			

Mutant	0 (0.0%)	28 (100.0%)	28 (45.2%)
Wildtype	34 (100.0%)	0 (0.0%)	34 (54.8%)
MGMT Status			
N-Miss	13	21	34
Methylated	11 (52.4%)	4 (57.1%)	15 (53.6%)
Unmethylated	10 (47.6%)	3 (42.9%)	13 (46.4%)
Adjuvant XRT TMZ			
Both	34 (100.0%)	27 (96.4%)	61 (98.4%)
Neither	0 (0.0%)	0 (0.0%)	0 (0.0%)
Temozolomide Only	0 (0.0%)	0 (0.0%)	0 (0.0%)
Preoperative contrast-enhancing postgadolinium enhancement			
Mean (SD)	16.0 (21.9)	37.0 (47.4)	25.5 (36.9)
median	9.4	15.0	10.8
Q1, Q3	2.2, 17.3	2.4, 54.6	2.4, 25.9
Range	0.2 - 82.7	0.2 - 160.9	0.2 - 160.9
Preoperative non-enhancing hyperintensity			
Mean (SD)	30.6 (32.4)	106.9 (63.8)	65.6 (62.1)
median	23.3	103.2	43.1
Q1, Q3	9.3, 35.0	50.1, 156.3	17.9, 103.8
Range	5.0 - 147.9	6.4 - 217.6	5.0 - 217.6
Postoperative contrast-enhancing postgadolinium enhancement			
Mean (SD)	0.2 (0.4)	1.3 (2.2)	0.7 (1.6)
median	0.0	0.1	0.0
Q1, Q3	0.0, 0.2	0.0, 1.3	0.0, 0.5
Range	0.0 - 1.8	0.0 - 8.3	0.0 - 8.3
Postoperative non-enhancing hyperintensity			
Mean (SD)	2.5 (1.7)	30.7 (36.5)	15.2 (28.1)
median	2.3	17.1	3.7
Q1, Q3	1.0, 3.8	6.5, 40.9	1.6, 9.5
Range	0.0 - 5.4	0.1 - 146.1	0.0 - 146.1
Contrast-enhancing extent of resection, % by volume			
Mean (SD)	96.4 (11.9)	92.0 (16.4)	94.5 (14.1)
median	100.0	99.8	100.0
Q1, Q3	98.2, 100.0	96.4, 100.0	96.8, 100.0
Range	31.6 - 100.0	33.1 - 100.0	31.6 - 100.0
Non-enhancing extent of resection, % by volume			
Mean (SD)	85.8 (15.7)	69.1 (28.5)	78.2 (23.8)

median	92.0	79.0	90.0
Q1, Q3	85.0, 95.0	51.5, 93.0	67.0, 95.0
Range	40.0 - 100.0	0.0 - 100.0	0.0 - 100.0

eTable 6. Hazard Ratios for 4 Risk Groups for UCSF Subset Newly Diagnosed After 2005 and Known Tumor *IDH* Status

Hazard ratios and 95% confidence intervals for the four risk groups defined by the recursive partitioning tree (in Manuscript Figure 2) for Post-2005/IDH known patients in UCSF subset were calculated via the Cox proportional hazards model. Group 3 is considered baseline as that group has the expected median survival for newly diagnosed GBM patients with mixed IDH-status. Risk groups are defined above Supplementary eTable 4.

A. Survival risk groups defined in Manuscript Figure 2 (n=434)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	3.31	2.31	4.74	<0.001
Group 2	1.45	1.15	1.83	0.002
Group 3	1.00			
Group 4	0.36	0.25	0.51	<0.001

B. Survival risk groups and MGMT Status (n=197)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	2.67	1.54	4.62	<0.001
Group 2	1.50	1.07	2.13	0.02
Group 3	1.00			
Group 4	0.25	0.14	0.46	<0.001
MGMT Methylated vs. Unmethylated	0.59	0.43	0.82	0.002

C. Survival risk groups, MGMT Status and KPS (n=125)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	2.85	1.38	5.87	0.005
Group 2	1.52	0.98	2.37	0.06
Group 3	1.00			
Group 4	0.25	0.13	0.51	<0.001
MGMT Methylated vs. Unmethylated	0.63	0.42	0.96	0.03
KPS under 100 vs. 100	0.31	0.11	0.86	0.02

D. Survival risk groups, MGMT Status, KPS and interaction with MGMT Status (n=125)

When an interaction between the risk groups and MGMT status was examined, the only risk group with a significant interaction was Group 1 (n=38), the patients who did not receive temozolomide regardless of extent of resection. The model indicates that those untreated with temozolomide patients whose tumor are MGMT methylated are at a higher risk than those who are unmethylated. However, it is clear from the confidence interval estimates that the power for this group is diminished; thus, this result needs to be further examined.

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	1.71	0.69	4.24	0.25
Group 2	1.92	1.08	3.42	0.03
Group 3	1.00			
Group 4	0.16	0.06	0.44	<0.001
MGMT Methylated vs. Unmethylated	0.55	0.30	1.01	0.06
KPS 100 vs. under 100	0.35	0.12	0.98	0.05
Group1: MGMT Methylated	21.29	4.41	102.81	<0.001
Group2: MGMT Methylated	0.65	0.27	1.60	0.35
Group4: MGMT Methylated	2.28	0.64	8.07	0.20

eTable 7. Demographic Table for the 4 Risk Groups for External Validation

Summary characteristics for the four risk groups in OBTS and Mayo external validation set defined by the RPA model (in Manuscript Figure 2). Group 1 had the worst survival, Group 2 had the next worse survival, Group 3 had intermediate survival and Group 4 had the best survival.

	Group 1 (N=38)	Group 2 (N=56)	Group 3 (N=92)	Group 4 (N=20)	p value
Age at Initial Diagnosis					< 0.0011
N-Miss	34	22	43	0	
(0,30]	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (25.0%)	
(30,50]	0 (0.0%)	0 (0.0%)	14 (28.6%)	5 (25.0%)	
(50,60]	0 (0.0%)	0 (0.0%)	22 (44.9%)	6 (30.0%)	
(60,70]	2 (50.0%)	20 (58.8%)	13 (26.5%)	4 (20.0%)	
(70,100]	2 (50.0%)	14 (41.2%)	0 (0.0%)	0 (0.0%)	
Survival status					0.041
ALIVE	1 (2.6%)	4 (7.1%)	13 (14.1%)	5 (25.0%)	
DEAD	37 (97.4%)	52 (92.9%)	79 (85.9%)	15 (75.0%)	
IDH status					< 0.0011
N-Miss	25	9	28	0	
Mutant	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (55.0%)	
Wildtype	13 (100.0%)	47 (100.0%)	64 (100.0%)	9 (45.0%)	
Temozolomide Treatment					< 0.0011
N-Miss	0	2	1	0	
No	38 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	0 (0.0%)	1 (1.9%)	11 (12.1%)	3 (15.0%)	
Yes	0 (0.0%)	53 (98.1%)	80 (87.9%)	17 (85.0%)	
Preoperative contrast-enhancing postgadolinium enhancement					0.832
Mean (SD)	35.8 (22.7)	33.1 (27.5)	37.6 (27.9)	36.3 (37.6)	
median	30.2	28.8	31.2	23.8	
Q1, Q3	19.2, 48.6	9.1, 46.4	14.7, 51.8	14.2, 39.6	
Range	3.1 - 90.8	1.1 - 125.2	2.6 - 112.8	2.8 - 125.0	
Preoperative non-enhancing hyperintensity					0.452
Mean (SD)	89.0 (51.4)	89.2 (60.1)	92.1 (54.1)	67.3 (52.5)	
median	90.3	89.5	93.5	58.6	
Q1, Q3	46.6, 122.4	37.0, 123.1	43.8, 129.5	22.0, 85.7	
Range	15.8 - 204.0	3.9 - 214.6	6.9 - 269.1	8.6 - 182.9	
Postoperative contrast-enhancing					0.052

postgadolinium enhancement					
Mean (SD)	4.9 (7.9)	2.5 (4.3)	4.0 (6.0)	0.8 (1.7)	
median	2.0	0.6	1.6	0.0	
Q1, Q3	0.2, 5.3	0.0, 2.9	0.0, 5.3	0.0, 0.7	
Range	0.0 - 39.0	0.0 - 17.2	0.0 - 34.9	0.0 - 7.2	
Postoperative non-enhancing hyperintensity					< 0.0012
Mean (SD)	65.0 (41.0)	49.3 (43.9)	53.3 (35.0)	12.0 (13.5)	
median	62.7	40.2	46.2	4.8	
Q1, Q3	25.1, 93.4	18.0, 61.2	28.7, 74.8	2.7, 25.1	
Range	6.4 - 145.8	0.4 - 180.3	5.8 - 163.0	0.1 - 36.8	
Contrast-enhancing extent of resection, % by volume					0.092
Mean (SD)	86.0 (15.3)	92.1 (12.8)	86.8 (20.5)	96.4 (7.0)	
median	94.0	98.0	95.0	100.0	
Q1, Q3	73.8, 100.0	88.5, 100.0	87.0, 100.0	96.0, 100.0	
Range	47.0 - 100.0	28.0 - 100.0	6.0 - 100.0	76.0 - 100.0	
Non-enhancing extent of resection, % by volume					< 0.0012
Mean (SD)	26.4 (17.4)	48.7 (23.4)	37.7 (22.3)	81.1 (19.3)	
median	22.0	53.0	37.0	90.0	
Q1, Q3	14.0, 33.2	32.5, 64.0	20.0, 54.2	71.0, 94.8	
Range	9.0 - 73.0	8.0 - 91.0	-6.0 - 81.0	41.0 - 99.0	

1. Pearson’s Chi-squared test
2. Linear Model ANOVA

eTable 8. Hazard Ratios for Risk Groups for External Validation

Hazard ratios and 95% confidence intervals for the four risk groups defined by the recursive partitioning tree for the external validation set were calculated via the Cox proportional hazards model (n=206).

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	6.17	4.08	9.33	<0.001
Group 2	1.58	1.11	2.25	0.01
Group 3	1.00			
Group 4	0.54	0.31	0.94	0.03

eTable 9. Demographic Table for 4 Risk Groups for UCSF Subset With Tumor *IDH* Wildtype (Any Year of Diagnosis)

Recursive partitioning analysis (RPA) and survival curves for IDH wildtype (any year of diagnosis) patients (n=478) found four risk groups based on adjuvant temozolomide-treatment (TMZ Post-op), age at diagnosis, and pre-operative non-enhancing tumor volume (NE Pre-op), extent of resection of contrast-enhancing tumor (CE EOR), and residual non-enhancing tumor volume (NE Post-op). Groups are denoted by number and color. Group 1 (black in Supplementary eFigure 3) are the patients who did not receive temozolomide and had more than 73.8mL non-enhancing tumor pre-operatively. Group 2 (red in Supplementary eFigure 3) included three groups of patients: those who did not receive temozolomide with less than 73.8mL non-enhancing tumor pre-operatively; those over 65 years of age who did receive temozolomide; and those less than 65 who received temozolomide and had less than 77% contrast-enhancing tumor resected. Group 3 (green in Supplementary eFigure 3) are temozolomide-treated patients and under 65 years of age with more than 77% of contrast-enhancing tumor resected and more than 5.4mL residual non-enhancing-tumor. Group 4 (blue in Supplementary eFigure 3) is the temozolomide-treated patients, under 65 years of age with more than 77% of contrast-enhancing tumor resected and less than 5.4mL residual non-enhancing. Group 1 had the worst survival, Group 2 had the next worse survival, Group 3 had intermediate survival, Group 4 had the best survival.

	Group 1 (N=25)	Group 2 (N=200)	Group 3 (N=217)	Group 4 (N=36)	Total (N=478)
Sex					
Female	11 (44.0%)	66 (33.0%)	93 (42.9%)	11 (30.6%)	181 (37.9%)
Male	14 (56.0%)	134 (67.0%)	124 (57.1%)	25 (69.4%)	297 (62.1%)
Age at Diagnosis					
Mean (SD)	68.4 (11.0)	66.7 (9.6)	53.9 (8.0)	55.4 (7.7)	60.1 (10.9)
Median	67.6	68.1	55.2	57.3	60.6
Q1, Q3	58.4, 77.5	65.1, 72.7	49.0, 60.1	51.6, 60.9	52.7, 67.6
Range	51.2 - 89.0	32.8 - 85.3	26.9 - 65.0	30.5 - 64.8	26.9 - 89.0
Diagnosis Year 2005					
Post 2005	17 (68.0%)	169 (84.5%)	184 (84.8%)	33 (91.7%)	403 (84.3%)
Pre 2005	8 (32.0%)	31 (15.5%)	33 (15.2%)	3 (8.3%)	75 (15.7%)
KPS Preoperative Cat					
N-Miss	7	76	100	14	197
<=70	10 (55.6%)	35 (28.2%)	22 (18.8%)	1 (4.5%)	68 (24.2%)
70-80	6 (33.3%)	47 (37.9%)	24 (20.5%)	8 (36.4%)	85 (30.2%)
90-100	2 (11.1%)	42 (33.9%)	71 (60.7%)	13 (59.1%)	128 (45.6%)
Tumor Location By Lobe					
N-Miss	1	9	19	0	29

Brainstem, insular, basal ganglia, or thalamus	0 (0.0%)	7 (3.7%)	1 (0.5%)	1 (2.8%)	9 (2.0%)
Cerebellum	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Frontal	5 (20.8%)	72 (37.7%)	81 (40.9%)	14 (38.9%)	172 (38.3%)
Occipital	3 (12.5%)	13 (6.8%)	12 (6.1%)	3 (8.3%)	31 (6.9%)
Parietal	6 (25.0%)	38 (19.9%)	34 (17.2%)	4 (11.1%)	82 (18.3%)
Temporal	10 (41.7%)	60 (31.4%)	70 (35.4%)	14 (38.9%)	154 (34.3%)
Tumor Location By Hemisphere					
N-Miss	1	9	19	0	29
Bilateral	0 (0.0%)	0 (0.0%)	4 (2.0%)	1 (2.8%)	5 (1.1%)
Left	12 (50.0%)	91 (47.6%)	98 (49.5%)	23 (63.9%)	224 (49.9%)
Right	12 (50.0%)	100 (52.4%)	96 (48.5%)	12 (33.3%)	220 (49.0%)
IDH Status					
Mutant	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Wildtype	25 (100.0%)	200 (100.0%)	217 (100.0%)	36 (100.0%)	478 (100.0%)
MGMT Status					
N-Miss	18	111	143	16	288
Methylated	3 (42.9%)	40 (44.9%)	32 (43.2%)	10 (50.0%)	85 (44.7%)
Unmethylated	4 (57.1%)	49 (55.1%)	42 (56.8%)	10 (50.0%)	105 (55.3%)
Adjuvant XRT TMZ					
N-Miss	0	7	3	0	10
Both	0 (0.0%)	160 (82.9%)	210 (98.1%)	36 (100.0%)	406 (86.8%)
Neither	9 (36.0%)	9 (4.7%)	0 (0.0%)	0 (0.0%)	18 (3.8%)
Radiation Only	16 (64.0%)	21 (10.9%)	2 (0.9%)	0 (0.0%)	39 (8.3%)
Temozolomide Only	0 (0.0%)	3 (1.6%)	2 (0.9%)	0 (0.0%)	5 (1.1%)
Preoperative contrast-enhancing postgadolinium enhancement					
Mean (SD)	49.7 (27.6)	28.9 (24.0)	33.4 (25.9)	15.4 (21.3)	31.0 (25.6)
Median	43.2	22.1	28.8	8.8	24.1
Q1, Q3	28.7, 73.2	10.9, 43.0	14.3, 43.7	2.6, 16.2	11.5, 43.7

Range	10.8 - 116.7	0.4 - 118.6	0.1 - 172.1	0.2 - 82.7	0.1 - 172.1
Preoperative non-enhancing hyperintensity					
Mean (SD)	135.7 (44.1)	76.2 (53.1)	88.6 (50.7)	29.6 (31.7)	81.5 (53.9)
Median	125.6	61.6	81.7	20.7	73.1
Q1, Q3	93.6, 177.0	36.9, 109.6	49.4, 121.5	9.4, 34.9	38.3, 118.5
Range	86.4 - 217.1	1.2 - 266.3	10.2 - 255.1	5.0 - 147.9	1.2 - 266.3
Postoperative contrast-enhancing postgadolinium enhancement					
Mean (SD)	8.1 (14.0)	4.6 (7.8)	1.6 (3.4)	0.2 (0.4)	3.1 (6.7)
Median	2.8	1.1	0.5	0.0	0.6
Q1, Q3	0.5, 8.6	0.2, 5.2	0.0, 1.8	0.0, 0.2	0.0, 3.0
Range	0.0 - 55.8	0.0 - 57.6	0.0 - 38.4	0.0 - 1.8	0.0 - 57.6
Postoperative non-enhancing hyperintensity					
Mean (SD)	60.6 (38.3)	38.7 (33.4)	41.0 (28.7)	2.4 (1.7)	38.2 (32.2)
Median	51.7	32.6	35.3	2.1	32.5
Q1, Q3	30.5, 86.7	12.8, 53.3	18.8, 54.9	1.0, 3.7	12.8, 53.2
Range	9.8 - 159.8	0.7 - 200.3	5.4 - 138.4	0.0 - 5.4	0.0 - 200.3
EOR contrast-enhancing postgadolinium enhancement					
Mean (SD)	81.2 (23.7)	83.2 (21.6)	95.8 (5.2)	97.9 (4.5)	89.9 (16.7)
Median	88.0	93.0	98.0	100.0	97.0
Q1, Q3	67.0, 99.0	75.0, 99.0	93.0, 100.0	98.0, 100.0	88.0, 100.0
Range	20.0 - 100.0	10.0 - 100.0	78.0 - 100.0	79.0 - 100.0	10.0 - 100.0
EOR non-enhancing hyperintensity					
Mean (SD)	56.1 (21.7)	49.8 (23.6)	54.1 (17.7)	85.5 (16.0)	54.7 (22.2)
Median	60.0	52.5	54.0	92.0	55.0
Q1, Q3	35.0, 76.0	35.0, 67.0	44.0, 67.0	85.0, 95.0	41.0, 70.5
Range	21.0 - 90.0	0.0 - 97.0	0.0 - 88.0	40.0 - 100.0	0.0 - 100.0

eTable 10. Hazard Ratios for 4 Risk Groups for UCSF Subset With Tumor *IDH* Wildtype (Any Year of Diagnosis)

Hazard ratios and 95% confidence intervals for the four risk groups defined by the recursive partitioning tree for UCSF subset with IDH wildtype tumor (any year of diagnosis) were calculated via the Cox proportional hazards model. Interaction between risk groups and MGMT Status was not significant (data not shown). Risk groups are defined above in Supplementary eTable 9.

A. Survival Risk Groups (n=478)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	17.26	10.67	27.91	<0.001
Group 2	1.82	1.49	2.23	<0.001
Group 3	1.00			
Group 4	0.56	0.38	0.84	0.005

B. Survival Risk Groups and MGMT Status (n=190)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	18.69	7.63	45.76	<0.001
Group 2	1.76	1.26	2.45	<0.001
Group 3	1.00			
Group 4	0.34	0.18	0.64	<0.001
MGMT Methylated vs. Unmethylated	0.56	0.41	0.78	<0.001

C. Survival Risk Groups, MGMT Status, and KPS (n=118)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	12.85	4.08	40.50	<0.001
Group 2	1.79	1.16	2.76	0.009
Group 3	1.00			
Group 4	0.35	0.16	0.78	0.01
MGMT Methylated vs. Unmethylated	0.58	0.38	0.88	0.01
KPS under 70 vs. above 70	2.64	1.33	5.25	0.005

D. Survival Risk Groups and MGMT Status interaction, and KPS (n=118)

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	11.45	2.97	44.05	<0.001
Group 2	1.88	1.06	3.32	0.03

Group 3	1.00			
Group 4	0.20	0.07	0.64	0.006
MGMT Methylated vs. Unmethylated	0.53	0.27	1.07	0.08
KPS under 70 vs. above 70	2.61	1.29	5.28	0.008
Group1: MGMT Methylated	1.51	0.21	10.84	0.68
Group2: MGMT Methylated	0.91	0.38	2.19	0.83
Group4: MGMT Methylated	3.33	0.75	14.87	0.11

eTable 11. Analysis by Age for UCSF Subset With Tumor *IDH* Wildtype (Any Year of Diagnosis)

Hazard ratios and corresponding 95% confidence intervals for IDH wildtype newly diagnosed glioblastoma patients from UCSF cohort.

Age	Number of patients	Variables	Hazard Ratio	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value	Assumption of proportional hazards met
>65	**167**	**Contrast-enhancing Extent of resection**	**0.96**	**0.97**	**0.99**	**<0.001**	□
	70	**Contrast-enhancing Extent of resection**	**0.97**	**0.95**	**0.96**	**0.02**	□
		MGMT Status Unmethylated vs. Methylated	0.39	0.22	0.69	0.001	□
	166	Non-enhancing Extent of resection	0.99	0.99	1.00	0.42	□
	70	Non-enhancing Extent of resection	0.99	0.99	1.01	0.57	□
		MGMT Status Unmethylated vs. Methylated	0.41	0.23	0.71	0.002	×
<=65	311	**Contrast-enhancing Extent of resection**	**0.99**	**0.98**	**0.99**	**<0.001**	×
	117	**Contrast-enhancing Extent of resection**	**0.98**	**0.97**	**0.99**	**0.001**	□
		MGMT Status Unmethylated vs. Methylated	0.70	0.46	1.06	0.09	□
	309	**Non-enhancing Extent of resection**	**0.99**	**0.98**	**0.99**	**<0.001**	□
	116	**Non-enhancing Extent of resection**	**0.99**	**0.98**	**0.99**	**0.003**	□
		MGMT Status Unmethylated vs. Methylated	0.70	0.46	1.07	0.1	□

eTable 12. Demographic Table for 3 Risk Groups for UCSF Subset With Tumor Methylation Status–Methylated

Recursive partitioning analysis (RPA) and survival curves for MGMT methylated patients (n= 94) found three risk groups based on adjuvant temozolomide treatment (TMZ Post-op), enhancing residual tumor (CE Post-op). Groups are denoted by number and in Supplementary eFigure 4.Group 1 patients had the poorest survival and were those not treated with temozolomide (Group 1: median OS 3.9mo (95% CI 2.4 - NA)). Group 2 patients had better survival than Group 1 patients and were treated with temozolomide with over 1.7mL enhancing residual tumor (median OS: 12.8mo (95% CI: 10.0 - 21.5)). Group 3 patients fared the best and were temozolomide-treated with less than 1.7mL enhancing residual tumor (median OS: 28.4mo (95% CI 22.3 - 42.9)). Similar to the previous models, patients with the best survival (Group 3) had the highest median enhancing tumor resected (100%) and non-enhancing tumor (63%).

	Group 1 (N=10)	Group 2 (N=26)	Group 3 (N=58)	Total (N=94)
Sex				
Female	5 (50.0%)	10 (38.5%)	24 (41.4%)	39 (41.5%)
Male	5 (50.0%)	16 (61.5%)	34 (58.6%)	55 (58.5%)
Age at Initial Diagnosis				
Mean (SD)	69.7 (10.8)	60.4 (13.1)	59.4 (11.3)	60.7 (12.1)
median	69.8	62.3	61.4	62.3
Q1, Q3	66.6, 75.5	51.0, 71.6	52.1, 67.6	52.0, 69.8
Range	52.1 - 85.3	32.8 - 82.2	24.1 - 81.7	24.1 - 85.3
Diagnosis Year 2005				
Post 2005	10 (100.0%)	26 (100.0%)	58 (100.0%)	94 (100.0%)
KPS Preop cat				
N-Miss	4	9	19	32
<60	2 (33.3%)	2 (11.8%)	0 (0.0%)	4 (6.5%)
60	0 (0.0%)	2 (11.8%)	2 (5.1%)	4 (6.5%)
70	0 (0.0%)	2 (11.8%)	6 (15.4%)	8 (12.9%)
80	3 (50.0%)	6 (35.3%)	8 (20.5%)	17 (27.4%)
90	1 (16.7%)	5 (29.4%)	19 (48.7%)	25 (40.3%)
100	0 (0.0%)	0 (0.0%)	4 (10.3%)	4 (6.5%)
Tumor Location By Lobe				
Frontal	4 (40.0%)	9 (34.6%)	24 (41.4%)	37 (39.4%)
Brainstem, insular, basal ganglia, or thalamus	1 (10.0%)	1 (3.8%)	1 (1.7%)	3 (3.2%)
Cerebellum	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Occipital	1 (10.0%)	3 (11.5%)	3 (5.2%)	7 (7.4%)
Parietal	3 (30.0%)	5 (19.2%)	9 (15.5%)	17 (18.1%)
Temporal	1 (10.0%)	8 (30.8%)	21 (36.2%)	30 (31.9%)
Tumor Location By Hemisphere				
Bilateral	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Left	2 (20.0%)	11 (42.3%)	27 (46.6%)	40 (42.6%)
Right	8 (80.0%)	15 (57.7%)	31 (53.4%)	54 (57.4%)
IDH status				
N-Miss	2	0	3	5
Mutant	0 (0.0%)	0 (0.0%)	4 (7.3%)	4 (4.5%)

Wildtype	8 (100.0%)	26 (100.0%)	51 (92.7%)	85 (95.5%)
MGMT Status				
Methylated	10 (100.0%)	26 (100.0%)	58 (100.0%)	94 (100.0%)
Unmethylated	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adjuvant XRT TMZ				
Neither	0	1	1	2
Both	0 (0.0%)	24 (96.0%)	56 (98.2%)	80 (87.0%)
Neither	7 (70.0%)	0 (0.0%)	0 (0.0%)	7 (7.6%)
Radiation Only	3 (30.0%)	0 (0.0%)	0 (0.0%)	3 (3.3%)
Temozolomide Only	0 (0.0%)	1 (4.0%)	1 (1.8%)	2 (2.2%)
Preoperative contrast-enhancing postgadolinium enhancement				
Mean (SD)	31.8 (20.8)	46.9 (31.8)	25.0 (26.5)	31.8 (28.9)
median	32.6	44.2	17.6	24.8
Q1, Q3	23.1, 36.5	18.8, 63.3	4.6, 35.9	8.9, 44.4
Range	4.1 - 79.5	10.9 - 130.6	0.3 - 126.9	0.3 - 130.6
Preoperative non-enhancing hyperintensity				
Mean (SD)	96.0 (59.6)	101.4 (52.5)	66.0 (50.0)	79.0 (53.8)
median	62.9	100.5	52.2	65.1
Q1, Q3	59.9, 120.1	57.8, 144.5	26.4, 100.0	37.7, 118.6
Range	38.3 - 217.1	15.3 - 196.6	1.2 - 185.1	1.2 - 217.1
Postoperative contrast-enhancing postgadolinium enhancement				
Mean (SD)	3.9 (4.4)	7.4 (7.3)	0.3 (0.4)	2.7 (5.1)
median	3.0	4.4	0.1	0.6
Q1, Q3	0.4, 6.1	2.5, 10.5	0.0, 0.5	0.0, 2.8
Range	0.0 - 14.3	1.8 - 35.2	0.0 - 1.7	0.0 - 35.2
Postoperative non-enhancing hyperintensity				
Mean (SD)	43.4 (22.8)	49.1 (36.8)	23.7 (23.8)	32.8 (30.0)
median	43.2	41.0	15.5	25.9
Q1, Q3	26.8, 58.3	29.4, 57.1	5.3, 32.6	9.2, 47.3
Range	10.0 - 86.8	2.8 - 146.2	0.2 - 89.3	0.2 - 146.2
Contrast-enhancing extent of resection, % by volume				
Mean (SD)	85.2 (13.8)	79.3 (20.2)	94.7 (13.9)	89.5 (17.2)
median	85.2	88.3	99.5	95.9
Q1, Q3	81.8, 95.0	72.4, 92.2	95.8, 100.0	88.2, 100.0
Range	52.8 - 100.0	20.5 - 96.1	26.9 - 100.0	20.5 - 100.0
Non-enhancing extent of resection, % by volume				
Mean (SD)	49.6 (25.2)	51.3 (21.2)	62.7 (22.3)	58.1 (22.8)
median	59.0	52.5	62.5	60.0
Q1, Q3	31.5, 65.2	41.5, 64.8	47.5, 81.2	44.2, 73.8
Range	1.0 - 78.0	1.0 - 90.0	0.0 - 99.0	0.0 - 99.0

eTable 13. Hazard Ratios for 3 Risk Groups for UCSF Subset With Tumor Methylation Status Methylated

Hazard ratios and 95% confidence intervals for the three risk groups defined by the RPA tree for UCSF MGMT methylation-methylated subset in Supplementary eFigure 4 were calculated via the Cox proportional hazards model.

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	3.20	1.50	6.80	0.003
Group 2	1.00			
Group 3	0.36	0.21	0.61	<0.001

eTable 14. Demographic Table for 2 Risk Groups for UCSF Subset With Tumor Methylation Status–Unmethylated

Recursive partitioning analysis (RPA) and survival curves for MGMT unmethylated patients (n= 111) found two risk groups based on age at diagnosis and enhancing residual tumor(CE Post-op). Groups are denoted by number and in Supplementary eFigure 6. Group 1 patients had the poorest survival and included two types of patients: those older than 65; or, those less than or equal to 65 with more than 0.4mL residual enhancing tumor (median OS: 11.4mo (95% CI 9.5 - 12.8)). Group 2 patients had the best survival and were those under 65 with less than 0.4mL enhancing residual tumor (median OS: 20.9mo (95% CI: 17.5 - 31.7)). That is, these younger patients with complete resection (median 100% enhancing resection and median 64% enhancing resection) with an MGMT-unmethylated tumor had survival more similar to those with MGMT-methylation, temozolomide treated patients over the first 3 years of treatment (Supplementary eFigure 4).

	Group 1 (N=75)	Group 2 (N=36)	Total (N=111)
Sex			
Female	28 (37.3%)	13 (36.1%)	41 (36.9%)
Male	47 (62.7%)	23 (63.9%)	70 (63.1%)
Age at Initial Diagnosis			
Mean (SD)	61.7 (11.9)	55.6 (8.1)	59.7 (11.1)
median	65.4	56.8	60.3
Q1, Q3	55.1, 69.9	51.1, 61.8	54.3, 67.2
Range	26.9 - 84.9	30.5 - 65.2	26.9 - 84.9
DiagnosisYear 2005			
Post 2005	75 (100.0%)	36 (100.0%)	111 (100.0%)
KPS Preop cat			
N-Miss	28	13	41
<60	3 (6.4%)	0 (0.0%)	3 (4.3%)
60	3 (6.4%)	0 (0.0%)	3 (4.3%)
70	8 (17.0%)	3 (13.0%)	11 (15.7%)
80	12 (25.5%)	4 (17.4%)	16 (22.9%)
90	18 (38.3%)	14 (60.9%)	32 (45.7%)

100	3 (6.4%)	2 (8.7%)	5 (7.1%)
Tumor Location By Lobe			
Frontal	32 (42.7%)	14 (38.9%)	46 (41.4%)
Brainstem, insular, basal ganglia, or thalamus	4 (5.3%)	2 (5.6%)	6 (5.4%)
Cerebellum	0 (0.0%)	0 (0.0%)	0 (0.0%)
Occipital	3 (4.0%)	2 (5.6%)	5 (4.5%)
Parietal	10 (13.3%)	6 (16.7%)	16 (14.4%)
Temporal	26 (34.7%)	12 (33.3%)	38 (34.2%)
Tumor Location By Hemisphere			
Bilateral	3 (4.0%)	0 (0.0%)	3 (2.7%)
Left	33 (44.0%)	20 (55.6%)	53 (47.7%)
Right	39 (52.0%)	16 (44.4%)	55 (49.5%)
IDH status			
N-Miss	2	1	3
Mutant	2 (2.7%)	1 (2.9%)	3 (2.8%)
Wildtype	71 (97.3%)	34 (97.1%)	105 (97.2%)
MGMT Status			
Methylated	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unmethylated	75 (100.0%)	36 (100.0%)	111 (100.0%)
Adjuvant XRT TMZ			
N-Miss	0	1	1
Both	66 (88.0%)	31 (88.6%)	97 (88.2%)
Neither	3 (4.0%)	0 (0.0%)	3 (2.7%)
Radiation Only	2 (2.7%)	4 (11.4%)	6 (5.5%)
Temozolomide Only	4 (5.3%)	0 (0.0%)	4 (3.6%)
Preoperative contrast-enhancing postgadolinium enhancement			
Mean (SD)	36.5 (31.7)	19.8 (20.6)	31.1 (29.5)
median	29.6	11.4	22.0
Q1, Q3	13.1, 48.2	7.5, 24.5	10.4, 46.4
Range	1.4 - 172.1	0.1 - 82.7	0.1 - 172.1
Preoperative non-enhancing hyperintensity			
Mean (SD)	88.9 (56.9)	61.6 (51.7)	80.0 (56.5)
median	75.6	49.2	64.4
Q1, Q3	41.7, 134.1	24.7, 87.5	32.6, 118.5
Range	10.2 - 219.4	5.6 - 255.1	5.6 - 255.1
Postoperative contrast-enhancing postgadolinium enhancement			
Mean (SD)	5.2 (8.9)	0.1 (0.1)	3.5 (7.7)
median	1.8	0.0	0.4

Q1, Q3	0.4, 5.4	0.0, 0.0	0.0, 3.1
Range	0.0 - 47.0	0.0 - 0.4	0.0 - 47.0
Postoperative non-enhancing hyperintensity			
Mean (SD)	42.8 (38.1)	21.3 (24.4)	35.7 (35.6)
median	32.4	11.1	25.6
Q1, Q3	15.8, 60.0	4.8, 32.6	10.0, 47.4
Range	0.7 - 200.3	0.0 - 105.5	0.0 - 200.3
Contrast-enhancing extent of resection, % by volume			
Mean (SD)	85.9 (17.1)	99.2 (2.5)	90.2 (15.4)
median	93.2	100.0	98.2
Q1, Q3	77.7, 98.5	100.0, 100.0	86.5, 100.0
Range	38.3 - 100.0	86.3 - 100.0	38.3 - 100.0
Non-enhancing extent of resection, % by volume			
Mean (SD)	54.0 (23.2)	63.5 (25.0)	57.1 (24.1)
median	58.0	63.5	59.0
Q1, Q3	40.0, 68.0	44.0, 86.2	40.8, 73.0
Range	0.0 - 97.0	4.0 - 100.0	0.0 - 100.0

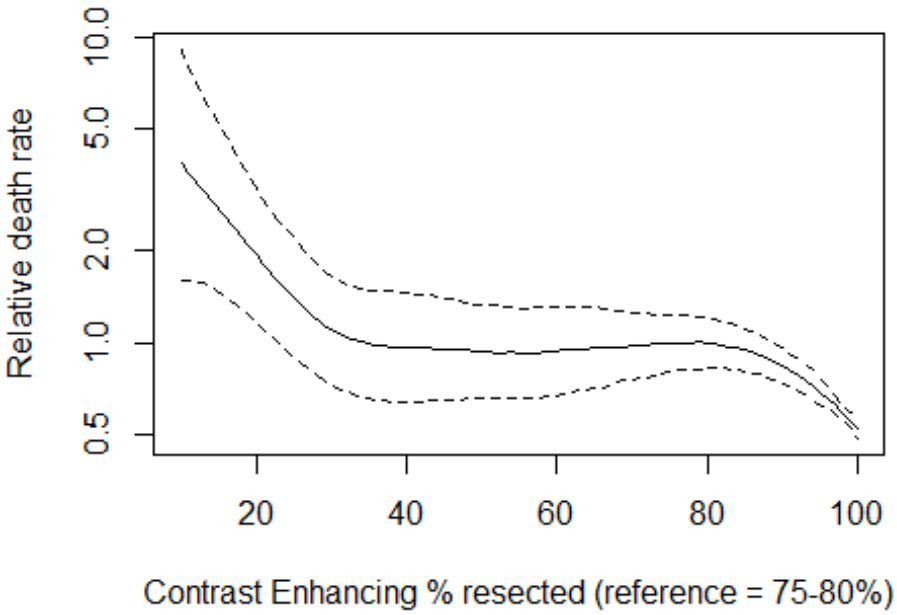
eTable 15. Hazard Ratios for MGMT-Unmethylated Risk Groups

Hazard ratios and 95% confidence intervals for the two risk groups defined by the RPA tree for UCSF MGMT methylation-unmethylated in Supplementary eFigure 6 subset were calculated via the Cox proportional hazards model.

Risk Group	Hazard Ratio (univariable)	Lower Confidence Limit (95%)	Higher Confidence Limit (95%)	p-value
Group 1	1.00			
Group 2	0.28	0.18	0.46	<0.001

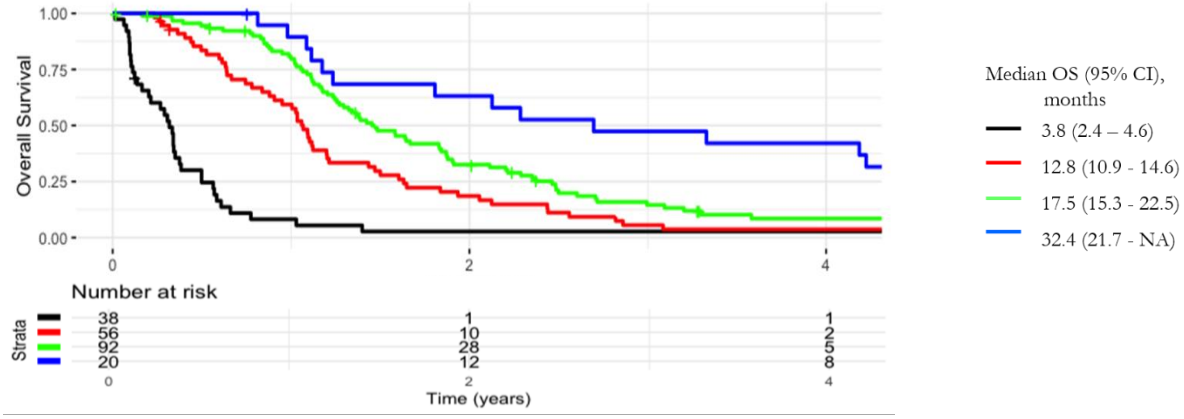
eFigure 1. Univariate Survival Analysis for Contrast-Enhancing Volumetric Resection via Splines

The univariate effect of the percent of contrast-enhancing resected on the relative death rate is shown in a solid line. The reference is a 75-80% reduction (Sanai N 2008) which has a relative death rate of 1. Resections below 40% result in an escalated death rate while those over 80-85% result in a reduced death rate. The 95% upper and lower confidence intervals are shown in dotted lines.



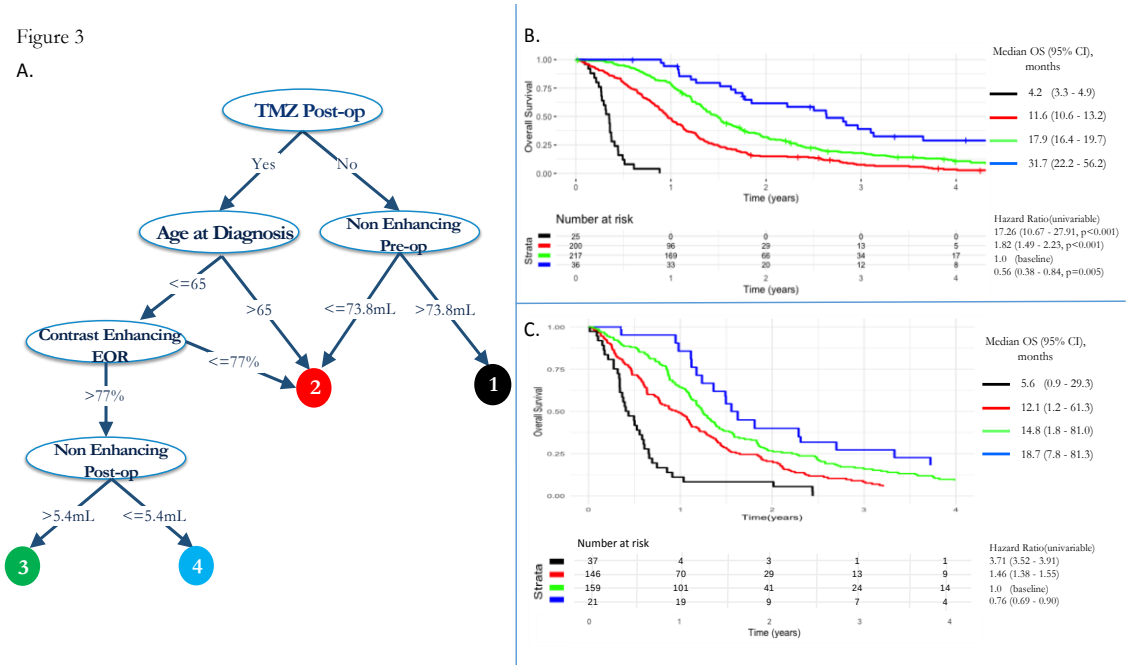
eFigure 2. Survival Curves for External Validation of the Risk Groups

Kaplan-Meier curves, number at risk, median overall survival and hazard ratio for external validation subset.

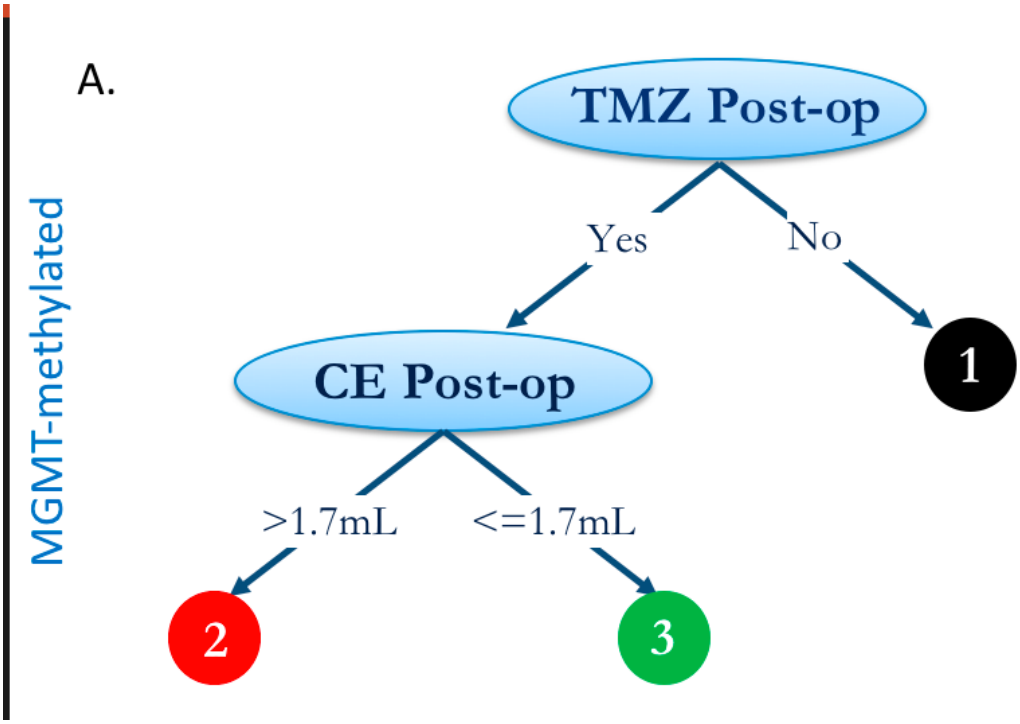


eFigure 3. Recursive Partitioning Analysis and Survival Curves for *IDH*-Wildtype for Risk Groups

Recursive partitioning analysis (RPA) and survival curves for IDH-wildtype subset (n=478). A) Four risk groups were determined by RPA based based on adjuvant temozolomide-treatment (TMZ Post-op), age at diagnosis, and pre-operative non-enhancing tumor volume (NE Pre-op), extent of resection of contrast enhancing tumor (CE EOR), and residual non-enhancing tumor volume (NE Post-op). Groups are denoted by number and color. Group 1 (black) are the patients who did not receive temozolomide and had more than 73.8mL non-enhancing tumor pre-operatively . Group 2 (red) included three groups of patients: those who did not receive temozolomide with less than 73.8mL non-enhancing tumor pre-operatively; those over 65 years of age who did receive temozolomide; and those less than 65 who received temozolomide and had less than 77% contrast enhancing tumor resected. Group 3 (green) are temozolomide-treated patients and under 65 years of age with more than 77% of contrast-enhancing tumor resected and more than 5.4mL residual non-enhancing-tumor. Group 4 (blue) is the temozolomide-treated patients, under 65 years of age with more than 77% of contrast-enhancing tumor resected and less than 5.4mL residual non-enhancing . B.) Kaplan-Meier curves, number at risk, median overall survival and hazard ratio for the four risk groups as determined in A. C.) Kaplan-Meier curves, number at risk, median overall survival and hazard ratio for the validation sets: Mayo Clinical (n=96), Ohio Brain Tumor Study (n=31), and UCSF imputed IDH-unknown glioblastoma patients (on average 230 patients per 1,000 iterations).



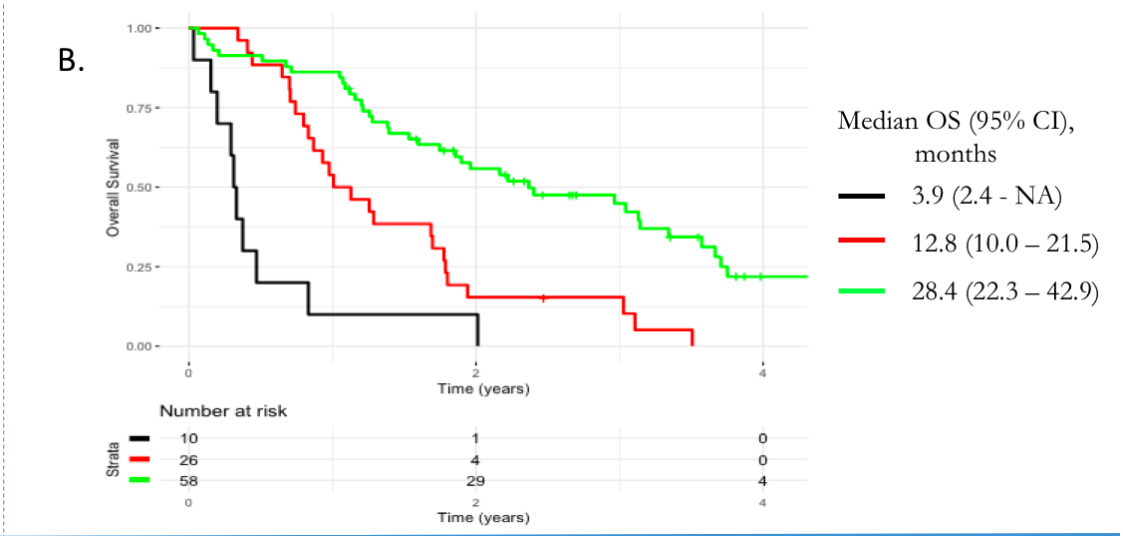
eFigure 4. Recursive Partitioning Analysis for MGMT-Methylated for Risk Groups



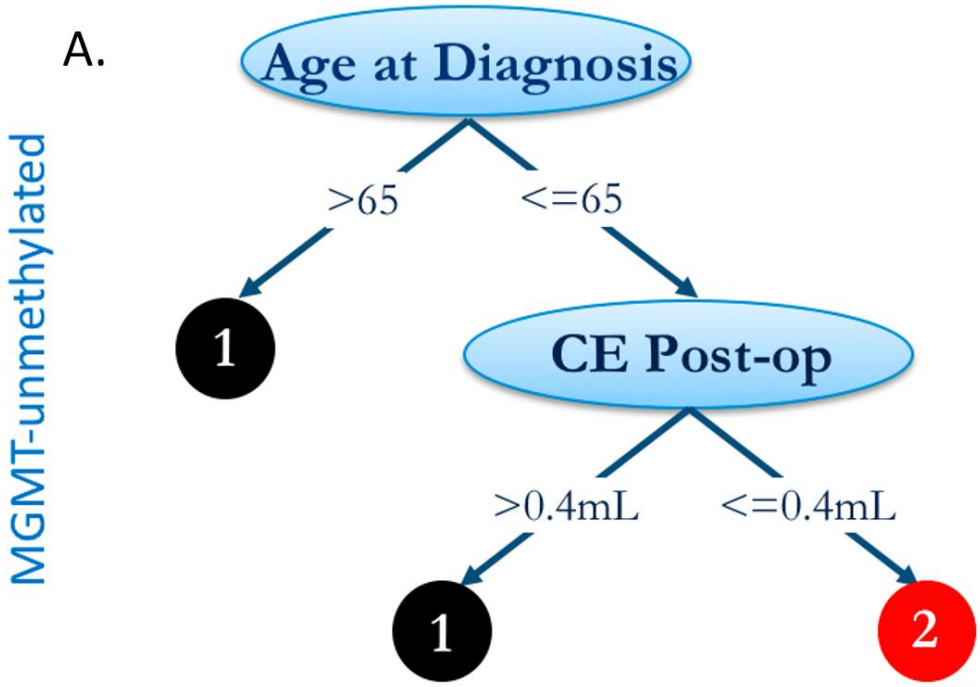
In our subset of patients whose tumors had undergone MGMT methylation analysis (n=205), there were 94 whose tumors were MGMT methylated and 111 whose tumors were MGMT unmethylated. For the patients with MGMT methylated tumors, there were three risk groups by RPA (Supplementary eFigures 4 and 5). Group 1 patients had the poorest survival and were those not treated with temozolomide (Group 1: mOS 3.9mo (95% CI 2.4 - NA)). Group 2 patients had better survival than Group 1 patients and were treated with temozolomide with over 1.7mL enhancing residual tumor (median OS: 12.8mo (95% CI: 10.0 - 21.5)). Group 3 patients fared the best and were temozolomide-treated with less than 1.7mL enhancing residual tumor (median OS: 28.4mo (95% CI 22.3 - 42.9)). Similar to the previous models, patients with the best survival (Group 3) had the highest median enhancing tumor resected (100%) and non-enhancing tumor (63%). Clinical characteristics and HRs are shown in eTables 12 and 13. For the patients with unmethylated tumors, there were two risk groups by RPA (eFigures 6 and 7). Group 1 patients had the poorest survival and included two types of patients: those older than 65; or, those less than 65 with more than 0.4mL residual enhancing tumor (median OS: 11.4mo (95% CI 9.5 - 12.8)). Group 2 patients had the best survival and were those under 65 with less than 0.4mL enhancing residual tumor (median OS: 20.9mo (95% CI: 17.5 - 31.7)). That is, these younger patients with complete resection (median 100% enhancing resection and median 64% enhancing resection) with an MGMT-unmethylated tumor had survival more similar to those with MGMT-methylation, temozolomide treated patients over the first 3 years of treatment (aFigure 4). Characteristics and HRs are shown in Supplementary aTables 14 and 15.

eFigure 5. Survival Curves for MGMT-Methylated Risk Groups

Kaplan-Meier curves, number at risk, median overall survival and hazard ratio for UCSF MGMT-methylated subset.

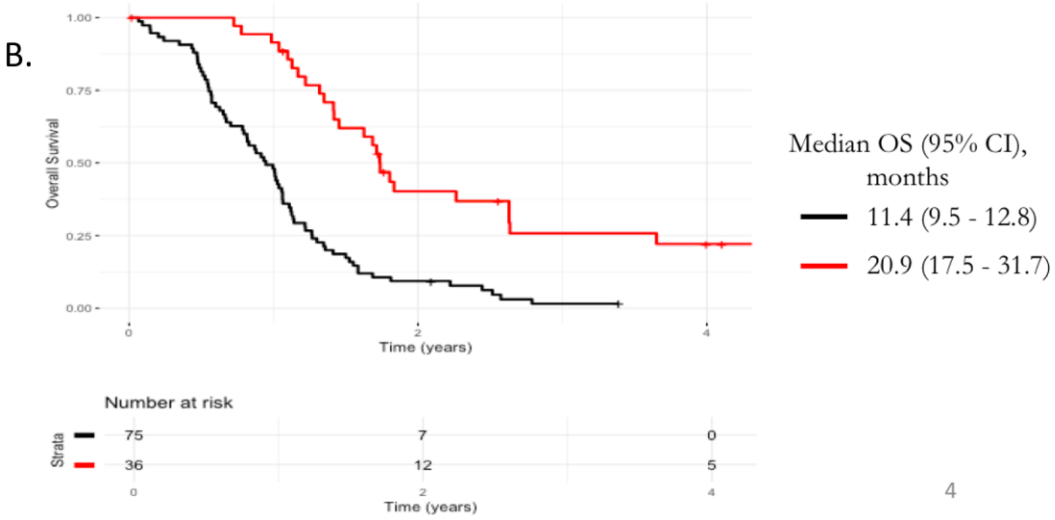


eFigure 6. Recursive Partitioning Analysis for MGMT-Unmethylated for Risk groups



eFigure 7. Survival Curves for MGMT-Unmethylated Risk Groups

Kaplan-Meier curves, number at risk, median overall survival and hazard ratio for UCSF MGMT-unmethylated subset.



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