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Extent of resection as an independent predictor of survival for patients with glioblastoma as defined by the new WHO 2021 classification

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OBJECTIVE Extent of resection (EOR) has previously been demonstrated to have an impact on survival in patients with glioblastoma (GBM). However, with the World Health Organization (WHO) 2021 reclassification of GBMs based on IDH-mutation status, patients with "IDH-mutant GBMs," who typically survive long term, were reclassified as WHO grade 4 IDH-mutant astrocytomas and removed from the GBM taxonomy. Therefore, it is unknown whether the previously reported impact of resection on survival was a false-positive result due to the inclusion of the less aggressive IDH-mutant tumors in previous datasets. This study aimed to determine the extent to which EOR remains an independent predictor of survival in patients with WHO 2021 GBM after the reclassification of IDH-mutant grade 4 astrocytomas.

METHODS All cases of GBM tumors (based on the pre-2021 GBM classification) that were newly diagnosed between 2005 and 2021 were identified in our institutional database and subsequently reclassified based on the updated WHO 2021 criteria using IDH status. Multivariable statistical analyses of demographic information, survival time, and EOR based on volumetric MRI were performed to determine the independent predictors of survival for the whole group of patients and for IDH-wildtype GBM patients exclusively. Additional analyses were performed to identify an EOR threshold for improvement in survival.

RESULTS Of the 523 tumors classified as GBM based on the pre-2021 taxonomy, 52 (9.9%) cases were reclassified as WHO grade 4 IDH-mutant astrocytomas, and the median survival of patients in this group was 7.9 years, whereas median survival of the IDH-wildtype GBM patients was 1.4 years. Multivariate analyses of the whole group demonstrated that IDH-mutant astrocytomas were associated with reduced hazard of death. In both the whole group (n = 523) and in IDH-wildtype GBMs (n = 471), higher EOR of the contrast-enhancing (CE) tumor was associated with reduced hazard of death, whereas older age or male sex was associated with increased hazard of death. Because most patients (90%) had high EOR values (> 81%), a statistically meaningful EOR threshold could not be established.

CONCLUSIONS These analyses demonstrated that EOR of the CE tumor is an independent predictor of survival and that greater EOR is associated with improved survival in WHO 2021 IDH-wildtype GBMs even after excluding grade 4 IDH-mutant astrocytomas. However, an absolute EOR threshold below which resection did not improve survival could not be established, raising concerns about prior cutoff assessments.

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KEYWORDS glioblastoma; IDH-wildtype; extent of resection; oncology; tumor

The long-standing debate surrounding the impact of the extent of resection (EOR) on survival in patients with glioblastoma (GBM) was seemingly settled by the seminal work of Lacroix et al.[1] in 2001, which provided the strongest data until then showing a direct correlation between the EOR of the contrast-enhancing (CE) portion of the tumor and patient survival. Specifically, EOR was found to be an independent predictor of survival, with sta-

ABBREVIATIONS AIC = Akaike information criterion; CE = contrast-enhancing; EOR = extent of resection; GBM = glioblastoma; KPS = Karnofsky Performance Status; NCE = non–contrast-enhancing; WHO = World Health Organization.

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tistically significant improvement in survival associated with ≥ 89% resection (median survival 10.9 months, $p < 0.04$)[1] and highly significant differences associated with ≥ 98% resection (median survival 13 months, $p < 0.0001$). Subsequent studies confirmed this result,[2–4] although the minimum EOR, or cutoff, varied, with Sanai et al. suggesting that ≥ 78% resection provides statistically significant survival benefit, whereas below 78% did not improve survival.[3] These insights have driven advances in surgical techniques to maximize safe tumor removal.[5–8]

As the role of surgery in the management of GBM has evolved, the classification of GBM has also evolved. Traditional histological features that define GBM, including nuclear pleomorphism, frequent mitotic figures, microvascular proliferation, and necrosis, have been augmented by new genetic information. The most impactful of these has been the identification of mutations in the gene encoding isocitrate dehydrogenase (*IDH*),[9] which includes *IDH-1* and its paralogue, *IDH-2*, with mutational hotspots around arginine 132 (R132) in *IDH-1* and R140/R172 in *IDH*-2. Mutations in *IDH-1* were first identified in 2008 in 12% of tumors classified histologically as GBM.[10] *IDH* mutations lead to the production of the oncometabolite, D-2-hydroxyglutarate, which induces epigenetic and metabolic changes[11] that drive tumorigenesis.[12] IDH-mutant astrocytomas with histological features of GBM (necrosis, microvascular proliferation) were previously designated by the World Health Organization (WHO) classification as GBM. However, extensive work has led to the recognition that *IDH* mutations are a defining feature of lower grade astrocytomas, and patients with IDH-*1*/IDH-*2* GBM live significantly longer compared with those with IDH-wildtype GBM (31 months vs 15 months according to the literature).[13] Consequently, in the new WHO 2021 classification,[14] IDH-mutant tumors with histological features of GBM are now classified as "grade 4 IDH-mutant astrocytomas," removing these IDH-mutant tumors from the GBM taxonomy. Since 2011, classifying a tumor as a GBM requires the presence of a wildtype *IDH* gene.

Reclassification of IDH-mutant GBMs as WHO 2021 grade 4 IDH-mutant astrocytomas, and IDH-wildtype GBMs as "true" GBMs,[14] raises the question of whether the association between greater EOR and longer survival in prior GBM studies[1] was merely the result of including the biologically favorable, less aggressive IDH-mutant tumors in these analyses, as IDH status was not considered a variable. This question is even more pertinent given reports indicating that these less aggressive IDH-mutant tumors are more amenable to resection than IDH-wildtype tumors.[15] Whereas a few studies have explored the role of EOR in IDH-wildtype tumors,[5,16–18] detailed analyses of datasets built on pre-2021 GBMs and reclassified based on the post-2021 taxonomy have not been reported. Additionally, no study has addressed the question of a specific cutoff for EOR in WHO 2021 IDH-wildtype GBMs.

Therefore, the objective of this study was to reexamine the impact of EOR on survival in the context of the new WHO 2021 classification of GBM and to determine the minimum EOR at which survival benefit is observed for patients with IDH-wildtype GBMs, similar to the minimum EOR established by previous studies.[1–4] Specifically, we sought to test the null hypothesis that greater EOR is not associated with longer survival once the biologically favorable WHO 2021 grade 4 IDH-mutant astrocytomas are removed from the analysis. We identified a large cohort of patients whose tumors were originally classified as GBM based on pre-2021 WHO classification schemes (similar to the study by Lacroix et al.[1]) and reclassified these tumors as IDH-wildtype GBM or grade 4 IDH-mutant astrocytoma based on the newest 2021 WHO criteria. We then undertook analyses to determine the extent to which increased EOR correlated with improved survival. Our analyses confirmed that EOR was an independent predictor of survival after accounting for IDH-mutant astrocytomas and that greater EOR was associated with improved survival specifically in WHO 2021 IDH-wildtype GBMs.

Methods

Study Design and Patients

A retrospective analysis of prospectively collected data was performed, reclassifying GBM based on the WHO 2021 criteria for IDH-wildtype GBM and grade 4 IDH-mutant astrocytoma. Data were rigorously collected at the time of surgery, routine clinic visits, procedures, or clinical changes to cover patient history and follow-up status with very little missing information. Data were obtained from the patients' medical and imaging records, institutional tumor registry, and the neurosurgery database at MD Anderson under an IRB-approved data collection and banking protocol and data review protocol, both with waivers of informed consent and authorization. For each patient, information was obtained on sex, race, age at surgery, Karnofsky Performance Status (KPS), symptoms and postoperative complications, anatomical tumor location, tumor functional location (noneloquent, near eloquent, eloquent), CE and non–contrast-enhancing (NCE) tumor volumes, IDH status, date of surgery, and date of death or last follow-up. Postoperative KPS was assessed within 48 hours of surgery. The initial data query was limited to patients with histological grade 4 "glioblastoma" who underwent index surgery at MD Anderson between June 1, 2005, and June 30, 2021, allowing for at least 1 year of follow-up and ensuring that all patients had received radiation and temozolomide as standard of care.[19,20] Index surgery was defined as a primary resection or a secondary resection following biopsy or as insufficient resection at another facility but prior to initiation of chemotherapy and radiation. Each patient was then followed until death or censoring occurred.

IDH Status

IDH status was obtained from the pathology reports (immunohistochemistry for IDH-mutant protein and clinically available gene mapping reports) or by directly importing IDH status from an internally maintained molecular databank (MOCLIA Portal). IDH status retrieved using one of the above methods was verified for each patient and cross-checked for inconsistencies, which were then reconciled by manual review of original reports or actual tumor specimens. Only patients with known IDH status were included in the study.

Imaging and Volumetric Data

MR images were reviewed visually to confirm tumor location and functional grade. Quantitative volume assessment was performed as reported previously.[1,21] Imaging data extracted for this study included pre- and postoperative T1-weighted hypointense tumor volume, as well as pre- and postoperative T1-weighted hyperintense tumor volume after intravenous infusion of gadolinium (CE and pre- and postoperative T2-weighted/FLAIR volumes). Preoperative imaging was performed typically within 1 week of the operation and postoperative imaging was performed within 48 hours.

Volumetric data were examined and compared pre- and postoperatively for associations with overall survival. Raw and $\log_2$-transformed volumes were used alone (e.g., preoperative CE volume) and relative to other volumes (i.e., fraction of CE to NCE volume). It was assumed that all NCE volume was tumor volume, and "NCE tumor" refers to T2-weighted/FLAIR volume minus CE volume, while "total tumor volume" refers to total T2-weighted/FLAIR volume including CE volume, per previously published work.[15] Residual tumor was defined by the postoperative volume. EOR of CE tumor was defined by preoperative CE tumor volume minus residual CE tumor volume divided by preoperative CE volume.

Survival Time

Survival analyses began at the date of the index surgery and ended at the date of death. If the date of death was not known, the patient was censored at the date of last follow-up.

Statistical Analysis

Demographic and clinical characteristics were summarized as number (%) or mean (SD), both altogether and separately by tumor type (IDH-wildtype GBM vs grade 4 IDH-mutant astrocytoma). Differences between tumor types were assessed with the chi-square test (discrete variables) or with the t-test and Wilcoxon test (continuous variables). Preoperative and residual CE tumor volume and residual NCE tumor volumes were $\log_2$ transformed to reduce skewness. The time to death or last follow-up by tumor type was summarized with scatterplots and Kaplan-Meier methods.[22] Univariate Cox models[23] were used to assess the association between time to death or last follow-up with each of the variables. For discrete variables with more than two categories, Dunnet-adjusted p values were reported for differences with relation to a reference category. To determine the set of variables that optimally predicted time to death or last follow-up, exhaustive variable selection was performed by fitting the Cox models of all possible combinations of variables, with selection of the optimal predictors based on the combination that yielded the minimum Akaike information criterion (AIC). AIC is an estimation of prediction error that provides information about the strength of the model, where the lowest AIC value corresponds to the best fit. To determine the EOR threshold or cutoff associated with highly significant increase in survival, covariate-adjusted models were generated over a range of EOR thresholds between 20% and 99% (at each 1% increment), where continuous EOR was replaced in the models by the binary threshold. Corresponding accelerated failure time models with log-logistic distributions were utilized to predict median survival at each threshold; the log-logistic distribution was chosen as optimal based on the minimum AIC and residual distribution.

Results

Patient Demographic Characteristics, Imaging, and Molecular Reclassification

From our database, we identified 1234 patients with GBM, classified using pre-2021 WHO criteria, who underwent surgery from 2005 to 2021 (Fig. 1). After the exclusion of patients with missing IDH status (n = 677), missing imaging (n = 29), and incomplete data (n = 5), 523 patients were included in the final analysis (Table 1). All patients were newly diagnosed, underwent surgery, and were treated with concurrent radiation and temozolomide chemotherapy per the current standard of care (Stupp protocol).

The tumors of these 523 patients were reclassified using the WHO 2021 criteria into grade 4 IDH-mutant astrocytoma (n = 52 patients [9.9%]) or IDH-wildtype GBM (n = 471 [90.1%]). The two reclassified groups are compared in Table 1. There were notable differences between IDH-wildtype GBMs and grade 4 IDH-mutant astrocytomas in pre- and postoperative imaging characteristics, preoperative KPS, EOR, residual NCE tumor volumes, and follow-up time. The majority of patients in both groups were White, consistent with the rarity of this disease in other races.

Survival Analysis

Before reclassification, the median (95% CI) overall survival for all 523 patients was 1.5 (1.4–1.7) years. The 1-year, 2-year, and 5-year survival rates were 70.3% (95% CI 66.3%–74.4%), 38.5% (95% CI 34.4%–43.2%), and 18.0% (95% CI 14.5%–22.5%), respectively. After reclassification, the median overall survival for IDH-wildtype GBM patients was 1.4 years (95% CI 1.3–1.6 years) and the 1-year, 2-year, and 5-year survival rates were 68.2% (95% CI 64.0%–72.7%), 34.1% (95% CI 29.8%–39.0%), and 12.0% (95% CI 8.7%–16.6%), respectively. The median overall survival of patients with grade 4 IDH-mutant astrocytomas was 7.9 (95% CI 4.6 to ∞) years, and the 1-year, 2-year, and 5-year survival rates were 86.3% (95% CI 77.3%–96.3%), 73.6% (95% CI 62.2%–87.0%), and 56.9% (95% CI 44.0%–73.5%). The data indicate a clear biological difference between these two tumor types, supporting the exclusion of IDH-mutant tumors from the GBM nomenclature (Fig. 2).

Predictors of Survival: Analysis of Entire Cohort

To determine whether EOR was an independent predictor of survival in the whole cohort (n = 523), we undertook univariate analysis with Cox modeling of survival for each variable listed in Table 1, which revealed that EOR of the CE tumor volume (as a continuous variable), lower postoperative residual tumor volume, classification as a grade 4

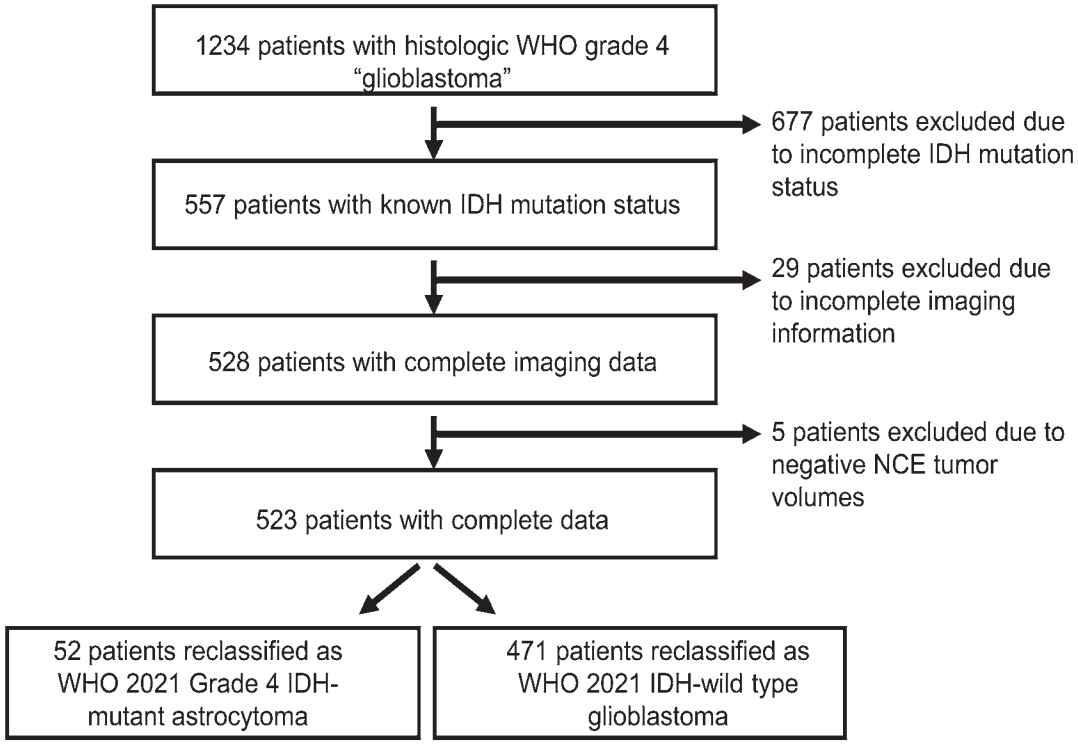

FIG. 1. Patient selection flow diagram. In total, 1234 patients with newly diagnosed GBM who underwent surgery between 2005 and 2021, whose tumors were classified using pre-2021 WHO criteria, were identified in the database maintained by the Department of Neurosurgery at MD Anderson. Patients with missing IDH status (n = 677), missing imaging (n = 29), and incomplete data (n = 5) were excluded, and 523 patients were included in the final analysis.

IDH-mutant astrocytoma, higher preoperative KPS, higher postoperative KPS, and younger age were associated with significantly reduced hazard of death, whereas male sex, presence of preoperative memory loss, and larger preoperative tumor volumes were associated with increased risk of death (Table 2). Additional univariate predictors of survival evaluated in this study are also shown in Table 2.

Multivariate analysis revealed that older age and male sex remained independent predictors of shorter survival (Table 3). Most importantly, classification as a grade 4 IDH-mutant astrocytoma was the strongest predictor of improved survival (HR 0.326, range 0.207–0.513, $p < 0.0001$) and greater EOR (as a continuous variable) of the CE tumor volume was a strong independent predictor of longer survival (HR 0.989, range 0.981–0.996, $p = 0.004$).

Predictors of Survival: Analysis of IDH-Wildtype GBM Exclusively

To determine whether EOR was an independent predictor of survival exclusively in patients with WHO 2021 IDH-wildtype GBM, we repeated the Cox modeling of survival including only WHO 2021 IDH-wildtype GBM. In addition to age and sex, EOR of the CE tumor volume (as a continuous variable) was a statistically significant predictor of improved survival in both univariate (HR 0.99, range 0.093–0.998, $p = 0.017$) (Table 4) and multivariable (HR 0.989, range 0.981–0.997, $p = 0.006$) (Table 5) analyses. These results demonstrate that EOR of the CE tumor volume is an independent predictor of survival even after excluding the biologically favorable grade 4 IDH-mutant astrocytomas from the analysis.

EOR Threshold in IDH-Wildtype GBM

Prior studies suggested a discrete threshold or cutoff for EOR of the CE tumor volume of GBM, below which there was no statistically significant evidence for improved survival, but these studies included both IDH-wildtype and IDH-mutant tumors. To determine the EOR threshold associated with a significant increase in survival in WHO 2021 IDH-wildtype GBM patients (n = 471), we used covariate-adjusted models generated over a range of binary EOR thresholds. Our results demonstrated that ≥ 81% EOR of the CE tumor volume in IDH-wildtype patients was associated with significant survival advantage (Table 6), indicating that EOR values below 81% do not result in statistically significant increase in survival. In addition, consistent with our previous study, patients with ≥ 98% EOR in the IDH-wildtype GBM group had a highly significantly reduced hazard of death ($p < 0.00001$) (Table 6).

Analysis of the EOR values in our dataset raised concerns about potential statistical bias with regard to these threshold values, specifically because few patients had EOR values below 81% (i.e., only 50/471 [10.6%]), as shown in Fig. 3A. This observation raised the possibility that the survival benefit seen above the cutoff value

TABLE 1. Variable frequencies and descriptive statistics by tumor type

	Grade 4 IDH-Wildtype GBM (n = 471)	Grade 4 IDH-Mutant Astrocytoma (n = 52)	p Value
Male sex	292 (62)	35 (67)	0.548
Age at index surgery, yrs	59.7 [11.8]	41.4 [14.8]	<0.001
Symptoms			
Vision symptoms	46 (10)	5 (10)	>0.99
Speech symptoms	72 (15)	3 (6)	0.099
Memory loss	45 (10)	2 (4)	0.267
Weakness	112 (24)	11 (21)	0.802
Seizures	57 (12)	10 (19)	0.215
Other symptoms	263 (56)	31 (60)	0.709
Race			0.441
Asian	14 (3)	4 (8)	
Black or African American	14 (3)	1 (2)	
Hispanic or Latino	13 (3)	2 (4)	
White	403 (86)	43 (83)	
Other/unknown	27 (6)	2 (4)	
Tumor side			0.418
Bilat	18 (4)	4 (8)	
Lt	244 (52)	26 (50)	
Rt	209 (44)	22 (42)	
Tumor functional grade			0.066
Noneloquent	114 (24)	11 (21)	
Near eloquent	152 (32)	25 (48)	
Eloquent	205 (44)	16 (31)	
Preop KPS	84.5 [12.8]	88.3 [10.6]	0.038
Preop subfalcine herniation	46 (10)	5 (10)	>0.99
Preop CE mismatch, cm^3	0.5 [0.3]	0.2 [0.3]	<0.001
Preop NCE tumor vol, cm^3	40.2 [34.3]	88.7 [64.7]	<0.001
Preop CE tumor vol, cm^3	35.1 [27.9]	21.9 [30.2]	0.001
Preop log_2-transformed CE tumor vol, cm^3	4.5 [1.6]	3.2 [2.1]	<0.001
Preop NCE tumor vol, cm^3	75.4 [48.7]	110.6 [69.2]	<0.001
Preop log_2-transformed NCE tumor vol, cm^3	5.8 [1.2]	6.5 [1.1]	<0.001
Preop midline shift, cm	0.2 [0.4]	0.5 [0.7]	<0.001
Postop subfalcine herniation	16 (3)	8 (15)	<0.001
Adverse events	83 (18)	8 (15)	0.833
MGMT promotor methylation	89 (45)	9 (50)	0.869
EOR ≥99%	313 (67)	44 (85)	0.012
KPS ≥90	255 (54)	33 (64)	0.256
Died	355 (75)	24 (46)	<0.001
Time to death or last follow-up, yrs	1.8 [1.7]	4.4 [2.9]	<0.001
Postop KPS	82.6 [11.9]	85.2 [9.8]	0.127
CE EOR, %	94.6 [11.6]	95.7 [13.9]	0.509
EOR of total tumor vol, %	65.9 [22.3]	66.8 [28.6]	0.788
Postop CE mismatch, cm^3	0.1 [0.2]	0.03 [0.1]	0.045
Residual NCE tumor vol, cm^3	26.3 [25.6]	40.7 [45.6]	0.001
Postop midline shift, cm	0.2 [0.4]	0.5 [0.7]	<0.001
Residual CE tumor vol, cm^3	2.1 [5.5]	1.7 [7.1]	0.555
Residual log_2-transformed CE tumor vol, cm^3	0.8 [1.3]	0.4 [1.2]	0.059

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TABLE 1. Variable frequencies and descriptive statistics by tumor type

	Grade 4 IDH-Wildtype GBM (n = 471)	Grade 4 IDH-Mutant Astrocytoma (n = 52)	p Value
Residual total tumor vol, cm^3	28.4 [26.6]	42.3 [46.2]	0.001
Residual log_2-transformed total tumor vol, cm^3	4.0 [2]	4.3 [2.3]	0.355

Categorical variables are displayed using number (%), and continuous variables are displayed using mean [SD].

resulted from an imbalance in sample distribution rather than a true therapeutic effect of surgery. To demonstrate the impact of the distribution of EOR values, we determined the AIC for each model fit to each 1% increment of EOR threshold (EOR thresholds ranged between 20% and 99% at 1% increments, with a separate covariate-adjusted model fit for each threshold) in our dataset (see *Methods*). We observed that the lowest AIC value (strongest model) occurred at EOR > 98% (Fig. 3B, blue line) that coincided with the EOR value at which the majority of data were found (i.e., 323/471 [69%] patients with EOR above 98%), indicating that the EOR threshold was influenced by the distribution of the data. Furthermore, analysis of HR graphed as a function of EOR of the CE tumor volume (Fig. 3B, black line) demonstrated that HR below 81% had wide 95% confidence intervals, leading to low confidence in these threshold values. Next, covariate-adjusted accelerated failure time models were used to predict median survival times as a function of EOR threshold, and the data were graphed as either above or below the threshold (Fig. 3C, red line vs black line). Above a threshold EOR of 81%, we observed increased survival with fairly narrow confidence intervals due to the fact that the analysis included large numbers of patients at each threshold value. In contrast, graphs showing survival time as a function of less than the threshold EOR demonstrated increasingly wide confidence intervals with lower EOR values due to the limited number of data points for EOR values < 81%. Taken together, our results suggest that attaining statistical significance below EOR of 81% in this study was limited by the distribution of the data (few data points < 81%) and not as a result of any intervention. Therefore, while increased EOR of the CE volume above 81% in this cohort of patients was associated with reduced hazard of death, there is little statistical confidence in this value as a "threshold" value given that there were insufficient EOR data points below 81%. Therefore, it is not statistically feasible to identify a cutoff below 81%, although one might exist if such data were available.

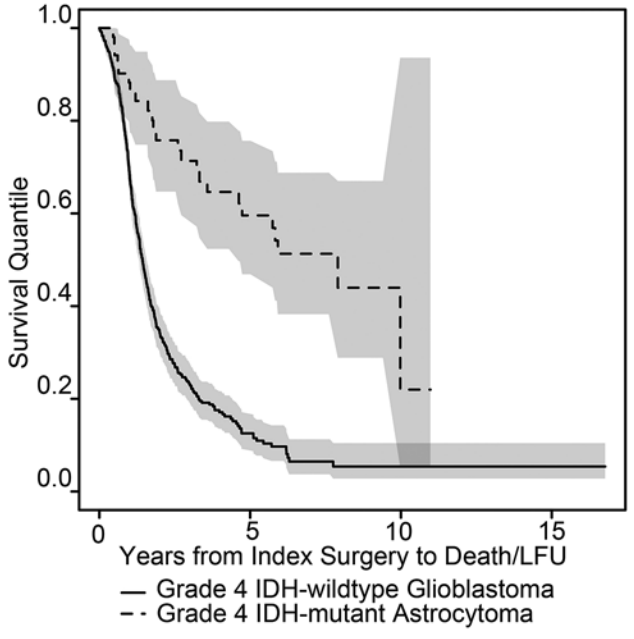

FIG. 2. Patient survival by tumor type: WHO 2021 IDH-wildtype GBM versus WHO 2021 grade 4 IDH-mutant astrocytoma. Unadjusted Kaplan-Meier plot of survival quantile by tumor type, with *shaded* 95% confidence intervals. LFU = loss to follow-up.

Discussion

Previous studies have demonstrated that EOR correlates with extent of survival, although the EOR threshold or cutoff above which this effect is seen varies between studies.[1–4] Importantly, these prior studies predate WHO 2021 reclassification of GBM into IDH-wildtype GBM and IDH-mutant grade 4 astrocytoma, which have significantly different survival outcomes.[14] Although several recent studies have suggested the benefit of increased EOR in IDH-wildtype GBM,[5,16–18] we undertook the current study to fully understand the role of resection in WHO 2021 IDH-wildtype GBM and to determine whether a minimum threshold EOR for survival benefit exists for this group of patients. Specifically, we sought to test the null hypothesis that greater EOR is not associated with longer survival once the biologically favorable WHO 2021 grade 4 IDH-mutant astrocytomas are removed from the analysis. We identified a cohort of 523 patients whose tumors were originally classified as GBM based on pre-2021 criteria and reclassified these tumors based on IDH mutation status as WHO 2021 IDH-wildtype GBM (n = 471) or WHO 2021 IDH-mutant grade 4 astrocytoma (n = 52). Consistent with recent studies, grade 4 IDH-mutant astrocytomas were biologically favorable with a median survival of over 7 years compared with just over 1 year for IDH-wildtype GBM. Multivariable analysis of all 523 patients demonstrated that increased EOR of the CE tumor volume is a predictor of longer survival, independent of tumor type (GBM or grade 4 astrocytoma), confirming prior studies demonstrating the impact of EOR of the CE tumor volume on survival. Importantly, we demon-

TABLE 2. Univariate predictors of survival in all patients (n = 523)

Continuous Variables	HR (range)*	p Value
Older age at surgery	1.026 (1.018–1.035)	**<0.0001**
Grade 4 IDH-mutant astrocytoma	0.265 (0.174–0.405)	**<0.0001**
Preop KPS	0.985 (0.977–0.992)	**<0.0001**
Postop KPS	0.976 (0.967–0.985)	**<0.0001**
Postop KPS >90	0.723 (0.59–0.884)	**0.002**
Preop CE tumor vol	1.004 (1.001–1.007)	**0.012**
Postop CE tumor vol	1.015 (1.002–1.029)	**0.027**
EOR of CE tumor†	0.989 (0.982–0.996)	**0.003**
EOR on T2-weighted FLAIR	1.00003 (0.99993–1.00014)	0.57
Preop midline shift	0.916 (0.72–1.166)	0.48
Postop midline shift	0.921 (0.725–1.172)	0.50
Postop log_2-transformed T1-weighted hyperintense vol	1.187 (1.107–1.274)	**<0.0001**
Postop T2-weighted FLAIR vol	1.001 (0.998–1.004)	0.58
Postop log_2-transformed T2-weighted FLAIR vol	1.026 (0.975–1.079)	0.32
Residual vol on T2-weighted FLAIR only	0.994 (0.99–0.999)	**0.010**
Binary Variables	**HR (range)**	**p Value**
Symptoms		
Visual symptoms	1.085 (0.778–1.511)	0.63
Speech symptoms	1.037 (0.778–1.384)	0.80
Weakness	0.861 (0.674–1.098)	0.23
Memory loss prior to surgery	1.655 (1.196–2.29)	**0.002**
Seizure	0.964 (0.718–1.296)	0.81
Other symptoms	1.016 (0.83–1.245)	0.88
Male sex	1.421 (1.146–1.762)	**0.001**
Preop subfalcine herniation	0.784 (0.472–1.302)	0.35
Postop subfalcine herniation	0.832 (0.508–1.361)	0.46
Postop events	1.115 (0.862–1.444)	0.41
Categorical Variables	**HR (range)**	**p Value**
Race (compared w/ White)		
Asian	0.388 (0.192–0.784)	**0.03**
Black or African American	0.89 (0.511–1.55)	0.96
Hispanic or Latino	1.822 (1.022–3.25)	0.14
Other/unknown	0.676 (0.388–1.177)	0.44
Tumor side		
Lt (vs bilat)	0.614 (0.383–0.984)	0.08
Rt (vs bilat)	0.682 (0.424–1.098)	0.21
Tumor location/functional grade		
Near eloquent (vs noneloquent)	1.054 (0.802–1.386)	0.89
Eloquent (vs noneloquent)	1.189 (0.916–1.543)	0.33

Boldface type indicates statistical significance ($p < 0.05$).

* HR < 1 indicates increased survival.

† HR for EOR of CE tumor refers to HR for EOR as a continuous variable; for every 1% increase in EOR, the HR changes by a factor of 0.989. Therefore, a larger increase in EOR is associated with a larger decrease in HR (e.g., 10% increase in EOR would be associated with $0.989^{10} = 0.895$ HR).

strated that greater EOR remained a significant predictor of longer survival in the subgroup of IDH-wildtype GBM patients. These findings agree with prior studies in favor of complete resection of the CE portion of IDH-wildtype GBM. The completeness of our data allowed us to develop well-adjusted models, adding confidence to the results. Of note, although we attempted to analyze the impact of EOR on survival of the patients with WHO 2021 grade 4 IDH-mutant astrocytoma, the small sample size (n = 52 patients) precluded such an analysis. We are currently pro-

TABLE 3. Multivariate predictors of survival in all patients (n = 523)

Variable	HR (range)*	p Value
Older age at surgery	1.016 (1.007–1.026)	**0.0007**
Male sex	1.603 (1.287–1.996)	**<0.0001**
Grade 4 IDH-mutant astrocytoma	0.326 (0.207–0.513)	**<0.0001**
EOR of CE tumor†	0.989 (0.981–0.996)	**0.004**

Boldface type indicates statistical significance ($p < 0.05$).
* HR < 1 indicates increased survival.
† HR for EOR of CE tumor refers to HR for EOR as a continuous variable; for every 1% increase in EOR, the HR changes by a factor of 0.989. Therefore, a larger increase in EOR is associated with a larger decrease in HR (e.g., 10% increase in EOR would be associated with $0.989^{10} = 0.895$ HR).

spectively accruing cases of WHO 2021 grade 4 astrocytomas for this analysis.

It is important to note that, in our analyses of EOR, the HR for EOR of the CE tumor was calculated as a continuous variable. In our multivariable analysis of the 471 patients with IDH-wildtype GBM, the HR was 0.989. Because EOR was a continuous variable, this result implies that for every 1% increase in EOR of the CE tumor, the HR changes by a factor of 0.989. Therefore, a larger change in EOR is associated with a larger HR. For example, a 10% increase in EOR would be associated with an HR of 0.895 (i.e., HR 0.989^{10}). This increase in HR with incremental increase in EOR is borne out in Table 6, where the HRs are calculated for each EOR. Therefore, increasing EOR is quite impactful on patient outcome.

Given the importance of neurological function for survival, we included postoperative complications and postoperative KPS in our analysis. No statistical association between postoperative complications and survival outcomes was observed in either the whole group of patients or the IDH-wildtype patients, likely due to the relatively low number of significant neurological complications after surgery. Interestingly, lower postoperative KPS was a statistically significant predictor of worse survival in the univariate analysis but was not statistically significant in the multivariate analysis, highlighting both the importance of postoperative neurological function as it relates to survival and the complexity of assessing this outcome.

A second goal of our study was to identify an EOR threshold, below which resection offers minimal survival benefit. Prior studies have differed in terms of the minimum EOR required for significant improvement in survival.[1–4] Using covariate-adjusted models generated over a range of binary EOR thresholds for the CE tumor volumes, we demonstrate that for our dataset ≥ 81% EOR of the CE tumor of WHO 2021 IDH-wildtype GBM is associated with significant survival advantage, whereas resection below this threshold does not show evidence of improved survival. However, an unbiased dive into the analysis revealed that this cutoff was mostly a function of the distribution of the EOR values in our dataset rather than the result of our therapeutic intervention. Specifically, very few of our patients underwent resection < 81%, so there was little statistical power to adjudicate the effects

TABLE 4. Univariate predictors of survival in IDH-wildtype patients (n = 471)

Continuous Variables	HR (range)*	p Value
Older age at surgery	1.017 (1.007–1.027)	**0.0005**
Preop KPS	0.988 (0.981–0.996)	**0.002**
Postop KPS	0.979 (0.969–0.988)	**<0.0001**
Postop KPS >90	0.757 (0.615–0.933)	**0.009**
Preop CE tumor vol	1.002 (0.998–1.006)	0.28
Postop CE tumor vol	1.001 (0.997–1.005)	0.51
EOR of CE tumor†	0.99 (0.983–0.998)	**0.017**
EOR on T2-weighted FLAIR	1 (0.995–1.005)	>0.99
Preop midline shift	0.999 (0.748–1.335)	0.99
Postop midline shift	1 (0.748–1.336)	>0.99
Postop $\log_2$-transformed T1-weighted hyperintense vol	1.166 (1.08–1.258)	**<0.0001**
Postop T2-weighted FLAIR vol	1 (0.996–1.004)	0.92
Postop $\log_2$-transformed T2-weighted FLAIR vol	1.013 (0.961–1.068)	0.64
Residual T2-weighted FLAIR vol only	1.003 (0.997–1.009)	**0.270**
Binary Variables	**HR (range)**	**p Value**
Symptoms		
Visual symptoms	1.082 (0.77–1.522)	0.65
Speech symptoms	0.993 (0.743–1.327)	0.96
Weakness	0.827 (0.642–1.063)	0.14
Memory loss prior to surgery	1.493 (1.07–2.084)	**0.018**
Seizures	1.054 (0.766–1.448)	0.75
Other symptoms	1.028 (0.834–1.268)	0.79
Male sex	1.492 (1.195–1.864)	**0.0004**
Preop subfalcine herniation	0.93 (0.509–1.698)	0.81
Postop subfalcine herniation	0.93 (0.509–1.698)	0.81
Postop events	1.115 (0.854–1.454)	0.42
Categorical Variables	**HR (range)**	**p Value**
Race (compared w/ White)		
Asian	0.454 (0.214–0.963)	0.13
Black or African American	0.711 (0.399–1.266)	0.58
Hispanic or Latino	1.476 (0.785–2.775)	0.55
Other/unknown	0.593 (0.333–1.058)	0.23
Tumor side		
Lt (vs bilat)	0.524 (0.314–0.876)	**0.026**
Rt (vs bilat)	0.564 (0.336–0.945)	**0.056**
Tumor location/functional grade		
Near eloquent (vs noneloquent)	1.099 (0.827–1.459)	**0.73**
Eloquent (vs noneloquent)	1.149 (0.878–1.503)	**0.5**

Boldface type indicates statistical significance ($p < 0.05$).
* HR < 1 indicates increased survival.
† HR for EOR of CE tumor refers to HR for EOR as a continuous variable; for every 1% increase in EOR, the HR changes by a factor of 0.99. Therefore, a larger increase in EOR is associated with a larger decrease in HR (e.g., 10% increase in EOR would be associated with $0.99^{10} = 0.903$ HR).

TABLE 5. Multivariate predictors of survival in IDH-wildtype patients (n = 471)

Variable	HR (range)*	p Value
Older age at surgery	1.017 (1.007–1.027)	**0.0009**
Male sex	1.582 (1.262–1.982)	**<0.0001**
EOR of CE tumor†	0.989 (0.981–0.997)	**0.006**

Boldface type indicates statistical significance ($p < 0.05$).
* HR < 1 indicates increased survival.
† HR for EOR of CE tumor refers to HR for EOR as a continuous variable; for every 1% increase in EOR, the HR changes by a factor of 0.989. Therefore, a larger increase in EOR is associated with a larger decrease in HR (e.g., 10% increase in EOR would be associated with $0.989^{10} = 0.895$ HR).

of resecting < 81% of the tumor. Indeed, the lowest AIC was seen at the EOR values for which we had the most data (i.e., high EOR values). In other words, because most patients had ≥ 81% EOR, it is not surprising that 81% EOR was the statistical threshold EOR value for significant improvement in survival. As such, given the imbalance in the distribution of EOR values in our dataset (only 50/471 patients [10.6%] had resections between 10% and 80%), it is not possible to statistically exclude an EOR threshold of < 81%. From this perspective, the best we can conclude from our data, given the statistical limitations, is that an EOR of 98% corresponds to the lowest HR with the best fit model based on the AIC, suggesting that in this dataset

TABLE 6. Survival by EOR threshold in patients with IDH-wildtype GBM

EOR, %	HR	Min 95% CI	Max 95% CI	p Value	AIC
20	0.203713	0.027932	1.485719	0.12	3250.07
30	0.46703	0.114342	1.907582	0.29	3250.746
40	0.46703	0.114342	1.907582	0.29	3250.746
50	0.626183	0.30795	1.273279	0.20	3250.187
60	0.595524	0.323716	1.095553	0.10	3249.249
70	0.910792	0.568502	1.459171	0.70	3251.495
71	0.864589	0.545565	1.370165	0.54	3251.274
72	0.852446	0.543653	1.336632	0.49	3251.179
73	0.785701	0.51008	1.210254	0.27	3250.519
74	0.736857	0.493793	1.099566	0.13	3249.578
75	0.736857	0.493793	1.099566	0.13	3249.578
76	0.735433	0.499785	1.082187	0.12	3249.398
77	0.735433	0.499785	1.082187	0.12	3249.398
78	0.71129	0.486026	1.040961	0.08	3248.826
79	0.733441	0.508915	1.057024	0.10	3249.084
80	0.717627	0.502055	1.025761	0.07	3248.586
81	0.653986	0.468395	0.913111	0.01264	3246.008
82	0.653986	0.468395	0.913111	0.01264	3246.008
83	0.644282	0.462555	0.897404	0.00931	3245.527
84	0.629854	0.458464	0.865315	0.00433	3244.309
85	0.658779	0.487892	0.88952	0.00645	3244.853
86	0.701205	0.521231	0.943323	0.01900	3246.546
87	0.721274	0.537064	0.968668	0.02989	3247.242
88	0.698411	0.526929	0.925698	0.01252	3245.851
89	0.738958	0.560731	0.973833	0.03169	3247.299
90	0.68333	0.52502	0.889375	0.00463	3244.167
91	0.666552	0.515342	0.86213	0.00200	3242.755
92	0.656544	0.50985	0.845445	0.00111	3241.761
93	0.668079	0.520101	0.858158	0.00159	3242.341
94	0.643695	0.504752	0.820885	0.00038	3239.882
95	0.655961	0.515966	0.833941	0.00058	3240.519
96	0.671796	0.531142	0.849697	0.00090	3241.219
97	0.614633	0.489004	0.772537	0.00003	3235.235
98	0.603919	0.481518	0.757434	0.00001	3233.65
99	0.638914	0.510582	0.799502	0.00009	3236.977

Shaded cells indicate increased survival advantage for that EOR.

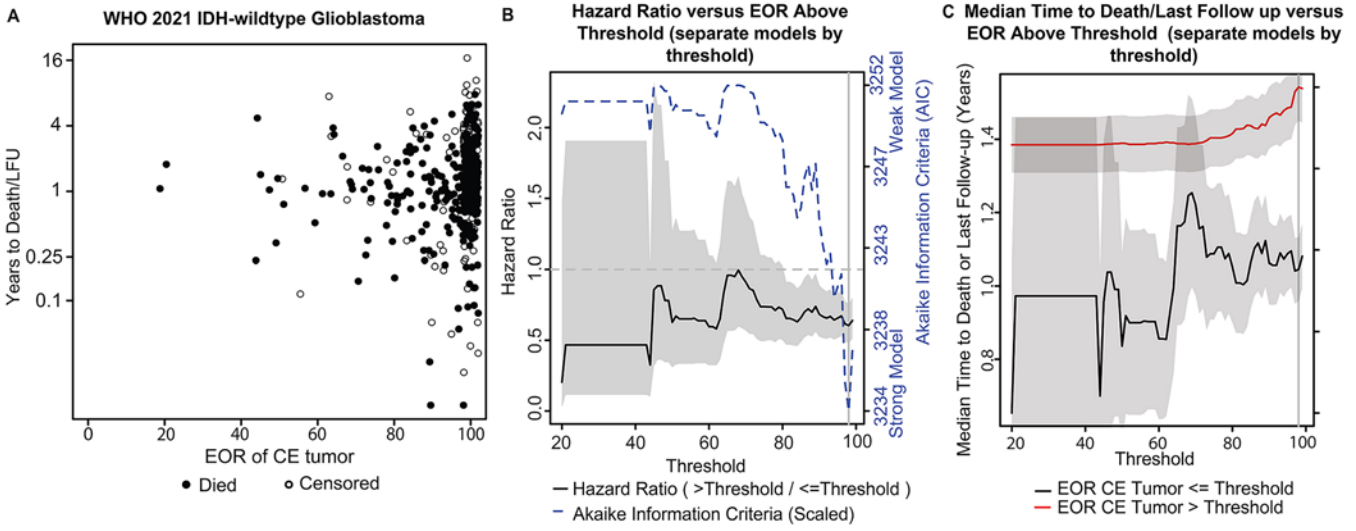

FIG. 3. A: Distribution of patients by EOR and number of years to death or to loss of follow-up (points at 99% EOR have been randomly jittered horizontally ± 2% for clarity). **B:** HR with 95% confidence region (*shaded*) across EOR thresholds (separate models per threshold) and AIC (*blue line*). **C:** Model prediction of median time to death or to loss to follow-up based on EOR thresholds (separate models per threshold) with the standard error (*shaded*) of the confidence regions.

98% is the EOR most reliable threshold value that leads to a highly significant improvement in survival. However, this does not mean that 98% is an *absolute* threshold or that lower EOR values do not result in improved survival. The EOR value at which there is no benefit, or minimal benefit, cannot be adjudicated with our dataset given the limitations of the distribution of the EOR values.

Our data analysis calls into question the cutoffs determined in previous studies because most patients in these prior studies, like those in our study, also had imbalanced EOR distributions that favored high EOR values in most patients. In our study, after exclusion of patients with incomplete imaging data or missing IDH status, we reviewed EOR in 523 patients, and the mean EOR of CE tumor was 94.7% ± 11.9%, and the median was 100%. Other studies that assessed EOR thresholds had similarly high EOR distributions. Specifically, Lacroix et al. (n = 416) reported a mean ± SD EOR of CE tumor of 89% ± 18%.[1] Likewise, Sanai et al. (n = 500) reported a median EOR of CE tumor of 96%,[3] and Molinaro et al. (n = 761) reported a mean EOR of CE tumor of 89.6% ± 17.2% and median 97.5%.[5] These findings suggest that a similar situation around the distribution of the data drove the conclusions reached in these previous studies that attempted to establish an absolute EOR threshold. In other words, in all these previous studies, few patients had resections in the 30%–60% range, for example, and therefore, the studies all lacked statistical power to assess an EOR threshold in this low range. Based on this analysis, we suggest caution when concluding from our data and all previous data that there is a known absolute cutoff below which there is no benefit of surgery. This result does not imply that such a cutoff does not exist but suggests that it has not been accurately defined based on current datasets. In fact, our data suggest that a cutoff below 70% or 80% may exist and may be biologically relevant.

Conclusions

This study establishes EOR of CE tumor as an independent predictor of survival in patients with WHO 2021 IDH-wildtype GBM and challenges the idea of an absolute cutoff for EOR for survival benefit in GBM patients. Our analysis suggests that the reported "cutoff" values are likely driven not by the therapeutic effect of surgery but by the limitation of the statistical analysis, which is dependent on the distribution of data points. Therefore, resection below previously defined "thresholds" may in fact provide a survival advantage. Nevertheless, our data reinforces that the goal of surgery should be as high an EOR as is safely possible, as higher EOR confers increasing survival benefit. Of course, preservation of neurological function should always be part of the decision-making around EOR. A similar analysis of WHO 2021 grade 4 IDH-mutant astrocytoma is warranted.

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Disclosures

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Conception and design: Lang, Catalino, Ballester. Acquisition of data: Catalino, Suki, Prabhu, McCutcheon, Demonte. Analysis and interpretation of data: Lang, Catalino, Andersen, Ramadoss, Poon. Drafting the article: Lang, Catalino, Andersen, Weinberg, Poon, Ferguson. Critically revising the article: Lang, Catalino, Andersen, Ramadoss, Weinberg, Poon, Cezayirli, Brahimaj, McCutcheon, Ferguson, Ene. Reviewed submitted version of manuscript: Lang, Catalino, Andersen, Ramadoss, Prabhu, Weinberg, Poon, Cezayirli, McCutcheon, Ferguson, Ene, Kim, Raza, Demonte. Approved the final version of the manuscript on behalf of all authors: Lang. Statistical analysis: Catalino, Andersen. Administrative/technical/material support: Lang, Catalino, Ramadoss, McCutcheon. Study supervision: Lang, Catalino.

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