

An extent of resection threshold for newly diagnosed glioblastomas

Clinical article

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Object. The value of extent of resection (EOR) in improving survival in patients with glioblastoma multiforme (GBM) remains controversial. Specifically, it is unclear what proportion of contrast-enhancing tumor must be resected for a survival advantage and how much survival improves beyond this threshold. The authors attempt to define these values for the patient with newly diagnosed GBM in the modern neurosurgical era.

Methods. The authors identified 500 consecutive newly diagnosed patients with supratentorial GBM treated at the University of California, San Francisco between 1997 and 2009. Clinical, radiographic, and outcome parameters were measured for each case, including MR imaging–based volumetric tumor analysis.

Results. The patients had a median age of 60 years and presented with a median Karnofsky Performance Scale (KPS) score of 80. The mean clinical follow-up period was 15.3 months, and no patient was unaccounted for. All patients underwent resection followed by chemotherapy and radiation therapy. The median postoperative tumor volume was 2.3 cm³, equating to a 96% EOR. The median overall survival was 12.2 months. Using Cox proportional hazards analysis, age, KPS score, and EOR were predictive of survival ($p < 0.0001$). A significant survival advantage was seen with as little as 78% EOR, and stepwise improvement in survival was evident even in the 95%–100% EOR range. A recursive partitioning analysis validated these findings and provided additional risk stratification parameters related to age, EOR, and tumor burden.

Conclusions. For patients with newly diagnosed GBMs, aggressive EOR equates to improvement in overall survival, even at the highest levels of resection. Interestingly, subtotal resections as low as 78% also correspond to a survival benefit. (DOI: 10.3171/2011.2.JNS10998)

KEY WORDS • oncology • glioblastoma multiforme • extent of resection • survival analysis • volumetric measurement

STANDARD treatment for GBM, the most common primary malignant brain tumor, includes microsurgical resection followed by concomitant chemotherapy and radiation therapy.⁹ Unfortunately, despite decades of refinement, this multimodal approach still leads to a mean survival time of 12–14 months, except for a select group of patients who have methylguanine methyltransferase promoter methylation and are treated with temozolomide (46% 2-year overall survival).^{2,9} Beyond establishing the histological diagnosis and decompressing tumor mass effect, the value of microsurgical resection of GBMs remains controversial. However, in the last decade, mounting evidence suggests that the surgical EOR is associated with better survival of patients with GBM.⁴ Although these data have helped establish a

precarious, and frequently debated, consensus that GBM resection improves patient outcome, the impracticality of conducting a randomized clinical trial limits our ability to quantify the value of greater tumor resection. Simply put, how much tumor resection is enough to make a difference?

To date, only 1 study has attempted rigorous quantification of the survival benefit of a subtotal microsurgical resection for patients with GBM.³ A retrospective analysis combining 416 patients with newly diagnosed and recurrent GBM concluded that a $\geq 98\%$ EOR is necessary to improve survival significantly. In the modern era, this report serves as a critical study of reference for the neurosurgical community, justifying an “all-or-none” approach commonly practiced in the surgical management of GBM.¹² However, although a mixture of newly diagnosed and recurrent GBMs amplified the overall sample size in this study, considerable differences in demographic characteristics, biological features, and outcome distinguish these 2 populations. Furthermore, a subsequent subgroup

Abbreviations used in this paper: EOR = extent of resection; GBM = glioblastoma multiforme; KPS = Karnofsky Performance Scale; RPA = recursive partitioning analysis; 5-ALA = 5-aminolevulinic acid.

analysis of 233 patients with newly diagnosed GBM was probably insufficiently powered, given that nearly half (46%) of the patients had a $\geq 98\%$ tumor resection. Weakness in statistical methodologies also plagued both approaches, because the value of the EOR was assessed using a minimum probability value method.¹ This putative strategy attempts to define a statistical cutoff by arbitrarily categorizing the data set into 2 groups on the basis of a single variable (for example, EOR). Unfortunately, previous oncology studies have demonstrated that this statistical strategy can be misleading and is associated with a 10-fold increase in the false-positive rate.¹ Furthermore, inclusion of a cutoff determined in such a way as a binary variable in a Cox multiple regression analysis can lead to an inflated effect at the expense of other variables that may be more important. Taken together, these study design deficiencies severely hampered a valuable opportunity to detect the “threshold value” beyond which EOR improves outcome in GBMs. Nevertheless, in the absence of a more comprehensive analysis, this EOR study has endured for nearly a decade as a mainstay in our current glioblastoma management paradigm.

Thus, study design sensitivity and certain statistical methodologies can limit the ability to detect small yet meaningful improvements in outcome in patients with GBM following microsurgical resection. This masking effect is likely to be worsened by both the short life expectancy of these patients and the highly aggressive nature of the disease. These formidable limitations, however, can be overcome with a statistically robust analysis of a large, homogeneous population of patients with GBM. Thus, to determine whether a threshold for efficacy exists beyond a complete resection for GBM, the current study focuses on a uniform population of 500 consecutive newly diagnosed adult patients with GBMs treated with immediate microsurgical resection followed by a standard chemotherapy and radiation therapy regimen.

Methods

Patient Population

Between June 1997 and January 2009, 500 consecutive adult patients with newly diagnosed supratentorial GBMs underwent surgery at the University of California, San Francisco Medical Center, followed by standard chemotherapy and radiation therapy. A small number of patients ($< 5\%$) had prior biopsy procedures performed at another institution, but none had undergone previous resection or neoadjuvant therapy. Central pathology review was performed based on WHO guidelines to confirm that all patients had a WHO Grade IV glioma (GBM). In light of evidence suggesting that the gliosarcoma variant differs significantly in biological characteristics and clinical behavior from GBM, patients with gliosarcoma were excluded from the analysis. Clinical, radiographic, and outcome data were collected from inpatient and outpatient records, telephone interviews, and the Centers for Disease Control National Death Index. Patient and treatment characteristics identified for each case included age, KPS score, pre- and postoperative tumor volumes,

adjuvant therapy, volumetric EOR, sites of tumor infiltration (frontal, temporal, parietal, occipital, insular, and/or corpus callosum), and eloquence of tumor location. The institutional review board of the University of California, San Francisco approved this retrospective study. All patients gave written informed consent for the procedure; however, because of the study's retrospective nature, the requirement for informed consent for this study was waived by the institutional review board.

Tumor Volume and EOR

The EOR was determined by comparing MR imaging studies obtained before surgery with those obtained within 48 hours after surgery. A 3D volumetric measurement of pre- and postoperative MR imaging studies was retrospectively conducted by a neurosurgeon in a blinded fashion. Manual segmentation was performed with region-of-interest analysis to measure tumor volumes (in cubic centimeters) on the basis of contrast-enhancing tissue seen on T1-weighted MR imaging. Extent of resection was calculated as follows: (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume. Determination of volumes was made without consideration of clinical outcome.

Statistical Analysis

Age, percent EOR, KPS scores, and tumor volumes were analyzed as continuous variables. To summarize patient and treatment characteristics, medians and ranges were calculated for continuous variables, whereas counts and percentages were defined for categorical variables. Comparison of patient and treatment characteristics among groups was done using the Wilcoxon rank-sum test for continuous or ordinal variables. The Kendall tau correlation was used to assess the correlation between 2 continuous variables.

To evaluate the prognostic value of the variables under consideration, we adopted 2 approaches to tease out both strong and weak associations between EOR and overall GBM survival. The first approach follows the standard method of the Cox proportional hazards model and identifies all EOR categories associated with improved survival. Variables that were significant at the $\alpha = 0.2$ level in the univariate analysis were entered into a multivariate model for consideration. The forward stepwise selection technique was then used to select the final variables to retain. We chose to include only variables that are statistically significant at the $p = 0.01$ level in the final model. Kaplan-Meier curves were then constructed to summarize the relative impact of each EOR category and to identify an EOR threshold, defined by the point at which the survival curves crossed.

A second approach then used RPA to identify the combined prognostic category associated with the maximal impact on overall GBM survival. Our analysis followed the method of exponential scaling,¹⁰ in which the survival time was prescaled to fit a parametric exponential model. Ten-fold cross-validation was used. The program was constrained to have a minimum final node size of 20 patients. The maximum-size tree for which the complex-

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ity parameter exceeds the $p < 0.01$ threshold was chosen as the final tree. Once the tree was selected, the log-rank test with significance level $p < 0.01$ was used to confirm the difference for each split identified by the tree. Any split that did not satisfy this criterion was discarded. The terminal nodes were then compared again, using the log-rank test with the $p < 0.01$ criterion. Final nodes that did not meet the criterion were combined.

Results

For the 500 patients with GBM identified in this study, the median age was 60 years (range 21–90 years), and they presented with a median KPS score of 80 (range 20–100). The mean clinical follow-up duration among surviving patients was 15.3 months (range 5.3–64.2 months), and no patient was lost to follow-up. The median preoperative tumor volume was 65.8 cm³ (range 0.3–476.1 cm³), the most common area of tumor infiltration was the temporal lobe (198 patients [40%]), and most tumors (346 [69%]) occupied an eloquent territory. Intraoperative motor mapping was conducted in 116 patients (23%), language mapping in 43 patients (9%), and subcortical mapping in 34 patients (7%). All patients underwent image-guided microsurgical resection followed by chemotherapy and radiation therapy. The use of different chemotherapeutic agents and radiation therapy protocols was coded for subgroup analysis, although no specific variation was predictive of outcome. The median postoperative tumor volume was 2.3 cm³ (range 0–80 cm³), equating to a 96% median EOR (range 10%–100%). The median overall survival was 12.2 months (range 0.4–142 months) (Fig. 1).

Univariate Cox proportional hazards model analysis was used to examine each collected variable and identify those that are statistically significant at the $p = 0.20$ level (Table 1). These variables were age ($p < 0.0001$), KPS score ($p < 0.0001$), EOR ($p < 0.0001$), preoperative tumor volume ($p = 0.01$), postoperative tumor volume ($p < 0.0001$), tumor eloquence ($p = 0.12$), frontal lobe infiltration ($p = 0.08$), and corpus callosum infiltration ($p = 0.004$). Based on this preliminary survey, a multivariate Cox proportional hazards analysis was built based on the forward stepwise selection technique, with the final model retaining only variables significant at the $p = 0.01$ level. This final analysis designated age ($p < 0.0001$), KPS score ($p = 0.001$), EOR ($p = 0.004$), and postoperative tumor volume ($p < 0.0001$) as predictors of overall survival in patients with GBM.

For specific delineation of the relative impact of subtotal resections, serial Kaplan-Meier survival curves were generated at 2% EOR intervals. A significant survival advantage was seen with as little as 78% EOR, which was associated with a 12.5-month median survival, although the difference in median overall survival widened successively with higher EOR (Figs. 2 and 3). An EOR $\geq 80\%$ equated to a 12.8-month median survival, whereas an EOR $\geq 90\%$ led to a 13.8-month median survival, and EOR of 100% carried a 16-month median survival. Interestingly, stepwise improvement in overall survival was evident even within the 95%–100% range ($p < 0.0001$) (Fig. 4), suggesting a place for additional risk-group stratification within this EOR subgroup.

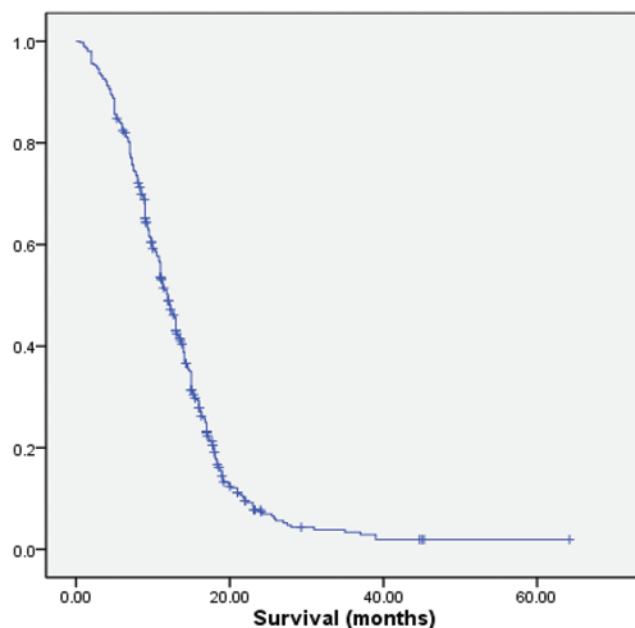


Fig. 1. Kaplan-Meier survival curve for all 500 newly diagnosed patients with GBM, demonstrating a median overall survival of 12.2 months. Numbers on the y axis represent percent survival throughout.

An RPA was then constructed to do the following: 1) validate our statistical analysis described above; 2) identify the EOR category with the largest measurable effect on overall survival; and 3) stratify patients by risk within this highest level of EOR (Fig. 5). The results exactly matched the multivariate Cox proportional hazards analysis, identifying patient age, KPS score, EOR, and tumor volume as each predictive of overall survival ($p < 0.0001$). Also, as indicated by the Kaplan-Meier survival curve analysis, an EOR $\geq 95\%$ had the largest impact on overall survival, with the 316 patients in this EOR category demonstrating a median overall survival of 14.5 months. Within this cohort, RPA branching defined 4 risk groups with successively worse outcomes: Group 1 (EOR $\geq 95\%$, age < 34 years); Group 2 (EOR $\geq 95\%$, age 34–57 years); Group 3 (EOR $\geq 95\%$, age ≥ 58 years, preoperative volume < 13.7 cm³); and Group 4 (EOR $\geq 95\%$, age ≥ 58 years, preoperative volume ≥ 13.7 cm³). Thus, for patients with 95%–100% EOR, these statistically significant stratifications correspond to low-, low-to-moderate,

TABLE 1: Results of a multivariate Cox proportional hazards analysis to assess effect of EOR on survival in patients with GBM*

Variable	HR (95% CI)	p Value
age	1.01 (1.01–1.02)	<0.0001
KPS score	0.99 (0.98–0.99)	0.001
EOR	0.99 (0.98–0.99)	0.004
log (postop tumor vol +1)	1.07 (1.04–1.11)	<0.0001

* This final analysis designated age ($p < 0.0001$), KPS score ($p = 0.001$), EOR ($p = 0.004$), and postoperative tumor volume ($p < 0.0001$) as predictors of overall survival in patients with GBM.

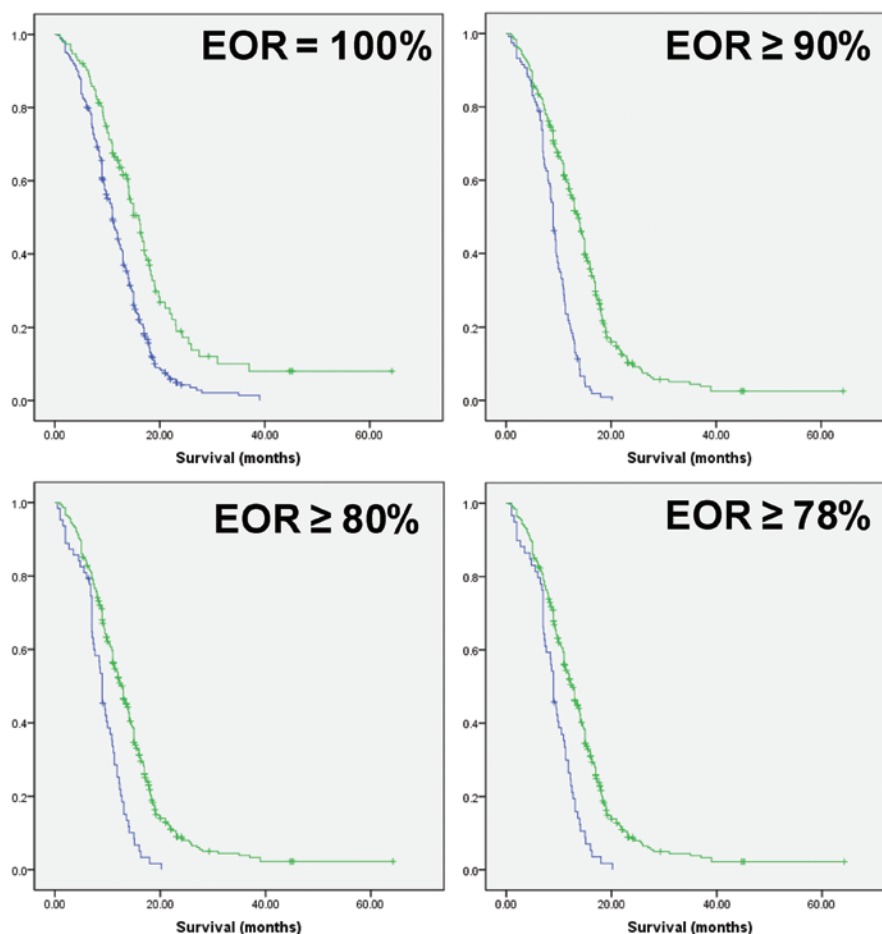


FIG. 2. Select Kaplan-Meier survival curves for 100%, 90%, 80%, and 78% EOR thresholds. Corresponding overall survival times beyond each threshold value were 16, 13.8, 12.8, and 12.5 months, respectively.

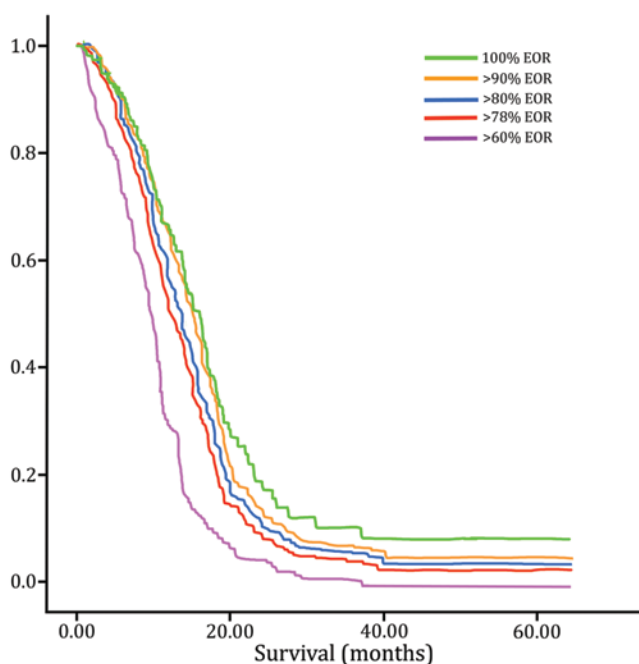


FIG. 3. Overlay of survival curves for total, subtotal, and partial resections.

moderate-to-high, and high-risk subgroups. The 6-month overall survival rates were 100%, 94%, 81%, and 76%, respectively, whereas 2-year overall survival rates were 55%, 16%, 7%, and 0%, respectively (Fig. 6).

Discussion

The value of EOR for gliomas has remained a long-standing topic of debate. Interestingly, the most compelling evidence exists for low-grade gliomas,⁴ where volumetric analyses have shown, both in hemispheric⁶ and insular⁵ low-grade gliomas, that greater EOR portends better overall survival, progression-free survival, and malignant progression-free survival. For high-grade gliomas, however, the evidence has been less consistent and robust. Class I evidence is scarce, due at least in part to the ethical and logistical challenges related to randomizing a subtotal resection. However, 1 prospective, randomized study does exist, comparing biopsy versus debulking for elderly patients with GBM.¹¹ Although the results indicated a survival benefit (5.7 vs 2.8 months) in favor of EOR, the study was unblinded, underpowered, and without adjuvant chemotherapy.

More recently, the ALA-Glioma Study Group evaluated EOR in the context of 260 patients enrolled in a

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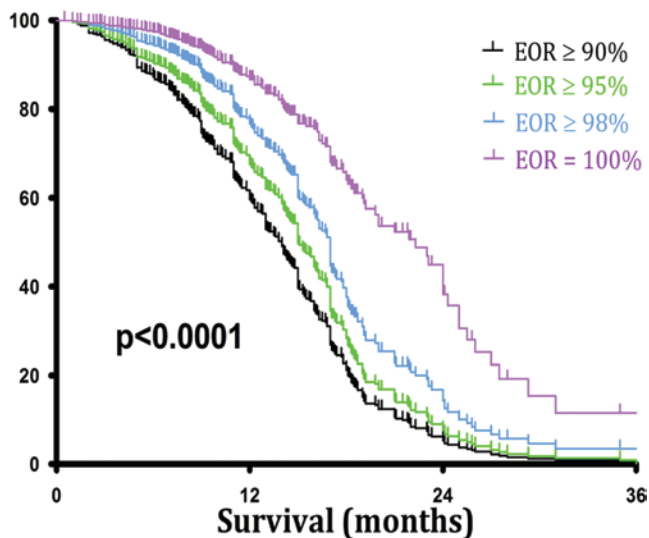


FIG. 4. Stepwise improvement in overall survival when comparing 90%, 95%, 98%, and 100% EOR thresholds.

prospective, randomized multicenter trial examining intraoperative 5-ALA-mediated tumor fluorescence versus conventional white light for high-grade glioma resection.⁷ Although the difference in observed rates of complete resection (65% for 5-ALA vs 36% for white light) presented an unprecedented opportunity to study the impact of EOR, this study was limited by several factors, including investigator bias (surgeons were unblinded), absence of intraoperative neuronavigation, a minimal ($< 10\%$) rate of adjuvant chemotherapy, and use of 6-month progression-free survival as its sole outcome measure. In a follow-up study, however, a more stringent analysis of the original data set was performed, focusing on the 243 randomized patients with WHO Grade IV gliomas and restratifying

them on the basis of complete versus incomplete resection.⁸ Sixteen pre- and postoperative variables were then controlled for across both groups, producing one of the most controlled EOR analyses to date. However, although a 4.9-month survival benefit (16.7 months for complete resections vs 11.8 months for incomplete resections) was reported, the value of a subtotal resection was not assessed beyond these 2 categories.

As described earlier, the most comprehensive work to date on the value of EOR suggests that $\geq 98\%$ is necessary to impact survival in patients with GBM.³ Although these data are valuable, the results nonetheless offer little hope for patients without a complete radiographically confirmed resection. Nevertheless, the “all or none” conceptualization of glioma management has filtered into the mainstream of medical literature. One recent high-grade glioma case analysis published in the *Journal of the American Medical Association* concluded that “Data presented so far show no continuous correlation between the extent of resection and survival; only maximal or gross-total resections affect survival.”¹²

Our findings, based on a more comprehensive and homogeneous patient population, challenge this doctrine by demonstrating that an EOR $\geq 78\%$ can impact patient survival, and that this trend continues even at the highest levels of resection. These data represent the largest reported volumetric outcome study for patients with newly diagnosed GBM, and suggest that EOR is a significant predictor of survival, even when a gross-total resection is not possible. Our statistical analysis also underscores the value of reducing tumor burden to shape outcome, particularly because tumor responses to radiation and chemotherapy are probably nonlinear and are affected by the quantity and distribution of remaining tumor cells. Whereas the 78% threshold represents the minimum value at which any survival benefit is seen, RPA selected

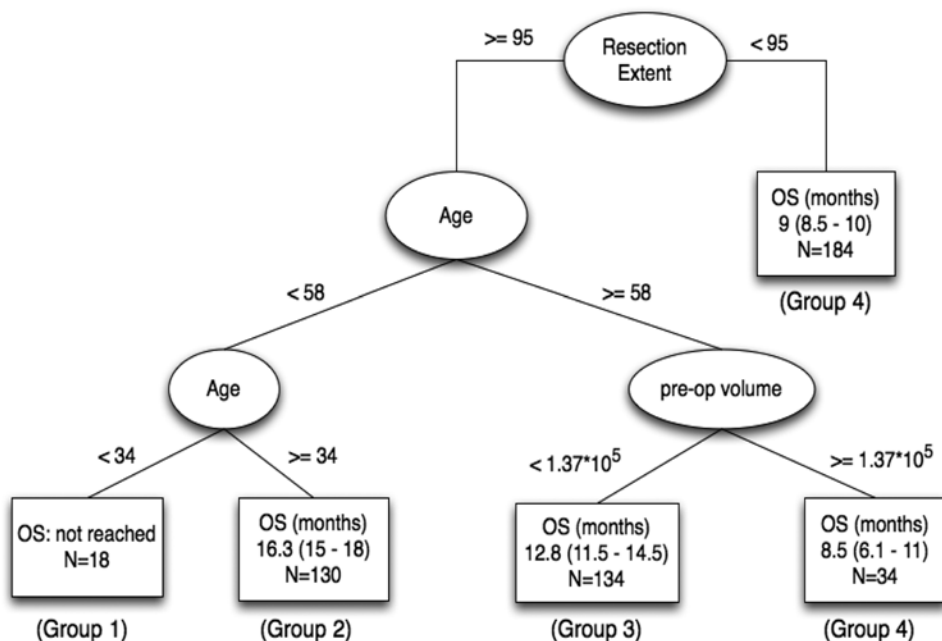


FIG. 5. The RPA results identify each of the following: patient age, KPS score, EOR, and tumor volume as predictive of overall survival (OS) ($p < 0.0001$). Four distinct risk groups are each predictive of outcome.

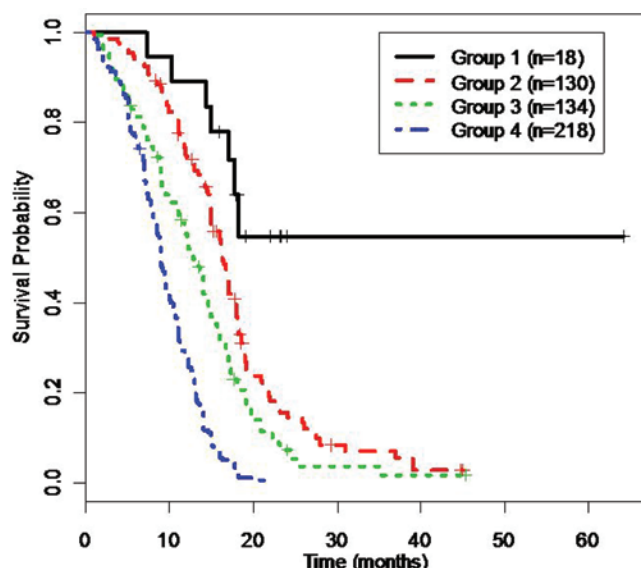


Fig. 6. Kaplan-Meier survival curves for each RPA stratification group demonstrate a stepwise improvement in overall survival.

95% as the most significant predictor of survival in patients with GBM, emphasizing the added value of a complete resection and raising the possibility that additional confounders could impact a lower EOR. Nevertheless, the usual limitations of a retrospective analysis still apply, particularly with respect to the risk of selection bias. Taken together, this analysis supports the value of microsurgical resection for newly diagnosed GBMs when at least 78% of the tumor volume can be resected. In cases in which this does not seem possible, tumor debulking remains a reasonable option to alleviate symptoms due to mass effect and to establish a diagnosis.

Conclusions

The value of EOR for GBMs remains a topic of debate, particularly for incomplete resections. Previous work has fueled this controversy by concluding that a survival advantage is seen only beyond a 98% EOR. Our findings, based on a larger and more homogeneous population of patients with newly diagnosed GBMs, demonstrate that an EOR $\geq 78\%$ impacts patient outcome, and that this trend continues even at the highest levels of resection. Thus, attaining an EOR beyond this threshold should be of critical concern to the neurosurgeon treating a patient with newly diagnosed GBM.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Berger, Sanai. Acquisition of data: Sanai. Analysis and interpretation of data: Berger, Sanai. Drafting the article: Sanai. Critically revising the article: Berger. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Sanai, Polley. Study supervision: Berger, McDermott, Parsa.

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