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Diffusion Magnetic Resonance Imaging Phenotypes Predict Overall Survival Benefit From Bevacizumab or Surgery in Recurrent Glioblastoma With Large Tumor Burden

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BACKGROUND: Diffusion magnetic resonance (MR) characteristics are a predictive imaging biomarker for survival benefit in recurrent glioblastoma treated with anti-vascular endothelial growth factor (VEGF) therapy; however, its use in large volume recurrence has not been evaluated.

OBJECTIVE: To determine if diffusion MR characteristics can predict survival outcomes in patients with large volume recurrent glioblastoma treated with bevacizumab or repeat resection.

METHODS: A total of 32 patients with large volume (>20 cc or > 3.4 cm diameter) recurrent glioblastoma treated with bevacizumab and 35 patients treated with repeat surgery were included. Pretreatment tumor volume and apparent diffusion coefficient (ADC) histogram analysis were used to phenotype patients as having high (>1.24 μm^2/ms) or low (<1.24 μm^2/ms) ADC_L, the mean value of the lower peak in a double Gaussian model of the ADC histogram within the contrast enhancing tumor.

RESULTS: In bevacizumab and surgical cohorts, volume was correlated with overall survival (Bevacizumab: $P = .009$, HR = 1.02; Surgical: $P = .006$, HR = 0.96). ADC_L was an independent predictor of survival in the bevacizumab cohort ($P = .049$, HR = 0.44), but not the surgical cohort ($P = .273$, HR = 0.67). There was a survival advantage of surgery over bevacizumab in patients with low ADC_L ($P = .036$, HR = 0.43) but not in patients with high ADC_L ($P = .284$, HR = 0.69).

CONCLUSION: Pretreatment diffusion MR imaging is an independent predictive biomarker for overall survival in recurrent glioblastoma with a large tumor burden. Large tumors with low ADC_L have a survival benefit when treated with surgical resection, whereas large tumors with high ADC_L may be best managed with bevacizumab.

KEY WORDS: Diffusion MRI, ADC histogram analysis, T1 subtraction, Recurrent glioblastoma, Bevacizumab

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Glioblastoma continues to be a devastating disease with a uniformly poor prognosis of 14 to 21 mo from diagnosis[1-3] and only a small proportion of patients survive more than 5 yr.[1-3] Standard of care for patients with newly diagnosed glioblastoma includes concurrent temozolomide plus radiation therapy, followed by temozolomide with or without tumor treating fields.[1-3] Upon recurrence few effective treatment options exist, and this is acutely true in patients with large volume recurrence, who are more likely to be transitioned to supportive care.[4] Bevacizumab was approved for use in recurrent GBM in 2009 after it was shown to improve progression-free survival[5,6]; however, randomized phase II trials have not demonstrated an overall survival (OS) benefit when including all patients with recurrent GBM[5,7]

ABBREVIATIONS: ADC, apparent diffusion coefficient; **BTIP,** brain tumor imaging protocol; **MGMT,** 06-methylguanine-DNA methyltransferase; **MR,** magnetic resonance; **MRI,** magnetic resonance imaging; **OS,** overall survival; **VEGF,** vascular endothelial growth factor; **VOI,** volume of interest

despite widespread exploration of a number of anti-vascular endothelial growth factor (VEGF) therapies in recurrent GBM.

Although bevacizumab remains an important therapeutic agent for treatment of recurrent GBM, as almost all patients will be exposed to bevacizumab sometime during treatment of their disease, contemporary use in the academic centers in the US tends to be limited to patients who have had multiple relapses or treatment failures, patients who have large tumors or extensive cerebral edema, and/or patients who otherwise have no other treatment or clinical trial options, with additional use among less specialized practitioners.[8] Therefore, there is a significant clinical need to identify large volume recurrent GBM patients that may have a significant survival benefit from treatment of anti-VEGF therapy to guide therapy at this clinical junction.

One strategy to identify these patients is to use pretreatment imaging as a proxy for underlying biologic characteristics. One example of this is the use of diffusion magnetic resonance imaging (MRI). Diffusion MRI serves as biomarker for glioma cellularity, with clinical apparent diffusion coefficient (ADC) and tumor cell density being negatively correlated.[9] These areas, hypothesized to be areas of active and rapid cell growth are important targets for surgical resection, with residual low ADC/high cellularity areas serving as a poor prognostic marker.[4,10,11] The connection between differences in diffusion imaging and underlying tumor biology may allow diffusion MRI to serve as a prognostic marker.

Extensive retrospective data in both single-center and multi-center phase II trials in recurrent GBM have suggested that pretreatment diffusion MRI characteristics are predictive of overall survival when treated with anti-VEGF therapies including bevacizumab, cediranib, cabozantinib, and aflibercept; but are not predictive of overall survival when treated with cytotoxic chemotherapies.[12-14] Specifically, patients with elevated ADC_L, the mean value of the lower peak in a double Gaussian mixed model applied to ADC measurements in contrast enhancing tumor, were found to have a significant survival benefit in recurrent GBM treated with anti-VEGF therapy compared to patients with a low ADC_L. Therefore, we hypothesize contemporary recurrent GBM patients with large tumor burden exhibiting high ADC_L will have a significant survival advantage when treated with bevacizumab compared to large tumors with low ADC_L. Additionally, since low ADC_L may imply a more densely packed tumor, we hypothesize that patients with low ADC_L may benefit from an additional surgery compared to treatment with bevacizumab. Therefore, the objective of the current retrospective study was to first confirm that diffusion magnetic resonance (MR) phenotypes can predict survival in large recurrent GBMs treated with bevacizumab and second to test whether these same phenotypes can predict patients who may have value a survival benefit from an additional surgical resection.

METHODS

Patient Population

Institutional review board approval was obtained for this study. Written consent was obtained from all patients prior to treatment. We retrospectively gathered clinical and imaging data for patients treated with recurrent glioblastoma at our institution. Clinical decision making to treat with bevacizumab or repeat surgery was not informed by diffusion MRI phenotypes analysis and was the decision of the care provider team.

Bevacizumab-Treated Recurrent GBM

Written consent was obtained from all patients prior to treatment. A total of 80 recurrent glioblastoma patients from our institution who were treated with bevacizumab over the past 5 yr with high quality anatomic and diffusion MRI data were included. Specifically, inclusion criteria included: 1) pathologically confirmed glioblastoma with recurrence based on MR imaging; 2) no previous exposure to anti-VEGF therapy; 3) treatment with bevacizumab (5-10 mg/kg body weight with or without adjuvant chemotherapy) occurring at least 3 mo after completion of radiation therapy to decrease the chance of treatment-induced pseudoprogression; and 4) pretreatment MR imaging including diffusion MR images available. Of the 80 patients identified, 32 had large contrast enhancing tumors (>20 cc or > 3.4 cm diameter, group average) for use in final analyses. Of these 32 patients, 19% patients were treated with bevacizumab monotherapy while 81% of patients were treated with bevacizumab and concurrent chemotherapy including temozolomide and small molecular inhibitors.

Recurrent GBM Treated with Additional Surgical Resection

A total of 71 patients with recurrent GBM underwent a repeat surgical resection and met the following inclusion criteria: 1) pathologically confirmed glioblastoma with recurrence based on MR imaging; 2) no previous exposure to anti-VEGF therapy; 3) pretreatment MR imaging including diffusion MRI available; and 4) underwent repeat second surgical resection at least 3 mo after completion of radiation therapy. Of these 71 patients, 35 patients had large (>20 cc or 3.4 cm diameter) contrast enhancing tumors for use in the final analysis. Of these 35 patients, 60% received bevacizumab sometime during the course of their disease, after repeated resection surgery, while 40% did not receive bevacizumab.

Anatomic and Diffusion MRI Acquisition

Standard and diffusion MR data were acquired in a manner previously used for ADC analysis.[12-14] Specifically, MR data were acquired using either a 1.5T or a 3T MR scanner from an MR scanner manufactured by Siemens Healthcare (Erlangen, Germany) or GE Medical Systems (Waukesha, Wisconsin). All patients received pre- and postcontrast T1-weighted images (gadopentetate dimeglumine [Magnevist; Berlex], at a concentration of 0.1 mmol/kg) along with T2-weighted and T2-weighted FLAIR images according to the standardized brain tumor imaging protocol (BTIP).[15] In addition, all patients received either diffusion weighted imaging according to BTIP recommendations[15] (3 mm slice thickness with no interslice gap with b-values of 0, 500, and 1000 s/mm^2) or diffusion tensor imaging with 64 directions and 2 mm isotropic resolution with b-values of 0 and 1000 s/mm^2. ADC maps were calculated offline using $b = 0$ s/mm^2 and $b = 1000$ s/mm^2

images. Anatomical T2-weighted and T2-weighted FLAIR images were not used in the current study. All examinations were acquired within 14 d of starting therapy.

Contrast-Enhanced T1-Weighted Digital Subtraction Maps (T1 Subtraction Maps)

We have previously described our methods for creation of T1 subtraction maps.[12,16,17] Briefly, T1-weighted MR images with and without contrast were registered using FSL (FLIRT; FMRIB Software Library, Oxford, England; http://www.fmrib.ox.ac.uk/fsl/). Intensities were normalized using the National Institutes of Mental Health Magnetoencephalography 3Core Facility (3dNormalize; NIMH MEG Core, Bethesda, Md; *kurage.nimh.nih.gov/meglab/Med/3dNormalize*) and the following equation: $[S_{Nor}(x, y, z) = S(x, y, z)/\sigma_{WB}]$ (S_{Nor} = *normalized image intensity; S = unnormalized image intensity; WB = whole brain).* These normalized images underwent voxel by voxel subtraction of intensities (Figure 1A and 1B). The resultant subtraction map was manually reviewed for quality control and contrast enhancing regions were identified to signify a volume of interest for further analysis (Figure 1C and 1D).

ADC Histogram Analysis

We have previously described our methods for ADC Histogram Analysis.[12,16,17] ADC characteristics within T1 subtraction-defined enhancing tumor volumes were used for ADC histogram analysis (Figure 1E-1H). Nonlinear regression using a double Gaussian mixed model was performed to parameterize ADC histograms using GraphPad Prism, Version 4.0c (GraphPad Software, San Diego, California) or MATLAB (Release 2018b Version 9.5.0). The double Gaussian equation used was:

$$p(ADC) = f\,.\,N(\mu_{ADC_L}, \sigma_{ADC_L}) + (1 - f)N(\mu_{ADC_H}, \sigma_{ADC_H})$$

In this equation, p(ADC) = ADC probability; f = lower histogram members (voxels); $N(\mu, \sigma)$ = normal Gaussian distribution; ADC_L = lower Gaussian distribution; ADC_H = upper Gaussian distribution (Figure 1I, 1J). These regressions were manually reviewed for quality control and fit was evaluated with adjusted $R^2 > 0.7$.[12,13,18-20]

Statistical Analyses and Interpretation

Analysis was carried out between ADC_L phenotypes (low or high ADC_L) and treatment groups (bevacizumab or surgery). Unpaired *t*-tests with and without Welch's correction for unequal variance were used to test differences in tumor measurements and demographic characteristics between treatment groups. Continuous values of volume and ADC_L phenotypes using a previously described threshold of 1.24 μm^2/ms were used to predict OS for each therapy using a combination of log-rank analyses on Kaplan Meier data and Cox proportional hazard models of age, tumor volume and ADC_L phenotypes. For all analyses, $P < .05$ was considered statistically significant. No corrections for multiple comparisons were performed. Statistical analyses were performed with Stata 12 (2011; College Station, Texas) or GraphPad Prism v6.0 h (GraphPad Software, Inc., La Jolla, California) All errors are presented in standard error of the mean.

RESULTS

We identified 80 patients receiving bevacizumab and 71 patients receiving repeat surgery within our Neuro Oncology Database in whom the initial inclusion criteria were satisfied; of which 32 bevacizumab patients (40%) and 35 surgical patients (49%). The overall group average was 20 cc or ~3.4 cm in diameter and this was used as a cut off for large tumor recurrence. No difference in volume (Figure 2A and Table 1; $P = .536$) was observed between the bevacizumab-treated patients with large tumors (average = 43.7 cc, range 20-144 cc) or large tumors treated with repeat resection (average = 39.9 cc, range 20-93 cc), nor was there any significant difference in ADC_L (Figure 2B; $P = .085$) or average age (Table 1; $P = .982$). Patients treated with bevacizumab had an average of 2.0 recurrences prior to treatment whereas surgical patients had an average of 1.3 ($P < .001$). There were no significant differences in prognostic genetic characteristics between two groups including IDH mutation (3.1% vs 5.7%; $P = .615$) and 06-methylguanine-DNA methyltransferase (MGMT) promoter methylation (31.3% vs 25.7%; $P = .622$). High ADC_L tumors were associated with higher rates of IDH mutation, but this was not statistically significant (5.3% vs 3.5% $P = .727$). There was no significant difference in prior salvage therapy. This included lomustine (28.1% vs 20%; $P = .444$), Toca 511/FU (9.4% vs 8.6%; $P = .910$), checkpoint inhibitors (pembrolizumab, nivolumab, 18.8% vs 20%; $P = .899$), and EGFR inhibitors (9.8% vs 5.7%; $P = .576$). There was no difference between time from initial treatment to treatment for large volume recurrence (either bevacizumab or repeat surgery) (16.51 vs 16.50 mo; $P = .999$). According to our data, patients with large enhancing tumors, in general, had a significant survival advantage if treated with repeat surgical resection compared with bevacizumab (Figure 2C; Log-rank, $P = .0376$, HR = 1.65, median OS = 7.6 vs 4.3 mo). Given the importance of initial extent of resection on overall survival in glioblastoma, we evaluated whether initial extent of resection affected overall survival after large volume recurrence. Gross total resection was achieved in 41 (62%) patients, subtotal resection in 22 (33%) and biopsy only in 4 (6%). There was no significant difference in overall survival from recurrence in patients who had initial gross total or subtotal resection (median survival 5.8 vs 5.5 mo; Log-Rank $P = .732$). However, there was a trend towards increased survival advantage was larger in patients with gross total resection relative to subtotal resection on repeat surgery (median survival 8.3 vs 5.8 mo; Log Rank $P = .516$). There was no difference in ADC phenotypes in patients with gross total resection or subtotal resection (42.8% each; $P > .99$). There were no new permanent postoperative neurologic deficits after repeat surgery.

Effects of Pretreatment Tumor Volume on Survival

Cox proportional hazard regression analyses considering the effects of age and pretreatment tumor volume were carried out separately for bevacizumab and surgical patients. Results

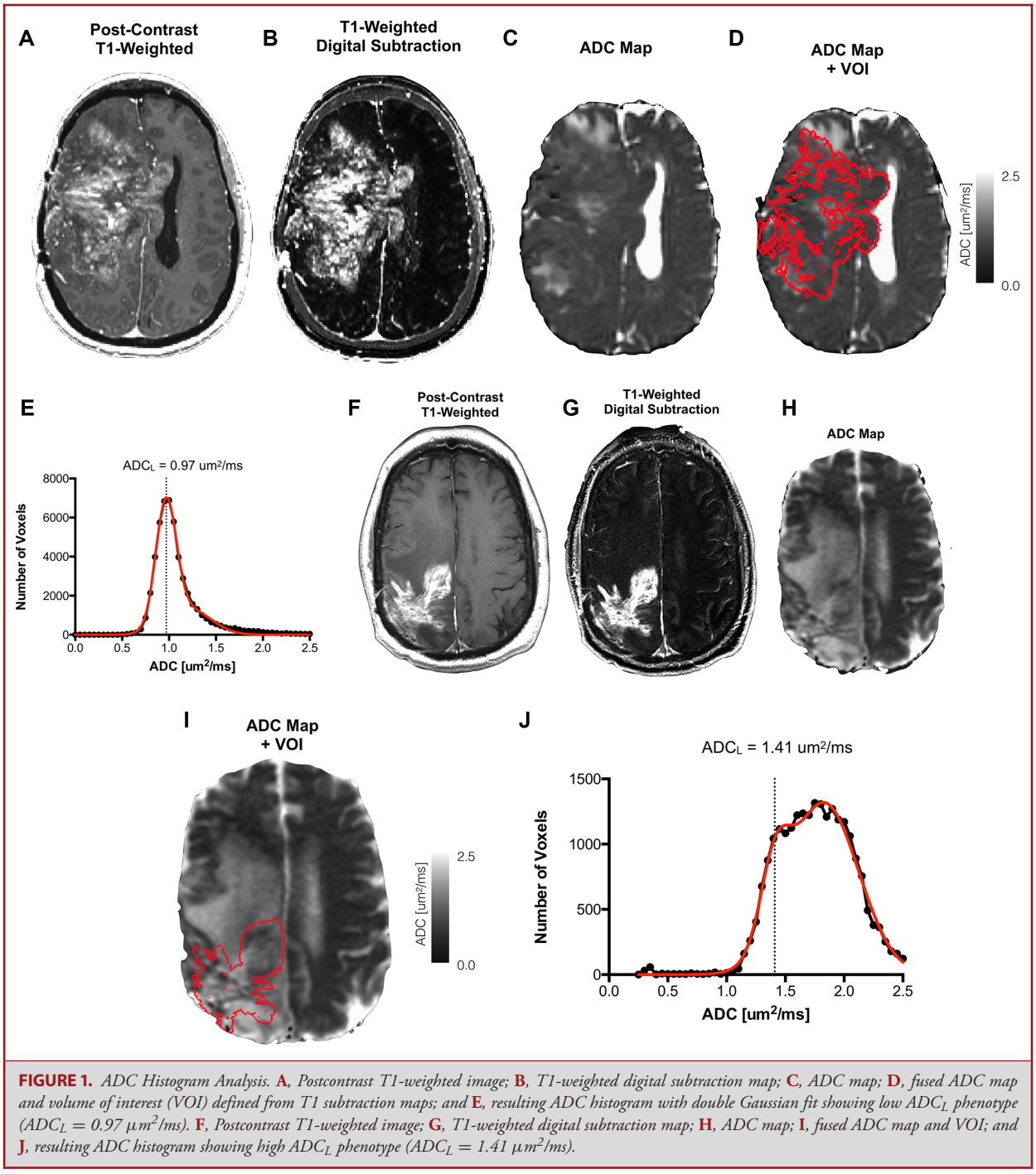

FIGURE 1. *ADC Histogram Analysis.* **A**, *Postcontrast T1-weighted image;* **B**, *T1-weighted digital subtraction map;* **C**, *ADC map;* **D**, *fused ADC map and volume of interest (VOI) defined from T1 subtraction maps; and* **E**, *resulting ADC histogram with double Gaussian fit showing low ADC_L phenotype ($ADC_L = 0.97\ \mu m^2/ms$).* **F**, *Postcontrast T1-weighted image;* **G**, *T1-weighted digital subtraction map;* **H**, *ADC map;* **I**, *fused ADC map and VOI; and* **J**, *resulting ADC histogram showing high ADC_L phenotype ($ADC_L = 1.41\ \mu m^2/ms$).*

indicated that tumor volume was a significant predictor of survival in both groups (Table 2); however, bevacizumab-treated patients had worse outcome with increasing tumor burden (Cox, $P = .009$, HR = 1.02), whereas patients treated with repeated resection had better outcome if they were larger prior to surgery (Cox, $P = .006$, HR = 0.96).

Diffusion MR Phenotypes Predict Survival in Recurrent GBM Treated With Bevacizumab

A total of 15 of the 32 (47%) bevacizumab treated patients and 15 of the 35 (43%) patients treated with surgery had a low ADC_L phenotype (<1.24 $\mu m^2/ms$). Cox regression including age, tumor volume, and ADC_L phenotype confirmed that both

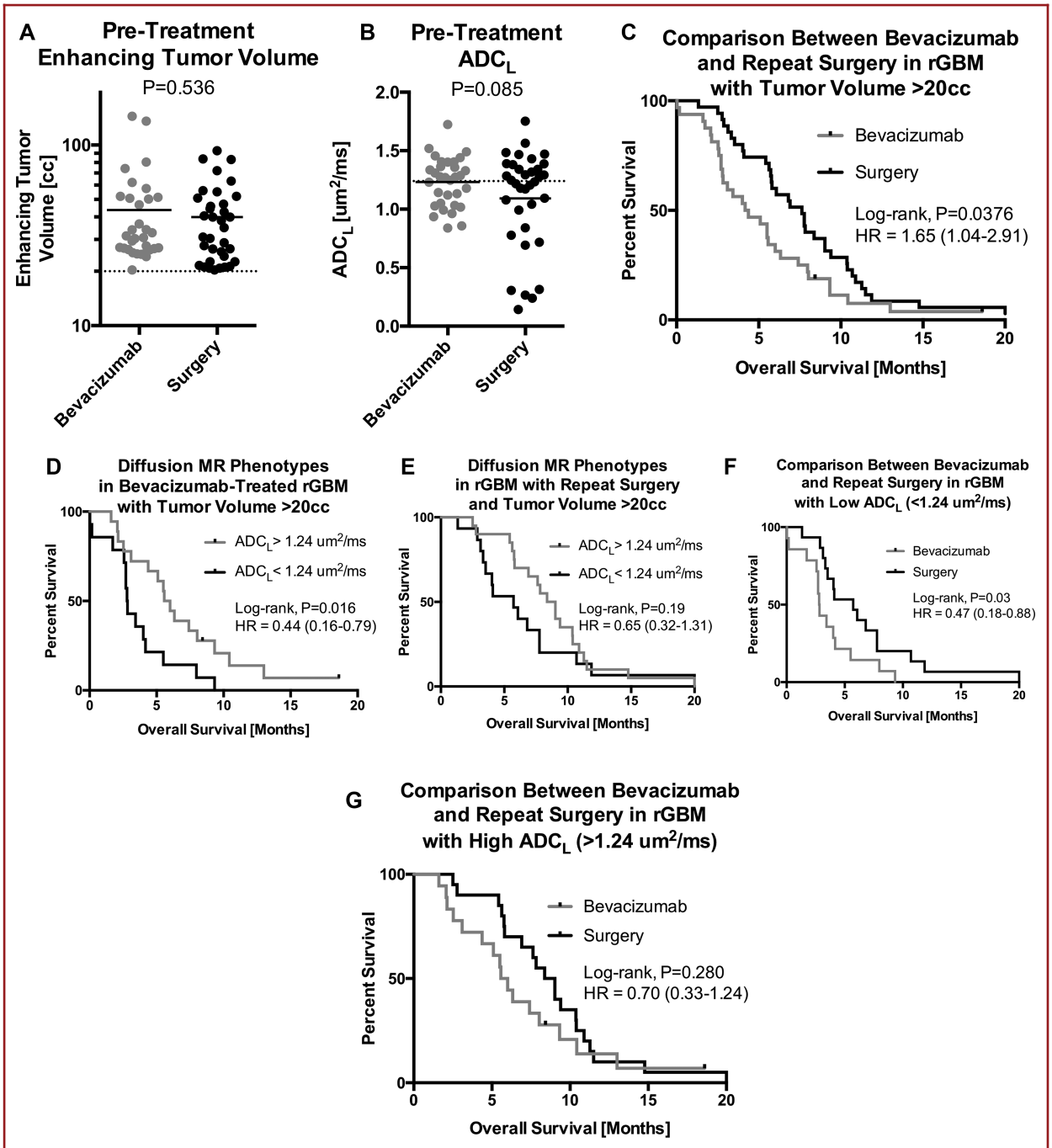

FIGURE 2. **A**, *Comparison of pretreatment tumor volume between bevacizumab-treated recurrent GBM and recurrent GBM treated with repeat surgical resection (P = 6.53).* **B**, *Comparison of ADC$_L$ between bevacizumab-treated recurrent GBM and recurrent GBM treated with repeat surgical resection (P = .085).* **C**, *Kaplan-Meier curves comparing survival between bevacizumab and surgery in recurrent GBM with large tumor burden (>20 cc) (P = .0376).* **D**, *Kaplan-Meier curves comparing survival differences between diffusion MR phenotypes in large, recurrent GBM treated with bevacizumab (P = .016).* **E**, *Kaplan-Meier curves comparing survival differences between diffusion MR phenotypes in large, recurrent GBM treated with repeat surgical resection (P = .19).* **F**, *Kaplan-Meier curves comparing survival differences between bevacizumab and surgery within large, recurrent GBM with low ADC$_L$ (P = .03).* **G**, *Kaplan-Meier curves comparing survival differences between bevacizumab and surgery within large, recurrent GBM with high ADC$_L$ (P = .280).*

TABLE 1. Cohort Characteristics

Characteristic	Bevacizumab (n = 32)	Surgical (n = 35)	*P* value
Age (y)	55.1	55.2	.982
Tumor volume (cc)	43.7	39.9	.536
ADC_L (μm^2/ms)	1.23	1.09	.092
Initial GTR	47%	74%	.021
IDH mutation	3.1%	5.7%	.615
MGMT methylation	31.3%	25.7%	.622
Prior salvage therapy			
Chemotherapy	28.1%	20%	.444
Toca 511/FU	9.4%	8.6%	.910
Immunotherapy	18.8%	20%	.899
EGFR inhibitors	9.8%	5.7%	.576
Time from initial treatment to recurrence (mo)	16.51	16.50	.999
Adjuvant therapy after 2nd resection			
Chemotherapy		40%	
Immunotherapy		29%	
EGFR inhibitors		17%	
Bevacizumab		60%	

TABLE 2. Volume Survival Analysis

Variable	*P* value	Hazard ratio	CI
Bevacizumab cohort			
Age	.423	0.985	0.95-1.02
Tumor volume	**.009**	1.02	1.01-1.04
Surgical cohort			
Age	.379	1.01	0.99-1.04
Tumor volume	**.006**	0.96	0.94-0.99

CI, Confidence interval.
Bold indicates statistical significance ($P < .05$).

pretreatment tumor volume (Table 3; Cox, $P = .021$, HR = 1.02) and ADC_L phenotype ($P = .049$, HR = 2.25) were predictive of survival in patients treated with bevacizumab (Figure 2D). Log-rank analysis based only on ADC_L phenotype also stratified long and short-term survivors ($P = .016$, HR = 0.44, median OS = 5.8 vs 2.8 mo). Results also indicated that presurgical tumor volume was an independent predictor of survival benefit in patients treated with repeated resection (Table 3; Cox, $P = .008$, HR = 0.97), with larger tumors benefiting more than smaller tumors, but ADC_L phenotype ($P = .273$) and age ($P = .586$) were not independently predictive of outcome. Unlike bevacizumab-treated patients, ADC_L phenotype alone was not predictive of outcome in patients treated with surgery (Figure 2E), although there was a similar trend toward better outcomes in patients with higher ADC_L (Log-rank, $P = .19$, HR = 0.65, median OS = 8.7 vs 5.7 mo).

TABLE 3. Diffusion Phenotype Survival Analysis

Variable	*P* value	Hazard ratio	CI
Bevacizumab cohort			
Age	.930	0.99	0.96-1.04
Tumor volume	**.021**	1.02	1.01-1.04
ADC_L	**.049**	2.25	1.03-5.49
Surgical cohort			
Age	.586	1.01	0.98-1.04
Tumor volume	**.008**	0.97	0.94-0.99
ADC_L	.273	1.50	0.73-3.08

CI, Confidence interval.
Bold indicates statistical significance ($P < .05$).

TABLE 4. Survival Analysis Stratified by Diffusion Phenotype

Variable	*P* value	Hazard ratio	CI
$ADC_L < 1.24$ Cohort			
Surgery	**.036**	0.433	0.20-0.95
$ADC_L > 1.24$ cohort			
Surgery	.284	0.693	0.36-1.36

CI, Confidence interval.
Bold indicates statistical significance ($P < .05$).

Recurrent GBM With Low ADC_L Benefits From Repeat Surgical Resection

Patients with large enhancing tumors and a low ADC_L phenotype appear to have a significant survival advantage when treated with surgery compared with bevacizumab treatment (Figure 2F and Table 4; Log-rank, $P = .03$, HR = 0.47). No survival difference was observed between treatment arms in tumors with high ADC_L (Figure 2G; Log-rank, $P = .280$, HR = 0.70).

DISCUSSION

This study shows that preoperative MR phenotype using diffusion sequences of large (>20 cc) recurrent GBM can predict overall benefit when treated with bevacizumab. This is consistent with numerous reports demonstrating this to be the case with anti-VEGF therapy for recurrent GBM,[12,13,19,20] but also suggests this to be the case even among contemporary patients with very large tumors, which are often treated with bevacizumab when other treatment options are off the table. Additionally, previous studies have suggested this diffusion phenotype is predictive for anti-VEGF therapies but not prognostic for all therapies including systemic chemotherapies[12,13] (eg, lomustine or temozolomide). Results from the current study support these previous findings, suggesting that diffusion MRI is predictive of

outcome in recurrent GBM treated with bevacizumab, but not repeat surgical resection.

While a significant difference in survival was observed between the two treatment arms regardless of similar distributions in tumor size, age, and diffusion characteristics, patients with unfavorable diffusion phenotypes[4,10,11] ("low ADC", $ADC_L < 1.24\ \mu m^2/ms$) may significantly benefit from surgical resection, if safely possible, compared with bevacizumab treatment. It is important to note, however, that there also appeared to be a trend toward better survival in patients treated with surgery in patients with a favorable diffusion phenotype; this benefit to repeat resection has been previously described.[21]

While both tumor and treatment related factors effect survival, certain tumor related characteristics such as location, infiltration, gliomatosis, and volume are extremely important in prognostication.[22] Multiple studies have demonstrated that patients with larger tumors generally do worse when treated with systemic chemotherapies than patients with smaller tumors in both newly diagnosed GBM[22] and at first or second relapse.[17] Interestingly and perhaps counterintuitively, results from the current study suggest patients with larger tumors actually have a better outcome than smaller tumors when treated with repeat surgical resection. Despite our efforts to match patient demographics (age, previous salvage therapy, initial extent of resection) and tumor imaging characteristics, this difference may speak to some potential bias in our data, as patients with large tumor burden that appear eligible for re-resection are likely to have slower growing tumors or tumors distal from eloquent structures.[23]

Our study provides data to help clinicians make evidence-based treatment decisions in recurrent GBM. However, management strategy in recurrent large volume GBM is a complex clinical decision that includes several factors. One major consideration is relief of current or expected symptomatic mass effect that could help prevent loss of functional independence and therefore quality of life.[21,24,25] As we identified in this study, patients with repeat craniotomy had further adjuvant therapy including repeat chemotherapy, small molecular inhibitors, and immunotherapy and therefore repeat surgery could allow for re-analysis of recurrent tumor for selection and monitoring of adjuvant therapy. Lastly, as seen in this study, several patients with repeat surgery received adjuvant bevacizumab, but the reverse was not seen as in many cases this precludes surgery even if there was increased symptomatic mass effect. Therefore, our results represent a quantitative tool in the complex management paradigm of recurrent GBM that requires combination of survival data and clinical situation.

Limitations

In addition to potential bias in the surgical cohort, recent evidence suggests MGMT promoter methylation status may predict response to bevacizumab.[26,27] Although a potential limitation, this was not examined in the current study as there is no evidence to suggest MGMT status has an impact on surgical efficacy. Another potential limitation to the current retrospective study is the potential impact from the sequence of therapies in each patient. As mentioned above, approximately 60% of patients in the surgical arm actually received bevacizumab sometime during their care. Potential changes in diffusion MR phenotypes at the time of bevacizumab initiation were not considered but may have changed as a result of prior therapy or resection. In addition, further treatment after bevacizumab therapy may not affect survival in a significant manner. Last, given small sample size, statistical control for multiple comparisons could not be performed and these data should be evaluated in a larger, prospective manner.

CONCLUSION

Diffusion MR phenotypes predict overall survival in recurrent GBM patients with large tumor burden (>20 cc) that are treated with bevacizumab or surgical resection. Patients with low ADC_L have a significant survival advantage when treated with repeat surgery, while patients with high ADC_L have favorable survival when treated with bevacizumab.

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COMMENTS

The authors report a retrospective series of patients in which they investigate the apparent diffusion coefficient (ADC) on MRI and its relationship to responsiveness of large (>20 cc) recurrent glioblastoma to bevacizumab and surgery. They found that patients with high ADC (>1.24 μm^2/ms) had better response to bevacizumab than those with low ADC and that patients with low ADC responded better to surgery than those with high ADC in terms of survival.

This study illustrates how magnetic resonance imaging sequences can be related to tumor biology and how understanding this biology can contribute to understanding patient outcome. As the authors explain in their introduction, diffusion MRI can indicate the tumor cell density. In a simplistic view, high ADC is associated with less tumor cell density and low ADC with high tumor cell density. In keeping with this simplistic explanation, it makes sense that bevacizumab would have more efficacy than surgery when tumor cell density is less (and therefore more normal brain may be interspersed amongst the tumor cells) and that surgery would be more effective than pharmacology when a dense block of tumor cells can be removed. Additional insights could be gained by examining the effects on neurological functioning tumor resections involving eloquent portions of the brain. One might hypothesize that neurological deficits would be increased in surgical resection of high ADC tumors compared to low ADC tumors. Thus, MRI characteristics of tumors, beyond just examining enhancement patterns, can help guide clinical decision-making and lead to better patient outcomes.

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This retrospective study looks at the role of diffusion MR phenotypes in predicting survival in recurrent GBMs treated with bevacizumab and repeated surgical resection.

Every clinical scenario of recurrent GBM is unique. Variable factors include the biological profile of the tumor, patient characteristics, tumor location, and extent of first tumor resection. Treatment scenarios similarly vary case by case and it is still unclear how each different treatment ultimately affects the OS/PFS. While definitive answers will not come without prospective and multicentric studies, small retrospective and meta-analytical ones, such as this one, can furnish important new insights.

This study confirms that pre-treatment diffusion MR characteristics within large (>20cc) contrast enhancing tumors are a predictive imaging biomarker for overall survival benefit in recurrent GBM patients treated with bevacizumab. The authors also suggest that unfavorable diffusion phenotypes (low ADCL) may significantly benefit from surgical resection.

While both tumor-related and treatment-related factors play a role in clinical outcomes, certain tumor-related characteristics have a greater effect on tumor progression and survival than reoperation itself. The small sample size of this study is an important limit in this regard, but it is balanced out by the rigorous reporting of all the tumor-related features (including MGMT/IDH status, timing of repeated surgery, extent of first and next resections, treatment received in between surgeries, patient age, etc).

This study highlights how emerging advancements in radiomics can enhance our understanding of tumor and patient variables and can thus improve the management and prognosis of each different case of recurrent GBM.

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