

Survival prediction based on qualitative MRI diffusion signature in patients with recurrent high grade glioma treated with bevacizumab

Pradeep Goyal¹, Mary Tenenbaum^{2,3}, Sonali Gupta⁴, Puneet S. Kochar⁵, Alok A. Bhatt³, Manisha Mangla⁶, Yogesh Kumar⁷, Rajiv Mangla^{3,8}

¹Department of Radiology, St. Vincent's Medical Center, Bridgeport, CT, USA; ²Department of Radiology, UMMS-Baystate Regional Campus, Springfield, MA, USA; ³Department of Radiology, University of Rochester Medical Center, Rochester, NY, USA; ⁴Department of Medicine, St. Vincent's Medical Center, Bridgeport, CT, USA; ⁵Department of Radiology, Yale New Haven Health Bridgeport Hospital, Bridgeport, CT, USA; ⁶Department of Public Health, SUNY Upstate Medical University, Syracuse, NY, USA; ⁷Department of Radiology, Columbia University at Bassett Healthcare, Cooperstown, NY, USA; ⁸Department of Radiology, SUNY Upstate Medical University, Syracuse, NY, USA

Correspondence to: Pradeep Goyal, MD. Department of Radiology, St. Vincent's Medical Center, Bridgeport, CT 06606, USA.
Email: pradeepgoyal78@gmail.com.

Background: Bevacizumab was approved by the FDA for the treatment of recurrent or progressive glioblastoma (GBM). Imaging responses are typically assessed by gadolinium-enhanced MRI. We sought to determine the significance of qualitative diffusion signature (manifest as variable degree of dark signal) on ADC maps in recurrent gliomas after treatment with bevacizumab.

Methods: We performed an institutional review board (IRB) approved retrospective study on patients who underwent MRI of the brain after 8 weeks of receiving bevacizumab for recurrent glioma. Patients were divided into three groups based on qualitative diffusion signature: (I) lesion not bright on diffusion weighted imaging (DWI) suggestive of no restricted diffusion (FDR₀); (II) lesion bright on DWI with corresponding homogenous dark signal on apparent diffusion coefficient (ADC) maps suggestive of focal restricted diffusion likely due to bevacizumab induced necrosis (FDR_n); and (III) lesion bright on DWI with corresponding homogenous faint dark signal on ADC maps suggestive of focal restricted diffusion likely due to viable tumor or heterogeneous spectrum of dark and faint dark signals on ADC maps suggestive of focal restricted diffusion likely due to viable tumor surrounding the bevacizumab induced necrosis (FDR_v).

Results: Based on the qualitative signal on diffusion weighted sequences after bevacizumab therapy, total number of patients in group (I) were 14 (36%), in group (II) were 17 (44%); and in group (III) were 8 (20%). The median overall survival (OS) from the time of recurrence in patients belonging to group (II) was 364 days *vs.* 183 days for those with group (I) *vs.* 298 days for group (III). On simultaneous comparison of survival differences in all three groups by Kaplan-Meier analysis, group (II) was significant in predicting survival with P values for the log-rank tests <0.033.

Conclusions: In patients with recurrent glioma treated with bevacizumab, the presence of homogenous dark signal (FDR_n) on ADC maps at 8 weeks follow-up MRI correlated with a longer survival. Thus, use of this qualitative diffusion signature in adjunct to contrast enhanced MRI may have the widest potential impact on routine clinical care for patients with recurrent high-grade gliomas. However, prospective studies analysing its predictive value are warranted.

Keywords: Recurrent glioblastoma multiforme (GBM); bevacizumab; median survival; diffusion weighted imaging (DWI); apparent diffusion coefficient (ADC)

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Introduction

Glioblastoma (GBM) is the most common primary malignant CNS tumor with poor prognosis even after standard treatment of surgery, postoperative temozolomide (TMZ) sensitized radiochemotherapy followed by TMZ monotherapy with a median survival of 14 months (1). At recurrence, patients typically survive only another 30 weeks (2-4). In recurrent or progressive GBM following the standard therapy, several biological therapeutic agents were tested, out of which the angiogenesis inhibitor bevacizumab (Avastin) was approved by the FDA in 2009 (5). There has been improved radiographic response, progression-free survival (6) but inconsistent improvements of overall survival (OS) in patients with recurrent GBM on bevacizumab (7-11). Tumor treatment response is typically assessed by gadolinium enhanced MRI. However, when treatment with anti-VEGF agents such as bevacizumab is utilized there is a common phenomenon of marked decrease in enhancement post treatment known as pseudoresponse. Pseudoresponse relates to block of neovascularization with abnormally permeable microvessels and is mostly noted with antiangiogenic treatment. This leads to a rapid decrease in contrast leakage of gadolinium, but it does not reflect the decrease in tumor activity or size (12). Therefore, the traditional method of evaluating response by evaluating for decrease in enhancing tumor may not be accurate when antiangiogenic treatments utilized, and other methods of evaluation are needed. As a result, Response Assessment for Neuro-Oncology (RANO) response criteria added some new suggestions that include anti-angiogenic therapy (13).

Though, diffusion imaging once gained attraction as an alternative marker to assess treatment response and tumor progression, however in last few years, there has been great interest in applying other multi-parametric MRI sequences in detecting infiltrative tumor and determining treatment response. Dynamic susceptibility weighted magnetic resonance (DSC-MR) perfusion imaging have been shown to be effective at measuring the response to bevacizumab (14-16). Advanced DWI techniques such as graded functional diffusion maps, ADC histogram analysis within both enhancing and non-enhancing components of tumor can be used to predict the response to bevacizumab in recurrent GBMs (17-20). More recently, another advanced DWI technique restriction spectrum imaging (RSI) which along with DSC-MR perfusion study could differentiate Bevacizumab related necrosis from viable tumor (21). However, measurement of all these advanced perfusions and

DWI techniques is cumbersome and requires additional software's and expertise to familiarize with concepts. Moreover, routine diffusion sequences (DWI and ADC maps) are routinely performed as part of every brain study in all clinical and research settings, whereas MR perfusion and advanced DWI techniques are not. Finding early and easy to interpret imaging biomarkers for GBM progression may have a significant impact on clinical treatment decision-making, especially during bevacizumab therapy.

We hypothesized that qualitative focal diffusion restriction, in and around the enhancing tumor, may be a useful predictor of survival. Therefore, our purpose was to determine the utility of qualitative diffusion signature at initial 8 weeks MRI follow-up to assess treatment response to anti-VEGF therapy (bevacizumab) in patients with recurrent GBM. In addition, we sought to assess patient survival following the appearance of restricted diffusion during the course of treatment for recurrent GBM. There have been reports which suggest that progressing bevacizumab-related FDR is associated with coagulative necrosis surrounded by viable tumor and worst OS (22) whereas stable FDR lesions were associated with greatest OS (22,23). However, survival prediction in these studies was based on serial MRI studies. We hereby, hypothesized that even a single qualitative diffusion weighted imaging (DWI) at initial 8 weeks follow-up can predict median OS or effectiveness of bevacizumab in recurrent tumor.

Methods

Patients and follow-up

We performed an IRB approved, retrospective study on patients who underwent MRI of the brain around 8 weeks after starting treatment with bevacizumab for recurrent gliomas. Patients were retrospectively selected from institution's neuro-oncology database and data acquisition was performed in compliance with all applicable regulations of the Health Insurance Portability and Accountability Act (HIPAA) from December 2009 to March 2015. All patients were treated with maximal gross tumor resection and radiation therapy (60 Gy given over 6 weeks)/temozolomide (TMZ) + adjuvant TMZ at time of initial tumor presentation. A total of n=47 patients who met the following criteria were initially selected: (I) had pathologically confirmed initial high grade gliomas with recurrence based on MRI, clinical data and in some cases with histology; (II) were regularly treated every 2 weeks per

Table 1 Demography of the patients

| Characters | FDR ₀ (n=14) | FDR _n (n=17) | FDR _i (n=8) |
|---|-------------------------|-------------------------|------------------------|
| Age (years) at death, mean (SD, range) | 49 (15, 32–74) | 52 (9, 31–64) | 58 (7, 49–72) |
| Gender | | | |
| Male | 12 | 9 | 3 |
| Female | 2 | 8 | 5 |
| Initial pathology | | | |
| Grade 3 | 0 | 2 | 1 |
| Grade 4 | 14 (100%) | 15 (88%) | 7 (87.5%) |
| Initial MGMT methylation/unmethylation (n=21) | | | |
| Meth | 2 | | |
| Umeth | 3 | 11 | 5 |
| Initial IDH-1 mutation | 0 | 4 | 2 |
| Initial therapy (surgery + XRT/TMZ+ adjuvant TMZ) | 14 | 17 | 8 |
| Glucocorticoid use anytime during therapy | 14 | 17 | 8 |
| Karnofsky performance score (KPS) >70 | 2 (14%) | 14 (82%) | 6 (75%) |

SD, standard deviation; MGMT, O6-methylguanine DNA methyltransferase; IDH-1, isocitrate dehydrogenase; XRT, radiation therapy; TMZ, temozolomide.

cycle with bevacizumab (Avastin, Genentech; 5 or 10 mg/kg body weight) alone or in combination with chemotherapy; (III) had baseline (pre-bevacizumab treatment) and minimum of 1 follow-up MRI scan near 8 weeks post bevacizumab therapy. We excluded patients who received bevacizumab within 3 months of completing radiotherapy, since pseudoprogression typically occurs within the first three months following radiotherapy. Of these recurrent GBM patients, n=39 had good-quality diffusion-weighted images before and after initiation of bevacizumab treatment and were retrospectively assessed to determine if focal diffusion-restricted (FDR) lesions developed in or adjacent to the tumor following treatment onset.

Of these 39 retrospective patients, status of initial tumor's isocitrate dehydrogenase (IDH-1) mutation and O6-methylguanine DNA methyltransferase (MGMT) promoter methylation (described elsewhere) (24) was available only in 21 patients. An additional analysis was done assessing Karnofsky performance score. Demography of patients is described in *Table 1*.

Patients were divided into three groups based on qualitative diffusion signature: (I) lesion not bright on isotropic diffusion map (DWI) suggestive of no restricted diffusion (FDR₀); (II) lesion bright on DWI with

corresponding dark signal on apparent diffusion coefficient (ADC) maps suggestive of focal restricted diffusion, likely due to bevacizumab induced necrosis (FDR_n) (*Figure 1*); and (III) lesion bright on DWI with corresponding homogenous faint dark signal on ADC maps suggestive of focal restricted diffusion, likely due to viable tumor or heterogeneous spectrum of dark and faint dark signals on ADC maps suggestive of focal restricted diffusion, likely due to viable tumor surrounding the bevacizumab induced necrosis (FDR_i) (*Figures 2,3*). No patient had clinical signs or symptoms of acute/sub-acute ischemic stroke as an alternative explanation for restricted diffusion, and on MRI dark-ADC lesions were not explained by subacute haemorrhage, ischemia, or postoperative changes.

MR imaging

Various MR imaging sequences were obtained on a 1.5/3 T MR scanner (Signa LX Scanner, and DiscoveryTM 750; GE Healthcare, Milwaukee, Wisconsin, USA) with the help of standard 8-channel head coil. All studies were performed according to a standardized protocol that included conventional sequences such as axial T1 FSE, T2FLAIR and T2 FSE as well as DWI, ADC maps, and triplane contrast

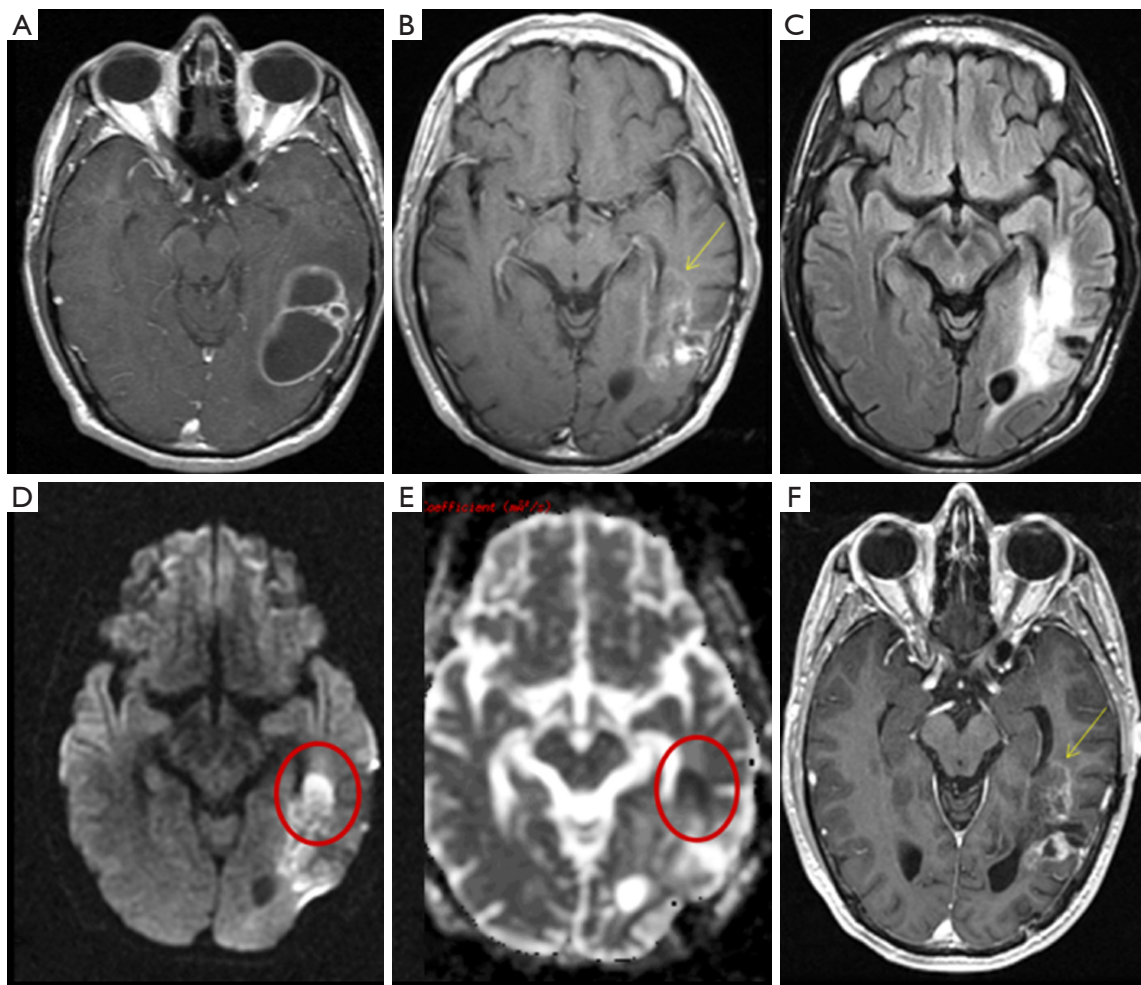


Figure 1 Development of acute infarct phenotype diffusion restriction in a 57-year-old male with recurrent GBM following 2 months of bevacizumab. Pre-treatment Post Gad T1WI demonstrating peripheral enhancement surrounding the surgical cavity in the left posterior temporal lobe suggestive of recurrent GBM (A). After 2 months of treatment (B-E). Post Gad T1WI demonstrating shrinkage of cavity and slightly decreased surrounding enhancement compared to pre-treatment with more focal enhancement posterolaterally (B), non-enhancing high FLAIR signal adjacent to residual cavities (C) and small area of high signal on DWI (D) adjacent to temporal horn of left ventricle with corresponding dark signal on ADC (E) akin to acute infarct phenotype (red circles) suggestive of focal diffusion restriction due to necrosis (FDR_n). Post Gad T1WI after 6 months of bevacizumab (F) demonstrating no progression/increased enhancement in the area of FDR_n noted at 2 months (yellow arrow). GBM, glioblastoma.

T1-weighted images. DWI were collected using single-shot echo-planar imaging with TE/TR =100 ms/8,000 ms, FOV =240 mm using a twice refocused spin-echo echo planar preparation, number of excitations (NEX) =1, 5-mm section thickness with 1 mm intersection gap, matrix size =128×128 (reconstructed images were interpolated to 256×256). Post-contrast T1-weighted images in 3 planes were acquired immediately after contrast injection using standard doses of 0.1-mmol/kg gadodiamide (Omniscan; Winthrop

Laboratories, Rensselaer, New York, USA).

Image registration

ADC maps were calculated from DWI using commercially available software (FuncTool, GE Healthcare) and the equation $ADC = (1/1,000) \cdot \ln(b_0/b_{1000})$. Morphologic and diffusion images were co-registered, allowing for the production of ADC maps.

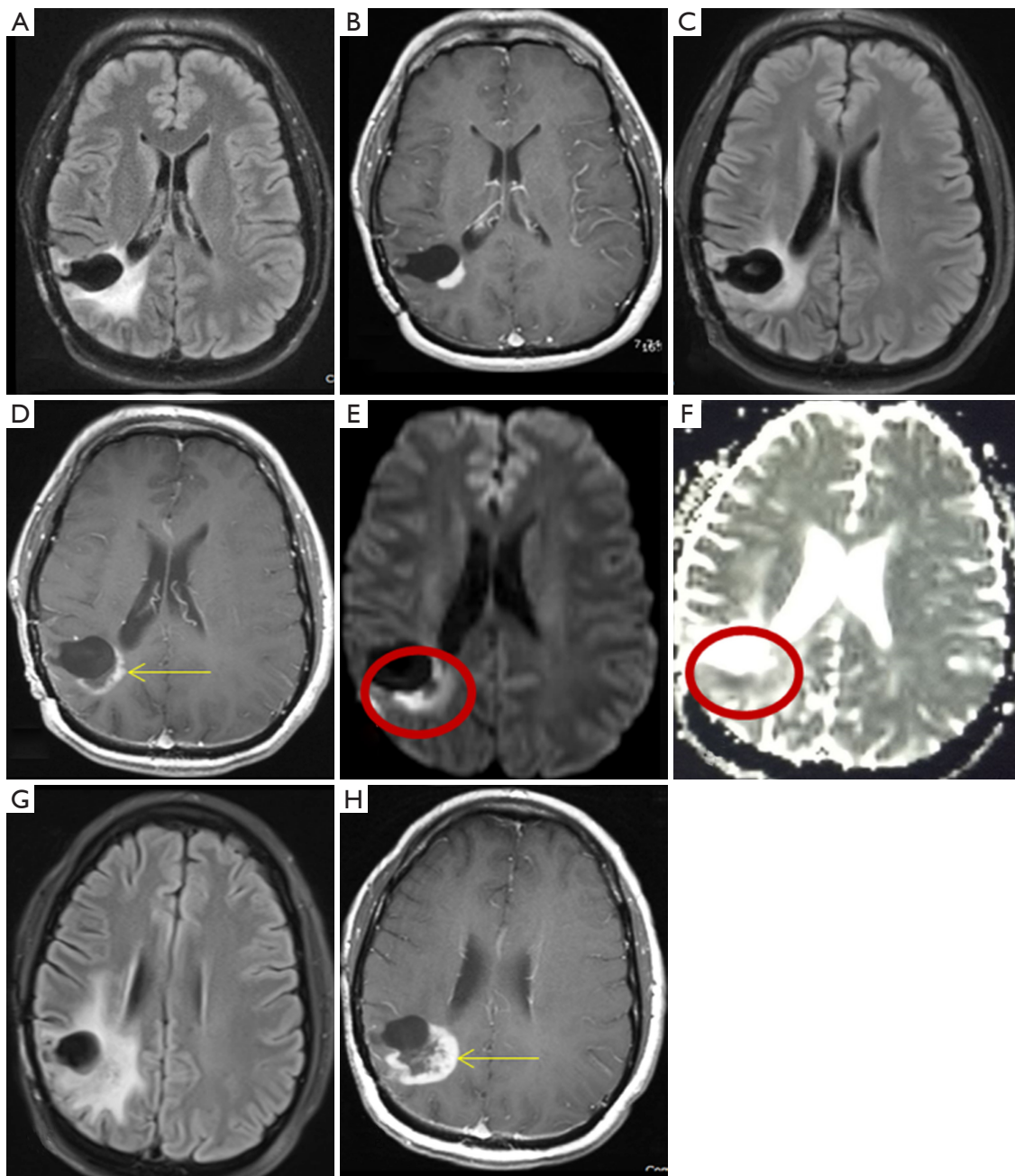


Figure 2 Development of subacute infarct phenotype diffusion restriction in a 54-year-old male with recurrent GBM following 2 months of bevacizumab. Pre-treatment (A,B), non-enhancing high FLAIR signal adjacent to the surgical cavity in the right parietal lobe (A) and peripheral enhancement adjacent to posterior margin of surgical cavity on post Gad T1WI (B), suggestive of recurrent GBM. After 2 months of treatment (C-F), decreased non-enhancing high FLAIR signal adjacent to the surgical cavity (C) and resolution of previously seen surrounding enhancement however there is new faint enhancement along the posterior margin of surgical cavity on Post Gad T1WI (D), and small area of high signal on DWI (E) adjacent to posterior margin of cavity with corresponding faint dark signal on ADC (F) akin to subacute infarct phenotype (red circles) suggestive of focal diffusion restriction due to viable tumor (FDR_t). Post Gad T1WI after 6 months of bevacizumab (G-H) demonstrating progression: increased enhancement (G) and increased non-enhancing high FLAIR signal (H) in the area of FDR_t noted at 2 months (yellow arrow). GBM, glioblastoma; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient.



| Appearance on DWI | Morphologic appearance on ADC maps | Visual color appearance on ADC | Lesion |
|-------------------|--|--|--|
| Bright | Homogenous dark signal |  | Coagulative necrosis FDR _n |
| Bright | Homogenous faint dark or heterogeneous dark and faint signals with even small faint dark component |  | Viable tumor component FDR _t |

Figure 3 Diffusion signature demonstrating FDR_n and FDR_t.

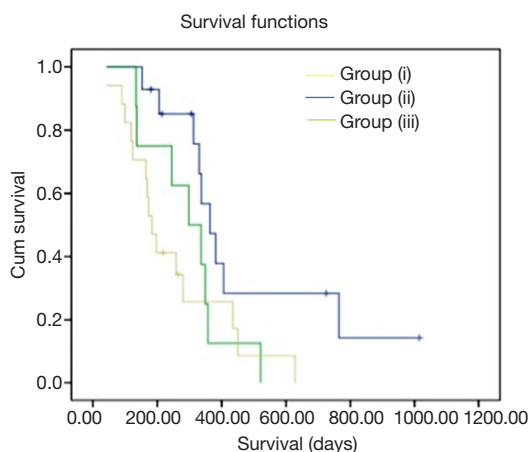


Figure 4 Kaplan-Meier survival curve demonstrating median overall survival in days from time of recurrence.

Image interpretation

Two experienced board certified neuroradiologists (RM and MF) with 8 and 3 years of experience in MRI post-processing, performed ADC analyses (RM holds a Certificate of Added Qualification in Neuroradiology). The DWI and axial contrast-enhanced T1-weighted images were transferred to an off-line workstation and analyzed using available commercial software (Nordic ICE, Nordic Neuro-Lab). ADC maps were calculated from the DWI and

low-ADC lesions in and around the tumor area were noted.

Statistical analysis

Differences in OS between the three groups were calculated using Kaplan-Meier Survival curves (Figure 4) and Log-rank t-test via IBM SPSS 22 (Chicago, IL, USA). The time between the date of start of bevacizumab and that of death was defined as the event time. Survival was determined by both documented date of death in the patient’s medical record and by the Social Security Death Index if this information was not available in the medical record. A P value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Based on the qualitative diffusion signature manifested by variable degrees of dark signal on ADC maps after bevacizumab therapy, total number of patients with no restriction FDR₀ n=14 (36%), with FDR_n n=17 (44%); and with FDR_t n=8 (20%). For all patients, median OS =313 days (95% CI, 232–393 days) from the time of the first bevacizumab treatment. The median OS from the time of recurrence in patients belonging to FDR_n was 364 days (95% CI, 295–432 days) vs. FDR₀ 183 days (95% CI, 145–220 days) vs. FDR_t 298 days (95% CI, 171–424 days) (Table 2).

Table 2 Means and medians for survival time of all three groups

| Group | Estimate | Std. error | Median* | |
|---------|----------|------------|-------------------------|-------------|
| | | | 95% confidence interval | |
| | | | Lower bound | Upper bound |
| I | 183 | 19.208 | 145.353 | 220.647 |
| II | 364 | 35.124 | 295.157 | 432.843 |
| III | 298 | 64.347 | 171.880 | 424.120 |
| Overall | 313 | 41.234 | 232.182 | 393.818 |

*, estimation is limited to the largest survival time if it is censored.

Table 3 Overall comparisons

| Variable | Chi square | df | Sig. |
|-----------------------|------------|----|-------|
| Log rank (Mantel-Cox) | 6.833 | 2 | 0.033 |

Test of equality of survival distributions for the different levels of group.

On simultaneous comparison of survival differences in all three groups by Kaplan-Meier analysis, group (II) was significant in predicting survival with P values for the log-rank tests <0.033 (Table 3). Tumor samples from 2 of 14 patients in the no diffusion restriction group (I) were found to be MGMT methylated, whereas 3 of 14 patients of group (I), 11 of 17 patients of group (II) and 5 of 8 patients of group (III) were found to be MGMT un-methylated (Table 1). None of group (I) patients had IDH-1 mutation whereas mutation was present in 4 patients from group (II) and 2 patients from group (III).

Discussion

Based on our and others experience, often quantitative measurement of ADC values from the ADC map can be challenging even to experienced personnel due to heterogeneous distribution of nests of tumor cells within the tumor, the presence of tumor necrosis, hemorrhage and ischemia, and may cause significant sampling bias. We tried to explore if morphologic diffusion signature rather than quantitative ADC values can be used to assess tumor progression in recurrent GBM. Because our study was retrospective and our patients didn't undergo autopsy due to medicolegal and other reasons, we utilized cut-off values of mean ADC reported previously (22) which were determined from autopsy samples of coagulative necrosis and viable tumor.

Our study explored qualitative diffusion signature manifested by variable degrees of dark signal on ADC maps following bevacizumab treatment. Earlier glioma studies have found an inverse correlation between ADC and cellularity tumor grade, and Ki-67 proliferation indices (25,26). Besides increasing cellularity and subsequent decreases in the free extracellular space and water proton diffusivity, low ADC values in GBMs are possibly related to relative tumor ischemia (25,26). However, mean ADC values of hypercellularity of GBM has been reported to be near $0.9 \times 10^{-3} \text{ mm}^2/\text{s}$ (22) which is closer to mean ADC value of early subacute infarct (27), so should match phenotypically with early subacute infarct (variable degrees of faint dark signal on ADC maps) (Figure 3).

Anti-VEGF therapy associated tumor necrosis has been found to be coagulative necrosis (22), and in contrast to liquefactive necrosis which is associated with radiation necrosis in brain and TACE (trans-arterial chemoembolization)/ablation associated necrosis of hepatocellular carcinoma or other solid tumors (28). Whereas liquefactive necrosis is associated with high diffusion and consequent bright signal on ADC images, coagulative necrosis on the other hand is associated with restricted diffusion with low ADC values (22). There are few theories regarding the mechanism behind diffusion-restriction in coagulative necrosis. Jeyaretna *et al.*, in their case report hypothesized that focal regions of coagulative necrosis may result from exacerbated radiation necrosis by bevacizumab (29). Others hypothesized that such regions result from bevacizumab-induced chronic hypoxia (30). Moreover, lack of hypoxia expression within recurrent high-grade glioma following bevacizumab has also been suggested by prior investigations using ^{18}F Fluoromisonidazole (FMISO) positron emission tomography and MR imaging (31). We believe the reason

behind diffusion restriction is bevacizumab induced tumor ischemia. This concept of tumor ischemia is supported by histopathologic findings of perivascular tumor deposits, vasculopathy, and small brain infarcts in bevacizumab-treated patients (32). Mean ADC value in pathologically confirmed bevacizumab coagulative necrosis is reported to be in the range of 0.63×10^{-3} – 0.736×10^{-3} mm²/s (22) which is closer to mean ADC value of acute infarct (0.57 ± 0.16) $\times 10^{-3}$ mm²/s (27), so it should match phenotypically with acute infarct (dark on ADC) (Figure 3).

Although there has been a suggestion of role of pre and post treatment quantitative DWI (33,34), qualitative diffusion signatures are not fully explored and not commonly implemented into treatment decision-making trees due to the controversial significance of new restricted diffusion during antiangiogenic treatment in recurrent GBM. There are several studies showing both increased and decreased survival associated with diffusion restriction in patients receiving bevacizumab (12–15,19–21,23,29,30,35–40). However, recent reports suggest that progressing bevacizumab related FDR lesions due to coagulative necrosis surrounded by viable tumor are associated with worst OS (22) whereas stable FDR lesions are associated with greatest OS (22,23). In our study, we found that FDR_n group (OS =364 days), which should correspond to coagulative necrosis, was associated with better OS than FDR_t group (OS =298 days), which corresponds to the combination of viable tumor and coagulative necrosis. However, contrary to results of Nguyen *et al.* (22), OS of our patients with no restriction (those who did not develop lesions in first 2 months) in FDR₀ group was shorter than FDR_t group (183 *vs.* 298 days). We think poor survival in group (I), despite younger mean age among all three groups, might be due to unfavorable tumor biology, as 100% were grade IV and most of them were probably primary due to the absence of IDH-1 mutation (Table 1). Moreover, Karnofsky performance scores were also poor in group (I) compared to group (II) and (III) patients. Leaving aside the group (I) due to the unbalanced distribution of prognostic factors, our study is of value for all other patients with restricted diffusion during antiangiogenic treatment in recurrent GBM, where the most controversy exists. Survival differences in group (II) and group (III) in our study should be considered significant as the distribution of various other prognostic markers which can influence survival such as age, performance status, tumor biology including MGMT methylation as well IDH-1 mutation status were balanced (Table 1).

Our study is different from other recent studies in which

survival prediction or effectiveness of bevacizumab was based on serial MRI studies which can result in the loss of valuable time. Whereas, based on our study we can predict statistically significant OS even on a single MRI follow-up at 8 weeks. GBM progresses with time as evident from natural history, and it is true even for recurrent GBM on combination chemotherapy including anti-VEGF. Lesions which demonstrate FDR_n within 2 months eventually will develop viable tumor with longer time duration and will show heterogeneous spectrum of dark and faint dark signals on ADC due to the combination of FDR_n and FDR_t. So, the importance of morphologic diffusion signature decreases with longer or serial follow-up period.

Our study suggests that on ADC maps, the patients with the homogenous dark signal (like acute infarct phenotype), should have better OS than with patients with homogenous faint dark signal (subacute phenotype) or heterogeneous spectrum of dark and faint dark signals (like both acute and subacute phenotype). Though there is no doubt about the importance of quantitative cut-off ADC value of 0.736×10^{-3} mm²/s separating diffusion-restricted necrosis and viable hypercellular tumor which is based on autopsy analysis by Nguyen *et al.* (22), there is limitation of universal application of quantitative ADC values as: (I) there is reported variability in ADC values among and even within vendors (41); (II) also, they measured the ADC values in the region of autopsy confirmed coagulative necrosis and viable tumors, whereas most common method of ADC value measurement is ADC_{min}, in which out of 4–5 low ADC values, the lowest ADC value is taken into consideration. This method is good for grading of gliomas and should be considered when done for initial evaluation of tumor. However, it can give false negative result in recurrent gliomas with coagulative necrosis surrounded by viable tumor, as there is a possibility that one or all the 4–5 measurements may be taken from coagulative necrosis and lowest ADC value come below cut-off ADC value of 0.736×10^{-3} mm²/s. Whereas, our method of diffusion signature which manifest as variable degrees of dark signals on ADC maps is though subjective, the lesions in group (II) and group (III) were visibly apparent and clearly abnormal even without any quantitative measurements and could predict statistically significant median OS. On the other hand, we do not undermine the importance of quantitative measurement, but suggest caution while interpreting the ADC values in recurrent gliomas, and recommend if there is heterogeneous spectrum of dark and faint dark signals on ADC maps, ADC values should be taken from most

dark and least dark area and instead of considering the lowest of 4–5 ADC values (ADC_{min}), mean of 4–5 ADC values (ADC_{mean}) should be taken into consideration and value above cut-off is suggestive of viable tumor or worse prognosis. Interpretation of homogenous dark signal is straightforward, however though rarely, there might come difficulty in interpretation of a lesion which demonstrates homogenous intermediate dark signal on ADC maps; in that case also, quantitative ADC_{mean} can be helpful. Moreover, if need arises, morphologic diffusion signature can also be used for tissue sampling in regions of FDR_t as this could reduce the likelihood of false-negative results.

There are few limitations in our study; one potential limitation is the relatively small patient cohort. Despite the small numbers, we achieved statistically significant results. However, worst OS in those with no restriction in our study was unexpected, likely reasons behind this, already explained earlier. Further research is necessary to establish the biological basis for bevacizumab causing these lesions. Another potential limitation is the lack of locus-specific histopathologic correlation in our series to confirm the homogenous dark signal (FDR_n) lesions as coagulative necrosis rather than viable tumor. However, others have reported histologic proof of restricted diffusion with mean ADC values below $0.736 \times 10^{-3} \text{ mm}^2/\text{s}$ as coagulative necrosis, which correspond to dark signal on ADC maps. Larger prospective trials are needed to confirm our findings, but our data support the role of using diffusion signature in predicting median OS of recurrent GBM on bevacizumab at early follow-up within 8 weeks. Additionally, our study is limited to the biologic effect of bevacizumab therapy with and without TMZ in recurrent GBM, however due to current practice of different combination adjuvant therapy, biological effects may vary and further research is necessary to establish the effects of different combination adjuvant therapy in recurrent GBM.

Therefore, recognitions of these qualitative diffusion signatures have the widest potential impact on routine clinical care for patients with recurrent GBMs without requiring any additional imaging time or imaging technique beyond standard practice.

Conclusions

DWI is routinely performed as part of every brain study in all research and clinical settings; whereas MR perfusion and other advanced DWI techniques are not universally performed. As everyone is familiar with the appearance

of acute and subacute infarct on ADC maps, we tried to use diffusion signature as an easy method to interpret imaging biomarkers for GBM progression. We proposed if lesions demonstrating homogenous dark signal (acute infarct phenotype) on diffusion map will have better survival than both the lesions with a faint dark signal (subacute phenotype) or heterogeneous spectrum of dark and faint dark signals (subacute and acute phenotypes) and the lesions with no restriction. The use of survival prediction in patients with recurrent gliomas may have a significant impact on clinical treatment decision-making, especially as early as 8 weeks of bevacizumab therapy. This prediction of tumor response is especially important given a recent meta-analysis that showed an associated increase in treatment-related mortality for bevacizumab when added to other chemotherapy as compared to chemotherapy alone (6). Therefore, if bevacizumab is to be used as a major treatment, it is essential to identify patients who will respond well to therapy versus those who are unlikely to respond as early in the course of treatment as possible.

Therefore, the recognition of this qualitative diffusion signature in adjunct to contrast enhanced MRI has the widest potential impact on routine clinical care for patients with recurrent GBMs, without requiring any additional imaging time or imaging technique beyond standard practice. Prospective studies analysing its predictive value are warranted.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by University of Rochester Medical Center, Rochester, New York, USA.

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