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CLINICAL-PATIENT STUDIES

Time course of imaging changes of GBM during extended bevacizumab treatment

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Abstract Glioblastoma multiforme (GBM) are morphologically heterogeneous tumors, with varying amounts of necrosis, and edema. Previous studies have shown that treatments incorporating the VEGF antibody bevacizumab can reduce edema and tumor burden in GBM. Additionally it has been suggested that bevacizumab regimen treatment reduces the percent of tumoral necrosis. Therefore we sought to (1) determine the time course of change in necrosis, tumor, and edema volume in patients who respond to bevacizumab regimen treatment and (2) determine if GBM that progress following a response to bevacizumab regimen treatment are morphologically different from their appearance at prior tumor progression. Therefore, we retrospectively assessed tumor, necrosis, and edema volumes on MRI scans from 15 patients with recurrent GBM who responded to bevacizumab regimen treatment, and had extended (>7 month) follow-up. We found that the median time to best tumor response was 158 days (range, 16–261, SD = 63). The median best response was 72.1% reduction in tumor volume and 72.8% reduction in peritumoral edema. Most tumors (77.8%) showed resolution of necrotic areas. The relative reduction of edema and necrosis was sustained, even in patients ($n = 7$) who developed tumor progression. Thus the mean ratio of edema-to-tumor volume at progression on bevacizumab regimen treatment was 38.4% lower than that for the same tumors seen on progression scans following prior chemotherapy. The percentage of necrotic tumor also was diminished following progression on bevacizumab regimen treatment. These findings illustrate the time course of changes in edema and tumor volume with prolonged bevacizumab regimen treatment, and support the conclusion that the morphology of recurrent GBM following bevacizumab regimen therapy is distinct from that on other chemotherapy.

Keywords Bevacizumab · GBM · Glioma · VEGF · Tumor · Edema · Necrosis · Volume analysis

Abbreviations

GBM	Glioblastoma multiforme
VEGF	Vascular endothelial growth factor
MRI	Magnetic resonance imaging
TTR	Time to partial tumor response
TTP	Time to tumor progression
RT	Radiation therapy
RECIST	Response evaluation criteria in solid tumors

Introduction

Glioblastoma multiforme (GBM) are the most aggressive and infiltrative of primary brain tumors. Heterogeneous in appearance and gene expression, GBM share a poor prognosis [1]. VEGF and its receptors are more highly expressed in GBM than in other brain tumors [2]. VEGF is a potent mediator of cerebrovascular permeability and is thought to play a significant role in tumor progression through regulation of endothelial cell permeability, activation, survival, proliferation, invasion, and migration [3]. Cerebrovascular

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permeability also results in interstitial edema. Clinical data show that peritumoral edema in high-grade glioma patients correlates with poorer survival [4]. Hypoxia leads to necrosis, and also induces VEGF production by tumor cells [5]. Increased VEGF and necrosis are both associated with a poorer prognosis [6, 7].

Bevacizumab (Avastin) is a non-selective monoclonal antibody to VEGF [8]. Bevacizumab has previously been shown to reduce tumor and edema in GBM patients, with an approximately 50% response rate [9, 10]. The time course of this response is not well characterized. In addition to changes in tumor size, previous studies have raised the possibility that bevacizumab regimen treatment significantly diminishes the percent of necrotic tissue in these tumors [9]. In this study, we have investigated the time course of change in edema, tumor, and necrosis, using volumetric MRI analysis in patients undergoing extended bevacizumab regimen therapy, to assess these changes quantitatively, both during response to treatment, and at recurrence.

Materials and methods

Patients

Patients were retrospectively selected from the our institution's neuro-oncology database, and all have signed institutional review board consent. All patients ($n = 15$) who met the following criteria were selected: (1) pathology confirmed GBM with recurrence following chemotherapy and radiation therapy (RT), (2) no prior surgical resection in the 180 days preceding the start of bevacizumab regimen treatment (Avastin, Genentech, Inc., San Francisco, CA), and no surgical resection for the duration of the study, (3) regularly treated every 2 weeks per cycle with bevacizumab (5 mg/kg body weight) alone or in combination with chemotherapy (carboplatin, irinotecan, etoposide, lomustine), (4) initial response to bevacizumab regimen treatment with reduction in tumor or edema as documented in the radiology report for the first follow-up scan, and no tumor progression for at least 4 months following start of bevacizumab regimen therapy, and (5) baseline and five follow-up MRI scans at approximately 1, 3, 5, 7, and 9 months from start of bevacizumab regimen therapy available for review. RT ranged from 45 to 60 Gy. No patients had radiosurgery. Three patients were placed on dexamethasone (Decadron) treatment before starting bevacizumab regimen therapy. They all received diminished steroid dose as the study progressed. Five patients were placed on dexamethasone during the course of follow-up for this study. This began following recurrent disease in each of these patients, occurring more than 7 months (range 7–11 months) following start of bevacizumab regimen treatment. Dosages for all steroid-treated patients ranged from 0.5 to 36 mg/day (Table 1).

Imaging

MRI scans were read by a board-certified neuroradiologist (W. P.) blinded to patient outcome. MRI sequences were acquired on a 1.5T scanner and included axial T1-weighted (TR 532, TE = 15, slice thickness 5 mm), T2-weighted fast spin-echo (TR 5020, TE 97–134.6, slice thickness 5 mm) and gadolinium-DPTA (Omniscan, Amersham Health, Princeton, NJ, 10–20 ml) enhanced axial T1-weighted images, with a field of view of 24 cm and a matrix size of 256 × 256.

Volume acquisition

Necrosis volume was defined as the area of non-enhancement surrounded by an enhancing rim with an irregular margin on T1-weighted post-contrast images. Edema was defined as the area of very high T2-weighted signal intensity (approaching that of cerebrospinal fluid) surrounding the tumor which was confined to the white matter (i.e., demonstrated "fingers of edema," [11]). Non-enhancing tumor was defined as regions of moderate T2-weighted hyperintensity, significantly less bright that CSF, which clearly demonstrated mass effect as evidenced by, e.g., sulcal effacement, midline shift, ventricular compression etc., and that also blurred the gray–white junction but lacked "fingers of edema." The presence of non-enhancing tumor in GBM has previously been shown to be prognostically significant and detectable with a high degree of inter-observer reliability [4]. Enhancing necrotic tumor was defined as enhancing tumor on post-contrast T1-weighted images that contained measurable (>0.5 ml) necrosis. Necrosis volume was subtracted from the enhancing necrotic tumor volume to obtain the volume of enhancing tissue for the tumor. The sum of non-enhancing and enhancing tumor volumes was considered as total tumor volume for each patient. All measurements excluded resection cavities.

ROIs were manually drawn in each image slice using the Freeform tool, followed by the Surface and Measure tools for surface rendering and volume determination on a Vitrea 2 Workstation (Vital Images, Minnetonka, MN). ROI selection was verified by a board-certified neuroradiologist (W.·P.) and confirmed to be consistent between the scans for each patient, i.e., areas that were determined to be enhancing or non-enhancing tumor or edema on the baseline scan were similarly designated on the follow-ups. This planimetry method for GBM volume determination has previously been proven to be superior to the simple diameter method for quantitative evaluation of tumors [12].

Table 1 Baseline patient demographics and response to Bevacizumab

Patient	Age	Sex	Recurrence	Steroid dose (decadron mg/d)	Treatment prior to baseline recurrence	Baseline KPS[a] (%)	Baseline necrosis volume (cc)	Baseline tumor volume (cc)	Baseline edema volume (cc)	Days on bevacizumab	Combination therapy during measured scans	Best response[b]
1	68	F	2nd	0	Temsirolimus and erlotinib	90	0.5	11.3	60.8	464	Irinotecan	PR
2	61	F	2nd	8–12[c]	AEE-788	90	1.5	92.6	66.0	346	Irinotecan; carboplatin	PR
3	61	M	1st	0	Temozolomide and regional RT	70	4.3	34.8	76.2	449	Irinotecan; lomustine	PR
4	54	F	1st	36 to >8	Temozolomide and regional RT	60	3.7	87.8	95.6	332	Irinotecan; carboplatin; lomustine; irinotecan	PR
5	47	F	1st	1–32[c]	Temozolomide and conformal RT	90	1.3	20.4	99.2	320	Irinotecan; carboplatin; lomustine	PR
6	84	M	1st	8–16[c]	Temozolomide and regional/stereotactic RT	80	0.0	17.6	44.7	234	Lomustine	PR
7	43	M	2nd	0	Gefitinib and rapamycin	90	7.2	104.4	19.5	229	Irinotecan	SD
8	62	F	1st	0	Temozolomide regional RT and 13-cis-retinoic acid	90	0.0	6.2	18.7	586	Irinotecan; carboplatin	PR
9	67	F	1st	0	Temozolomide and conformal RT	90	0.0	19.1	49.0	381	Irinotecan	CR
10	52	F	1st	8 to >0.5	Temozolomide and regional RT	90	3.0	51.7	155.9	311	Irinotecan; lomustine	PR
11	75	M	1st	12 to >2	Temozolomide and stereotactic RT	80	1.7	20.3	73.9	260	Lomustine	SD
12	39	F	1st	0	Temozolomide and regional RT	90	0.8	23.1	49.5	421	Irinotecan; carboplatin; rapamycin	PR
13	54	M	4th	2–24[c]	Carboplatin	90	0.0	9.0	62.4	277	Irinotecan; etoposide	PR
14	90	F	2nd	0	Lomustine	40	0.0	17.3	142.7	234	None	PR
15	39	M	2nd	8–16[c]	Interleukin-13 immunotoxin	80	0.0	5.6	0.8	273	Lomustine; irinotecan; carboplatin	SD

[a] KPS: Karnofsky performance status

[b] According to the response evaluation criteria in solid tumors: CR: Complete response = −100% change in volume from the baseline; PR: Partial response = ≤ −65% change in volume from baseline; PD: Progressive disease = ≥ +73% change in volume from the best response; SD: >−65% change in volume from the baseline and <+73% change in volume from the best response

[c] Patients started on steroids at recurrence, minimum 7 mos after start of bevacizumab therapy

Arrows in steroid column indicate dose at start of bevacizumab treatment followed by ending dose

Statistical methods

Time to response (TTR) and time to progression (TTP) from the baseline were determined based on the change in volume and the Response evaluation criteria in solid tumors definitions (RECIST). Previous studies have shown that volumetric measurements agree well with RECIST 1-D measurement on gadolinium-enhanced images in assessing response and progression in gliomas [13–16]. Since RECIST criteria were established for 1-D measurements, we used the volume conversion table as in reference [13, 14]. Partial tumor response was therefore defined as $\geq$65% decrease in volume from the baseline. Response status was confirmed by a minimum interval of 4 weeks from the baseline. Progression was defined as $\geq$73% increase in volume from the best response or the appearance of a new lesion. Stable disease was confirmed by a minimum interval of 6–8 weeks without progression or partial/complete tumor response. The best response was that recorded before tumor progression. Student's 2-tailed paired *t*-test was used to determine statistical significance at the 5% level. The 95% confidence intervals for means and differences were determined by the *t*-distribution.

Results

Patient characteristics

Table 1 shows the baseline characteristics, volumes, and responses of the recurrent GBM patients in this study. For the cohort, the median baseline age was 61 years (range, 39–90 years). In addition, 60.0% of the patients started bevacizumab regimen treatment upon first tumor recurrence, 33.3% upon second tumor recurrence, and the remaining patient at fourth recurrence. The treatment at the time of tumor recurrence prior to starting bevacizumab is listed. The median baseline KPS was 90% (range, 40–90%). All patients were treated with bevacizumab alone or in combination with chemotherapy for at least 4 months without tumor progression. The median time on bevacizumab was 320 days (range, 229–586, SD = 102). The most frequently used combination chemotherapies were irinotecan, carboplatin, and lomustine. The median necrosis volume was 1.7 ml (range, 0.5–7.2 ml), the median tumor volume was 20.3 ml (range, 5.6–104.4 ml), and the median edema volume was 62.4 ml (range, 0.8–155.9 ml). Nine patients had tumors with necrosis at baseline. In addition to the baseline MRI scan, 5 follow-up MRI scans were volumetrically analyzed for each patient over approximately 300 days of bevacizumab regimen treatment. Out of 15 patients, 10 (66.7%, 95% CI = 58.5–78.9%) showed at least a partial tumor response by median 81 days (range, 14–165, SD = 60) per RECIST criteria. Out of seven patients with baseline tumor volumes below the median, six showed a partial response. Half of the 10 partial responders had necrotic tumors. One partial responder eventually had a complete response.

Rapid response to bevacizumab with sustained reduction of necrosis volume overall

In order to determine the radiographic response to bevacizumab regimen treatment, we measured the volumes of total tumor (enhancing + non-enhancing), peritumoral edema and necrosis for each patient at each follow-up scan (Fig. 1). Tumor, edema and necrosis volumes among all patients rapidly responded to bevacizumab regimen therapy by the 1st follow-up scan. For instance, the tumor with the best response at 1st follow-up had a 89.8% reduction in tumor volume, and overall there was a median 52.6% reduction in tumor volume for all patients at 1st follow-up ($P = 0.003$). The median reduction in tumor volume was maximal at the 3rd follow-up scan (70.0% reduction in tumor volume, $P = 0.001$), before subsequently increasing. The median best response (over the entire follow-up period) was 67.7% (95% CI = −58.9 to −80.9%) reduction in total tumor volume, and 72.8% (95% CI = −48.1 to −83.6%) reduction in edema volume, compared to baseline. The median time to best tumor response was 158 days (range, 16–261, SD = 63).

Reductions in edema persisted throughout the treatment, even in tumors that subsequently progressed. The edema volumes decreased by as much as 87.6% by the first follow-up scan (median = −46.1%, $P = 0.001$). This reduction was sustained through the 3rd follow-up scan, where the median reduction in volume reached 68.7% ($P = 0.001$). Scans thereafter showed complete or near complete resolution of edema. The low baseline edema volume in patient 15 was an outlier as it did not respond to bevacizumab treatment. The edema volume change from the baseline was significant at the 5% level throughout the study.

Necrosis completely resolved in the majority of necrotic tumors (seven out of nine). From the nine patients with necrotic tumors at baseline, the mean change in necrosis volume was −69.1% at the 2nd follow-up scan ($P = 0.0005$), −77.0% at the 3rd follow-up scan ($P < 0.0001$) and −86.4% by the 5th follow-up scan ($P = 0.0003$), compared to the baseline volumes. In comparison, the mean change in tumor volume in these patients was −59.9% at the 3rd follow-up scan ($P = 0.0001$) and increased to −6.2% by the 5th follow-up scan ($P > 0.05$). Thus necrosis remained diminished, even when there was tumor progression.

Figure 2 illustrates the best tumor response observed in this study. Time to partial tumor response was 81 days

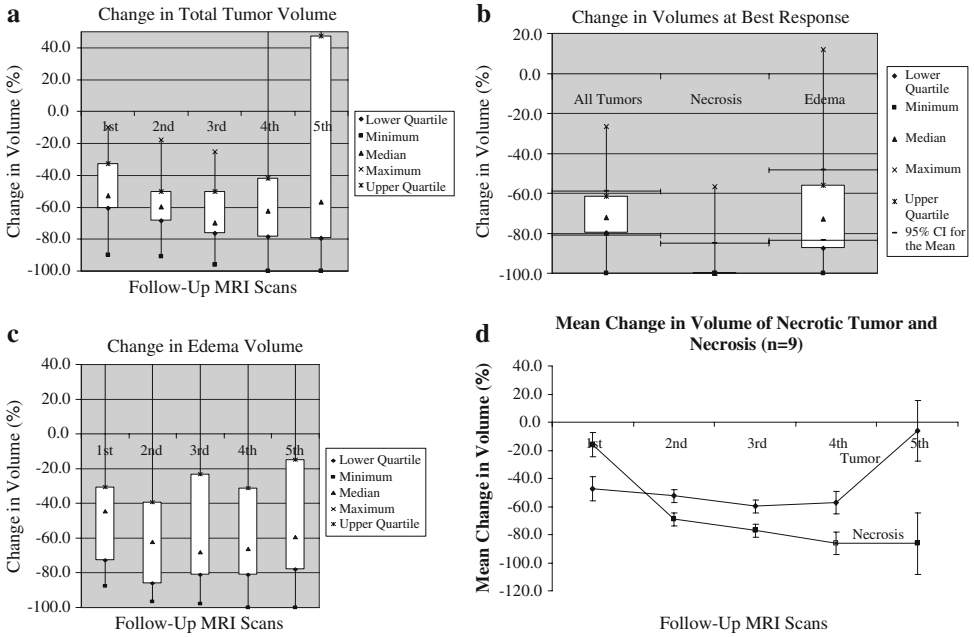


Fig. 1 Change in volume compared to the baseline volume for All GBM patients ($n = 15$). Box and whisker plots show rapid and significant response to bevacizumab by (**a**) total tumor volume changes (compared to baseline, $P < 0.05$ at 1st to 4th); (**b**) best responses of total tumor, necrosis, and peritumoral edema volumes among patients over median follow-up of 259 days (horizontal bars represent upper and lower 95% confidence limits for the mean); (**c**) peritumoral edema volume changes (compared to baseline, $P < 0.05$ at 1st to 5th); (**d**) temporal relationship between change in necrosis volume (compared to baseline, $P<0.05$ at 2nd to 5th) and change in tumor volume (compared to baseline, $P < 0.05$ at 1st to 4th) in patients with necrotic tumors is shown ($n = 9$, data represented as mean ±95% confidence interval for the difference)

from the baseline. By this time, tumor volume decreased by 83.8% and edema volume decreased by 69.2% from the baseline. The tumor completely responded by 202 days from the baseline.

Tumor progresses more rapidly than edema and necrosis in patients with progressive disease

Figure 3 displays the analysis of patients who showed tumor progression during bevacizumab treatment. In this study, 7 out of 15 (46.7%, 95% CI = 38.0–55.4%) patients showed tumor progression between approximately 180 and 270 days of bevacizumab regimen therapy (range, 185–260, SD = 25). Tumor progression occurred at the site of original presentation, except in the case of Patient 2, where the appearance of two small enhancing nodules in the left hemisphere marked progression on day 236 of bevacizumab regimen treatment, while the original tumor in the right hemisphere showed sustained response. Of the seven progressing patients, five had necrotic tumor at baseline, but none had necrotic tumor at progression on bevacizumab treatment. The edema to tumor volume also was reduced at progression on bevacizumab compared to progression on prior chemotherapy by approximately 38.4% (see below). Figure 4 shows an example of sustained edema volume reduction despite tumor progression.

Differential responses of tumor and edema volumes

Since the patients in this study were treated with bevacizumab regimen therapy after progression on other chemotherapy, the baseline volumes represented a standard for comparison within each patient. In order to assess the relationship between tumor and edema volumes in response to bevacizumab and how this compares to the baseline volumes, the mean volumes at each follow-up scan were normalized to the respective mean baseline volumes. In Fig. 5, the baseline-normalized mean edema volume from all patients ($n = 15$) at each follow-up scan did not increase beyond 0.48. On the other hand, the baseline-normalized tumor volume from all patients ($n = 15$) increased to 0.72. The 95% confidence intervals of the difference between the mean tumor and mean edema volumes did not overlap. Overall, tumor volume increased at a faster rate than edema volume during the later part of bevacizumab treatment.

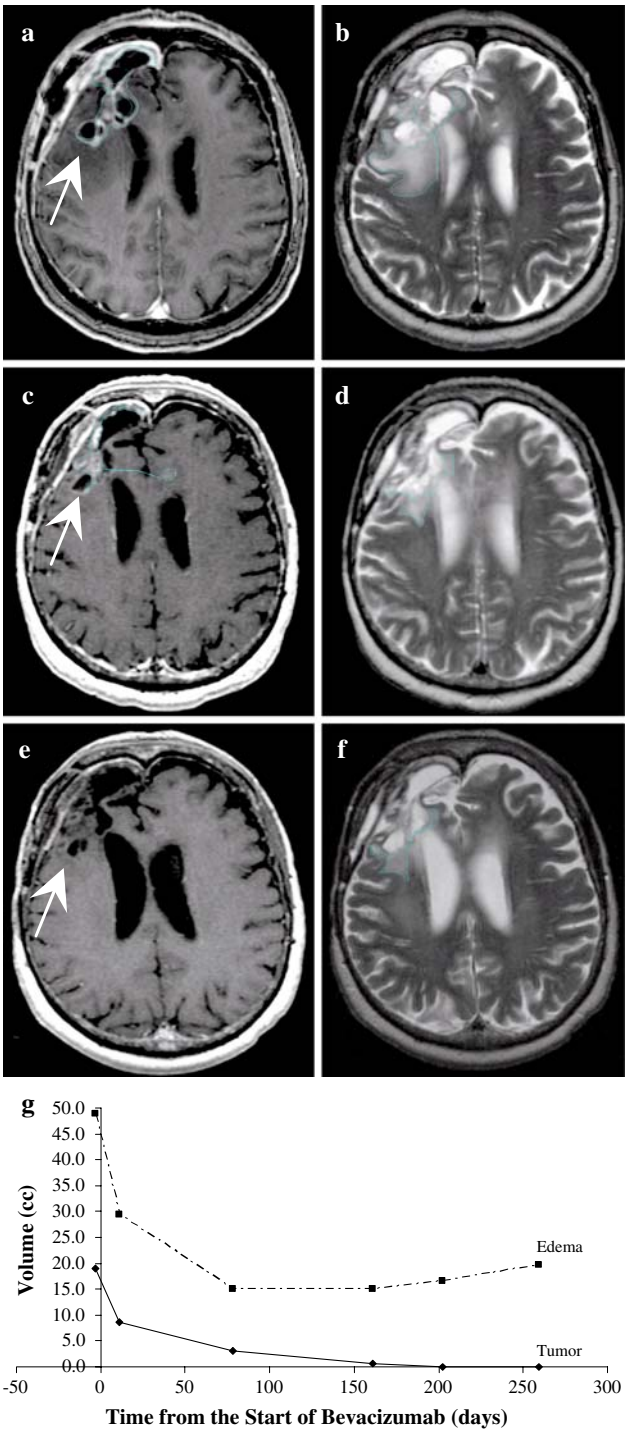


Fig. 2 Patient with complete response of GBM to bevacizumab. Paired axial T1 post-contrast (left) and corresponding T2 (right) MRI scans of patient 9. (**a**, **b**) 31 days before starting bevacizumab, the patient showed right frontal irregular contrast enhancement (arrow). (**c**, **d**) By day 78 of the treatment, the tumor volume decreased by 83.8% from the baseline. (**e**, **f**) By day 202, the tumor completely responded. (**g**) Temporal relationship between tumor (solid line) and edema volumes (dashed line) over time. The complete response of the tumor remained at day 340. The patient was on bevacizumab for 381 days and taken off due to stroke. T2 images d and f show stable peritumoral T2-weighted signal change following significant edema volume reduction from b

Discussion

In patients with recurrent GBM, bevacizumab regimen treatment has been shown to improve both progression-free and overall survival in comparison to historical controls [10]. Response can occur quickly; reduction in tumor volume has been documented within 6 weeks of therapy initiation [9]. In addition to diminished tumor size, bevacizumab regimen treatment also can result in a dramatic reduction in edema [9]. The time course and extent of these responses to bevacizumab is not well characterized. In the current study we used MRI and volumetric analysis to quantitatively assess response and progression in recurrent GBM patients undergoing extended bevacizumab regimen treatment.

Our retrospective analysis was designed to follow patients who successfully continued bevacizumab regimen treatment for at least 4 months. It should be noted that the study was not designed to determine response rates in an unselected cohort of GBM cases, but rather characterize the time course of tumor, edema, and necrosis volume reductions in a selected group of patients that showed an initial response to bevacizumab regimen treatment. We showed a rapid and significant median reduction of tumor and edema volumes from the baseline in patients by the 1st (approximately 1 month) follow-up scan, in agreement with a previous non-quantitative report [9]. The rate of tumor progression also was similar that observed for patients in prior studies [10]. Our finding that maximal reduction in tumor volume in patients with an initial response to bevacizumab treatment can occur as early as 16 days, but on average takes approximately 5 months, and that all patients had a maximal response within approximately 8 months, adds insight into the time course of the response to bevacizumab regimen treatment. Additionally, the finding that the average maximal reduction in tumor volume was approximately 66%, helps define what can be considered a "good" response to bevacizumab regimen treatment.

One caveat to our findings is that there was a high degree of variability of treatment in our patient group. In particular, multiple chemotherapy regimens were used in combination with bevacizumab therapy. Historical data from other chemotherapy regimens suggests a response rate of less than 20% [17, 18]. However, it is not known what portion of patient response is due to bevacizumab alone, versus synergistic effects with the other chemotherapies used. Ongoing trials of bevacizumab alone versus bevacizumab in addition to irinotecan for recurrent GBM should allow for a more definitive answer to this important question. Even though the treatment regimen was heterogeneous, our results are comparable to other studies in which all patients received the same chemotherapy combination (e.g., bevacizumab and irinotecan as in Ref. [10]). Although limited by small numbers, we did not find a

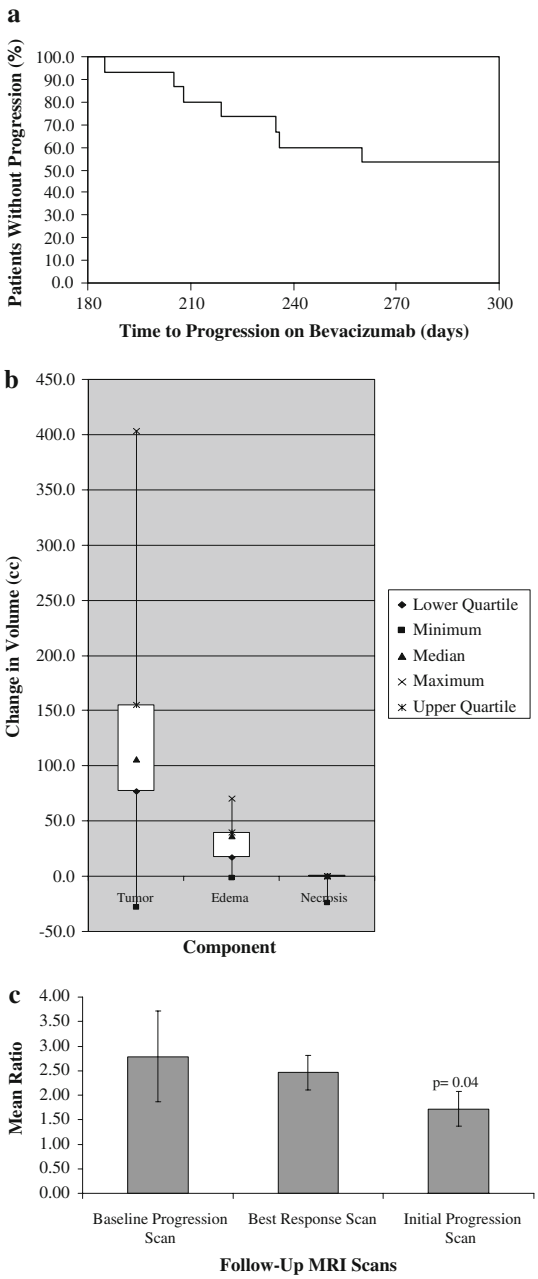


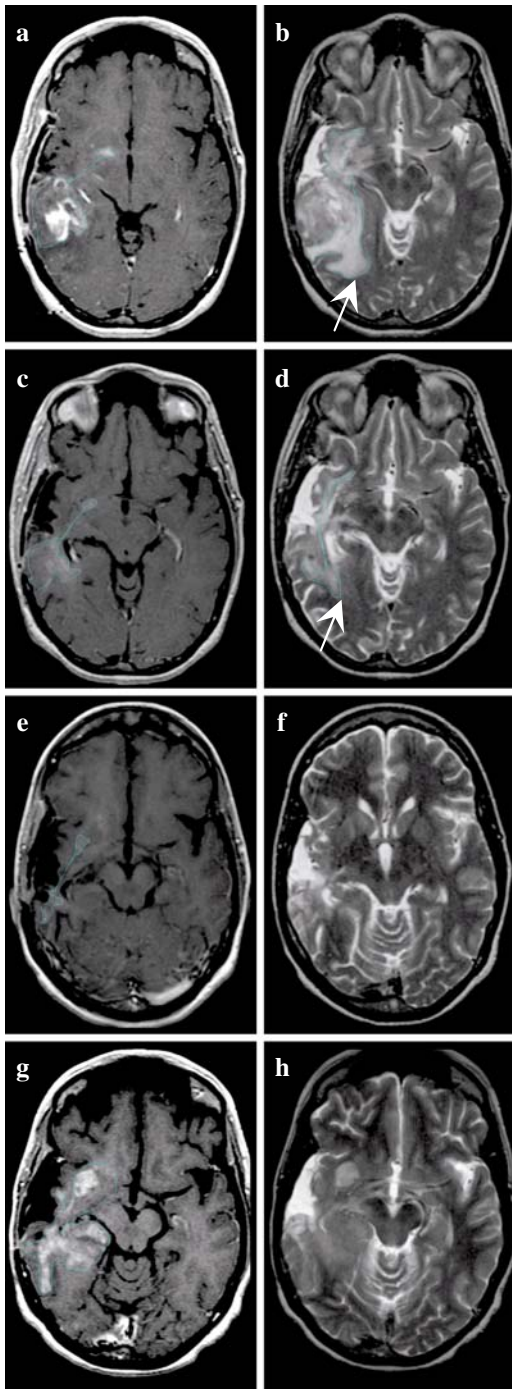
Fig. 3 Greater progression of tumor than edema. (**a**) Kaplan–Meier progression-free survival was plotted as patients without progression (% of $n = 15$) over time to progression (TTP) from the start of bevacizumab treatment, according to the date of the initial scan showing tumor progression by RECIST definitions. (**b**) Box and whisker plots show the distribution of change in tumor, edema ($n = 7$) and necrosis ($n = 5$) volumes from volumes at the best tumor response scan. (**c**) Ratio of edema-to-tumor volume was calculated at the tumor progression scan and at the best tumor response scan for each progressing patient ($n = 7$). The difference between ratios was significant at the 5% level ($P = 0.04$). Both ratios were lower than the baseline ratio from progression on other chemotherapy. Data are expressed as mean ratio ±95% confidence interval for the true mean difference

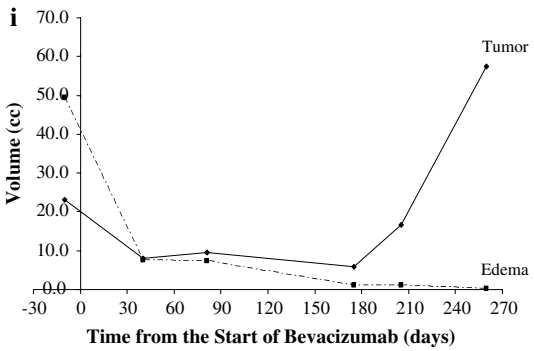
significant difference between response and bevacizumab regimen treatment based upon prior/cotemporaneous chemotherapy regimens or recurrence number.

Another important issue in interpreting the data is the possibility of resolving pseudo-progression from prior RT accounting for some of the reduction in tumor and edema volumes during follow-up scans. Pseudo-progression typically occurs within 3 months of RT [19]. In our cohort, the majority of patients (10/15) were started on bevacizumab regimen treatment more than 3 months after the end of RT. Median reduction in both tumor and edema on the initial follow-up scan was similar for the two groups of patients, i.e., those treated within 3 months of RT (33% for edema and 53% for tumor) and those treated more than 3 months after RT (39% for edema and 49% for tumor). Others have reported decrease in enhancement and FLAIR signal change in a small cohort of GBM patients treated with bevacizumab and chemotherapy exhibiting MRI findings compatible with radiation necrosis [20]. The time between RT and bevacizumab treatment was not defined in that study, but potentially could be longer that 3 months. However, the majority of patients in our study lacked some or all of the imaging characteristics of radiation necrosis, such as "areas of abnormal enhancement at a distance from the primary tumor." In fact only one of our patients met that criterion. Additionally, improvement in radiation necrosis would be unlikely to explain the survival benefit seen with bevacizumab regimen therapy. However, it is important to note that bevacizumab could indeed have similar effects on necrotic areas, regardless of whether they are due to tumor, radiation, or a combination of the two.

In agreement with previous qualitative data [9], we found in the current study a significant reduction in edema in bevacizumab regimen treated GBM. Eight out of 15 of our patients received steroids during the study, which also acts to reduce edema. Three of these were started on steroids prior to bevacizumab regimen treatment and had their doses tapered during the course of the study. The other five patients were placed on steroids after having recurrent tumor, more than 7 months after the start of bevacizumab regimen treatment in each case. Thus the early and progressive reduction in edema and tumor in 12 of the patients cannot be explained by steroid effect. Additionally, the tapering of steroid dose in the remaining three patients while on bevacizumab regimen therapy suggests that bevacizumab treatment may reduce the requirement for steroid treatment.

The reduction in edema was rapid and sustained, even for patients with tumor progression. Tumor progression also lacked necrosis, unlike recurrence with other chemotherapies. This finding supports previous work suggesting that bevacizumab regimen treatment reduces the necrotic component of tumor preferentially [9]. However, bevacizumab regimen treatment also was effective in tumors that lacked necrosis at baseline. The sustained reduction in edema and necrosis at tumor recurrence may signify an





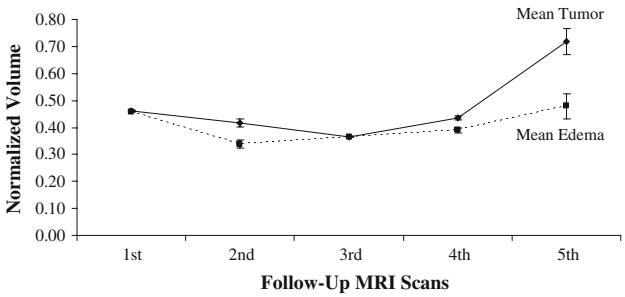


Fig. 5 Temporal relationship between tumor and edema volumes in all patients ($n = 15$). Data represented as baseline-normalized mean volume ±95% confidence interval for the difference

important change in tumor morphology and underlying tumor biology. One possibility is that the reduction in necrotic tumor has to do with the link between VEGF and hypoxia. Hypoxia induces increased VEGF expression [21]. It is possible that the inhibition of VEGF by bevacizumab results in a "normalization" of the vasculature which reduces hypoxia. As hypoxia is associated with a more aggressive phenotype [22, 23], this may explain, at least in part, the potential survival benefit of anti-VEGF therapy, i.e., anti-VEGF therapy shifts tumor biology toward as less malignant course. Additionally, reduction in hypoxia could promote better response to radiation treatment. Potentially DNA array analysis before and subsequent to bevacizumab regimen treatment could be used to determine what genetic changes underlie these phenotypic differences.

Although our study was limited by small sample size, we showed quantitatively that there was sustained reduction of edema and necrosis volumes overall in GBM with bevacizumab regimen treatment, even following recurrence. We also characterized the extent and time course of these changes, which may provide a benchmark useful in judging an individual patient's response to bevacizumab regimen therapy.

◀ **Fig. 4** Steady decline of peritumoral edema with bevacizumab treatment over time despite tumor progression. Axial T1 post-contrast (left) and T2 (right) MRI scans of patient 12. (**a**, **b**) 10 days before the start of bevacizumab treatment, the patient showed large heterogeneously enhancing tumor and significant peritumoral edema (arrow). (**c**, **d**) By day 40 of bevacizumab treatment, necrosis volume reduction was complete and tumor volume reduction was 64.9%, coupled with significant edema reduction from the baseline (arrow). (**e**, **f**) By day 175, the tumor's best response was measured. (**g**, **h**) By day 260, there was further progression of the non-enhancing and nonnecrotic tumor in the right temporal lobe. (**i**) Temporal relationship between total tumor (solid line) and peritumoral edema (dashed line) volumes was measured. By day 205, the patient showed tumor progression while edema volume reduction was sustained (scan not shown)

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