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Journal
Clinical Neurology and Neurosurgery, 115(9)

ISSN
0303-8467

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Publication Date
2013-09-01

DOI
10.1016/j.clineuro.2013.04.017

Peer reviewed

HHS Public Access

Author manuscript

Clin Neurol Neurosurg. Author manuscript; available in PMC 2017 August 21.

Published in final edited form as:

Clin Neurol Neurosurg. 2013 September ; 115(9): 1795–1801. doi:10.1016/j.clineuro.2013.04.017.

Disseminated progression of glioblastoma after treatment with bevacizumab

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Abstract

Objectives—Reports of glioblastoma (GBM) progression following treatment with bevacizumab indicate that a subset of patients develop disseminated, often minimally enhancing tumors that differ from the typical pattern of focal recurrence. We have reviewed our institutional experience with bevacizumab for GBM to evaluate the prognostic factors and outcomes of patients with disseminated progression.

Patients and methods—Medical records of patients treated for GBM at the University of California San Francisco from 2005 to 2009 were reviewed. Patients receiving bevacizumab for focal disease were evaluated and imaging was reviewed to identify patients who progressed in a disseminated pattern. Tumor and treatment factors were compared between focal and disseminated progressors to identify predictive factors for dissemination. Clinical outcomes were compared between progression groups.

Results—Seventy-one patients received adjuvant bevacizumab at some point in their disease course in addition to surgical resection and standard chemoradiotherapy. Of these, 12 patients (17%) had disseminated progression after bevacizumab. There were no differences in patient demographics, surgical treatment, or bevacizumab administration between disseminated and focal progressors. Length of bevacizumab treatment for disseminated progressors trended toward increased time (7.4 vs. 5.4 months) but was not statistically significant ($p = 0.1$). Although progression-free survival and overall survival did not differ significantly between progression groups (median survival from progression was 3.8 vs. 4.6 months, $p = 0.5$), over 30% of focal progressors had a subsequent resection and enrollment in a surgically based clinical trial, whereas none of the disseminated progressors had further surgical intervention. Compared to previously published reports of GBM dissemination with and without prior bevacizumab treatment, our patients had a rate of disease dissemination similar to the baseline rate observed in patients treated without bevacizumab.

Conclusion—The risk of dissemination does not appear to be considerably increased due to the use of bevacizumab, and the pattern of disease at progression does not affect subsequent survival.

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Conflict of interest

The authors declare they have no conflicts of interest.

Therefore, the risk of dissemination should not influence the decision to treat with bevacizumab, especially for recurrent disease.

Keywords

Glioblastoma; Bevacizumab; Progression; Craniotomy

1. Introduction

Despite advances in surgical techniques and adjuvant therapies, the prognosis for patients with glioblastoma (GBM) remains universally poor. Standard therapy at diagnosis consists of maximal safe surgical resection followed by radiation with concurrent temozolomide (TMZ), providing a median survival of 15 months [1]. Patients with GBM inevitably recur, at which point median survival is approximately 6 months [2,3]. In the United States only two drugs are approved for recurrence: implantable chemotherapy wafers (polifeprosan 20 with carmustine, Gliadel®) and bevacizumab (Avastin®), a humanized monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A). Prior to its use in GBM, bevacizumab demonstrated improved progression-free survival (PFS) in phase III trials of metastatic breast [4] and renal [5] cancers as well as prolonged overall survival in metastatic colorectal [6,7] and non-small-cell lung cancers [8]. Bevacizumab was first assessed in patients with recurrent GBM in combination with the topoisomerase inhibitor irinotecan in 2007 [9]. Early phase II studies demonstrated that bevacizumab alone was well tolerated in patients with GBM and provided a 6-month PFS that exceeded that of salvage chemotherapy and irinotecan alone [10–13]. It was, therefore, approved as a single-agent for recurrent GBM in 2009.

Since bevacizumab did not undergo a phase III placebo-controlled trial for GBM prior to approval, the patterns of progression and clinical outcomes after treatment failure have not been systematically reviewed in a prospective fashion. However, numerous retrospective studies have described atypical patterns of progression after bevacizumab treatment, including multifocal and widely disseminated disease [14–17]. It is now generally accepted that a subset of patients receiving bevacizumab will develop disseminated tumors at progression, with reports ranging from 16 to 73% [14,15,18–23]. Unfortunately, there is little data on the rate of spontaneous dissemination in patients not treated with bevacizumab, and the limited number of studies of tumor progression after bevacizumab demonstrate conflicting results [14,15,22]. Additionally, the radiographic appearance of recurrent tumors has been shown to change after bevacizumab treatment. In one study 35% of patients who progressed on bevacizumab developed non-enhancing tumor with increased T_2-wieghted FLAIR signal, which differed from the typical recurrence pattern of focal enhancement at the site of initial disease [14]. The Response Assessment in Neuro-Oncology (RANO) criteria were established to address T_2 hyperintensity in recurrent lesions and account for the progression of non-enhancing tumor, partially in response to the effects of bevacizumab [24]. Application of these criteria to patients has resulted in recognition of decreased response rates and progression-free survival [25].

The implications of disseminated progression after bevacizumab on subsequent treatment and overall survival remain ambiguous. The majority of studies reporting dissemination after treatment for recurrent GBM do not show an effect on survival [19–23]. However, with the increased use of bevacizumab as upfront therapy following initial resection, the true incidence of disseminated progression and its effect on subsequent treatment options becomes an important question. In this study we retrospectively reviewed our institutional experience with bevacizumab for newly diagnosed and recurrent tumors. We assessed the clinical characteristics and outcomes of patients in relation to their pattern of progression. The incidence of dissemination and repeat surgical resection, as well as the time to progression and survival from progression was evaluated.

2. Materials and methods

2.1. Patient selection and evaluation

All patients undergoing craniotomy for resection of a GBM at the University of California, San Francisco Medical Center from January 2005 to December 2009 were retrospectively reviewed for this study. Eligible patients were identified using the operating room log cross-referenced to a pathology database. A histopathologic diagnosis of GBM, according to the World Health Organization classification system, was confirmed for each patient. Medical records and imaging studies were reviewed for demographic and treatment information to identify patients with de novo GBM treated at our institution for their entire disease course. Patients with incomplete medical records were excluded. Neuro-oncology treatment records were then used to identify patients who received bevacizumab chemotherapy at any time in their treatment course. Demographic information including age, sex, presenting symptoms, tumor anatomic and functional location, and Karnofsky Performance Status (KPS) were obtained from the medical records. All patients underwent initial surgical resection of their tumor followed by fractionated conformal radiotherapy and TMZ chemotherapy in accordance with the Stupp protocol [1]. Some patients underwent one or more repeat operations for recurrent tumor. A variety of adjuvant chemotherapy protocols were given, with all identified patients receiving bevacizumab alone or in combination with other agents at some point in their disease course. Bevacizumab was administered as 10 mg/kg every 2 weeks. The total time and number of bevacizumab doses administered for each patient was recorded.

Magnetic resonance imaging (MRI) studies before and after each operation, as well as at each identified tumor progression time point were reviewed. Volumetric extent of resection from each operation was calculated from pre and post-operative imaging and categorized as gross-total (>95% by volume) or subtotal (≤95% by volume). Imaging identifying tumor progression prior to initiation of bevacizumab therapy was reviewed to ensure focal disease. Patients who received bevacizumab for multifocal or disseminated disease were excluded from this study. All subsequent imaging following initiation of bevacizumab was reviewed to determine the time and nature of progression after the start of therapy. Tumor progression was defined radiographically according to RANO criteria and confirmed by multi-disciplinary clinical assessment of the neuro-oncology tumor board. Radiographically, progression was classified as focal or disseminated (Fig. 1). Focal progression was defined

as tumor recurrence or growth contiguous with the prior tumor that remained confined to a single lobe or less than 2 cm margin from the original tumor (both contrast-enhancement and mass-like FLAIR signal). Disseminated recurrence was defined as contiguous tumor growth involving the majority of two or more lobes, expansion beyond a 2 cm margin, spread to the contralateral hemisphere, or multifocal disease (either contrast-enhancing or non-enhancing mass-like FLAIR signal). For disseminated tumors, the degree of contrast enhancement was graded as focal nodular, diffusely patchy, or non-enhancing. The time to progression from initiation of bevacizumab therapy was calculated for each patient, and the survival from progression was determined by locating the official date of death for each patient from the Social Security Death Index. All medical record and imaging reviews were conducted with approval from the University of California San Francisco Committee on Human Research (CHR #H41995-35483-01).

2.2. Statistical methods

Differences in patient demographic and clinical variables between progression groups were compared using an independent samples *t*-test for continuous variables and Pearson's Chi-square test for dichotomous variables. Fisher's exact test was used when the expected frequency was less than 5. The Kaplan–Meier method was used to estimate PFS and overall survival from progression, and a log-rank test was performed to determine statistically significant differences between groups. Statistical tests were considered significant for $p < 0.05$. All statistical tests were performed using SPSS version 20 (IBM).

3. Results

3.1. Patient population

The review of our surgical database identified 354 patients who underwent craniotomies for newly diagnosed GBM from 2005 to 2009. Of these, 81 patients were treated with bevacizumab through a variety of clinical protocols. Eleven patients (14%) received bevacizumab in combination with TMZ and erlotinib before progression as part of a clinical trial for the treatment of newly diagnosed GBM. The remaining 70 patients (86%) received bevacizumab for recurrent disease. Two patients were lost to follow-up during treatment and were excluded due to incomplete medical records. Six patients were treated with bevacizumab for multifocal recurrence and were excluded from the analysis, and two other patients had not yet progressed at the time of data analysis and were excluded. The remaining 71 patients met the inclusion criteria and were evaluated.

3.2. Demographics

Of the 71 patients who received bevacizumab for focal GBM, 59 (83%) had focal tumor progression and 12 (17%) had disseminated tumor at progression. The demographic characteristics of the patients and their tumors are shown in Table 1. There were no significant differences in patient age, gender, or anatomic/functional tumor location between focal and disseminated progressors. The median KPS for patients in both groups was 90 prior to bevacizumab treatment, and an equal proportion of each group had a prior gross-total resection.

3.3. Bevacizumab administration

The patients included in this study represent a heterogeneous group who received bevacizumab chemotherapy in combination with multiple other therapies at different times in their disease course. Table 2 shows the breakdown of prior surgical treatment and concurrent chemotherapy given with bevacizumab stratified by type of progression. Among disseminated progressors, 4/12 (33%) received bevacizumab after only a single tumor resection, with the remaining 67% undergoing two or more operations prior to bevacizumab. In contrast, 36/59 (61%) of focal progressors had only a single resection before treatment, however these differences were not statistically significant ($p = 0.21$). Additionally, there was no statistical correlation between concurrent chemotherapies and the type of progression after bevacizumab. There was a trend toward increased treatment time among disseminated progressors, who received an average of 7.4 months of bevacizumab therapy as compared to 5.4 months in focal progressors; however, this trend did not reach statistical significance ($p = 0.12$). Additionally, the time to progression from initiation of therapy was not statistically different between progression groups (Table 3).

3.4. Outcomes after bevacizumab therapy

In developing this study, we hypothesized that disseminated recurrence after bevacizumab would lead to a decrease in repeat resections at progression and might affect overall survival. As shown in Table 3, none of the disseminated progressors underwent repeat resection after bevacizumab therapy. This is expected, as the diffuse nature of the recurrence limits the capacity for a safe resection. In contrast, 19/59 (32%) patients with focal recurrence underwent further surgical resection. Repeat resection was not limited to patients who had previously only had a single operation. Of the 19 patients with re-operations after bevacizumab, 6 had previously undergone 2 or more resections and were re-resected for enrollment in a surgically based clinical trial.

Overall, focal progressors had a median post-progression survival of 4.6 months with a 6-month survival of 35%, as compared to disseminated progresssors with a median survival of 3.8 months and a 6-month survival of 25%. These differences were not significant (log-rank, $p = 0.78$).

3.5. Patterns of recurrence

Disseminated progression following bevacizumab therapy has been primarily reported as non-enhancing or minimally enhancing disease with extensive mass-like T_2 signal best appreciated on FLAIR imaging [14–17]. In our series, we identified three patterns of enhancement in disseminated progressors. The majority of patients had either non-enhancing tumors (17%) or diffuse patchy enhancement within a larger non-enhancing tumor (50%). Only 33% of patients had focal or multi-focal nodular enhancement, which is typical of recurrent tumors. Despite the focality of the enhancement, these patients still had diffusely infiltrative disease seen on T_2-weighted FLAIR that extended beyond the margins of the enhancement. Pattern of enhancement was not associated with differences in survival ($p = 0.31$).

3.6. Role of treatment protocol

Of the patients included in this study, 11/71 (15.5%) were treated with bevacizumab upfront at diagnosis following initial resection and 60/71 (84.5%) were treated at first or subsequent recurrence. Since the biology of recurrent glioblastoma and its response to bevacizumab may differ from newly diagnosed disease, we investigated differences in outcomes between patients treated in the upfront vs. recurrent setting. Patient demographics including age, gender, KPS, and extent of tumor resection did not significantly differ between patients treated at new diagnosis or recurrence (Supplementary Table S1). Newly diagnosed patients did receive significantly longer treatment with bevacizumab, averaging 11.1 months of treatment vs. 4.7 months in recurrent GBM patients ($p < 0.001$). As expected, patients with newly diagnosed disease had significantly longer progression-free survival compared to recurrent disease (12.5 vs. 4.5 months, $p = 0.001$). However, overall survival from progression after bevacizumab and absolute overall survival from diagnosis did not differ between groups (Supplementary Table S2). Additionally, the pattern of recurrence following bevacizumab treatment was similar, with 18% disseminated disease in patients treated upfront compared to 17% dissemination in patients treated at recurrence ($p = 0.90$).

4. Discussion

The prognosis for GBM patients at recurrence remains poor with a median PFS of 8–9 weeks and a median OS of 17–25 weeks [2,26]. Effective options for the treatment of recurrent GBM are limited, and two therapies are approved for this indication, with bevacizumab widely becoming accepted as the emerging standard of care. Phase II studies of bevacizumab with and without additional chemotherapy for recurrent GBM have demonstrated 6-month PFS of 29–46%, median PFS of 17–24 weeks, and median OS of 36–42 weeks [9,10,13,15,27]. When combined with fractionated radiotherapy, 6-month PFS rates increase to 65% with median PFS of 28 weeks and median OS of 65 weeks [28]. This compelling data prompted approval of bevacizumab for recurrent GBM without a controlled phase III trial, and has driven investigational studies of bevacizumab as adjuvant therapy for newly diagnosed GBM. Initial phase II data in newly diagnosed tumors demonstrates median PFS of 13.6–14.2 months and median OS of 16.6–21.1 months [29,30]. Lai et al. compared their outcomes with upfront bevacizumab combined with TMZ and radiotherapy to a non-randomized group of contemporary patients treated without bevacizumab and found increased PFS without an effect on overall survival [30]. To definitively address the true benefit of bevacizumab for newly diagnosed disease, two randomized, controlled phase III clinical trials are currently underway in the United States and Europe: RTOG 0825 (NCT00884741) and AVAglio (NCT00943826) [31].

Regardless of the outcome of the on-going clinical trials, it is important to note that bevacizumab is not without risk. Although generally well tolerated, the drug has been reported to cause a number of adverse events including hypertension, seizures, intracranial hemorrhage, and arterial or venous thromboembolism [9,10,29]. Additionally, administration of bevacizumab peri-operatively has been shown to impair wound healing. In one retrospective study, 35% of patients who received bevacizumab prior to craniotomy developed wound-healing complications compared to 10% in patients who were

bevacizumab naïve prior to surgery [32]. Complications included infection (29%), wound dehiscence (12%), CSF leak (24%), pseudomeningocele (18%), and osteomyelitis (18%).

Another perceived risk of bevacizumab is the conversion of local disease to widely disseminated tumor. This perception has arisen from early reports of invasive, often non-enhancing tumor arising at progression after bevacizumab [14]. Multiple studies have since reported disseminated progression following bevacizumab treatment of newly diagnosed or recurrent GBM. Estimates of the frequency of disease dissemination range from 21 to 73% [14,15,18–23]. Unfortunately, there is no uniform definition of dissemination. Some studies differentiate between multi-focal, distant, and disseminated recurrence, defining dissemination as tumor extending more than 2–3 cm from the margin of the primary site/resection cavity and greater than 50% of the margin having a poorly defined border [21,22]. Others differentiate between radiographic patterns of progression based on degree of contrast enhancement, which has been associated with underlying genetic differences in the tumor [14,33]. DeLay and colleagues reported differential upregulation of a number of genes that promote migration through the extracellular matrix, including integrin α5, fibronectin1, neutrophin 3, PDGFRβ, and CXCL12 in non-enhancing recurrent tumors after bevacizumab [33]. In this study we have defined dissemination as tumor extending more than 2 cm from the primary site with greater than 50% of the margin poorly defined. Additionally, we excluded patients with multifocal or disseminated disease at initiation of bevacizumab treatment to assess the population of patients with focal disease who converted to a disseminated phenotype. We found that 17% of patients treated with bevacizumab had widely disseminated tumor at recurrence, and that 67% of these tumors had patchy or no enhancement.

A summary of the results from all of the substantial case series evaluating disseminated progression after bevacizumab has been compiled in Table 4. When data was available, we adjusted the disseminated progression rates to eliminate patients with pretreatment multi-focal disease such that these results represent the true conversion rates of focal to distant/disseminated disease. The majority of studies examining disseminated progression, including our own, represent single cohort retrospective studies with no control group of non-bevacizumab treated patients [18–21,23]. There is a paucity of data in the literature regarding the spontaneous rates of dissemination at progression in patients treated without bevacizumab, making the true impact of bevacizumab difficult to assess. Only 2 studies by Norden et al. [15] and Wick et al. [22] evaluated a concurrent group of non-bevacizumab treated patients. Both studies found no statistical difference in the rate of disseminated progression with the use of bevacizumab. The rate of spontaneous dissemination in their non-bevacizumab patients was 18–21%, which was similar to the rate of dissemination with bevacizumab in single arm studies reported by Pope et al., Chamberlin et al., and our results in this study [18,21].

Additionally, none of the studies examining the frequency of disseminated progression have found a difference in overall survival for patients with focal vs. disseminated progression, regardless of the definition criteria or observed frequency of dissemination. In our study as well, progression pattern was not associated with a difference in survival. Admittedly, the majority of our patient population received bevacizumab for recurrent disease, as was the

case with nearly all of studies reporting progression patterns after bevacizumab [15,18,19,21–23]. Given the limited survival of patients with recurrent disease, differences in survival due to progression pattern may be difficult to resolve. A single study by Narayana et al. included a substantial number of patients with newly diagnosed tumors (38%) as well as recurrent tumors [20]. Although they did not stratify their results on the basis of newly diagnosed vs. recurrent tumor, they also found that recurrence pattern did not affect overall survival. In our study, the same frequency of dissemination was observed in patients receiving bevacizumab at new diagnosis and at recurrence. Overall survival was not altered by the timing of bevacizumab administration or the pattern of recurrence after bevacizumab.

Anecdotal reports of disseminated progression after treatment with bevacizumab, coupled with laboratory studies demonstrating that VEGF inhibition can lead to increased glioma invasiveness have led to a perception that bevacizumab increases the risk of disease dissemination; however, the results of this study and others do not support the perception. Although some studies have shown rates of dissemination as high as 73%, their findings are biased by their definition of dissemination and do not control for the rate of spontaneous dissemination in non-bevacizumab patients [20,23]. The few controlled studies have not found a significant increase in dissemination and their control groups demonstrate spontaneous dissemination rates around 20%, similar to the rate of dissemination found in our study [15,22]. Importantly, no study has demonstrated decreased survival associated with disseminated disease after bevacizumab. Taken together, these data suggest that the risk of dissemination should not influence the decision to give bevacizumab as treatment for recurrent GBM. To date, the published clinical trials of bevacizumab for newly diagnosed GBM have not addressed the patterns of recurrence or the frequency of dissemination at progression [30,34,35]. Our results in this study demonstrate, as expected, that patients with disseminated progression are significantly less likely to undergo further resection. The lack of surgical options and eligibility for clinical trials may adversely affect outcomes for patients with disseminated progression related to bevacizumab use after initial diagnosis. This factor will need to be closely examined when the outcomes of the ongoing phase III trials for bevacizumab in newly diagnosed GBM are reported.

5. Conclusion

Nearly 20% of patients who received bevacizumab progressed in a disseminated pattern. This rate of dissemination is similar to rates previously reported for bevacizumab treatment and non-bevacizumab treated control. Pattern of recurrence did not influence overall survival from progression. Therefore, the risk of dissemination should not influence the decision to treat a patient with recurrent GBM using bevacizumab. The data for patients with newly diagnosed GBM is insufficient to affect treatment recommendations at this time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures

This work was supported by a grant from the Reza and Georgianna Khatib Endowed Chair in Skull Base Surgery (A.T.P.). Dr. Berger is a consultant for Ivivi Health Sciences and Pharmaco-Kinesis Corporation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clineuro.2013.04.017.

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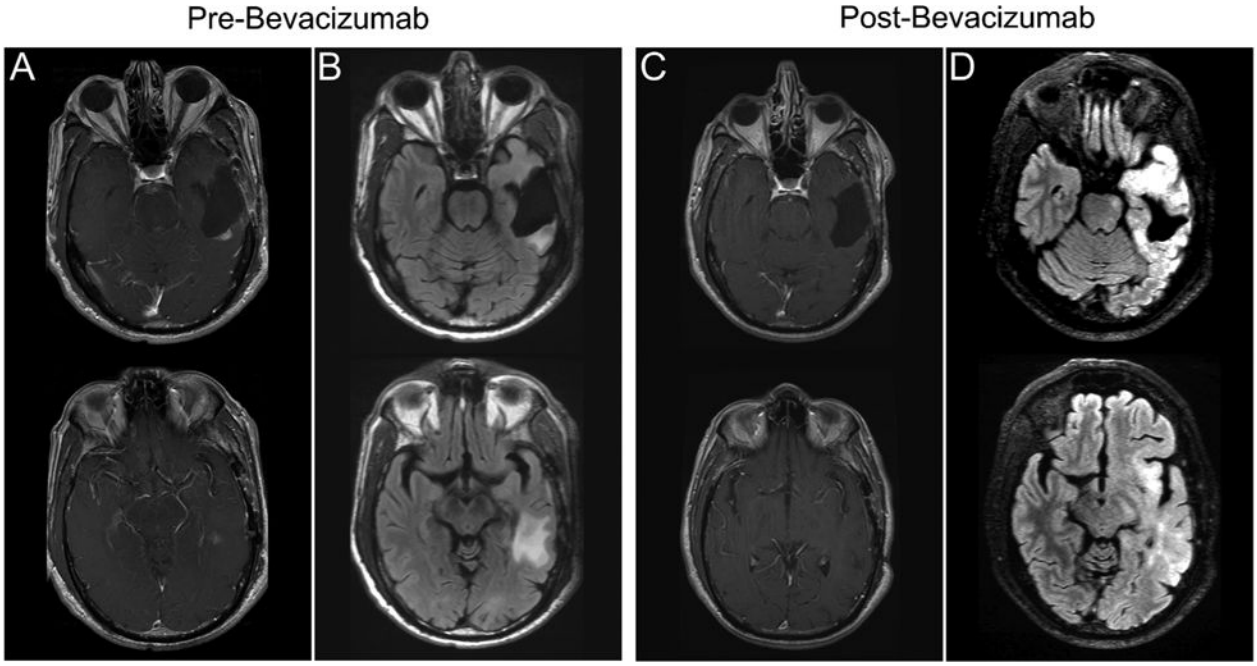

Fig. 1.

Disseminated progression following bevacizumab chemotherapy. T_1-weighted gadolinium enhanced (A) and T_2-weighted FLAIR (B) images of a recurrent glioblastoma in the left temporal lobe prior to bevacizumab therapy. After 12 months of bevacizumab therapy T_1-weighted gadolinium enhanced (C) and T_2-weighted FLAIR (D) images demonstrate non-enhancing disseminated tumor in the entire left temporal lobe extending into the left insula and cerebral peduncle.

Table 1

Characteristics of bevacizumab-treated patients by progression type.

Characteristic	Progression		*p* value
	Diffuse (*n* = 12) No. pts (%)	Focal (*n* = 59) No. pts (%)	
Age			
Mean (years)	49.1	54.7	0.12
Range	21–71	25–83	
Sex			
Male	8 (67)	36 (61)	0.71
Female	4 (33)	23 (39)	
Anatomical location			
Frontal	2 (17)	25 (42)	0.10
Temporal	8 (66)	20 (34)	
Parietal	2 (17)	14 (24)	
Occipital	0 (0)	0 (0)	
Functional location			
Eloquent	7 (58)	32 (54)	0.80
Non-eloquent	5 (42)	27 (46)	
Presenting symptom			
Headache	2 (17)	3 (5)	0.45
Seizure	4 (33)	15 (25)	
Cognitive deficit	2 (17)	10 (17)	
Speech deficit	3 (25)	14 (24)	
Motor deficit	0 (0)	13 (22)	
Sensory deficit	1 (8)	2 (3.5)	
Other	0 (0)	2 (3.5)	
KPS			
Median	90	90	0.43
Range	70–90	70–90	
Initial tumor resection			
Gross total	7 (58)	28 (47)	0.68
Subtotal	5 (42)	31 (53)	

Table 2

Characteristics of bevacizumab administration by progression type.

	Progression		*p* value
	Diffuse (*n* = 12)No. pts (%)	**Focal (*n* = 59)No. pts (%)**	
Resection prior to bevacizumab			0.21
Single resection	4 (33)	36 (61)	
Two resections	7 (59)	20 (34)	
Greater than two resections	1 (8)	3 (5)	
Bevacizumab combined with			0.46
Alone	2 (17)	24 (41)	
Temozolomide	2 (17)	8 (14)	
Irinotecan	4 (33)	18 (30)	
Erlotinib + Temozolomide	3 (25)	7 (12)	
Carboplatin or Lomustine	1 (8)	2 (3)	
Length of treatment			
Mean (months)	7.4 ± 1.6	5.4 ± 0.5	0.12

Table 3

Outcomes of bevacizumab patients by progression type.

	Progression		*p* value
	Diffuse (*n* = 12)No. pts (%)	**Focal (*n* = 59)No. pts (%)**	
Re-resection after progression			
Yes	0 (0)	19 (32)	0.03
No	12 (100)	40 (68)	
Progression-free survival			
Median, month (95% CI)	6.3 (4.3–8.3)	4.9 (3.3–6.5)	0.63
6-Month PFS (%)	58	45	
Overall survival from progression following bevacizumab			
Median, month (95% CI)	3.8 (1.2–6.4)	4.6 (3.5–5.7)	0.78
6-Month survival (%)	25	35	
Overall Survival from diagnosis			
Median, month (95% CI)	19.3 (9.4–29.1)	20.0 (17.6–22.3)	0.73
12-Month survival (%)	92	93	
24-Month survival (%)	42	34	

Table 4

Published studies of glioblastoma dissemination after bevacizumab.

Author and year	No. pts	Treatment regimen	Patients with dissemination (%)		
			Bev Tx (%)	Non-bev (%)	Diff
Norden et al. (2008)	55	Bev + multiple agents	31	21	$p = 0.48$
Iwamoto et al. (2009)	37	Bev + multiple agents	51		
Narayana et al. (2009)	61	Bev + irinotecan or carboplatin	30		
Zuniga et al. (2009)	51	Bev + irinotecan	60.5		
Chamberlin (2011)	80	Bev alone	21		
Pope et al. (2011)	88	Bev ± irinotecan	23–55		
Wick et al. (2011)	88	Bev + multiple agents	22	18	$p > 0.05$
Narayana et al. (2012)	162	Bev + multiple agents	73		
Current study	71	Bev + multiple agents	17		