Case Report

Stereotactic Radiosurgery and Bevacizumab for Recurrent Glioblastoma Multiforme

Alvin R. Cabrera, MD[a]; Kyle C. Cuneo, MD[a]; James J. Vredenburgh, MD[b,c,d]; John H. Sampson, MD, PhD[a,c,d]; and John P. Kirkpatrick, MD, PhD[a,d]

Abstract

Despite contemporary surgery, image-guided radiotherapy, and chemotherapy, glioblastoma multiforme (GBM) persists or relapses in nearly all patients, and tumors almost always recur locally. Management of recurrent GBM is variable, but approaches include best supportive care, reoperation, reirradiation, and/or systemic therapy. Promising novel therapies include antiangiogenic agents and stereotactic radiosurgery, which have cytotoxic effects on tumor microvasculature. Emerging data suggest the safety and efficacy of bevacizumab and radiosurgery either alone or in combination. This report presents the case of a man with locally recurrent GBM treated with stereotactic radiosurgery and concurrent bevacizumab, and reviews the preclinical and clinical data supporting this approach. (*JNCCN* 2012;10:695–699)

Case Report

A 58-year-old man with hypertension presented to his primary care provider with right leg weakness. On physical examination, he had diminished right hip flexion and dorsiflexion. Spine MRI showed degenerative disc disease, and his physician prescribed prednisone for presumed lumbar radiculopathy. His symptoms resolved, but recurred on tapering the prednisone. A week later, he presented to the emergency department with repetitive right arm and leg movements suggestive of a seizure. Head CT showed a ring-enhancing lesion in the left frontal lobe. Brain MRI showed a 2.6 × 1.8–cm, peripherally enhancing, centrally necrotic mass in the left posterior frontal lobe with surrounding vasogenic edema (Figure 1). Body CT showed no other tumors. Neurosurgery performed gross total resection via craniotomy, and pathologic examination revealed glioblastoma multiforme (GBM; WHO grade IV). Polymerase chain reaction assay detected methylation of the O(6)-methylguanine-DNA methyltransferase (MGMT) gene. A 24-hour postoperative MRI showed no residual tumor, and his neurologic symptoms resolved.

The patient enrolled in an institutional clinical trial investigating a novel adjuvant regimen: radiotherapy with concurrent temozolomide and bevacizumab, followed by temozolomide, bevacizumab, and irinotecan (CPT-11). Four weeks after surgery, he began radiotherapy (volumetric modulated arc therapy), receiving 50.4 Gy to the left frontoparietal region with a 9-Gy boost to the tumor bed over 6.5 weeks. During radiotherapy, he received metronomic temozolomide (75 mg/m^2/d) and 3 doses of bevacizumab (10 mg/kg every 2 weeks). After radiotherapy, he continued temozolomide along with CPT-11 (124 mg/m^2) and bevacizumab (10 mg/kg) every 2 weeks. During the second cycle of CPT-11 and bevacizumab, he developed deep venous thrombosis in his right leg. He began anticoagulation with enoxaparin, and CPT-11 and temozolomide were dose-reduced.

The patient completed 8 cycles of adjuvant chemotherapy over 6 months. Brain MRI 3 months after completion of radiotherapy showed no disease. Temozolomide caused significant nausea and fatigue, however, so he discontinued temozolomide and CPT-11 after 8 cycles, withdrawing himself from the clinical trial. He continued single-agent bevacizumab off-protocol

From the Departments of [a]Radiation Oncology, [b]Medicine, and [c]Surgery, Duke Cancer Institute, and the [d]Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, North Carolina.

Submitted March 27, 2012; accepted for publication April 11, 2012.

Drs. Cabrera, Cuneo, and Sampson have disclosed that they have no financial interests, arrangements, or affiliations with the manufacturers of any products discussed in this article or their competitors. Dr. Vredenburgh has disclosed that he serves as a consultant and is on the advisory board for Genentech, Inc. Dr. Kirkpatrick has disclosed that he receives research support from Genentech, Inc.

Correspondence: Alvin R. Cabrera, MD, Duke University Medical Center, Morris Clinic Building, Box 3085, Durham, NC 27710. E-mail: alvin.cabrera@duke.edu

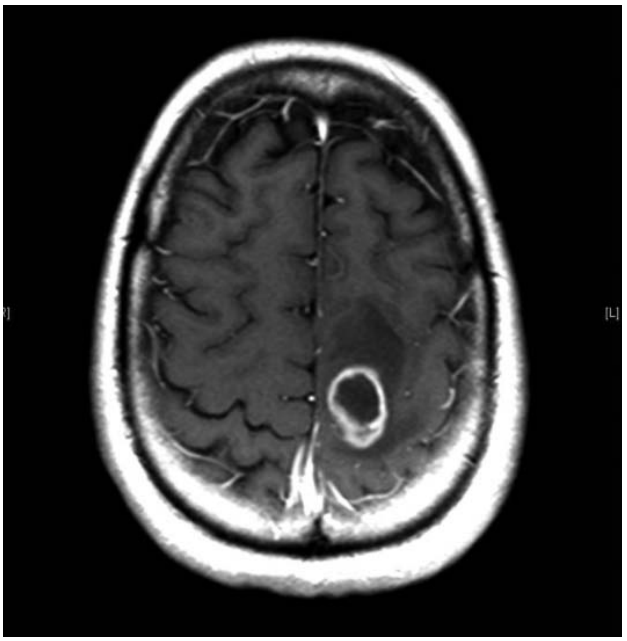

Figure 1 Initial imaging. Axial T1-weighted postgadolinium MRI showed a ring-enhancing, centrally necrotic mass in the left posterior frontal lobe with surrounding vasogenic edema.

(15 mg/kg every 4 weeks) for 10 months. Remaining clinically stable and without evidence of disease on brain MRI or PET, he then also discontinued bevacizumab.

Eight months after stopping systemic therapy, brain MRI showed a 0.4-cm area of faint enhancement at the superior aspect of the resection cavity. PET showed no abnormal FDG avidity and the patient had no new symptoms, and therefore observation was continued. Three months later, MRI showed growth of the enhancing lesion to 1.4 × 0.7 × 0.4 cm and development of surrounding edema (Figure 2A). MRI-guided stereotactic biopsy revealed recurrent GBM.

To treat the locally recurrent nodule, the patient received stereotactic radiosurgery with concurrent bevacizumab (10 mg/kg just before radiosurgery). He received 18 Gy in a single fraction via 5 dynamic conformal arcs using a high-definition multileaf collimator on the linear accelerator–based Novalis Tx radiosurgery system (BrainLAB AG, Munich, Germany and Varian Medical Systems, Palo Alto, CA). Gross tumor volume (GTV) was defined as the enhancing volume on MRI, and planning target volume (PTV) created by uniformly expanding GTV by 1 mm. Of the PTV, 99.9% received prescription dose, with a conformity index of 2.0 and a 21-Gy maximum dose to the PTV (Figure 2B). Other than 2 minor headaches relieved with acetaminophen, the patient experienced no adverse effects. Two weeks later, he began adjuvant temozolomide (200 mg/m^2, days 1–5 every 28 days) and bevacizumab (10 mg/kg, every 14 days).

Two months later, brain MRI showed decreased size of the enhancing nodule to 0.9 × 0.5 × 0.6 cm (Figure 2C). MRI 4 months after radiosurgery showed no progression.

The patient remains clinically stable 4 months post-radiosurgery, 3 years and 1 month since initial diagnosis.

Discussion

Primary treatment of GBM in patients with good performance status involves maximally safe resection followed by fractionated external beam radiotherapy with concurrent and adjuvant temozolomide.[1] Unfortunately, disease persists or recurs in nearly all. Despite contemporary surgery, image-guided radiotherapy, and concurrent/adjuvant chemotherapy, the overall survival rate at 5 years is only 10% and the progression-free survival rate is less than 5%. In the EORTC-NCIC trial, which showed the efficacy of adding temozolomide to radiotherapy and established the current standard of care, methylation of the MGMT promoter was the strongest predictor of outcome, improving median survival from 15 to 23 months. But even among patients with methylated MGMT, the survival rate at 5 years was only 14%.[2] Efforts to improve primary treatment outcomes with radiation dose escalation beyond 60 Gy have failed, even with radiosurgical boost doses of up to 24 Gy.[3]

GBM tends to recur locally, with 90% of relapses occurring within 2 cm of the original tumor.[4] As reflected in the NCCN Clinical Practice Guidelines in Oncology for Central Nervous System Cancers, therapies are variable and depend on the extent of recurrence and the patient's performance status (to view the most recent version of these guidelines, visit NCCN.org).[1] Reoperation may benefit certain patients with locally recurrent disease,[5] but poor performance status, large tumor volume, and involvement of specific critical brain areas are associated with unfavorable surgical outcomes.[6] Patients with a reasonable performance status often receive systemic therapies, such as temozolomide, nitrosoureas, procarbazine/lomustine/vincristine, cyclophosphamide,

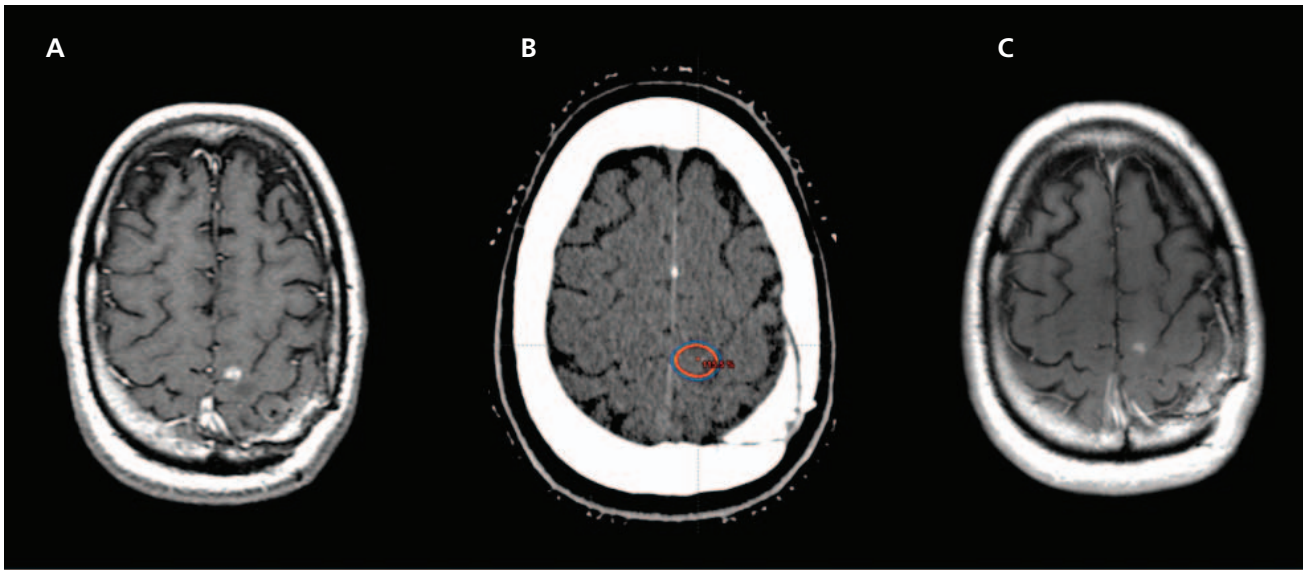

Figure 2 Imaging response to radiosurgery plus bevacizumab. (A) Axial T1-weighted postgadolinium MRI showed an enhancing lesion at the superior aspect of the resection cavity. Biopsy confirmed recurrent glioblastoma. (B) Isodose lines from the radiosurgery plan overlie this axial slice from the patient's simulation CT. The inner red line is the 100% isodose line, within which all voxels receive at least 100% of the prescription dose. The outer blue line is the 80% isodose line. Dose declines rapidly beyond the target volume. (C) Axial T1-weighted postgadolinium MRI obtained 4 months after radiosurgery plus bevacizumab shows a smaller area of enhancement.

platinum-based regimens, irinotecan, or etoposide.[1] Salvage therapies for recurrent GBM have historically achieved radiographic response rates of 5% to 10%, and 6-month progression-free survival rates of 10% to 15%, conferring a median overall survival of approximately 25 weeks.[2,7]

Poor prognosis with conventional treatments has compelled the development of novel therapies. Antiangiogenesis has been an active area of investigation, because GBM is among the most angiogenic of malignancies. High-grade gliomas overexpress vascular endothelial growth factor (VEGF), resulting in a dense network of leaky and unstable vessels engendering tumor hypoxia and increased interstitial pressure, which contribute to radio- and chemoresistance.[8] In animal models of high-grade glioma, antiangiogenic agents reduce vascular density, increase perivascular tumor cell apoptosis, inhibit tumor growth, and extend survival.[9] The first clinically available angiogenesis inhibitor in the United States was bevacizumab, a humanized monoclonal antibody targeting VEGF. Two single-arm, prospective phase II trials investigating bevacizumab and CPT-11 in recurrent glioma patients showed 6-month progression-free survival rates of 38% to 46% and median overall survival of 40 to 42 weeks.[10,11]

Two additional phase II studies confirmed the efficacy of bevacizumab and formed the basis for accelerated approval of single-agent bevacizumab for recurrent GBM by the FDA in 2009. The first, a single-arm evaluation of bevacizumab monotherapy in 48 heavily pretreated recurrent GBM patients, showed radiographic response in 35%, a 6-month progression free survival rate of 29%, and median overall survival of 31 weeks.[12] The second trial, which randomized 167 patients with recurrent GBM to single-agent bevacizumab versus bevacizumab plus CPT-11, showed radiographic response in one-third, respective 6-month progression-free survival rates of 43% and 50%, and respective median survivals of 37 and 35 weeks, all superior to historical controls.[13] Adding CPT-11 to bevacizumab did not improve outcomes and was associated with more frequent adverse effects. Bevacizumab itself was associated with thromboembolic events, hypertension, and a low risk of intracranial hemorrhage (< 3%).

Another novel therapy is stereotactic radiosurgery, which delivers a high dose of radiation to the tumor in a single fraction (or up to 5 fractions for larger tumors). Conformity of dose to tumor is essential; normal tissue toxicity would be otherwise prohibitive. Radiosurgery plans typically use mul-

tiple narrow photon beams delivered in noncoplanar arcs, which concentrate the dose to the tumor with a rapid lowering of dose just beyond the target. Radiosurgery requires highly accurate beam delivery, so patients' heads are immobilized by a metal ring screwed into the skull or by a tight, customized, thermoplastic mask. These devices are "stereotactic," in that they allow precise 3-dimensional mapping during initial imaging, target localization, and patient setup, conferring submillimeter treatment accuracy.

Radiosurgery is a promising approach for recurrent high-grade gliomas because recurrences almost always occur in previously irradiated areas. Reirradiating brain with large-field, full-dose, conventional radiotherapy carries a high risk of cognitive/neurologic deficits or radionecrosis, which can be debilitating. Through sparing adjacent normal brain, radiosurgery can deliver a high dose in a short time. Unlike surgical resection, stereotactic radiosurgery need not delay systemic therapy.

Several institutions have published promising results with stereotactic radiosurgery or hypofractionated radiotherapy for recurrent high-grade gliomas. Retrospective series involving a total of 145 patients from Brigham and Women's Hospital, University of Heidelberg, and University of Minnesota each reported a median survival of 10 months from salvage radiosurgery.[14–16] A retrospective study from Thomas Jefferson University of 147 patients treated with hypofractionated stereotactic radiotherapy (median dose, 35 Gy in 3.5-Gy fractions) reported a median survival of 11 months from time of salvage.[17] A prospective cohort study from Korea involving 114 consecutive patients with recurrent grade III to IV gliomas also showed favorable outcomes with radiosurgery. Among the 65 patients with GBM, median survival was 13 months from radiosurgery and 23 months from diagnosis, compared with 12 months from diagnosis among historical controls ($P < .0001$). Of the patients who underwent radiosurgery, 24% developed radiation necrosis on follow-up MRI, but only 2 of the 22 cases were confirmed histologically.[18]

Emerging evidence suggests that pairing radiosurgery with bevacizumab improves outcomes compared with either therapy alone. The rationale for combining these modalities derives from unique interactions between radiotherapy and vasculature. Radiation induces angiogenesis through increasing hypoxia-inducible factor-1, effectively protecting tumor blood supply.[19] Concurrent administration of antiangiogenic drugs could mitigate this effect. Anti-VEGF agents have been found to sensitize endothelial cells to radiotherapy, targeting tumor vessels.[20] Radiosurgery, compared with conventional radiotherapy, may itself be cytotoxic to vascular cells, because high doses of radiation cause microvascular endothelial apoptosis.[21] Moreover, bevacizumab may reduce the risk of radionecrosis, a significant dose-limiting toxicity.[22,23]

Clinical outcomes from radiosurgery plus bevacizumab have been encouraging. A retrospective analysis from the Duke Cancer Institute of patients with recurrent GBM treated with stereotactic radiosurgery included 33 who received bevacizumab during radiosurgery or shortly thereafter, and 16 who did not. Although the groups had similar pretreatment characteristics, median survival of the patients who received bevacizumab was significantly longer (11 vs. 4 months). Multivariate analysis found a significantly reduced risk of death or progression with the addition of bevacizumab to radiosurgery, with a risk ratio of 0.37 ($P = .015$) and 0.45 ($P = .043$), respectively. Patients who received bevacizumab also had lower rates of radionecrosis (5% vs. 19%).[24]

Based on this experience, Duke conducted a pilot study to prospectively evaluate the safety of stereotactic radiosurgery plus bevacizumab for recurrent high-grade gliomas.[25] Fifteen patients (9 grade IV, 6 grade III) participated. Lesions smaller than 2 cm and 2 to 2.9 cm received a single fraction of 24 and 18 Gy, respectively. Lesions measuring 3 to 5 cm received 25 Gy in 5 fractions. Patients received 10 mg/kg of bevacizumab intravenously on the day of radiosurgery and again 14 days later. No grade 4 or 5 adverse events occurred. One patient experienced a grade 3 headache, requiring hospitalization and steroids. Two experienced grade 2 toxicities consisting of moderate cognitive disturbance and moderate dizziness. The 6-month progression-free survival rate was 27%. At a median follow-up of 15 months, median survival from time of radiosurgery was 13 months (95% CI, 6–16 months).

Memorial Sloan-Kettering Cancer Center also published results from a prospective study of bevacizumab and radiosurgery for recurrent high-grade gliomas, in which 25 patients (20 grade IV, 5 grade III) received bevacizumab 10 mg/kg intravenously every 2 weeks until tumor progression, along with 30 Gy in 5 fractions after the first cycle of bevacizumab. Three

discontinued treatment because of grade 3 intratumoral hemorrhage, wound dehiscence, and bowel perforation. Radionecrosis was not observed. For the GBM cohort, the 6-month progression-free survival rate was 65% and median survival 12.5 months.[26]

Conclusions

Management of recurrent GBM may include best supportive care, surgical resection, systemic therapies, and/or radiotherapy. Preclinical and clinical data show the efficacy of antiangiogenic agents and stereotactic radiosurgery, which may be administered individually or concomitantly. At the authors' institution, if tumor size and location are amenable to reirradiation, stereotactic radiosurgery with concurrent and adjuvant bevacizumab are usually recommended. Patients also receive a variety of systemic therapies, preferably in the context of a clinical trial.

Despite recent advances, the prognosis for GBM remains poor. Larger prospective studies are needed to confirm the safety and efficacy of radiosurgery plus bevacizumab for recurrent GBM. Continued exploration of novel therapeutic approaches is essential.

References

1. Nabors LB, Ammirati M, Bierman PJ, et al. NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 1, 2012. Available at: NCCN.org. Accessed March 19, 2012.
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459–466.
3. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys 2004;60:853–860.
4. Hochberg FH, Pruitt A. Assumptions in the radiotherapy of glioblastoma. Neurology 1980;30:907–911.
5. Barker FG II, Chang SM, Gutin PH, et al. Survival and functional status after resection of recurrent glioblastoma multiforme. Neurosurgery 1998;42:709–720; discussion 720–723.
6. Park JK, Hodges T, Arko L, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol 2010;28:3838–3843.
7. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. J Clin Oncol 1999;17:2572–2578.
8. Reardon DA, Turner S, Peters KB, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. J Natl Compr Canc Netw 2011;9:414–427.
9. Pluderi M, Lucini V, Caronzolo D, et al. Long-term inhibition of glioma growth by systemic administration of human PEX. J Neurosurg Sci 2003;47:69–78.
10. Vredenburgh JJ, Desjardins A, Herndon JE II, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res 2007;13:1253–1259.
11. Vredenburgh JJ, Desjardins A, Herndon JE II, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007;25:4722–4729.
12. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009;27:740–745.
13. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009;27:4733–4740.
14. Cho KH, Hall WA, Gerbi BJ, et al. Single dose versus fractionated stereotactic radiotherapy for recurrent high-grade gliomas. Int J Radiat Oncol Biol Phys 1999;45:1133–1141.
15. Combs SE, Widmer V, Thilmann C, et al. Stereotactic radiosurgery (SRS): treatment option for recurrent glioblastoma multiforme (GBM). Cancer 2005;104:2168–2173.
16. Shrieve DC, Alexander E III, Wen PY, et al. Comparison of stereotactic radiosurgery and brachytherapy in the treatment of recurrent glioblastoma multiforme. Neurosurgery 1995;36:275–282; discussion 282–284.
17. Fogh SE, Andrews DW, Glass J, et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. J Clin Oncol 2010;28:3048–3053.
18. Kong DS, Lee JI, Park K, et al. Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. Cancer 2008;112:2046–2051.
19. Moeller BJ, Cao Y, Li CY, et al. Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. Cancer Cell 2004;5:429–441.
20. Mauceri HJ, Hanna NN, Beckett MA, et al. Combined effects of angiostatin and ionizing radiation in antitumour therapy. Nature 1998;394:287–291.
21. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 2003;300:1155–1159.
22. Torcuator R, Zuniga R, Mohan YS, et al. Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis. J Neurooncol 2009;94:63–68.
23. van Bruggen N, Thibodeaux H, Palmer JT, et al. VEGF antagonism reduces edema formation and tissue damage after ischemia/reperfusion injury in the mouse brain. J Clin Invest 1999;104:1613–1620.
24. Cuneo KC, Vredenburgh JJ, Sampson JH, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 2012;82:2018–2024.
25. Cuneo KC, Cabrera AR, Sampson J, et al. Bevacizumab and radiosurgery for recurrent malignant glioma: toxicity results from a prospective pilot study. Int Radiat Oncol Biol Phys 2011;81:S185.
26. Gutin PH, Iwamoto FM, Beal K, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 2009;75:156–163.