

Outcomes of Salvage Fractionated Reirradiation Combined With Bevacizumab for Recurrent High-grade Gliomas That Progressed After Treatment With Bevacizumab

Hajime Yonezawa

National Cancer Center Hospital

Makoto Ohno

National Cancer Center Hospital <https://orcid.org/0000-0001-8031-4306>

Hiroshi Igaki

National Cancer Center Hospital

Yasuji Miyakita

National Cancer Center Hospital

Masamichi Takahashi

National Cancer Center Hospital

Yukie Tamura

National Cancer Center Hospital

Satoshi Shima

National Cancer Center Hospital

Yuko Matsushita

National Cancer Center Hospital

Koichi Ichimura

National Cancer Center Research Institute

Yoshitaka Narita (✉ yonarita@ncc.go.jp)

National Cancer Center Hospital

Research

Keywords: reirradiation, bevacizumab, recurrent high-grade glioma, failure, progression

Posted Date: January 18th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-147697/v1>

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Abstract

Background: This study evaluated the outcomes of reirradiation combined with bevacizumab (Bev) for patients with recurrent high-grade gliomas that progressed after treatment with Bev.

Methods: Between January 2015 and September 2019, 14 patients who experienced progression after Bev treatment were treated with reirradiation consisting of 25 Gy in five fractions combined with Bev (ReRT/Bev). The isocitrate dehydrogenase (IDH) 1/2 mutation status was analysed by pyrosequencing.

Results: The diagnoses of 14 patients at the time of reirradiation included six cases of glioblastoma (GBM) with IDH-wildtype, four cases of GBM with IDH-mutant, one case of anaplastic astrocytoma (AA) with IDH-wildtype, one case of AA with IDH-mutant, and one case of GBM not otherwise specified (NOS), and one case of radiologically diagnosed brainstem glioma. The median overall survival (OS) and progression-free survival (PFS) times with ReRT/Bev were 6.1 months and 3.8 months, respectively. The 6-month OS and PFS rates were 54.5% and 15.7%, respectively. The median OS and PFS did not differ significantly between patients with IDH-wildtype (N=7) and IDH-mutant (N=5) (OS: 7.3 [wildtype] vs 6.0 [mutant] months, $p = 0.64$; PFS: 3.8 [wildtype] vs 3.7 [mutant] months, $p = 0.56$). The median OS and PFS did not differ significantly between patients with a diagnosis of GBM (N=6) and those with a diagnosis of non-GBM (N=7) (OS: 9.3 [GBM] vs 6.0 [non-GBM] months, $p = 0.19$; PFS: 4.0 [GBM] vs 3.8 [non-GBM] months, $p = 0.31$). Four patients (28.6%) achieved a complete or partial radiological response and three patients (21.4%) experienced improvement after ReRT/Bev. Tumor recurrences were observed in 12 patients, including 3 (21.4%) in-field recurrence; 5 (35.7%) marginal recurrence, 3 (21.4%) out-field recurrence, and 1 (7.1%) had in-field and out-field recurrence. Grade 3/4 toxicities included leukopenia in four patients (28.6%), hypertension in three (21.4%), proteinuria in one (7.1%), and gastrointestinal haemorrhage in one (7.1%) with ReRT/Bev.

Conclusions: ReRT/Bev for patients with high-grade glioma who experienced progression after Bev was effective and involved acceptable toxicities.

Introduction

Recurrent high-grade gliomas have a poor prognosis and limited treatment options, including re-resection, systemic therapy, and reirradiation [1, 2]. Bevacizumab (Bev), an antiangiogenic monoclonal antibody that binds to vascular endothelial growth factor (VEGF), is one of the most commonly used treatment options for patients with recurrent high-grade gliomas. Several studies demonstrated favorable 6-month progression-free survival rates of 20.9–42.6% and median survival times of 7.1 to 12 months with Bev for recurrent glioblastomas (GBM) [3]. However, it has been reported that GBM that progressed after Bev tended to be refractory to further treatment, resulting in limited treatment options and a poor prognosis [4–6]. A review of 16 phase II trials that investigated the efficacy of Bev with or without additional chemotherapy after the failure of the initial Bev treatment showed a median survival time of 3.8 months

and no discernible activity with continued Bev for this patient population [7]. It is critical to establish the optimal treatment option for patients with disease progression after Bev treatment.

Salvage reirradiation is a treatment option for recurrent high-grade gliomas [2]. Recently, reirradiation has become increasingly available due to advances in technology and imaging. Several studies showed that reirradiation for recurrent high-grade gliomas is well-tolerated and feasible, resulting in a median survival time of approximately 9.7 to 12.2 months after reirradiation [8–10]. Moreover, an investigation of the combination of reirradiation and Bev (ReRT/Bev) indicated favorable outcomes [11–13]. Shapiro et al. treated 24 patients with recurrent high-grade gliomas using fractionated stereotactic radiotherapy (FSRT) consisting of 30 Gy in five fractions combined with Bev and reported a median survival time of 12.2 months and an objective response rate of 54.1% [13]. However, there is no clear evidence of the optimal timing or survival benefits of reirradiation [14, 15]. We hypothesised that ReRT/Bev for patients with high-grade gliomas that progressed after Bev may result in improved patient outcomes. There have been few reports regarding ReRT/Bev for patients with high-grade gliomas that progressed after Bev [6, 7, 11, 16–19]; therefore, we evaluated the potential efficacy and safety of our therapeutic approach.

In this study, we retrospectively analysed the treatment outcomes of patients with high-grade glioma that progressed after Bev and were treated with ReRT/Bev (25 Gy in five fractions).

Patients And Methods

Patient characteristics

Thirty-four patients were diagnosed with recurrent high-grade gliomas and underwent reirradiation at our center between January 2015 and September 2019. Among these patients, 20 were excluded from this study for various reasons (ReRT/Bev without preceding Bev for 9 patients; ReRT/Bev for new enhancing lesions out of the initial radiation field for 6 patients; reirradiation regimen not 25 Gy in five fractions for 2 patients; loss to follow-up for 2 patients; and reirradiation alone for 1 patient). The remaining 14 patients with glioma progression after Bev who were administered ReRT/Bev (hypofractionated reirradiation consisting of 25 Gy in five fractions) were included in the study. All patients were diagnosed by neuropathologists at our hospital according to the revised 4th edition of the World Health Organization classification scheme [20].

Clinical and radiological information of the patients were reviewed. Data regarding the clinical history, pathological diagnosis at initial presentation and at the time of reirradiation, Karnofsky performance status (KPS) at 3 months before and 6 months after the time of reirradiation, number of recurrences at the time of reirradiation, date of Bev initiation, date of reirradiation initiation, date of completion of initial radiotherapy, date of tumor recurrence, date of death or last hospital visit, reirradiation modality, and clinical and planned target volumes were collected.

Treatment

When tumor recurrence was observed with Bev administration, patients received ReRT/Bev. The dose of Bev was 10 mg/kg every 2 weeks or 15 mg/kg every 3 to 4 weeks. Blood tests and urinalyses were performed before each Bev administration. Bev was continued until disease progression after ReRT/Bev administration.

All patients received hypofractionated radiotherapy consisting of 25 Gy at the isocenter in 5-Gy daily fractions for the planning target volume ($D_{95\%}$) using an intensity-modulated or stereotactic radiotherapy technique or at the isocenter using a three-dimensional conformal radiotherapy technique with four or more portals, including non-coplanar beams. Target volumes were determined based on computed tomography (CT) and magnetic resonance imaging (MRI) at the time of tumor progression with Bev. The gross tumor volume was defined as the contrast-enhanced lesion on contrast-enhanced T1-weighted images. The clinical target volume was defined as the gross tumor volume and area of hyperintensity on T2-weighted images or fluid-attenuated inversion recovery images. The planning target volume was defined as the clinical target volume plus a 0.5-cm margin. Irradiation fields were modified, if necessary, through the dose-volume histogram evaluation of the organs at risk, such as the brainstem, optic nerve, optic chiasm, retina, and lens. The lens was shielded by multileaf collimators when possible through the eye view of the beam.

Response and recurrent pattern evaluation

Patients were evaluated using contrast-enhanced T1-weighted MRI performed 1 month after the completion of ReRT and every 2 months thereafter or according to clinical symptom development. Disease progression was evaluated according to the Response Assessment Criteria for High-Grade Gliomas (RANO) [21]. Briefly, a complete response was defined as the complete disappearance of all enhancing measurable and non-measurable lesions for at least 4 weeks. A partial response was defined as $\geq 50\%$ decreased lesion size compared to baseline as measured by summing the products of the perpendicular diameters of all measurable lesions that were sustained for at least 4 weeks and no new lesions or progression of non-measurable disease observed. Progressive disease was defined as $\geq 25\%$ increased sum of the products of the perpendicular diameters of the enhancing lesions compared with the smallest tumor measurement, a significant non-enhancing lesion on T2-weighted or fluid-attenuated inversion recovery images, the appearance of new lesions, definite clinical deterioration not attributable to causes other than the tumor, or death. If there was uncertainty regarding whether there was progression, then close observation was performed. If follow-up imaging studies showed progressive enlargement, then tumor recurrence was diagnosed. Stable disease was defined as not meeting any of the criteria for complete response, partial response, and progressive disease [21].

Recurrences were defined as in-field if the 95% isodose surface contained $> 80\%$ of the tumor recurrence and as marginal if the 95% isodose surface contained 20–80% of the recurrence volume. In all other cases, recurrences were considered outside the radiation field [13].

IDH1/2 mutation analysis

The IDH1/2 mutation status was determined as previously described [22, 23]. Briefly, DNA was extracted from frozen tissue samples or paraffin-embedded specimens using the DNeasy Blood & Tissue kit (Qiagen, Germantown, MD, USA). Polymerase chain reaction (PCR) was performed to amplify a 129-bp fragment of IDH1 containing codon 132 or a 150-bp fragment of IDH2 containing codon 172. The PCR products were purified using the QIAquick PCR Purification kit (Qiagen). DNA sequencing of the IDH1/2 gene was performed using the same primers used for PCR [22, 23].

Statistical analysis

The OS time was calculated from the date of reirradiation to the date of death or last follow-up. The PFS time was calculated from the date of reirradiation to the date of detection of progression or the date of death or the last follow-up. The time from the first administration of Bev to the time of irradiation was calculated from the date of Bev initiation to the date of reirradiation. The survival time from the first administration of Bev was calculated from the date of Bev initiation to the date of death or last follow-up. The time from the completion of initial radiotherapy to irradiation was calculated from the date of completion of the initial radiotherapy to the date of reirradiation. These were calculated using the Kaplan-Meier method. Analyses were conducted using JMP® 8 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism® version 6.0 (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics and treatments

Patient characteristics are summarised in Table 1. The 14 patients had a median age of 46 years (range, 22–81 years) and median KPS of 70 (range, 40–80). At the time of reirradiation, 6 patients (42.9%) had GBM with IDH-WT, 4 patients (28.6%) had GBM with IDH-mutant, 1 patient (7.1%) had anaplastic astrocytoma (AA) with IDH-WT, 1 patient (7.1%) had AA with IDH-mutant, 1 patient (7.1%) had GBM not otherwise specified (NOS), and 1 patient had a brainstem glioma based on the radiographical diagnosis. All patients experienced progression after Bev treatment. The median number of prior recurrences was three (range, 2–5). The median time from completion of radiotherapy to reirradiation was 24.8 months (range, 11.0–99.0 months). The median time from the first Bev administration to reirradiation was 4.2 months (range, 1.6–15.7 months) (Table 1).

Outcomes

The median OS time was 6.1 months (Fig. 1A) and the median PFS time was 3.8 months (Fig. 1B). The 6-month and 12-month OS rates were 54.5% and 23.4%, respectively. The 6-month PFS rate was 15.7%. The median OS time for patients with IDH-mutant (N = 5) was 6.0 months, whereas the median OS time for patients with IDH-WT (N = 7) was 7.3 months; this difference was not statistically significant ($p = 0.64$) (Fig. 1C). The median PFS times for patients with IDH-mutant (N = 5) and IDH-WT (N = 7) were 3.7 and 3.8 months, respectively; again, this difference was not statistically significant ($p = 0.56$) (Fig. 1D). The median OS times for patients with a diagnosis of GBM (N = 6) and non-GBM (N = 7) at the time of

reirradiation were 9.3 months and 6.0, respectively ($p = 0.19$) (Fig. 1E). The median PFS times for patients with a diagnosis of GBM ($N = 6$) and non-GBM ($N = 7$) at the time of reirradiation were 4.0 months and 3.8, respectively ($p = 0.31$) (Fig. 1F). Tumor recurrence patterns of 12 patients after ReRT/Bev treatment were evaluated by radiological examinations: 3 (21.4%) had in-field recurrence; 5 (35.7%) had marginal recurrence, 3 (21.4%) had out-field recurrence, and 1 (7.1%) had in-field and out-field recurrence. One patient (7.1%) had clinical progression without clear radiological tumor recurrence and one patient (7.1%) did not have recurrence at the time of the last visit (Table 2). The best radiological responses were complete response for 1 patient (7.1%), partial response for 3 patients (21.4%), stable disease for 7 patients (50%), and progressive disease for three patients (21.4%). A spider plot showed changes in the KPS at 3 months before and 6 months after the time of ReRT/Bev initiation for 14 patients with recurrent malignant gliomas (Fig. 2). Three patients (21.4%; red line with triangle, yellow line with inverted triangle, green line with rhombus in Fig. 2) had improved KPS after ReRT/Bev. Three representative patients with complete response or partial response are described in Supplementary Fig. 1.

Toxicities

Toxicities are summarised in Table 3. During ReRT/Bev treatment, 4 patients (28.6%) experienced grade 3/4 leukopenia, 3 patients (21.4%) had hypertension, and 1 patient (7.1%) had proteinuria and gastrointestinal haemorrhage. One patient (7.1%) experienced an intratumoral haemorrhage 1 month after termination of ReRT/Bev treatment due to tumor progression. No grade 3/4 neutropenia, thrombocytopenia, or anemia was observed. We did not observe wound dehiscence or radiation necrosis.

Discussion

The prognosis of patients with high-grade gliomas that progressed after Bev is poor and there is no standard treatment. We studied ReRT/Bev after Bev failure and showed that the median OS and PFS times were 6.1 and 3.8 months, respectively, and that the 6-month OS and 6-month PFS rates were 54.5% and 15.7%, respectively. Additionally, we observed a radiological response (complete response and partial response) in four patients (28.5%) and KPS improvement in three patients (21.4%).

A few studies have investigated the outcomes of ReRT/Bev for patients with high-grade gliomas that progressed after Bev (Table 4) [6, 7, 11, 16–19]. The median survival times after ReRT/Bev ranged from 3.3 to 14.7 months, and the median PFS times ranged from 2.6 to 6.3 months. Torcuator et al. retrospectively analysed 23 patients treated with either FSRT or stereotactic radiosurgery (SRS) with Bev after progression after the initial Bev regimen and compared them with another 23 patients treated with Bev-based chemotherapy without FSRT or SRS [19]. They reported significantly increased OS and PFS times for patients who received FSRT or SRS (OS: 7.2 [FSRT] vs 3.3 [SRS] months, $p = 0.03$; PFS: 2.6 [FSRT] vs 1.7 [SRS] months, $p = 0.009$) [19]. Bergman et al. conducted a randomised phase II trial involving patients with high-grade gliomas that progressed after Bev and compared the outcomes of FSRT comprising 32 Gy in four fractions with Bev-based chemotherapy with those of Bev-based chemotherapy alone [16]. They observed significantly increased PFS times for patients treated with FSRT compared to those for patients treated with Bev-based chemotherapy alone (5.1 vs 1.8 months; $p < 0.001$)

and an increased trend in OS (7.3 vs 4.8 months; $p = 0.11$); therefore, they concluded that FSRT with Bev-based chemotherapy might be a valuable option for extending PFS and improving local control [16]. Our results indicating that the median OS and PFS were 6.1 and 3.8 months, respectively, are comparable to those of previous studies. Moreover, the 28.5% radiological response and 21.4% KPS improvement after ReRT/Bev were clinically meaningful benefits for this challenging patient population. Because there is no effective treatment option for patients with high-grade glioma progression after Bev, our study suggests that ReRT/Bev might be a promising option for these patients.

In our analysis, we found no statistically significant differences in OS or PFS according to the IDH mutation status and diagnosis at the time of reirradiation. No reports have addressed how the IDH mutation status impacts the outcomes of ReRT/Bev for patients with high-grade glioma progression after Bev. Our observation indicated that the IDH mutation status does not affect the outcomes of ReRT/Bev. Shi et al. performed a multivariate analysis of 36 patients with high-grade gliomas that progressed after Bev and reported that histology results at the time of recurrence of GBM and anaplastic astrocytoma were not prognostic factors [6]. Their results could support our observation that there were no statistically significant differences in the OS and PFS for those diagnosed with GBM and non-GBM. Collectively, ReRT/Bev would be indicated regardless of the IDH mutation status and diagnosis at the time of reirradiation. Further studies are needed to find predictive factors that more clearly define patients who could derive potential benefits from ReRT/Bev treatment.

The optimal timing of reirradiation is controversial [14–16]. Palmer et al. retrospectively analysed 114 patients who received sequential reirradiation and Bev for disease recurrence or progression and reported that the median survival times from recurrence were 13.9 months for patients administered reirradiation first and 13.3 months for those administered Bev first ($p = 0.75$), indicating that the sequence of reirradiation and Bev does not matter [14]. Recent preliminary results of comparing Bev alone and Bev with reirradiation for patients with Bev-naïve recurrent glioblastomas showed that the addition of reirradiation improved the PFS time (7.1 months with the combination vs 3.8 months with Bev alone; $p = 0.05$) but not the OS time (10.1 months with the combination vs 9.7 months with Bev alone; $p = 0.46$). These results suggest that ReRT/Bev prolongs PFS but does not have survival benefits compared to Bev alone for Bev-naïve patients with recurrence [15]. Bergman et al. reported that ReRT/Bev-based chemotherapy also increased PFS, and that it tended to prolong OS compared to Bev-based chemotherapy alone for patients with progression after Bev [16]. Although the optimal timing of reirradiation before and after Bev remains unclear, based on our results and those of Bergman, differing reirradiation after Bev might be a preferred option to minimise the potential risk of radiation necrosis. Further studies are needed to clarify the optimal timing of reirradiation that balances the risks and benefits.

The most important limitation of ReRT/Bev is out-field tumor recurrence. In this study, we observed out-field recurrence in 21.4% and in-field and out-field recurrence in 7.1%, whereas in-field recurrence and marginal recurrence occurred in 21.4% and 35.7%, respectively. This frequent out-field recurrence might reflect the invasive nature of high-grade gliomas that might be enhanced by preceding Bev [24]. Iwamoto

et al. reported that after Bev failure, 35% of patients had progression of a predominantly non-enhancing tumor, 16% had progression as a new enhancing lesion outside the initial site, and 46% had progressive enhancement at the initial site, suggesting that tumor cells might distribute in the non-enhancing area on MRI and that some out-field recurrence could be inevitable in patients with progression with Bev [24]. It is important to understand the possibility of developing out-field recurrence when following-up patients after ReRT/Bev treatment.

Reirradiation could have a risk of radiation necrosis. Fetcko et al. reported that 5.9% of patients developed radiation necrosis and 3.3% had major neurological deficits after SRS treatment for recurrent high-grade gliomas [25]. Shanker et al. also reported that the radiation necrosis rates after reirradiation for recurrent high-grade gliomas were 7.1 % for FSRT, 6.1% for SRS, and 1.1% for conventional radiotherapy [10]. In our study, we did not observe radiation necrosis in any patient. Previous reports of ReRT/Bev for patients with high-grade gliomas that progressed after Bev also showed low rates of radiation necrosis (0–11.1%) (Table 4). One of the reasons for the low rates of radiation necrosis may be the short survival time after reirradiation, which varies from 3.3 to 14.7 months [6]. Another reason could be the addition of Bev to reirradiation. Cuneo et al. observed radiation necrosis diagnosed by imaging or repeat biopsy in 19% of patients who received SRS without Bev and in 5% of those who received SRS with Bev [11]. This result supports the hypothesis that the use of Bev combined with reirradiation might reduce the risk of developing radiation necrosis. Our results suggest that ReRT/Bev is feasible and poses a low risk of radiation necrosis.

Bev-related toxicities are another concern associated with ReRT/Bev treatment. We observed grade 3/4 leukopenia in 28.6% of patients, hypertension in 21.4%, and proteinuria in 7.1% during ReRT/Bev treatment. Nagane et al. reported that grade 3/4 toxicities of single-agent Bev included hypertension in 9.7%, leukopenia in 3.2%, thromboembolism in 3.2%, and congestive heart failure in 3.2%, but not proteinuria and haemorrhage, of patients with recurrent malignant gliomas [26]. Although we observed more frequent leukopenia, hypertension, and proteinuria, all these toxicities were manageable. Based on our results, ReRT/Bev seems to be well-tolerated. Two of our patients experienced haemorrhagic toxicities (gastrointestinal haemorrhage and intratumoral haemorrhage). Gastrointestinal haemorrhage occurred during ReRT/Bev treatment, and we assumed it to be a consequence of Bev administration. Intratumoral haemorrhage occurred 1 month after termination of ReRT/Bev due to tumor recurrence. Because tumor progression was rapid in this patient, it was difficult to conclude that intratumoral haemorrhage was related to ReRT/Bev treatment. However, we should be aware of the potential risk of these haemorrhagic complications and carefully observe patients.

Our study had some limitations. First, we did not compare our results with those of the control treatment, for example, Bev-based chemotherapy. However, this patient cohort has a generally poor prognosis and it is difficult to conduct a controlled trial. Second, our cohort was too small to achieve definitive conclusions. The purpose of this study was to provide the preliminary results of ReRT/Bev for patients with high-grade gliomas that progressed after Bev. Further studies are needed to confirm the efficacy and feasibility of this treatment.

In conclusion, there is no effective treatment option for patients after Bev failure, however, our study indicates that ReRT/Bev is a potential option for these patients. The ReRT/Bev approach for patients with high-grade gliomas that progressed after Bev is feasible and could improve the prognosis because of its clinically meaningful benefits for patients with advanced disease.

Abbreviations

GBM, glioblastoma; AA, anaplastic astrocytoma; Bev, bevacizumab; IDH, isocitrate dehydrogenase; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; KPS, Karnofsky performance status; MRI, magnetic resonance imaging; RANO, Response Assessment Criteria for High-Grade Gliomas; IDH-mutant, isocitrate dehydrogenase mutation; IDH-WT, isocitrate dehydrogenase wildtype; ReRT/Bev, reirradiation combined with bevacizumab

Declarations

Acknowledgments

This study was presented at the 29th Annual Meeting of the Japanese Society of Stereotactic Radiosurgery. We would like to thank Editage (www.editage.com) for English language editing.

Author contributions

MO and YN designed the study. HY and MO collected and interpreted the data and performed the biostatistical analysis. MO, YM, MT, HI, YT, SS and YN contributed to the treatment and management of patients. YM and KI identified the IDH1/2 mutations status. HY, MO, and HI wrote the manuscript. YN supervised the writing of the manuscript. All the authors reviewed and approved this manuscript.

Funding

None to report

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and the 1964 Helsinki declaration and its later amendments. This study was approved by the internal review board of the National Cancer Center (2004-066 or 2007-086). Written informed consent was obtained from all individual participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest in association with this paper.

References

1. Birk HS, Han SJ, Butowski NA. Treatment options for recurrent high-grade gliomas. *CNS Oncol.* 2017;6:61-70.
2. Scoccianti S, Francolini G, Carta GA, Greto D, Detti B, Simontacchi G, et al. Re-irradiation as salvage treatment in recurrent glioblastoma: A comprehensive literature review to provide practical answers to frequently asked questions. *Crit Rev Oncol Hematol.* 2018;126:80-91.
3. Narita Y. Drug review: Safety and efficacy of bevacizumab for glioblastoma and other brain tumors. *Jpn J Clin Oncol.* 2013;43:587-95.
4. Quant EC, Norden AD, Drappatz J, Muzikansky A, Doherty L, Lafrankie D, et al. Role of a second chemotherapy in recurrent malignant glioma patients who progress on bevacizumab. *Neuro Oncol.* 2009;11:550-5.
5. Reardon DA, Turner S, Peters KB, Desjardins A, Gururangan S, Sampson JH, et al. A review of VEGF/VEGFR-targeted therapeutics for recurrent glioblastoma. *J Natl Compr Canc Netw.* 2011;9:414-27.
6. Shi W, Blomain ES, Siglin J, Palmer JD, Dan T, Wang Y, et al. Salvage fractionated stereotactic re-irradiation (FSRT) for patients with recurrent high grade gliomas progressed after bevacizumab treatment. *J Neurooncol.* 2018;137:171-77.
7. Magnuson W, Ian Robins H, Mohindra P, Howard S. Large volume reirradiation as salvage therapy for glioblastoma after progression on bevacizumab. *J Neurooncol.* 2014;117:133-9.
8. Chapman CH, Hara JH, Molinaro AM, Clarke JL, Oberheim Bush NA, Taylor JW, et al. Reirradiation of recurrent high-grade glioma and development of prognostic scores for progression and survival. *Neurooncol Pract.* 2019;6:364-74.
9. Navarria P, Minniti G, Clerici E, Tomatis S, Pinzi V, Ciammella P, et al. Re-irradiation for recurrent glioma: outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). *J Neurooncol.* 2019;142:59-67.
10. Shanker M, Chua B, Bettington C, Foote MC, Pinkham MB. Re-irradiation for recurrent high-grade gliomas: a systematic review and analysis of treatment technique with respect to survival and risk of radionecrosis. *Neurooncol Pract.* 2019;6:144-55.
11. Cuneo KC, Vredenburgh JJ, Sampson JH, Reardon DA, Desjardins A, Peters KB, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2012;82:2018-24.

12. Gutin PH, Iwamoto FM, Beal K, Mohile NA, Karimi S, Hou BL, et al. Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys.* 2009;75:156-63.
13. Shapiro LQ, Beal K, Goenka A, Karimi S, Iwamoto FM, Yamada Y, et al. Patterns of failure after concurrent bevacizumab and hypofractionated stereotactic radiation therapy for recurrent high-grade glioma. *Int J Radiat Oncol Biol Phys.* 2013;85:636-42.
14. Palmer JD, Bhamidipati D, Song A, Eldredge-Hindy HB, Siglin J, Dan TD, et al. Bevacizumab and re-irradiation for recurrent high grade gliomas: does sequence matter? *J Neurooncol.* 2018;140:623-28.
15. Tsien C, Pugh S, Dicker A, Raizer J, Matuszak M, Lallana E, et al. ACTR-232. NRG Oncology RTOG 1205: randomized phase II trial of concurrent bevacizumab and re-irradiation versus bevacizumab alone as treatment for recurrent glioblastoma. *Neuro Oncol.* 2019;21:vi 20.
16. Bergman D, Modh A, Schultz L, Snyder J, Mikkelsen T, Shah M, et al. Randomized prospective trial of fractionated stereotactic radiosurgery with chemotherapy versus chemotherapy alone for bevacizumab-resistant high-grade glioma. *J Neurooncol.* 2020;148:353-61.
17. Cabrera AR, Cuneo KC, Desjardins A, Sampson JH, McSherry F, Herndon JE, 2nd, et al. Concurrent stereotactic radiosurgery and bevacizumab in recurrent malignant gliomas: a prospective trial. *Int J Radiat Oncol Biol Phys.* 2013;86:873-9.
18. Conde-Moreno AJ, Garcia-Gomez R, Albert-Antequera M, Almendros-Blanco P, De Las Penas-Bataller R, Gonzalez-Vidal V, et al. Fractionated stereotactic radiotherapy plus bevacizumab after response to bevacizumab plus irinotecan as a rescue treatment for high-grade gliomas. *Rep Pract Oncol Radiother.* 2015;20:231-8.
19. Torcuator RG, Thind R, Patel M, Mohan YS, Anderson J, Doyle T, et al. The role of salvage reirradiation for malignant gliomas that progress on bevacizumab. *J Neurooncol.* 2010;97:401-7.
20. Louis DN, Ohgaki H, Wiestler OD, WK C. WHO classification of tumours of the central nervous system. Revise 4th edition. . Lyon: IARC Press. 2016.
21. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28:1963-72.
22. Arita H, Narita Y, Matsushita Y, Fukushima S, Yoshida A, Takami H, et al. Development of a robust and sensitive pyrosequencing assay for the detection of IDH1/2 mutations in gliomas. *Brain Tumor Pathol.* 2015;32:22-30.
23. Ohno M, Narita Y, Miyakita Y, Matsushita Y, Arita H, Yonezawa M, et al. Glioblastomas with IDH1/2 mutations have a short clinical history and have a favorable clinical outcome. *Jpn J Clin Oncol.* 2016;46:31-9.
24. Iwamoto FM, Abrey LE, Beal K, Gutin PH, Rosenblum MK, Reuter VE, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. *Neurology.* 2009;73:1200-6.
25. Fetcko K, Lukas RV, Watson GA, Zhang L, Dey M. Survival and complications of stereotactic radiosurgery: A systematic review of stereotactic radiosurgery for newly diagnosed and recurrent

high-grade gliomas. *Medicine (Baltimore)*. 2017;96:e8293.

26. Nagane M, Nishikawa R, Narita Y, Kobayashi H, Takano S, Shinoura N, et al. Phase II study of single-agent bevacizumab in Japanese patients with recurrent malignant glioma. *Jpn J Clin Oncol*. 2012;42:887-95.

Tables

Due to technical limitations, table xlsx is only available as a download in the Supplemental Files section.

Figures

Figure 1

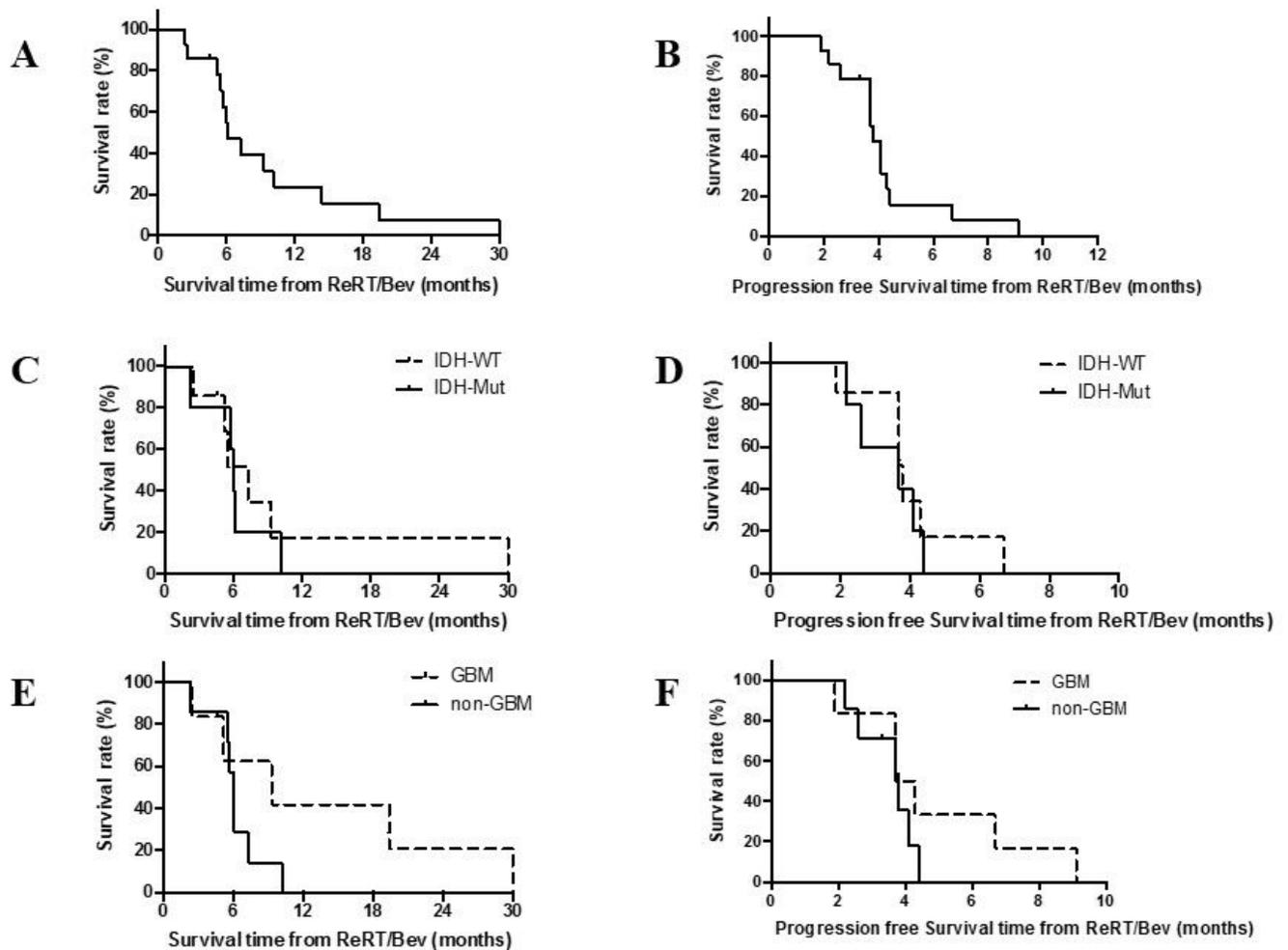


Figure 1

Kaplan-Meier curves of overall survival (A, C, E) and progression-free survival (B, D, F). (A) The median survival time was 6.1 months. (B) The median progression-free survival time was 3.8 months. (C) The median survival times were 6.0 months for patients with IDH-mutant (N=5) and 7.3 months for those with

IDH-WT (N=7) ($p=0.64$). (D) The median progression-free survival times were 3.7 months for patients with IDH-mutant (N=5) and 3.8 months for those with IDH-WT (N=7) ($p=0.56$). (E) The median survival times were 9.3 months for patients with a diagnosis of GBM (N=6) and 6.0 months for those with non-GBM (N=7) ($p=0.19$). (F) Median progression-free survival times were 4.0 months for patients with a diagnosis of GBM (N=6) and 3.8 months for those with non-GBM (N=7) ($p=0.31$).

Figure 2

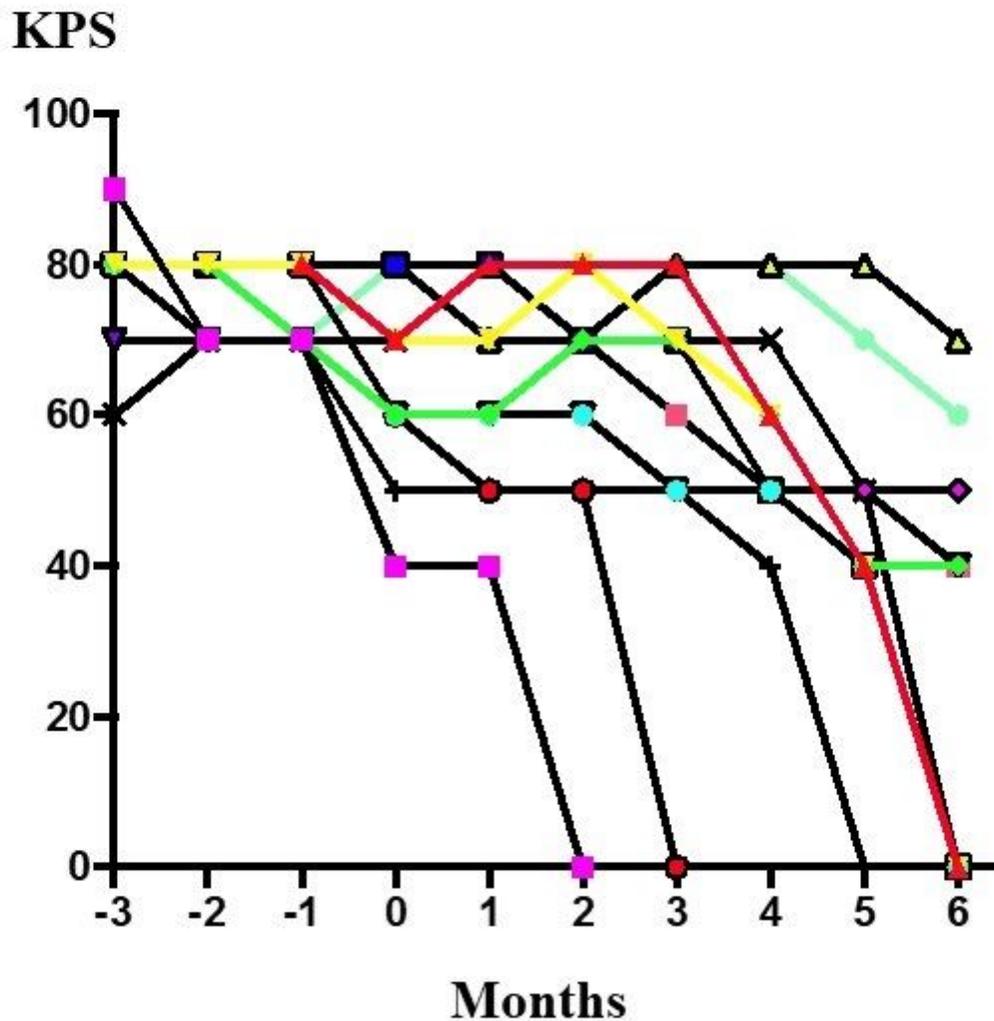


Figure 2

A spider plot shows changes in KPS at 3 months before and 6 months after the time of ReRT/Bev in 14 patients with recurrent malignant gliomas. Three patients (red line with triangle, yellow line with inverted triangle, green with rhombus) had improved KPS after ReRT/Bev. The X-axis indicates months and 0 indicates the time of ReRT/Bev. The Y-axis indicates KPS.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [210110ReRTBevTableROver1.0.xlsx](#)
- [SFigure1.jpg](#)