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Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas

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Salvage therapy for recurrent high grade gliomas (HGG) includes surgery, radiotherapy and chemotherapy, however, standard treatment does not exist. We evaluated the tolerability and efficacy of re-irradiation (re-RT) with hyperthermia (HT) for patients with recurrent HGG. From September 2010 to July 2015, 20 patients with recurrent HGG were treated with re-RT and HT. The radiotherapy dose of 30 Gray (Gy) was delivered with 2 Gy per fraction daily, and HT was performed twice weekly. Primary endpoints were treatment compliance and toxicity. Second endpoints were overall survival (OS) and progression free survival (PFS). The median interval between initial RT and re-RT was 11 months. During re-RT with HT, there were no significant acute morbidities over grade 3. Median overall survival (OS) from re-irradiation was 8.4 months and the 6 and 12 months survival rate were 67% and 30%, respectively. The median progression free survival (PFS) from re-irradiation was 4.1 month. Our findings suggested that concurrent re-RT with HT was a safe and well-tolerated. In addition, the combination re-RT and HT could be a valuable salvage treatment option for selected recurrent HGG patients with poor performance status.

Key words: recurrent high-grade glioma, re-irradiation, hyperthermia

High-grade gliomas (HGG) comprise both glioblastoma multiforme (GBM) and anaplastic glioma. The standard treatment of HGG is surgical resection of the tumor to the maximum extent that is safely possible, followed by radiotherapy (RT) and chemotherapy (CT) with temozolomide (TMZ) [1, 2]. Local control and survival in patients with HGG is poor even after multimodality treatment, and 90% of HGG patients experience recurrence within 2 years of the initial therapy [3].

Treatment options for recurrent HGG are surgical resection, re-irradiation (re-RT), cytotoxic agents, anti-angiogenic agents, and combination therapies. Although many approaches for recurrent HGG have been evaluated, no standard treatment option exists [4]. Surgery is favorable for a limited group of patients, such as those with higher performance status or a smaller lesion, as well as for younger patients [5]. The re-RT dose is limited because of the risk of toxicity in brain tissue previously exposed to high-dose conventional RT. Consequently, hypofractionated stereotactic radiotherapy (HFSRT) or stereotactic surgery (SRS) is often employed. However, re-RT have revealed that the overall survival (OS) after treatment is 8–10 months in patients with HGG [6].

Hyperthermia (HT) has a synergic effect that improves re-oxygenation of the tumor and sensitizes tumor cells to RT [7-9]. In addition, HT inhibits the repair of sub-lethal and lethal damage to tumor cells by inhibiting DNA repair pathways [10]. A previous study evaluated HT combined with brachytherapy for patients with GBM, and the 2-year OS rate increased significantly in patients treated with HT and RT [11]. HT is a safe method because most normal tissues are not damaged during treatment, and side effects such as burns, discomfort, and pain are temporary.

We have used a combined treatment of HT with re-RT for patients with recurrent HGG and analyzed the outcome.

Patients and methods

Patients. Between September 2010 and July 2015, 20 patients received re-RT with HT in our institution. Before treatment, all patients were discussed by a multidisciplinary

decision-making team comprising neuro-oncology surgeons, medical oncologists and radiation oncologists, among others. Re-RT with HT was offered to patients who could not receive surgery or chemotherapy because of poor general well-being, such as a low Karnofsky Performance Score (KPS) or a salvage operation history for recurrent HGG. Patients initially diagnosed with HGG received gross total resection, subtotal resection, or biopsy when possible. After surgery, brain radiation was performed with a dose of up to 60 Gy in 30 daily fractions. The patients received TMZ-based chemotherapy concurrently with RT followed by maintenance chemotherapy for 5 days every 4 weeks after radiation. Treatment outcomes were evaluated by follow-up brain magnetic resonance imaging (MRI) every 3 months. If patients displayed symptoms indicating tumor progression, an evaluation including imaging was performed. The diagnosis of tumor recurrence was based on changes in the tumor volume detected using dynamic contrast-enhanced MRI, and additionally considering the standardized uptake value (SUV) on ^{18}flurodeoxyglucose-positron emission tomography [12]. The failure pattern was defined as "in field" if more than 80% of the recurrent tumor was inside the initial planning target volume (PTV); it was considered "marginal" if 20% to 80% of the lesion was inside the previous PTV [13]. The other cases were defined as "outside field". Clinical data were obtained from patients' electronic medical records. This study was reviewed and approved by the institutional review board of our institution.

Radiotherapy. Patients underwent a simulation in the supine position with a mask device using a Philips Big Bore Brilliance computed tomography (CT) scanner with 3-mm slice intervals for three-dimensional RT planning. The initial clinical target volume (CTV) contained the tumor bed and edema on T2-fluid-attenuated inversion recovery (FLAIR) imaging. The PTV was defined as CTV plus a 20-mm margin. After recurrence, the gross tumor volume (GTV) was delineated based on the contrast-enhanced tumor on T1-weighted gadolinium-enhanced MRI registered with the CT planning images. The PTV was defined as the GTV plus a 5-mm margin. This margin was modified around natural barriers such as the skull, ventricles, and falx. Organs at risk (OAR) were defined as the brain stem, optic nerves, and optic chiasm. The maximum dose for OAR was 30 Gy for the brain stem and 25 Gy for the optic components. RT was delivered to the PTV at a dose of 30 Gy using 6-MV photon beams applied in multiple fields. The defined PTV was encompassed by the 97% isodose line. The Eclipse External Beam Planning System ver. 7.1 (Varian Medical Systems, Palo Alto, CA, USA) was used.

Hyperthermia. The HT treatment was given for 40–60 minutes twice a week up to 1 hour before RT. HT for recurrent HGG was achieved with a Celsius 42+ (Celsius 42+, GmBH, Köln, Germany) device during RT. The patient's position during treatment was right or left lying down according to the GTV location. The system used 150-mm electrodes coupled with a distilled water bolus to deliver radiofrequency at 13.56 MHz, which, in principle, can penetrate deep-situated regions [14]. The electrodes were placed at the center of the treatment plan for re-RT, and treatment fields covered the entire target area. Temperatures at the three sites (in the ear, skin tumor site, and treatment center) were measured before, during, and after treatment. Heating was started at 25 W during the first 20 minutes. Patients were instructed to report any discomfort due to high temperatures, which could induce a skin reaction in normal tissues. To avoid skin burns and reach higher thermotolerance in patients, a cooling system was created by flowing cooled water between each electrode and the patient's body. Power and phase treatment settings were adjusted according to the patient's condition. If there was no complaint, the power was increased by 5 W every 5 minutes, up to 45 W for 60 minutes each. The treatment goal was to achieve 40–43°C as consistently as possible [15].

Endpoints and statistical analysis. The primary endpoints were treatment compliance and toxicity of HT combined with external RT for patients with recurrent HGG. Toxicity was estimated using the Common Terminology Criteria for Adverse Event (CTCAE) 4.0. Treatment compliance was evaluated upon completion of the planned treatment. The secondary endpoints were OS and progression-free survival (PFS). OS was defined as survival from the start of re-RT and HT until death or the final follow-up. PFS was defined as progression of disease, based on MRI imaging every 3 months. A survival analysis was performed by the Kaplan-Meier method. All statistical analyses were performed with IBM SPSS statistics ver. 19.0 software (IBM SPSS, Inc., Armonk, NY, USA). Two-sided p-values <0.05 were considered statistically significant.

Results

Twenty patients (8 male and 12 female patients) with recurrent HGG were analyzed in the study. The median patient age was 56 years (range, 36–77 years). The median KPS was 60 (range, 30–90) and 7 patients (35%) had a KPS below 50 at re-RT. The *MGMT* methylation status was assessed in 14 patients, and 5 patients (25%) had positive results. Fifteen patients had previously undergone debulking surgery, whereas the other 5 had undergone biopsy at the initial surgery (Table 1). Patients had initially received 60 Gy external RT and concomitant TMZ. Maintenance TMZ was administered at an average of 6 cycles (range, 0–12 cycles). Regarding the failure pattern of patients, 70% of these were located in-field (14 patients), 10% were marginal (2 patients) and 20% were out-field (4 patients). The median interval between initial RT and re-RT was 11 months (range, 4–26 months).

RT was delivered to the brain at a dose of 30 Gy (range, 16.0–40 Gy). HT was performed 6 times (range, 3–12 times) twice per week during RT. The median cumulative doses were 89.4 Gy (range, 76.0–100.0) for 2 radiotherapy sessions and 172.9 Gy (range, 152.0–200.0) for biologically effective dose (BED) (α/β=2 Gy). Salvage surgery before re-RT was performed for 6 (30%) patients. Fourteen patients (70%) did not undergo surgery because of poor general well-being, such

as a low KPS, renal failure, hepatitis, or a lesion in a critical location. Chemotherapy was administered to 8 patients (40%) before RT, with TMZ (N=6) and procarbazine, lomustine, and vincristine (N=2).

All patients completed the prescribed treatment program except for 1 patient who received 15 Gy of RT and 3 times of HT because of general deterioration. During re-RT with HT, no acute toxicity over grade 3 occurred (Table 2). The main adverse event was grade 2 anemia, which was observed in 6 patients. Grade 2 toxicity was observed in 2 patients (10%), and headache and nausea were observed in 3 patients (15%). Grade 2 thermal burns occurred in 1 patient (5%) and they healed with medical intervention.

The median follow-up duration from re-RT was 8.4 months (range, 1.3–18.1 months). The median OS was 8.4 months (95% confidence interval [CI]: 6.9–9.9 months) (Figure 1). The 6- and 12-month survival rates were 67% and 30%, respectively. The median PFS was 4.1 months (95% confidence interval [CI]: 3.4–4.7 months) and the 6-month PFS was 13%.

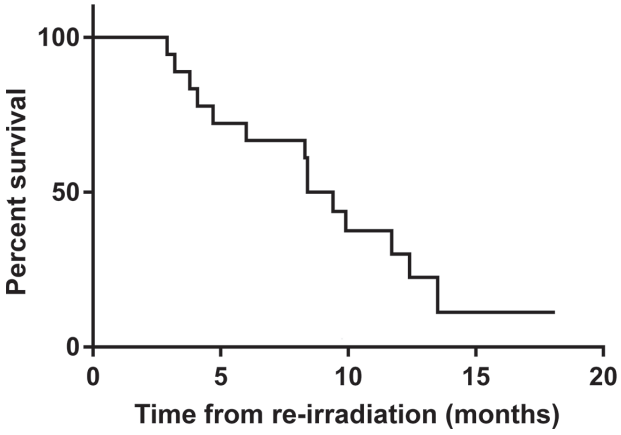

Figure 1. Kaplan–Meier curve of overall survival (OS) for patients with recurrent high grade glioma (HGG) treated with re-irradiation (re-RT) and hyperthermia (HT).

Table 1. Patient baseline Characteristics (n=20)

Characteristics	No. of patients (%)
Age, years	
Median (range)	56 (36 – 77)
Sex	
Male	8 (40)
Female	12 (60)
KPS	
Median (range)	60 (30 – 90)
Initial WHO grade	
III	16 (80)
IV	4 (20)
MGMT methylation	
Methylated	9 (45)
Unmethylated	5 (25)
Unknown	6 (30)
Salvage surgery	
Yes	7 (35)
No	13 (65)
Local failure pattern	
In field	14 (70)
Marginal	2 (10)
Out field	4 (20)
Interval between RT	
Median (range)	11.0 (3.1- 26.1)
Initial RT dose ,Gy	
Median (range)	59.4 (59.4 – 60)
Initial TMZ cycle	
Median (range)	6 (0-12)
Re-irradiation dose,Gy	
Median (range)	30 (16-40)
Hyperthermia fraction	
Median (range)	6 (3-12)

Abbreviations: KPS, Karnofsky Performance Score at re-irradiation; TMZ, temozolomide

Discussion

Salvage therapy for recurrent HGG includes surgery, radiotherapy, and chemotherapy, however, there is no standard treatment. We performed re-RT with HT for patients who could not undergo surgery or chemotherapy because of poor general well-being or patient refusal. During re-RT with HT, no acute toxicity over grade 3 occurred. The median OS from re-RT was 8.4 months, and the 6- and 12-month survival rates were 67% and 30%, respectively.

In previous studies, chemotherapy was the most commonly used therapy for treating recurrent malignant glioma, and an alkylating agent was the first-line therapy. Nitrourea, TMZ, and bevacizumab (BVZ), alone or in combination, have been used to treat patients with recurrent HGG [16-18]. Additionally, BVZ combined with irinotecan resulted in 6-month PFS and OS rates of 46% and 77%, respectively [19, 20]. A surgical approach was possible for selected patients, but not for patients

Table 2. Toxicities during treatment

Toxicity	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	1(5)	6(30)	-	-
Leukopenia	1(5)	1(5)	-	-
Neutropenia	-	-	-	-
Thrombocytopenia	-	-	-	-
Dizziness	1(5)	1(5)	-	-
Headache	-	2(10)		-
Nausea	-	3(15)	-	-
Vomitus	1(5)	-	-	-
Skin burn	-	1(5)-	-	-

whose tumors had reached critical regions that may be associated with high morbidity [21].

Many studies have compared the survival benefits of RT-based treatment modalities in patients with recurrent HGG (Table 3). Because additional conventional courses of irradiation to a previous treatment field carry an increased risk of toxicity, short-course fractionation and stereotactic radiotherapy of small volume were often administered. Combs et al. reported a median OS of 8 months with 36 Gy irradiation at 2 Gy per fraction [22]. Fogh et al. found that patients with GBM treated with HFSRT of 35 Gy at 3.5 Gy per fraction had a median survival of 8 months from the start of treatment [23]. In another study, patients receiving RT with 30 Gy in 5 fractions had a median OS of 7.9 months after re-RT [24]. Ciamella et al. found that the median OS was 9.5 months in a HFSRT study with 25 Gy administered in 5 fractions [25].

Because the treatment dose of re-RT is limited and as malignant gliomas are diffuse and infiltrative, previous studies have evaluated the synergic effect of re-RT with a systemic response modulator. Concomitant RT and chemotherapy, such as TMZ or BVZ, has been used in patients with recurrent HGG. Combs et al. confirmed a median survival of 8 months and a 12-month survival rate of 25% when 25 patients received 36 Gy of fractionated RT in 2-Gy fractions combined with TMZ [26]. In another study, patients received re-RT (37.5 Gy in 2.5-Gy fractions) with concomitant TMZ followed by adjuvant TMZ. The median OS was 9.7 months, and the 12-month survival rate was 33% [27]. BVZ sensitizes the tumor endothelium to RT by depleting vascular endothelial growth factor levels, and also lowers the RT dose required to control 50% of the tumor [28, 29]. Consequently, the combination of BVZ and radiotherapy results in a synergic effect and a superior outcome compared to single modality therapy [30]. Gutin et al. reported a median survival of 12.5 months and a 12-month survival rate of 63% in 25 patients who received 30 Gy HFSRT in 5 fractions, along with BVZ [12]. However, BVZ was associated with side effects including impaired wound healing, hemorrhage, and gastrointestinal perforation.

The results of our study combining HT with re-RT in patients with recurrent HGG were similar to those of previous studies (Table 3). Furthermore, the median OS was longer than that of patients receiving supportive care (8.4 vs. 2.5 months) [25]. However, in the previous study, the majority of patients had a KPS of over 60 [12, 23, 25, 27], with 92% patients having a KPS of more than 70 [26]. By comparison, in our study, the median KPS was 60 (range, 30–90) and 8 patients (40%) had a KPS of more than 60. In addition, patients who underwent salvage surgery before RT have a superior prognosis compared to those who did not undergo the operation. In previous studies, surgical resection was performed for patients over 60% [23, 24, 26]. In contrast, in the present study, surgery for a recurrent lesion was performed in 7 patients (35%) because of comorbidity and poor overall health.

Treatment-induced complications have long been a concern for patients with recurrent malignant glioma. In a study of irinotecan in combination with TMZ, 1 of 12 patients developed grade 4 lymphopenia and neutropenia, and grade 3 thrombocytopenia. In particular, 1 patient died of grade 5 pneumonia caused by *Legionella* [31]. Kreisl et al. used BVZ in combination with irinotecan for patients with recurrent GBM, and thromboembolic events occurred in 6 patients (12.5%) [20]. Radiation-induced necrosis occurred in 8% of patients who received fractionated RT and TMZ, and moderate and severe fatigue was reported in 41% of patients [27]. Gutin et al. used HSRT with BVZ. Three of 25 patients discontinued treatment because of grade 3 intratumoral hemorrhage, wound dehiscence, or bowel perforation [12]. The treatment discontinuation in these patients with recurrent HGG was associated with prognosis [32]. Unlike in previous studies, no patient in the present study discontinued treatment because of a treatment-related toxicity. Steroid was used during RT and Radiation-induced headache occurred in only 2 patients (10%). One patient in our study did not complete the planned treatment because of deteriorated general performance.

A limitation of this study was that the choice of treatment modality (surgery, chemotherapy, or RT) was determined by

Table 3. Clinical therapeutic outcomes based on radiotherapy for recurrent malignant glioma.

Authors	N	Re-irradiation dose	KPS	Concomitant therapy	Median OS (months)	Treatment completion
Combs et al. [22]	53	36 Gy/18 Fr	≥80:87% <80:13%	None	8.0	Not evaluated
Fogh et al. [23]	105	35 Gy/10 Fr	≥60	None	11.0	Completion
Vodermark et al. [24]	14	30 Gy/5 Fr	≥60	None	7.9	Not evaluated
Ciamella et.al [25]	15	25 Gy/5Fr	≥70	None	9.5	Completion
Combs et al. [26]	25	36 Gy /18 Fr	≥70 : 92% <70 : 8%	TMZ	8.0	Completion
Minniti et al. [27]	54	37.5 Gy/15 Fr	≥60	TMZ	9.7	Completion
Gutin et al. [12]	20	30 Gy /5 Fr	≥70	BVZ	12.5	Discontinuation
This Study	20	30 Gy /15 Fr	≥30	HT	8.4	Completion

Abbreviations: N, numbers at re-irradiation; KPS, Karnofsky Performance Score at re-irradiation; TMZ, temozolomide; BVZ, bevacizumab; HT, hyperthermia

the multidisciplinary team (neurosurgeon, hemato-oncologist, and radiation oncologist). Therefore, clinical features such as patient performance and co-morbidities were considered for the decision of the treatment regimen. It was ultimately decided that patients with poor prognosis with limited salvage treatment options would be selected. The median KPS of patients receiving re-RT with HT was 60, lower than that in previous studies [25, 27]. Furthermore, we did not compare the combination of RT and HT with RT alone. A future randomized study comparing the re-RT alone and re-RT with HT could help identify any synergic effects of HT.

Conclusion. It was suggested that concurrent re-RT with HT was safe and well-tolerated treatment option for patients with recurrent HGG in our study. Moreover, although patients with poor performance status were selected, the combination of HT with RT resulted in equivalent survival rates when compared with those described in previous studies. Concurrent re-RT and HT could therefore be a valuable therapeutic option for HGG patients in poor health status. Further studies are needed to evaluate the potential advantages of re-RT with HT for recurrent HGG.

References

[1] STUPP R, MASON WP, VAN DEN BENT MJ, WELLER M, FISHER B et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med 2005; 352: 987–996. https://doi.org/10.1056/NEJMoa043330

[2] NISHIKAWA R. Standard therapy for glioblastoma--a review of where we are. Neurol Med Chir 2010; 50: 713–719. https://doi.org/10.2176/nmc.50.713

[3] MINNITI G, AMELIO D, AMICHETTI M, SALVATI M, MUNI R et al. Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide. Radiother Oncol 2010; 97: 377–381. https://doi.org/10.1016/j.radonc.2010.08.020

[4] WELLER M, CLOUGHESY T, PERRY JR, WICK W. Standards of care for treatment of recurrent glioblastoma--are we there yet? Neuro Oncol 2013; 15: 4–27. https://doi.org/10.1093/neuonc/nos273

[5] BRANDES AA, BARTOLOTTI M, FRANCESCHI E. Second surgery for recurrent glioblastoma: advantages and pitfalls. Expert Rev Anticancer Ther 2013; 13: 583–587. https://doi.org/10.1586/era.13.32

[6] PATEL M, SIDDIQUI F, JIN JY, MIKKELSEN T, ROSENBLUM M et al. Salvage reirradiation for recurrent glioblastoma with radiosurgery: radiographic response and improved survival. J Neurooncol 2009; 92: 185–191. https://doi.org/10.1007/s11060-008-9752-9

[7] SONG CW, PARK H, GRIFFIN RJ. Improvement of tumor oxygenation by mild hyperthermia. Radiat Res 2001; 155: 515–528. https://doi.org/10.1667/0033-7587(2001)155[0515:IOTOBM]2.0.CO;2

[8] BRIZEL DM, SCULLY SP, HARRELSON JM, LAYFIELD LJ, DODGE RK et al. Radiation therapy and hyperthermia improve the oxygenation of human soft tissue sarcomas. Cancer Res 1996; 56: 5347–5350.

[9] VUJASKOVIC Z, POULSON JM, GASKIN AA, THRALL DE, PAGE RL et al. Temperature-dependent changes in physiologic parameters of spontaneous canine soft tissue sarcomas after combined radiotherapy and hyperthermia treatment. Int J Radiat Oncol Biol Phys 2000; 46: 179–185. https://doi.org/10.1016/S0360-3016(99)00362-4

[10] RAAPHORST GP, NG CE, YANG DP. Thermal radiosensitization and repair inhibition in human melanoma cells: a comparison of survival and DNA double strand breaks. Int J Hyperthermia 1999; 15: 17–27. https://doi.org/10.1080/026567399285828

[11] SNEED PK, STAUFFER PR, MCDERMOTT MW, DIEDERICH CJ, LAMBORN KR et al. Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/- hyperthermia for glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1998; 40: 287–295. https://doi.org/10.1016/S0360-3016(97)00731-1

[12] GUTIN PH, IWAMOTO FM, BEAL K, MOHILE NA, KARIMI S 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. https://doi.org/10.1016/j.ijrobp.2008.10.043

[13] LEE SW, FRAASS BA, MARSH LH, HERBORT K, GEBARSKI SS et al. Patterns of failure following high-dose 3-D conformal radiotherapy for high-grade astrocytomas: a quantitative dosimetric study. Int J Radiat Oncol Biol Phys 1999; 43: 79–88. https://doi.org/10.1016/S0360-3016(98)00266-1

[14] CHEUNG AY, NEYZARI A. Deep local hyperthermia for cancer therapy: external electromagnetic and ultrasound techniques. Cancer Res 1984; 44: 4736s-4744s.

[15] ROUSSAKOW S. The History of Hyperthermia Rise and Decline. Conference Papers in Medicine 2013; Article 428027. https://doi.org/10.1155/2013/428027

[16] BRADA M, HOANG-XUAN K, RAMPLING R, DIETRICH PY, DIRIX LY et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. Ann Oncol 2001; 12: 259–266. https://doi.org/10.1023/A:1008382516636

[17] REITHMEIER T, GRAF E, PIROTH T, TRIPPEL M, PINSKER MO et al. BCNU for recurrent glioblastoma multiforme: efficacy, toxicity and prognostic factors. BMC Cancer 2010; 10: 30. https://doi.org/10.1186/1471-2407-10-30

[18] FRANCESCONI AB, DUPRE S, MATOS M, MARTIN D, HUGHES BG et al. Carboplatin and etoposide combined with bevacizumab for the treatment of recurrent glioblastoma multiforme. J Clin Neurosci 2010; 17: 970–974. 10.1016/j.jocn.2009.12.009 https://doi.org/10.1016/j.jocn.2009.12.009

[19] FRIEDMAN HS, PRADOS MD, WEN PY, MIKKELSEN T, SCHIFF D et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009; 27: 4733–4740. https://doi.org/10.1200/JCO.2008.19.8721

[20] KREISL TN, KIM L, MOORE K, DUIC P, ROYCE C 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. https://doi.org/10.1200/JCO.2008.16.3055

[21] PARK JK, HODGES T, ARKO L, SHEN M, DELLO IACONO D et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol 2010; 28: 3838–3843. https://doi.org/10.1200/JCO.2010.30.0582

[22] COMBS SE, GUTWEIN S, THILMANN C, HUBER P, DEBUS J et al. Stereotactically guided fractionated re-irradiation in recurrent glioblastoma multiforme. J Neurooncol 2005; 74: 167–171. https://doi.org/10.1007/s11060-004-2463-y

[23] FOGH SE, ANDREWS DW, GLASS J, CURRAN W, GLASS C et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. J Clin Oncol 2010; 28: 3048–3053. https://doi.org/10.1200/JCO.2009.25.6941

[24] VORDERMARK D, KOLBL O, RUPRECHT K, VINCE GH, BRATENGEIER K et al. Hypofractionated stereotactic re-irradiation: treatment option in recurrent malignant glioma. BMC Cancer 2005; 5: 55. https://doi.org/10.1186/1471-2407-5-55

[25] CIAMMELLA P, PODGORNII A, GALEANDRO M, D'ABBIERO N, PISANELLO A et al. Hypofractionated stereotactic radiation therapy for recurrent glioblastoma: single institutional experience. Radiat Oncol 2013; 8: 222. https://doi.org/10.1186/1748-717X-8-222

[26] COMBS SE, BISCHOF M, WELZEL T, HOF H, OERTEL S et al. Radiochemotherapy with temozolomide as re-irradiation using high precision fractionated stereotactic radiotherapy (FSRT) in patients with recurrent gliomas. J Neurooncol 2008; 89: 205–210. https://doi.org/10.1007/s11060-008-9607-4

[27] MINNITI G, ARMOSINI V, SALVATI M, LANZETTA G, CAPORELLO P et al. Fractionated stereotactic reirradiation and concurrent temozolomide in patients with recurrent glioblastoma. J Neurooncol 2011; 103: 683–691. https://doi.org/10.1007/s11060-010-0446-8

[28] GORSKI DH, BECKETT MA, JASKOWIAK NT, CALVIN DP, MAUCERI HJ et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. Cancer Res 1999; 59: 3374–3378.

[29] KOZIN SV, BOUCHER Y, HICKLIN DJ, BOHLEN P, JAIN RK et al. Vascular endothelial growth factor receptor-2-blocking antibody potentiates radiation-induced long-term control of human tumor xenografts. Cancer Res 2001; 61: 39–44.

[30] CUNEO KC, VREDENBURGH JJ, SAMPSON JH, REARDON DA, DESJARDINS A 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. https://doi.org/10.1016/j.ijrobp.2010.12.074

[31] REYNES G, BALANA C, GALLEGO O, IGLESIAS L, PEREZ P et al. A phase I study of irinotecan in combination with metronomic temozolomide in patients with recurrent glioblastoma. Anticancer Drugs 2014; 25: 717–722. https://doi.org/10.1097/CAD.0000000000000059

[32] CHA Y, KIM YJ, LEE S-H, KIM T-M, CHOI SH et al. Post-bevacizumab Clinical Outcomes and the Impact of Early Discontinuation of Bevacizumab in Patients with Recurrent Malignant Glioma. Cancer Res Treat 2017; 49: 129–140. https://doi.org/10.4143/crt.2015.466