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Retreatment in Recurrences of High Grade Gliomas: Feasibility of Re-Irradiation and Concomitant Chemotherapy

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Abstract

Purpose: Treatment approaches for high grade gliomas recurrences include second surgery, re-irradiation, systemic therapies and supportive cares. We retrospectively investigated the feasibility of a second irradiation with or without chemotherapy for patients with recurrence of high grade glioma.

Methods and Materials: Thirty patients with recurrence of high-grade gliomas received a median re-irradiation dose of 36 Gy (34 – 41.1 Gy) with conventional fractionation (1.8 – 2 Gy/die) at our institution. Median age at the recurrence was 53 years (range 21-75 years). Twelve patients received chemotherapy (Temozolomide) as concomitant and adjuvant treatment, 8 patients received re-irradiation followed by adjuvant chemotherapy (Fotemustine), 10 patients received re-irradiation alone. Overall survival was calculated with Kaplan-Meier method. Neurocognitive evaluation (Mini-mental test and quality of life evaluation) was carried out with psycho-oncologist and patients underwent a neurocognitive rehabilitation therapy.

Results: Mean time between radiation therapies was 36 months (6-176 months). All patients carried out re-irradiation, with no cases of Grade ≥ 3 toxicity. At a follow up of 15 months, overall survival was 8 months (1-95 months). The group treated with concomitant chemo-radiotherapy shows a better overall survival compared with the group treated with only re-irradiation (16 *vs.* 7 months); 1 year-OS was 57.1% *vs.* 35.7% and 2 years-OS was 47.6% *vs.* 26.8%. From neurocognitive evaluation we report a good feasibility of re-irradiation, with good compliance to neurocognitive rehabilitation therapy.

Conclusion: In our experience, re-irradiation associated with chemotherapy (Temozolomide) for recurrent high grade gliomas represents a good treatment option, with better OS. Patients selection is important to identify those patients who benefit from this approach.

Keywords: High grade gliomas; Re-irradiation; Chemotherapy; Radiotherapy; Quality of life; Neurocognitive evaluation

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Introduction

Glioblastoma is the most common primary malignant brain tumor in adults, counting 16% of all primary Central Nervous System (CNS) tumors. Despite diagnostic and treatment developments, almost all patients undergo disease progression with nearly total mortality: The median survival from first diagnosis is less than 15 months and the 2-year survival rate is about 26-33% [1]. Median survival after progression for patients initially treated with Temozolomide and radiotherapy is very poor (6.2 months in the EORTC/NCIC-CTG trial) [2,3]. Treatment of recurrent CNS tumors is historically a challenge due to the remarkable toxicity which negatively affects quality of life (QoL), with no significant advantages on survival. Treatment approaches for high grade

gliomas recurrences include second surgery, re-irradiation, systemic therapies and supportive cares. Treatment must be tailored to each individual patient and requires consideration of tumor size and location, previous treatments, age, Karnofsky performance score (KPS), patterns of relapse and prognostic factors. Surgery remains an important option but radical surgery can be achieved only in a few patients. Re-irradiation (ReRT), with the advancement of radiation techniques and imaging, has become a valid salvage option with limited side effects [4-11]. Chemotherapy can also be used, either alone or in combination with radiotherapy. However, currently there is no standardized treatment for recurrent CNS tumors outside of protocols or clinical studies.

The aim of this retrospective analysis is to evaluate:

1. The feasibility and the safety of Re-RT in terms of toxicity and treatment related side effects and the association with chemotherapy.
2. Treatment outcomes (disease free survival, DFS, overall survival, OS) of Re-RT with or without chemotherapy.
3. Quality of life (QoL) and neuropsycological assessment related to second line therapies.

Methods and Materials

Patient population

From 2011 to March 2018, thirty-six patients (21 males, 15 females) with recurrent gliomas received Re-RT with external beam radiotherapy at our Department of Radiation Oncology. Thirty patients (18 males, 12 females) with recurrent high grade gliomas (HGG) received intensity modulated radiotherapy (IMRT) and were included in this evaluation whereas six patients (15%) with recurrence of low-grade gliomas were not included in our study. At the initial diagnosis all patients underwent neurosurgery followed by adjuvant radiotherapy (30/30 patients) and most of them received also concomitant chemotherapy with Temozolomide and adjuvant chemotherapy (23/30 patients) (STUPP Protocol). Patient characteristics at first diagnosis and at the recurrence are shown in **Table 1**.

The inclusion criteria for our study were: age ≥ 18 years at diagnosis; Karnofsky performance status (KPS) score ≥ 60; confirmed primary CNS tumor with GBM histology or others aggressive histological subtypes (anaplastic astrocytoma, anaplastic oligodendroglioma); disease evidence at both at disease debut and recurrence on gadolinium-enhanced MRI; adequate hematologic, renal, and liver parameters: an absolute neutrophil count (ANC) ≥ 1500/mm^3, platelets ≥ 100,000/mm^3, hemoglobin ≥ 10 g/dL, blood urea nitrogen, creatinine, total bilirubin, and direct bilirubin levels 1.5 times the upper normal laboratory value, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase levels 3 times the upper normal laboratory value; recurrence HGG treated with Re-RT with or without previous re-operative surgery and followed or not by adjuvant CT.

Table 1 Patient characteristics at Re-RT (re-RT) n=30.

Characteristics	Number
Age (Years)	
Median	53
Range	21 - 75
Sex	
Male	18
Female	12
Karnofsky performance status	
Median	80
Range	60 - 100
Histology	
Glioblastoma (St. IV)	18
Anaplastic astrocitoma (St. III)	12
Number of resections prior to re-RT	11
Complete	6
Partial/Subtotal	5
Interval between primary radiation and Re-RT	
Median	36.3
Range	6 - 176
Delivered RT dose (Gray)	
Median	36
Range	34 - 41.1
Re-RT plus concomitant TMZ	12
Glioblastoma (St. IV)	6
Anaplastic astrocitoma (St. III)	6
Re-RT and adjuvant Fotemustine	8
Glioblastoma (St. IV)	5
Anaplastic astrocitoma (St. III)	3
Re-RT alone	10
Glioblastoma (St. IV)	7
Anaplastic astrocitoma (St. III)	3

Neuro-imaging

A multidisciplinary staff (composed of neuro-radiologists, neuro-surgeons and neuro-radiation oncologists) reviewed MRIs prospectively and one investigator retrospectively performed measurements on T1 and/or T2-weighted and FLAIR sequences while blinded to individual diagnosis. For each patient, MRI examinations were performed for tumor location and after each therapeutic intervention: after surgery and before the radiation therapy to determine the extent and radicality of resection; after first line therapies to evaluate tumor response. Contrast enhancement on radiological images was noticed as absent or faint and patchy. Tumor response to radiotherapy plus concomitant chemotherapy was estimated with analysis of tumor variation on images studies. FLAIR sequences were chosen because they adequately show the areas of infiltration and/or edema. A complete response (CR) was defined as disappearance of all enhancing disease, whereas a partial response (PR) described a reduction > 30% in lesion size using bi-dimensional measurements.

Surgical procedures

At first diagnosis patients underwent functional-based surgery (awake craniotomy) using a method of intraoperative functional mapping or surgery with general anesthesia. Awake craniotomy is a neurosurgical intervention aimed at identifying and preserving the eloquent functional brain areas during resection of tumors located near the cortical and subcortical language centers. Before resection the cortex was mapped for language and sensorimotor sites. When the procedure was performed under general anesthesia only motor sites were mapped. A bipolar electrode with 5 mm tip spacing was utilized for functional mapping with a biphasic current intensity while patients performed functional tasks. In patient at rest, involuntary movements or paresthesis were induced with stimulation of primary motor or sensory sites respectively. A cortical site was considered positive when any interference in sensorimotor or language functions was observed at stimulations followed by normalization. The resection cavity was extended up to the functional boundaries, with no margin, so that maximal resection was obtained while preserving essential cortical and subcortical functional eloquent structures. At disease recurrence only eleven patients underwent a second surgery with six complete resection.

Neuropathology and molecular genetics methods

All tumors were firstly diagnosed on specimens' formalin fixed and paraffin-embedded slides and reviewed by a staff of experienced neuropathologists, according to the 2007 and 2016 WHO classifications of CNS tumors. The analyzed indices were: 1-expression of p53 (samples were taken as negative when no cell was labeled, positive when > 10% of cells were labeled); 2-expression of Ki-67 or MIB1 (proliferation rates were estimated with an index of MIB-1 immunostaining in the tumor area with the highest MIB-1 positive cell density); 3-loss of heterozygosity (LOH) on chromosomes 1p and 19q, evaluated on tumor DNA samples using polymorphic markers; 4-DNA methylation status of MGMT -promoter tested with polymerase chain reaction (PCR) followed by separation on 4 % agarose gel; 5-A fragment spanning wild-type R132 of IDH1 was amplified using a 5'-3' sense primer in PCR and samples were then investigated for mutation of the exon 4 of the *IDH2* gene using 5'-3' sense and 5'-3' antisense primers.

Radio-chemotherapy and adjuvant chemotherapy in first line and second line therapies

Patients were treated at initial diagnosis with standard external beam radiotherapy (EBRT, delivered dose 60 Gy with 2 Gy/die), with or without concomitant oral chemotherapy (Temozolomide at the dose of 75 mg/mq/daily during EBRT). For each patient dose-fractionation schemes, any delay in therapy supply and/or any toxicities were recorded. Adjuvant CT based on TMZ at the dose of 200 mg/mq for 5 consecutive days every 28 days was administered for eligible patients, until progression of disease at MRI or severe toxicity or until the maximum number of 12 CT cycles of adjuvant TMZ.

At recurrence, all patients received Re-RT at conventional fractionation with median dose of 36 Gy (range 34-41.1 Gy). RT was delivered after simulation using axial computerized tomography (aCT), segmentation of target and organs at risk (OARs) by the Radiation Oncologist and treatment planning by medical physics, using Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), with Trilogy® System Linear Accelerator and Tomotherapy®. Treatment plans were discussed, modified and finally approved by the Radiation oncologist. Before, during and after treatment, all patients underwent several physical, neurological and psychological examinations to promptly detect any side effects which may arise. Twelve patients received Re-RT plus concomitant and adjuvant chemotherapy (Temozolomide), eight patients received Re-RT and adjuvant chemotherapy (Fotemustine) and ten patients received only radiotherapy **(Table 1)**. At the onset of hematological toxicity, whenever possible, chemotherapy was given at reduced dose and then, in case of index and/or symptoms worsening, definitively stopped. Toxicity and adverse effects were graded according to the NCI-CTC (National Cancer Institute-Common Toxicity Criteria) and to RTOG (RadioTherapy Oncology Group)-EORTC (European Oncology RadioTherapy Group) grading system.

Neuropsycological and Quality of Life (QoL) assessment

Neuropsychological examinations and tests were carried out before, during and after each treatment (surgery, radiotherapy +/-chemotherapy, adjuvant chemotherapy) and were aimed at evaluating global efficiency, pre-morbid intelligence, laterality in handedness as well as seven cognitive domains: information processing/psychomotor speed, attention, episodic memory (verbal and non verbal), working memory (verbal and non verbal), language, visuo-spatial abilities and executive functions. Before, during and after radiotherapy several tests were administer to evaluate neuropsycological functions and depressive or anxious symptoms. First step is to administer a screening tool designed by Randolph named "RBANS" (Repeatable Battery for the Assessment of Neuropsychological Status): it is a short and complete neuropsycological battery of questions and exercises, divided into two parts (i.e., A and B) of equal difficulty, each one subdivided in 12 subtests suitable for patients from twenty to eighty years and able to evaluate 5 different cognitive domains: attention, language, visuospatial ability, visuoconstructive ability, immediate and deferred memory. The subtests constituting each of the two parts are: 1. Learning of word lists; 2. Prose memory; 3. Copy figures; 4. Orient lines; 5. Denomination; 6. Semantic fluency; 7. Digit span; 8. Association of symbols with numbers; 9. Re-enacting word list; 10. Word list recognition; 11. Prose re-enacting; 12. Shapes re-enacting. These tests can be grouped according to the neurocognitive function to be assessed: Immediate memory (1-2); Visual-spatial + visual-constructive ability (3-4); Language ability (5-6); Attention (7-8); Deferred memory (9-12) [12].

With regard of psycho-emotional evaluation the emotional

distress have been measured through the HADS (Hospital Anxiety and Depression Scale), composed by 2 subscales lasting about ten minutes, designed for the measurement of distress (theorized as the presence of anxiety and/or depression) in patients hospitalized and/or suffering from physical diseases, consisting of 14 items [13].

In addiction the "EORTC QLQ-30" questionnaire is given to patients in order to evaluate the quality of life (QoL), it lasts about ten minutes: it is a 30-items questionnaire comprising several domains divided in 3 different scales and items (functional scale, symptoms scale and global health status/QoL items). Functional scales provide 5 scores concerning physical functioning (PF), role (PF2), emotional functioning (EF), cognitive functioning (CF) and social functioning (SF). Symptomatic scales offer 3 scores about fatigue (FA), nausea and vomit (NV), pain (PA), whereas symptomatic items afford 6 scores inherent dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), financial impairments (FI). Last two groups of items give a score on health status and quality of life with seven point visual scale [14].

Neurological examinations and psycological assessments were performed at least two times for each patient (at the start of radiation therapy and during follow up), except in cases of evident worsening of neurological conditions. Psychotherapeutic interviews were performed once a week during all this period, unless the patient showed the need for closer encounters. During the considered period different questionnaires were administered with the aim of finding the more useful tests.

Statistical analysis

Comparison between Re-RT alone or with adjuvant chemotherapy (Fotemustine) and concomitant radiochemotherapy (Temozolomide) plus adjuvant chemotherapy were performed using Kaplan-Meyer method. Comparison of survivals curves according to various parameters were achieved using a log-rang test. A significant level was set at value of $p<0.05$.

Results

From 2011 to March 2018, 30 patients with a median age of 53 years (range 21 -75 years) received Re-RT for recur-rence of high-grade gliomas. The median interval between primary RT and Re-RT was 36.3 months. Eight patients were alive at the time of the analysis, 22 patients died of tumour progression during the follow-up.

After a median follow up of 15 month the overall survival was 36%, with a median overall survival of 9 months. **(Figure 1)** When we compared the treatments at HGG recurrence, we observed a difference in term of overall survival, with a benefit from Re-RT plus concomitant and adjuvant chemotherapy (Temozolomide), nearly to statistical significance (p= 0.052) **(Figure 2)**. When we compared patients treated with Re-RT and concomitant and adjuvant chemotherapy *vs.* patients treated with Re-RT only or Re-RT and adjuvant chemotherapy (Fotemustine), we observed a difference in term of overall survival, with a benefit for patients treated with Re-RT plus concomitant chemotherapy (Temozolomide), with a significant statistical difference (p= 0.027) **(Table 2 and Figure 3)**. Sex, age, KPS and histology did not show any effect on survival.

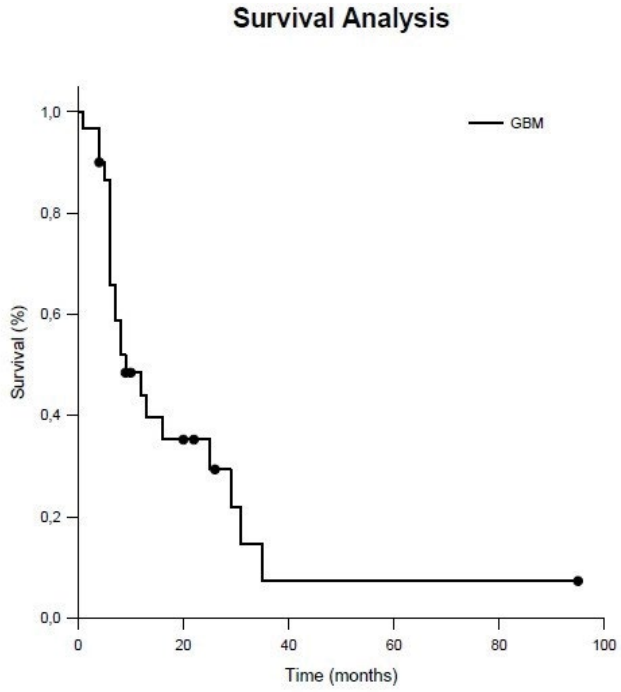

Figure 1 Kaplan-Meier analysis of overall survival of population (30 patients) after Re-RT for recurrent high grade gliomas.

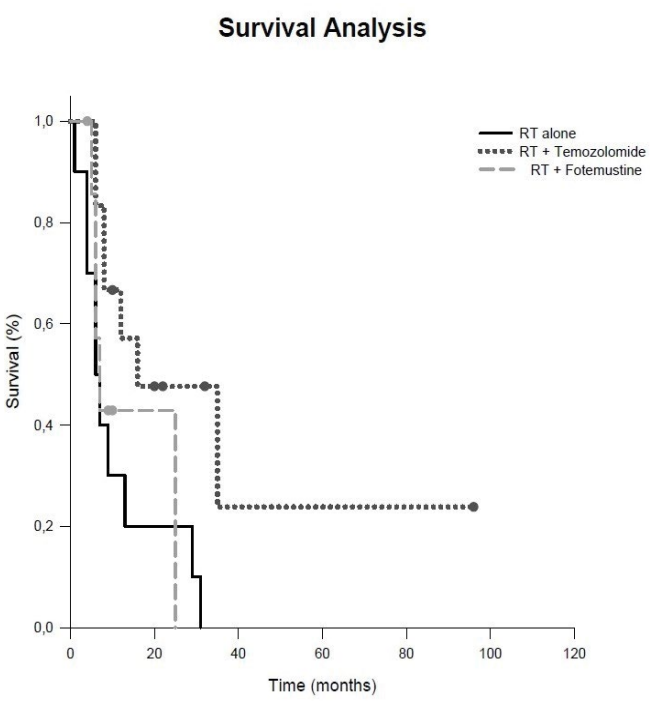

Figure 2 Kaplan-Meier analysis of overall survival of population (30 patients) after Re-RT for recurrent high grade gliomas according to three treatment approaches at recurrence (p=0.052).

Table 2 OS after Re-RT for high grade gliomas recurrences.

Treatment approach	OS	Univariate analysis p	OS a 1 year
	Median months		Median %
Re-RT plus concomitant TMZ	16	0.052	57.1
Re-RT and adjuvant Fotemustine	7		42.9
Re-RT alone	6		30
Re-RT plus concomitant and adjuvante TMZ	16	0.027	57.1
Re-RT alone and with adjuvant Fotemustine	7		35.7

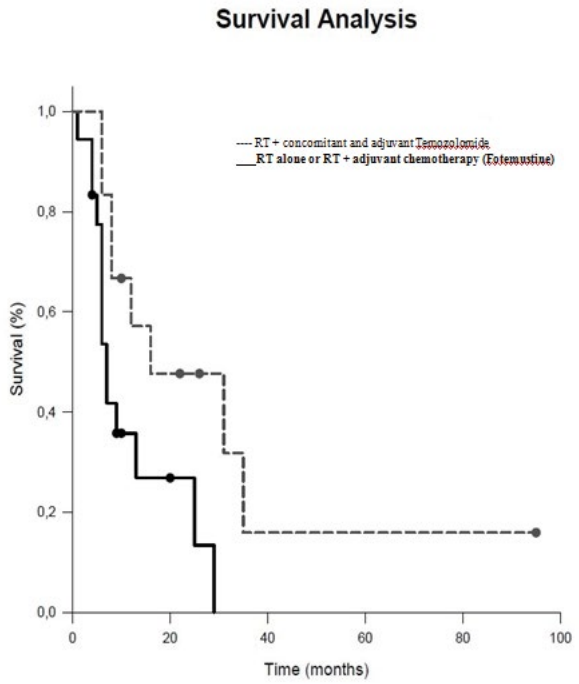

Figure 3 Kaplan-Meier analysis of overall survival of population (30 patients) after Re-RT for recurrent high grade gliomas (p= 0.027).

Toxicity

In general, Re-RT with conventional fractionation was well tolerated and all patients completed the panned treatment without any interruption. No grade ≥ 3 toxicities were reported. The most common adverse event was a moderate fatigue, which occurred in 11 patients (36.7%). One patient had grade 2 thrombocytopenia. During follow up no radione-crosis was observed on magnetic resonance.

As for neurological examinations and psychological assessments, each patient was evaluated at least twice (at the start of radiation therapy and during follow up). However because of the set of different questionnaires administered to patients at different time point, a quantitative evaluation was not appropriate or possible to achieve. In general, none of the different evaluation s reported relevant neurological toxicities and/or severe neuropsychological dysfunctions (in our group of patients).

Discussion

Almost all patients with glioblastoma undergo disease progression after first treatment (surgery and radiochemotherapy). Treatment approaches for high grade gliomas recurrences represent a challenge for physician: These include second surgery, re-irradiation, systemic therapies and supportive cares.

Several radiation techniques have emerged as a feasible treatment for recurrent brain tumors previously exposed to high doses of RT. Many clinical studies and reviews are reported in the literature on Re-RT of gliomas [4-11,15,16]. The majority of these studies have the limitations that are retrospective in design and encompass a variety of techniques, including brachytherapy, fractionated stereotactic radiotherapy, radio surgery and conformal or intensity-modulated radiotherapy with or without new systemic agents.

In addition to the great variety of radiation techniques, the published studies include a wide range of doses, thus indicating that a standard radiation approach is still lacking. Compared to stereotactic techniques, conventional RT reduces the risk of both radionecrosis and toxicity [5,7]. In studies considering stereotactic techniques, the most reported severe toxicity was radionecrosis: in some series radionecrosis was detected with imaging techniques with a rate ranging from 20% to 31.3%, whereas some authors reported data of histologically proven radionecrosis but with a lower incidence rate (1.6% -7.6%) [15-18]. In patients who were treated with conventionally fractionated techniques the authors reported a very low rate of severe toxicity (1.7%), despite the large median tumour size [5]. In our series, where patients were treated with conventional fractionated ReRT, we reported no cases of radionecrosis.

Few studies have addressed the combination of chemotherapy with Re-RT [4,11,15,19,20]. The association of concomitant Temozolomide to radiotherapy was based on the observation that concurrent chemotherapy can potentiate the cytotoxic effects of radiation [3]. Temozolomide and Re-RT have been found to be safe and effective. In a study combining fractionated stereotactic radiotherapy and concomitant temozolomide in 25 patients with recurrent gliomas, median survival from Re-RT was 8 months [11]. Planned treatment was completed in all patients with some interruptions no longer than 3 days and without any severe side effect. Minniti et al. published their results on 36 patients who were treated with fractionated stereotactic radiotherapy and concomitant Temozolomide, for a total dose of 37.5 Gy delivered in 15 fractions [15]. They reported a median overall survival of 9.7 months with neurological deterioration due to radiation-induced necrosis in three patients (8%). Published data suggest that combined chemoradiation in patients with recurrent high grade gliomas is more effective than radiation alone and our results are in line with these outcomes, reporting a greater survival benefit with the addition of TMZ to ReRT. In our series we evaluated patients with different toxicities from previous treatments, including patients with severe acute hemathologic toxicity, and we observed no difference in toxicity events during patient retreatment.

A low incidence of acute and late toxicity in patients with recurrent high grade gliomas using conventional fractionated radiotherapy in association with TMZ has been reported previously, suggesting that this approach, with fractions of 2-3.5 Gy to a total dose less than 40 Gy, may be a feasible and safe option for patients with larger tumors or tumors located in eloquent structures [5,7,11,17-20].

In our evaluation different neuropsychological tests were used but no severe neurological deterioration was observed. We identified a few series of useful tests to be administered to patients with recurrent high grade glioma: RBANS, HADS and EORTC-QLQ 30, with a total execution time of 30 minutes [12-14]. Neuropsychological evaluation is not only feasible but is especially useful for identifying patients with distress or deteriorations in cognitive functions, who could be included in psychological or cognitive rehabilitation.

Conclusion

Treatment of high grade gliomas' recurrences is still a challenge for physicians. Treatment of rGBM requires a delicate balance between aggressiveness of treatment, outcome, cost of care, quality of life and a multidisciplinary evaluation. In our retrospective, mono-institutional analysis, Re-RT associated with concomitant chemotherapy is a safe tool and pro-vides better outcomes compared to radiation therapy only or radiotherapy with adjuvant chemotherapy. Prospective trials are required to evaluate the treatment for recurrent high grade glioma.

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