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Original research article

Fractionated stereotactic radiotherapy plus bevacizumab after response to bevacizumab plus irinotecan as a rescue treatment for high-grade gliomas



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radiotherapy**ABSTRACT**

Aim: To evaluate the possibility of implementing a new scheme of rescue treatment after relapse or progression of high-grade glioma (HGG) treated at the first-line with bevacizumab and irinotecan (BVZ+CPT11), evaluating the response and toxicity of associating BVZ and fractionated stereotactic radiotherapy (BVZ+FSRT).

Materials and methods: We retrospectively analysed data from 59 patients with relapse of HGG. Nine patients with HGG relapse after treatment using the Stupp protocol that were treated with BVZ+CPT11 for progression between July 2007 and August 2012, after which the response was assessed according to the Revised Assessment in Neuro-Oncology (RANO) criteria. BVZ was administered at a dose of 10 mg/kg and FSRT up to a prescribed dose of 30 Gy, 500 cGy per fraction, three days a week. The median follow-up was 38 months.

Results: The treatment was well-tolerated by all patients. The response after nuclear magnetic resonance imaging (MRI) at 3–6 months was progression in two patients, stable disease in four, and three patients had a partial response. The median overall survival (OS) from diagnosis until death or the last control was 36.8 months. The median progression-free survival (PFS) was 10.8 months. The results from tumour sub-group analysis indicated that the PFS was not statistically significant although it seemed that it was higher in grade-III. The OS was higher in grade-III gliomas.

Abbreviations: HGG, high-grade glioma; BVZ, bevacizumab; CPT11, irinotecan; FSRT, fractionated stereotactic radiotherapy; RANO, revised Assessment in Neuro-Oncology; MRI, magnetic resonance imaging; OS, overall survival; PFS, progression-free survival; TMZ, temozolamide; KPS, Karnofsky Performance Scale; VEGF, vascular endothelial growth factor; PTV, planning target volume; CAT, computed axial tomography; GTV, gross tumour volume; SEOM, Sociedad Española de Oncología Médica; ASCO, American Society of Clinical Oncology; CTCAE, common terminology criteria for adverse events; PET, positron emission tomography; CI, confidence interval; MGMT, O-6-methylguanine-DNA methyltransferase; HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; SRS, stereotactic radiosurgery; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

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Conclusions: The combination of BVZ+FSRT as a second-line HGG relapse rescue treatment is well-tolerated and seems to offer promising results. We believe that multi-centre prospective studies are needed to determine the long-term efficacy and toxicity of this therapeutic approach.

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1. Background

High-grade gliomas (HGGs) are heterogeneous entities that comprise primary glioblastomas, anaplastic oligodendroglomas and gliomas, and secondary glioblastomas, together representing 25% of primary central nervous system tumours.¹ Among patients affected with glioblastoma, less than 10% of those treated with the standard Stupp protocol² (maximal surgical resection, external radiotherapy, and concomitant and adjuvant temozolomide [TMZ]) survive more than five years from diagnosis.³

HGG relapse treatment is changing. Although surgical resection is an option in relapse, the infiltrative nature of glioma makes complete tumour resection difficult during the rescue surgery and chemotherapy is being used with modest success because of chemoresistance and accumulated toxicity. Advances in the biology of HGGs allow targeted therapies to be developed, such as the use of bevacizumab (BVZ), a humanised monoclonal antibody against the vascular endothelial growth factor (VEGF) expressed in HGG cells, which used alone or in combination with external radiotherapy, is offering promising results.⁴

Fractionated stereotactic radiotherapy (FSRT) provides local control in HGG relapses with minimal morbidity. Case series and prospective and retrospective studies demonstrate efficacy and acceptable FSRT toxicity in the treatment of this disease.⁵

The purpose of this work was to evaluate the possibility of implementing a new relapse or progression treatment-scheme for HGG treated at the first-line with BVZ+CPT11, evaluating the response and toxicity of associating BVZ and fractionated stereotactic radiotherapy (BVZ+FSRT).

2. Materials and methods

2.1. Patient selection

This retrospective study was conducted with permission from the institutional review and ethics board of our centre; thus, we analysed data from 59 patients treated for HGG relapse between 2007 and 2014, of whom we found nine whose progression was treated with compassionate use with BVZ+CPT11 after a relapse following original Stupp protocol treatment, response was assessed using the RANO criteria (Table 1). After assessment by a multidisciplinary committee which discarded the possibility of any other type of treatment, BVZ was administered (dose of 10 mg/kg) on day two on the first day FSRT was started, FSRT was administered at a prescribed dose of 30 Gy,

500 cGy per fraction, three times a week, between July 2007 and August 2012.

After the initial diagnosis, all the patients were treated by a total tumour excision followed by conventional external radiotherapy and concomitant and adjuvant TMZ (except for patient one where adjuvant chemotherapy was suspended because of haematological toxicity). All of them had relapsed after primary treatment, which was confirmed with nuclear magnetic resonance imaging (MRI) neuroimaging techniques.

The median follow-up was 38 months. All of them were in a good general condition, with no neurological deficits after primary treatment, with a Karnofsky Performance Scale (KPS) score above 70%, MGMT status was not tested; rescue surgery was discarded as the first option and was reserved as an option for use after the second-line treatment response in all of them.

2.2. Patient characteristics

The mean patient age was 54.8 years and the cohort consisted of five men and four women. The histology was: 2 patients with anaplastic oligodendrogloma, 2 grade II glioma and 3 glioblastoma. In 88.8% of the patients the primary tumour was located in a single cerebral lobe, presenting in the left frontal lobe in two patients, right temporal lobe in four of them, the right frontal lobe in one, and the right parietal lobe in the other. The primary location of the tumour was multiple in only one case. In eight patients the relapse was located at the base of or near the tumour, and of all the patients studied, 22.2% presented leptomeningeal spread (Table 2).

66.6% of the patients received less than 10 neoadjuvant BVZ+CPT-11 cycles and the average time between administration of the Stupp scheme and the relapse treatment with BVZ+FSRT was 17.8 months. Systemic treatment scheme was based on recently published studies¹³ and it followed BVZ 10 mg/kg (1st and 15th day of 28 days) plus irinotecan 125 mg/m². About patients evaluation, no quality of life specific tests were applied. A toxicity follow-up was performed in all cases, using the Barthel escala, Mini-Mental Score and ECOG performance status. The average FSRT dose administered to these patients was 29.2 Gy (covering the lesion with an isodose of between 95 and 103% with a planning target volume [PTV] of between 85 and 95%), this dose being less than 29 Gy in 55.5% of the patients.

2.3. Fractionated stereotactic radiotherapy technique

All patients underwent a computed axial tomography (CAT) simulation for radiotherapy treatment planning with cuts every 1.5 mm using a thermoplastic immobilisation mask (Brain-Lab system), as well as a T1-sequence gadolinium-contrast brain MRI with cuts every 1.5 mm, these

Table 1 – RANO criteria.

Criterion	CR	PR	SD	PD
T1 gadolinium-enhancing disease activity	None	≥50%↓	<50%↓ but <25%↑	≥25%↑ ^a
T2/FLAIR disease activity	Stable or ↓	Stable or ↓	Stable or ↓	↑ ^a
New lesion	None	None	None	Present ^a
Corticosteroids	None	Stable or ↓	Stable or ↓	NA ^b
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓ ^a
Response-requirement	All	All	All	Any ^a

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

^a Progression occurs when this criterion is present.

^b Increased in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

images were merged with those from the CAT simulation. The gross tumour volume (GTV) was determined as the lesion captured by the T1 contrast sequence and the PTV was defined as the GTV plus a 4 mm margin. The treatment planning was carried out using a Brain SCAN planning system (Brainlab).

An overall dose of 30 Gy was administered (5 Gy per fraction in 6 fractions every other day; one patient received 6 Gy per fraction in 5 fractions) as determined by an isodose of 100%, using a single isocenter and an average of 13 non-coplanar beams (8–17 beams). The mean GTV was 11.14 cc (0.24–65.02 cc). Daily treatment positioning verification was performed using the ExactTrac® system. All the patients received corticosteroid therapy during the FSRT treatment period.

Table 2 – Characteristics of the study patients.

	n	%
Sex		
Men	5	55.5
Women	4	44.4
Age		
<50 years	2	22.2
≥50 years	7	77.7
Primary tumour location		
Single lobe	8	88.8
Multiple lobes	1	11.1
Relapse location		
Original tumour site or close	8	88.8
In another location	1	11.1
BVZ+CPT11 cycles		
<10	6	66.6
≥10	3	33.3
Toxicity ^a		
Attributable to the treatment	0	0
Not attributable to the treatment	9	100
Time elapsed ^b		
<12 months	5	55.5
≥12 months	4	44.4
Radiological response ^c		
CR	0	0
PR	3	33.3
SD	4	44.4
PD	2	22.2
Average FSRT dose ^d		
<29 Gy	5	55.5
≥29 Gy	4	44.4

^a Radio-necrosis confirmed by biopsy, a multiparametric nuclear magnetic resonance (MRI) study, or positron emission tomography (PET). BVZ, bevacizumab; CPT11, irinotecan.

^b Time between initial Stupp scheme treatment and administration of rescue treatment with BVZ+FSRT.

^c According to Revised Assessment in Neuro-Oncology (RANO) criteria.

^d Isodose of 95–103% to cover the lesion and 85–95% to cover the planning target volume (PTV).

2.4. Systemic therapies and toxicity

We reviewed the clinical histories of all the patients to determine which systemic therapies were received by each of them before and after BVZ+FSRT treatment. Administration of systemic therapies was directed by the Medical Oncology service of the Castellon Provincial Hospital Consortium according to the therapeutic protocols recommended by the Spanish Society of Medical Oncology (Sociedad Española de Oncología Médica; SEOM) and the American Society of Clinical Oncology (ASCO) in coordination with the multidisciplinary neuro-oncology committee from the Provincial and General hospitals in Castellon.

Toxicity was determined based on the common terminology criteria for adverse events (CTCAE, version 4), which defines it as the appearance of new symptoms or the worsening of previous symptoms after administration of the treatment. Symptoms which were caused by progression of the disease were excluded.

2.5. Statistical analysis

Overall survival (OS) was considered from diagnosis and from the point of BVZ+FSRT treatment to death or last control and progression-free survival (PFS) were considered from diagnosis and from the point of BVZ+FSRT treatment to the date of diagnosis of tumour recurrence. Survival functions were calculated using the Kaplan-Meier method. For comparison of survival curves, a log-rank test was used.

The limit of statistical significance was established as a p value of alpha = 0.05. Statistical analysis was performed using SPSS (Statistical Package for Social Science) for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA) and R software version 2.15.1.

3. Results

3.1. Response to rescue treatment with bevacizumab and fractionated stereotactic radiotherapy

At 3–6 months the disease progressed in two patients, was stable in four, and a partial response was obtained in three (according to the RANO criteria) as detected by MRI. When clinical or radiological progression was detected, a second round of BVZ+CPT11 treatment was administered in three cases and BVZ only in the other three after a new multidisciplinary committee evaluation.

Both treatments were administered every 15 days, with an average of 5.5 cycles (range: 2–8 cycles).

When the final clinical history of the patients was analysed, six had deceased, one had a partial response, and two remained with stable disease criteria.

3.2. Toxicity

The treatment was well-tolerated by all of the patients and the toxicity could not be clearly attributed to either of the two treatments. One patient presented with a diagnosis of radionecrosis indicated by an imaging test performed in another centre (non-multiparametric MRI). Clinically, this patient presented with occasional sphincter incontinence, bradypsychia, and clumsiness when walking which was attributed to the possible presence of radionecrosis and not to disease progression, but, as indicated, this could not be confirmed by biopsy or multiparametric MRI or positron emission tomography (PET) studies. No grade 4–5 toxicities occurred in relation to administration of BVZ or FSRT.

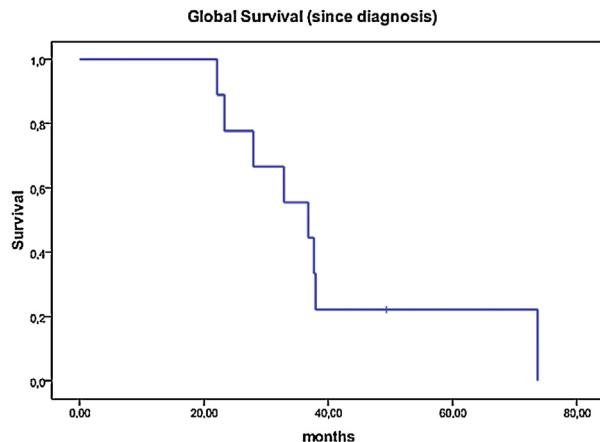
3.3. Survival

The median OS from diagnosis to death at the last control was 36.8 months (95% confidence interval [95% CI]: 25.3–48.3). The estimated mean OS was 40.7 months (95% CI: 27.8–53.6; Fig. 1).

The median progression-free survival (PFS) from the point of BVZ+FSRT treatment was 6.4 months (95% CI: 2.0–10.8). The estimated average PFS was 12.1 months (95% CI: 4.4–19.7; Fig. 2).

The differences in PFS (since diagnosis) between the tumour subgroups were 5.3 months for grade-IV gliomas (95% CI: 4.0–6.6), 12.1 months for grade-III-OA gliomas (95% CI: 6.2–18.0), and the highest PFS was for grade-III gliomas at 15.4 months (95% CI: 1.4–29.4; Fig. 3).

The median progression-free survival (PFS) from the point of diagnosis to the first disease progression was 10.1 months (95% CI: 6.2–14.0). The estimated average PFS was 14.7 months (95% CI: 8.6–20.8). The differences in PFS between the tumour subgroups were higher for grade-III anaplastic oligodendroglomas. The mean survival after BVZ+FSRT treatment was 15.3 months for grade-IV gliomas (95% CI: 3.8–26.8), 10 months for grade-III gliomas (95% CI: 2.86–17.40), and the highest PFS was for grade-III-OA gliomas at 23 months (95% CI: 8.8–37.13; Fig. 4).



	Mean	Std. Error	CI 95%		Median	Std. Error	CI 95%
OS	42,25	5,56	32,35 – 54,15	OS	37,8	6,25	25,73 – 50,23
PFS	14,69	3,11	8,59 – 20,79	PFS	10,1	2,01	6,15 – 14,02

Fig. 1 – Overall survival from high-grade glioma diagnosis until death.

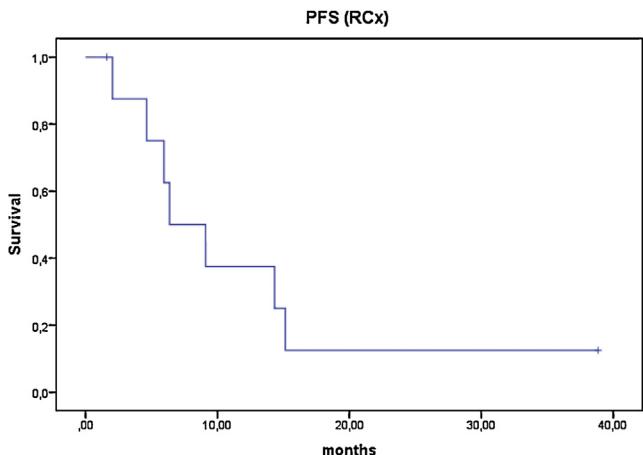


Fig. 2 – Progression-free survival after bevacizumab and fractionated stereotactic radiotherapy treatment.

The OS was higher in grade-III gliomas (OS = 54.5 m) and anaplastic oligodendroglomas (OS = 37.4 m) compared to grade-IV gliomas (OS = 24.5 m; Fig. 5).

It was clinically observed that the presence of more than one tumour lesion increases the risk of death and that this had a direct impact on the OS.

Glioma grade	Mean	Std. Error	CI 95%
G3	15,400	7,123	1,44 – 29,36
G3-OA	12,123	3,023	6,20 – 18,05
G4	5,290	0,657	4,00 – 6,58
Global	12,053	3,888	4,43 – 19,67

Fig. 3 – Progression-free survival by tumour subgroups.

Glioma grade	Mean	Std. Error	CI 95%
G3	10,127	3,709	2,86 – 17,40
G3-OA	22,965	7,228	8,80 – 37,13
G4	15,266	5,866	3,77 - 26,76
Global	14,693	3,112	8,59 – 20,79

Fig. 4 – Overall survival by tumour subgroup after BVZ+FSRT treatment.

Glioma grade	Mean	Std. Error	CI 95%
G3	54,497	11,802	31,37 – 77,63
G3-OA	37,388	0,591	36,23 – 38,55
G4	24,487	1,753	21,05 - 27,92
Global	40,692	6,589	27,78 – 53,61

Fig. 5 – Overall survival by tumour subgroup since diagnosis.

4. Discussion

The treatment choices for relapse patients with high-grade glioma are limited. The treatments used include surgical resection and systemic treatment with chemotherapy drugs or new molecular therapy agents until the administration of a second brain irradiation dose.

4.1. Rescue with surgery

The value of surgery has been considered controversial in the past and few studies have demonstrated promising results after surgery for relapsed HGG patients.

In general terms, the results are poor and surgical resection is sometimes associated with a higher risk of secondary effects given the naturally infiltrative nature of the disease.⁶

Park et al. recently generated an interesting tool to determine a prognostic scale applicable to the surgical intervention results from patients with relapsed glioma. This work took into account relevant factors that influence brain resection, such as the tumour volume, location, its association with vital brain areas, and factors related to the clinical condition of the patient, such as the KPS. They developed a point score index ranging from 0 to 3, good to poor, and demonstrated that patients with a final score of 3 benefitted very little from a surgical approach to their disease, and assert that the decision of which treatment to apply should be individualised for each patient taking the previously mentioned factors into account.⁷

4.2. Rescue with radiotherapy

With regard to administration of radiotherapy as a rescue treatment in relapsed HGG patients, conventional external radiotherapy is not generally possible because of the elevated risk of toxicity to the brain which can provoke an increase in neuro-cognitive deficits and necrosis induced by radiation.⁸

Multiple studies have demonstrated the security and efficacy of cerebral re-irradiation with distinct treatment

schemes, including FSRT, radiosurgery, or non-conventional fractionation techniques; this second irradiation is always performed six months after the first irradiation with conventional external radiotherapy.⁶ However there is little experience of these studies and to date no phase-III trials have been published in the literature. Given that there are no randomised trials, data on the role of re-irradiation after progression of the disease or the appearance of radiation-induced cancers are scarce and poorly defined. The literature is limited to a series of small retrospective clinical case studies, which makes their interpretation difficult.⁹

Brachytherapy, which aims to deliver a localised dose of high-level radiation targeted at the tumour while protecting the normal cerebral tissue, points towards a modest improvement in the OS but has shown an elevated risk of cerebral necrosis (which lowers its percentage of effectiveness if tumour debulking has previously been performed). Chan et al. carried out a study on 24 relapsed HGG patients, administering low-dose rate brachytherapy with I^{125} (GliaSite®) in the previously operated area and evaluated the secondary effects (acute and delayed) and the OS. The majority of these effects were mild, infrequent, and were resolvable with symptomatic treatment, except in two cases that presented with symptoms of radio-necrosis. They observed that these two patients had received a dose of 50 Gy or more at a prescribed dose depth of more than 1 cm: the presence of an increased amount of tumour in these patients meant that they had to administer higher doses. They concluded that because they did not demonstrate an increase in OS at doses higher than 45 Gy, this might be a sufficient treatment dose with minimal risk of developing toxicity, provided that an initial optimal tumour resection is performed leaving minimal tumour residue.¹⁰

4.3. Re-irradiation and radio-necrosis

There is level-1 evidence for BVZ as a radio-necrosis treatment, the main risk of cerebral re-irradiation^{11,12}. It has been demonstrated that molecular therapy with BVZ reverses the effects of radio-necrosis because (VEGF) is altered in radio-necrosis and BVZ acts on this factor. As described in their article, Chao et al. administered BVZ to 8 patients with cerebral radio-necrosis and showed a reduction in MRI contrast in all of them (T2 fluid-attenuated inversion recovery [FLAIR] and T1 post-gadolinium imaging). Moreover, it also helped reduce the corticosteroid dose. Levin et al.¹² demonstrated that in a series of 14 patients all those treated with BVZ showed improvement in neurological signs and symptoms, but that there was no alteration in those treated with the placebo. Therefore, performing a second irradiation seems justified and safe if it is administered along with BVZ.

4.4. Molecular therapy

BVZ has shown an anti-tumour effect in HGG relapses,¹³ although the results are not clear in first-line treatment, as shown in the AVAglio and RTOG studies^{14,15}. In the AVAGlio study on HGG patients previously treated with surgery, the addition of BVZ to the adjuvant treatment with TMZ+External beam Radiation Therapy (EBRT) did not significantly increase the OS, although it did increase the PFS by 4.4 months with

an HR of 0.61, and improved the quality of life as shown by maintenance of a stable KPS score in this period, and reduced corticosteroid doses. However, this benefit was not seen as clearly in the RTOG 0825 study in which the patients' symptoms and neuro-cognitive function deteriorated with BVZ. The justifications for these differences include, among others, statistical anomalies in the analysis of a data subset, given that studies on *Quality of Life* and *Neuro-cognitive* tests were only performed on a subgroup of patients in both studies, coupled with possible differences in the statistical methods used. The AVAglio study focussed only on the quality of life and not on neurocognitive data, and so, given that BVZ produces a larger gap at the blood-brain barrier and lowers gadolinium MRI-enhancement, there could have been radiologically occult disease progression in these patients which would justify the worsening of neuro-cognitive function observed in the RTOG 0825 study. Regarding the failure to increase OS, it is important to note that different factors can act to modify the response in different patients, such as the study design, treatment cross-effects, the presence of distinct patient molecular sub-types, or the presence of suboptimal BVZ concentrations at the site of action. Therefore, it is inevitable that VEGF may not be considered an optimal target in all HGG cases, or at least, not at all points of the disease, which would justify the appearance of the 10–20% prolongation of PFS and OS in patients treated with TMZ+EBRT+BVZ for recurrent glioblastoma.^{16,17} All of this makes it essential to know the molecular HGG profile of individual patients so as to be able to individualise the treatment and optimise resources.

4.5. Associated therapy

Turning to associated therapy (FSRT ± BVZ), there are multiple studies in the literature. The first one, a prospective study with 25 patients, was published in 2009 by Gutin et al. and they concluded that BVZ associated with FSRT in HGG relapse treatment was safe and well-tolerated.¹⁸ Niyazi et al. carried out a retrospective study with 30 patients, demonstrating that OS was higher in patients in whom BVZ was associated with the rescue treatment, and that the OS was also affected by the tumour grade and general condition of the patients.¹⁹ Several studies posit that the OS and the PFS are the highest where BVZ is associated with radiosurgery or FSRT (Table 3).

One retrospective study, performed by Torcuator et al., compared 23 patients treated with either FSRT or stereotactic radiosurgery (SRS) after progression on an initial bevacizumab regimen to other 23 patients who, after progression to BVZ+chemotherapy, continued with more BVZ+chemotherapy. Patients treated with FSRT/SRS/BVZ had a longer median progression-free period (2.6 vs. 1.7 months), longer median post FSRT/SRS treatment survival (7.2 vs. 3.3 months) and higher radiographic response rate (22 vs. 0%). Thus, they concluded that FSRT or SRS followed by bevacizumab+chemotherapy may have a role for patients who progress on bevacizumab.²⁰ Our modest study of 9 patients with HGG tumour relapse treated with FSRT+BVZ after a response with BVZ+CPT11, also showed higher OS and PFS figures, similar to those studies where FSRT+BVZ were performed as initial treatment in HGG relapse (Table 4).

Table 3 – Studies associating bevacizumab with radio-surgery or fractionated stereotactic radiotherapy.

Study	Patient No.	Treatment	Age (years)	KPS	Tumour volume n (cm ³)	RTX dose (Gy)	Time between initial diagnosis and salvage RTX (months)	PFS (months)	OS from salvage RTX (months)	OS from initial diagnosis (months)	Radiation necrosis
Hall et al.	26	SRS (LINAC)	47	70	28	20	10	NR	6.5	18	14%
Sheirive et al.	86	SRS (LINAC)	46	80	10.1	13	10.3	NR	10.2	NR	16%
Combs et al.	32	SRS (LINAC)	56	NR	10	15	10	5	10	22	0%
Hsieh et al.	26	SRS (LINAC)	58	70	21.6	12	NR	NR	10	16.7	31%
Mahajan et al.	41	SRS (LINAC)	54	NR	NR	NR	11	NR	11	26	NR
Vordemark et al.	14	HFSRT	50	90	15	30	19	4.6	7.9	NR	0%
Kong et al.	65	SRS (GK)	49	100	10.6	16	NR	4.6	13	23	24.4%
Patel et al.	10	HFSRT	44	90	51.1	NR	14.9	NR	7.4	24.1	NR
Patel et al.	26	SRS	53	80	10.4	18	12.5	NR	8.4	24.4	7.6%
Gutin et al.	20	HFSRT+BVZ	56	80	34	30	14.5	7.3	12.5	NR	0%
Fogh et al.	105	HFSRT	53	NR	22	35	8	NR	11	23	NR
Cuneo et al.	42	SRS (LINAC)+BVZ	47	80	4.5	15	21	5.2	11.2	47	5%

BVZ, bevacizumab; GK, gamma knife; HFSRT, hypofractionated stereotactic radiation therapy; KPS, Karnofsky performance status; LINAC, linear accelerator; OS, overall survival; PFS, progression free survival; RTX, radiation therapy; SRS, stereotactic radiosurgery; NR, not record.

Table 4 – Studies in which combined therapy is associated with high-grade glioma rescue treatment.

Centre/author	Scheme	n	OS	OS after FSRT	PFS after FSRT
CHP Castellón-Eresa/Conde et al.	(BVZ+CPT11)	9	36.8 m	15.7 m	6.4 m
	BVZ+FSRT				
MSKCC/Gutin et al.	BVZ+FSRT	24	32.1 m	12.2 m	7.5 m
	BVZ+FSRT				
LMU	BVZ+FSRT	20	–	12 m	8.1 m
	FSRT				
Munich/Niyazi et al.	FSRT	7	–	4.7 m	5.8 m
Michigan/Cabrera et al.	BVZ+FSRT	15	–	14.4 m	3.9 m
	(After progression to BVZ)				
Torcuator et al.	BVZ+FSRT/SRS	23	–	7.2 m	2.7 m

In 2013, the Memorial Sloan Kettering Cancer Centre published an update on its 2009 study on 22 patients in which they evaluated their clinical and radiological progression, showing that radiological progression is the only variable related with PFS.⁴ In the same year, Cabrera et al. observed, in a prospective study on 15 patients, that combined therapy did not produce grade 4–5 toxicity, neuro-cognitive deterioration, or a KPS decrease, and that there was a decrease in the MRI perfusion after radio-surgery or FSRT.³

To date, our retrospective study is the first to evaluate results from FSRT+BVZ after response to neoadjuvant therapy with BVZ+CPT11 in relapsed HGG in patients where FSRT was discarded as the first treatment to recurrence. Remaining tumour could not be identified on the control MRI in one patient after having received FSRT+BVZ treatment for six cycles. Another showed a 0.8 mm reduction in the size of the lesion after receiving 10 cycles and yet another showed a complete tumour response after 8 cycles. However, we do not yet have clear data which can guide us on what strategy should be followed after a response to BVZ+CPT11: if treatment should be continued or discontinued until progression, or if another type of treatment should be assessed.

Other factors which must be taken into account are response evaluation criteria. Several of referenced studies followed Macdonald criteria, but it is known that the RANO criteria are more suitable to evaluate response to anti-VEGF treatment. Therefore, these criteria were used in our study as in other studies, such as S. Comas et al., in which it is shown T2-Flair MRI sequence role in order to evaluate response, especially in neoadjuvant treatment.²¹

4.6. Prognostic scales

Various prognostic models have been developed to predict survival in patients newly diagnosed with HGG, above all, at the time of first-line treatment. Weller et al. evaluated the prognostic value of 11 molecular markers in patients treated with the Stupp scheme, reaching the conclusion that the only factor with prognostic significance was O-6-methylguanine-DNA methyltransferase (MGMT) gene methylation,²² which was associated with longer survival.²³ In glioblastomas a DNA test can be carried out to determine if the MGMT gene promoter is methylated or not: a prognosis of significantly longer survival is associated with MGMT gene promoter methylation HGG patients compared to those with an unmethylated MGMT gene promoter, because the former can benefit from a better response to TMZ treatment.²⁴

To improve prognostic predictions, these models have to be updated with data about HGG relapses. Thus Gorlia et al.

conducted a combined study on the EORTC trials which analysed HGG relapses with the aim of validating the existing clinical prognostic factors, identifying markers which might be useful as future predictive factors for OS and PFS. Three hundred relapsed HGG patients were recruited to eight phase-I and -II studies (carried out by the EORTIC tumour group), in which the patients' age, sex, clinical status (based on their performance status score), the presence of neurological deficits, the history of their disease, use of corticosteroid or anti-epileptic drugs, and the disease characteristics were measured. The analysis demonstrated that performance status, but not age, is a prognostic factor for OS and PFS in HGG relapses and that patients with large and multiple lesions are at a higher risk of death.²⁵

5. Conclusions

OS and PFS in HGG relapse after treatment with surgery and FSRT+BVZ is very limited. We believe that after a first-line response to BVZ+CPT11, another option might be to explore the other types of treatments which were initially excluded. Rescue treatment with FSRT+BVZ was well-tolerated in this series of patients and seems to increase the OS and PFS. This was a retrospective study in which the administration of FSRT+BVZ was assessed only in patients who had had a second-line response and those in whom a surgical option was again discarded; hence, the low number of patients included, and this bias may explain the differences between different patient series in different studies, meaning that a prospective multicentre study is necessary to address this issue. Tissue and serological markers associated with the response should be evaluated, as well as changes in the CAT-MRI perfusion pattern in order to search for the optimum timing for administration of relapse rescue treatment in HGG relapse patients.

Conflict of interest

None declared.

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