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Glioblastoma Re-Irradiation: Impact of Concomitant Bevacizumab - Retrospective Series of 61 Cases

Research Article

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Abstract

Purpose: Glioblastoma is the most common primary brain tumor with a poor prognosis. Although the standard of initial treatment is well defined, no recommendation exists in the relapse setting. This work focuses on the optimal strategy for recurrent glioblastoma.

Methods: We performed a retrospective monocentric analysis of all recurrent glioblastoma adult patients treated since 2000 in one neuro-oncology center by re-irradiation, alone or combined with chemotherapy and/or surgery at first or second relapse.

Results: Overall, 61 patients underwent a re-irradiation for glioblastoma relapse. Patient median age at diagnosis was 55 (27 to 76), 44% were women. At diagnosis, 77% underwent surgical resection and 23% were biopsied. Most of them (95%) received a Stupp regimen. After a median follow-up of 31.1 months, 44 patients (72%) had died and the median overall survival (mOS) was 39.8 months. Regardless of the time of treatment (first or second relapse), patients treated with radiation therapy concomitant to bevacizumab (RTbev, n=36) showed superior survival data compared to patients treated with radiation therapy alone (RTalone, n=17). At first relapse, median progression free survival (mPFS) of RTbev (n=19) was 9.9 versus 3.6 months for RTalone (n=6) (OR=3.98 (3.14-61.81); p=0.001). At second relapse, mPFS of RTbev (n=17) was 9.2 versus 5.4 months for RTalone (n=11) (OR=2.31 (1.18-7.75); p =0.03), and mOS of RTbev was 15.2 versus 9.1 months for RTalone (OR=3.60 (2.17-18.13); p=0.001).

Conclusion: This retrospective monocentric analysis reports a favorable impact of bevacizumab adjunction to re-irradiation. The high mOS may be due to patient selection, but emphasis the relevance of a multidisciplinary approach.

Keywords: Radiotherapy; Bevacizumab; Glioblastome; Recurrence; Neoplasm Mortality

Abbreviations: RTbev: Patient Treated with Radiation Therapy Concomitant to Bevacizumab; RTalone: Patient Treated with Radiation Therapy; mOS: Median Overall Survival; mPFS: Median Progression Free Survival; EGFR: Epidermal Growth Factor Receptor

Introduction

Glioblastoma is the most common malignant brain and central nervous system tumor and accounts for more than 60% of all gliomas [1,2]. It affects slightly more men than women and can occur at any age with a maximum incidence between 55 and 60 years of age [3,4]. This disease is responsible for aggressive clinical manifestations causing significant morbidity, handicap and short- to intermediate-term mortality. Since 2005, the standard of first line treatment is defined by maximal surgical resection followed by radiation therapy with concomitant and adjuvant temozolomide, according to Stupp regimen, resulting in 14.6 months of median overall survival (mOS) and about 10% of survival

rate after 5 years [5,6]. Furthermore, in spite of this treatment, most patients will relapse after a median progression free survival (mPFS) of 6.9 months [5,7].

In relapse setting, numerous treatment strategies have been studied over the past years such as surgery, radiation or systemic therapy [8]. A second surgery seems to give encouraging results in terms of survival rate and quality of life but is indicated in only 10 to 30% of relapsing patients [9-11]. A second irradiation is also a possible option despite the risk of post radiation necrosis [12]. Systemic therapy, either by chemotherapy, targeted or antiangiogenic agents such as bevacizumab is also an interesting option. The latter has been approved by the US Food and Drug Administration since 2009 in this indication [13] but not by the European authorities due to the lack of direct evidence of increased survival and the absence of comparison with an arm without bevacizumab. In addition, anti-angiogenic treatment targeting VEGF and radiation therapy could act synergistically and their combination would give better results in terms of tumor control. One of the hypotheses put forward would be that bevacizumab would allow transient normalization of uncontrolled tumor vascularization, by restoring the abnormal structure and function of tumor vessels to a more normal state. During this time called the "normalization window", there is a temporary increase in blood flow and therefore in tumor oxygenation, which is well known to increase DNA damage induced by radiation and thus radiation-induced death of tumor cells [14,15].

Unfortunately, in spite of all these encouraging recent results, none of these strategies have shown a superiority in terms of OS [8]. Thus, no standard second-line treatment has yet been determined. However, it seems essential to have a multidisciplinary discussion at each stage of patient management in order to choose the best therapeutic sequence. The objective of this work is to assess the impact of concomitant bevacizumab on the outcome of adult patients treated by re-irradiation for recurrent glioblastoma.

Material and Methods

Patients selection

We conducted a retrospective monocentric observational study from 2000 to 2018 in a single French expert center of neuro-oncology. During this period, all patients, treated at Gustave Roussy Cancer Campus by re-irradiation for a recurrent glioblastoma, alone or combined with chemotherapy and/or surgery, at first or second relapse, were included. Patients with histology other than glioblastoma were excluded.

Data collection

A search in the Gustave Roussy Cancer Campus intranet database by one physician with the key words "glioblastoma" and "re-irradiation" was performed. Information on each patient such as medical history, demographic status, clinical characteristics, therapeutic intervention and survival data were then collected and analysed. At diagnosis and at each new event, each patient file was discussed to the weekly multidisciplinary neuro-oncology tumor board, which included neuro-oncologists, radiation-oncologists, neuro-surgeons and neuro-radiologists. All medical decisions regarding treatment, initially or at relapse, were taken in accordance with current scientific data, the patient general condition, any contraindications to treatment and her or his willingness to follow the decision. A certain number of patients were present and seen right after the decision. Over the course of treatment or during the monitoring phases, patients were regularly followed-up by one of the expert neuro-oncologists at the Gustave Roussy Cancer Campus, both clinically and by brain imaging, to detect recurrent disease, progression or toxicity as early as possible. Every two to three months or according to clinical symptoms, magnetic resonance imaging were performed.

Patient management

The RTbev group was composed of all patients treated with radiation therapy concomitant to bevacizumab and without surgery (except for initial treatment) for their first or second recurrence. The group of patients treated by radiation therapy concomitant to bevacizumab at first recurrence represented the RTbev1 group and at second relapse, the RTbev2 group. Bevacizumab was delivered at the dose of 15mg/kg for 30 minutes every 3 weeks, concomitantly throughout the period of radiotherapy and then continued alone in maintenance until disease progression, unacceptable toxicity or patient's willingness.

All patients treated with radiation therapy alone for first or second recurrence and without surgery (except for initial treatment) composed the RTalone group. RTalone1 group was made of the patients treated with radiation therapy alone at first recurrence and RTalone2 group at second recurrence.

Evaluated outcomes

PFS1 was defined as the time between diagnosis and first recurrence, PFS2 between first and second recurrence and PFS3 between second and third recurrence. OS represented the time between diagnosis and date of last news, OS1 between first recurrence and date of last news, OS2 between recurrence 2 and date of last news and OS3 between third recurrence and date of last news. For each patient, the date of last news was defined as the date of mortality or the last clinic visit.

Statistical analysis

Descriptive statistics were calculated for all quantitative variables as medians with their respective interquartile ranges. Kaplan-Meier survival curves and crude log rank tests were calculated for all variables and association with OS and PFS were evaluated. All statistical analyses were two-tailed and a p value of less than 0.05 was considered as statistically significant. To perform these analyses, PrismGraphPad® was used.

Compliance with ethical standards

The ethics committee of Gustave Roussy Cancer Campus approved our study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the retrospective design of our study and in agreement with the ethics committee of Gustave Roussy Cancer Campus, no informed consent had to be obtained from any individual participants included in the study.

Results

Patient characteristics

A total of 284 patient files were screened and 61 were included in the final analysis. Reasons of exclusion (n=223) were missing data, no glioblastoma or no re-irradiation for salvage treatment (Figure 1).

Median age of the 61 patients was 55 years (range 27 to 76) and 48% were female. The most common tumor locations were temporal (39%) and frontal (31%). IDH mutation status was known for 21 (34.4%) and positive for 3 of them (14.3%). Five (8.2%) patients were tested for MGMT promoter methylation status and 4 (80.0%) of them were positive. The majority of the patients underwent initial surgery (77%), among them, 83% were considered radiologically complete. In contrast, 23% of patients were only biopsied. The totality were treated with adjuvant radiation therapy, either according to the Stupp regimen with concomitant and adjuvant temozolomide for most of them (95%), or with temozolomide plus Cilengitide (3%) or radiation therapy alone (2%). Median dose of radiation therapy was 60Gy (range 54 to 60) in 30 fractions (range 26 to 30) (Table 1).

Relapse management modalities

At first relapse, most of the patients were fit: 55 of them (90.2%) were ECOG performans status (PS) 0 or 1, 4 (6.6%) were ECOG PS 2 and none of them were above. PS is unknown for 2(3.3%) of them. The mPFS1 of the overall cohort was 14.7 months (range 3.2 to 73.1). At first recurrence, every patient underwent salvage therapy:

concomitant chemo-radiation therapy (n=20), chemotherapy alone (n=20), radiation therapy alone (n=6), surgery and chemotherapy (n=6), surgery and radiation therapy (n=5), surgery alone (n=3), or surgery, radiation therapy and chemotherapy (n=1). No patients received Cilengitide. The drugs received by the 20 patients treated with chemotherapy alone were bevacizumab in combination with another chemotherapy (n=14) or alone (n=1). The other 5 patients did not receive bevacizumab-based chemotherapy.

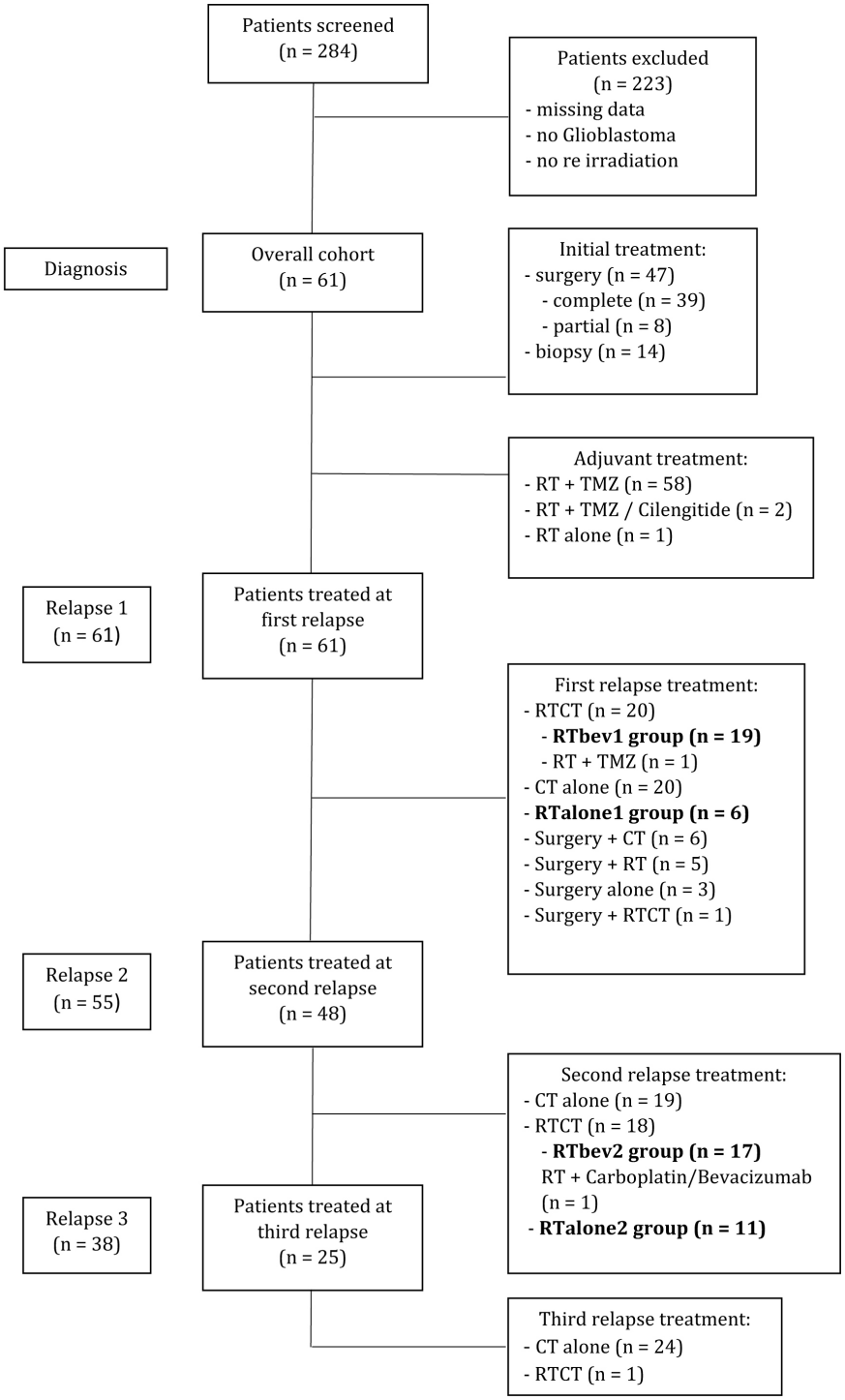

Figure 1: Flow chart.

Fifty-for of the 61 patients (89%) underwent a second recurrence. The mPFS2 of this cohort was 9.2 months (range 1.0 to 26.8). Among them, 48 (89%) received a second active salvage therapy: chemotherapy alone (n=19), radiation therapy and chemotherapy (n=18) or radiation therapy alone (n=11) among the ones who did not receive radiation therapy for the first relapse. None of them were operated for the second relapse and 6 (11%) only received best supportive care. In the group of patients treated with chemotherapy alone, bevacizumab was used alone (n=3) or in combination with another drug (n=2), 14 patients did not receive bevacizumab-based chemotherapy.

A third relapse was diagnosed in 38 patients with a mPFS3 of 6.0 months (range 0.2 to 20.6). Among them, 66% (n=25) received a third active salvage therapy based on chemotherapy for the majority (n=24) and radio-chemotherapy for the last one.

Overall, the median time between first and second irradiation (which could have been delivered at first or second relapse), was 18.0 months (range 4.6 to 84.0). The median total dose of radiation therapy delivered was 100Gy (range 80 to 120) with a median number of 40 fractions (range 33 to 63).

Table 1: Patients demographic characteristics and treatment modalities

Diagnosis	Median(range) or n(%)
Total	**61**
Age	55 years (27-76 years)
Gender	
Male	32(52%)
Female	29(48%)
Localization	
Temporal	24(39%)
Frontal	19(31%)
Parietal	9(15%)
Occipital	2(3%)
Multiple or unknown	7(11%)
First treatment	
Resection	
Surgery	47(77%)
Complete	39(83%)
Partial	8(17%)
Biopsy	14(23%)
Adjuvant radiotherapy	
With Temozolomide alone	58(95%)
Cycle	6(0-12)
With Temozolomide and other	2(3%)
Alone	1(2%)
Adjuvant radiation †	
Dose	60Gy (54 - 60)
Fraction	30(26-30)
First relapse	
Total	61
Treatment	61
Radiation † plus chemotherapy	20(33%)
Dose	40Gy (30 - 50)
Bevacizumab	19(95%)
Temozolomide	1(5%)
Chemotherapy alone	20(33%)
Radiation † alone	6(10%)
Dose	10Gy (5 - 15)
Surgery plus chemotherapy	6(10%)
Surgery plus radiation †	5(8%)
Dose	35Gy (30 - 40)
Surgery alone	3(5%)
Surgery plus chemotherapy plus radiation †	1(2%)
Second relapse	
Total	**55**
Treatment	48
Chemotherapy alone	19(40%)
Radiation † plus chemotherapy	18(38%)
Dose	40.5Gy (30-50)
Bevacizumab	17(94%)
Bevacizumab plus Carboplatine	1(6%)
Radiation † alone	11(23%)
Dose	40.5Gy (20-60)
Surgery alone	0
No treatment	6
Third relapse	
Total	38
Treatment	25
Chemotherapy alone	24(96%)
Radiation † plus chemotherapy	1(4%)

†Radiation: radiation therapy

Prognostic factors

After a median follow-up of 31.1 months, 44 patients (72%) had died consecutively to a relapse and 17 patients (28%) were still alive at the time of the analysis. The mOS of the overall cohort was 39.8 months (Figure 2). Tumor location was the only prognostic factor at diagnosis and surgery was the only at one first relapse. Indeed, patients with tumors of exclusive frontal location (n=19) at diagnosis had longer OS than patients with exclusive non-frontal tumors (n=42) (mOS: 54.0 months versus 36.0 months (p=0.0175). Moreover, at first relapse, patients treated with surgery alone or in combination with radiation therapy and/or chemotherapy (n=15), had a better survival than patients who didn't underwent a second surgery (n=46) regardless of the treatment, i. e. radiation therapy, chemotherapy or both (mOS: 28.4 months versus 16.8 months (p=0.045), mPFS1: 11.2 months versus 8.9 months (p=0.616)). However, we didn't identify prognostic factors at diagnosis among sex, age (with the cut off of 65 years) or surgery status (complete versus incomplete) and at the first relapse, other location than frontal or early versus late relapse with the cut off of 12 months or symptom (Table 2).

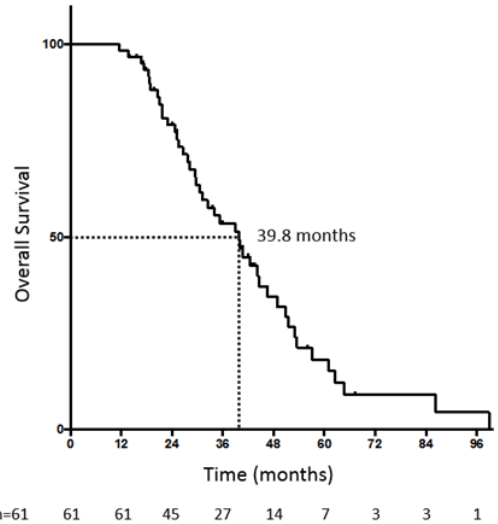

Figure 2: Overall survival.

Kaplan–Meier estimates of overall survival of the overall cohort. The dashed line indicates the median. The analysis was performed with the use of a log-rank.

Group of interest

Radiation therapy and concomitant bevacizumab: RTbev group.

Overall, 38 patients were treated with radiation therapy plus concomitant chemotherapy for the first or second relapse and without surgery (except for the initial treatment). RTbev group was composed of 36 patients, 1 patient was treated with concomitant temozolomide and the last one with bevacizumab plus carboplatin.

Table 2: Prognostic factors.

		PFS	p	OS	p
At diagnosis					
Gender			0.784		0.939
	Male	14.50		35.40	
	Female	14.70		40.70	
Age			0.856		0.350
	< 65 years	14.55		39.80	
	> 65 years	15.10		38.90	
Tumor Location			0.778		0.382
	Temporal	16.70		35.40	
	Frontal	14.95		44.50	
			0.6073		0.3942
	Temporal excl.	15.97		36.0	
	Non temporal excl.	14.60		45.0	
			0.3971		**0.0175**
	Frontal excl.	15.33		**54.0**	
	Non frontal excl.	14.63		**36.0**	
Surgery status			0.319		0.914
	Complete	15.00		40.10	
	Incomplete	13.98		34.00	
At first relapse					
Time to relapse			0.974		0.699
Early relapse	< 12 months	8.00		16.80	
Late relapse	> 12 months	10.60		18.80	
Symptoms			0.142		0.778
	Yes	9.90		16.80	
	No	9.00		18.30	
Surgery			0.616		**0.045**
	Yes	11.20		**28.40**	
	No	8.90		**16.80**	

excl. = exclusive. Crude log rank tests were calculated for all variables and association with OS and PFS were evaluated. A p value of less than 0.05 was considered as statistically significant.

Nineteen patients represented the RTbev1 group. Median radiation therapy dose at first relapse was 40Gy (range 30 to 50) with a median number of 10 fractions (range 6 to 20). The median number of bevacizumab cycles was 7 (range 1 to 21). Thirteen patients stopped chemotherapy because of progressive disease or death (68%), 3(16%) for toxicity (2 proteinuria, 1 for unknown reason) and the last 3 patients stopped bevacizumab after completing radiation therapy as planned by the multidisciplinary board.

Seventeen patients composed the RTbev2 group. Median radiation therapy dose at second relapse was 40.5Gy (range 30 to 50) with a median number of 15 fractions (range 5 to 33). The median number of bevacizumab cycle was 5 (range 2 to 18). Thirteen patients stopped chemotherapy for progression disease or death (76%), 3 stopped after complete radiation therapy as planned (18%) and the last one was followed in another center. None of them stopped because of toxicity.

Radiation therapy alone: RTalone group

Among the RTalone group (n=17), patients of the RTalone1 group (n=6) received a median dose of radiation therapy of 38Gy (range 30 to 45) in 10 fractions (5 to 15) and those of the RTalone2 group (n=11) received a median dose of radiation therapy of 40Gy (range 20 to 60) in 10 fractions (5 to 30).

As shown in Table 3, there were no statistical differences between the group RTbev and RTalone.

rtBEV group versus RTalone group outcomes

Regardless of the time of treatment, at first or second relapse, patients of the RTbev groups showed a superior OS and PFS compared to patients of the RTalone groups. Indeed, RTbev1 group showed a superior mPFS2 than RTalone1 (9.9 months versus 3.6 months (OR=3.98 (3.14-61.81); p=0.001)). The difference was not significant in terms of mOS1 (16.2 months versus 18.4 months; OR=1.09 (0.36-3.36); p=0.875)) (Figure 3). However, there was a significant superiority of RTbev2 group versus RTalone2 group in terms of mPFS3 (9.2 months versus 5.4 months (OR= 2.31 (1.18-7.75); p =0.029)), and for mOS2 (15.2 months versus 9.1 months (OR= 3.60 (2.17-18.13); p=0.001)) (Figure 3).

Therapeutic sequence

There was no significant difference in terms of OS or PFS between RTbev1 (n=19) and RTbev2 (n=17) groups: mPFS2 RTBev1 9.9 months versus mPFS3 RTbev2 9.2 months, p=0.5009, mOS RTbev1 16.2 months versus RTbev2 15.2 months, p=0.4168.

Long-term survivals

Interestingly enough and in line with the literature, 6 patients of our cohort, representing nearly 10% of the whole population, had a survival of more than 5 years, one of them still being alive at the time of the analysis. Nevertheless, it is impossible to extrapolate the role of a particular treatment in this sub-population in view of the heterogeneity of the therapies received as none of the 6 patients underwent the same treatment sequence at first and second relapse. In addition, two patients are "*extreme long-term survivors*" with a survival of 7.20 and 8.25 years.

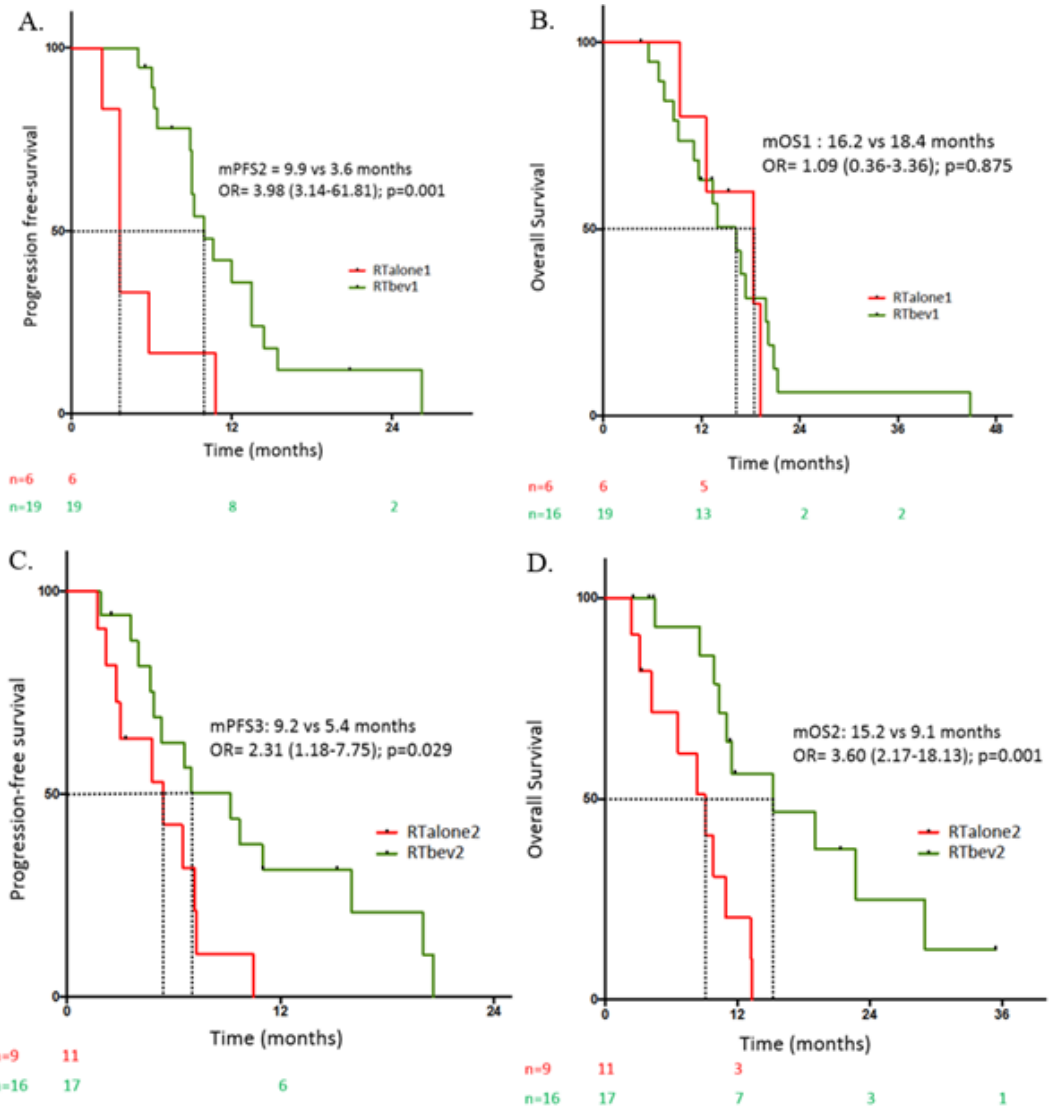

Figure 3: Overall Survival and Progression Free Survival of RTbev and RTalone groups.

Kaplan–Meier estimates survival of RTbev1 (n=19) versus RTalone1 (n=6) groups C. and D. RTbev2 (n=17) and RTalone2 (n=11). The dashed line indicates the median. The analysis was performed with the use of a log-rank. mPFS2 was defined as the median time between first and second relapse, mOS1 as the time between the first relapse and the latest news. mPFS3 was defined as the median time between second and third relapse, mOS2 as the time between the second relapse and the latest news.

Discussion

Despite a standardized first line of treatment, patients with glioblastoma eventually relapse, which explains the poor prognosis of this disease. To date, there are no clear recommendations for their management at first relapse and beyond (8). From our series and in accordance with the literature, surgery at relapse whenever possible seems beneficial [16,17]. In addition, combining bevacizumab with radiation therapy tends to provide better survival results than radiation therapy alone while maintaining a good tolerance.

Interestingly, we observe in this selected cohort, long mOS and mPFS1 for patients with glioblastoma (39.8 months and 14.6 months respectively), which is notably higher than the historical data from the Stupp et al study with less than 15 and 7 months for OS and PFS respectively [5]. Several points can explain such a difference. First, the patients in the Stupp cohort were patients with newly diagnosed glioblastoma, while the patients in our series were selected on the presence of a second irradiation during their treatment. Therefore, they correspond to a sub-population that has probably a better prognosis. Second, in Stupp trial, patients were included between August 2000 and March 2002, while we included the majority (93.4%) of our patients between 2011 and 2018. It is clear that between these two periods, overall care has improved. Indeed, the different treatment techniques, such as surgery or radiotherapy, as well as supportive care have greatly evolved, improving survival. Finally, we studied patients from a single expert center, while the recruitment of the patients in the Stupp study was done by 85 centers in 15 countries, not necessarily all experts in the management of glioblastoma. It is likely that in our center, beyond the first standardized line, decisions have been more favorable to aggressive management (new surgery and re-radiation in particular) of patients. These data are consistent with those of a similar study recently carried out in our center [18]. Nevertheless, in other similar studies, re-irradiation plus bevacizumab does not show this delta of benefit in survival in the same indication [19,20].

The feasibility of combining radiation therapy with bevacizumab in patients with recurrent glioblastoma has been reported in several studies and showed relatively good tolerance. Indeed, in the series of Cabrera et al. [18] no grade 4 or 5 adverse event was reported, the most severe toxicity being limited to one headache [19]. This is also the case for Schernberg et al who noted no toxicity of grade 3 or higher. Niyazi et al. [21] reported for their part, a single and debatable grade 4 toxicity (5%) for a wound dehiscence. The data in our series are consistent with the favorable safety pattern, with less than 10% of treatment stopped due to toxicity, mainly for proteinuria. As cure is rarely a reasonable aim facing a relapse of glioblastoma, maintaining a good quality of life is critical for patients.

Table 3: Comparison of the characteristics of the RTbev and RTalone groups.

Median (range) or n (%)			
Groups	**RTbev**	**RTalone**	**Log rank p**
Total	36	17	
Diagnosis			
Age	55(29 – 76)	60(27 – 69)	0.67
<65 years	28(78%)	13(76%)	0.92
>65 years	8(22%)	4(24%)	0.92
Sex			
Male	19(53%)	12(71%)	0.22
Female	17(47%)	5(29%)	0.22
Location			
Temporal	15(42%)	7(41%)	0.97
Frontal	12(33%)	5(29%)	0.78
Parietal	3(8%)	4(24%)	0.13
Occipital	1(3%)	0	0.49
Multiple or unknown	5(14%)	1(6%)	0.39
IDH			
Muted	2(6%)	1(6%)	0.96
Non muted	11(30%)	2(12%)	0.14
Unknown	23(64%)	14(82%)	0.17
MGMT			
Methylated	1(3%)	1(6%)	0.58
Non methylated	1(3%)	0	0.49
Unknown	34(94%)	16(94%)	0.96
Initial resection			
Surgery	25(69%)	14(82%)	0.32
Complete	21(84%)	10(71%)	0.97
Incomplete	4(16%)	4(29%)	0.24
Biopsy	11(31%)	3(18%)	0.32
Second radiation therapy			
Age	57(30 – 79)	63(28 – 72)	0.61
Performance status			
0	15(42%)	10(59%)	0.24
1	18(50%)	4(23%)	0.07
2 and more	2(5%)	2(12%)	0.42
Unknown	1(3%)	1(6%)	0.57
Radiation therapy dose (Gray)	40.5(30 – 50)	40(20 – 60)	0.14
Radiation therapy split	15(5 – 33)	10(5 – 30)	0.12
For line of treatment	**16(44%)**	**8(47%)**	**0.86**

Our series finds a superiority of the combination of radiation therapy with bevacizumab over radiotherapy alone. However, the combination at first or second recurrence seems to provide identical results in terms of OS and PFS. Given that glioblastoma is responsible for a rapid decline of patient general condition, it seems convenient to propose the combination as soon as possible rather than wait with the risk that the patient will no longer be able to receive the full treatment.

The relevance of this therapeutic combination is supported by a strong biological rationale. Indeed, where anti-angiogenic treatments targeting VEGF have been shown to be synergistic with radiotherapy in several tumor types [21-23], the mechanism of action of this synergy is still not fully understood. One of the identified mechanisms concerns intra-tumor cellular hypoxia due to the creation of non-functional neo-vessels, which represents one of the major factors of resistance to radiotherapy. Due to their action on VEGF, anti-angiogenic treatments would be responsible for a temporary normalization of intra-tumor vascularization by destroying immature neo-vessels and decreasing interstitial pressure. This would then allow a transient increase in oxygenation, called normalization window, responsible for improving the efficacy of acute radiotherapy [24,25]. Another hypothesis concerns the increase of cell death in the later phase by the stimulation of angiogenesis by radiation therapy, called vascular rebound effect [26]. Indeed, it has been shown that radiation therapy can also influence angiogenesis by inducing the expression of pro-angiogenic growth factors such as VEGF by cells in the tumor microenvironment. This results in an increase in tumor perfusion and therefore a reduction in hypoxia, mechanisms that are blocked by the anti-angiogenic agents, which explains the synergy of the two treatments.

Our study is limited by its monocentric and retrospective design. In addition, the limited data available on IDH and MGMT status makes this analysis uninterpretable, depriving us of information that could represent a confounding bias. The molecular testing has been used more intensively over the past few years but since our database includes patients from 2000, most of the old samples were not tested. As demonstrated in several studies, methylation of the MGMT gene promoter is an important prognostic factor of better response to temozolomide-based chemotherapy in glioblastoma. However, the efficacy of bevacizumab is not known to be related to the MGMT promoter methylation status and IDH mutation status.

As glioblastoma is responsible for a rapid decline of cognitive function and general condition, the study of disease at the stage of recurrence is difficult due to the small number of patients who are healthy enough to benefit from second- and third-line treatments. It should also be noted that the different therapies offered to patients at different stages of their disease (surgery, radiation therapy, chemotherapy, alone or in combination) increase the heterogeneity of the groups and sometimes make it difficult to analyze the data. Therefore, small groups of homogeneously treated patients tend to yield to uninterpretable data.

Despite these different limitations, the strength of our study is its relatively large cohort of homogeneously treated patients in the same center. Indeed, we restricted our analysis from the beginning of the 2000s in order to make the various radiation therapy techniques as homogeneous as possible and to avoid the biases related to constant technological improvements. This allowed us to form two interest groups (RTbev and RTalone groups) of sufficient size to highlight a statistically relevant difference. This is probably due to the long screening period (almost 20 years) as well as the absence of negative selection criteria: all patients treated by radiation therapy for recurrence glioblastoma at the Gustave Roussy Cancer Campus being included in our series. Finally, the median follow-up of 2.5 year, a relatively long time for a disease such as glioblastoma, allowed us to report a significant number of events (nearly 3/4 of patients died at the time of analysis).

Our series highlights a minority but interesting subpopulation of long-term survivors. Although the treatments patients received are too heterogeneous to be able to draw any conclusions about the role of any of them, the existence of histological or mutational features may be questioned. This point has been addressed by different teams, with interesting and sometimes contradictory emerging data. This is particularly the case for the IDH mutation, identified as a prognostic marker according to some [27] but not to others [28,29].

The methylation of the MGMT promoter appears, for its part, to be a strong candidate [28-30]. Michaelsen et al. [31] have highlighted the role of CD34 while according to Geisenberger et al. [32], co-gain of chromosomes 19 and 20 remains a significant prognostic factor. Identifying other prognostic factors of long survivors is an important issue in order to better adapt the treatments to be offered to patients.

Anti-angiogenic agents in glioblastoma are still controversial. In our center, bevacizumab is still prescribed in relapse setting, due to the lack of therapies in brain tumors. As about 50% of glioblastoma present an epidermal growth factor receptor (EGFR) amplification [33-35], a novel antiangiogenic agent, Depatuxizumab mafodontine (ABT-414), a humanized antibody (ABT-806) conjugated to a cytotoxin, monomethylauristatin-F has been investigated with positive results in relapse setting in combination with temozolomide [36-38]. However, the Phase 3 INTELLANCE 1 trial evaluating ABT-414 in newly diagnosed glioblastoma patients combined with the Stupp regimen failed to demonstrate efficacy. In addition, regorafenib, a multi-kinase inhibitor including those involved in the angiogenesis pathway (VEGFR1, 2 and 3), was recently tested in a Phase II trial in relapsed glioblastoma patients. In this study, patients treated with regorafenib demonstrated significantly better overall survival than patients in the control group treated with lomustine (7.4 versus 5.6 months respectively, HR 0.50, p=0.0009). All these results seem to position anti-angiogenic treatments in relapse situations in the treatment of glioblastoma and not as first-line treatment and perhaps more particularly in combination with re-irradiation. Therefore, it appear relevant that future glioblastoma trials should test anti-angiogenic treatments at the time of relapse after treatment according to the Stupp protocol and to test associations between this type of treatment and radiotherapy.

Finally, a major area of future research seems to be the relationship between anti-angiogenic treatment and the tumor microenvironment. Indeed, a number of studies have demonstrated a significant impact of the latter, particularly of the endothelium, on the regulation of immune mechanisms and the establishment of an immunosuppressive environment. Anti-angiogenic treatment could therefore represent a way to reactivate the failing immune system [21,39,40]. The combination of radiotherapy and Bevacizumab could then act as a booster of immune checkpoint inhibitors. Therefore, it seems interesting to us in the future to study this association in greater depth.

Overall, this retrospective study emphasizes the feasibility and relevance of combining radiation therapy with bevacizumab in patients with recurrent glioblastoma. Given the complexity of managing these patients, our work also reinforces the importance of a multidisciplinary approach in expert centers. However, it should be noted that the size of the cohorts of our study, although large enough to show a statistically significant difference, remains small (less than 20 patients per subgroup). The power of our study has therefore to be moderated. Based on this results, it could be considered as a gateway to other, more powerful and larger prospective studies studying the place of bevacizuamb associated to radiation therapy versus radiation therapy alone in this indication, when surgery is not feasible. In the era of immunotherapy and because of the close relationship between anti-angiogenic treatment and tumor microenvironment, it also seems interesting to focus future research on the combination of radiotherapy/anti-angiogenic treatment and immune checkpoint inhibitors.

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Disclosure of Potential Conflicts of Interest

All the authors declare that there is no conflict of interest.

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