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Multimodal treatment for local recurrent malignant gliomas: Resurgery and/or reirradiation followed by chemotherapy

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Abstract. The therapeutic management of recurrent malignant gliomas (MGs) is not determined. Therefore, the efficacy of a multimodal approach and a combination systemic therapy was investigated. A retrospective analysis of 26 MGs patients at first relapse treated with multimodal therapy (chemotherapy plus surgery and/or reirradiation) or chemotherapy alone was performed. Second-line chemotherapy consisted of fotemustine (FTM) in combination with bevacizumab (BEV) (cFTM/BEV) or followed by third-line BEV (sFTM/BEV). Subgroup analyses were performed. Multimodal therapy provided a higher overall response rate (ORR) (73 vs. 47%), disease control rate (DCR) (82 vs. 67%), median progression-free survival (mPFS) (11 vs. 7 months; P=0.08) and median overall survival (mOS) (13 vs. 8 months; P=0.04) compared with chemotherapy. Concomitant FTM/BEV resulted in higher ORR (84 vs. 36%), DCR (92 vs. 57%), mPFS (10 vs. 5 months; P=0.22) and mOS (11 vs. 5.2 months; P=0.15) compared with sFTM/BEV. Methylated patients did not experience additional survival benefits with multimodality treatment but had higher mPFS (10 vs 7.1 months; P=0.33) and mOS (11 vs. 8 months; P=0.33) with cFTM/BEV. Unmethylated patients experienced the greatest survival benefit with the multimodal approach (mPFS: 10 vs. 5 months; mOS 11 vs 6 months; both P=0.02) and cFTM/BEV (mPFS: 5 vs. 2 months; mOS 6 vs. 3.2 months; both P=0.01). In conclusion, in recurrent MGs, multimodal therapy and cFTM/BEV provide survival and response benefits. Methylated patients benefit from a cFTM/BEV but not from a multimodal approach. Notably, unmethylated patients had the highest survival benefit with the two strategies.

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Introduction

Malignant gliomas (MGs) are the most common primary malignant brain tumours and include anaplastic gliomas (AG) and glioblastoma multiforme (GBM) (1). Maximal safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide (TMZ) is the standard first-line treatment of GBM (2), leading to a median overall survival (mOS) of 12-15 months (3). Despite the optimal standard treatment, the local infield recurrence rate remains high (~90%), and despite the molecular advances, no standard therapies are established for recurrent MGs. Different options are under investigation, including resurgery, reirradiation and chemotherapy, as well as their combinations (3,4).

A recent review of the literature (5) showed a survival benefit and an improved functional status after resurgery followed by adjuvant treatments, with a higher OS in selected patients with favourable clinical and radiological characteristics at the time of recurrence. Preoperative Karnofsky Performance Status (KPS>70%) and age (<60 years) are important predictors of longer survival (5-7). Multiple studies have also demonstrated that a greater extent of resection is associated with better survival outcomes (8-10). However, prospective data are lacking to confirm resurgery as an independent predictor of survival (11,12).

Focal radiotherapy is a similarly controversial option due to the lack of prospective randomised trials and the risk of toxicity, regarding radionecrosis and neurocognitive impairment. Recent

advances in radiotherapy techniques, including stereotactic and hypofractionated treatments, allow for more precise treatment, sparing healthy surrounding tissue and reducing late toxicity (13). Younger age (<70 years) and good performance status (PS) (KPS>60%) are the most important predictors of longer survival for reirradiation (14). Multiple trials have studied the combination of radiotherapy and systemic therapy, such as bevacizumab (BEV) and TMZ (13,15,16). Proton-beam therapy (PBT), a type of radiation treatment, has the advantage over photon-therapy of sparing considerable volumes of previously irradiated healthy tissue (13,15). Survival and clinical benefits of PBT, alone or in association with chemotherapy, have been studied in newly diagnosed and recurrent MGs (17-20).

Many clinical trials on recurrent GBM studied the efficacy of single and/or combined chemotherapy agents, including nitrosoureas, and of targeted therapies, such as BEV, alone or associated with chemotherapy, with encouraging results (6,21,22). Nitrosoureas, mainly fotemustine (FTM) (23), have been employed either in monotherapy or in combination with other agents (21), including BEV, showing potential survival benefit (21,24-27).

Improved outcomes with a multimodality management of recurrent MGs have been reported in a few trials (28-30), but no standard treatment algorithm has been defined.

The aim of this study is to analyse the efficacy of the multimodal treatment as a combination of chemotherapy, as FTM and BEV in combination or in sequence, and resurgery and/or reirradiation, including PBT, in MGs patients at first recurrence.

Patients and methods

Study population. This study was conducted at the Department of Medical Oncology of Policlinico Umberto I of Rome and Latina, both of Sapienza University of Rome. The study was approved by the Institutional Review Board of Latina.

From August 2011 to August 2017, we retrospectively analysed recurrent MGs patients at first relapse treated with multimodal therapy as a combination of resurgery and/or reirradiation, including PBT, followed by chemotherapy or chemotherapy alone. All patients underwent first-line therapy with surgery followed by radio-chemotherapy according to Stupp protocol (2).

The initial diagnosis was established by magnetic resonance imaging (MRI) and histologically using WHO criteria (31). Diagnosis of recurrence was assessed by MRI in all patients and by histological examination when resurgery was performed. Clinical data included patients' characteristics, tumour characteristics and treatment information (Table I).

Treatment plan. At first recurrence, patients received either a multimodal therapy consisting of chemotherapy preceded by resurgery and/or reirradiation or chemotherapy alone. Resurgery consisted of maximal safe surgical resection. Reirradiation, including radiotherapy or PBT, was given prior to chemotherapy and after surgery. Reirradiation consisted of fractionated stereotactic radiotherapy (total dose of 60 Gy in 1.8 to 2.0 Gy fractions).

Chemotherapy consisted of FTM as second-line therapy in combination with BEV (concomitant FTM/BEV; cFTM/BEV) or as second-line therapy followed by third-line BEV (sequential FTM/BEV; sFTM/BEV).

The sequential treatment FTM, according to the Addeo schedule (23), consisted of an induction phase dose of 80 mg/mq every 2 weeks for 5 consecutive administrations followed by a 4-week rest period and a maintenance phase dose of 80 mg/mq every 4 weeks. BEV was administered at 10 mg/kg every 2 weeks, in off-label use. In patients who underwent resurgery, BEV commenced 4-6 weeks after surgery.

The cFTM/BEV therapy, according to the Soffietti schedule (24), consisted of an induction phase with BEV at 10 mg/kg on days 1 and 15 and FTM at 75 mg/mq on days 1 and 8, followed by a 3-week rest period and a maintenance phase with BEV at 10 mg/kg and FTM at 75 mg/mq every 3 weeks.

Response evaluation. Radiological evaluations consisted of 3-Tesla MRI scans (contrast-enhanced T1-weighted, T2/FLAIR-weighted, perfusion-weighted and diffusion-weighted scans and MR spectroscopy). MRI evaluations were made at baseline, between each treatment modality, after the first 2 cycles of BEV or after the induction phase of FTM and then after every two cycles of BEV or FTM in the maintenance phase. Evaluation response was assessed according to RANO criteria (32) as complete (CR) and partial (PR) response, stable (SD) and progression (PD) disease. Overall response rate (ORR) was defined as the sum of CR and PR and disease control rate (DCR) was defined as the sum of CR, PR and SD.

Statistical analysis. Survival analysis was conducted on the efficacy of multimodal therapy compared to chemotherapy alone in terms of median progression-free survival (mPFS) and OS (mOS) from diagnosis of recurrence disease and of cFTM/BEV versus sFTM/BEV in terms of mPFS and mOS from the start of chemotherapy. Median PFS and OS were estimated with a 95% confidence interval. Survival curves of PFS and OS were generated using the Kaplan-Meier method. Differences in PFS and OS were evaluated using the log-rank test (Mantel-Cox) for statistical significance, which was defined at the $P<0.05$ level (33).

Subgroup analyses according to treatment and O^6-methylguanine-DNA methyltransferase (MGMT) and isocitrate dehydrogenase 1 (IDH-1) status were performed. Other subgroup analyses according to surgery, radiotherapy and other biological markers were not possible to perform due to the low number of patients.

Toxicity evaluation. All adverse events were graded according to NCI-CTCAE, version 4.03 (34). Toxicity assessment was performed at each cycle or, if clinically indicated, at weekly intervals. Evaluation of quality of life was not performed due to the lack of questionnaires in clinical practice.

Results

Patient characteristics. Twenty-six MGs patients treated at first relapse with multimodal therapy or chemotherapy were included in the analysis. Patients' characteristics are summarised in Table I. The two treatment groups are balanced for demographic and clinical characteristics.

Table I. Patient characteristics and treatment at recurrence (n=26).

A, Patient characteristics at recurrence

Characteristics	n (%)
Sex	
Male	16 (62)
Female	10 (38)
Median age, years (range)	50 (26-67)
Karnofsky performance status	
Median (range)	80 (60-100)
90-100	9 (35)
70-80	16 (61)
60	1 (4)
Laterality	
Right	11 (42)
Left	15 (58)
Lobe	
Fronto-temporal	7 (27)
Parieto-temporal	5 (19)
Monolobar	13 (50)
Multilobar	1 (4)
Histotype	
Primary GBM	20 (77)
Secondary GBM	6 (23)
MGMT methylation status at diagnosis	
Methylated	16 (62)
Unmethylated	10 (38)
IDH-1 status at diagnosis	
Mutated	5 (19)
Non mutated	9 (36)
Unknown	12 (46)
First-line therapy	
Stupp protocol (RT/TMZ-TMZ)	26 (100)

B, Treatment at recurrence

Treatment	n (%)
Type of treatment at recurrence	
Multimodal therapy	11 (42)
Monotherapy	15 (58)
Surgery at recurrence	
Yes	7 (27)
No	19 (73)
Reirradiation at recurrence	
Yes	9 (35)
No	17 (65)
Type of reirradiation	
Photon-therapy	4 (15)
Proton-therapy	5 (19)
Chemotherapy at recurrence	
BEV + FTM	12 (46)
FTM → BEV	14 (54)

Table I. Continued.

B, Treatment at recurrence

Treatment	n (%)
No. of median cycles of chemotherapy received (range)	
BEV + FTM	8 (1-24)
FTM → BEV	5 (1-7)
FTM	
BEV	8 (2-40)

GBM, glioblastoma multiforme; MGMT, O6-methylguanine-DNA methyltransferase; IDH-1, isocitrate dehydrogenase 1; RT, radiotherapy; TMZ, temozolomide; BEV, bevacizumab; FTM, fotemustine.

Most patients were male (62%), median age was 50 years (range, 26-67 years) and median KPS was 80 (range, 60-100). All patients had a histological diagnosis of MGs (77% GBM and 23% grade-III gliomas). At first relapse all grade-III gliomas evolved into GBM (secondary GBM), a diagnosis that was made radiologically in 5 patients and histologically after resurgery in 1 patient.

The assessment of MGMT promoter status was conducted in all patients and resulted methylated in 16 patients (62%) and unmethylated in 10 patients (38%). The assessment of IDH status was conducted in 14 patients (54%) and resulted mutated in 5 patients (19%) and wild-type in 9 patients (35%).

Fifteen patients (58%) received chemotherapy alone and 11 patients (42%) received multimodal therapy. Of these, 2 patients (8%) underwent surgery followed by chemotherapy, 4 patients (15%) received reirradiation followed by chemotherapy and 5 patients (19%) underwent surgery followed by reirradiation and then chemotherapy. Twelve patients (46%) were treated with cFTM/BEV and 14 patients (54%) with sFTM/BEV.

Treatment response evaluation. All patients included in the study were assessable for response analysis (Table II). Multimodal therapy showed 1 vs. 0 CR (9 vs. 0%), 7 vs. 7 PR (64 vs. 47%) and 1 vs. 3 SD (9 vs. 20%) compared to chemotherapy alone. ORR and DCR of multimodal therapy were 73 and 82% compared to 47 and 67% with chemotherapy alone, respectively. Concomitant FTM/BEV resulted in 1 vs. 0 CR (8 vs. 0%), 9 vs. 5 PR (76 vs. 36%), 1 vs. 3 SD (8 vs. 21%) compared to sFTM/BEV. ORR and DCR of cFTM/BEV were of 84 and 92% respectively compared to 36 and 57% of sFTM/BEV.

General survival outcomes. All patients included in the study were assessable for survival analysis (Table II). Median PFS and OS from diagnosis of recurrence were 9 months (95% CI 6.5-11.5) and 11 months (95% CI 9.1-12.9) respectively, whereas mPFS and mOS from the start of chemotherapy were 7.1 months (95% CI 5.6-8.6) and 9.5 months (95% CI 5.1-13.9), respectively.

Table II. Results for objective response and survival outcomes according to type of approach and treatment.

Variables	Multimodal therapy (n=11)	Monotherapy (n=15)	Concomitant FTM/BEV (n=12)	Sequential FTM/BEV (n=14)
Objective response, n (%)				
CR	1 (9%)	0 (0%)	1 (8%)	0 (0%)
PR	7 (64%)	7 (47%)	9 (76%)	5 (36%)
SD	1 (9%)	3 (20%)	1 (8%)	3 (21%)
PD	2 (18%)	5 (33%)	1 (8%)	6 (43%)
ORR	73	47	84	36
DC	82	67	92	57
Survival data				
6 months-PFS, %	82	67	92	71
12 months-PFS, %	27	20	25	21
Median PFS, months	11	7	10	5
6 months-OS, %	91	73	83	50
12 months-OS, %	55	20	25	21
Median OS, months	13	8	11	5.2

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DC, disease control; FTM, fotemustine; BEV, bevacizumab; PFS, progression-free survival; OS, overall survival.

Survival outcomes according to treatment. Multimodal therapy reported better survival outcomes in terms of mPFS and mOS compared to chemotherapy alone. Median PFS was 11 months (95% CI 8-14) vs. 7 months (95% CI 4.2-9.8) (P=0.08) and mOS was 13 months (95% CI 11.2-14.8) vs. 8 months (95% CI 5.5-10.5) (P=0.04) (Fig. 1A and B). Concomitant FTM/BEV was associated with better survival outcomes in terms of mPFS of 10 months (95% CI 8.6-11.4) versus 5 months (95% CI 1-9) and mOS of 11 (95% CI 10.3-11.7) vs. 5.2 months (95% CI 1.7-8.7) compared to sFTM/BEV (P=0.22 and P=0.15, respectively) (Fig.1C and D).

Activity according to MGMT status. Methylated patients (n=16) experienced longer survival from the diagnosis of recurrence (both mPFS and mOS of 11 vs. 6 months; P=0.03 and P=0.05, respectively) and from the start of chemotherapy (mPFS: 8.2 vs. 3.8 months, P=0.11; mOS: 10.6 vs. 5 months, P=0.08), independently of the type of treatment. In methylated patients, multimodal treatment (n=8) was associated with similar mPFS (both 11 months) and mOS (12 vs. 11 months) compared to chemotherapy alone (n=8). Methylated patients experienced greater mPFS (10 vs. 7.1 months; P=0.33) and mOS (11 vs. 8 months; P=0.33) with cFTM/BEV (n=6) compared to sFTM/BEV (n=10) (Fig. 2A and B).

The greatest benefit was observed in unmethylated patients who experienced statistically significant longer survival with multimodal therapy and cFTM/BEV. Unmethylated patients experienced higher mPFS (10 vs. 5 months; P=0.02) and mOS (11 vs. 6 months; P=0.02) with multimodal therapy (n=3) compared to chemotherapy alone (n=7) and greater mPFS (5 vs. 2 months; P=0.01) and mOS (6 vs. 3.2 months; P=0.01) with cFTM/BEV (n=6) compared to sFTM/BEV (n=4) (Fig. 2C and D).

Toxicity evaluation. All patients were evaluated for safety. Concomitant FTM/BEV was well-tolerated with grade 1-2 myelotoxicities in 62 vs. 70% of patients, grade 3 myelotoxicity in 8 vs. 15% of patients and grade 1-2 hypertransaminasemia in 23 vs. 38% of patients compared to sFTM/BEV. Grade 1-2 fatigue was present in 30% of patients in both treatments. Grade 1-2 hypertension and proteinuria developed in 10 and 15% of patients in cFTM/BEV vs. 20% and 40% of patients in sFTM/BEV. No grade 4 adverse events were observed. None of the patients discontinued for toxicity.

Discussion

For recurrent MGs, different treatment strategies are available, such as resurgery, reirradiation and systemic chemotherapy, as well as their combinations, depending on clinical status, tumour location and extension and time interval since last treatment. Nonetheless, the optimal management of recurrent MGs has not yet been established, which represents a marked clinical challenge.

Local recurrence within 2 cm of the resection bed of the primary tumour is the most common pattern of failure. Therefore, local strategies such as surgical resection and/or radiotherapy in combination with systemic chemotherapy, in a multidisciplinary approach, may offer an advantage in local control and may improve survival outcomes.

Recent literature reviews and several retrospective studies suggest a survival benefit with reoperation at the time of recurrence. Favourable PS and extent of resection (gross total resection vs. partial surgery) are the main predictors of survival (5-10) and the addition of adjuvant treatments (chemotherapy and radiosurgery) prolongs survival (5,35,36).

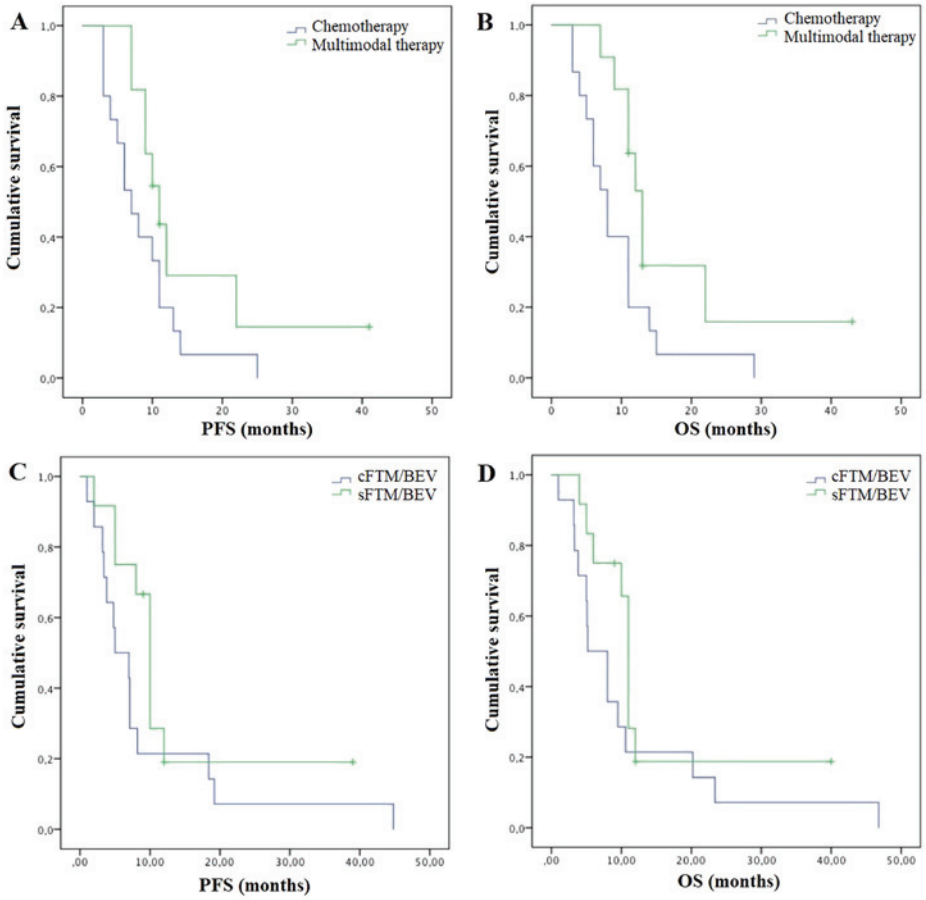

Figure 1. Survival outcomes according to treatment. Kaplan-Meier curves for (A) PFS and (B) OS in MGs patients treated with multimodal therapy compared to chemotherapy alone and for (C) PFS and (D) OS in MGs patients treated with concomitant FTM/BEV compared to sequential FTM/BEV. PFS, progression-free survival; OS, overall survival; MGs, malignant gliomas; FTM, fotemustine; BEV, bevacizumab.

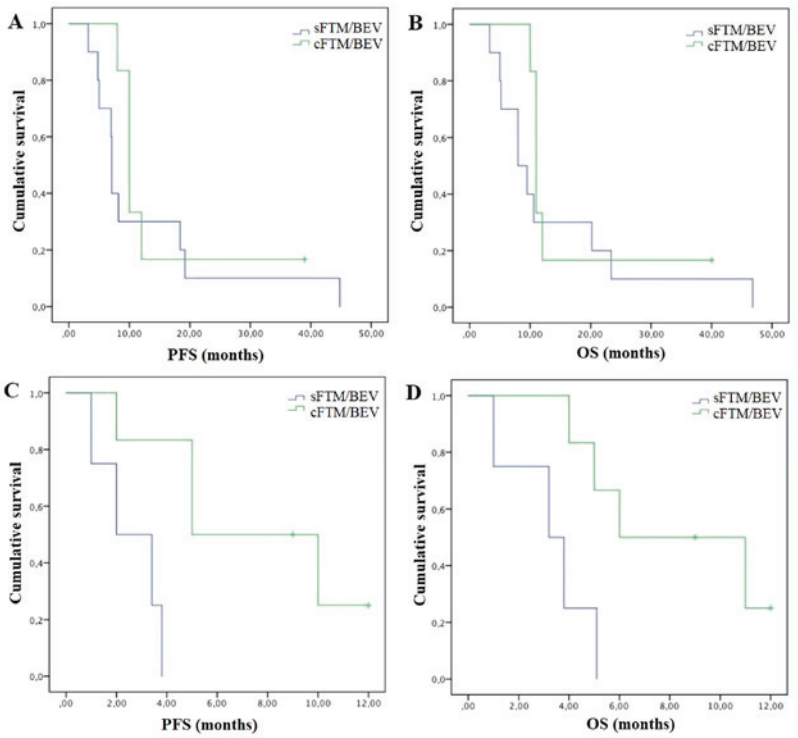

Figure 2. Survival outcomes according to MGMT-methylation. Kaplan-Meier curves for (A) PFS and (B) OS in methylated patients and for (C) PFS and (D) OS in non-methylated patients treated with concomitant FTM/BEV compared to sequential FTM/BEV. MGMT, O^6-methylguanine-DNA methyltransferase; PFS, progression-free survival; OS, overall survival; MGs, malignant gliomas; FTM, fotemustine; BEV, bevacizumab.

Table III. Clinical trials on concomitant FTM/BEV as second-line therapy in recurrent MGs.

Authors (years)	Type of study	No. of patients	Hystotype	RR (%)	DCR (%)	mPFS (months)	PFS-6 (%)	mPFS in patients (months)		mOS (months)	1-year OS (%)	mOS in patients (months)		(Refs.)
								Methylated	Unmethylated			Methylated	Unmethylated	
Soffietti *et al* (2012)	Prospective phase II study	32	Grade III gliomas	50.0	94.0	5.0	31.0	NA	NA	8.6	37.8	NA	NA	(24)
Soffietti *et al* (2014)	Prospective phase II study	54	GBM	52.0	89.0	5.2	42.6	NA	NA	9.1	29.7	NA	NA	(26)
Vaccaro *et al* (2014)	Observational prospective study	26	MGs (50% GBM)	31.0	92.5	4.0	23.1	NA	NA	6.0	20.5	NA	NA	(25)
Liu *et al* (2015)	Retrospective analysis	176	GBM	46.6	90.9	5.0	33.3	6	5	8.0	22.0	NA NA	NA NA	(27)
Present study	Retrospective analysis	12	MGs (77% GBM)	84.0	92.0	10.0	92.0	10	5	11.0	25.0	11	6	

MGs, malignant gliomas; GBM, glioblastoma mutiforme; RR, response rate; DCR, disease control rate; mPFS, median progression-free survival; PFS-6, progression-free survival at 6 months; mOS, median overall survival; NA, not available.

Table IV. Clinical trials on multimodal treatment as second-line therapy in recurrent MGs.

Authors (years)	Type of study	No. of patients	Hystotype	mPFS (months)	mPFS in methylated patients (months)	1-year PFS	mOS	mOS in methylated patients (months)	1-year OS	(Refs.)
Archavlis *et al* (2014)	Prospective study	17	GBM	7	NA	NA	7	NA	NA	(28)
Archavlis *et al* (2014)	Prospective study	66	GBM	7	NA	NA	8	NA	NA	(29)
Scorsetti *et al* (2015)	Retrospective study	21	GBM	15	NA	65%	17	NA	69%	(30)
Azoulay *et al* (2017)	Retrospective study	41	GBM	NA	NA	NA	10	NA	NA	(39)
Archavlis *et al* (2017)	Retrospective study	15	GBM	3	NA	NA	6	NA	NA	(46)
Present study	Retrospective study	11	MGs (77% GBM)	11	11	27%	13	12	55%	

MGs, malignant gliomas; GBM, glioblastoma mutiforme; RR, response rate; DCR, dsease control rate; mPFS, median progression-free survival; mOS, median overall survival; NA, not available.

Several trials suggest an improvement in survival and functional status with local reirradiation in younger patients with good PS, tumour size <4 cm and progression more than 6 months from first irradiation (14,37,38). Retrospective and prospective trials have investigated the benefits of reirradiation as adjuvant therapy after resurgery (36) or as part of a combined approach with chemotherapy (39). There is no consensus on one particular radiation regimen, but higher doses per fraction with modern precision radiotherapy (PBT, fractionated stereotactic radiotherapy or stereotactic radiosurgery), are associated with smaller recurrences and clinical efficacy with low toxicity rates. Systemic agents used as radiosensitizers in combination with radiotherapy are cytotoxic and targeted systemic agents, such as TMZ and BEV (38).

Systemic therapy, consisting of chemotherapeutic and anti-angiogenetic drugs, is the main treatment employed and investigated for recurrent gliomas as single agents or as combination regimens (21,30), but the optimal combination and sequencing have not yet been established. The most used drugs are rechallenge TMZ, nitrosoureas and BEV (40).

According to several systematic reviews and meta-analyses, BEV as a single agent and in combination with chemotherapy, both as first or second-line treatments, has been shown to be effective in terms of ORR, PFS and reducing symptoms, but not in terms of OS (5,41).

Interesting results were shown with the combination of BEV and nitrosoureas (41,42), such as lomustine and FTM. The BELOB phase II trial (42), the subsequent phase III trial EORTC-26101 (43) and two recent trials (44,45) showed that the combination BEV/lomustine at first recurrence was superior to BEV or lomustine monotherapy (41). Other interesting results were obtained by retrospective and prospective trials on the combination of BEV and FTM (24-27) (Table III). Soffietti et al. showed the efficacy of the association of BEV/FTM at first recurrence in recurrent grade-III gliomas (24) and GBM patients, in terms of survival outcome and response rate (26). Similar results were reported by a retrospective analysis conducted by Liu *et al* (27) and an observational prospective study by Vaccaro *et al* (25).

Several studies showed that the efficacy of systemic chemotherapy in terms of disease control and survival is improved by the combination with local treatments such as surgery and/or irradiation (28-30,39,46) (Table IV). In 2015 Scorsetti *et al* (30) evaluated 43 GBM patients treated by chemotherapy plus local treatment or chemotherapy alone, showing that the combined treatment achieved better survival results in terms of PFS (15 vs. 5 months) and OS (17 vs. 6 months).

Azoulay *et al* (39) conducted a retrospective study to assess the benefits of resurgery followed by chemotherapy and/or reirradiation compared to resurgery alone and chemotherapy and/or reirradiation. Median survival was superior in the multimodal treatment compared to the other treatment approaches (10 vs. 6.8 vs. 6.6 months).

Archavlis et al. showed in three clinical studies (28,29,46) that a combined therapy of resurgery, brachytherapy and chemotherapy achieved better survival outcomes compared to a historical control group of patients treated with TMZ.

We report our experience with the multimodal management of recurrent MGs, as the combination of resurgery and/or radiotherapy and chemotherapy, compared to chemotherapy alone. In regards to chemotherapy, we studied the efficacy of cFTM/BEV compared to sFTM/BEV, an idea born from the study of Piccioni *et al* (47), which demonstrated equal efficacy of BEV monotherapy on first, second or third recurrence in recurrent GBM.

We observed that multimodal therapy was associated with 25% higher response rates, 15% higher DCR and a survival improvement of 4 months in PFS and 5 months in OS compared to chemotherapy alone. Our results are in line with those reported by other retrospective and prospective trials on multimodal treatment (Table IV), showing the possibility of combining systemic chemotherapy with local treatment to improve local control of the disease and survival outcomes.

According to the type of chemotherapy, we observed ~50% higher response rates, 35% higher DCR and better survival outcomes with cFTM/BEV compared to sFTM/BEV. Our results seem to be stronger than those reported by other trials regarding cFTM/BEV (Table III), which was probably due to the addition of reirradiation, alone or after surgery.

Only recently, the DIRECTOR and the BELOB trials demonstrated the prognostic value of the MGMT methylation also in recurrent GBM (42,48,49). The AVAREG trial (50) demonstrated also that MGMT methylation status was predictive of efficacy of FTM in the recurrence setting. We observed an association between MGMT methylation and longer survival independent of the type of treatment. Methylated patients appear not to benefit from a multimodal approach, but a survival benefit was observed with the combination therapy compared to FTM alone, whereas unmethylated patients appear to benefit from both multimodal therapy and concomitant systemic therapy better than methylated patients. Subgroup analyses on MGMT methylation in this setting were not reported in other similar clinical trials (Table III-IV). Similar to the other trials on cFTM/BEV, the combination therapy was well-tolerated, with most frequent grade 3-4 toxicities related to chemotherapy.

The main limitations of this study are the low number of patients with small subgroups resulting in a lack of statistically significant results, the heterogeneity and non-standardisation in the therapeutic approach used, and the retrospective and non-randomised nature, resulting in possible selection biases for each treatment modality.

Despite these limitations our encouraging survival and local control results underlined that the management of recurrent MGs patients, especially those with a poorer survival such as unmethylated patients, should involve a multidisciplinary approach, associating local treatments (surgery and/or radiotherapy) to chemotherapy, or a combination of chemotherapies, whenever possible. Moreover, in this multimodal view of the treatment of MGs patients, molecular characteristics play a relevant role in the decision making to determine the best choice of treatment and the highest survival benefit possible.

Considering that no optimal treatment combinations and sequencing have been established, our results could be a starting point for further larger prospective studies.

In conclusion, our experience showed that in MG patients at first recurrence, multimodal treatment (chemotherapy plus surgery and/or radiotherapy) achieves better survival and response results compared to chemotherapy alone. Moreover, concomitant BEV/FTM provides higher survival benefit and

response rates, without adding higher toxicity, compared to the sequential approach. Better survival outcomes were observed in MGMT methylated patients but MGMT unmethylated patients have shown a greater survival benefit with both multimodal therapy and cFTM/BEV.

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Availability of data and materials

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

Authors' contributions

AP and SER were the major contributors in writing the manuscript, analysing and interpreting the patient data. MG, JRGB, SP and CF were involved in acquisition, analysis and interpretation of patient data. MS, ST, VB were involved in writing the manuscript and revising it critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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. Informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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