The Effect of Re-operation on Survival in Patients with Recurrent Glioblastoma

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Abstract. *Background: Treatment options for glioblastoma (GBM) at recurrence have limited efficacy. Re-surgery has been used for confirmation of recurrent disease and to provide relief of symptoms but the real impact on survival is unknown. Patients and Methods: A retrospective analysis was performed for GBM patients followed between 01/2005 and 06/2010 at our Institution. Results: Two hundred and thirty-two patients with recurrent GBM were evaluated. One hundred and two patients (44%) were treated with re-surgery followed by chemotherapy and 130 patients (56%) with chemotherapy alone. In multivariate analysis, no significant effect of re-surgery was found, with age (p=0.001), MGMT methylation (p=0.002) and PFS at 6 months (p=0.0001) being significant prognostic factors. Conclusion: Second surgery might have a limited impact in the clinical course of recurrent GBM patients.*

Glioblastoma (GBM) is the most frequent malignant tumor of the central nervous system (CNS) with an incidence of 4.8/100,000 cases per year (1). Surgical treatment followed by temozolomide (TMZ) concomitant with and adjuvant to radiotherapy (RT) is the cornerstone of treatment for newly-diagnosed GBM that allows for improvement in progression-free survival (PFS) and overall survival (OS). Nevertheless, despite optimal treatments, patients experience disease progression and median survival does not exceed 12-14 months with a 5-year survival rate of 10% (2, 3). The therapeutic options available at recurrence are scarce because the efficacy of chemotherapy is limited and neurologic deterioration is often severe and include systemic treatments with chemotherapy and/or bevacizumab and re-surgery.

Re-surgery is often used both for confirmation of recurrent disease and for debulking to provide symptoms relief; however, there is no evidence that re-surgery might increase survival. Since a randomized trial at recurrence comparing re-surgery versus chemotherapy is not feasible from an ethical standpoint, the only available data on second surgery derive from few retrospective studies (4-14).

Thus, in order to evaluate the impact of second surgery on the prognosis of patients with recurrent GBM, we performed a retrospective analysis on a cohort of GBM patients who were treated in our Center.

Patients and Methods

A retrospective analysis was performed on GBM patients treated between 01/2005 and 06/2010. Out of 1,006 screened patients, 232 were considered eligible (Figure 1). Eligibility criteria were: age ≥18; ECOG performance status (PS) 0-2; treatment at disease progression after RT/TMZ and data about second progression.

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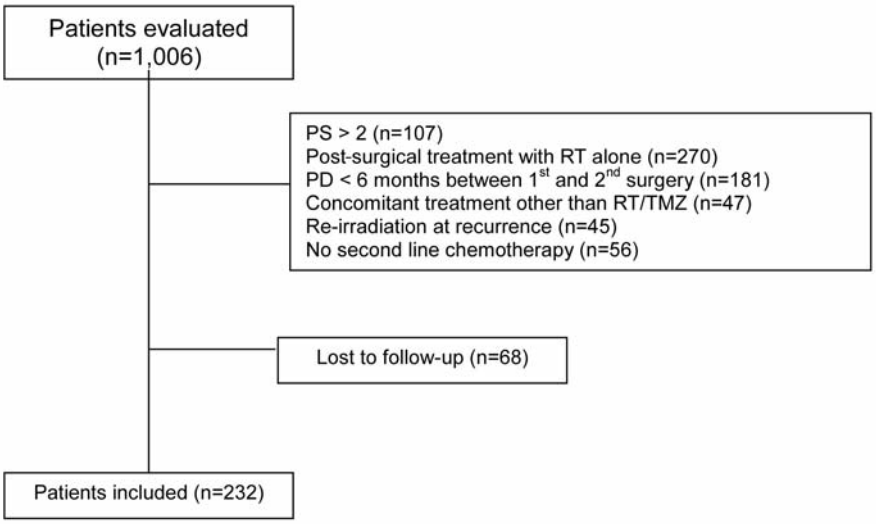

PS : Performance Status, RT : radiotherapy, PD : progressive disease, TMZ : temozolomide

Figure 1. *Patients' cohort*.

Moreover, patients were considered eligible if at least 6 months passed between 1st surgery and 1st progression.

End-points. Study end-points were OS and post-progression survival (PPS). OS was defined as the time from first diagnosis until death from any cause, while PPS was defined as time from first progression to death from any cause.

Response evaluation was based on MacDonald's criteria considering magnetic resonance imaging (MRI) measurements of contrast enhancing tumor size and recording the largest cross-sectional area of the tumor, patients' neurological status and corticosteroids' dose.

In case of lesion increase at first MRI after RT/TMZ, which may be due to potential pseudoprogressions, two more cycles were delivered followed by another MRI. After the MRI, these lesions were considered as pseudoprogressions if they were stable or had improved; otherwise they were recorded as progressive disease (PD).

Statistical analysis. Factors that were analyzed included: age, performance status, extent of resection, and MGMT methylation status

Univariate and multivariate analyses of OS and PPS for the chosen explanatory variables (age, PS, treatment characteristics and *MGMT* status) were performed using the Log rank test and the Cox proportional hazards regression model, respectively.

The extent of surgery was evaluated on the basis of the neurosurgical report. The Kaplan-Meier analysis was used to evaluate survival probabilities for OS and PPS. The significance level was set at $p<0.05$. All analyses were made using the SPSS software (Version 13.0, SPSS, Inc., Chicago, IL, USA).

Treatment. Patients with newly-diagnosed GBM received TMZ (75 mg/m^2/day) concurrent with RT at a dose of 60 Gy to the planned target volume in 30 fractions as primary treatment after surgery. Four weeks after completion of RT/TMZ, maintenance TMZ (150 to 200 mg/m^2 for 5 days every 28 days) was delivered up to 6 cycles. The dose was adjusted based on relevant blood tests. Treatment was suspended after 6 cycles only if the MRI showed no enhancement suggesting presence of tumor; otherwise, chemotherapy was delivered until complete response or clear disease progression. After recurrence, patients were treated with further chemotherapy or considered for surgery according to general conditions, extent and site of the recurrence. After surgery, all patients received further chemotherapy.

Histological evaluations. Evaluations were made on formalin-fixed, paraffin embedded tissues. Tumor tissue was classified and graded as GBM according to WHO 2007 guidelines. Diagnosis was based on conventional histological and immunohistochemical (IHC) procedures, including staining with haematoxylin and eosin, glial fibrillary acidic protein (GFAP) and p53.

The MGMT methylation status was evaluated with the methylation specific polymerase chain reaction (MSP) after a nested-polymerase chain reaction protocol. DNA from 10-μm paraffin sections of cerebral lesion was modified by sodium bisulfite, which converts unmethylated but not methylated cytosine to uracil, according to the procedure of Herman *et al*. (15).

Results

Patients' characteristics. Two hundreds and thirty-two patients with recurrent GBM were evaluated. Mean age was 52 years (range=18-77 years). The MGMT methylation status was determined on 165 patients (71%): 62 methylated (37.6%), 103 unmethylated (62.4%). At progression after RT/TMZ, 102 patients (44%) were treated with re-surgery

followed by chemotherapy and 130 patients (56%) with chemotherapy alone (Table I). Histology at the time of second surgery showed GBM in all the cases.

Overall survival. Median OS was 22.4 months (95% confidence interval (CI)=20-24.7). Univariate analysis evaluating age, PS, six-month progression-free survival (PFS-6), MGMT methylation, re-surgery, time between first and second surgery and type of chemotherapy for recurrent disease was performed. Median OS was 25.8 months (95%CI: 20.6-31) in patients who received second surgery at recurrence and 18.6 months (95%CI=17-20.1, p=0.003 – Table II) in patients who did not received re-surgery. However, a multivariate analysis showed that re-surgery did not affect survival (p=0.11), while age (p=0.001), *MGMT* methylation (p=0.002) and PFS-6 (p=0.0001) were significantly correlated with OS.

The median time between first and second surgery was 13.1 months, being significantly longer in patients with methylated *MGMT* than in patients with unmethylated MGMT (19.3 *vs*. 13 months, p=0.001).

Post-progression survival. Median PPS was 8.6 months (95%CI=7.4-9.8). In patients who received re-surgery, the median PPS was 9.6 months (95%CI=7.5-11.6), while in patients who did not receive re-surgery the median PPS was 7.5 months (95%CI=5.7-9.3, p=0.3 – Table II).

Table I. *Patients' characteristics*.

	Population (n=232)
MGMT methylation status	
Evaluable	165
Methylated	62 (37%)
Unmethylated	103 (62%)
Age	
Median (range)	52 (18-77)
Treatment at progression	
Re-surgery + Chemotherapy	102 (44%)
Chemotherapy	130 (66%)

Table II. *Median OS and PPS in patients who received or not re-surgery.*

	Re-surgery	No re-surgery	*p*
mOS (months)	25.8	18.6	0.003
mPPS (months)	9.6	7.5	0.3

mOS: Median overall survival, mPPS: median post-progression survival.

Discussion

Despite radical surgery and the efficacy of RT/TMZ, the vast majority of patients with GBM will experience disease progression or relapse during the course of the disease. Current treatment options include chemotherapy (such as lomustine (CCNU) (16), fotemustine (17), carboplatin-etoposide (18)), which allows obtaining objective responses; however, the impact on symptom control and survival is limited. Another promising agent is bevacizumab (19-21), which has been evaluated both in newly-diagnosed and recurrent GBM patients. While in newly-diagnosed GBM patients bevacizumab increases PFS but not OS (22, 23), in the recurrent setting, a recent randomized phase II trial (BELOB trial) (24), showed a median OS of 8 months for bevacizumab or CCNU alone and 12 months for the bevacizumab-CCNU combination. Therefore, this combination is under investigation in two phase III trials (EORTC 26101, NCT01290939; TAMIGA, NCT01860638).

It has long been debated whether surgery at recurrence could lead to a survival advantage in patients with recurrent GBM (26). The role of second surgery has been evaluated in few retrospective studies (Table III), the vast majority of which demonstrated no difference in survival between patients who received second surgery or not (5, 7, 8, 10, 11, 13, 14). A study by McGirt *et al*. (9) on 294 patients demonstrated an advantage in survival for those patients who underwent re-surgery with gross-total resection (GTR) or near-total resection (NTR) when compared to those who had small-total resection (STR) (11.9 *vs*. 5 months). GTR provided a 10% greater reduction of the risk of death than NTR, which provided a further 37% greater decrease that SRT. The authors concluded that an extensive resection could improve OS. In the present study, the accrual time went on for 10 years and patients enrolled had mixed histology (26% of grade 3 gliomas), while some of them (29%) had carmustine wafer implanted: these factors could have an impact on the outcome. Moreover, during the accrual time improvement of surgical techniques could have influenced the results. In another retrospective series of 76 recurrent GBM, De Bonis *et al*. (12) found an advantage in survival for patients undergoing re-operation and chemotherapy when compared to surgery alone, chemotherapy alone or no treatment. PS was an independent prognostic factor. Nevertheless, the small number of patients and the retrospective nature of the study limited the statistical power of the trial.

In a recent study by Michaelsen *et al*. (25), the authors performed an analysis of outcome according to the treatments at recurrence after standard therapy. The participating patients underwent surgery, therapy with bevacizumab + irinotecan (BEV/IRI), either treatments or none. Surgery and systemic therapy demonstrated better survival over no treatment. There was no difference between surgery + BEV/IRI or BEV/IRI

Table III. *Studies on surgical resection of recurrent GBM.*

Study by	Surgery (months)	No surgery	Post–surgical chemotherapy
McGirt (n=294)	~10 (Gross/near total) 5 (Partial/biopsy)	NA	yes
Clarke (n=247)	8	8	yes
Brandes (n=232)	10	8	yes
De Bonis (n=77)	14 (Surg→CT) 6 (Surg alone)	8 (with chemo) 5 (no chemo)	

alone. The combination of surgery and systemic treatment was superior to surgery alone.

In 2011, Clarke *et al*. (11) analyzed 758 patients with recurrent GBM, 208 of which underwent re-surgery at the time of disease progression. Patients who underwent surgery were compared with those who did not in terms of PFS-6 and OS. No difference was found between the surgical and nonsurgical groups, either for PFS and overall survival.

Gorlia *et al*. (14) made a pooled analysis of 300 patients enrolled in EORTC phase I/II trials for recurrent disease. In this study, 12% of patients underwent a re-surgery for recurrence but without a significant impact on survival (p=0.25).

The retrospective nature and the heterogeneity of populations are major limitations in these studies, which leave the questions about second surgery open. Nevertheless, these studies confirmed the role of PS and age as predictors of survival, as they resulted significantly associated with prognosis.

The majority of these studies found no advantage deriving from re-surgery. Few studies found an improvement of survival after re-operation but the advantage was often limited to a selected group of patients (*e.g*. patients with good PS or patients that could receive radical or near-radical surgery) (9, 12).

Our study is a large analysis on 232 patients with recurrent GBM who were treated in our Center. One hundred and two patients underwent re-surgery at the time of recurrence/progression. This study was set to determine the impact on survival of second surgery at recurrence and the weight of prognostic factors on the outcome of patients who undergo re-surgery. In accordance with the data reported by other authors, our study showed in multivariate analysis no benefit in terms of survival from second surgery in patients with recurrent GBM. It is a common idea that the patients who are selected for surgery (usually with local recurrences without bilateral disease of involvement of eloquent regions or the mid-brain and who were well enough to tolerate additional surgery) would have longer survival than their counterparts who were not selected for surgery. Despite the prolonged median survival in patients who underwent surgery (25.8 *vs*. 18.6 months), a multivariate analysis showed no impact of second surgery on survival (p=0.11). Prognostic factors that were related to improvement of survival were age, PS and *MGMT* methylation status.

Our series of patients showed a median OS that is longer than the survival commonly found in the literature. The patient population was influenced toward patients who would be expected to have better than average survival (good PS and over 6 months without evidence of progression). Moreover, to be enrolled, patients have to receive a second-line treatment. As a comparison, in the EORTC/NCIC CE.3 trial, only 57% of patients received a second-line treatment.

As re-operation does not appear to play a major role in increasing survival in general, it may be best used to determine a definitive diagnosis of tumor recurrence (vs. pseudoprogression) and to alleviate mass effect and symptoms in affected patients. Second surgery should be carefully evaluated, taking into account the characteristic of each patient, and could be an option for young patients with big tumor burden and compressive symptoms. The *MGMT* methylation status could be useful to select patients who are less likely to respond to chemotherapy, for whom surgery could be a therapeutic option. One of the major questions is represented by the selection of patients to propose for surgery rather than systemic treatments.

In 2013, Park *et al*. (26) proposed a 3-tier scale based on prognostic factors in order to determine the benefit of surgical management in recurrent GBM. Authors created a scale based on Karnofsky's performance score (KPS) and ependymal involvement distinguishing patients into three prognostic groups (good, with a median OS of 18 months; intermediate, with a median OS of 10 months; poor, with a median OS of 4 months). Authors concluded that patients with good prognosis could benefit from surgery, given longer life expectancy, while patients with intermediate prognosis would benefit from both surgery and adjuvant chemotherapy. On the other hand, surgery is not recommended for patients with poor prognostic score. These data were obtained in a small series of patients and need validation from perspective studies.

A more complicated scale was also suggested based on data of 34 patients who underwent re-operation of recurrent

GBM: tumor involvement of eloquent/critical brain regions (p=0.021), KPS <80 (p=0.030) and tumor volume ≥50 cm^3 were identified as factors associated with poor postoperative survival. Based on the combination of these factor the authors elaborated a preoperative scale that identified patients likely to have poor, intermediate and good relative outcomes after surgical resection of recurrent GBM (10).

In conclusion, our results are in accordance with many other studies present in literature. The role of second surgery in the treatment of recurrent GBM remains unclear and, at present, this therapeutic option could be carefully considered only for a selected subset of patients.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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