RESEARCH ARTICLE

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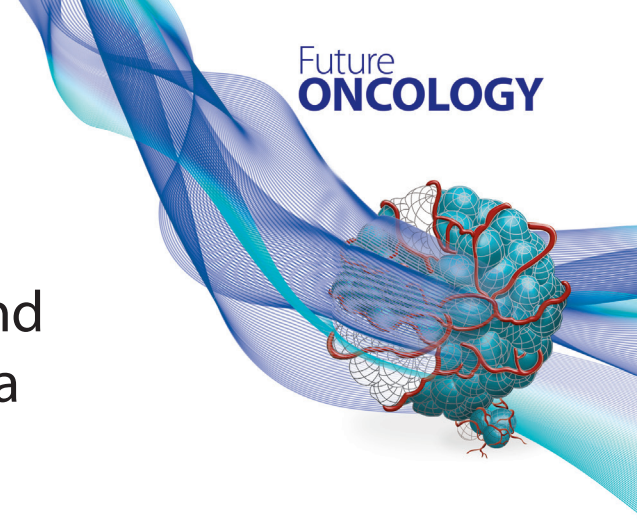

Patient outcomes following second surgery for recurrent glioblastoma

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Background: The most appropriate management of recurrent glioblastoma is still controversial. In particular, the role of surgery at recurrence remains uncertain. **Patients & methods:** From our Institutional data warehouse we analyzed 270 consecutive patients who received second surgery for recurrent glioblastoma, to assess survival after second surgery, and to evaluate prognostic factors. **Results:** Complete resection was found in 128 (47.4%) and partial resection in 142 patients (52.6%). Median survival from second surgery was 11.4 months (95% CI: 10.0–12.7). Multivariate analysis showed that age ($p = 0.001$), *MGMT* methylation ($p = 0.021$) and extent of surgery ($p < 0.001$) are associated with better survival. **Conclusion:** A complete resection should be the goal for second resection and younger age and *MGMT* methylation status might be considered in the selection of patients.

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KEYWORDS
• age • glioblastoma • *MGMT* • second surgery

Glioblastoma (GBM) is the most frequent malignant primary tumor of the CNS with an incidence of 4.8/100,000 cases per year [1]. Standard treatment for newly diagnosed GBM is represented by surgery followed by temozolomide (TMZ) concomitant with and adjuvant to radiotherapy (RT). Despite the improvement in overall survival (OS), most of the 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 at recurrence include systemic treatments, reirradiation and second surgery.

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The role of surgery at recurrence remains, to date, uncertain. Even though useful symptom relief, its benefit in terms of survival is not clear. Randomized trials comparing second surgery with chemotherapy at recurrence are not feasible from an ethical standpoint; for this reason data on the role of second surgery in GBM are lacking [4].

We performed an analysis on our institutional data warehouse evaluating all consecutive GBM patients who underwent second surgery for recurrence after standard treatment with radiotherapy and TMZ, in order to investigate the impact of second surgery and to evaluate prognostic factors for survival after second surgery.

Patients & methods

• Patients

From our institutional data warehouse 270 patients, who had been treated between June 2005 and June 2014 with the following eligibility criteria, were included: age ≥18 years, Eastern Cooperative Oncology Group performance status 0–2, previous treatment with TMZ concurrent with and adjuvant to radiotherapy after surgery and first disease recurrence after at least 3 months from completion of radiotherapy.

All patients underwent postoperative contrast CT scan within 48 h of surgery to determine the extent of tumor removal. The decision to repeat surgery was based on recommendations of an institutional interdisciplinary brain tumor board consisting of neurosurgeons, oncologists, neuroradiologists and radiation therapists. In general, criteria for second surgery were tumor location and acceptable clinical patient status (i.e., Karnofsky performance status [KPS] >60).

Based on postoperative CT scan the extent of resection for each patient was retrospectively classified by a neuroradiologist as complete (>90% resection by volume) or partial (≤90% resection by volume). The neuroradiologist was blinded to clinical information and outcomes.

A review of patient charts was conducted to obtain demographic information, including age, sex and surgical procedure description.

Histological evaluations were made on formalin-fixed, paraffin embedded tissues. Tumor tissue was classified and graded as GBM according to WHO 2007 guidelines.

The *MGMT* methylation status was evaluated with the methylation-specific PCR [5].

The study was approved by the institutional review board of the Azienda USL of Bologna, Italy.

• Objectives

The aim of this study was to assess survival after second surgery, defined as the time from surgery for recurrent GBM until death from any cause, and to evaluate potential prognostic factors.

• Statistical analysis

Data are reported as mean, range and frequency. Survival data (median survival times with 95% confidence interval) were computed by Kaplan–Meier procedure and were analyzed by Univariate and Backward Stepwise Multivariate Cox proportional hazards model. The hazard ratios (HRs) were computed together with their 95% CIs. *MGMT* methylation status, extent of first and second surgery, chemotherapy after second surgery, type of chemotherapy after second surgery, time between first and second surgery, gender and age were considered in univariate and multivariate analysis.

The SPSS (Version 13.0 for Windows; SPSS Inc., IL, USA) was used as a statistical package. Two-tailed p-values < 0.05 were considered significant.

Results

• Patients' characteristics

A total of 270 consecutive patients at first recurrence for GBM who underwent second surgery were evaluated. Histology at the time of second surgery confirmed GBM in all the cases. None of the patients was lost at follow-up.

Patients' characteristics are summarized in **Table 1**.

At time of first surgery *MGMT* was methylated and unmethylated in 46.0 and 54.0% of samples, respectively.

• Survival from first surgery

Median survival from first surgery was 27.6 months (95% CI: 25.0–30.3).

In univariate analysis, survival was significantly correlated with age ($p < 0.001$; HR: 1.023; 95% CI: 1.011–1.034), *MGMT* methylation ($p < 0.001$; HR: 0.505; 95% CI: 0.358–0.711), and time between first and second surgery ($p < 0.001$, HR: 0.958, 95% CI: 0.948–0.968). Multivariate analysis confirmed the role of age ($p = 0.006$; HR: 1.017; 95% CI: 1.005–1.030), *MGMT* methylation ($p < 0.001$; HR: 0.491; 95% CI: 0.346–0.696) and time between first and second surgery ($p < 0.001$; HR: 0.363; 95% CI: 0.275–0.480).

• Survival from second surgery

Median survival from second surgery was 11.4 months (95% CI: 10.0–12.7). Age, *MGMT* methylation, extent of second resection and chemotherapy after second surgery **(Table 2)** were analyzed in order to evaluate their prognostic role. Univariate analysis showed a significant correlation between the extent of second surgery (gross total resection: 15.4 months [95% CI: 13.5–17.2]; partial resection: 9.0 months [95% CI: 8.5–9.6]; $p < 0.001$), *MGMT* methylation at first surgery (*MGMT* methylated: 13.8 months [95% CI: 11.5–16.0], *MGMT* unmethylated 10.0 months [95% CI: 9.2–10.8]; $p = 0.003$) and age (continuous variable, $p = 0.001$) for survival from second surgery. There was no difference according to the delivery of chemotherapy after second surgery and the type of chemotherapy used following second surgery (TMZ vs nitrosoureas vs experimental agents). In total, 49 patients (18%) did not receive chemotherapy after second surgery due to postsurgical complications (18 patients), medical decision due to previous toxicities (14 patients), patients refusal (nine patients), neurological deterioration (eight patients).

Multivariate analysis confirmed the correlation for extent of second surgery, *MGMT* methylation status and age **(Table 2)**.

Table 1. Patients' characteristics.

Characteristics	Value (n = 270)
Age, mean (range); years	50.7 (18–74)
Gender, n (%):	
– Males	178 (65.9)
– Females	92 (34.1)
Karnofsky performance status, median (range)	80 (70–100)
MGMT at first surgery, (n = 161), n (%):	
– Methylated	74 (46.0)
– Unmethylated	87 (54.0)
MGMT at second surgery (n = 119), n (%):	
– Methylated	55 (46.2)
– Unmethylated	64 (53.8)
Extent of second surgery (n = 270), n (%):	
– Partial	142 (52.6)
– Gross total resection	128 (47.4)
Type of chemotherapy after second surgery (n = 266), n (%):	
– None	49 (18.4)
– Temozolomide	91 (34.2)
– Nitrosoureas	72 (27.1)
– Other (bevacizumab or experiments agents)	54 (20.3)

Discussion

Current treatment options in recurrent GBM include chemotherapy (lomustine [6], fotemustine [7]) and bevacizumab [8–10], or reirradiation while the role of surgery at recurrence in GBM remains a topic of debate and to evaluate who are the best candidates is of utmost interest.

In the prospectively compiled database named Glioma Outcome Project, the toxicity of second surgery was analyzed. Perioperative complications occurred in 33% of patients, 18% of patients displayed a worsened neurological status, 10% of patients had seizures, intracranial bleeding and systemic infection both occurred in 4% of patients. Depression occurred in 20% of patients, and the perioperative mortality rate was 2.2% [11].

So far, trials that explored second surgery were nonrandomized series with selected population (patients with resectable tumor, with sufficient functional status to safely undergo two surgeries), with younger age [12–15], good performance status [13,16] and a long survival from the time of first surgical resection [14–16]. However, many of these trials had several limitations, such as considering together different histologies [13], referring to a population treated in the nineties [17], or receiving different treatments after first surgery [13–15,18], or avoiding to assess extent of surgical resection at recurrence [16,19], or including patients who received surgery early for pseudoprogression (with histological findings of necrosis without tumor) [18,19].

In a recent paper by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons (AANS/CNS) Joint Guidelines Committee, authors stated that the available data on the role of second surgery in recurrent GBM were lacking high levels of evidence, but the review of the relevant literature suggested that second surgery might add a survival advantage of about 8–9 months in selected patients without significantly increasing morbidity or mortality [4]. At age of 50 years or under, a KPS score of greater than 60 or 70 and the site of the tumor, appear to contribute to an improved outcome. However, these features usually identify the vast majority of patients that underwent second surgery.

In 2010, the NIH developed a prognostic preoperative scale based on patients who underwent reoperation for recurrent GBM. Tumor involvement of eloquent/critical brain regions, KPS ≤80 and tumor volume ≥50 cm^3 were identified as factors associated with poor postoperative survival. Combining all these

Table 2. Results of univariate and multivariate analysis for prognostic factors.

Characteristics	Univariate†				Multivariate†		
	Median survival (95% CI); months	*HR*	*95% CI*	*p-value*	*HR*	*95% CI*	*p-value*
Age	–	1.020	1.009–1.032	<0.001	1.020	1.008–1.033	0.001
MGMT status first surgery:		0.595	0.421–0.843	0.003	0.662	0.466–0.940	0.021
– Methylated	13.8 (11.5–16.0)						
– Unmethylated	10.0 (9.2–10.8)						
Time between first and second surgery (months)	–	0.995	0.986–1.003	0.210	–	–	–
Extent of second surgery:		0.428	0.327–0.559	<0.001	0.456	0.348–0.598	<0.001
– Total	15.4 (13.5–17.2)						
– Partial	9.0 (8.5–9.6)						
Chemotherapy after second surgery	–	0.833	0.582–1.193	0.320	–	–	–
Type of chemotherapy after second surgery	–	–	–	0.673	–	–	–

†Cox proportional hazards model.

factors, the authors elaborated a preoperative scale that identified patients likely to have poor (3 points, median survival: 1.0 month), intermediate (1–2 points, median survival: 4.5 months) and good (0 points, median survival: 10.8) outcomes after surgical resection [20]. More recently, Woernle *et al.* suggested that the implementation of age might improve the prognostic power of the NIH scale [14]. In 2013, another preoperative scale was proposed by Park *et al.* [21] based on KPS and ependymal involvement.

However, these scales are not tested in a series of patients treated with chemotherapy alone and the prognosis of reoperated patients could be determined by these prognostic factors instead of undergoing second surgery.

Our study represents a large cohort of patients with defined inclusion criteria, who received second surgery for recurrent GBM after TMZ and radiotherapy, where pseudoprogressions were excluded (an increase in T1 contrast imaging was considered a disease progression only after 3 or more months from radiotherapy completion), where the extent of resection was assessed and *MGMT* status was assessed.

Due to the patients selection, patients in our study were young (mean age: 51 years), with high percentage of *MGMT* methylated tumors (45%) and achieved a long overall survival (27.6 months) with median survival from second surgery of 11.4 months.

These data are similar to those obtained with chemotherapy or bevacizumab [6–7,10,22] without second surgery, as showed by EORTC Brain Tumor Group and North American Brain Tumor Consortium (NABTC), where undergoing surgery for recurrence did not significantly impact survival [23,24].

As surgical treatment for newly diagnosed GBM [25], and also the extent of resection at recurrence might have a role [26], we obtained a median survival after second surgery of 15.4 and 9.0 in patients with complete or partial resection, respectively. If complete resection, which could be achieved in about 40% of patients, could be superior to the best systemic treatment it is still matter of debate. Moreover, we confirmed the prognostic value of *MGMT* methylation that was an independent predictor of survival both from time of initial surgery and from time of recurrence, while we were not able to find a significant role for KPS at time of second surgery.

We checked the data on the role of chemotherapy. However, due to the limited number of patients who did not receive chemotherapy after second resection (only 18%) we cannot draw any answer.

Conclusion

In conclusion, our study reports the outcome of a large series of consecutive patients with recurrent GBM that received second resection at recurrence. With the limitation of patients' selection, which is intrinsic in a study on second surgery for recurrent GBM, we showed that achieving a complete/gross total resection could provide a median survival of approximately 15 months. *MGMT* methylation and age might also be useful prognostic factors to identify patients with longer postoperative survival after second surgery

Future perspective

Improvements in neurosurgery (i.e., use of 5-amino levulinic acid fluorescence, or intraoperative MRI) might improve the resection rate of

recurrent GBM. Moreover, the refinement and application of prognostic preoperative scales will be crucial in selecting patients for second surgery.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

- The role of surgery at recurrence remains, to date, uncertain.
- We evaluated 270 patients at first recurrence for glioblastoma who underwent second surgery.
- Median survival from second surgery was 11.4 months (95% CI: 10.0–12.7).
- In multivariate analysis survival from second surgery was correlated with extent of surgery, *MGMT* methylation and age.

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