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Technical Notes & Surgical Techniques

Recurrent glioblastomas: Should we operate a second and even a third time?

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A B S T R A C T

Objectives: The aim of this study was i) to analyse the effect of repeat surgeries on the survival of patients with focally recurrent glioblastoma who have benefited from temozolomide treatment and ii) to identify potential prognostic factors for survival.
Patients and methods: Cases from 2005 to 2014 in the glioblastoma database of our department were retrospectively reviewed. The Kaplan-Meier method was used to estimate overall survival (OS) as a function of time after one, two and three surgical resections. All patients received the standard of care after the first surgery (temozolomide during and after radiotherapy) and adjuvant treatment after repeat surgeries.
Results: One hundred-thirty-two glioblastoma patients (median age: 57 years) were included in the study. Among them, 68, 53 and 11 patients underwent one, two and three surgical resections, respectively. The median OS was 11, 16 and 18 months, respectively, for patients who underwent one, two and three surgical resections. Patients who underwent two ($p < 0.001$) or three ($p < 0.01$) surgeries survived significantly longer than patients who underwent only one. No significant difference was observed between patients who underwent two versus three surgeries ($p = 0.76$). A second resection performed > 6 months after the initial resection was the only factor associated with prolonged survival ($p = 0.008$).
Conclusion: Glioblastoma patients who benefited from temozolomide treatment and underwent surgery for recurrent glioblastoma exhibited a significant increase in survival compared with patients who did not undergo a second surgery. By contrast, a third surgery for a second recurrence did not contribute to any significant survival benefit.

1. Introduction

Glioblastoma remains a devastating disease. In 2005, the current standard of care for newly diagnosed glioblastoma was established based on the trial of the European Organization for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), which demonstrated a prolonged median overall survival of 14.6 months by the addition of temozolomide (TMZ) during and after radiotherapy compared with radiotherapy alone (12.1 months) [1]. In 2017, the European Association for NeuroOncology published guidelines for the treatment of malignant gliomas [2]. Multiple retrospective studies have demonstrated that a more extensive surgical resection of the enhancing tumour component of the disease is associated with a longer survival [3–7]. In selected cases, the removal of tumour-infiltrated tissue outside of the tumour bulk is associated with an additional survival benefit [8].

However, malignant gliomas including glioblastomas are infiltrating tumours, and an actual complete surgical resection is difficult. Moreover, the remaining glioblastoma cells that migrate after debulking are resistant to conventional treatments [9]. Otherwise, the recurrent tumour may arise from both infiltrating tumour cells and from an interaction and recruitment of apparently normal cells in the peritumoural tissue by infiltrating tumour cells [10].

Glioblastoma recurrence occurs in almost all patients. Currently, no standard of care is established for recurrent or progressive glioblastoma [2,11], and the role of repeat surgery in patients with progressive or recurrent glioblastoma remains controversial. Some retrospective studies have proposed a survival benefit after reoperation [12–17] while others have not [18–20]. To our knowledge, the site of a third surgery for a second recurrence is rarely discussed. The aim of this study was i) to analyse the effect of repeat surgeries on the survival of patients with focally recurrent glioblastoma who benefited from temozolomide treatment and who received adjuvant treatment after new surgeries, and ii) to identify potential prognostic factors for survival in this specific glioblastoma population.

2. Patients and methods

2.1. Patients

The cases in the glioblastoma database of our neurosurgical department (Erasme Hospital/Brussels, Belgium) were retrospectively

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reviewed. In all, 211 consecutive patients were treated for glioblastoma according to the Stupp protocol [1] between 2005 and 2014.

Patients who were lost to follow-up or who had missing data were excluded from the study. This study was approved by the local ethical committee review board (Ref: P2017/159).

For each patient, the following data were collected: sex, age at diagnosis, tumour location, extent of resection (EOR) on early postoperative magnetic resonance imaging (MRI) (classified as gross-total (GTR)/subtotal resection (STR), partial resection (PR) or biopsy), functional status prior each surgery (assessed using the Karnofsky Performance Status (KPS)), postoperative complications, histopathological characteristics (isocitrate dehydrogenase (IDH) status, O(6)-methylguanine methyltransferase (MGMT) methylation status), adjuvant therapies after repeat surgeries, follow-up data, indication for reoperation, date of surgeries, time interval between the surgeries and overall survival (OS). Definition of tumour recurrence was made using the criteria suggested by the Response Assessment in Neuro-Oncology (RANO) Working Group. OS was defined as the time from first surgery to death. All patients received only the Stupp protocol before the second surgery.

2.2. Statistical analysis

Basic descriptive features of all patients were expressed as the median and interquartile range (IQR), and as frequencies. The Kaplan-Meier method was used to estimate the OS as a function of time, and survival curves were compared using the log-rank test. The Cox proportional-hazards model was used for multivariable analyses. Analyses were conducted using R statistical software. Statistical significance was accepted at $p < 0.05$.

3. Results

3.1. Demographics

Of the 211 patients assessed, 79 were excluded because of missing data or incomplete follow-up. As a result, 132 patients comprised the final study group. The patient demographics are summarized in Table 1.

The median age of the included patients was 57 years (*IQR* 50–65). Eighty-one patients were male (61%) and 51 were female (39%). Of the 132 patients, 68, 53 and 11 patients underwent one, two and three resections, respectively. The median age was 61 years (*IQR* 53–69), 56 years (*IQR* 49–65), and 52 years (*IQR* 43–55) at the first, second and third surgeries, respectively.

The mean preoperative KPS score was 70 for patients with one resection. The mean preoperative KPS was also 70 for patients who underwent two resections at both the first and the second surgeries. In patients with three resections, the mean preoperative KPS was 80 at the first, second and third surgeries. Postoperative complications were observed in 19 of the 132 patients (14%) after the first surgery, in 20 patients (31%) after the second surgery, and in one of 11 patients after the third surgery. STR to GTR was achieved in 45/68 patients with one resection (66%). PR was achieved in 15/68 patients (22%), and biopsy was performed in 8/68 (12%). Among patients who had two surgeries, GTR or STR was achieved in 81% of patients and PR was achieved in 19%. Among patients who had a third surgery, GTR or STR was achieved in 64% of patients (7/11) and PR was achieved in 36% (4/11). The indications for a second surgery were progression on MRI (using RANO criteria) in 28 patients and neurological symptoms (focal neurological deficit, seizure or intracranial hypertension) with radiological progression in 25 patients. Six patients underwent a third surgical resection driven by a radiological progression on MRI, while for 5 others, a third resection was performed due to radiological progression with neurological deficits.

Fifty-seven patients (59%) received second-line chemotherapy (lomustin and/or bevacizumab) after the second surgery and re-irradiation was never performed. By contrast, only 5 patients (95%) received chemotherapy after the third surgery because of rapid tumour progression.

Table 1
Patients' characteristics.

	Patients $N = 132$	One resection $N = 68$	Two resections $N = 53$	Three resections $N = 11$
Age (years) range (IQR)	57 (50–65)	61 (53–69)	56 (49–65)	52 (43–55)
Sex, *N* (%)				
Man	83 (62)	44 (64)	31 (58)	8 (71)
Women	64 (49)	24 (36)	22 (42)	3 (29)
Preoperative KPS	70	70	70	80
Extent of resection: *n* (%)				
Biopsy	8 (6)	8 (11)	0 (0)	0 (0)
Partial	36 (27)	15 (22)	10 (18)	4 (36)
Subtotal/total	88 (66)	45 (66)	43 (81)	7 (63)
Reoperation > 6 months, *n* (%)			36 (67)	7 (63)
IDH 1				
Muted	2			
Unmuted	51			
Unknown	79			
MGMT				
Methylated	32			
Unmethylated	18			
Unknown	82			

IDH-1 status was known in 53 patients (40%), and of these, 2 patients had an IDH-1 mutation. MGMT promoter methylation status was known in 50 patients (38%). MGMT was methylated in 32 patients (24%) and unmethylated in 18 patients (14%). The median interval between the first and second surgeries was 7 months (*IQR* 3–13.5), while the median interval between the second and third surgeries was 3 months (*IQR* 2–8).

3.2. Outcome

The median OS was 11, 16 and 18 months for patients who underwent one, two and three resections, respectively. Patients who had two surgeries survived significantly longer than patients who had one surgery ($p < 0.001$). Patients who had three surgeries also survived significantly longer than patients who had one surgery. However, patients who underwent a third surgery constitute a negligible group, therefore, statistical analyses for these patients are not applicable. Survival curves plotted according to the Kaplan-Meier method are shown in Fig. 1.

According to a multivariable Cox regression analysis, no statistically significant difference was observed in survival between patients who underwent three resections and patients who underwent two resections (hazard ratio 0.67; 95% CI 0.32–1.39; $p = 0.282$). KPS, EOR and the postoperative complication rate were not associated with survival. Information on IDH and MGMT methylation status cannot be used for statistical analyses since this information was missing for about 80 patients. A second resection performed > 6 months after the initial resection was the only factor associated with prolonged survival (hazard ratio 0.44; 95% CI 0.24–0.81; $p = 0.008$).

4. Discussion

Due to their spatial and temporal heterogeneity and their ability to infiltrate the surrounding brain tissue, the management of recurrent glioblastomas is challenging [11,21]. Numerous recent clinical trials using second-line chemotherapy [22] and new molecular drugs [23–25] including immunotherapy [26] have failed to improve survival.

Early retrospective studies in the pre-TMZ era have shown survival

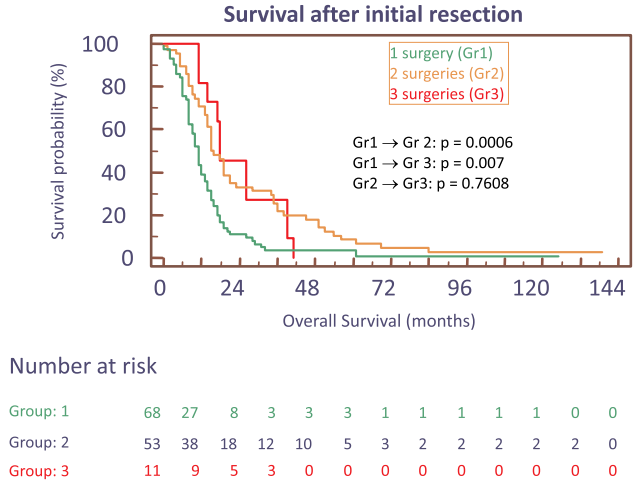

Fig. 1. Kaplan-Meier curves comparing overall survival between the reoperation and non-reoperation groups.

benefits from repeat surgeries in a small cohort of young glioblastoma patients with generally favourable KPS [27–30]. Similarly, Helseth et al. examined the effect of repeat surgery on survival in a retrospective analysis of 516 patients with glioblastoma. Sixty-five patients were subjected to repeat surgery for recurrent tumours and exhibited prolonged survival compared with patients who underwent only one resection (18.4 months 8.6 months). Their rate of repeat surgery for glioblastoma was 13%, and the main indications for a second surgery were increased intracranial pressure and increasing neurological deficits [31].

The National Comprehensive Cancer Network (NCCN 2016) guidelines indicate that a second surgery can be considered for local recurrence with level 2A evidence, but a consensus on how to select patients has not been established [32]. The only other specific recommendation is the Canadian Glioblastoma Recommendation Committee's position on second surgery, which states that with the lack of level I evidence, the impact of surgery on a patient's quality of life must be considered [33]. The limitations of most of the studies include a high probability of selection bias and a lack of reasonable controls for comparison [16].

In our retrospective study based on 132 glioblastoma patients, we show that patients receiving the Stupp treatment and who underwent surgery for recurrent glioblastoma ($n = 53 + 11$) exhibited a significant increase in survival compared with patients who did not undergo a second surgery (=68); this is in agreement with other published studies. Our rate of repeat surgery is 48%. We have to remark that from an initial database of 211 patients, we provide data on 132 cases: 37% of the patients were lost at follow-up. This could alter the results adding to the fact that the volume and the expertise of the treatment center should be further investigated as a prognostic factor [34]. After a search of the PubMed and Ovid Medline databases, we found a study by Montemurro et al. [35] in which the literature published over the previous seven years was reviewed. Their final analysis included 28 studies and 2279 patients who underwent a second surgery. The median overall survival from diagnosis and the median survival from the time of the second surgery were 18.5 months and 9.7 months, respectively. These authors showed that the extent of resection at reoperation improves overall survival, even in patients with subtotal resection during the initial surgery, and that preoperative performance status and age are important predictors of a longer survival [35].

The results of a multicenter study that included 503 patients with recurrent glioblastomas who underwent surgical resection were published by Ringel et al. [36]. This study is the largest study to evaluate the effect of repeat surgery in the TMZ era, and the results support the view that surgery for recurrent glioblastoma prolongs patient survival [36]. The median survival of the patients was 25 months after the first resection and 11.9 months after the second resection.

In that study, in addition to their initial surgery and resection of a recurrent tumour, 82, 11 and 2 patients underwent a third, fourth and fifth resection, respectively, for recurrent/progressive tumours. After a second resection for recurrence/progression, the median survival after reoperation and the median overall survival after initial surgery was 10.0 months (95% CI: 6.4–12.5 mo) and 29.3 months (95% CI: 24.9 40.6 mo), respectively; after a third reoperation, these values were 9.0 months [95% CI: 4.0-not available (NA)] and 34.3 months (95% CI: 34.3-NA), respectively, and after a fourth reoperation, these values were 3.5 months (95% CI: 2.0-NA) and 26.4 months (95% CI: 24.7-NA), respectively [36].

In a retrospective assessment of patients treated between 1997 and 2007, Chaichana et al. [37] identified 354, 168, 41, and 15 patients who underwent 1, 2, 3, or 4 resections, respectively. According to a multivariable analysis, patients who underwent only 1 resection experienced a shortened survival (relative risk [RR] 3.400, 95% CI 2.423–4.774; $p < 0.0001$) compared with patients who underwent 2 (RR 0.688, 95% CI 0.525–0.898; $p = 0.0006$), 3 (RR 0.614, 95% CI 0.388–0.929; $p = 0.02$), and 4 (RR 0.600, 95% CI 0.238–0.853; $p = 0.01$) resections [37]. These results were verified in a case-control evaluation that controlled for age, neurological function, periventricular tumour location, extent of resection, and adjuvant therapy. Patients who underwent 1, 2, or 3 resections had a median survival of 4.5, 16.2, and 24.4 months, respectively ($p < 0.05$) [37]. Additionally, the risk of infections or iatrogenic deficits did not increase with repeat resections in this patient population ($p > 0.05$) [37]. By contrast, we show that a third surgery for a second recurrence did not contribute any significant survival benefit, which could be explained by the small size of our cohort.

Few prospective data sets on repeat surgery are available. A prospective registry study of 764 patients with glioblastoma who were analysed over a 7-year period (2004–2010) in which one third of the patients underwent another surgery at recurrence did not suggest a benefit of repeat surgery (HR 1.02) [19]. However, no detailed patient stratification for prognostic variables was available [19]. Similarly, in a meta-analysis of 8 prospective phase I and II trials comprising 300 patients with recurrent glioblastoma, repeat surgery was not an independent predictor of PFS and OS [20].

A scale was suggested to select patients with recurrent/progressive glioblastomas for repeat resection. This study showed relative benefits for patients with a KPS > 80 who underwent resection of recurrent tumours < 50 cm^3 in size in non-eloquent areas compared with patients who did not full fill these criteria. The scale was modified to a score comprising the KPS and ependymal involvement for decision-making regarding reoperation based on retrospective data [38].

In the study by Ringel et al. [36], the following parameters were found to significantly influence survival after a second surgery: preoperative and postoperative KPS, EOR of the first reoperation, and chemotherapy after the first reoperation. In a review of 107 patients, Bloch et al. showed that GTR at recurrence was a predictor of improved survival regardless of EOR at the first surgery [13]. Therefore, tumour volume might be a predictor of chemotherapy outcome in patients with recurrent glioblastomas.

In a recent study, seventy-one patients received surgery at first recurrence. Prognostic factors, including age, MGMT promoter methylation, and KPS, were balanced among patients who did and did not undergo reoperation [15]. The outcomes in patients who underwent surgery at recurrence versus those who did not were similar with respect to PFS after initial progression (2.0 mo vs 1.9 mo, $p = 0.360$) and post recurrence survival (11.4 mo vs 9.8 mo, $p = 0.633$) [19]. Among patients who underwent a second surgery, post-surgery imaging was available in 59 cases. In these patients, complete resection of contrast-enhancing tumour ($n = 40$) versus residual detection of contrast enhancement ($n = 19$) was associated with improved post recurrence

survival (12.9 mo [95% CI: 11.5–18.2] vs 6.5 mo [95% CI: 3.6–9.9], $p < 0.001$) and better quality of life [15]. Incomplete tumour resection was associated with inferior post recurrence survival compared with patients who did not undergo surgery (6.5 vs 9.8 mo, $p = 0.052$). The quality of life was similar in these 2 groups [15].

The retrospective study by Brandes et al. on 270 patients showed that MGMT methylation ($p = 0.021$) and EOR ($p < 0.001$) were associated with better survival [39]. A recent short series of 121 glioblastoma patients of whom 31 (25%) underwent reoperation revealed that the reoperation group had a mean and a median increase in overall survival of 10.5 and 16.3 months, respectively [40]. A Cox multivariable analysis revealed that age at reoperation, extent of resection > 95% and complete adjuvant therapy were correlated with a higher OS [40].

Lu et al. [41] plan to publish a systematic review and meta-analysis. However, in a previous study, the authors described 8 observational studies that reported prognostic hazard ratios in 10 cohorts. This meta-analysis on 1906 recurrent glioblastomas with 709 (37%) patients who underwent further repeat surgery at recurrence suggested that repeat surgery in selected patients conferred a significant prognostic advantage with respect to OS that was independent of other prognostic factors [41].

In our study, the KPS, EOR and postoperative complication rate were not associated with survival probably because the study sample is too small. We showed that a second resection performed > 6 months after the initial resection was the only factor associated with prolonged survival (hazard ratio 0.44; 95% CI 0.24–0.81; $p = 0.008$).

The oncological benefits of a re-resection need to be balanced against the complication rates of repeat surgery. The publication by Hoover et al. on surgical outcomes in recurrent glioma (all grades) reported overall complication rates of 12.8%, 27.0%, 22.0% and 22.2% and neurological complication rates of 4.8, 12.1, 8.2 and 11.1% after the first, second, third and fourth or more surgeries, respectively [42]. De Bonis et al. showed that major surgical morbidity at tumour recurrence occurred in 16 out of 33 patients (48%) [43].

The complication rates of the series by Ringel et al. increased slightly from initial surgery to the first re-resection [36]. The non-neurological complication rate increased from 5% to 7%, while the rates of transient and permanent neurological deficits increased from 7% to 9% and from 5% to 8%, respectively.

However, besides a possible direct oncological effect, resampling of the recurrent tumour with a detailed pathological and molecular analysis might have an impact on the development, testing and validation of new salvage therapies.

In our series, all patients received the Stupp protocol post-operatively after the first surgery, but our study has several main limitations. One of the major limitations is the small sample of patients, particularly the number of patients who had a third surgery. Second, its retrospective design makes it more difficult to obtain stronger conclusions and to obtain a homogeneous group for analysis, which in turn makes standardization of postoperative treatment a challenge. The absence of an analysis of the MGMT methylation status and the IDH1 mutation status in many patients (data on MGMT methylation status and IDH1 mutation status missing in 62% and 60% of patients, respectively) is also a limitation.

5. Conclusion

This manuscript is trying to defend for surgery as an important therapy at glioblastoma local recurrence. However, same to the proof for primary surgery, no randomize trial can be organized for it. This study suffered from the intrinsic bias, selected patients, uncontrolled second line therapies and cross-over effect. However, this topic is worth discussing for its potential impact. The weight for second resection will increase when the options of second line adjuvant therapy increase. This study provided the surgical risk and benefit data upon second resection. And it carried higher surgical complication risk and lower benefit compared with 1st surgery.

Reoperation should be proposed if the tumour is amenable to a complete resection and should be followed by adjuvant therapy if prognostic factors suggest that the patient could benefit from a second surgery. However, it seems that a third surgery for glioblastoma recurrence may not be beneficial. In all cases, a re-resection should be part of a multidisciplinary therapeutic plan.

Proper patient selection, development of predictive biomarkers and randomized controlled studies are required to develop guidelines for recurrent glioblastoma.

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