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Research Article

The Impact of Surgery on the Survival of Patients with Recurrent Glioblastoma

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Abstract

Objective: The purpose of this study was to investigate the possible benefit of repeat surgery on overall survival for patients with recurrent glioblastoma multiforme (GBM). **Methods:** We performed a retrospective analysis of data from patients who presented with recurrent GBM over a 5-year period (n = 157), comparing baseline characteristics and survival for patients who had at least 1 new tumor resection followed by chemotherapy (reoperation group, n = 59) and those who received medical treatment only (no-reoperation group, n = 98) for recurrence. **Results:** The baseline characteristics of the two groups differed in terms of WHO performance status (better in the reoperation group), mean age (60 years in the reoperation group vs. 65 years in the no-reoperation group), mean interval to recurrence (3 months later in the reoperation group than in the no-reoperation group) and more gross total resections in the reoperation group. Nevertheless, the patients in the reoperation group had a higher rate [32.8%] of sensorimotor deficits than those of the no-reoperation group [14.2]. There was no significant difference in sex; tumor localization, side, or extent; MGMT status; MIB-1 labeling index; or Karnofsky Performance Status [KPS] score. After adjustment for age, the WHO performance status, interval of recurrence, and extent of resection at the first operation, multivariate analysis showed that median survival was significantly better in the reoperation group than in the no-reoperation group (22.9 vs. 14.61 months, $P < 0.05$). After a total of 69 repeat operations in 59 patients (10 had 2 repeat surgeries), we noted 13 temporary and 20 permanent adverse postoperative events, yielding a permanent complication rate of 28.99% (20/69). There was also a statistically significant ($P = 0.029$, Student's t-test) decrease in the mean KPS score after reoperation (mean preoperative KPS score of 89.34 vs. mean postoperative score of 84.91). **Conclusion:** Our retrospective study suggests that repeat surgery may be beneficial for patients with GBM recurrence who have good functional status (WHO performance status 0 and 1), although the potential benefits must be weighed against the risk of permanent complications, which occurred in almost 30% of the patients who underwent repeat resection in this series.

Keywords: *Extent of resection, glioblastoma, neuro-oncology, recurrence, redo surgery, reoperation*

Introduction

Glioblastoma multiforme (GBM) is one of the most challenging malignancies to treat. The incidence of new cases is approximately 3/100,000 persons,[1] and GBM accounts for 47.1% of malignant primary central nervous system tumors.[2] The first-line standard treatment is based on the most complete surgical excision, followed by concomitant radio-chemotherapy and adjuvant chemotherapy.[3] Age, Karnofsky Performance Status (KPS), and molecular findings (mainly methylguanine-DNA methyltransferase [MGMT] methylation status) have been found to be major predictors of survival.[4-7] The current evidence also support a survival advantage in patients who undergo more extensive surgery.[8-10]

In most cases, recurrence occurs within 8–10 months of initial resection.[11,12] The median survival for patients with recurrent glioblastoma is around 9 months.[13] To date, there is no standard management for recurrence. Repeat surgery is one of the treatment options for recurrent GBM and is suggested by some studies,[14-16] but there is currently no formal consensus about which patients may benefit from repeat surgery.

The aim of this study is to evaluate the impact of repeat resection on survival of patients with recurrent GBM in comparison

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to those who only received adjuvant therapy for tumor recurrence.

Methods

The review boards of our institutions (Centre Hospitalo-Universitaire for surgery and Institut Universitaire du Cancer for radio-and chemotherapy) approved (No. 09-516) this retrospective analysis. Only patients who underwent treatment and follow-up at our 2 institutions were included. All patients gave their informed consent before any surgical procedure.

We analyzed the clinical data of adult patients (age >18 years at the time of initial resection) who had previously undergone resection of histologically confirmed *de novo* GBM (based on the WHO classification system) and presented with recurrence over a 5-year period (from January 2008 to 2013). Patients for whom complete data were not available were excluded from the study (n = 68). A total of 157 patients qualified for inclusion. Fifty-nine of these patients underwent at least 1 repeat surgery for treatment of recurrent GBM (reoperation group), and 10 of these 59 patients underwent 2 reoperations, for a total of 69 repeat resection procedures. The remaining 98 patients did not undergo repeat surgery (no-reoperation group).

Information about the initial treatment protocol

No patient was treated using carmustine wafers during the first resection. All patients had a postoperative magnetic resonance imaging (MRI) within 48 h of each surgery. Gross-total resection (GTR) was defined as no residual tumor on the postoperative gadolinium-enhanced T1-weighted images. Subtotal resection included other types of resection with a residual enhancement of postoperative MRI. Surgical mortality was defined as operation-related death within 30 days.

After initial resection, all patients in this series underwent concomitant radiotherapy and temozolomide (TMZ) treatment followed by adjuvant TMZ in accordance with the Stupp protocol.[3] MGMT status (positivity cutoff of 8%) was not available for some of the earlier patients (14 of the 157 patients). Isocitrate dehydrogenase status of tumors only started to be available in our institution early in 2013, so we were unable to include this molecular marker in the current study.

Follow-up included clinical evaluation (monthly during the treatment period and every 3 months after the end of adjuvant therapy) and brain MRI every 3 months over the entire course of the disease.

Diagnosis and management of the recurrent glioblastoma multiforme

Recurrent GBM was defined as the reappearance of contrast enhancement in the tumor bed or the growth of the residual tumor without any evidence of pseudo-progression according to the Response Assessment in Neuro-Oncology (RANO) criteria.[17] When recurrence was confirmed, therapeutic options were discussed, including reoperation with or without carmustine implants, second-line chemotherapy or bevacizumab, re-irradiation, or supportive care. These therapeutic options were discussed by group of physicians including radiotherapists, neuro-oncologists, neuroradiologists and neurosurgeons. The decision to perform surgery at GBM recurrence was based on either (1) a combination of the patient's clinical condition (KPS score ≥70) and timing of recurrence (≥6 months after the first craniotomy) or (2) the need to treat high intracranial pressure.

At the time of recurrence, 98 patients were treated with systemic therapy only (chemotherapy or bevacizumab), and 59 underwent repeat resection. All patients in the reoperation group also received systemic therapy after each repeat resection.

Statistical analysis

Overall survival time was measured from the date of the first operation to the date of the patient's death; survival after repeated surgery was also measured. Median survival was compared between groups. Age (dichotomized as ≤65 vs. >65 years), KPS score, and extent of resection at reoperation were studied as possible independent prognostic factors. Survival was analyzed using the Kaplan–Meier method. Log-rank statistics were used for group comparison. We conducted a univariate analysis and all variables, except for sex (confounding factor), with a $P \leq 0.10$ in the univariate analysis were included for a multivariable analysis. Multivariate proportional-hazards regression was used to assess for association between repeat resection and survival.

A description of baseline patient characteristics was provided in terms of percentages, and differences between the groups were evaluated using the Fisher's exact test and Student's t-test. Median survival was estimated using the Kaplan–Meier method and the Cox proportional hazards model. The Kaplan–Meier method was used to obtain survival curves, median survival values, and survival probabilities at different time points (1, 2, and 3 years for overall survival). The Cox proportional hazards models provided hazard ratios (HRs) as relative risk estimates of survival for given combinations of adjustment values (age class, KPS class, WHO performance status) and predictive factors (sex, number of lobes involved [dichotomized as single or multiple], extent of resection, reoperation, and type of surgery [awake vs. under general anesthesia]).

Results

Overall, 157 patients were included (103 males and 54 females), with the mean age of 63 years old. The mean duration of follow-up was 28.5 months (range 24–59 months, SD 11.8 months). The survival probabilities were

63% (95% confidence interval [CI] 57%–71%) at 1 year, 23% (95% CI 18%–30%) at 2 years, and 8% (95% CI 6%–10%) at 3 years. At the last follow-up, 150 patients (95.5%) had died. All of the 7 patients still alive at the end of the study were in the reoperation group.

Comparison of baseline characteristics

The reoperation group and no-reoperation group were not strictly equivalent at recurrence [Table 1]; there were statistically significant differences in five variables: age, WHO performance status, interval of recurrence, and clinical symptoms. Patients in the reoperation group had overall better WHO performance status (mean WHO performance status of 2 in this group) and were slightly younger (60 vs. 65 years old). The initial extent of resection was also better in Group 1 (repeated surgery) than Group 2 (only one operation) as summarized in Table 2. The average length of time from initial GBM resection to recurrence was 12 months in the reoperation group versus 9 months in the no-reoperation group. On the other hand, patients in the

Table 1: Demographic and clinical characteristics of patients in this study

Characteristic	Reoperation (*n*=59), *n* (%)	No reoperation (*n*=98), *n* (%)	*P*
Sex			
Male	38 (65.5)	65 (66.3)	0.863
Age at recurrence in years			
Mean±SD	60±8.4	65.1±10.9	**0.003**
≤65	46 (78.0)	52 (53.1)	**0.002**
>65	13 (22.0)	46 (46.9)	
Morbidity at initial presentation			
Sensorimotor deficit	19 (32.8)	14 (14.2)	**0.008**
Aphasia	6 (10.3)	18 (18.4)	0.251
Headache	37 (63.8)	30 (30.1)	**<0.001**
Cognitive impairment	16 (27.6)	29 (29.5)	0.856
Generalized epilepsy	6 (10.3)	3 (3.0)	0.079
Focal epilepsy	16 (27.6)	28 (28.6)	1.000
KPS score			
Mean±SD	89.3±14.7	88.9±9.9	0.85
≤70	56 (94.9)	88 (89.8)	0.373
>70	3 (5.1)	10 (10.2)	
WHO performance status			
0	27 (46.6)	34 (34.7)	**0.011**
1	31 (53.4)	53 (53.8)	
2	0	11 (11.2)	
Tumor localization			
Frontal	20 (34.6)	37 (37.8)	0.985
Temporal	21 (36.3)	35 (35.7)	
Parietal	10 (17.3)	15 (15.3)	
Occipital	6 (10.1)	8 (8.2)	
Insular	1 (1.7)	2 (2.0)	
Deep	0 (0.0)	1 (1.0)	
Side			
Right	24 (40.3)	50 (51.0)	0.252
Left	35 (59.6)	48 (49.0)	
MGMT status			
Positive	27 (45.7)	42 (42.8)	0.893
Negative	26 (44.1)	48 (48.9)	
Unknown	6 (10.1)	8 (8.1)	
MIB-1 labeling index (%)			
<10%	15 (25.4)	23 (23.4)	0.745
>10%	44 (75.5)	75 (76.5)	
Number of lobes involved			
Multiple	16 (27.1)	21 (21.4)	0.442
Single	43 (72.9)	77 (78.6)	

Boldface type in the right column indicates statistical significance. KPS: Karnofsky Performance Status, MGMT: Methylguanine-DNA methyltransferase, SD: Standard deviation, MIB-1: Monoclonal antibody

Table 2: Data of the Gross total resection and sub-total resection in of 2 groups of patients

	Reoperation group		Non reoperation group
	1st operation	Redo	
GTR	42	33	52
STR	17	26	46
Total	59	59	98

Patients of Group 1 had more GTR (at first operation) than those of Group 2 (P=0.0248 test -khi2). GTR: Gross total resection, STR: Subtotal resection

reoperation group had significantly more clinical signs and symptoms (sensorimotor deficits and headache) before their repeat surgery. These symptoms could explain why redo surgery was preferentially proposed. There was no significant difference in other variables (localization, side, multiple-versus single-lobe tumor, KPS score, MGMT status, MIB-1 labeling index). Finally, as noted previously, 10 of the 59 patients in the re-resection group had two operations for GBM recurrence (a total of 69 repeat surgeries).

Survival

Since the comparison groups were not equivalent, we adjusted for four variables: age category (≤65 vs. >65 years), WHO performance status, time from initial resection to recurrence, and initial extent of resection. In multivariate analysis, the median survival of the patients who underwent repeat resection at recurrence was significantly better than that of those who did not (22.99 months [95% CI 20.20–28.85 months] vs. 14.61 months [95% CI 12.63–16.81 months], respectively; $P < 0.05$) [Figure 1]. The mean survival of patients in the reoperation and no-reoperation groups was found to be significantly different (based on an alpha of 0.05) using three different tests: likelihood ratio test, observed value 17.04 ($P < 0.001$); Wald test, 16.15 ($P < 0.001$); and log-rank test, 16.95 ($P < 0.001$). For patients in the reoperation group, the risk of death at any time was half that for the no-reoperation group (HR = 0.47 [95% CI 0.32–0.68], $P < 0.001$; based on multivariable analysis and adjusted for age, WHO performance status, and time to recurrence).

Type of surgery and extent of resection

Considering the overall group of 157 patients, only two factors were significant in multivariate analysis. First, patients who underwent awake surgery for initial GBM resection had better median survival than those operated on under general anesthesia [$P < 0.005$; Table 3]. Second, in patients with the single-lobe disease, the median survival was significantly better for those in whom GTR was performed than those in whom subtotal resection (STR) was performed (risk ratio [RR] = 0.50 [95% CI 0.25–0.99], $P = 0.028$). Conversely, in patients with multi-lobar tumors the median survival was worse for those who had GTR than for those who had STR (RR = 1.58 [95% CI 1.05–2.40], $P = 0.047$).

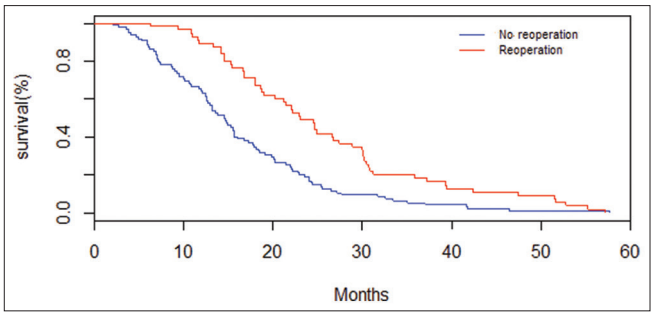

Figure 1: Survival curves for the 2 groups (patients who underwent reoperation at glioblastoma multiforme recurrence and those who did not)

Surgical morbidity and mortality associated with reoperation

There was no surgical mortality in this series. Since 10 of the 59 patients D underwent 2 repeat operations, we calculated the number of complications over 69 surgeries. Overall, considering all postoperative events, we had 13 temporary and 20 permanent postoperative events, yielding a permanent complication rate of 28.98% (20 of 69 reoperations) [Table 4].

Permanent postoperative morbidity mainly involved hemiparesis or aphasia. Finally, we noted that over the 69 operations for recurrent disease, the mean preoperative KPS score was 89.34 ± 1.91 and the mean postoperative score was 84.91 ± 1.21 - a significant decrease ($P = 0.029$, Student's t-test).

Discussion

In this retrospective study, our two groups of patients with recurrent glioblastoma (the reoperation group and the no-reoperation group) showed statistically significant differences in the WHO performance status, age, and time to recurrence, presumably reflecting, at least in part, selection bias with respect to resection. However, even after adjusting for these three variables, multivariate analysis showed that the patients who underwent repeat resection for GBM recurrence (the reoperation group) had significantly better median survival than those who received only chemo-and/or or radiotherapy for recurrent GBM (difference of 8 months). Nevertheless, repeat surgery was associated with temporary or permanent postoperative morbidity in a substantial number of cases.

Indications for repeat surgery in patients with recurrent glioblastoma multiforme

Despite significant therapeutic advances in recent years, tumor recurrence remains inevitable in patients with GBM, and there is no clear consensus on the benefits of reoperation and its potential role in association with other therapeutic options (such as chemotherapy, targeted therapy, or repeat radiation therapy). The peritumoral zone is often the origin of recurrent disease, even in cases in which the initial resection was considered total.[18,19] In

Table 3: Results of uni- and multivariate analyses[a]

Factor	Number of events	Kaplan-Meier univariable analysis		Multivariable Cox proportional hazard model	
		Median overall survival, in months (95% CI)	*P*	HR (95% CI)	*P*
Sex					
Female	52	18.3 (14.5-23.9)	0.280	1	0.055
Male	98	16.8 (15.3-20.2)		1.43 (0.99-2.06)	
Number of lobes involved					
Multiple	36	11.6 (10.5-12.7)	0.471	Data correlated with type of removal GTR/STR	**0.005**
Single	114	18.0 (15.3-20.2)			
Extent of initial resection					
STR	61	15.6 (13.4-19.0)			
GTR	89	18.5 (15.3-22.2)	0.100		
Type of surgery at initial resection					
Awake	23	22.1 (16.6-33.4)		1	
Not awake	127	16.0 (14.6 -19.0)	**0.040**	1.93 (1.19-3.14)	**0.005**
Group					
No reoperation	95	14.6 (12.6-16.8)		1	
Reoperation	55	23.0 (20.2-28.8)	**<0.001**	0.47 (0.32-0.68)	**<0.001**
Age (years)					
≤65	93	18.7 (15.6-22.2)		1	
>65	57	14.5 (12.4-18.5)	0.100	1.07 (0.73-1.56)	0.65
KPS score					
≤70	13	18.5 (13.0-17.9)		1	
>70	137	16.8 (15.3-20.0)	0.100	1.24 (0.67-2.29)	0.71
WHO Perfomance status					
1	57	16.6 (14.5-21.1)		1	
2	79	17.1 (13.0-30.0)		1.02 (0.71-1.46)	0.90
3	14	17.1 (13.0-30.0)	0.6	5.87 (0.75-46.17)	0.90

[a]The 7 patients who were still alive at the time of the analysis were included in the analysis but we showed for this analysis only the number of deceases. Thus, results are based on a total of 150 events. Boldface type indicates statistical significance. GTR: Gross total resection, STR: Subtotal resection, KPS: Karnofsky Performance Status, HR: Hazard ratio, CI: Confidence interval

Table 4: Complications associated with the 69 repeat surgeries

	Aphasia	Paresis	Aphasia and paresis	Cognitive deficit	Epilepsy	Surgical site complications	Total
Temporary	2				6	5*	13
Permanent	5	13	1	1			20

*We noted 3 postoperative infections, 1 subcutaneous hematoma, and 1 case of cerebrospinal fluid leakage

patients with GBM, the peritumoral zone at the margin of the resection cavity may have selected tumor clones and stromal cells with tumorigenic and angiogenic properties, and this issue has raised questions about the optimization of resection.[20] Moreover, the molecular profiles of cells in recurrent tumor evolve and differ from the initial tumor cells' gene expression profiles.[21] Recurrent GBMs acquire new genetic aberrations associated with tumor growth and therapy resistance.[22] For example, Christmann *et al*. found that >90% of their initial sample with MGMT promotor methylated primary GBM lost this methylation upon recurrence.[23]

Consensus has not yet been reached regarding indications for repeat resection. The rate of repeat craniotomy for recurrent GBM in France was around 9%,[13,24,25] which remained much lower than the Stark *et al*. study (27%)[26] and North American series (13%–31%).[27] Mandl *et al*., analyzed 32 cases of recurrent GBM and concluded that repeat surgery should be performed only for important symptomatic mass effects not responsive to steroids.[28] Like us, however, many other teams have suggested repeat surgery in patients with progression-free survival >6 months and KPS ≥70 at recurrence.[24,25,28,29] The goals of a repeat craniotomy are maximal resection to improve survival and obtaining tissue for new histology and molecular profiles, which allows adapting systemic treatment to the evolved genomic alterations of the recurrent tumor. The rate of permanent postoperative morbidity after repeat resection in patients was almost 30%, based on 69 repeat surgeries in 59 patients. In 2 review articles on recurrent surgery for GBM, Barbagallo *et al*. found a rate <20%,[30] and Robin *et al*. found a rate of 18.6%.[31] With 141 patients operated

on for primary resection of glioblastoma, Gulati *et al*. found a similar rate of perioperative complications of 19.4%.[32] Regarding the prognosis of GBM, we consider that the postoperative complications observed were acceptable to the large majority of our cohort. Patients who are willing to undergo repeat surgery and have a WHO status of 0 or 1 (even with neurological deficits) and a single-lobe tumor amenable to GTR could particularly benefit from a reoperation.

Improvement of survival

Our retrospective study found a significant gain in survival for patients who underwent reoperation compared with patients who underwent resection at first diagnosis only (almost 23 months vs. 14 months). This is in accordance with previously published studies showing that repeat surgery improves survival as well as symptoms related to mass effect.[8,9,33]

Woernle *et al*. found that the overall survival of patients with GBM was significantly longer in their repeat surgery group (18.8 vs. 14.8 months, $P < 0.001$).[34] Ening *et al*. also found that patients who underwent reoperation at recurrence survived significantly longer than patients who did not (19 vs. 13 months, $P = 0.002$).[35] In addition, Chaichana *et al*., showed the number of resections to be an independent predictor of prolonged survival. In their study, the median survival for patients who underwent 1, 2, 3, or 4 surgeries was 6.8, 15.5, 22.4, and 26.6 months, respectively ($P < 0.05$).[8] In accordance with studies by our group and others,[27,29,36,37] All of these authors stated that repeat surgery improved median survival. Similarly, Barker and coworkers found that the median survival was longer for their 46 patients who underwent reoperation than for their patients who only underwent 1 craniotomy.[26] However, other series found no association between median survival and repeat resection.[38,39] In a review of studies comparing several retreatment strategies for recurrent malignant glioma, Nieder *et al*. found no evidence for prolonged survival with repeat surgery[12] and in the analysis of 232 cases of recurrent GBM, Franceschi and coauthors concluded that repeat surgery "might have a limited impact" on the clinical course.[40] As with our study, the main limitations of most previously published studies are their retrospective nature and often-inevitable patient selection bias. Although our study is retrospective, we tried to overcome selection bias by careful statistical adjustment. An additional limitation of this study is that we did not include some new molecular markers, which are important indicators of patient outcome. As noted, these new markers were not always available at the beginning of the study period.

Conclusion

Despite modern therapies, the recurrence of GBM is inevitable. Strategies for treatment at recurrence can be controversial. Our retrospective study suggests that repeat surgery can be beneficial for patients with good functional status (WHO performance status of 0 or 1 and KPS score >70). Despite a poor prognosis, aggressive treatment with repeat surgery appears to prolong survival with a complication rate that we consider acceptable given the overall poor prognosis of GBM.

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Conflicts of interest

There are no conflicts of interest.

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