# Usefulness of Reintervention in Recurrent Glioblastoma: An Indispensable Weapon for Increasing Survival

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■ BACKGROUND: **Glioblastoma is the most frequent primary brain tumor and despite of complete treatment survival is still poor. The aim of this study is to define the utility of reoperation for improving survival in patients with recurrent glioblastoma, and determine other prognostic factors associated with longer survival.**

■ METHODS: **We performed a retrospective analysis of those patients who underwent surgery and compared those who were operated two or more times and those who received surgery only once. We studied overall survival (OS), progression-free survival (PFS), and clinical variables that could be related with higher survival.**

■ RESULTS: **A total of 121 patients were eligible for the study, of whom 31 (25%) underwent reoperation. The reoperation group had a mean and median increase survival of 10.5 and 16.4 months in OS and 3.5 and 2.7 months for PFS compared with the non-reoperation group ($P < 0.001$ and 0.01, respectively). Although complications were higher in patients that underwent reintervention (19.3%) there was no statistical difference with complication rate in first surgery (12.4%, $\chi^2 = 1.86$; $P = 0.40$). Cox multivariable analysis revealed that age (hazard ratio [HR] 1.03; 95% confidence interval [CI], 1.006–1.055; $P = 0.013$), reoperation (HR, 0.48; 95% CI, 0.285–0.810; $P = 0.006$), extent of resection >95% (HR, 0.547; 95% CI, 0.401–0.748; $P < 0.001$), and complete adjuvant therapy (HR, 0.389; 95% CI, 0.208–0.726; $P = 0.003$) were correlated with a higher OS.**

■ CONCLUSIONS: **Reoperation and the extent of resection (EOR) are the only surgical variables that neurosurgeons can modify to improve survival in our patients. Higher EOR and reoperation rates in patients who can be candidates for second surgery, will increase OS and PFS.**

## INTRODUCTION

Glioblastoma is the most common primary brain tumor in adults, with a devastating prognosis.[1,2] The incidence of glioblastoma is 5–10 cases per 100,000 persons per year, representing 65% of newly diagnosed gliomas.[3] Despite the efforts to improve survival in affected patients, life expectancy is limited, ranging from 12 to 15 months, with <10% of patients alive after 5 years.[4] Typically, glioblastoma recurs after 1 year despite maximal treatment when surgery, chemotherapy, and radiotherapy are administered.[4,5] To improve prognosis, new treatments and strategies have been developed for recurrence, based on the use of new angiogenesis inhibitors, targeted therapies, or gamma knife surgery.[6,7] Surgical treatment has become more aggressive, and reoperation is a more frequently used approach for these patients. In 1968, Pool[8] introduced reoperation for recurrent glioblastoma, and few studies have evaluated the impact of reoperation in glioblastoma recurrence, although it can be an important tool for increasing overall survival (OS) and progression-free survival (PFS) in selected patients. Some evidence has been published, mainly by Berger et al.[6,9-11] and also by other authors, indicating similar results.[12,13] However, there is a lack of information regarding the possible effectiveness of this strategy and possible

**Key words**
- Extent of resection
- Progression-free survival
- Recurrent glioblastoma
- Reoperation
- Survival

**Abbreviations and Acronyms**
**5-ALA**: 5-aminolevulinic acid
**CI**: Confidence interval
**ECOG**: Eastern Cooperative Oncology Group
**EOR**: Extent of resection
**GTR**: Gross total resection
**HR**: Hazard ratio
**KPS**: Karnofsky Performance Status
**OS**: Overall survival
**PFS**: Progression-free survival

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prognostic factors. The aim of the present study was to elucidate the impact of reoperation for recurrent glioblastoma and to identify prognostic factors that can improve survival in these cases.

## METHODS

We retrospectively reviewed all patients diagnosed with and treated for de novo glioblastoma at our institution between January 2010 and December 2015, certified after histopathological examination. The hospital's central database was reviewed for all patients who underwent surgery for intra-axial tumors. Those patients with complete medical records and confirmed glioblastoma, according to World Health Organization criteria, at the first surgery were eligible for the study. Patients who had incomplete records, were lost to follow-up, or underwent biopsy were excluded. The patients lost to follow-up were excluded as well. Patient survival was calculated between the time of surgery and last follow-up in those patients with complete follow-up.

Clinical variables collected included date of birth; sex; age; date of diagnosis; initial symptoms; tumor location; location in an eloquent area; intraoperative use of 5-aminolevulinic acid (5-ALA), carmustine, or neuromonitoring; and volume at diagnosis calculated with the 3 largest diameters in axial and coronal views using the formula for an ellipsoid volume: Volume = $4/3\pi$ (diameter 1 × diameter 2 × diameter 3), in $cm.^3$ In our postoperative protocol, all patients underwent postoperative magnetic resonance imaging at 48–72 hours to assess surgical resection, and postoperative volume was calculated again. The percent removal was calculated as follows: (preoperative tumor volume−postoperative tumor volume)/preoperative tumor volume. Functional status of the patient was calculated with preoperative and postoperative Karnofsky Performance Scale (KPS) and Eastern Cooperative Oncology Group (ECOG) performance status[14] at diagnosis. Date of surgery, complications after surgery, inpatient stay, and in those patients who were reoperated, date of second surgery, postoperative KPS and ECOG scores and the presence of new complications were also recorded. Patients were classified into 3 groups according to the adjuvant therapy received: complete, comprising patients receiving complete radiotherapy and chemotherapy after surgery following the Stupp protocol; only radiotherapy, comprising patients who completed radiotherapy after surgery; and no therapy, comprising patients who did not receive adjuvant therapy or did not complete it. The patients also were classified into 3 groups according to the extent of resection (EOR) at initial surgery: gross total resection (GTR; >95%), subtotal resection (50%–95%), and partial resection (<50%). Secondary variables analyzed were KPS score ≥80 or <80 and ECOG score <2 or ≥2.

OS was defined as the period from the initial diagnosis of the glioblastoma to the last follow-up or the date of death if registered, and PFS was defined as the period from the initial surgery to the date of recurrence.

Statistical analyses were performed with SPSS 21.0 (IBM, Armonk, New York, USA), with a P value ≤ 0.05 considered to indicate statistical significance. Student's *t* test and ANOVA were used for quantitative variables, and the $\chi^2$ test and Fisher's exact test were used for qualitative variables. OS and PFS were compared using the Kaplan-Meier test, and multivariable analysis was performed using Cox proportional hazards regression with 95% confidence intervals. All variables associated with survival in univariable analysis (P < 0.10) were included in the multivariable analysis.

## RESULTS

Between January 2010 and December 2015, 157 patients were diagnosed with glioblastoma at our institution. Of these, 31 (20%) received only biopsy as treatment at our department because of deep or inaccessible location, and 5 were lost to follow-up. The remaining 121 patients who underwent initial surgery were divided into 2 groups: those who underwent only 1 surgery (n = 90; 75%), and those who underwent 2 or more surgeries (n = 31; 25%).

Our patients' demographic and clinical data are summarized in Table 1. The mean patient age was 62.21 ± 12.34 years, and 71 were male (58.7%). Preclinical status, as defined by ECOG score <2, was seen in 76 patients (62.8%), and the median preoperative KPS score was 80 (range, 50–90). The most common location was the left temporal lobe (32 patients; 26.4%), followed by the right temporal lobe (27 patients; 22.3%) and the left frontal lobe (17 patients; 14%). Only 22 patients had a tumor located in an eloquent area (18.1%). The mean volume was 310 ± 246 $cm^3$, and the most frequent symptom was headache (33 patients; 27.3%), followed by hemiparesis (21 patients; 17.3%). In 38 patients (31.4%), 5-ALA was administered to guide the intervention, and intraoperative neuromonitoring was applied in 15 patients (12.4%). Gross total resection was achieved in 59 patients (48.8%), and EOR ≥50% was achieved in 104 patients (86%). Mean postoperative volume was 55.4 ± 88.3 $cm^3$, translating to a mean resection of 82.15% of the lesion. Splitting the cohort into 3 groups, the mean values were as follows: GTR, defined as a mean postoperative volume of 7.04 ± 6.4 $cm^3$ and 97.02 ± 2.4% of mean resection; subtotal resection, defined as a mean postoperative volume of 56.02 ± 47.4 $cm^3$ and 79.95 ± 14.4% of mean resection; and partial resection, defined as a mean postoperative volume of 221.46 ± 118.7 $cm^3$ and 36.36 ± 19.6% of mean resection. Morbidity and mortality occurred in 15 patients who experienced complications after surgery (12.4%), with 3 patients (2.4%) who died due to complications and were excluded from the posterior analysis. The causes of death were acute subdural hematoma in 1 patient and pulmonary embolism in 2 patients. Other complications included hemiparesis in 4 patients (4.4%), acute subdural hematoma in 2 patients (2.2%), and 1 patient each with recurrent seizures, pulmonary thromboembolism, epidural hematoma, wound infection, pseudomeningocele, and refractory edema necessitating decompressive craniotomy. The mean inpatient length of stay was 18 ± 9.6 days. At the end of this retrospective analysis, 111 patients had died (91.7%). Adjuvant therapy following the Stupp protocol, with complete temazolamide and radiotherapy treatment, was administered to 82 patients (67.8%).

Only 3 patients in the reoperation group underwent 3 surgeries (9.6%). The most common location was the right temporal lobe (8 patients; 25.8%), followed by the left temporal lobe (7 patients; 22.6%). Intraoperative neuromonitoring was performed in 4 patients (13.3%) because of tumor location. Intraoperative agents included 5-ALA in 17 patients (54.8%) and carmustine in 10 patients (32.2%). Postoperative complications after second surgery occurred in 19.3% of patients, including 3 patients with cerebrospinal fluid fistula and 3 patients with wound infection.