Survival outcomes following repeat surgery for recurrent glioblastoma: a single-center retrospective analysis

Paolo Perrini1 · Carlo Gambacciani1 · Alessandro Weiss1 · Francesco Pasqualetti2 · Durim Delishaj2 · Fabiola Paiar2 · Riccardo Morganti3 · Riccardo Vannozzi1 · Lodovico Lutzemberger1

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Abstract The aim of the present study is to evaluate the impact of extent of resection at initial and repeat craniotomy on overall survival of patients with recurrent glioblastoma. The authors retrospectively reviewed the records of all adults patients who underwent repeat resection of recurrent glioblastoma following radiation and chemotherapy at an academic tertiary-care institution between 2011 and 2015. We evaluated the survival outcomes with regard to extent of resection considering both the initial and repeat resections. The role of possible prognostic factors that may affect survival after repeat resection, including age, preoperative performance status, tumor location and adjuvant treatment, was evaluated using Cox regression analyses. Forty-eight patients were included in this study. The overall median survival of 14 patients who had subtotal resection at recurrence after initial subtotal resection did not statistically differ from seven patients who had gross-total resection at recurrence after initial subtotal resection (18 months vs. 22 months, \( p = 0.583 \)). The overall median survival of 13 patients who had gross-total resection at recurrence after initial gross-total resection was significantly increased compared with survival of 13 patients who had subtotal resection at recurrence after initial gross-total resection (47 months vs. 14 months, \( p = 0.009 \)). A Cox proportional hazards model was created demonstrating that preoperative performance status at recurrence (HR 0.418, \( p = 0.035 \)) and the extent of repeat resection (HR 0.513, \( p = 0.043 \)) were independent predictors of survival. Gross-total resection at repeat craniotomy is associated with longer overall survival and should be performed whenever possible in patients with recurrent glioblastoma and in good performance status.

Keywords Extent of resection · Glioblastoma · Recurrent glioma · Surgery · Survival

Introduction

Glioblastoma is the most common primary brain tumor in adults and its prognosis remains dismal due to the high propensity for tumor recurrence [1, 2]. The recurrence pattern after surgical resection and administration of temozolomide concurrent with radiation therapy is mainly local occurring within 2 cm of the tumor bed in approximately 80% of cases [3]. Over the recent years, treatment strategies have become more aggressive, with several studies reporting the clinical results of repeat surgery and salvage chemotherapy for recurrent high-grade gliomas. Recent investigations emphasized the importance of extent of resection (EOR) at the time of recurrence as an important predictor of overall survival [4, 5]. However, only few studies analyzed the effect of EOR considering both the initial and repeat resection [4]. In addition, the effective role of several variables, which may affect the prognosis of patients with recurrent glioblastoma, including age, preoperative performance status, tumor location and adjuvant treatment, are still matter of controversy. In this study we performed a retrospective analysis to evaluate the survival outcomes after reoperation...
in our series of 48 consecutively treated patients with recurrent glioblastoma.

Methods

Patient population

A retrospective analysis was performed on patients who underwent a planned resection of recurrent primary GBM at the Neurosurgical Department of the University of Pisa between January 2001 and December 2015. All patients with gliosarcoma and secondary glioblastoma were excluded from the analysis, as were those with initial multifocality. The patient’s age, sex, Karnofsky Performance Scale (KPS) score, tumor location, concomitant and adjuvant chemotherapy were recorded. All patients underwent a preoperative gadolinium (Gd)-enhanced magnetic resonance imaging scan of the whole brain on 1.5-tesla Magneton. Tumour volume was assessed on T1 Gd-enhanced imaging scans and measured with manual segmentation using the iplan cranial software (BrainLab). Extent of resection (EOR) [6] was calculated as (preoperative tumour volume-postoperative tumour volume)/preoperative tumour volume. The EOR was defined as gross-total resection (GTR) (>95% resection by volume) or sub-total resection (STR) (≤95% resection by volume). The functional grade as reported by Sawaya et al [7] and modified by Lacroix et al [8] was used to define the tumour with respect to the proximity to eloquent brain. A neuronavigation system was used in all cases and intra-operative neurophysiology was performed for tumours near eloquent areas. Neuropathological diagnoses of GBM were based on WHO criteria. All patients underwent postoperative computed tomography (CT) scans to exclude the occurrence of haematoma. Contrast-enhanced MRI study was obtained within 72 h to determine the extent of resection, one month after radiotherapy and thereafter in 3-month intervals until there was evidence of progression. All patients underwent postoperative radiotherapy plus concomitant and sequential temozolomide according to the Stupp regimen [9]. According to the RANO criteria, recurrence was defined as a significant increase in the volume of the enhancing lesion in T1 weighted images [10]. The endpoints studied included the progression-free survival (PFS), calculated as the time between the first surgery and the relapse, the overall survival (OS), defined as the time from the beginning of treatment to the last follow up or date patient’s death, and the survival following second surgery (SSS), defined as the time from the second surgery to the last follow-up. In addition, factors potentially affecting the outcome such as Karnofsky performance scale (KPS), EOR, patient age, tumor location and chemotherapy after surgery were investigated.

At the time of the data analysis, four patients (5%) were known to be alive and were appropriately censored in the survival analysis.

The local Institutional Review Board approved this study and all patients provided informed, written consent.

Statistical analysis

Before performing survival analysis an exploration phase was carried out. Categorical data were described by frequency, whereas continuous data by mean and median. To evaluate the normality of the quantitative data distributions, the Kolmogorov–Smirnov test was performed. The assessment of the qualitative variables such as sex, tumor location and secondary chemotherapy was realized by chi square test or Fisher exact test when appropriate, whereas the quantitative variables such as age and KPS were analyzed with t test (two-tailed) and Mann–Whitney test (two-tailed) respectively. Survival curves were calculated using the Kaplan–Meier method and the log-rank test was used to evaluate the differences between curves. Univariate analysis of PFS, OS and SSS was performed including each risk factor in a Cox regression model. All variables influencing survival (p <0.1) were analyzed together in a Cox regression model as multivariate analysis, with the aim of studying the independent contribution of each risk factor in explaining survival. Furthermore, the proportional hazard was always verified by using log(−log) curves. The results of the Cox regression were expressed by hazard ratios with its related confidence interval and related p value calculated by Wald test. Regression coefficients were also calculated. Differences were considered significant at p <0.05. Analyses were performed using the SPSS 22 technology.

Results

Patient population and survival outcomes

Forty-eight patients underwent a second tumour resection for histologically verified GBM during the study period (Table 1). According to the surgical treatment they received, patients were divided into four groups. Fourteen patients had STR at first and second resection, seven patients had STR followed by GTR at the time of reoperation, 13 patients had GTR at first and second resection and 14 patients had GTR followed by STR at the time of reoperation (Table 2). Age, median KPS score, eloquence of tumor location and adjuvant chemotherapy after reoperation did not statistically differ between groups. The extended survival following GTR at recurrence for patients with initial GTR (GTR/GTR) was significantly increased compared with STR at reoperation after initial GTR (GTR/
STR (mean survival from reoperation 47 months vs. 14 months, p=0.009) (Table 2). GTR at recurrence after STR at initial surgery (STR/GTR) provided a median OS advantage of 4 months compared to STR at recurrence after initial STR (STR/STR) which did not reach statistical significance (mean survival from reoperation 22 months vs. 18 months, p = 0.583) (Fig. 1). There was no statistically significant difference in PFS between the four groups although the median duration of PFS was longer in patients with GTR at recurrence (P=0.085) (Table 3). Surgical complications after first operation occurred in two patients (4.1%). One patient had an asymptomatic haemorrhage into a tumor resection cavity that was treated conservatively. The other patient developed hydrocephalus, which required ventriculoperitoneal shunt. Postoperative complications after reoperation occurred in one patient (2%), who experienced wound dehiscence requiring surgical revision. Following repeat resection 39 patients received a salvage systemic therapy. Accordingly, 25 patients (64.1%) received Fotemustine chemotherapy, nine patients (23.1%) received Fotemustine plus Bevacizumab, three patients (7.7%) received Temozolomide chemotherapy and two patients (5.1%) underwent re-irradiation with additional Temozolomide.

### Progression-free survival after first surgery and prognostic factors

Median PFS after initial resection was 8.5 months (range 2–67 months). Table 4 summarizes the association of potential prognostic factors with PFS. PFS was statistically significantly increased for initial GTR compared with STR (10 months vs. 6 months, p=0.020). Patient age, sex, KPS score before repeat surgery, and adjuvant chemotherapy appeared to be predictors of survival after resection of recurrent GBM. KPS score ≥80 provided a median SSS advantage of 8 months when compared to patients with

### Table 1: Preoperative characteristics of EOR groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>STR STR</th>
<th>STR GTR</th>
<th>p value</th>
<th>GTR STR</th>
<th>GTR GTR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>7</td>
<td>0.625</td>
<td>14</td>
<td>13</td>
<td>0.454</td>
</tr>
<tr>
<td>Age, mean (yrs)</td>
<td>0.625</td>
<td>0.454</td>
<td></td>
<td></td>
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<tr>
<td>First surgery</td>
<td>60</td>
<td>57.8</td>
<td>0.061</td>
<td>60.6</td>
<td>58</td>
<td>0.999</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
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<tr>
<td>Female</td>
<td>6</td>
<td>0</td>
<td></td>
<td>7</td>
<td>6</td>
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<td>Median KPS</td>
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<td></td>
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<tr>
<td>Initial</td>
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<td>85.7</td>
<td>0.749</td>
<td>84.6</td>
<td>85.4</td>
<td>0.831</td>
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<td>Recurrence</td>
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<td>0.158</td>
<td>78.5</td>
<td>82.3</td>
<td>0.581</td>
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<td>Eloquent</td>
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<td>3</td>
<td>0.765</td>
<td>5</td>
<td>6</td>
<td>0.884</td>
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<tr>
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<td>8</td>
<td>6</td>
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<tr>
<td>Near eloquent</td>
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<td>1</td>
<td>1</td>
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<td>6</td>
<td>0.624</td>
<td>11</td>
<td>12</td>
<td>0.596</td>
</tr>
<tr>
<td>No</td>
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<td></td>
<td>3</td>
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</tbody>
</table>

### Table 2: Patients outcomes of EOR groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Initial STR STR at recurrence</th>
<th>GTR at recurrence</th>
<th>p</th>
<th>Initial GTR STR at recurrence</th>
<th>GTR at recurrence</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (months)</td>
<td>18</td>
<td>22</td>
<td>0.583</td>
<td>14</td>
<td>47</td>
<td>0.009</td>
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<tr>
<td>1-year survival (%)</td>
<td>75</td>
<td>86</td>
<td></td>
<td>71</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2-year survival (%)</td>
<td>23</td>
<td>27</td>
<td></td>
<td>17</td>
<td>77</td>
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</tr>
</tbody>
</table>

**Note:** Table 3 and Table 5 are not provided in the image.
lower score (p = 0.014). Similarly, EOR with GTR provided a median SSS advantage of 8 months compared to patients with STR (p = 0.016). The treatment with adjuvant chemotherapy provided a median SSS advantage of 10 months when compared to patients without adjuvant chemotherapy (p = 0.007). Multivariate analysis revealed that only EOR at repeat surgery was significantly associated with improved SSS (HR = 0.516, 95% CI 0.250–0.964; p = 0.048).

Overall survival and prognostic factors

The overall survival for patients is summarized in Table 5. The median OS was 21 months according to Kaplan–Meier estimates. In univariate analyses, patients with KPS > 80 before second surgery presented a median OS advantage of 7 months (median 23 months) compared to patients with KPS ≤ 80 (median 16 months). This difference was statistically significant (p = 0.010). GTR at first surgery was associated with an OS of 24 months compared to 18 months following STR at first surgery, but this difference did not reach statistical significance (p = 0.082). GTR at recurrence provided a statistically significant longer OS compared to patients with STR (32 months vs. 17 months, p = 0.009). In a multivariate analysis KPS before second surgery (HR = 0.418, 95% CI 0.172–0.919; p = 0.035) and EOR at recurrence (HR = 0.513, 95% CI 0.253–0.939; p = 0.043) were associated with longer survival.

Discussion

Several clinical studies demonstrated that greater EOR is associated with increased overall survival in patients with glioblastoma. Lacroix and colleagues [8] first demonstrated that the EOR begins to be associated with a survival advantage at 89% of the tumor volume and that resection of 98% of tumor volume is a significant independent predictor of patient survival. Subsequently, other clinical investigators confirmed these findings supporting the value of an aggressive microsurgical resection in patients with glioblastoma [6]. In addition, in the contemporary era of aggressive interventions there is mounting evidence supporting the clinical value of repeat resection for recurrent high-grade glioma in selected patients. Several clinical studies after the introduction of the Stupp protocol described a survival benefit after reoperation for recurrent glioblastoma [19]. However, only recently the role of EOR at repeat surgery and the number of resections were evaluated [11, 12]. McGirt and colleagues [11] analysing a retrospectively collected database including 400 cases with recurrent high-grade glioma reported that GTR and near-total resection were independently associated with prolonged survival. Chaiciana and colleagues [12] demonstrated that repeated debulking
procedures, at least up to 4 times, are associated with improved chances of prolonged survival regardless of age and functional status. Surprisingly, before our study only in one retrospective analysis the impact of EOR was evaluated independently at initial and repeat craniotomy [4]. Bloch et al. [4] reviewed a series of 107 patients with recurrent glioblastoma and analysed the survival outcomes according to the EOR at initial operation (GTR vs. STR) and at the subsequent resection. They found that for patients with initial GTR, the EOR (GTR vs. STR) at recurrence doesn't
provide a statistically significant difference in survival. In contrast, they found that for patients with initial STR, GTR at recurrence significantly increased survival following repeat resection compared with STR at reoperation (median 19.0 vs. 15.9 months, p = 0.004). Paradoxically, they observed that the overall survival is statistically the same regardless of initial EOR, when GTR is achieved at repeat craniotomy. In our study we found that patients with GTR at initial surgery followed by GTR at recurrence (GTR/GTR) experienced the longest median overall survival and their survival was significantly increased compared with STR at recurrence (GTR/STR). According to our findings, when STR is achieved at initial resection, there is no statistically significant difference in survival after subsequent reoperation based on the EOR at repeat craniotomy. However, it is worthwhile that GTR at recurrence conferred the greatest survival advantage, regardless of EOR at initial resection. Consistent with previous reports [4], EOR at repeat craniotomy was an independent predictor of survival in both our univariate and multivariate analyses, supporting the role of GTR at repeat resection. In addition, according to our findings, the EOR was the only factor statistically influencing the PFS following initial surgery and affected SSS in both univariate and multivariate analyses. This association between survival outcome and EOR is thought to be due, at least in part, to reduced tumor burden, which seems to “reset the clock” prolonging recurrence and allowing for improved efficacy of radiation and chemotherapy [6, 8, 11, 12].

Besides the value EOR as independent predictor of improved survival, other reported prognostic factors in patients undergoing repeat resection for recurrent glioblastoma include age <50 years, preoperative KPS score ≥70, smaller tumor volume, radiation necrosis at the time of reoperation and longer interval between operations [4, 11, 13–20]. Prognostic factors are crucial to provide data-driven assessment of patients with recurrent glioblastoma in order to estimate preoperatively the patient’s postoperative survival. Park and colleagues [17] devised a preop- erative scale - the NIH Recurrent GBM scale—for use in counseling patients considering repeat surgery and their prognosis. They created a composite score assigning 1 point for the presence of each of the following characteristics: motor/speech/middle cerebral artery score >2, KPS score ≤80, and tumor volume ≥50 cm³. They found that patients with a score of three points experienced a poor survival (1-month median survival), those with scores of 1–2 experienced an intermediate outcome (4.5 months median survival) and those with score of zero presented a good outcome (10.8 months median survival). In our study we evaluated several potential predictors of improved survival in addition to EOR, including age, preoperative KPS, eloquence of tumor location and adjuvant chemotherapy at recurrence. In our analysis we found that preoperative KPS score >80 at repeat surgery was associated with longer OS and this association was statistically significant in both univariate and multivariate analysis. The association between higher KPS score and longer OS is consistent with previously reported studies [17, 21] and confirms the utility of the performance status for clinical decision making in patients with recurrent glioblastoma.

**Strength and limitations of the study**

The relevant finding in this study is that patients with an initial GTR had a maximized OS after a GTR at recurrence. These results support the previously reported data on initial EOR and provide some insights into conflicting data available in the recent literature regarding the cumulative effect of EOR at initial and repeat craniotomy on OS [4, 20]. Although in multivariate analysis we found that EOR at recurrence and not at first resection was associated with longer survival, these results support the role of maximal EOR in patients with recurrent glioblastoma and should provoke additional studies to assess the impact of EOR independently at initial and repeat resection. This study is retrospective and therefore entails several limitations. There may be a selection bias associated with patients selection, in which patients who were offered repeat craniotomy where those younger, with better functional status and longer survival outcomes. We acknowledge that patients with GTR at recurrence probably represent a selected cohort with a more favorable tumor location. Accordingly, absolute survival times after repeat resection should be considered with caution. In addition, the sample size is relatively small and only allows reduced statistical inference.

**Conclusion**

The results of this study confirm that EOR at recurrence is a significant predictor of outcome in patients with recurrent glioblastoma. According to our findings, patients in good performance status at the time of tumor recurrence should be offered repeat craniotomy with the aim of achieving a maximal resection when it is safe and feasible.

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**References**


