Supratotal Resection of Glioblastoma: Is Less More?

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ABSTRACT

Background: A relationship between the extent of resection (EOR) and survival has been demonstrated in patients with glioblastomas (GBMs). However, despite gross total resection (GTR) of the enhancing nodule (EN), GBMs usually relapse, generally near the surgical cavity.

Objective: The aim of this study was to determine the prognostic role of FLAIR resection of GBMs by analyzing pre- and post-operative MRIs to estimate the EOR of EN, FLAIR-hyperintense regions and total tumor volume (TTV).

Methods: Radiologic and clinical outcomes were analyzed retrospectively. Pre- and post-operative EN volume, pre- and postoperative FLAIR volume (POFV), and pre- and postoperative TTV were analyzed. EOR was then calculated for each component. Time-dependent ROC curves and cut-off values for pre- and post-operative volumes and EOR were calculated. A Kaplan-Meier analysis with the log-rank test and Cox regression analysis were then used to analyze progression-free survival (PFS) and overall survival (OS).

Results: We did not find any correlation between EOR of FLAIR-altered regions and patient survival. On the other hand, there were statistically significant relationships between the prognosis and both a preoperative EN volume less than 31.35 cm³ (p=0.032) and a postoperative EN volume less than 0.57 cm³ (p=0.015). Moreover, an EOR of EN greater than 96% was significantly associated with the prognosis (p=0.0051 for OS and p=0.022 for PFS).

Conclusion: Our retrospective, multi-center study suggests that survival in patients with GBM is not affected by the extent of resection of FLAIR-hyperintense areas.

INTRODUCTION

Primitive brain tumors are a terrible disease with a poor prognosis. They affect about 7/100,000 people/year and represent 25% of all childhood cases; the number of brain tumors diagnosed in all age groups has increased over the years, which has led to an increase in social costs. Patients with a newly diagnosed glioblastoma (GBM) have a median survival time of 14–16 months and an overall survival (OS) rate of 25% at 2 years. Furthermore, less than 10% of these patients live more than 5 years after treatment. Surgery is still the cornerstone of treatment because it provides a histological diagnosis and a molecular profile of the tumor, and cytoreduction has been proven to improve the efficacy of adjuvant therapies. A correlation has been found between the extent of resection (EOR) of gliomas and patient survival, as long as surgery does not result in iatrogenic damage: in fact, a good post-operative neurological status and a Karnofsky Performance Status (KPS) > 70 are generally considered to be primary requirements for adjuvant radiochemotherapy. In cases of GBM, an EOR of more than 78% of the enhancing nodule (EN) has been reported to increase patient survival. However, despite gross total resection (GTR), GBMs tend to relapse, and recurrent tumors usually arise close to the surgical cavity. There is some evidence that the stem cells responsible for tumoral growth and resistance to drugs and radiotherapy can be found all around the EN, in areas with altered signal intensity in FLAIR sequences.

To date, it has not been fully demonstrated that surgical resection of FLAIR-altered regions in GBM patients could improve patient survival. For many surgeons, this is not an issue, since a major surgical resection often carries a higher risk of post-operative deficit and the reversibility of which is still highly unpredictable. On the other hand, these tumors tend to rapidly cause neurological deficits. Therefore, the best approach to GBM surgery still needs to be clarified.

To shed light on this topic, we retrospectively analyzed our series of surgical cases to determine if FLAIR-guided resection in GBM patients could influence the prognosis. The EOR of EN, FLAIR-hyperintense regions and total tumor volume (TTV) (EN plus FLAIR) were calculated from pre- and post-operative MRI images and evaluated in terms of their associations with progression-free survival (PFS) and OS. The main purpose of this study was to determine whether overaggressive surgical resection could improve the oncological control.
MATERIALS AND METHODS

We retrospectively reviewed clinical and radiological data of all patients who underwent GBM resection from May 2015 to January 2018 at the Department of Neurosurgery of the University of Turin and from January 2016 to December 2017 at the Neurosurgical Department of the Catholic University of Rome.

The following inclusion criteria were considered: age over 18 years, histologically proven GBM (WHO 2016 classification), post-operative MRI within 48 h, post-operative adjuvant therapy with the Stupp regimen and follow-up performed at the corresponding facility.

Exclusion criteria consisted of recurrent GBM, post-operative KPS < 70, post-operative complications, adjuvant therapies at other hospitals and lack of follow-up.

The goal of surgery was a maximal safe resection. All procedures were performed with an OPMI Pentero microscope (Carl Zeiss Meditec AG, Jena, Germany) equipped with a Blue 400 fluorescence kit at University of Turin and a Leica 530 OHX (Leica Microsystems, Wetzlar, Germany) equipped with a Blue 400 fluorescence kit was used at University of Rome. Both centers used the guidance of SALA intraoperative fluorescence.

Tumor edges were also checked with neuro-navigation. Neurophysiological monitoring routinely included electrocorticography (ECoG), MEPs, SEPs and direct electrical stimulation (DES) of the cortex and subcortical fascicles. Surgery was stopped in the proximity of eloquent areas to avoid post-operative neurological deficits.

Tumor volume was calculated by neurosurgeons and radiation oncologists with experience in neuro-oncology using Horos® software (The Horos Project) for MacOs (Apple Inc., Cupertino, California) for manual segmentation of T1 and FLAIR 3D volumetric images. EN, FLAIR volume and TTV were calculated for both pre- and post-operative MRI images. Necrotic and cystic areas eventually present in EN were also considered in the evaluation of EN volume. T1 without gadolinium and T2 sequences were evaluated to distinguish blood from postoperative residual tumor. Postoperative diffusion-weighted imaging (DWI) was also considered to rule out postoperative ischemic injury.

The EOR was then calculated as

\[
EOR = \left( \frac{\text{preopVol} - \text{postopVol}}{\text{preopVol}} \right) \times 100.
\]

OS was calculated starting from the date of surgery, while PFS was calculated from the date of surgery to the date of radiological progression disease (PD) according to the RANO criteria. All MRIs were checked with the senior neurooncologist to establish the correct PD time.

All neuroradiological, clinical and histological data were collected and analyzed retrospectively.

Informed consent was obtained from all participants in the study. The study was conducted in accordance with our institution’s ethical standards and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

STATISTICAL ANALYSIS

Data are expressed as mean (±standard deviation) or median [25th;75th percentile] values for continuous variables, as appropriate, and as frequencies and percentages (%) for categorical data. Theoretical cut-offs for EN EOR, FLAIR EOR and TTV EOR were defined using literature data,4,10,14 and the Kruskal–Wallis test, χ² test or Fisher’s exact test was performed as appropriate to determine significant differences among groups in terms of demographics and pathological characteristics.

A time-dependent ROC curve analysis was performed to evaluate the prognostic value of preoperative volumes. A time point was chosen for median survival (i.e., 16 months) and attempts were made to identify the optimal preoperative volume cut-off for every preoperative volume value (FLAIR, EN and TTV). The optimal cut-off value was defined as the point where the True Positive (TP) rate + (1-False Positive) rate was maximal. The obtained cut-off was used to create two groups of patients: those with values less than or equal to the cut-off and those with values greater than the cut-off. A Kaplan–Meier analysis and log-rank test were used to compare OS and PFS between the two groups. Finally, a multivariate Cox regression analysis was performed to assess the associations of the different groups with OS and PFS, while estimating the HRs adjusted for age and O6-methylguanine DNA methyltransferase (MGMT).

The same statistical analysis was carried out to evaluate the prognostic value of post-operative volumes and EOR. All analyses were performed using R, version 3.2.5 (R Core Team, 2018). A p-value <0.05 was taken as the level of significance.

RESULTS

Among the 64 GBM patients included in our retrospective multi-center study, the median age was 64.5 years.

Table I

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total n=64</th>
<th>EOR:99% n=21</th>
<th>EOR:99% n=39</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>64.5[55;70.2]</td>
<td>63[56;69.5]</td>
<td>66[55;73]</td>
<td>0.670</td>
</tr>
<tr>
<td>Female</td>
<td>66[56;70.5]</td>
<td>63[56;69.5]</td>
<td>66[55;73]</td>
<td>0.670</td>
</tr>
<tr>
<td>Sex</td>
<td>63[56;69.5]</td>
<td>66[55;73]</td>
<td>0.670</td>
<td></td>
</tr>
<tr>
<td>MGMT</td>
<td>0</td>
<td>21(53.8)</td>
<td>18(46.2)</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>20(51.3)</td>
<td>19(48.7)</td>
<td>0.725</td>
</tr>
</tbody>
</table>

Data are reported as number of patients (%), mean (±standard deviation) or median [25th;75th percentile], as appropriate. p-values are based on the Kruskal–Wallis test, χ² test or Fisher’s exact test, as appropriate. The series included 4 patients with non-enhancing GBM.
(range 22–81 years), 23 (36%) were female and 41 (64%) were male. All GBMs were IDH1 wild type.

Tables I, II, and III show that the EOR groups were homogenous with respect to age, sex and MGMT.

The mean clinical follow-up duration was 10.66 months (range 0.99–30.05 months) for the entire cohort and 11.56 (range 2.89–30.05 months) months for surviving patients. At the last observation, 44 patients (69%) were alive. No post-operative complications were recorded in this series.

The median preoperative EN volume was 23.14 cm³ (range 0–106.56 cm³), the median preoperative FLAIR volume was 55.20 cm³ (range 5.70–179.17 cm³) and the median preoperative TTV was 99.06 cm³ (range 9.24–227.70 cm³). The median postoperative EN volume was 0 cm³ (range 0–7.50 cm³), the median POFV was 25.40 cm³ (range 0–152.20 cm³) and the median postoperative TTV was 27 cm³ (range 0–152.75 cm³).

The median EOR of EN was 100% (range 39.08%–100%), the median EOR of FLAIR tumor was 49.69% (range 0.17%–100%) and the EOR of total tumor was 65.26% (range 22.73%–100%). The estimated median OS was 16.18 months and the estimated median PFS was 7 months (Fig. 1).

The time-dependent ROC curve analysis showed that, at 16 months (the median OS value in our sample and the value reported in the literature as median of survival), the optimal cut-off for preoperative FLAIR volume was...
Figure 2. Kaplan–Meier survival curves for OS and PFS. The relations of preoperative FLAIR volume (a), postoperative FLAIR volume (b) and FLAIR EOR (c) with OS and PFS were not significant.

Figure 3. Time-dependent ROC curve to evaluate the accuracy of preoperative EN volume for predicting OS at 16 months (a). Kaplan–Meier survival curves (b) for preoperative EN volume (≥31.35 cm³ vs. <31.35 cm³)
All patients were divided into two groups (preoperative FLAIR ≥ 47.87 cm³ and preoperative FLAIR < 47.87 cm³), and no significant differences were found in the corresponding OS distributions (p=0.8). With regard to PFS, a time-dependent ROC curve analysis at 7 months (the median value in our sample) identified an optimal cut-off preoperative FLAIR volume of 52.84 cm³, and no significant differences were found between the high and low groups (p=0.55).

As for the prognostic value of postoperative FLAIR volumes, a time-dependent ROC curve analysis identified an optimal cut-off of 9.46 cm³ for OS and 42.67 cm³ for PFS. In both cases, the differences in the distributions were not significant.

Finally, the prognostic value of FLAIR EOR for OS and PFS was analyzed, and no significant differences were found (Fig. 2).

Next, we investigated whether there was a relationship between EN volume and OS or PFS. A time-dependent ROC curve analysis identified, at 16 months, an optimal cut-off for preoperative EN volume of 31.35 cm³. Patients with a preoperative EN volume < 31.35 cm³ had a significantly longer OS than those with ≥ 31.35 cm³ (p=0.032) (Fig. 3). The multivariate Cox proportional hazards assessment estimated an adjusted HR of 3.11 (95% CI: 1.09–8.88; p = .034) for preoperative EN volume ≥ 31.35 cm³.

A time-dependent ROC curve analysis for PFS identified an optimal cut-off for preoperative EN volume of 32.23 cm³. While the difference between the high and low groups was not significant in a univariate analysis, the adjusted HR for EN volume ≥ 32.23 cm³ was significant (3.83; 95% CI: 1.35–10.87; p = .011).

As for the prognostic value of postoperative EN volume, a time-dependent ROC curve analysis identified an optimal cut-off of 0.57 cm³ for the postoperative EN volume. The OS distributions of patients with postoperative EN ≥ 0.57 cm³ and postoperative EN < 0.57 cm³ were significantly different (p=0.015) (Fig. 4). The adjusted HR for postoperative EN volume ≥ 0.57 cm³ was 3.79 (95% CI: 1.35–10.65; p = .012). PFS also differed according to the post-operative EN volume, with a cut-off of 1.69 cm³ (p=0.022). The estimated adjusted HR for postoperative EN volume ≥ 1.69 cm³ was 10.82 (95% CI: 3.16–36.97; p <0.001).

The prognostic value of EN EOR with respect to OS and PFS was analyzed. A time-dependent ROC curve analysis identified the same optimal cut-off percentage (96%) for both OS and PFS. OS and PFS were significantly longer in patients with an EN EOR ≥ 96% (p <0.001).

Figure 4. Time-dependent ROC curve to evaluate the accuracy of post-operative EN volume for predicting OS at 16 months (a). Kaplan–Meier OS curves for post-operative EN volume (≥ 0.581 cm³ vs. <0.581 cm³) (b). Time-dependent ROC curve to evaluate the accuracy of post-operative EN volume for predicting PFS at 7 months (c). Kaplan–Meier PFS curves for post-operative EN volume (≥ 1.69 cm³ vs. <1.69 cm³) (d).
≥96% (p=0.0051 for OS and p=0.022 for PFS) (Fig. 5). For EN EOR ≥96%, the estimated adjusted HR was 5.35 (95% CI: 1.79–16.03; p = .003) for OS and 2.36 (95% CI: 1.13–4.96; p = .023) for PFS.

Finally, pre-operative and post-operative volumes and EOR of the TTV volume were studied, and no significant relationships were found between the obtained values, for both OS and PFS.

**DISCUSSION**

The prognostic value of EOR for GBMs has remained a longstanding issue. There is a lot of evidence in the literature that, for low-grade gliomas (LGGs), there are correlations between EOR (and supratotal resection) and clear improvements in OS, PFS and the time-delay in malignant transformation. However, there is no similar robust literature for GBMs. For LGGs, FLAIR abnormality is used to delineate the tumor burden and the completeness of resection, whereas for GBMs, only ENs are used and FLAIR perinodular hyperintensity is generally ignored. In a retrospective study on 416 GBM patients, Lacroix et al. showed that an EOR of 98% of the EN was associated with a survival advantage. In this study, aggressive resection of 98% or more of the EN was a significant independent predictor of patient survival in the overall patient population. In a retrospective study on 500 patients, Sanai and co-workers challenged the doctrine of all-or-none, and demonstrated that an EOR greater than 78% of the EN is related to an improvement in OS.

These studies illustrate the prognostic value of surgery. However, even in cases of GTR, patients experience relapse. In particular, 80% of the recurrences materialized within peritumoral FLAIR hyperintensity, about 2 cm from the surgical cavity. This suggests that peritumoral edema/infiltration may influence OS and PD. Several studies, in which biopsy of the non-enhancing area surrounding the EN was performed, confirmed that this region is usually infiltrated by tumor cells. In a single-center retrospective study on 1229 patients, Li et al. showed that resection of ≥ 53.21% of the surrounding FLAIR-hyperintensity beyond EN GTR was associated with a significant prolongation of OS compared with less-extensive resection (median survival time of 20.7 vs. 15.5 months, respectively). Pessina et al. retrospectively analyzed a cohort of 282 patients and confirmed the value of supratotal resection of EN.
removal threshold for predicting survival was 45%. Kotrotsou et al. recently correlated residual post-operative FLAIR volume (POFV) with OS and showed that a POFV less than 0.70.2 cm³ is associated with a better prognosis. In their retrospective analysis of 245 GBM patients, Mampre et al. reported that resection of the FLAIR region beyond EN did not correlate with OS or recurrence.

In our series, correlations were found between patient survival and both EN volume and EN EOR. Our results suggest that a preoperative EN volume greater than 31.35 cm³ and a postoperative EN volume below 0.57 cm³ are correlated with a better prognosis regarding OS, while a residual EN volume lower than 1.69 cm³ is related to a longer PFS. Moreover, an EOR greater than 96% of EN was associated with longer OS and PFS. However, we failed to demonstrate that supratotal resection of the EN would give better oncologic control of the disease (Figs. 6,7).

Our study has some limitations, partly due to the limited number of patients and events (deaths). This is related to the rarity of this pathology and the strict inclusion/exclusion criteria used to select a homogenous sample. Moreover, some limitations are intrinsic to the retrospective design of the study and the lack of an a priori power analysis to determine the sample size.

However, our findings open the way for further investigations to determine if supratotal resection of EN has prognostic value.

### CONCLUSION

In this study, we did not find a correlation between FLAIR resection and survival time in patients with GBM. The data showed a better prognosis in patients with a preoperative EN volume less than 31.35 cm³, a postoperative EN volume less than 0.57 cm³ and an EOR of EN greater than 96%. Further studies, including prospective, double-blind studies, with more patients should be carried out to confirm the prognostic value of FLAIR component resection in GBM patients.

### AUTHORS’ DISCLOSURES

The authors declare that there are no conflicts of interest.

### REFERENCES