Is There a Role for Surgical Resection of Multifocal Glioblastoma? A Retrospective Analysis of 100 Patients

# Is there a role for surgical resection of multifocal Glioblastoma Multiforme? A retrospective analysis of 100 patients

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**KEYWORDS:**

Extent of Resection; Glioblastoma multiforme (GBM); multifocal GBM; multicentric GBM; Survival; Brain Tumor

**CONFLICT OF INTEREST:**

None.

**DISCLOSURE OF FUNDING:**

None.

## ABSTRACT

**Background.** Glioblastoma with multiple localizations (mGBM) can be defined as multifocal, where enhancing lesions present a connection visible on MRI FLAIR imaging, or multicentric, in absence of a clear dissemination pathway.

**Objectives.** To evaluate the role of the extent of resection (EOR) in the treatment of mGBMs and its correlation with overall survival (OS) and progression free survival (PFS).

**Methods.** One hundred patients with mGBMs were treated at our Institution between 2009 and 2019. Clinical, radiological and follow-up data were collected. EOR of the contrast-enhancing part of lesions was classified as gross total resection (GTR, absence of tumor remnant), subtotal resection (STR, residual tumor <30% of the initial mass), partial resection (PR, residual tumor >30% of the initial mass) and needle- or open-biopsy (residual tumor >75% of the initial mass).

**Results.** 15% of patients underwent GTR, 14% STR, 32% PR and 39% biopsy. OS was 17 months for GTR, 11 months for STR, 7 months for PR and 5 months for biopsy, with significantly increased OS with greater EOR ($p < 0.001$). Patients receiving resection showed longer PFS with progressively greater EOR ($p = 0.04$). EOR was an independent prognostic factor influencing the PFS (p=0,029; HR 1,335; 95% CI 1,029-1,731) and the OS ($p = 0.005$; HR = 1.598; 95% CI 1.155-2.211).

**Conclusion.** Our study suggests that EOR is a significant predictor of survival in patients with mGBM similarly to patients with unifocal GBM, with greater EOR (gross total and subtotal resection) being positively correlated with longer PFS and OS.



**Keywords**: Extent of Resection; Glioblastoma multiforme (GBM); multifocal GBM; multicentric GBM; Survival; Brain Tumor

## Introduction

Glioblastoma (GBM) is the most frequent malignant primary brain tumor[1]. It has the poorest prognosis among brain malignancies[2, 3], with an overall survival (OS) ranging from 3-18 months[4] and a 2-year survival rate of only 5–10%[5, 6]. Patients with GBM usually present a single enhancing lesion but may also harbour a discrete number of enhancing foci[7]. GBMs with multiple localizations (mGBM) can either be defined as multifocal, where enhancing lesions present a connection visible on MRI FLAIR imaging[8], or multicentric, where multiple lesions do not present a continuity on FLAIR or a clear dissemination pathway (i.e. white matter tracts, cerebrospinal fluid, hematogenous spread, local extension)[8, 9]. Multifocal GBMs account for 12-35% of cases, while true multicentric GBMs are rare, with an incidence of 2-6% of patients[8].

The standard of care for newly diagnosed unifocal GBM is represented by maximal safe surgical resection, followed by chemo-radiation as per Stupp protocol[10, 11, 12, 13]. Over the last years, a growing evidence highlighted the correlation between the extent of resection (EOR) and survival[14, 15, 16, 17]. However, the relevance of the EOR in mGBMs remains unclear so well as the role of surgery itself. The aim of our study was to evaluate the role of EOR in the context of multi-modal treatment of mGBMs and its correlation with overall survival (OS) and progression free survival (PFS).

## Methods

### Study design and setting

A retrospective analysis of patients with a histological diagnosis of GBM (grade IV, WHO 2016) consecutively treated at Institute of Neurological Sciences of Bologna from January 2009 to December 2019 was performed. A total of 624 adult patients (>18 years) who underwent surgical resection of GBM was identified. Of these, 100 patients presented with a mGBM and were included in the study. Patient who underwent prior surgery for GBM were excluded.

### Ethics

The study was approved by the local IRB (Nr. 186/2019/OSS/AUSLBO-19031; March 2019). All patients signed a written consent for the use of their clinical data for scientific purposes. Further consent for this study was waived because of the retrospective observational nature of the study.

### Definitions

mGBMs were classified as multifocal or multicentric depending on the presence of a FLAIR-signal alteration connecting discrete enhancing lesions on T1-weighted images, according to previous studies[7, 8, 9, 18]. Multicentric GBMs presented with absence of connections on FLAIR sequences (**Figure 1**). The shortest distance between the foci in axial, coronal or sagittal plane was measured and stratified as <10 mm or >10 mm in multifocal lesions. Multicentric lesions were considered separately. If there were more than two lesions, the greatest distance was considered. Data concerning the hemisphere involved, number of lesions, localization, maximum diameters (on axial, coronal and sagittal view) and volumetric data of each lesion were collected.

**Data sources**

Past medical history, neurological status, symptoms and Karnofsky performance status (KPS) at presentation were collected from patient charts. For each patient, neuroradiological imaging was reviewed by neurosurgeons and neuroradiologists to classify lesions as multifocal or multicentric and to calculate distances, diameters, and volumes as described above.

Histological and molecular markers data, and surgical and medical complications occurred in the post-operative period were collected. Post-operative imaging was performed for each patient, along with neurological and clinical examination and KPS evaluation.

Pre- and post-operative tumor volume analyses were performed to calculate the extent of resection (EOR), that was classified as gross total resection (GTR: absence of tumor remnant), subtotal resection (STR, residual tumor <30% of the initial mass), partial resection (PR, residual tumor >30% of the initial mass) and needle- or open-biopsy (residual tumor >75% of the initial mass). EOR was referred to the contrast-enhancing part of lesions.

Furthermore, data regarding adjuvant therapies (radiotherapy, chemotherapy, re-do surgery) and clinical follow-up (date of progression, last clinical or radiological follow-up, performance status, date of death) were recorded.

**Statistical Methods**

Descriptive data are presented as median when non-normally distributed, and as mean when normally distributed. Pearson's Chi-square test was used for comparisons of categorical variables. The survival function was calculated with Kaplan-Meier curves and compared for each variable (extent of tumor resection and multicentricity/multifocality) using the log-rank test. Finally, multivariate analyses between variables related to the survival function were performed using Cox Regression. Analyses were performed with IBM SPSS Statistics 27 for Mac (IBM, Armonk, New York).

## Results

In our series, 100 patients met the inclusion criteria. The incidence of newly diagnosed multifocal or multicentric GBM was 16% (100/624). Eighty-two patients presented with multifocal GBM (13.1%), while a multicentric GBM was found in 18 patients (2.88%).

### Clinical Characteristics

The median age at presentation was 62 years (range 38-80). There were 63 male and 37 female patients (M:F = 1.7). The most common general symptoms at presentation were seizure (33%), headache (22%), confusion (20%), cognitive decline (17%) and mood changes (12%). At the pre-operative neurological examination, the majority of patients (70%) presented with focal neurological deficits, related to the localization of the lesions. Median KPS score was 80 (range 50-100). Pre-operative clinical characteristics of patients are summarized in Table 1.

### Radiological and histological findings

Seventy-six percent of patients presented with a single hemisphere involvement, while both hemispheres were involved in 21% of cases. Two patients (2%) presented a midline mGBM and one (1%) showed a posterior fossa extension. The vast majority of patients presented with 2 lesions (n = 62), while more than 2 discrete contrast-enhancing masses were detected in 38 patients (multifocal = 5, multicentric = 33). In the multicentric cohort, all the 18 patients presented with a distance between masses greater than 15 mm, with a distance >20 mm in 16 patients. Midline shift was identified in 21 pre-operative MRI. Corpus callosum invasion was observed in 32 patients. The mean total volume was 42.09 cm3. A summary of radiological features is detailed in Table 2.

Based on the available data, MGMT promoter methylation was present in the 45% of cases. One patient presented an IDH-1 mutation, and no one showed an IDH-2 mutation, as summarized in Table 2. There were no differences of MGMT methylation and IDH1 mutation in patients receiving resection versus biopsy and according to the EOR at Pearson's Chi Square test (MGMT for intervention: $X^2 = 2.429$, $p = 0.119$; MGMT for EOR: $X^2 = 0.634$, $p = 0.426$; IDH1 for intervention: $X^2 = 1.381$, $p = 0.24$; IDH1 for EOR: $X^2 = 0.536$, $p = 0.464$).

### Surgical and clinical outcome

GTR of the contrast-enhancing lesions was achieved in 15 patients (multifocal = 13; multicentric = 2). All patients who underwent GTR presented lesions in non-eloquent areas, therefore a greater resection was feasible without post-operative sequelae. All patients in which GTR was obtained

presented a post-operative KPS >70. STR was achieved in 14 patients (multifocal = 11; multicentric = 3) while 32 patients underwent a PR (multifocal = 25; multicentric = 7). Thirty-nine patients underwent biopsy (multifocal = 33; multicentric = 6). In the STR and PR groups, the resection was arrested to preserve eloquent areas identified during pre- and intra-operative evaluation. The different extent of resection in mGBMs groups are summarized in Table 3.

After surgery, every patient underwent a neurological examination to assess neurological outcome and to evaluate the post-operative KPS, as described in Table 4. In the 77% of the patients, the post-operative neurological status was unchanged. The vast majority of patients (72%) presented a stable KPS (n = 72). The KPS score of 6 patients improved after surgery, due to the reduction of the mass effect, while in 22 patients the KPS worsened. Ten of these presented a post-operative KPS <70. Only 4 of these patients, however, presented a pre-operative KPS >70.

The overall surgical morbidity was 8% (all patients presented multifocal disease) and there were no peri-operative deaths. Most complications did not result in permanent sequelae and included 3 post-operative bleeding that required a prompt surgical evacuation, 1 deep venous thrombosis, 2 post-operative pneumonia and 1 systemic infection that were resolved with antibiotic therapy. One patient presented post-operative seizure that required anti-epileptic drugs treatment.

**Adjuvant therapies**

Adjuvant therapies included radiotherapy, chemotherapy (temozolomide and/or experimental agents) and redo-surgery. Seventy-five patients (75%) received adjuvant therapies (multifocal = 59; multicentric = 16). Of these 75 patients, 48 underwent a resection (GTR, STR, PTR) while 27 a biopsy. Pearson's Chi-square test analysis revealed a significant correlation between resection and subsequent start of adjuvant therapies ($p = 0.028$). Twenty-five patients were excluded from post-operative radio-chemotherapies because of a rapid neurological decline. The vast majority of the patients (73 out of 75) underwent both radiotherapy and chemotherapy as per Stupp protocol.

**Follow-up and survival analyses**

Median length to last follow up was 6 months (range from 2 to 57). Status at last follow-up was defined as stable disease, progression, and death. Kaplan-Meier curves were generated for patients receiving biopsy, PR, STR and GTR, and compared using log-rank tests (**Fig. 2**). The median progression-free survival (PFS) was 9 months for GTR, 5 months for STR, 2 months for PR and biopsy. Patients receiving resection, therefore, showed higher PFS with progressively greater EOR ($p = 0.04$). Kaplan-Meier curves showed the same for OS. In fact, the median OS was 17 months for

GTR, compared to 11 months for STR, 7 months for STR and 5 months for biopsy. There was a significantly increased overall survival (OS) with greater EOR (p = <0.001).

The multivariate Cox Regression was performed to produce survival curves and hazard function for treatment groups adjusted for age at presentation, KPS, MGMT methylation, IDH-1 mutation and complementary therapies (**Fig. 3**). Multivariate models show that EOR is an independent prognostic factor that significatively influence the PFS (p=0.029; HR 1.335; 95% CI 1.029-1.731). On the Multivariate Cox Regression, the EOR was significantly related to the OS (p = 0.005; HR = 1.598; 95% CI 1.155-2.211). Others independent prognostic factors related to greater OS were lower age (p = 0.002; HR = 1.064; 95% CI 1.024-1.106) and adjuvant therapies (p = 0.009; HR = 0.319; 95% CI 0.135-0.755).

Comparison between multifocal and multicentric groups in terms of PFS and OS are shown in **Figure 4**. There were no differences in median PFS (3 months for multifocal; 1 months for multicentric; p = 0.699) and OS (8 months for multifocal; 9 months for multicentric; p = 0.9). No significant differences between these two groups were found with the multivariate model.

## Discussion

In this study, we collected the largest series of mGBMs reported in the literature. Multiple-lesions GBMs accounted for 16% of all GBM patients who underwent surgery in a 10 years period at our Institution. The circumstance of multifocality appears, therefore, only relatively rare and the criteria adopted to classify this subgroup of tumors play a major role in the evaluation of their impact. Our criteria were borrowed from previous studies[7, 8, 9, 18]. Furthermore, the incidences of multifocal GBMs (13.1%) as well as that of multicentric GBMs (2.9%) are consistent with those reported in the literature[19, 20, 21]. This corroborates the appropriateness of our definition of multiple GBMs.

GBM is often a diffuse disease at time of diagnosis and it is likely that a microscopic invasion of white matter can lead to the development of multifocal masses. These tumors are often considered inoperable because of the supposed widespread diffusion around the brain, the dismal prognosis[22], and the frequent involvement of eloquent areas[23]. Thus, a conservative attitude is often adopted, resulting in a biopsy-based approach followed by adjuvant treatment.

However, simple biopsy results in a reported median OS of only 6.6 months, and even if followed by chemo-radiation in good performing patients, median OS remains of only 9.4 months[24]. EOR has been proven to positively influence survival in GBM. Several studies have analysed such a correlation, also identifying specific thresholds of resection above which better outcomes are obtained, established first at 98% by Lacroix et al.[14] and later at 78% by Sanai et al.[15].

Although the exact role of surgical resection in multifocal GBMs is not clear, it is reasonable that EOR may influence the outcome also in these lesions. Beyond the effects of EOR on tumor repopulation, surgical cytoreduction improves the efficacy of adjuvant therapies by reducing hypoxic behaviour of tumor cells, facilitating diffusion of chemotherapeutic agents, and relieving symptoms of the disease[24, 25] along with mass effect. In a recent study on the topic, Di et al.[18] analysed 34 patients with mGBMs receiving resection and biopsy from 2011 to 2019 and identified a correlation between resection and increased OS, suggesting that grater resection may confer increased OS even in patients with mGBMs compared to biopsy only, similarly to what is found in unifocal tumors[26, 27, 28, 29]. Our findings substantially confirm these results providing further evidence of a favourable effect of EOR on OS and PFS in these patients.

Whether EOR plays a different role in multifocal versus multicentric tumors is another important issue. The comparative analysis of those two entities showed that PFR and OS between these two groups respond similarly to different EOR degrees (**Fig. 3**). This result is consistent with previous observations[7, 9]. On this basis, multifocal and multicentric GBM may be considered a subgroup of GBM sharing similar outcome in relation to EOR.

Our results suggest that greater EOR are associated to longer PFS and OS, and that this apply specifically to younger patients and to those who retain the possibility to receive adjuvant therapies. In our series, median pre-operative KPS was 80, and post-operatively we found that 78% of patients had an unchanged or improved performance status, freed from excess morbidity and perioperative mortality. Thus, treatments were in line with the principles of maximal safe resection[30], allowing access to adjuvant treatments in 75% of cases in our series.

## Limitations

The study presents limitations that need to be addressed. Firstly, its retrospective design could have affected results by generating biases, including an effect of age, eloquence, tumor volume and performance status on the selection of the surgical strategy (i.e. biopsy versus attempted GTR). We tried to reduce the influence of this effect through use of multi-variate analysis to evaluate the role of age at diagnosis, number of lesions, location of the lesions, and pre-operative tumor volume.

We included in this series patients with tumoral foci distant less than 10 mm each other, which pose surgical issues more similar to those of unifocal tumors than to those of multicentric GBM. Nevertheless, our interpretation reflects a general definition of the problem present in the literature. Furthermore, we separated patients in two categories according to distance among tumor foci. Results suggest that the benefits of greater degrees of EOR are similar in patients with close or distant lesions.

## Conclusions

Multiple glioblastomas still raise questions about their management and the standard of care for this disease has yet to be clarified. The role of surgery remains controversial, with a biopsy-only approach widely adopted. Our results suggest that EOR is a significant predictor of survival also in patients with mGBM, with greater EOR (gross total and subtotal resection) being positively correlated with longer OS and PFS. This study therefore suggests a more resolved approach in the surgical treatment of mGBMs.

## Disclosures

Nothing to Disclose.

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419 **FIGURE LEGENDS**

420

421 **Table 1.** Pre-operative clinical characteristics.

422

423 **Table 2.** Radiological and histological findings.

424

425 **Table 3.** Extent of resection in the multicentric and multifocal GBMs cohorts.

426

427 **Table 4.** Post-operative evaluation.

428

429 **Figure 1. A-D.** Pre- and post-operative MRI of mGBMs. **A-B.** Pre- and post-operative imaging of a
430 left frontal and temporal multifocal GBM. The patient underwent awake craniotomy to monitor
431 speech function. The resection of the frontal nodule was possible without postoperative deficits. **C-**
432 **D.** Pre- and post-operative imaging of a patient with bi-parietal multicentric GBM who underwent
433 gross total resection under motor function mapping. Gross total resection was achieved without new
434 neurological deficits.

435

436 **Figure 2. A-B.** Kaplan-Meier curves comparing Progression Free Survival and Overall survival.
437 There was significantly media PFS (p = 0.04, **A**) and median OS (p = <0.001, **B**) between the EOR
438 groups.

439

440 **Figure 3. A-B.** Hazard Function curves comparing OS and PFS between the EOR groups.
441 Multivariate Cox Regression was performed for treatment groups and adjusted for: age at surgery,
442 KPS, adjuvant therapies, MGMT methylation and IDH1 mutation. **A.** Cox regression analysis showed
443 that EOR is an independent factor that significatively influence the PFS (p=0,029; HR 1,335; 95% CI
444 1,029-1,731). **B.** The Cox regression found an increased hazard of death for biopsy compared to the
445 other groups (p = 0.005; HR = 1.598; 95% CI 1.155-2.211).

446

447 **Figure 4.A-D.** Kaplan-Meier and Hazard Function curves comparing Progression Free Survival and
448 Overall survival in multifocal and multicentric groups. **A-B.** There were no differences in PFR (p =
449 0.699) and OS (p = 0.9) between the two groups. **C-D.** Multivariate Cox Regression did not show
450 significant differences.

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