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

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35 **KEYWORDS:**

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

38

39 **CONFLICT OF INTEREST:**

40 None.

41

42 **DISCLOSURE OF FUNDING:**

43 None.

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45

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

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Introduction

Glioblastoma (GBM) is the most frequent malignant primary brain tumor¹. It has the poorest prognosis among brain malignancies^{2,3}, with an overall survival (OS) ranging from 3-18 months⁴ 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 foci⁷. GBMs with multiple localizations (mGBM) can either be defined as multifocal, where enhancing lesions present a connection visible on MRI FLAIR imaging⁸, 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 patients⁸.

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.

122

123 **Data sources**

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

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

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

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

139

140 **Statistical Methods**

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

147

148 **Results**

149

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

153

154 **Clinical Characteristics**

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

161

162 **Radiological and histological findings**

163 Seventy-six percent of patients presented with a single hemisphere involvement, while both
164 hemispheres were involved in 21% of cases. Two patients (2%) presented a midline mGBM and one
165 (1%) showed a posterior fossa extension. The vast majority of patients presented with 2 lesions (n =
166 62), while more than 2 discrete contrast-enhancing masses were detected in 38 patients (multifocal =
167 5, multicentric = 33). In the multicentric cohort, all the 18 patients presented with a distance between
168 masses greater than 15 mm, with a distance >20 mm in 16 patients. Midline shift was identified in 21
169 pre-operative MRI. Corpus callosum invasion was observed in 32 patients. The mean total volume
170 was 42.09 cm³. A summary of radiological features is detailed in Table 2.

171 Based on the available data, MGMT promoter methylation was present in the 45% of cases. One
172 patient presented an IDH-1 mutation, and no one showed an IDH-2 mutation, as summarized in Table
173 2. There were no differences of MGMT methylation and IDH1 mutation in patients receiving
174 resection versus biopsy and according to the EOR at Pearson's Chi Square test (MGMT for
175 intervention: $X^2 = 2.429$, $p = 0.119$; MGMT for EOR: $X^2 = 0.634$, $p = 0.426$; IDH1 for intervention:
176 $X^2 = 1.381$, $p = 0.24$; IDH1 for EOR: $X^2 = 0.536$, $p = 0.464$).

177

178 **Surgical and clinical outcome**

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

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

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

193 The overall surgical morbidity was 8% (all patients presented multifocal disease) and there
194 were no peri-operative deaths. Most complications did not result in permanent sequelae and included
195 3 post-operative bleeding that required a prompt surgical evacuation, 1 deep venous thrombosis, 2
196 post-operative pneumonia and 1 systemic infection that were resolved with antibiotic therapy. One
197 patient presented post-operative seizure that required anti-epileptic drugs treatment.

198

199 **Adjuvant therapies**

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

207

208 **Follow-up and survival analyses**

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

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

217 The multivariate Cox Regression was performed to produce survival curves and hazard
218 function for treatment groups adjusted for age at presentation, KPS, MGMT methylation, IDH-1
219 mutation and complementary therapies (**Fig. 3**). Multivariate models show that EOR is an
220 independent prognostic factor that significantly influence the PFS ($p=0.029$; HR 1.335; 95% CI
221 1.029-1.731). On the Multivariate Cox Regression, the EOR was significantly related to the OS ($p =$
222 0.005 ; HR = 1.598; 95% CI 1.155-2.211). Others independent prognostic factors related to greater
223 OS were lower age ($p = 0.002$; HR = 1.064; 95% CI 1.024-1.106) and adjuvant therapies ($p = 0.009$;
224 HR = 0.319; 95% CI 0.135-0.755).

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

229

230 **Discussion**

231

232 In this study, we collected the largest series of mGBMs reported in the literature. Multiple-lesions
233 GBMs accounted for 16% of all GBM patients who underwent surgery in a 10 years period at our
234 Institution. The circumstance of multifocality appears, therefore, only relatively rare and the criteria
235 adopted to classify this subgroup of tumors play a major role in the evaluation of their impact. Our
236 criteria were borrowed from previous studies^{7,8,9,18}. Furthermore, the incidences of multifocal GBMs
237 (13.1%) as well as that of multicentric GBMs (2.9%) are consistent with those reported in the
238 literature^{19,20,21}. This corroborates the appropriateness of our definition of multiple GBMs.

239 GBM is often a diffuse disease at time of diagnosis and it is likely that a microscopic invasion of
240 white matter can lead to the development of multifocal masses. These tumors are often considered
241 inoperable because of the supposed widespread diffusion around the brain, the dismal prognosis²²,
242 and the frequent involvement of eloquent areas²³. Thus, a conservative attitude is often adopted,
243 resulting in a biopsy-based approach followed by adjuvant treatment.

244 However, simple biopsy results in a reported median OS of only 6.6 months, and even if
245 followed by chemo-radiation in good performing patients, median OS remains of only 9.4 months²⁴.
246 EOR has been proven to positively influence survival in GBM. Several studies have analysed such a
247 correlation, also identifying specific thresholds of resection above which better outcomes are
248 obtained, established first at 98% by Lacroix et al.¹⁴ and later at 78% by Sanai et al.¹⁵.

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

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

264 Our results suggest that greater EOR are associated to longer PFS and OS, and that this apply
265 specifically to younger patients and to those who retain the possibility to receive adjuvant therapies.
266 In our series, median pre-operative KPS was 80, and post-operatively we found that 78% of patients
267 had an unchanged or improved performance status, freed from excess morbidity and perioperative
268 mortality. Thus, treatments were in line with the principles of maximal safe resection³⁰, allowing
269 access to adjuvant treatments in 75% of cases in our series.

270

271 **Limitations**

272

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

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

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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 significantly 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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452