ISSN 1220-8841 (Print)
ISSN 2344-4959 (Online)

ROMANIAN
NEUROSURGERY

Vol. XXXVII | No. 2 June 2023

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DOI: 10.33962/roneuro-2023-034

Romanian Neurosurgery (2023) XXXVII (2): pp. 190-197
DOI: 10.33962/roneuro-2023-034
www.journals.lapub.co.uk/index.php/roneurosurgery

Role of extent of resection on the survival of glioblastoma multiforme. A monocentric retrospective study

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Abstract

Background. Glioblastoma Multiforme (GBM) is the most prevalent form of brain cancer. The effect of Extent of Resection (EOR) on GBM survival is controversial. EOR degree, pre- and postoperative tumour volume estimation, and significance to residual tumour volume are still challenged. GBM has a 14-month Overall Survival (OS) rate. There is no evidence of a link between EOR and OS survival. We wish to determine whether GBM tumour removal increases survival.

Methods. At the Regional Center for Neurosurgery and Neurology in Uzhhorod, Ukraine, we conducted a retrospective evaluation of 86 consecutive patients diagnosed with glioblastoma who underwent surgery between January 1, 2010, and December 31, 2020, and who are being followed until January 1, 2022. Patients were selected if they met the following criteria: they were at least 18 years old, they had a diagnosis of glioblastoma (primary, secondary, or recurrent), they were either IDH mutants or wild types, they had an MRI within 2 weeks before surgery, and they had another MRI within 72 hours after surgery. Before and after surgery, we did a volumetric analysis of gadolinium-enhanced T1 MRI scans of the tumour to figure out EOR. Partial resection (PR) is <70%, sub-total resection (STR) is 70-90%, near-total resection (NTR) is 91-99%, and gross total resection (GTR) is >99%. By comparing pre- and post-operative volumes with the EOR, the Kaplan-Meier survival curve and Cox's regression analysis determined the impact of the EOR on survival rates. Many researchers considered a p value of 0.05 or below to be significant.

Results. A total of 86 patients were included in the analysis after being subjected to the criteria used to narrow the pool of potential participants. The average length of time people lived was 15 months. For PR patients, the median survival time was 3 months, for STR patients it was 10 months, and for NTR patients it was 16 months. Patients receiving GTR, on the other hand, had a considerably better outcome, with a median survival time of 36 months. This data demonstrate a direct correlation between EOR and survival rates. It was discovered that EOR improvement affected post-op survival. High EOR patients have a better prognosis for survival. Adjuvant therapy, pre- and post-operative KPS score, pre- and post-operative tumour volume, and gender also contributed significantly to enhanced survival.

Conclusion. Patients with glioblastoma appear to benefit from a more aggressive treatment strategy that combines maximal safe resection with the use of salvage adjuvant therapy. There was a correlation between complete resection (gross total resection) of intracranial GBM and improved survival. Whenever feasible, complete surgical removal of the tumour is recommended.

Keywords
glioma,
GBM,
extent of resection,
glioblastoma multiforme

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ISSN online 2344-4959
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First published
June 2023 by
London Academic Publishing
www.lapub.co.uk

Introduction

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults [1]. There is currently no agreed-upon drug, surgery, or radiation therapy regimen for treating GBM [2]. The surgical component of treatment may consist of anything from a craniotomy to a minimally invasive biopsy (GTR).

However, not all patients have a radical resection [3], despite improvements in 5-aminolevulinic acid-guided intraoperative procedures that increase the EOR that can be achieved during surgery. Large retrospective cohort studies in the field of neuro-oncology have shown better survival with greater EOR in patients with a newly diagnosed GBM, and mathematical modeling of retrospective data implies incremental gains in survival with EORs ranging from 78% to 98% [4,5].

The current set of known predictive markers for glioblastoma includes age, preoperative health performance status, tumor resection, and postoperative adjuvant therapy [6-9]. It is challenging to achieve entire excision of tumors despite evidence that it can improve overall survival (OS) [10,11,12] because to the risk of neurologic function deficiencies such as paralysis, aphasia, and others, which can reduce quality of life and finally limit longevity.

However, reaching this goal of GTR can be challenging due to the peculiarities of brain anatomy and the fear of damaging expressive structures, lowering life quality. Pathologic and radiologic investigations show that GBM often invades multiple lobes and both hemispheres at diagnosis [13-16].

Age, [17] preoperative performance status according to the KPS,[18] tumor location,[19] and preoperative MR imaging characteristics of the tumor,[20] and whether radiation therapy or chemotherapy is delivered affect a patient's prognosis after being diagnosed with GBM. Due to the interconnectedness of these characteristics, a multivariate analysis is required to identify the influence of surgical resection on survival and the subset of patients for whom extensive resection is most advantageous. We wanted to establish if surgical resection, as assessed by preoperative and postoperative tumor volumes, has predictive significance and to examine survival durations in defined patient subpopulations in relation to tumor resection. Finding out what aspects of life are connected to EOR was the driving force behind this research. Time-to-event analysis is a useful tool for studying GBM patients, but it should only be used when the confounders have been properly addressed.

Patients and methods

Materials and methods:

The Uzhhorod Regional Center of Neurosurgery and Neurology cared for 120 patients diagnosed with GBM between 2010 and 2020. For this statistical analysis, we did not include 86 individuals who had been lost to follow-up, had insufficient information, or were younger than 18 years old. Eighty-six patients' medical records were examined in retrospect. The patients who participated in our study broke down as follows: 55 men (63.95 percent), with a mean age of 52.76, and 31 women (36.05 percent), with a mean age of 50.32. Our inclusion criteria meant that these patients' records met our minimum standards for inclusion, thus we used them in our analysis. We performed surgery on adults diagnosed with GBM (astrocytoma, grade IV, as determined by histopathology). Results were tracked until January 2022. Patients were enrolled if a full clinical dossier was available, including information about the patient's background, current condition, previous medical history, radiographic results, surgical specifics, tumor features, and pathology reports.

Diagnosis and follow-up

All patients were judged to have the potential for headache and other regional neurological abnormalities. All patients who met these criteria underwent a preoperative MRI with and without gadolinium. No surgical patient was allowed to wait longer than 72 hours before undergoing an MRI scan. Patients were followed for a median of 36 months (range: 2-144 months) after hospital discharge. All patients were followed up with serial MRI scans. Moreover, data on postoperative quality of life and recurrence was gathered via telephone interviews, clinical examinations, and imaging. The aberrant mass was initially revealed by a T1-weighted magnetic resonance imaging scan, and a resection biopsy was used to confirm the diagnosis, as previously described in the medical literature. Independent neuroradiologists evaluated preoperative T1 contrast-enhanced MRI sequences

to quantify tumor volume. Using T1 contrast-enhanced images in the axial (A), sagittal (B), and coronal planes, the tumor's maximum diameters were measured, and the tumor's volume was then computed using the volumetric approach, as V = (AxBxC/2) cm3. Within 72 hours of the procedure, we took a second MRI scan (post-operative) and used the same volumetric method as before to determine the post-operative volume. Patients who underwent follow-up MRI were monitored for recurrence, clinical symptoms, and mortality through January 2022. Family members, phone calls, and messages were used to verify all deaths.

Data management and analysis

The size of the tumor before surgery (X) was divided into four groups: 1) less than 20 cm3, 2) between 20 and 50 cm3, 3) between 51 and 100 cm3, and 4) greater than 100 cm3, while the size of the tumor after surgery (Y) was divided into groups ranging from 1 to 10 cm3, 20 to 50 cm3, and 51 to 100 cm3. The EOR was calculated using the volume before and after surgery (X-Y/X*100%). After obtaining EOR% once more, we categorized our data as follows: 1) Gross total resection (GTR), 2) Near complete resection (NTR), 3) Sub-total resection (STR), 4) Partial resection (PR), and 5) Biopsy for outcomes with EOR% of 70% or lower. Our study focused primarily on how long patients lived after surgery. The data allowed us to conduct a Kaplan-Meier analysis of survival for GBM patients, with survival time measured in months post-op and separated into groups based on the percentage of endotracheal intubation used (EOR). We used a log-rank test to determine the effect of EOR percentage on survival, and we used COX regression analysis models to determine the effect of pre- and post-op volumes on median survival time.

Results

When strict inclusion criteria were applied, only 86 patients were considered for further study. For the population as a whole, the median survival time was 15 months. Those diagnosed with PR lived an average of 3 months longer than those diagnosed with STR or NTR, while those diagnosed with NTR lived 16 months longer than those diagnosed with PR. But patients who had GTR had a much better outcome, with a median survival time of 36 months. It reveals that there is a linear link between survival and EOR. Longevity post-operation was observed to be affected by an increase in EOR. High EOR predicts a higher life expectancy for patients.

Survival outcomes

Kaplan-Meier Analysis with EOR

The Kaplan-Meier test was used to compare the median post-operative survival times of patients in each EOR group. The significance level for the log rank test was high (X^2 (4) = 118.03, p .001). (Table 1). It demonstrates that there is a statistically significant variation in death rates among EOR categories. Patients who had BIOPSY had a median survival time of 12 months after surgery. Patients with an EOR of 70% or lower had a median survival duration of 3 months. With an EOR of 70-90%, patients had a median survival period of 10 months after surgery. Patients with 91-99% EOR levels have a median survival time of 16 months following surgery. However, for those with an EOR of >99%, the median time to death is 36 months (Table 2). It shows that there is a linear relationship between survival and EOR. Increase in EOR was found to have an influence on the time of survival since operation (Fig 1). Patients with high EOR are more likely to survive longer.

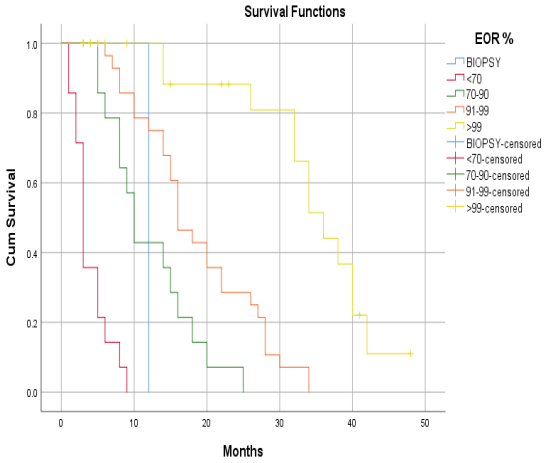

Figure 1. Kaplan-Meier Survival Graph with EOR as Factor Variable for GBM

Table 1. Log Rank Test for EOR and Survival for GBM

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	118.032	4	.000
Test of equality of survival distributions for the different levels of EOR %.			

Table 2. Median Survival Time Based on EOR Levels for GBM

EOR %	Median			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
BIOPSY	12.000	.	.	.
<70	3.000	.359	2.297	3.703
70-90	10.000	.926	8.185	11.815
91-99	16.000	1.583	12.897	19.103
>99	36.000	2.416	31.265	40.735
Overall	15.000	1.274	12.503	17.497

Cox Regression with Pre-Op Tumour

Cox regression indicated that there is a significant impact of pre-op tumor volume on survival time of patients as Omnibus test was significant ($\chi 2$ (3) = 20.444, p < .001) (Table 3). The results also indicated that patients with pre-op tumor volume of >100 were approximately 7.7 times more likely to die compared to those having pre-op tumor volume of <20 (B = 2.041, SE = .536, Wald (1) = 14.502, *Odds Ratio* = 7.699, p < .001) (Table 4) (Fig 2-3).

Table 3. Omnibus Test for Pre-Op Volume and Survival for GBM

Omnibus Tests of Model Coefficients[b]										
Step	-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
		Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
1[a]	479.921	20.444	3	.000	10.861	3	.013	10.861	3	.013
a. Variable(s) Entered at Step Number 1: PRE-OP VOLUME										
b. Beginning Block Number 1. Method = Forward Stepwise (Conditional LR)										

Table 4. Coefficients for Pre-Op Volume and Survival for GBM Sheet

Variables in the Equation									
		B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
								Lower	Upper
Step 1	Pre-op volume			15.522	3	.001			
	Pre-op volume(1)	.081	.300	.073	1	.787	1.084	.602	1.954
	Pre-op volume(2)	.330	.316	1.088	1	.297	1.391	.748	2.584
	Pre-op volume(3)	2.041	.536	14.502	1	.000	7.699	2.693	22.012

Cox Regression with Post-Op Tumor

The results indicated that there is a significant impact of post-op tumor volume on survival of patients as Omnibus test was significant ($\chi 2$ (3) = 41.181, p < .001) (Table 5). Patients with post-op tumor volume of 10.1-50 are 6.7 times more likely to die than those with post-op tumor volume of 0 (B = 1.908, SE = .564, *Wald* (1) = 11.456, *Odds Ratio* = 6.737, p < .001) (Table 6). Similarly, patients with post-op tumor volume of 50.1-100 are approximately 36 times more likely to die compared to those who had 0 post-op tumor (B = 3.579, SE = .926, *Wald* (1) = 14.946, *Odds Ratio* = 35.841, p < .001) (Fig 4-5).

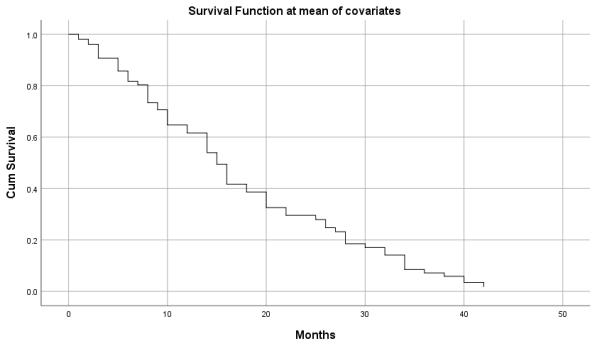

Figure 2. Survival Graph for Pre-Op Volume for GBM

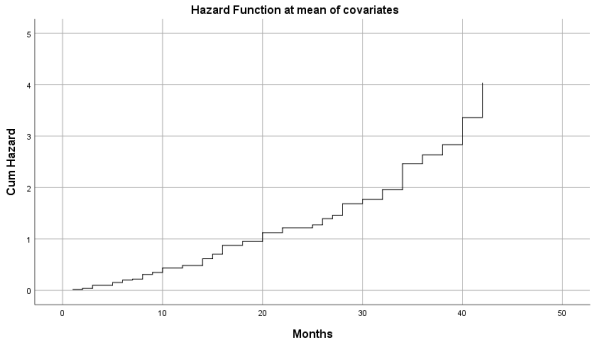

Figure 3. Hazard Graph for Pre-Op Volume for GBM

Table 5. Omnibus Test for Post-Op Volume and Survival for GBM

Omnibus Tests of Model Coefficients[b]										
Step	-2 Log Likelihood	Overall (score)			Change From Previous Step			Change From Previous Block		
		Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
1[a]	470.384	41.181	3	.000	20.398	3	.000	20.398	3	.000
a. Variable(s) Entered at Step Number 1: POST-OP VOLUME										
b. Beginning Block Number 1. Method = Forward Stepwise (Conditional LR)										

Table 6. Coefficients for Post-Op Volume and Survival for GBM

Variables in the Equation									
		B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
								Lower	Upper
Step 1	Post-op volume			27.508	3	.000			
	Post-op volume(1)	.521	.470	1.229	1	.268	1.684	.670	4.232

	Post-op volume(2)	1.908	.564	11.456	1	.001	6.737	2.232	20.332
	Post-op volume(3)	3.579	.926	14.946	1	.000	35.841	5.839	220.003

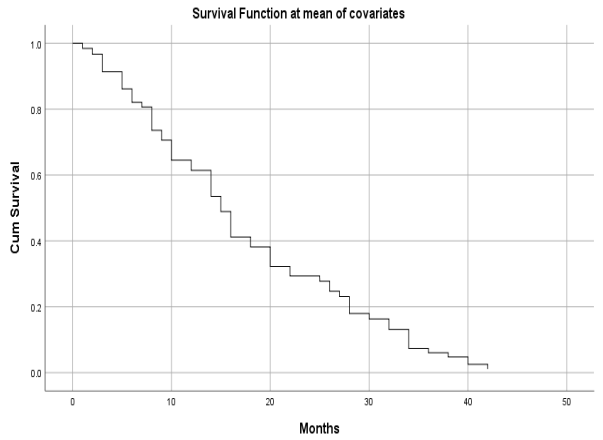

Figure 4. Survival Graph for Post-Op Volume for GBM

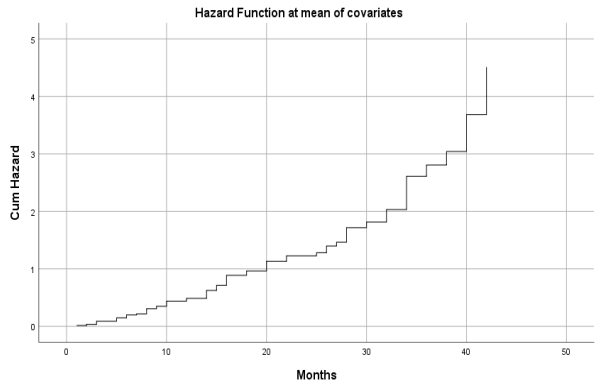

Figure 5. Hazard Graph for Post-Op Volume for GBM)

Discussion

In our study, we reported the median survival time following excision of a glioblastoma multiforme. Our analysis also shows that the size of the surgical resection affects post-operative survival rates. Surprisingly, both the pre- and post-tumor volume were linked to the median survival time following surgery.

The EOR has been demonstrated to be a significant survival predictor [23-27]. Total tumor resection rates for GBM, an infiltrative tumor, have been reported to be between 17.4% and 40% [27, 28]. Multiple variables affect EOR in practice, although no proof has been documented in the literature. Most studies relying on volumetric evaluation conclude that extensive surgical resection is linked to increased survival rates for high-grade gliomas [28,29].

Total resection was also substantially correlated with a tumor volume of 30 mL in GBM. Tumors that are less massive are easier to operate on [29,30]. Brain edema and midline displacement were found to be substantially linked with the size of the GBM, and both adversely affected the extent to which the tumor could be removed. In addition, the prognostic factor most strongly linked to complete resection in GBM was a tumor volume of 30 mL or less. Surgery is easier to do on smaller tumors than on larger ones [31,32]. Brain edema and midline displacement were found to be strongly linked with the size of the GBM and to have a direct impact on the extent to which the tumor could be resected in this investigation [33]. In our data, we found that patients with post-op tumor volume of 10.1-50 cm3 are 6.7 times more likely to die than those with post-op tumor volume of 0 cm3. Similarly, patients with post-op tumor volume of 50.1-100 cm3 are approximately 36 times more likely to die compared to those who had 0 cm3 post-op tumor

We discovered that a substantially higher likelihood of survival was associated with an EOR of 98%. This agrees with the findings of a comprehensive study on the volumetric tumor assessment of 416 GBM patients, conducted by Lacroix et al. at MD Anderson Cancer Center in 2001 [34]. In a study of 92 patients with GBM, Keles et al. [35] analyzed how EOR affected survival. Among the 5 "percent of resection" groups studied, those with a 100% EOR had a median survival time of 93 weeks, whereas those with a 75%-99% EOR had a median survival time of 88.5 weeks. The median survival time is just 62.9 weeks, based on an EOR of 50-74%.

In a review of the literature, Sanai and Berger (2008) contrasted studies that did and did not measure tumor volume (high- and low-grade gliomas). A total of 25 trials supported the idea of maximum EOR, while 13 did not show a clear preference for either resection group [36].

McGirt et al. [37] did a retrospective analysis with a large group of 1215 patients who had malignant glioma. In this study, resections were put into one of three groups based on MRIs taken soon after surgery: near-total resection (NTR), subtotal resection (STR), or gross-total resection (GTR). After a GBM primary tumor was removed, the average survival time was 11 months for GTR, 9 months for NTR, and 5 months for STR. This was linked to GTR vs. NTR and NTR vs. STR. But in our data, 86 patients

were considered for further study. For the population as a whole, the median survival time was 15 months. Those diagnosed with PR lived an average of 3 months longer than those diagnosed with STR or NTR, while those diagnosed with NTR lived 16 months longer than those diagnosed with PR. But patients who had GTR had a much better outcome, with a median survival time of 36 months. It reveals that there is a linear link between survival and EOR.

Adjuvant therapies, such as chemotherapy and radiation, have a significant impact on patient survival, progression-free survival, and overall survival [38-41], and should be included in the standard of care for GBM patients alongside surgical treatment modalities. With a focus on the SVZ and high-dose proton beam treatment, Matsuda et al. [42] found that patients with newly diagnosed GBM who had GTR had a median overall survival of 36.9 months, compared to 26.2 months for patients who got standard radiation therapy.

Kaplan-Meier estimates from our sample agree with those from the literature that link EOR and survival. According to Sanai et al. [43], we saw survival improve linearly with EOR. Full resection should be pursued whenever possible because of the survival data reported here and the evidence supporting the need of optimizing EOR to prolong survival in glioblastoma patients. These promising findings highlight the need to maximize resection with cutting-edge techniques; Future study should focus on GBM microenvironment and, if needed, surgery and despite the difficulty of treating GBM, the latter should not be ignored.

Conclusions

Removing 99% or more of a glioblastoma multiforme (GBM) tumor is associated with improved survival, according to volumetric analyses. We advise a gross-total resection for these patients whenever possible, but never at the expense of their ability to think and move normally. The primary objective of surgical treatment for GBM should be GTR with an emphasis on cerebral function preservation, as an EOR 99% has been found to greatly enhance patient survival. Small pre- and post-operative tumor volume considerably increases survival, as does an EOR of 99%. Patients with glioblastomas now use EOR as a prediction of survival, therefore it's important to learn what factors influence surgical success.

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