

Prognostic Factors in Glioblastoma: Is There a Role for Epilepsy?

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Abstract

The prognostic relevance of epilepsy at glioblastoma (GBMs) onset is still under debate. In this study, we analyzed the value of epilepsy and other prognostic factors on GBMs survival. We retrospectively analyzed the clinical, radiological, surgical and histological data in 139 GBMs. Seizures were the presenting symptoms in 50 patients out of 139 (35.9%). 123 patients (88%) were treated with craniotomy and tumor resection while 16 (12%) with biopsy. The median overall survival was 9.9 months from surgery. At univariable Cox regression, the factors that significantly improved survival were age less than 65 years ($P = 0.0015$), focal without impairment of consciousness seizures at presentation ($P = 0.043$), complete surgical resection ($P < 0.001$), pre-operative Karnofsky performance status (KPS) > 70 ($P = 0.015$), frontal location ($P < 0.001$), radiotherapy (XRT) plus concomitant and adjuvant TMZ ($P < 0.001$). A multivariable Cox regression showed that the complete surgical resection ($P < 0.0001$), age less than 65 years ($P = 0.008$), frontal location ($P = 0.0001$) and XRT adjuvant temozolomide (TMZ) ($P < 0.0001$) were independent factors on longer survival. In our series epilepsy at presentation is not an independent prognostic factor for longer survival in GBM patients. Only in the subgroup of patients with focal seizures without impairment of consciousness, epilepsy was associated with an increased significant overall survival at univariate analysis ($P = 0.043$). Main independent factors for relatively favorable GBMs outcome are complete tumor resection plus combined XRT-TMZ, frontal location and patient age below 65 years old.

Key words: epilepsy, glioblastoma, prognostic factor

Introduction

Glioblastoma (GBM) is the most common and malignant form of primary brain tumors. Despite recent progress in their treatment, median survival is still under 2 years. Nowadays, the main factors for increased survival rates in GBM are extensive surgical resection, age less than 65 years and combined adjuvant radio-chemotherapy.¹⁾

From 23% to 50% of GBM patients, seizures were the onset symptom of tumor.²⁾ Epilepsy at presentation was associated with longer survival in some studies.^{2–6)} However, the prognostic value of this finding remains controversial.⁷⁾

The aim of this study is to assess the prognostic relevance of epilepsy on survival in GBMs patients and its relationship with other clinical, radiological and surgical factors.

Materials and Methods

The study population included 139 patients with histologically confirmed de novo supratentorial GBM treated at our Institution from January 2006 to December 2008. The study follow-up cut-off point was October 2009. Age, sex, Karnofsky performance status (KPS) at admission and at discharge, presentation symptoms (including presence of seizures or not), tumor location, type of surgery (resection or biopsy), extent of resection and adjuvant therapy were retrospectively collected and evaluated.

Seizures were classified according to the 2010 criteria of the International League Against epilepsy:

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- focal without impairment of consciousness
- focal with impairment of consciousness
- focal evolving to bilateral convulsive seizure

We routinely give anti-epileptic drugs (AEDs) as prophylaxis in all operated patients even if they have not history of seizures. In all patients, we administer Levetiracetam.

In addition, all patients were evaluated for treatment with AEDs.

Pre-operative magnetic resonance imaging (MRI) imaging was carried out with 1.5-T system in all patients and the following features were evaluated: tumor size, location, invasion, extension, peritumoral edema, necrosis, bleeding and contrast enhancement.

Surgery consisted of either resection or biopsy. Extent of resection was classified according to post-operative computed tomography (CT) or MRI with contrast as follows:

- Gross total resection (GTR): lack of contrast enhancement
- Subtotal resection (STR): presence of contrast medium enhancement in less than 10% of the surgical cavity
- Partial resection (PR): contrast medium enhancement in less than 30% of the surgical cavity

The standard treatment following surgical resection includes radiotherapy (XRT) plus concomitant and adjuvant temozolomide (TMZ), according to Stupp's protocol.⁸⁾ Oncologic treatment was considered complete in patients who had received at least one full cycle of XRT and TMZ.

Tumor progression was diagnosed through clinical and radiological assessment at regular intervals (usually by monitoring MR images every three months) during the follow-up.

The outcome was evaluated by analyzing the overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the first surgery to death or until October 31, 2009, the cut-off point of follow-up. PFS was defined as the time from the first surgery to first evidence of tumor progression on CT or MR.

Survival was analyzed according to Kaplan–Meier survival curves using the log-rank test to determine statistical significance between groups and simple Cox models to assess differences in continuous variables. Multivariate analysis was performed using an adjusted Cox regression model in order to identify factors independently associated with better rates of survival during follow-up. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 17.0 for Mac.

Results

A complete follow-up was achieved for all 139 patients. At the end of the follow-up, 129 patients were dead (92.8%) and 10 were alive (7.2%). The study population included 85 males and 54 females with a mean age of 62 years (range from 25 to 86 years).

The most frequent clinical onset symptoms were focal neurological deficits, mainly motor deficit, followed by hemianopsia, sensory symptoms and aphasia occurred in 64 patients (46%). Epileptic seizures were the second most common presenting symptom occurred in 50 patients out of 139 (35.9%). Finally, at clinical onset 25 patients out of 139 (18%) showed headache and deterioration of consciousness.

The most frequent type of seizures was focal evolving to bilateral convulsive seizure (27 patients, 54%), with impairment of consciousness (13 patients, 26%) and finally focal seizure without impairment of consciousness (10 patients, 20%).

Status epilepticus with convulsive features was observed as onset symptom in only one patient with lumbar trauma with paraparesis. This patient underwent immediate surgical vertebral decompression and stabilization with screws and rods for unstable L1 burst fracture.^{9,10)} During chemotherapy the same patient developed L1 spondylodiscitis, level of previous surgery, treated with antibiotic therapy without hardware removal.¹¹⁾

Before surgery, 102 patients (73%) presented a KPS > 70 while 37 patients (27%) a KPS < 70. The location of GBM was: temporal in 53 patients (39%), frontal in 49 patients (35%), parietal in 21 patients (15%). The remaining 16 cases included lesions deeply seated (such as those located in the basal ganglia and/or corpus callosum) and/or lesions with multicentric locations and they were treated with biopsy.¹²⁾

123 patients (88%) were treated with craniotomy and tumor resection while 16 (12%) with biopsy. Extension of resection was total in 62 patients (44%), subtotal with residual <10% in 30 patients (22%) and partial in 31 patients (22%).

85 patients (61%) had radiotherapy (XRT) plus concomitant and adjuvant temozolomide (TMZ) according to Stupp's protocol, 13 (9%) and 16 (12%) respectively only XRT or chemotherapy (CT) and finally 25 patients (25%) did not receive adjuvant therapy at all.

The median OS in the total cohort of patients was 9 months from surgery. Survival probabilities to 1, 2 and 3 years were 35%, 8% and 4%, respectively.

At univariable Cox regression, the factors that significantly improved the OS were aged below 65 years ($P = 0.0015$), complete surgical resection ($P < 0.001$), pre-operative Karnofsky performance status (KPS) > 70 ($P = 0.015$), frontal location ($P < 0.001$), XRT plus concomitant and adjuvant TMZ ($P < 0.001$).

Epilepsy was not significantly associated with longer OS, with a median survival in the epilepsy group of 10 months versus 7 months for patients without epilepsy ($P = 0.07$).

Only in the subgroup of patients with focal seizures without impairment of consciousness, epilepsy was associated with an increased significant OS at univariate analysis ($P = 0.043$).

Multivariable Cox regression showed that complete surgical resection ($P < 0.0001$), age below 65 years ($P = 0.008$), frontal location ($P = 0.0001$) and XRT plus concomitant and adjuvant TMZ ($P < 0.0001$) were independent factors of longer survival.

These results were summarized in Table 1.

The mean PFS in our series was 5 months with 16 patients (12%) without tumor progression at 1 year from surgery. The univariate PFS analysis showed that complete surgical resection ($P < 0.0001$), age below 65 years ($P = 0.002$), frontal location ($P = 0.0001$), pre-operative KPS > 70 ($P = 0.004$) and XRT plus concomitant and adjuvant TMZ ($P = 0.0001$) were significant predictors of lengthier PFS.

Table 1 Results of univariable and multivariable Cox regression of the main factors that affect median overall survival

Variable	No. of patients	Median overall survival (months)	Univariate analysis	Multivariate analysis
Age			0.0015	0.008
<65 years	69	12 ± 2.1		
>65 years	70	8 ± 1.8		
KPS			0.013	>0.05
>70	102	10 ± 1.7		
<70	37	6 ± 1.2		
Location			<0.0001	0.0001
Frontal	49	11 ± 1.9		
Temporal	53	10 ± 2.1		
Parietal	21	8 ± 2.4		
Occipital	4	3 ± 0.7		
Bilateral	3	2 ± 0.9		
Multicentric	9	3 ± 1.1		
Extent of Resection			<0.0001	<0.0001
GTR	62	14 ± 2.9		
STR, partial, biopsy	77	6 ± 1.6		
Adjuvant Therapy			<0.0001	<0.0001
XRT+TMZ	85	12 ± 2.2		
XRT	13	7 ± 1.6		
CT	16	6 ± 1.4		
No adjuvant therapy	25	3 ± 0.9		
Epilepsy at presentation			0.07	>0.05
Yes	50	10 ± 2.3		
No	89	7 ± 1.6		
Type of Seizure at Presentation			0.043	>0.05
Focal without impairment of consciousness	10	14 ± 2.3		
Focal with impairment of consciousness	13	8 ± 1.5		
Focal evolving to bilateral convulsive seizure	27	6.5 ± 1.1		

CT: chemotherapy, GTR: gross total resection, STR: subtotal resection, TMZ: temozolamide, XRT: radiotherapy.

Multivariate analysis confirmed all the above-mentioned variables except the pre-operative KPS as independent predictors of longer PFS.

Finally, we analyzed the age, KPS, tumor location, extent of resection and adjuvant therapy as prognostic factors categorizing two groups of patients according to epileptogenic GBM (epilepsy+ vs epilepsy-). Age and extent of resection are statistically significant factors for the prognosis: epileptic patients are younger than non-epileptic ($P = 0.0001$) and presented an increased rate of gross total tumor resection ($P = 0.017$) with subsequent better prognosis. These data are summarized in Table 2.

Discussion

In neuro-oncology the identification of prognostic factors is essential to stratify patients in relatively homogeneous classes of therapies.

In the recently published guideline by the European Association for Neuro-Oncology (EANO) for diagnosis and treatment of adult astrocytic and oligodendroglial gliomas, age and pre-operative KPS together with genetic and molecular markers (such as IDH mutation and 1p/19q codeletion), are the guide for adjuvant or palliative therapies after surgery for GBMs.¹³⁾ Furthermore, these guidelines point out the extent of resection as a positive prognostic factor for survival and recommended maximum safe resection in all patients with newly diagnosed gliomas, including GBM.^{2-7,13,14)}

In our series, the extent of resection was an independent prognostic factor both for OS and PFS. In fact, the GTR patients group presented a median OS of 14 months compared to the 6 months of non-GTR group (STR, PR or biopsy). In relation to PFS, GTR group had a median of 9 months free from GBM progression while non-GTR group had

Table 2 Characteristics of subgroups analyzed in this study and the data of median overall survival in the subgroup of epileptogenic GBM and non-epileptogenic GBM

Variable	No. of patients	Epilepsy group (50 patients)	Median overall survival (months)	No epilepsy group (138 patients)	Median overall survival (months)	P value	Odds ratio	CI 95%
Age			12 ± 2.2		8 ± 2.4	0.0001	4.36	2.06–9.26
<65 years	69	36		33				
>65 years	70	14		56				
KPS			10 ± 1.7		7 ± 1.2	0.6	1.24	0.56–2.74
>70	102	38		64				
<70	37	12		25				
Location			10 ± 2.1		8 ± 2.4	0.83	1.18	0.48–5.26
Frontal	49	24		25				
Temporal	53	20		33				
Parietal	21	6		15				
Occipital	4	0		4				
Bilateral	3	0		3				
Multicentric	9	0		9				
Extent of resection			14 ± 2.9		7 ± 1.6	0.017	2.34	1.16–4.75
GTR	62	29		33				
STR, partial, biopsy	77	21		56				
Ajuvant therapy			12 ± 2.2		11 ± 1.9	0.38	2.48	0.78–8.49
XRT+TMZ	85	31		54				
XRT	13	10		3				
CT	16	3		13				
No adjuvant therapy	25	6		19				

CT: chemotherapy, GTR: gross total resection, STR: subtotal resection, TMZ: temozolamide, XRT: radiotherapy.

PFS time of 3 months. In the non-GTR group we included patients treated with STR, PR or biopsy because the median OS was similar in both groups (6 months).

Younger age and better KPS are well-known important positive prognostic factors for GBMs in literature.^{2-5,13} In the present study only age below 65 years was a significant prognostic factor for longer OS both in uni and multivariate analysis. Pre-operative KPS was associated with better OS only at univariate Cox regression. This issue may be explained by the fact that in our series nearly every patient had a KPS > 70 (102 patients out of 139) with subsequent reduction of statistical significance.

Among prognostic factors, onset epilepsy has been associated with longer survival in several studies.²⁻⁶ However, its prognostic relevance in GBM is still controversial.⁷

Some authors hypothesized that seizures at clinical onset lead to tumor early diagnosis and this leads to longer survival.^{2,6} However, this is not proven yet.

In this regard, Toledo et al.⁶ in a prospective observational study recruited 56 patients with GBM and seizures as presenting symptoms were observed in 26.6% patients. In this study, epilepsy was associated with longer survival only in patients younger than 60 years. However, the imaging and histological features found no evidence indicating that epileptogenic GBM is at an earlier stage at the time of the diagnosis.

Moreover, a recent retrospective series of 647 consecutive patients diagnosed with de novo GBMs showed a favorable association between epilepsy at clinical presentation and prolonged survival.⁴ This positive correlation is independent of age, sex, KPS, extent of resection, adjuvant therapy, tumor location and volume. For these reasons, the authors postulated that this positive association cannot be attributed solely to early diagnosis, but it might result from distinct genetic and biological features of epileptogenic GBMs.

The present study investigates the clinical features of seizures in GBMs and the value of epilepsy on GBMs survival time. Epilepsy in our series was the second most common presenting symptoms (36% of patients) in GBMs followed by neurological deficit, which occurred in 64 patients (46%). At univariate analysis, epilepsy at clinical presentation was not significantly associated with longer OS. These data do not appear in line with recent literature showing an association between epileptic onset and longer survival, except for a 2016 study of Shin (at any time during the course of glioblastoma) in which seizure was associated with significantly increased survival.⁷

In this scenario, Flanigan et al.⁵ recently published a retrospective series of 443 patients with pre-operative rate of seizure of 28% in which multivariate analysis revealed pre-operative epilepsy to be independently associated with increased survival. However, the same authors reported that, in case of longer delay between time of epilepsy at clinical onset and surgery, the prognostic benefit of pre-operative seizure does not seem significant. The same authors explain also that seizures usually arise from small lesions so their prognostic benefit only occurs when surgical intervention is prompt before more symptoms, a marker of tumor progression.

The present study analyzes the impact of epilepsy among different types of clinical onset: in this case the relative better OS in the epilepsy group was not significant compared to the neurological deficit group with respectively a median OS of 10 and 7 months. Moreover, in our study only 29 patients out of 50 with epilepsy were treated with GTR. This issue was correlated to the higher number of epileptogenic GBMs located close to eloquent areas. This observation has not been previously reported. In this study epilepsy was not significantly associated with longer survival, the median survival in the epilepsy group was 10 months versus 7 months for patients without epilepsy at clinical onset ($P = 0.07$).

In our study, the analysis of all epileptic patients (50 pts) does not show any statistically positivity because probably many patients (27 out of 50) had bilateral convulsive seizure due to a wide diffusion of the tumor in the brain (late stage of disease). A second hypothesis is that the small number of patients do not allow a relevant and specific statistical analysis.

Finally, only in the subgroup of patients with focal seizures without impairment of consciousness, epilepsy was associated with an increased significant OS at univariate analysis ($P = 0.043$). This could be explained by the fact that partial focal seizures without impairment of consciousness at presentation would lead to detection of the tumor at an earlier stage and this factor would imply longer survival.

In our series, young epileptogenic and high resected tumors had a good prognosis because epilepsy as presenting symptom allows a prompt diagnosis so in young patients without comorbidities the maximal surgical and adjuvant therapy may be feasible.

Conclusions

In our series epilepsy at clinical presentation is not an independent prognostic factor for longer survival in GBM patients. Only in the subgroup of patients with focal seizures without impairment

of consciousness, epilepsy was associated with an increased significant OS at univariate analysis ($P = 0.043$).

The main independent factors that predict a relatively favorable outcome in GBMs remain complete tumor resection, followed by combined XRT-TMZ, frontal location and patient under 65 years old.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest Disclosure

None.

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