Impact of seizures and antiseizure medication on survival in patients with glioma

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Abstract

Purpose

Seizures are a common presenting symptom among patients with low- and high-grade glioma. However, the impact and inter-relationship between the presence of seizures, anti-seizure medication and survival are unclear. We retrospectively analyzed the incidence of seizures and identified the pattern and relationship of anti-seizure medication on survival in our cohort of patients with glioma.

Methods

We evaluated all glioma patients who underwent treatment at the University of Malaya Medical Centre (UMMC) between 2008 to 2020. Demographic and clinical data of seizures and pattern of ASM administration in comparison to overall survival were analyzed.

Results

A total of 239 patients were studied, with a minimum of one year clinical follow-up post-treatment. The mean survival for low-grade glioma was 122 months whereas high-grade glioma was 47 months. One-third of our glioma patients (n=72) presented with seizures. All patients with seizures and a further 49.2% of patients without seizures were started on anti-seizure medication preoperatively. Seizure and Levetiracetam (LEV) were significantly associated with OS on univariate analysis. However, only LEV (p=0.019; HR 0.53;95%CI: 0.31-0.90) was significantly associated with OS on multivariate analysis. Once ASM was adjusted for relevant factors and each other, LEV was found to be protective in all grade gliomas (p=0.012; HR 0.50; 95% CI: 0.30-0.86) and specifically high-grade gliomas (p=0.00; HR 0.44; 95% CI: 0.25-0.77).

Conclusions

Pre-operative seizures among patients with glioma indicated a better overall prognosis. The administration of ASM, specifically LEV demonstrated a significant survival advantage in our retrospective cohort of patients.

Introduction

Gliomas account for more than 65% of all primary brain tumors. Glioblastoma is the most common (65%) and most malignant histopathological type [1]. Survival of patients varies significantly by grade across all glioma subtypes. There is a striking contrast when comparing survival rates in low and high-grade glioma patients. Patients with low-grade gliomas have longer survival compared to patients with high-grade gliomas, with a median survival of 14 years with optimal treatment [2, 3].

Seizure is the most common presenting symptom among 15 to 50% of newly diagnosed glioma patients, and 83% among low-grade glioma (LGG) patients [4, 5]. History of seizures was suggested as a good

prognostic factor in both low and high-grade gliomas as early as 1980 by Scott et al [6-9]. Since seizures are directly linked to a patient's quality of life, it's important to control the clinical seizure manifestation throughout glioma treatment [10]. Complete seizure control achieved with a single drug is the aim of seizure therapy in patients with LGG. Currently available ASMs are quite effective in this aspect, whereas the main treatment methods for LGG (surgery and radiation therapy) have a beneficial impact on seizure control [11]. On the other hand, antiseizure drugs remain the primary modality of seizure control in HGG [12]. The impact on survival was more significant in low-grade glioma, especially those with focal seizures without impairment of consciousness. [13]. Nevertheless, the management of seizures in these patients is often opportunistic and not evidence-based or uniform.

Anti-seizure medicine (ASM) has shown variable effectiveness in treating seizures in patients with glioma [14, 15]. While there are many ASM routinely used by clinicians, the common drugs prescribed to glioma patients include Phenytoin (PHT), Valproic acid (VPA), Carbamazepine (CBZ), Lamotrigine (LTG), and Levetiracetam (LEV) [16-18]. Some clinical studies imply that patients with glioblastoma multiforme (GBM) who are treated with VPA have better outcomes than those treated with other ASM [19-22]. Other papers have suggested that combined treatment of Levetiracetam and Temozolomide has reduced seizures [23-25], improved the efficacy of chemotherapy and prolonged the survival of GBM patients [26-28]. In contrast to these studies, Knudsen-Baas KM and Hirotomo Tanaka et al found that ASMs had no significant effect on OS in GBM patients [26, 29].

The current literature on seizures and ASM in glioma patients has shown a somewhat mixed picture of the impact of seizures and the utility of ASM beyond seizure control in patients with glioma. This study identifies the impact of seizures and ASM in relation to survival in our cohort of glioma patients.

Methodology

Study Design

This is a retrospective single-centre cohort study of glioma patients who underwent treatment at the University of Malaya Medical Centre (UMMC) between 2008 to 2020. Ethical approval was obtained from the Medical Research Ethics Committee, UMMC (No. 2020930-9118). Informed consent was not required as this was a retrospective anonymous design study.

Sample recruitment

Glioma patients were identified from the neurosurgical patient database. A total of 239 patients with histopathologically confirmed glioma diagnosed between January 2008 to December 2020, were included in this study. A neurologist or a neurosurgeon confirmed the pre-operative diagnosis of seizures based on a documented clinical history of seizures or electroencephalographic (EEG) findings. Clinical data of the included patients were collected using electronic medical records. Patients with a single ASM

were defined as monotherapy while patients with more than one ASM at any one time were defined to be on polytherapy.

Statistical analyses

All statistical evaluations were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0. The univariate analysis evaluated age, gender, ethnicity, tumor grade, epileptic seizures, tumor site, and the type of anti-seizure medication (ASM). Cox proportional hazards model and hazard ratios with a 95% confidence interval were used in the multivariate analysis (CI). A p-value of 0.05 or less was regarded as significant. The correlation between the use of ASM and survival was examined using the Kaplan Meier method, and the findings were compared using the log-rank test. In this analysis, not all patients had full ASM data. From the final study, 15 patients having insufficient ASM data were left out. Overall survival was determined as the time from surgery to the final check-up or the time until death from any cause (OS). Using Cox regression, the impact of ASMs like valproic acid, levetiracetam, phenytoin, and carbamazepine on survival was evaluated. Due to a lack of data, other ASMs weren't examined.

Results

A total of 239 patients with gliomas were recruited for this study. Table 1 summarizes the baseline characteristics of this study cohort. Younger glioma patients (< 65 years old) were more likely to present with seizures preoperatively. Patients with GBM were less prone to develop seizures preoperatively (20%) compared to lower-grade gliomas. The most common location in relation to presentation with seizures was the frontal lobe (50.6%). All patients who presented with seizures were started on ASM, while 58 patients (35%) without seizures were started on ASM prophylactically. The majority of our patients were on monotherapy (n=69) whereas patients with highly resistant seizures (n=49) were started on polytherapy, ranging between 2 to 4 ASMs.

Table 1: Baseline clinical characteristics of glioma patients.

Variables	Total	Seizure (n=72), N (%)	No seizure (n=167), N (%)	P value
Sex				
Male	125	41 (32.8)	84 (67.2)	0.705
Female	114	31 (27.2)	83 (72.8)	
Ethnic				
Malay	79	26 (32.9)	53 (67.1)	0.413
Indian	58	17 (29.3)	41 (70.7)	
Chinese	97	29 (29.9)	68 (70.1)	
Others	5	0 (0.00)	5 (100)	
Age group				
<65 years old	201	67 (33.3)	134 (66.7)	0.036
>65 years old	38	5 (13.2)	33 (86.8)	
Grade				
Low grade	83	31 (37.3)	52 (62.7)	0.076
High grade	156	41 (26.3)	115 (73.7)	
Tumor location				
Frontal	79	40 (50.6)	39 (49.4)	0.000
Temporal	38	13 (34.2)	25 (65.8)	0.831
Parietal	71	19 (26.8)	52 (73.2)	0.461
Occipital	16	5 (31.3)	11 (68.8)	0.919
Administration of ASM				
Yes	118	60 (50.8)	58 (49.2)	0.000

No	106	0	106 (100)	
ASM				
Monotherapy	69	32 (46.38)	37 (53.62)	0.000
Polytherapy	49	27 (55.10)	22 (44.90)	
Types of ASM				
LEV	56	31 (57.4)	23 (42.6)	0.000
PHT	54	20 (35.7)	36 (64.3)	0.163
VPA	34	23 (67.6)	11 (32.4)	0.000

Abbreviations: ASM, Antiseizure medication; LEV, Levetiracetam; PHT, Phenytoin; VPA, Valproate.

ASM data is available in 224 cases only

Patients with seizures have significantly longer mean overall survival than patients without seizures, according to an analysis of the effect of seizures on overall survival (Figure 1) (91.3±8.9 vs. 68.7±5.9 months, respectively). Using the log-rank approach, a Kaplan-Meier survival analysis revealed a statistically significant difference (p=0.017).

A wide variety of ASM was used by patients in our cohort. 69 patients with polytherapy were administered between 2 to 4 ASMs throughout their treatment (Table 2). In total, 56 PHT, 54 LEV, 34 VPA, and 13 CBZ were administered to the patients while the other less common ASM ranged from 1 to 7 occurrences. Phenytoin was the most common ASM prescribed followed by Levetiracetam. Most patients were on monotherapy (69 vs 49) whereas the number of drugs was higher in the polytherapy group (69 vs 112).

Table 2: Type and number of anti-seizure medications prescribed to patients.

ASMs	Monotherapy (n=69)	Polytherapy (n=49)	Total
Carbamazepine	5	8	13
Clonazepam	0	3	3
Gabapentin	1	2	3
Lamotrigine	0	4	4
Lorazepam	2	5	7
Levetiracetam	20	**34**	54
Phenobarbital	0	1	1
Phenytoin	**26**	**30**	**56**
Sodium Valproate	15	19	34
Topiramate	0	3	3
Oxycarbamazepine	0	1	1
Zonisamide	0	1	1

Older age (p=0.005; HR, 1.92 (1.22-3.01)), high grade glioma (p=0.000; HR 5.19 (3.12-8.64)), tumor location in the parietal lobe (P=0.013; HR1.60 (1.10-2.33), patients with seizure, (p=0.017; HR 0.59 (038-0.91)) anti-seizure drugs usage (p=0.032; HR 0.56 (0.33-0.96)), and levetiracetam administration (p=0.019; HR 0.53 (0.31-0.90)) were correlated with the overall survival on univariate analysis. Further multivariate analysis between these factors revealed high grade glioma (p=0.000; HR17.07 (5.74-50.71)) and Levetiracetam administration (p=0.003; HR 0.39 (0.22-0.73**))** to be significantly associated with OS.

Table 3: Associated factors for glioma patients' overall survival

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	**HR (95% CI)**	p-value
Sex				
Male	1			
Female	0.94(0.65-1.35)	0.733		
Ethnic				
Malay	1			
Indian	1.20(0.74-1.92)	0.461		
Chinese	1.07(0.70-1.65)	0.744		
Others	0.85(0.21-3.52)	0.822		
Age group				
<65 years old	1			
>65 years old	**1.92(1.22-3.01)**	**0.005**	1.26(0.63-2.51)	0.512
Grade				
Low grade	1			
High grade	**5.19(3.12-8.64)**	**0.000**	**17.07(5.74-50.71)**	**0.000**
Tumor location				
Frontal	0.98(0.66-1.44)	0.896		
Temporal	1.44(0.91-2.30)	0.123		
Parietal	**1.60(1.10-2.33)**	**0.013**	1.12(0.76-1.65)	0.578
Occipital	1.53(0.78-3.03)	0.220		
Preoperative seizure				
No	1			
Yes	**0.59(038-0.91)**	**0.017**	1.09(0.60-1.95)	0.785
Administration of ASM				
No	1			

Yes	**0.56(0.33-0.96)**	**0.032**	0.76(0.31-1.88)	0.553
Types of ASM				
LEV	**0.53(0.31-0.90)**	**0.019**	**0.39(0.22-0.73)**	**0.003**
PHT	1.19(0.79-1.80)	0.414		
VPA	0.77(0.45-1.32)	0.339		

Kaplan Meier survival analysis for all grade glioma based on the 4 most common anti-seizure medication used in our cohort is presented in Figure 2. LEV (Fig a) showed a significant survival benefit (p=0.019; HR 0.53; 95% CI: 0.31-0.90)) while PHT (Fig b) (p=0.414; HR 1.19; 95% CI: 0.79-1.80)), VPA (Fig c) (p=0.339; HR 0.77; 95% CI: 0.45-1.32)) were not significant. Based on cox regression analysis, in LGG (Fig d) LEV (p=0.012; HR 0.5, CI 0.30-0.86)) was the most favorable ASM in terms of survival compared to CBZ (p=0.226; HR 0.54; 95% CI: 0.20-1.47)), VPA (p=0.303; HR 0.75; CI: 0.44-1.30)) and PHT (p=0.180; HR 1.34; CI: 0.87-2.06)). LEV (p=0.000; HR 0.44; 95% CI: 0.25-0.77)) also showed similar results for HGG (Fig e) compared to other VPA (p=0.876; HR 0.95; 95% CI: 0.51-1.77)), PHT (p=0.583; HR 1.14; 95% CI: 0.72-1.80)) and CBZ (p=0.824; HR 0.89; 95% CI: 0.32-2.47)).

Discussion

Our study showed that glioma patients with seizures had significantly longer survival compared to patients without seizures. In the current era of modern ASM, there is a variety of medications that can provide patients with greater seizure control while not compromising the quality of life or concurrent adjuvant treatment for glioma patients. Our findings suggest that treatment with LEV was associated with longer survival compared to other ASMs that are available, irrespective of whether ASM monotherapy or polytherapy was utilized.

The risk of seizures in glioma patients is generally assumed to be high. In our study we accumulated data on 239 patients with glioma, spanning 12 years between 2008 to 2020, diagnosed and treated in a single centre. Of these 239 patients, 30% patients had seizure onset at presentation or some point in their pre-surgical period. All patients with seizures were started on at least one ASM among a variety that was available in our centre. The choice of ASM was variable, depending on familiarity and ease of prescription by the treating clinician. Of the remaining 70% with no seizures, one-third (35%) were also started on ASM preoperatively. Thus, most patients with glioma (52.6%) in our cohort received ASM irrespective of the seizure status. Current existing guidelines do not favour the administration of prophylactic ASM in the perioperative period [30-32].

There has been discussion on whether and why seizures may improve overall survival in glioma patients [33, 34]. In our cohort, the presence of presurgical seizures was a protective factor (HR 0.59) in univariate analysis for survival. While this has been established in patients from high-income countries,

similar data have been lacking in low- and middle-income countries where access to medical facilities and optimal medical diagnosis may not be as easily available [33, 35-37]. The reason for the protective nature of seizures in patients with glioma is still not established. Among the postulated hypothesis include early tumor detection due to the visible physical manifestation that may lead to early treatment and longer survival time [34, 38, 39]. Glutamate, an excitatory neurotransmitter, is crucial for the emergence of seizures [40]. Increased expression of particular glutamate receptor subtypes, low glutamine synthetase activity, high glutamate concentrations in glioma cells, essentially nonexistent intracellular uptake, and excessive extracellular glutamate levels are all abnormalities. These modifications may have an impact on tumor and are correlated with increased seizure frequency [37].

For glioma patients with epilepsy, the choice of an ASM is influenced by a number of variables, including accessibility, tolerability, effectiveness, comorbidity, costs, the convenience of administration, titration plans, and finally, the preference of the treating physician [41]. In our cohort, Phenytoin and Levetiracetam were commonly used to treat seizure patients with glioma. Phenytoin was widely used as it is affordable although it has side effects such as headache, nausea, vomiting, constipation, dizziness, or nervousness. On the other hand, levetiracetam is being used with increasing frequency in these patients due to the expected low side effect profile, fewer interactions with other medications and simplicity of dose titration [42, 43].

The grade of glioma, specifically high-grade glioma had a significant impact on survival as expected. More interestingly, we found the use of LEV had a significant impact on survival in both univariate and multivariate analyses among patients with glioma. This was confirmed by cox regression analysis which revealed a significantly lower hazard ratio for the use of LEV compared to three other commonly used ASM. Previous papers have alluded to possible mechanisms of action in which LEV may provide a beneficial effect including as a temozolomide chemosensitizer or by repressing the MGMT expression [29]. VPA has been previously suggested to carry a potential anti-tumor effect. However, we did not find a similar effect in our cohort of patients.

The use of ASM seems to be very varied among our cohort of patients, with 12 different ASM being used in various permutations of monotherapy and polytherapy. Tumor-related epilepsy is frequently drug-resistant and may require higher doses as well as multiple drugs to achieve reasonable control [44]. Furthermore, this variability in its use, especially in a prophylactic fashion is due to the lack of clear guidelines on tumor-related epilepsy management.

Limitations of the study

The findings in this study are limited by the small sample size and heterogenicity of associated factors. Some data were not available due to the retrospective nature of the data collected. The impact of individual ASMs could not definitively be determined because many patients were on ASM polytherapy. These limitations can be overcome with a prospectively designed study that may be able to determine the impact and benefit of ASMs in patients with glioma.

Conclusion

The presence of preoperative seizures among patients with glioma indicated a better overall prognosis. The administration of ASM preoperatively, especially LEV demonstrated a significant survival advantage in our cohort of patients. The findings in this study improve our understanding of the impact of seizures, the pattern of ASM usage and its association with survival in glioma patients in our cohort. Further large prospective randomized trials should be conducted taking into account all the prognostic factors for validating the benefits of LEV on survival in glioma.

Declarations

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Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval: Ethical approval was obtained from the Medical Research Ethics Committee, UMMC (No. 2020930-9118).

Consent to participate: Informed consent was not required as this was a retrospective anonymous design study.

Consent to publish: No individual data was used in this paper.

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Figures

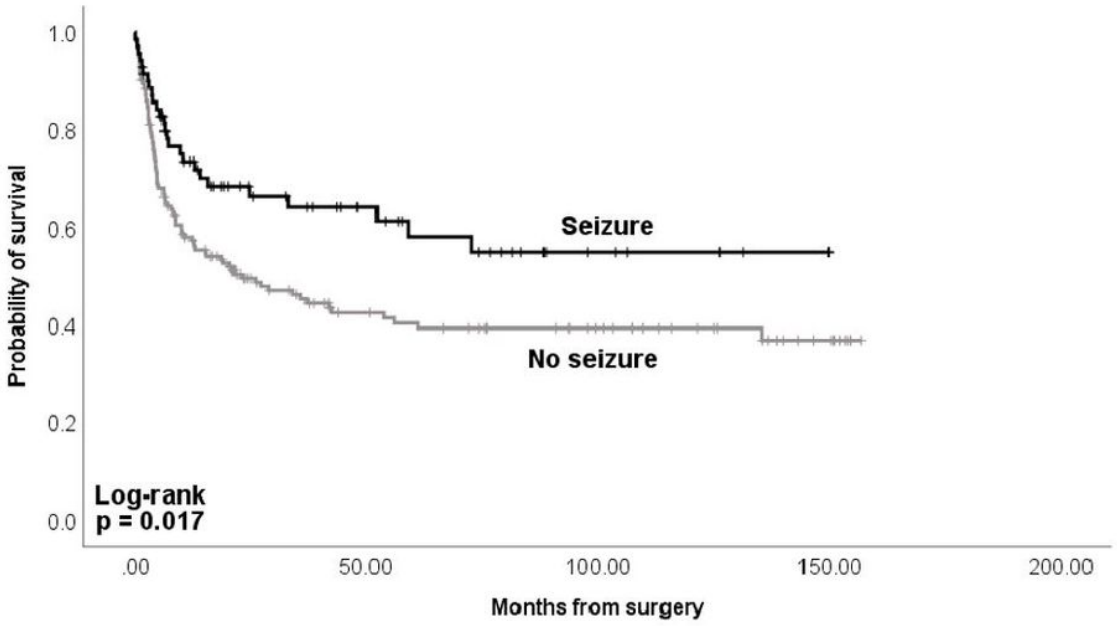

Figure 1

Kaplan–Meier plot with survival duration based on the preoperative seizure.

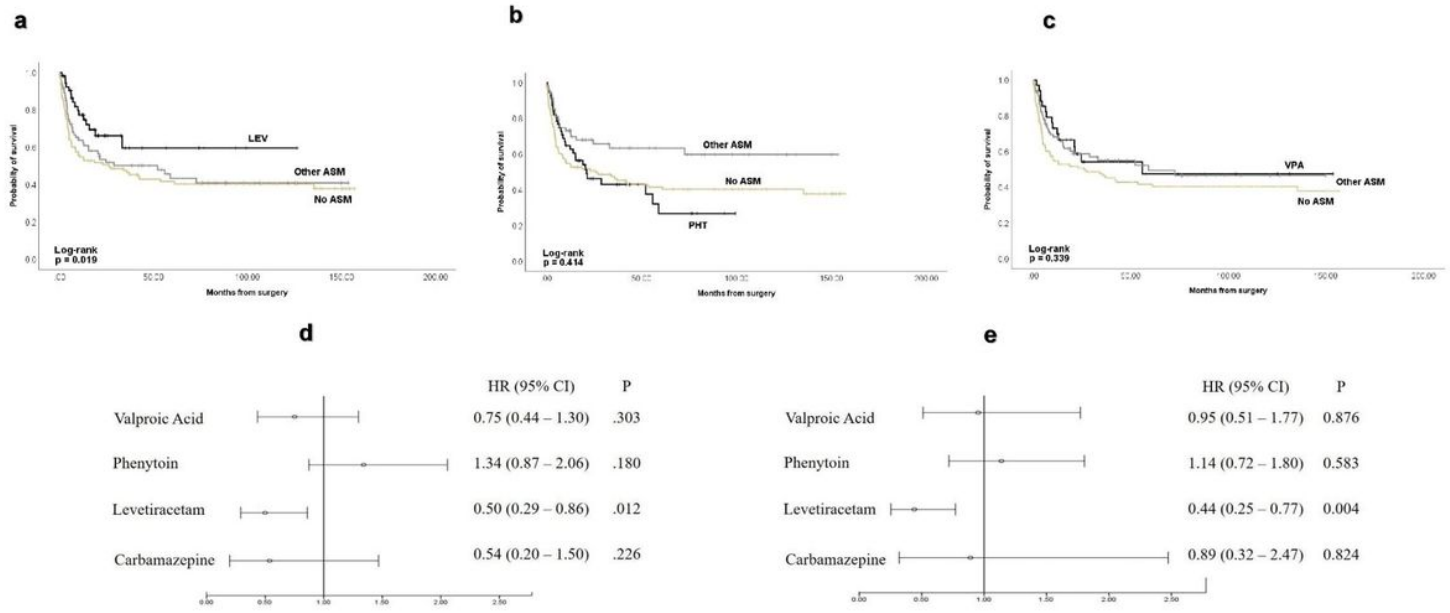

Figure 2

Kaplan–Meier survival curves show the overall survival of patients. (A) K-M plot of patients with and without Levetiracetam. Survival was significantly different between the 2 groups (p<0.001). (B) K-M plot of glioma patients treated with and without Phenytoin. (C)K-M plot of glioma patients treated with and without Valproate. (D) K-M survival plot shows ASMs in all grade glioma and LEV is significant compared to other drugs (p<0.012). (E) K-M survival plot shows ASM in only high-grade glioma. The plot shows that LEV is significant compared to other drugs (p<0.004).