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Cumulative seizure occurrence and the predictors of seizure in low- and high-grade gliomas

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Abstract

Objective: We aimed to determine the cumulative seizure occurrence, 1-year, and 5-years of preoperative seizures in gliomas, and an update on the predictors. *Methods:* This was a retrospective analysis of 239 patients with histopathologically confirmed gliomas in University Malaya Medical Centre, Malaysia, between 2008-2020. Kaplan-Meier curves were used to determine the cumulative incidence of seizures. Logistic regression was performed to determine the predictors of preoperative seizures. *Results:* A total of 80/239 patients (33.5%) had preoperative seizures. They were more commonly seen in those with younger age of presentation (40.0% in those <40 years old vs. 26.9% in ≥40 years old, $p<0.05$) and low-grade tumors (42.2% vs. 28.8% in high-grade tumors). Those with cortical involvement, especially the frontal lobe, or without focal deficit, headache, nausea, or vomiting were more likely to have seizures preoperatively. Logistic regression identified three significant predictors for preoperative seizure: absence of focal deficits at presentation (OR 6.090, 95% CI 3.110-11.925, $p<0.001$), cortical location (OR 3.834, 95% CI 1.363-10.786, $p<0.05$) and absence of headache at presentation (OR 2.487, 95% CI 1.139-5.431, $p<0.05$). The cumulative incidence of seizure was 29% at one year and 32% at 5-year for gliomas. Specifically, the seizure incidence was higher in low-grade gliomas (39% at 1-year) and certain tumor types such as ganglioglioma (50%), oligodendroglioma (48%), and astrocytoma (45%).
Conclusion: The cumulative incidence of preoperative seizures in low-grade gliomas and certain tumor types is high. The predictors included cortical involvement and absence of focal neurological deficit or headache at presentation.

Keywords: Brain tumor, glioma, epilepsy, cumulative incidence

INTRODUCTION

Gliomas account for almost 30% of all primary brain tumors. These tumors arise from neurological stem or progenitor cells and are classified histologically into astrocytomas, oligodendrogliomas, mixed oligoastrocytic gliomas or ependymomas based on morphological similarities to the neuroglial cell type found in the brain. In recent years, there has been substantial progress in understanding the molecular pathogenesis of gliomas. These advances have resulted in improved diagnostics and classification systems based on mutational profiles, which will complement histology-based classification.[1]

Patients with brain tumors will present in various ways and seizure is one of the most common manifestations. Seizure, when manifested, can be a good prognostic factor for these patients as it is associated with earlier detection of the brain tumor and the disease can be intervened early. The prevalence of seizure as the presenting symptom in glioma patients ranges from 60-100% among low-grade gliomas and between 40-60% in high-grade gliomas.[2]

Besides, numerous studies have investigated the factors associated with epileptic seizures in both low-grade (World Health Organisation, WHO

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grade I and II) and high-grade gliomas (WHO grade III and IV).[3] The identified factors can be classified into sociodemographic (age of onset and gender), tumor type (histopathological and WHO grading), clinical manifestation (neurological deficit, pre-operative seizures, headache), and tumor characteristics on neuroimaging (tumor location, diameter, enhancement, and features of increase intracranial pressure).[4,5] However, there were very few studies[4-7] that looked at the specific predictors that predominantly carries a higher risk for seizure occurrence in brain tumor.

The co-existence of seizures in patients with gliomas affects their quality of life and leads to debilitating consequences.[8] Nonetheless, there are yet any consensus guidelines on screening, prophylaxis, or treatment of seizures in this cohort of patients. This is mainly because the risk of seizure in individuals with glioma is variable depending on various factors such as the tumor type and grade, as well as studied populations and design. Furthermore, since the cumulative incidence of preoperative seizure in brain tumor was not reported in most studies, making it difficult to estimate the seizure occurrence risk over time.

Seizure prophylactic treatment in brain tumors is highly dependent on the probability of seizure occurrence. In the latest definition of epilepsy (2014), a person with one unprovoked seizure can be diagnosed with epilepsy if the probability of further seizure is at least 60% which will require ASM as treatment.[9] Therefore, knowing the cumulative seizure incidence in brain tumors will guide the use of antiepileptic drugs as prophylaxis.

Furthermore, by recognizing the predictors and the cumulative incidence of seizures, effective individualized treatment strategies that are tailored to the patient can be studied. Understanding the epileptogenesis and predictors of seizure in gliomas will guide future advances in personalised medicine. Moreover, seizure prediction in glioma will help to raise awareness and early detection of subtle seizures by the clinician, patients, or caregiver, and as well as guide prophylactic treatment.

Thus, the present study was conducted to determine the cumulative incidence and the significant predictors for preoperative seizure among patients with brain tumors.

METHODS

Study design

This was a retrospective single-centre cohort study of glioma patients who attended and underwent treatment at the University of Malaya Medical Centre, a tertiary care specialist centre in Malaysia. Approval of the study was obtained from the Medical Research Ethics Committee, University of Malaya Medical Centre (No. 2020930-9118). Due to the retrospective anonymous design, informed consent was not indicated.

Sample recruitment

Eligible patients were identified from the neurosurgical operation database. A total of 239 patients with gliomas diagnosed between January 2008 to December 2020, with histopathological confirmation, were included in this study. The diagnosis of epilepsy was confirmed by a neurologist or a neurosurgeon, based on the clinical history of seizures or electroencephalographic (EEG) findings.

Clinical data collection

The demographics and clinical information were collected using electronic medical records. Patients' age was categorized into (<40 and ≥ 40 years old) before being included in the analysis. Brain gliomas were graded into WHO grades I – IV. Grade I and II gliomas were categorised as low-grade, and grade III and IV as high-grade. Tumors are classified based on WHO 2021 tumor classification without incorporating molecular markers.[10] Recorded neuroimaging characteristics included the number of lobes involved, cortical involvement, lobe involvement, tumor characteristics, and tumor size (mean the largest diameter in three directions) are based on MRI findings. Cortical tumors are tumors that involve grey matter. For patients who have multilobe involvement tumors, each tumor location was tabulated separately.

Statistical analyses

SPSS Version 26 (IBM inc) was used for statistical analyses. All *p*-values are two-tailed and $p<0.05$ was considered statistically significant. A descriptive analysis was used to characterize the study population regarding the sample size, demographics, variables, and seizure incidences. The cumulative incidence of seizure in patients with brain tumors was estimated using Kaplan-Meier curves. Univariate analyses were performed using the chi-square test for dichotomous variables, and T-test for continuous parametric data. Significant variables associated with seizures in univariate analysis ($P<0.05$) were then included in a logistic regression analysis.

RESULTS

A total of 239 patients with gliomas were recruited, with a mean age of 39.3 ± 22.6 years, of which 83 patients (34.7%) had low-grade tumors and 156 (65.3%) had high-grade. Preoperative seizures were present in 80/239 patients (33.5%), including 35/83 (42.2%) with low-grade and 45/156 (28.8%) with high-grade tumors. Among these, 47 (58.8%) had seizures as their first presentation, 22 (27.5%) had generalized tonic-clonic seizures, and 10 (12.5%) had status epilepticus. At presentation, low-grade gliomas had significantly higher mean seizure frequency than high-grade gliomas (11 ± 14.06 vs 3 ± 6.7 seizures per month, $p<0.05$). EEG was performed in 29 cases with seizures (36.3%), of which 27 (93.1%) had abnormal findings including 13 (44.8%) with epileptiform discharges.

Factors associated with preoperative seizures

Preoperative seizures were more commonly seen in patients with younger age at presentation (40.0% in those <40 years old vs. 26.9% in ≥40 years old, $p<0.05$) and low-grade tumors (42.2% vs. 28.8% in high-grade tumor). Astrocytoma, oligodendroglioma, and ganglioglioma were the three tumor subtypes that had higher percentages of seizures (46.7%, 53.3%, and 60%, respectively). Those with cortical involvement, especially the frontal lobe, or without focal deficit, headache, nausea, or vomiting, were more likely to have seizures preoperatively. (Table 1)

Table 1: Sociodemographic, histopathological, clinical and neuroimaging characteristics of glioma-related pre-operative seizures. (N=239)

		Total	Seizure (n=80), N (%)	No Seizure (n=159) N (%)	p
Socio-demographic					
Age of onset	<40 years old	120	48 (40.0)	72 (60.0)	0.032
	≥40 years old	119	32 (26.9)	87 (73.1)	
Gender	Male	125	46 (36.8)	79 (63.2)	NS
	Female	114	34 (29.8)	80 (70.2)	
Ethnic	Malay	79	30 (38.0)	49 (62.0)	NS
	Chinese	97	32 (33.0)	65 (67.0)	
	Indian	57	18 (31.0)	40 (69.0)	
	Others	5	0	5 (100.0)	
Histo-pathological					
WHO Grade	I	35	13 (37.1)	22 (62.9)	0.023
	II	48	22 (45.8)	26 (54.2)	
	III	46	19 (41.3)	27 (58.7)	
	IV	110	26 (23.6)	84 (76.4)	
Grade	Low grade	83	35 (42.2)	48 (57.8)	
	High grade	156	45 (28.8)	111 (71.2)	0.038
Subtype	Adult-type diffuse gliomas	182	60 (33.0)	122 (67.0)	NS
	Circumscribed astrocytic gliomas	25	8 (32.0)	17 (68.0)	
	Ependymal tumors	19	5 (26.3)	14 (73.7)	
	Glioneuronal and neuronal tumors	13	7 (53.8)	6 (46.2)	
Tumor type	Glioblastoma	110	26 (23.6)	84 (76.4)	0.001
	Astrocytoma	45	21 (46.7)	24 (53.3)	
	Oligodendroglioma	30	16 (53.3)	14 (46.7)	
	Ganglioglioma	10	6 (60)	4 (40)	
	Pilocytic astrocytoma	22	5 (22.7)	17 (77.3)	
	Ependymal tumors	19	5 (26.3)	14 (73.7)	
	Others*	3	1 (33.3)	2 (66.7)	

Clinical **					
Focal deficit	Yes	113	9 (8.0)	104 (92.0)	<0.001
	No	101	58 (57.4)	43 (42.6)	
Headache	Yes	60	12 (20.0)	48 (80.0)	0.002
	No	154	66 (42.9)	88 (57.1)	
Nausea or vomiting	Yes	35	6 (17.1)	29 (82.9)	0.009
	No	179	72 (40.2)	107 (59.8)	
Neuroimaging					
No of lobes	Mean + SD		1.19±0.45	1.16±0.44	NS
Cortical involvement	Involved	198	73 (37.1)	125 (62.9)	0.014
	Not involved	41	7 (17.1)	34 (82.9)	
Tumor location	Frontal	80	42 (52.5)	38 (47.5)	<0.001
	Temporal	39	14 (36.8)	25 (64.1)	NS
	Parietal	71	21 (29.6)	50 (70.4)	NS
	Occipital	16	5 (31.3)	11 (68.8)	NS
	Basal ganglia	20	2 (10)	18 (90)	NS
	Cerebellum	8	1 (12.5)	7 (87.5)	NS
	Brainstem	9	1 (11.1)	8 (88.9)	NS
	Suprasellar	7	2 (28.6)	5 (71.4)	NS
Tumor characteristics	Midline shift	70	22 (31.4)	48 (68.6)	NS
	Oedema	70	21 (30.0)	49 (70.0)	NS
	Enhancement	29	7 (24.1)	22 (75.9)	NS
	Bleeding	10	2 (20.0)	8 (80.0)	NS
Tumor diameter, cm	Mean + SD		4.37±1.73	4.86±1.68	NS

NS, not significant; *papillary and rosette-forming glioneuronal tumor ** Data is available in 214 cases only

Predictors of preoperative seizures

Logistic regression was performed to determine the predictors for preoperative seizures in gliomas. The model contained seven independent variables (Table 2). The full model was statistically significant, $\chi 2\,(7, N = 213) = 66.7$, $p<0.001$. There were three significant predictors for preoperative seizure in this model: absence of focal deficits at presentation (OR 6.090, 95% CI 3.110-11.925, p<0.001), cortical location (OR 3.834, 95% CI 1.363-10.786, $p<0.05$) and absence of headache at presentation (OR 2.487, 95% CI 1.139-5.431, $p<0.05$).

Cumulative incidence of seizure in patients with gliomas

The cumulative incidence of seizure was 30% at one year and 32% at 5-year for all gliomas; specifically, 39% for low-grade tumors at both 1 and 5 years. Seizure occurrences in certain tumor types were higher, especially ganglioglioma (50% at 1-year), oligodendroglioma (48%), and astrocytoma (45%). For glioblastoma, despite a low survival rate at 1-year (28.4%), the cumulative 1-year seizure incidence was 18%. Those with tumors located at the cortical region, especially the frontal lobe (45% at 1-year), and those without focal neurological deficit (54%) had higher seizure occurrences. (Table 3 and Figure 1)

DISCUSSION

About one-third (33.5%) of our cohort had preoperative seizures, this finding is comparable to the reported rates in the literatures.[3,6,7,11,12] Half of these patients had seizures as their first presentation. The 1-year seizure occurrence rates were 39% for low-grade tumors and 30% for all gliomas. Specifically, the seizure occurrences were higher in certain tumor types such as ganglioglioma (50%), oligodendroglioma (48%), and astrocytoma (45%). Meanwhile, it is known that glioblastoma has a poor survival rate, however, we found that the cumulative incidence of seizure in glioblastoma was not low (18%).

Liigant *et al*.[13] reported higher occurrences of seizures in certain cortical regions especially frontal and temporal lobes, in a series of 165 cases with brain tumors. In our study, seizure occurrence was closely related to cortical involvement,

Table 2: Logistic regression analysis of factors related to the occurrence of the preoperative seizure (N=213)

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
Tumor grading: Low Grade	0.455	0.387	1.378	1	0.240	1.576	0.738	3.367
Age of onset: <40 years old	0.633	0.372	2.896	1	0.089	1.883	0.908	3.904
Tumor location: Cortical	1.344	0.528	6.484	1	0.011	3.834	1.363	10.786
Tumor location: Frontal	0.659	0.359	3.377	1	0.066	1.933	0.957	3.903
Focal deficit: Absence	1.807	0.343	27.764	1	0.000	6.090	3.110	11.925
Headache: Absence	0.911	0.399	5.224	1	0.022	2.487	1.139	5.431
Nausea/Vomiting: Absence	0.196	0.509	0.148	1	0.700	1.217	0.448	3.301
Constant	-5.197	0.888	34.230	1	0.000	0.006		

especially in the frontal lobe, which is consistent with other published literature.[5,14] This could be because of the relationship between the location of certain histopathological subtypes and seizure occurrence. For example, low-grade gliomas with IDH1 mutation that was shown to be associated with seizures are also commonly located in the frontal lobe.[15] Other locations that were reported to have a high seizure occurrence are the temporal and insular regions.[3] This is most likely due to the inherent epileptogenicity of the structures in these regions.

The findings of higher seizure occurrence among those with absent focal deficit and headache in our study, are likely due to the slow-growing nature of low-grade gliomas that are less likely to cause functional deficits or increased intracranial pressure.[16] Additionally, the association between the younger age of presentation and pre-operative seizure is also likely because highly epileptogenic low-grade gliomas tend to occur in younger age groups.[6,17]

EEG was rarely performed as a routine procedure in patients with brain tumors unless they presented with clinical seizures. In addition, seizure semiology especially non-motor focal seizures could be subtle or missed and not investigated further with EEG.[18] However, in our study, most EEGs were abnormal and nearly half had epileptiform discharges. Thus, it is essential to perform EEGs if subtle seizures are suspected especially among the high-risk group with cortical involvement and no focal deficit.

To date, meta-analyses showed that there was

Table 3: Seizure occurrence at 1-year and 5 years according to tumor grade, types, and locations.

	1-year, %	5-year, %
Tumor grading		
– Low grade	39.0	39.0
– High grade	22.0	32.0
Tumor types		
– Astrocytoma	45.0	48.0
– Oligodendroglioma	48.0	54.0
– Ganglioglioma	50.0	50.0
– Pilocytic astrocytoma	19.0	19.0
– Glioblastoma	18.0	24.0
– Ependymal tumors	24.0	30.0
Tumor location (cortical)		
– Frontal	45.0	54.0
– Temporal	24.0	29.0
– Parietal	28.0	29.0
– Occipital	20.0	20.0

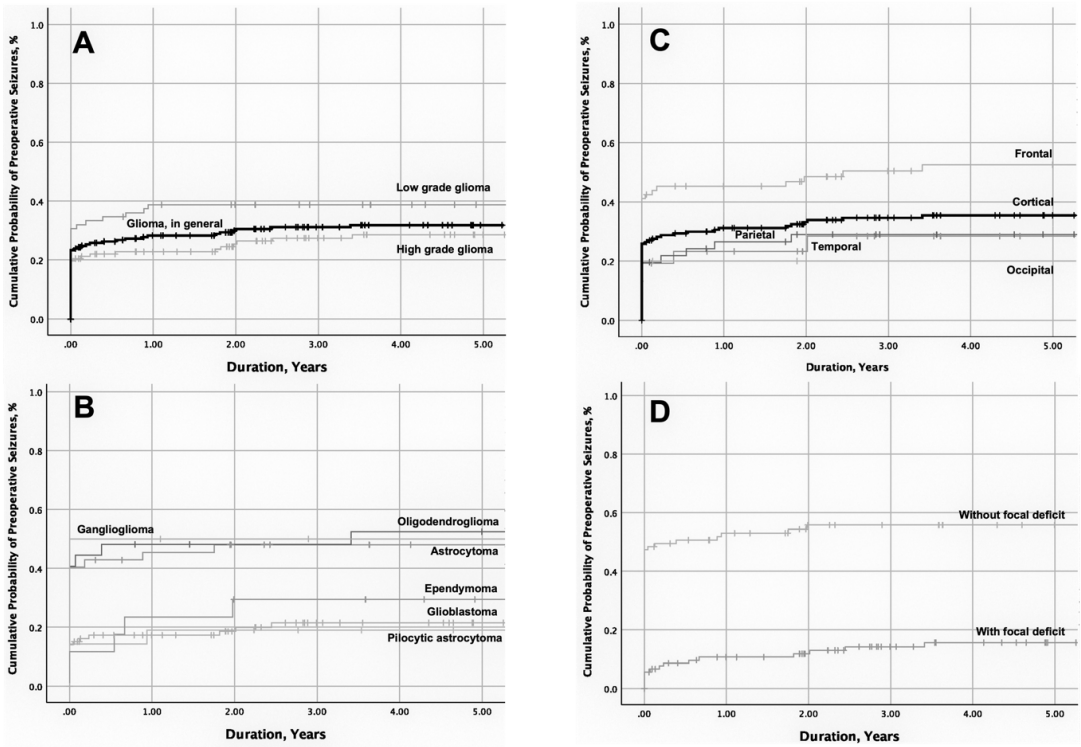

Figure 1: Cumulative incidence of seizure in 5 years for patients with (A) gliomas in general, and specifically low- and high-grade gliomas, (B) various tumor types, (C) cortical involvement and tumor location, and (D) focal deficits.

no benefit from seizure prophylaxis[19] and no consensus on the use of prophylactic treatment in those without seizures. However, our study showed certain subgroups of glioma patients had a seizure occurrence risk as high as 50%. Thus, it is essential to screen these high-risk groups for subtle seizures and consider EEG and seizure prophylaxis.

This study is limited by the small sample size and heterogenicity of the cohort. However, heterogenicity is essential to determine the variation of seizure occurrences in different tumor grades and types, and predictors. As this is a retrospective study, molecular data was not able to be collected.

The prevalence and predictors identified in this study may provide a basis for the development of a seizure prediction model in gliomas. This will guide the clinician to screen for subtle seizures either by asking for seizure symptoms or performing an EEG, especially in those with risk factors. In addition, this will guide future study and practice on AED prophylaxis in those with gliomas.

In conclusion, the prevalence of preoperative seizures in gliomas is high, especially in low-grade gliomas and certain tumor types. The key predictors included cortical involvement and absence of focal neurological deficit or headache. Seizure screening and anti-seizure prophylaxis should be considered in the high-risk group.

DISCLOSURE

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