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The potential of seizure to predict prognosis in glioblastoma patients: A retrospective study

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Abstract

Aim: Glioma, particularly glioblastoma (GBM), represents a prevalent and aggressive primary brain tumor with limited curative options. Epileptic seizures often manifest as a common clinical symptom in these patients, but their prognostic significance remains debated. This study aimed to retrospectively analyze the clinical presentations, tumor characteristics, and the impact of seizures on the prognosis of GBM patients.

Materials and Methods: A total of 113 adult patients with histologically confirmed GBM treated between April 2018 and January 2022 were included in this retrospective analysis. Data encompassed clinical symptoms, preoperative and postoperative seizures, tumor localization, overall survival (OS), and other relevant factors. Statistical analysis was performed to assess the relationships between seizures and various prognostic parameters.

Results: Seizures were present in 39.8% of GBM patients, with 20 patients experiencing both preoperative and postoperative seizures. Preoperative and postoperative seizures were not significantly associated with differences in prognosis ($p>0.05$). Tumor localization, OS, Karnofsky performance score, and length of hospital stay showed significant differences between patients with and without seizures ($p<0.05$). Complete resection was achieved in 90.3% of patients, leading to a relatively lower incidence of postoperative seizures.

Conclusion: Seizures in GBM patients are associated with OS, Karnofsky performance score, and hospitalization duration, independently of other factors. The presence of seizures serves as a valuable prognostic indicator for GBM, prompting further investigation into its influence on patient outcomes, quality of life, and socioeconomic aspects of survival. These findings emphasize the importance of early seizure management in GBM patients and the need for tailored treatment strategies.

Introduction

Glioblastoma (GBM) is a mortal malignant brain tumor predominantly found in adults, characterized by an exceptionally poor prognosis, with a median survival period of just 14 months [1]. Glioblastoma is categorized as a high-grade glioma, specifically designated as WHO grade IV [2]. It afflicts approximately five individuals per 100,000, making it the most prevalent malignant brain tumor in adults [3]. GBM constitutes nearly half, specifically 47.7%, of malignant tumors within the primary central nervous system (pCNS) of adults and, regrettably, continues to elude curative treatment [3]. The current standard of care for GBM patients entails a combination of safe and extensive surgical removal, followed by adjuvant therapies such as radiation and chemotherapy. Unfortunately, even with these optimal surgical and postoperative treatments, glioblastomas remain overwhelmingly fatal due to their invasive and aggressively progressive characteristics [1,4].

Seizures are more commonly associated with lower-grade gliomas, affecting over 80% of patients [5]. However, in glioblastoma, seizures also occur quite frequently, serving as the initial symptom in 20% to 40% of cases [6]. Interestingly, the mechanisms behind seizures may differ between low-grade and high-grade gliomas [5,6]. The influence of tumor location and size on seizure occurrence varies depending on the tumor's grade. In lower-grade gliomas, seizures are often associated with larger tumors. On the other hand, in high-grade gliomas, seizures are more likely to occur in smaller tumors. Specifically, these seizures tend to manifest in tumors that are not deeply seated in the pericallosal regions [7].

Although not fully understood, epilepsy related to brain

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tumors is believed to result from molecules released by the tumor, rendering the tumor or surrounding tissue more susceptible to seizures [5,7]. It may also result from the mechanical compression of normal brain tissue, leading to reduced blood flow and oxygen levels, thus increasing epileptogenic tendencies. In glioblastoma, the dominant mechanism of epileptogenesis is likely the disruption of subcortical electrical networks due to the tumor's rapid growth and invasive nature, leading to an imbalance between inhibitory and excitatory neural networks [8,9].

While seizures in lower-grade gliomas have been extensively studied, there is limited research on seizures as a prognostic factor in glioblastoma [7,10]. To the best of our knowledge , there have been no investigations into seizures within the context of other preoperative symptoms. Preoperative symptoms can provide insights into tumor characteristics, such as size and growth rate, and can also influence the clinical course, affecting the timing of glioblastoma detection and prognosis. By examining the distinctions between patients with tumors that solely cause seizures preoperatively and those with tumors causing seizures along with other symptoms, we aim to shed light on the importance of timely surgical intervention in managing glioblastoma patients with preoperative seizures.

In this research endeavor, we undertook a retrospective analysis of patients diagnosed with glioblastoma and treated at our medical facility. Our examination encompassed a thorough evaluation of various aspects, including clinical manifestations, initial symptoms, tumor localization, the occurrence of seizures, the timing of diagnosis, and the overall survival (OS) of these patients. The clinical examination of patients and the presence of seizures are easily accessible parameters, making them ideal indicators. Establishing a link between GBM patient symptomatology and prognosis may provide a robust and prompt means to predict patient outcomes. This, in turn, can offer clinicians valuable data for forecasting prognosis and devising treatment strategies following a GBM diagnosis.

Materials and Methods

This retrospective research study was conducted in medical facilities specifically dedicated to neurooncology. The analysis focused on 113 consecutive adult patients (age $\geq$18 years) with confirmed histological diagnoses of glioblastoma (GBM). These patients were treated and monitored at University of Health Sciences, Ankara Bilkent City Hospital between April 2018 and January 2022.We obtained Institutional Review Board approval for this retrospective study and secured written informed consent from each participating patient specifically for the surgical intervention and study participation. In addition, all patients underwent preoperative and periodic postoperative imaging, including contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) scans. For further treatment and follow-up, we collaborated with the medical oncology and radiation oncology departments.

The study excluded individuals below the age of 18, those who had previously undergone surgery for a low-grade glioma, patients who did not consistently attend follow-up appointments and treatment sessions, and individuals for whom the date of death was uncertain. Comprehensive records were meticulously maintained and compiled for all patients, encompassing detailed cranial imaging, blood tests, and thorough neurological examinations during follow-up, assessment of the presence and frequency of seizures both before and after surgery, postoperative pathology evaluations, and subsequent treatment and follow-up care.

Patients who experienced at least one seizure prior to surgery, which was not linked to conditions such as epidural or subdural hematoma, parenchymal hematoma, or subarachnoid hemorrhage, and was not associated with factors raising intracranial pressure, such as hydrocephalus, or metabolic factors like electrolyte imbalances, were categorized as having had a preoperative seizure (PreS).

All patients underwent a surgical resection procedure that prioritized safety and aimed for the most extensive removal of the tumor while preserving neurological function. Subsequently, they received a combination of chemotherapy and radiotherapy as part of their treatment plan. In cases where patients presented with preoperative deficits, the primary goal during surgery was to achieve maximal tumor resection while avoiding the introduction of additional deficits. If more than 95% of the tumor was resected, it was considered complete resection. 50%-95% resection was called subtotal resection and 10%-50% resection was called partial resection. $<$10% resection was considered as biopsy. The date on which cranial imaging confirmed the presence of a brain tumor was considered the date of diagnosis. The period from this date until the date of death was calculated as the overall survival (OS) time for each patient.

The diagnosis of epilepsy primarily relied on clinical symptoms as the initial assessment. Patients showing any suspicion of seizures underwent electroencephalogram (EEG) evaluations. Those with suspected epileptic symptoms collaborated with the neurology department to confirm the diagnosis, evaluate the semiology of seizures, and tailor the treatment accordingly. Postoperative seizures (PostS) were defined as epileptic seizures that manifested within a window of up to three weeks after surgery or before the commencement of chemoradiotherapy.

All prospective prognostic variables, whether preoperative or postoperative, were analyzed to assess their impact on OS rates.

Statistical analysis

Data analysis was conducted using statistical software packages, specifically IBM SPSS 25.0 (Armonk, NY: IBM Corp.) and MedCalc 15.8 (MedCalc Software bvba, Ostend, Belgium). In addition to employing descriptive statistical methods, such as frequency, percentage, mean, standard deviation, median, minimum-maximum values, and others, the study used Chi-Square tests (including Pearson's Chi-Square Test, Yates' Corrected Chi-Square Test, and Fisher's Exact Test) to compare qualitative data. Various statistical tests, including the Smirnov test, measures of skewness and kurtosis, and graphical methods

(such as histograms, Q-Q Plots, Stem-and-Leaf plots, and Boxplots), were assessed.

For comparing normally distributed quantitative data between groups, the study employed Independent Samples t-test, while the Mann-Whitney U test was used for comparing non-normally distributed data between groups. The relationships between variables were evaluated using Spearman's rho Correlation test. The statistical significance level was set at α=0.05.

Power analysis

Power analysis was conducted using the G*Power 3.1.9.7 statistical software package (Franz Foul, Universitat Kiel, Germany), with the following parameters: n1=87, n2=26, α=0.05, Effect Size (d)= 0.73, resulting in a power of 84%.

Results

In our study, a total of 113 patients were included in the analysis, comprising 45 (39.8%) females and 68 (60.2%) males. The average age of the patients was 61.1 ± 13.2 years. Among these patients, 45 (39.8%) had a history of seizures, with 32 patients experiencing seizures before surgery (PreS) and 33 patients having seizures after surgery (PostS). Notably, 20 patients had both PreS and PostS. When comparing the outcomes of PreS and PostS individually, no statistically significant differences were observed in terms of prognosis (p>0.05).

The mean Karnofsky performance score (KPS) was 67.4 ± 16.2 before surgery and 72.7 ± 18.9 after surgery. Regarding tumor localization, 55 (48.7%) tumors were situated in the right hemisphere, while 58 (51.3%) were in the left hemisphere. The overall survival rate for the cohort was 8.5 ± 5 months. On average, patients underwent 1.3 ± 0.5 surgical operations for the treatment of glioblastoma. The average duration of hospitalization during the perioperative period was 19.5 ± 22.7 days. A concise summary of patient characteristics is provided in Table 1.

Symptom presentation varied among patients, and some had multiple symptoms. Four patients (4.08% of the sample) were asymptomatic. Headache was reported by 58 patients (51.3%), while 58 patients (51.3%) had motor deficits. Thirty-two patients (28.4%) experienced preoperative seizures, and 32 patients (28.4%) reported neurocognitive impairment symptoms. Visual impairment was observed in six patients (5.3%), and speech disorders were present in six patients (5.3%).

When assessing the surgical procedures conducted, it was observed that complete resection was achieved in 102 patients (90.3%), with the remaining 11 patients undergoing different levels of resection (1 patient underwent biopsy, 2 patients had partial resection, and 8 patients underwent subtotal resection). All patients received combined chemotherapy and radiotherapy through coordinated efforts between the medical oncology and radiation oncology departments.

Comparing various groups according to location and seizure status, no statistically significant differences were observed in terms of gender, age, comorbidities, tumor localization, histologic tumor marker positivity (Gfap, p53,

Table 1. Patient characteristics and clinical presentations.

		Number	%
Sex	Female	45	39.8
	Male	68	60.2
Age (years)*		61.1 ± 13.2	64.0 (18.0 – 85.0)
Pre-op Seizure	No	81	71.6
	Yes	32	28.4
Post-op Seizure	No	80	70.7
	Yes	33	29.3
Seizure frequency	No	68	60.2
	Just one	8	7.1
	1 time per 3 month	5	4.5
	1 time per month	21	18.5
	3 times per day	4	3.5
	5 times a day	4	3.5
	1 time per week	3	2.7
Comorbidity			
No		61	54.0
Yes		52	46.0
Hypertension (HT)		16	30.7
Diabetes Mellitus (DM)		7	13.5
Other		14	26.9
HA + DM		4	7.7
HT + other		7	13.5
HT + DM + other		4	7.7
Pre-operative Neurologic deficits	No	55	48.7
	Yes	58	51.3
Post-operative Additional Neurologic deficits	No	48	42.4
	Yes	65	57.6
Localisation	Right	55	48.7
	Left	58	51.3
	Frontal	31	20.0
	Parietal	48	31.0
	Temporal	37	23.9
	Occipital	24	15.5
	Deep	11	7.1
	Post Fossa	4	2.5
Kİ67	<%10	7	6.2
	%10-19	13	11.5
	≥%20	87	77.0
	Other	6	5.3
Olig-2	(-)	103	91.2
	(+)	10	8.8
Idh-1	NOS	95	84.1
	Mutant	18	15.9
Overall Survival*		8.5 ± 5.0	8.0 (4.0 – 9.0)
Karnofsky Performance Score*	Pre-op	67.4 ± 16.2	60.0 (60.0 – 70.0)
	Post-op	72.7 ± 18.9	80.0 (80.0 – 80.0)
	Radiotherapy/ Chemotherapy	63.1 ± 17.1	70.0 (50.0 – 70.0)
Duration of Hospitalization (Days)*		19.5 ± 22.7	20.0 (6.5 – 20.0)
Operation number*		1.3 ± 0.5	1.0 (1.0 – 2.0)

*: Mean ± Standard Deviation / Median (Min – Max).

Table 2. Comparisons by Seizure Status.

		Seizure		p
		No (n=68)	Yes (n=45)	
Sex	Female	30 (44.1%)	15 (33.3%)	0.237[a]
	Male	38 (55.9%)	30 (66.7%)	
Age (years)*		61.9 ± 12.3	58.0 ± 15.4	0.490[b]
Pre-operative Seizure	No	68 (100.0%)	13 (28.9%)	--
	Yes	--	32 (71.1%)	
Post-operative Seizure	No	68 (100.0%)	12 (26.7%)	--
	Yes	--	33 (73.3%)	
Overall Survival		6.0 (3.0 – 8.0)	8.0 (8.0 – 14.0)	**<0.001**[c]
Karnofsky Performance Score	Pre-op	65.0 ± 20.2	59.2 ± 10.4	0.071[b]
	Post-op	68.0 ± 22.6	78.0 ± 15.3	**0.041**[b]
	After radiotherapy/ Chemotherapy treatment	66.0 ± 18.1	68.6 ± 15.2	0.582[b]
Duration of Hospitalization (Days)		14.0 (5.0 – 20.0)	18.0 (20.0 – 20.0)	**0.005**[c]
Operation number		1.3 ± 0.6	1.3 ± 0.5	0.512[b]

Note: Data are expressed as (a) n (%), (b) Mean ± Standard Deviation, (c) Median (Q1 -Q3). *: Comparison was made by combining 1.0 and 1.5 groups.
[a]: Chi-Square Test, [b]: IndependentSamples t Test, [c]: Mann-Whitney U Test.

Ki67, Vimentin, Atrx, Olig-2, Idh-1), KPS, and the number of operations ($p>0.05$). However, statistically significant differences ($p<0.05$) were found between the groups in terms of seizures, OS, postoperative KPS, and length of hospital stay. Specifically, patients with seizures had lower OS, postoperative KPS, and their hospital stays were longer (see Table 2).

Anti-epileptic drug therapy was initiated for all patients who experienced seizures. Furthermore, 51 patients with tumors located in the frontal and temporal lobes, who had not yet experienced seizures, were proactively started on prophylactic anti-epileptic drugs. The anti-epileptic treatment regimen encompassed a range of medications, with levetiracetam and phenytoin being the most frequently prescribed drugs.

Discussion

GBM is the most aggressive pCNS neoplasm. In general, it is one of the leading tumors in terms of mortality, even among all neoplasms. The incidence of GBM does not rely upon geographical or ethnic factors. GBMs are most commonly occur in the 6th and 7th decades of life [4,11]. Glioblastomas are diffuse infiltrative tumors. As a result, curative resection or tumor-free surgery are rarely possible for these neoplasm [12]. In the current treatment approach, key goal of primal treatment of GBM is maximal safe resection that can be described as balancing resection limits of tumor and neurological dysfunctions. Various advanced pre-operative neuroimaging, neuronavigation systems and neuromonitoring have been included in patient management to acquire the goal of safe maximal resection [13,14].

In our study, we retrospectively reviewed the characteristics, preoperative/postoperative neuroimaging, and pathological/histological features of the patients that operated for GBM in our clinic. The effects of these parameters on the course of the disease were evaluated by comparing them with prognostic and socioeconomic factors such as overall survival, length of hospital stay, and KPS.

When the symptoms before the diagnosis of GBM were evaluated, seizure gave more significant results in terms of prognosis than other symptoms. It is also useful for early diagnosis of GBM, as the presence of seizures causes patients to admit the hospital earlier and prompts doctors to perform a cranial imaging. Although seizure helps in early diagnosis, some articles show that seizure is an indicator of poor outcome in malign pCNS tumors. In the same studies, it was shown that cognitive impairment precedes neuroimaging progression [11]. Except seizure, patients with other symptoms may not apply to evaluation sooner, as the patient may be in denial phase.

Although its pathogenesis is not understood, the relationship between seizure and prognosis has been examined in many publications in the literature and statistically significant results have been obtained [12,13]. Numerous studies have addressed the relationship between longer OS in patients with PreS [5,8]. In despite of, there are few publications that do not confirm the positive prognostic effect of PreS on patient survival [9,11]. On the other hand, some authors showed the presence of pre/postoperative seizures as a generally poor prognosis, as in this study [12]. It was observed that the seizure decreased OS and KPS, and consequently prolonged the hospitalization period. When compared with delayed seizures that cause postoperative tumor progression, the incidence and occurrence of early postoperative seizures (epileptic seizures up to three weeks after surgery or before the start of chemoradiotherapy) is less known. Unlikely, PostS was more associated with preoperative/postoperative systemic diseases such as anemia, systemic infection, impaired liver homeostasis due to anesthesia and drugs and operative stress. Some authors reported that several systemic dysfunctions such as serum electrolyte imbalance, hormone imbalance, organ dysfunction and failure, autoimmune disorders, and paraneoplastic syndromes lower the seizure threshold [5,15]. Therefore, we initiate early anti-epileptic therapy to reduce the risk of PostS after GBM surgery. Seizures seen in the early period despite prophylactic anti-epileptic drug therapy are associated with particularly poor prognosis. As expected, the relationship of PostS with extension of resection and OS is well known. The relationship between partial tumor resection and the risk of postoperative seizures has already been reported for pCNS and metastatic brain tumors [10,16]. Given the high rate of complete resection at 90,3% among the patients in this study, the incidence of PostS was comparatively lower. In summary, the poorer OS observed in GBM patients with PostS could potentially be linked to partial tumor resection and the presence of the

systemic disorders mentioned earlier.

Recent reports have mentioned to the critical role of IDH1 mutation in pCNS tumor epileptogenesis [17]. We studied GFAP, p53, Ki67, Vimentin, Atrx, Olig-2 and Idh-1 mutations in this study. But, there is no statistically significant relationship with these parameters and seizure or OS. A study with a higher number of patients and a double-blind evaluation by independent pathologists will yield better results.

Conclusion

The presence of seizures in glioblastoma patients is significantly correlated with overall survival, KPS, and the length of hospital stay, regardless of other factors. Seizures prove to be a valuable indicator for predicting the prognosis of GBM and assessing the quality of life during the remaining life expectancy of patients. Our findings underscore the need for further research into the influence of perioperative seizures on glioblastoma survival, patient well-being, and the socioeconomic aspects of survival.

Disclosure and Conflicts of interest

The authors affirm that they have no actual or potential conflicts of interest pertaining to the research, authorship, and/or publication of this article.

Ethical approval

This study was approved by the Institutional Review Board (Ankara City Hospital No. 1 Clinical Research Ethics Committee, Decision no: E1/2410/2022).

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