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Tumour - Related Epilepsy and Post-Surgical Outcome: Tertiary Hospital Experience in Saudi Arabia

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Research article

Keywords: Epilepsy, brain tumor, pathology, surgery, Saudi Arabia, ILAE

Posted Date: August 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-53251/v1

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Abstract

Background Some studies have suggested that tumor pathology significantly influence freedom from seizures post epilepsy surgery; however, there is no consensus among researchers regarding this issue. This study aims to retrospectively look for different types of tumor- related epilepsy and their outcomes in the first-year post epilepsy surgery among both adults and children.

Methods In this hospital-based retrospective study, patients with drug resistant epilepsy due to brain tumor who underwent epilepsy surgery were included. Our patients underwent a thorough presurgical evaluation in an Epilepsy Monitoring Unit (EMU) before deciding to undergo surgical intervention, according to an epilepsy case-management conference. Four outcomes of interest were investigated during the first-year post epilepsy surgery.

Results One hundred patients with brain tumors were included in this study (male: female = 3:2); 45 patients were children. Most of the patients (93) had low-grade gliomas or glioneuronal tumors (G/GNT). No significant differences in outcome were observed between sex, age, or histopathological categories. However, during the first year after epilepsy surgery most of the low-grade G/GNT cases showed favorable outcomes of International League Against Epilepsy (ILAE) class 1 and 2 (61.3% and 9.7%, respectively), while high-grade gliomas and meningothelial tumors showed outcomes of ILAE class 1 (40% and 100%, respectively).

Conclusions One-year favorable outcome of post epilepsy surgery of different brain tumors have been achieved among both children and adults. Adequate presurgical evaluation in EMU (for long-term video-electroencephalography monitoring) to plan appropriate surgical strategy is advised. Tumor Pathology does not influence seizure outcome one-year post epilepsy surgery.

Introduction

Seizures have negative impact on quality of life, particularly in social, economic and cognitive domains and increases the risk of sudden unexpected death (SUDEP) in epilepsy has been established, [1] however post epilepsy surgery seizure reduction and/or freedom has been shown to improve quality of life.[2] While approximately 30–50% of patients with brain tumors have epilepsy as an initial presentation,[3] 6–45% of patients with brain tumors develop seizures later in their life.[4, 5] Although the exact mechanism of development of seizures in patients with brain tumors is not clearly understood, recent studies have identified that some changes in the peritumoral regions play a role in the release of neurotransmitters that lead to the development of seizures.[6]

Many studies have reported the relationship between the tumor type and seizure frequency. For example, low-grade gliomas and glioneuronal tumors (G/GNT) are associated with a high rate of seizure incidence (85–92%).[7-9] In contrast, glioblastomas, which are high-grade tumors, are associated with a low rate of seizure incidence (20–50%).[10, 11] The incidence rates of seizures in meningiomas, especially in atypical and malignant subtypes, remain understudied.[12]

The location of a tumor is also an important determinant of tumor-related epilepsy. Some authors reported that the proximity of a tumor to the cortical gray matter is an important factor influencing the development of epilepsy. Some studies indicate that the anatomical location of low-grade tumors related epilepsy is an important factor to be considered when choosing the optimal surgical strategy. For example, tumors in the frontal and temporal lobes, as well as those in the limbic system, are more likely to cause seizures than tumors in other locations.[13-15]

Tumor-related epilepsy is likely drug resistant; however, new generation antiepileptic drugs (AEDs) show good efficiency. For instance, metabolism of levetiracetam is not dependent on the P450 system; this drug is one of the attractive choices because drug interactions can be avoided.[3, 16, 17] When prescribing AEDs to patients with tumors related epilepsy, interactions between cytotoxic drugs and some AEDs—the modulation of metabolism of one another—should be taken into account.[18]

Treatment of tumor related epilepsy is a complex theme, however recent studies indicated that surgical management supersede medical management.[19] Reportedly, resection of the epileptogenic zone may lead to freedom from or significant control of seizures in 70–90% of patients.[20, 21] Furthermore, tumor type, seizure severity, early surgical intervention, frequency during the preoperative stage, histopathology of the tumors, and the extension of surgical resection to include peritumoral tissues are, reportedly, the factors that increase the likelihood of freedom from seizures postoperatively.[22] Two of the best predictors of freedom from seizures post-operation include a duration of less than 1 year since the onset of epilepsy and gross total surgical resection.[23, 24]

Some recent studies have suggested that tumor histopathology plays a significant role in predicting freedom from seizures post epilepsy surgery; however, there is no consensus among researchers regarding this issue.[25, 26] In this study we retrospectively looked for different brain tumors and their one-year post epilepsy surgery outcome.

Methods

Patients

A hospital-based retrospective study was conducted using secondary data from the epilepsy registry at King Faisal Specialist Hospital and Research Centre (KFSH&RC) over a 16-year period (1998–2014).

The study included patients with the diagnosis of brain tumor related epilepsy who underwent epilepsy surgery. The patients were admitted to the Epilepsy Monitoring Unit (EMU) for long-term video monitoring; they underwent presurgical evaluations such as surface EEG, 3-tesla brain MRI, and fluoro-deoxy-glucose positron emission tomography (PET) brain scan. Additionally, a qualified neuropsychologist was present during the evaluation of the enrolled patients with epileptic. In some patients, intracranial subdural recording, intracarotid amobarbital procedure (Wada test) and Electrocorticography (ECoG), and motor, sensory, and language mapping were performed.

Clinical data

Detailed information on the patients was collected. This included demographic characteristics (age, gender, handedness, age at onset of the disease) and history and clinical data (type of seizure and frequency, seizure observed at EMU, MRI findings, PET scan, ictal EEG (IEEG) location and type, subdural EEG recording, and inter-ictal EEG (IIEEG) location and type). Moreover, final diagnosis, surgical procedures, and pathology were recorded as the primary outcome. All tumor cases enrolled in this study were reviewed and graded independently by a neuropathologist according to the WHO classification.[27]

Epilepsy data were discussed in an epilepsy surgery conference with epileptologists, epilepsy surgeons, neuroradiologists, and neuropsychologists to determine the status and surgical candidacy of the patients.

According to the International League Against Epilepsy (ILAE) commission report (1997–2001), 6 outcomes of interest were proposed (table 1),[28] with certain modifications. While the definitions of classes 1, 2, and 3 remain the same, the remaining classes (4, 5, and 6) were merged into class 4. Thus, the definitions of the classes were as follow: class 1, patients who were completely seizure-free with no auras; class 2, patients with auras but no seizures; class 3, patients experiencing one to three seizure days per year with/without auras; and class 4, patients experiencing four or more seizure days per year to those experiencing ≥50% reduction of baseline seizure days, with/without auras. Furthermore, outcomes of classes 1 and 2 were considered favorable and those of classes 3 and 4 were considered unfavorable. These four outcomes were investigated during the first-year post surgery.

Statistical analysis

Statistical analysis through cross-tabulation of the tumor groups, pathologies, and progressive outcomes was performed (SAS software ver. 9.4). Due to small sample size, some of the subgroups, pathologies, and outcomes were collapsed. Proportional statistics, chi-squared test, and Fisher's exact test were used to explain the findings within a 95% CI. A *P*-value of less than 0.05 was considered statistically significant.

Results

Among the 100 patients with brain tumors related epilepsy included in this study, 59 (59%) were male patients and 41 (41%) were female patients. Regarding age classification, a lower rate of brain tumor incidence was reported among children than among adults (45% vs. 55%). However, there were no significant differences between sex and age and the histopathology categories ($P = 0.111$ and 0.878, respectively), as depicted in Table 1.

Table 1. Histopathologies of the brain tumors with patient characteristics (N = 100)

Characteristics	Low-grade G/GNT (n = 93)		High-grade Glioma (n = 5)		Meningioma (n = 2)		
	No.	%	No.	%	No.	%	*P* value
Male	58	62.4	1	20	0	0.0	0.111
Female	35	37.6	4	80	2	100	
Children (<18 years)	43	46.2	2	40.0	0	0.0	0.878
Adults (≥18 years)	50	53.8	3	60	2	100	

According to histopathological findings, the cases of brain tumor were grouped into three main categories (Figure 1). Most of the tumors (93%) were low-grade gliomas or glioneuronal tumors (G/GNT), followed by high-grade gliomas (5%); there were only two meningioma cases (2%).

Among the three main categories of brain tumors, low-grade G/GNT comprised 11 entities. Under this category, 40 tumors were gangliogliomas and 29 tumors were Dysembryoplastic neuroepithelial tumors (DNET). Among the 5 high-grade gliomas, 3 were astrocytic tumors. Interestingly, only 2 of meningiomas were found. Table 2 details the pathological categories.

Table 2. Subgroups of brain tumors among patients with epilepsy

Types of brain tumor	Subgroups	n	%
Low-grade Gliomas (93 cases)	Ganglioglioma	40	40.0
	DNET	29	29.0
	Oligodendroglioma	7	7.0
	Gangliocytoma	5	5.0
	Oligoastrocytoma	3	3.0
	Composite GG/DNET	3	3.0
	Diffuse Astrocytoma	2	2.0
	Ependymoma	1	1.0
	Neurocytoma	1	1.0
	PGNT	1	1.0
	Composite PXA and GG	1	1.0
High-grade Gliomas (5 cases)	Anaplastic Astrocytoma/GBM	4	4.0
	Anaplastic Oligodendroglioma	1	1.0
Meningiothelial tumors(2 cases)	Meningioma	2	2.0

In this study, the primary postoperative outcome was evaluated using the modified ILAE classification described in the methodology section. During the first-year post surgery, most patients with low-grade G/GNT experienced favorable outcomes (class 1, 61.3% and class 2, 9.7%) (Table 3). On the contrary, approximately 40% of the patients with high-grade gliomas showed favorable outcomes (ILAE class 1). Both meningioma cases (100%) showed outcomes of ILAE class 1.

Table 3. Seizure outcome one year after surgery according to histopathology

Group	1		2		3		4	
	No.	%	No.	%	No.	%	No.	%
Low-grade G/GNT	57	61.3	9	9.7	9	9.7	18	19.4
High-grade Gliomas	2	40	1	20	1	20	1	20
Meningiomas	2	100	0	0	0	0	0	0

(1) completely seizure free, no auras (2) only auras, no seizures (3) 1–3 seizure days per year ± auras (4) Four seizure days per year to 50% reduction of baseline seizure days; ±auras

Among the 100 patients with brain tumors, 71 (71%) patients—including 66 patients with low-grade G/GNT, 3 patients with high-grade gliomas, and 2 patients with meningiomas—experienced favorable outcomes during the one-year post-surgery period (Table 4). Moreover, incidence of favorable outcome was higher in adult patients than in children (52.2% vs. 47.8%) and in male patients than in female patients (41% vs. 30%). However, these differences in outcome depending on histopathological type, age, and sex were not statistically significant (P = 0.864, 0.559, and 0.159, respectively).

Table 4 Favorable and unfavorable outcomes one year after surgery

Characteristics	Favorable outcome (n = 71)		Unfavorable outcome (n = 29)		
Histopathological types	No.	%	No.	%	*P* value
Low-grade G/FNT	66	71.0	27	29.0	0.864
High-grade Gliomas	3	60.0	2	40.0	
Meningioma	2	100.0	0	0	
Age					
Adults	36	52.2	17	58.6	0.559
Children	33	47.8	12	41.4	
Gender					
Male	41	41.0	18	18.0	0.159
Female	30	30.0	11	11.0	

Discussion

From the epilepsy registry at KFSH&RC, 100 patients who underwent surgery for tumor-related epilepsy were included in this study. Our finding is consistent with other reports in the literature, were male patients found to be at a higher risk of developing brain tumors and have poor response to therapy than female patients.[25, 29-33]

Varying associations between different brain tumor types and epilepsy have been reported. Most studies showed gangliogliomas to be the most common tumor type associated with epilepsy, followed by DNET, oligodendrogliomas, and astrocytomas.[29, 34-36] These findings support our results, that is, most of our patients had low-grade G/GNT (93.0%), most of which were gangliogliomas (40%) followed by DNET (29%). Furthermore, Babini et al. reported that gangliogliomas (66.7% vs. 40%)[37] were the most frequent tumors among their patients; however, their sample size was smaller (30 cases) than that of our study. Contrary to our findings, Kahlenberg et al. reported that mixed oligo-astrocytomas were the most prevalent tumors followed by astrocytomas of grade II and oligodendrogliomas of grade II.[25] Incidence of high-grade gliomas was lower (5%) in our study than in a study by Michelucci et al. in Italy (77.0%), which can be attributed to a significantly high prevalence of high-grade gliomas in that area.[15]

Seizures and their management have a great impact on the quality of life of patients with brain tumors and weighs heavily on public health expenses . Epilepsy surgery, in many recent studies, was considered to relieve tumor-related epilepsy and achieve favorable outcome.[15, 38, 39] However, tumor related epilepsy in some cases is drug resistant by nature and it may persist even after resecting the primary focus.[25, 40] All of our patients underwent well-planned epilepsy surgery, which is defined as the

resection of the tumor and peritumoral tissues.[23] Consequently, our patients showed varying degrees of improvement during the first year post surgery depending on the type of brain tumor (low-grade G/GNT vs. high-grade gliomas- a difference not statistically significant, $P = 0.864$). It was reported in the some studies that, postoperative seizure outcome was independent of underlying pathology, although there was a trend in favor of better results with low-grade tumors, for example, patients with low-grade tumors, which were the most common type of tumors in our study (93 cases), showed favorable outcome during the first-year post epilepsy surgery with approximately 71% seizure freedom (class 1 and 2). Michelucci et al. reported findings that were similar to those of our study, that is, better outcomes were observed in patients with low-grade gliomas (76%).[15] On the contrary, Kahlenberg et al. showed that about half of their patients (30 out of 54; 55.6%) with brain tumor-related epilepsy showed a good outcome (seizure-free period > 12 months at the last follow-up) post epilepsy surgery.[25] Their proportions were lower than those observed in our study (55.6% vs. 71%).

In our opinion, the ILAE classification of the outcome of epilepsy surgery should be simplified, with only 4 categories rather than 6, to facilitate its application. Hence, whenever patients have four or more seizures (outcome 4, 5, and 6), they should be gathered under one category (to be called category 4). The currently used ILAE Commission on Neurosurgery in 2001,[28] still has some elements that make the use of category 4, 5, and 6 difficult to be measured and implemented in daily practice, particularly when include parameters related to quality of life. This suggested new modified classification could be easily implemented by other researchers in their ongoing studies.

Furthermore, few patients in our study had high-grade gliomas (5) and meningiomas (2). These patients showed favorable outcome during the first-year post epilepsy surgery (60% and 100%, respectively). Michelucci et al. reported similar results; 58% of their patients with high-grade glioma who became seizure free after tumor removal.[15]

Pediatric and adult groups showed no significant differences regarding seizure outcome during the first-year post surgery ($P = 0.559$), and thus, we cannot claim that surgery is more beneficial in pediatric patients. These findings were similar to those of other studies.[23]

Our study has three main limitations: Firstly, the sample size was small and included only 5 patients with high-grade gliomas and 2 patients with meningothelial tumors (2 cases); this makes comparison with low-grade G/GNT insufficient although our sample size (100 cases) is comparable to that of other studies. Secondly, this series of tumor-related epilepsy does not represent the population with epilepsy in Saudi Arabia, because not all patients with tumor-related epilepsy are eligible to be admitted to our institution, and thus, they are treated elsewhere. Finally, this is a retrospective study and it is associated with the possibility of bias occurring during data collection. Despite the above-mentioned limitations, we hope that our study provides valuable information on one of the most debatable topics in epilepsy surgery in the country and in the Middle East.

Conclusions

In this study, the most common tumor related epilepsy was low-grade G/GNT. Outcome of post epilepsy surgery independent of tumor pathology have been achieved with favorable outcome seen among both children and adults. Thus, thorough pre-surgical evaluation of patients with brain tumor-related epilepsy in EMU is highly recommended to enhance better post-epilepsy surgery outcome. Further studies are needed with a larger number of patients from multicenter to make the findings more generalizable in Saudi Arabia.

Declarations

Acknowledgement: We would like to thank Amal Abujaber, epilepsy coordinator, for her contribution to the study and data collection. We would also like to thank Edward Devol and Samia Al Hashim in KFSH&RC for facilitating the collection of required data for this study.

Ethical approval*:* The study was approved by IRB from the Office of Research Affairs in King Faisal Specialist Hospital and Research Centre (RAC # 2151084). As this is a retrospective study, secondary data has been collected from Epilepsy registry at King Faisal Specialist Hospital and Research Centre without identification of patient's data, hence no informed consent has been required.

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Figures

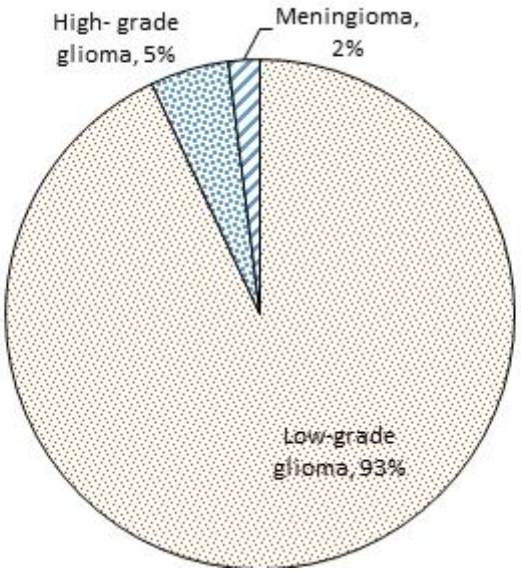

Figure 1

Main types of brain tumor histopathologies