Epilepsy & Behavior 158 (2024) 109919

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Research Paper

The course of tumor-related epilepsy in glioblastoma patients: A retrospective analysis

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ARTICLE INFO

Keywords:
Tumor-related epilepsy
Glioblastoma
Surgery
Radiochemotherapy

ABSTRACT

Purpose: Many patients with glioblastoma suffer from tumor-related seizures. However, there is limited data on the characteristics of tumor-related epilepsy achieving seizure freedom. The aim of this study was to characterize the course of epilepsy in patients with glioblastoma and the factors that influence it.
Methods: We retrospectively analyzed the medical records of glioblastoma patients treated at the University Hospital Erlangen between 01/2006 and 01/2020.
Results: In the final cohort of patients with glioblastoma (n = 520), 292 patients (56.2 %) suffered from tumor-related epilepsy (persons with epilepsy, PWE). Levetiracetam was the most commonly used first-line antiseizure medication (n = 245, 83.9 % of PWE). The onset of epilepsy was preoperative in 154/292 patients (52.7 %). 136 PWE (46.6 %) experienced only one single seizure while 27/292 PWE (9.2 %) developed drug-resistant epilepsy. Status epilepticus occurred in 48/292 patients (16.4 %). Early postoperative onset (within 30 days of surgery) of epilepsy and total gross resection (compared with debulking) were independently associated with a lower risk of further seizures. We did not detect dose-dependent pro- or antiseizure effects of radiochemotherapy.
Conclusion: Tumor-related epilepsy occurred in more than 50% of our cohort, but drug-resistant epilepsy developed in less than 10% of cases. Epilepsy usually started before tumor surgery.

1. Introduction

The majority of patients with glioblastoma experience tumor-related seizures, either as a presenting symptom or during the course of the disease [1,2]. It has been hypothesized that the development of epilepsy in individuals with glioblastoma depends on a combination of factors, including the inherent epileptogenic nature of tumor tissue, alterations in the tumor and surrounding microenvironment, and perturbations in the structure and function of neighboring brain regions [3].

Achieving durable seizure control is associated with reduced morbidity and improved quality of life and is an important treatment goal for patients with brain tumor-related epilepsy [4]. While numerous studies have analyzed the role of epilepsy in tumor prognosis [5–9] less is known about the prognosis of this type of epilepsy in terms of seizure freedom. Previous studies investigating the prognosis of brain tumor-related epilepsy have often been based on smaller, heterogeneous cohorts (low and high grade tumors) [2,10–12]. Seizure frequency is inversely correlated with tumor grade and growth rate [13–17]. A recent *meta*-analysis evaluating the efficacy of antiseizure medication (ASM) in patients with grade II-IV gliomas found that seizure freedom rates at 12 months exceeded 70 % for levetiracetam (LEV) monotherapy [10]. However, the characteristics that contribute to this favorable outcome

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https://doi.org/10.1016/j.yebeh.2024.109919
Received 5 February 2024; Received in revised form 7 May 2024; Accepted 22 June 2024
Available online 27 June 2024

and the factors that may lead to drug-resistant epilepsy in these patients are largely unknown.

We recently reported time-dependent risk factors for epileptic seizures in glioblastoma patients to address the question of how likely a patient is to have a seizure during a specific, defined interval of the glioblastoma disease course, namely preoperatively, early postoperatively, during or after radiochemotherapy. Using the same data set, this study aims to examine the course of epilepsy with seizure recurrence as the primary outcome parameter, while considering the time of first seizure as a covariate. In addition, we report on the occurrence of drug-resistant epilepsy and identify factors that may influence the course of tumor epilepsy. We examined various tumor-related characteristics, seizure patterns, and treatment efficacy to gain insight into the clinical interplay between tumor, oncologic treatment, and epilepsy.

2. Methods

We performed a retrospective analysis of the electronic medical records of patients with glioblastoma treated at our institution. The digital patient files included admissions and outpatient follow-up appointments. All consecutive cases of newly diagnosed de novo glioblastoma seen between January 2006 and January 2020 were included in this study. Exclusion criteria were: (a) patients younger than 18 years at diagnosis, (b) individuals with a history of epilepsy, and (c) those with infratentorial or extracranial tumors. The study adhered to the STROBE guidelines and was approved by the Institutional Ethics Committee of the University of Erlangen-Nürnberg (No. 390_20Bc). Records were analyzed for demographic information, Karnofsky Performance Scale (KPS) at admission, tumor characteristics, oncological treatment, seizure occurrence, seizure semiology and ASM treatment. Gross total resection was defined as the absence of tumor on postoperative MRI scans. Subtotal resection, or partial resection, was defined as the presence of tumor on postoperative imaging. The tumor volume was calculated on preoperative T1-weighted contrast-enhanced MRI using the ellipsoid volume formula: $\pi/6*D1*D2*D3$, where D1, D2, and D3 correspond to the largest diameter of the compartment measured in three-dimensional plans (axial, sagittal, and coronal reformations). In patients with multifocal lesions, all lesions were summed for comparison [18–20].

The diagnosis of epilepsy was made according to the International League Against Epilepsy (ILAE) criteria (19), i.e. if the patient had a seizure related to the brain tumor at any time during the course of the disease. Both focal seizures and focal to bilateral tonic-clonic seizures were included. Seizures that occurred before the first surgery (i.e., the surgery that led to the tumor diagnosis) and had no apparent cause other than the underlying oncological disease were considered preoperative seizures. Seizures that occurred after surgery and before the start of radiotherapy (RT) were considered "early postoperative seizures". This definition was chosen in order to safely exclude acute symptomatic seizures after craniotomy, which are typically defined as seizures occurring within 7 days after surgery [21], from other seizures as our previous work demonstrated that acute symptomatic seizures do not increase the risk of recurrence [22]. Seizures occurring during adjuvant RT or < 30 days after RT were classified as seizures during radiotherapy. Seizures occurring ≥ 30 days after primary oncological treatment (i.e., first surgery and adjuvant radiotherapy) were classified as post-therapeutic seizures.

Drug-resistant epilepsy was classified according to the ILAE definition in patients with epilepsy (PWE) who were not seizure-free after two ASMs [23].

To assess the risks associated with seizure recurrence, we compared patient characteristics of the group of PWE with a single documented seizure to those with more than one documented seizure (single versus recurrent seizures) using univariate and multivariate binary logistic regression analyses.

The multivariate analysis included significant clinical correlations and trends ($p < 0.1$) as well as oncologic parameters of first-line therapy (extent of surgery, radiation, chemotherapy) to assess their effect on seizure recurrence. We adjusted for age and follow-up time as potential confounders. In a second analysis, we analyzed the risks associated with drug-resistant epilepsy.

As this was an exploratory study, the significance level was set at $p < 0.05$ without correction for multiple testing.

Statistical analyses were performed using SPSS (version 26, SPSS Inc., IBM). Baseline characteristics of patients were expressed as percentage of patients, mean ± standard deviation (SD), median with interquartile range for data on overall survival, progression-free survival, and duration of follow-up.

We have previously published two analyses using this dataset investigating risk factors associated with seizures and status epilepticus [22,24]. Any data not published in the article will be made available in anonymized form upon reasonable request by the corresponding author.

3. Results

3.1. Patient population

After exclusion of ineligible cases (age < 18 years, $n = 13$; previous epilepsy, $n = 6$; extracerebral or infratentorial glioblastoma, $n = 14$), 520 individuals were included in the study (Fig. 1), of whom 292 (56.2 %) had tumor-related epilepsy. Median follow-up was 13 months (interquartile range 7–23 months, range 1–165 months). Table 1 shows the patient characteristics for PWE.

3.2. Epilepsy onset

The median time interval between primary surgery and first seizure was −2.5 days (range −250 – 1473 days, Fig. 2). Epilepsy onset was preoperative in 154/292 patients (52.7 %), early postoperative in 21/292 (7.2 %), during RT in 40/292 (13.7 %), posttherapeutic in 76/292 (26.0 %) PWE.

3.3. Semiology

150 of the 292 first seizures (51.3 %) were focal to bilateral tonic-clonic seizures. Throughout the disease course, 100/292 PWE (34.2 %) had only focal seizures and no bilateral tonic-clonic seizures. Seizure semiology was unknown in 15 PWE. In 18/292 PWE (6.2 %), the first seizure was status epilepticus (SE). Overall, SE occurred in 48/292 PWE (16.4 %) with a median time between first tumor diagnosis and SE occurrence of 142 days (range −99–1896 days), mostly after completion of primary oncologic therapy as previously published [24].

3.4. Antiseizure medication

Antiseizure medication (ASM) was started after the first seizure in the majority of patients with the exception of 13 (4.5 %) patients. Levetiracetam (LEV) was by far the most used drug initially (245 PWE, 83.9 %) with a median starting dosage of 1000 mg/d. Most PWE started with ASM monotherapy, with only 19/292 (6.5 %) receiving 2 ASM and 4/292 (1.3 %) receiving > 2 ASM right away. At the last follow-up, 117 PWE (40.1 %) were still taking their initial medication without any changes. 26 patients (8.9 %) were not taking any ASM at the last follow-up. Dual- or polytherapy was established in 15 % of PWE at the last follow-up. ASM therapy was continued without changes in 117/292 (40.1 %) PWE. Table 2 shows the initial ASM and the ASM documented at the last follow-up (see **Supplementary Table 2** for initial and last ASM in PWE with DRE).

3.5. Seizure freedom and drug-resistant epilepsy

136/292 PWE (46.6 %) remained seizure free after the first seizure

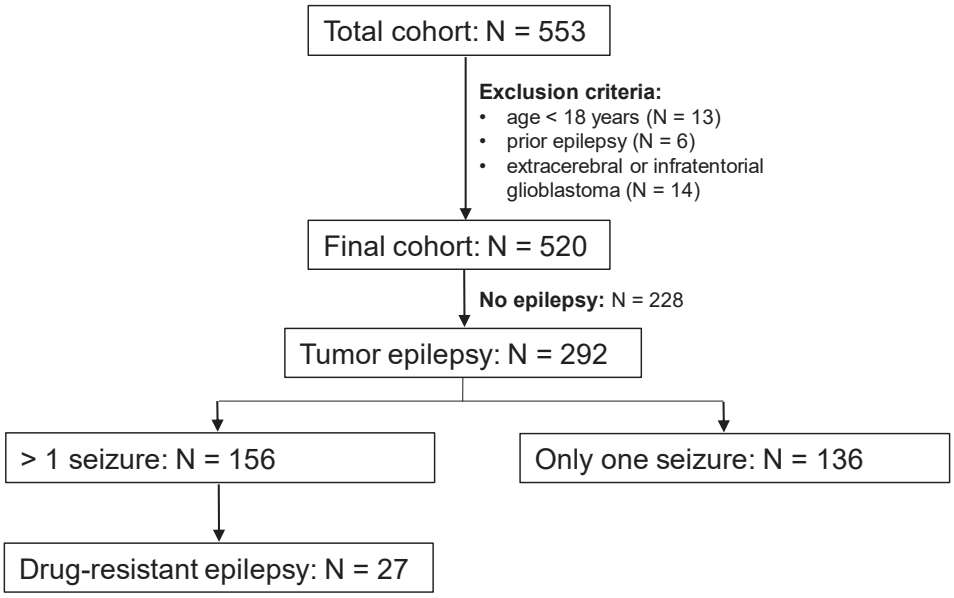

Fig. 1. Flow chart of the study cohort. Patients with glioblastoma (total cohort), after application of the exclusion criteria (final cohort), and glioblastoma patients suffering from epilepsy (tumor epilepsy).

throughout the follow-up period. Of the 150 patients with preoperative seizures, 19 had more than one seizure in the preoperative period. 156 patients had more than one seizure, but only 27/292 (9.2 %) developed drug-resistant epilepsy according to ILAE criteria. Status epilepticus occurred in 48/292 PWE (16.4 %) and was the first manifestation of epilepsy in 18/292 PWE (6.2 %).

3.6. Risk factors for recurrent seizures after a first seizure

In univariate analysis, occipital (odds ratio [OR] 0.517, p = 0.05) or multifocal (OR 0.540, p = 0.03) tumor location and early postoperative seizures (OR 0.323, p = 0.02) were associated with a lower risk of seizure recurrence. Preoperative seizures (OR 1.622, p = 0.04), longer follow-up (OR 1.021, p = 0.01), and longer time between first seizure and ASM onset (OR 1.011, p = 0.075) were associated with an increased risk of seizure recurrence.

In multivariate analysis, early postoperative epilepsy onset (adjusted odds ratio [aOR] 0.324, p = 0.05), longer follow-up (aOR 1.030, p = 0.005), and time from first seizure to ASM onset (aOR 1.020, p = 0.04) remained significant. The risk of seizure recurrence was significantly increased when debulking was performed instead of gross resection (aOR 1.993, p = 0.04, Table 3).

To address the issue of missing data on IDH mutation, we performed additional multivariate analyses including only patients with known negative IDH status (N = 344). Some results were no longer significant (such as follow-up and extent of resection), likely due to the reduced sample size leading to loss of power. However, there were no new or unexpected results.

3.7. Drug-resistant epilepsy and status epilepticus

Drug-resistant epilepsy (DRE) occurred in 27/292 PWE (9.2 %). At the last follow-up, LEV was the most commonly used drug, followed by benzodiazepines and lacosamide (LCM). 20/27 patients (74.1 %) were taking 2 ASMs, while 7/27 (25.9 %) were taking more than 2 ASMs at the last follow-up. The most frequently used combination in dual ASM therapy was LEV + benzodiazepine (9/27, 33.3 %), followed by LEV + LCM and LEV + OXC (4/27, 14.8 % each). On multivariate analysis, DRE was associated with younger age (aOR 0.964, p = 0.05) and status epilepticus as the first manifestation of tumor epilepsy (aOR 3.731, p = 0.04, Supplementary Table 1).

4. Discussion

We retrospectively analyzed the course of tumor epilepsy in patients with glioblastoma and the factors that influence it.

Approximately 60 % of all glioblastoma patients treated in our institution suffered from tumor epilepsy. More than 80 % of all PWE were treated with LEV. LEV is one of the first line ASM in focal epilepsies and has demonstrated efficacy in brain tumor-related epilepsy [10,25–27]. Our study was not designed or powered to compare different ASMs. Valproic acid was rarely used, probably because of concerns about its rare side effect of causing bleeding problems during surgery [28], while benzodiazepines were relatively frequently used.

Over 50 % of all PWE had epilepsy onset prior to surgery, consistent with previous findings [1,6,9]. Approximately 50 % of PWE experienced only a single seizure during the entire course of the disease, keeping in mind that most patients in our cohort were lost to follow-up within less than a year. Less than 10 % of PWE developed drug-resistant epilepsy (DRE) after failing 2 or more ASMs. In contrast, one third of the total population of PWE continue to have seizures despite ASM treatment, meeting the ILAE criteria for drug-resistant epilepsy [23,29]. This confirmed the good prognosis of tumor epilepsy, in contrast to the poor prognosis of the underlying disease, as recently observed in a *meta*-analysis of different tumor types [10]. However, data specifically addressing seizure freedom rates and DRE in glioblastoma patients are scarce; previous studies report seizure freedom rates of over 70 % at 12 months following surgery with DRE developing after surgery in up to 15 % of PWE [2,8,10,30].

A contributing factor to the good prognosis in terms of seizure control may be that nearly 50 % of the patients in our study underwent complete gross tumor resection, resulting in removal of the epileptogenic lesion. Compared to PWE with low-grade tumors, the time from first seizure to surgery is usually shorter in glioblastoma patients due to the characteristic presentation on MRI [31]. In our cohort, the median time between surgery and first seizure was −2.5 days. The lower survival rates and earlier resection in high-grade glioma patients may contribute to the lower seizure incidence and recurrence risk compared to low-grade glioma patients [1,13,32–34].

In the assessment of risk factors for recurrent seizures, we included

Table 1
Patients' characteristics.

Parameter	PWE, N = 292 N (%) or Mean (±SD)	PWE with 1 seizure N = 136	PWE with > 1 seizure N = 156	DRE N = 27
Age (years)	60.2 ± 12.1	60.5 ± 12.4	60.0 ± 11.9	57.0 +/- 11.57
Sex (% female)	119 (40.8 %)	56 (41.2 %)	63 (40.3 %)	13 (48.1 %)
KPS at admission < 70 %	69 (24.1 %) *Missing:* 6 (2.1 %)	36/132 (27.3 %) *Missing:* 4 (2.9 %)	33/154 (21.4 %) Missing: 2 (1.3 %)	6 (22.2 %)
Tumor location				
Frontal	115 (39.4 %)	47 (34.6 %)	68 (43.6 %)	9 (33.3 %)
Parietal	70 (24.0 %)	33 (24.3 %)	58 (37.2 %)	10 (37.0 %)
Temporal	116 (39.7 %)	58 (42.6 %)	37 (23.7 %)	9 (33.3 %)
Occipital	43 (14.7 %)	26 (19.1 %)	17 (10.1 %)	4 (14.8 %)
Right	137 (47.0 %)	63 (46.3 %)	73 (47.1 %)	11 (42.3 %)
Left	130 (44.7 %)	58 (42.6 %)	72 (46.5 %)	11 (42.3 %)
Multifocal	65 (22.3 %)	38 (27.9 %)	27 (17.3 %)	5 (18.5 %)
Extent of resection (EOR)				
Biopsy	70 (24.1 %)	35 (25.9 %)	35 (22.6 %)	9 (34.6 %)
Debulking	81 (27.9 %)	33 (24.3 %)	48 (31.0 %)	6 (23.1 %)
Gross total	139 (47.9 %) *Missing:* 2 (0.7 %)	67 (49.6 %) *Missing:* 1 (0.7 %)	72 (46.2 %) *Missing:* 1 (0.6 %)	11 (42.3 %) *Missing:* 1 (3.7 %)
Tumor volume (in cm^3)	25.7 ± 28.8 *Missing:* 29 (9.9 %)	28.0 ± 29.0 *Missing:* 13 (9.6 %)	23.71 ± 28.5 *Missing:* 16 (10.3 %)	20.2 ± 21.0 *Missing:* 0
Postsurgical Treatment				
None	6 (2.1 %)	5 (3.7 %)	1 (0.6 %)	0
RT only	20 (6.8 %)	7 (5.1 %)	13 (8.3 %)	2 (7.4 %)
RT + TMZ	266 (91.1 %)	124 (91.2 %)	142 (91.0 %)	25 (92.6 %)
RT total dose	56.8 ± 10.1	57.1 ± 9.6	56.6 ± 10.6	53.9 ± 14.9
RT single dose	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.3
TMZ courses	6.4 ± 5.2	6.0 ± 3.2	6.0 ± 6.3	6.8 ± 4.3
TTF	22 (7.5 %)	9 (6.6 %)	13 (8.3 %)	3 (11.1 %)
Molecular status				
MGMT	60 (45.8 %) *Missing:* 161 (55.1 %)	25 (41.7 %) *Missing:* 76 (55.9 %)	35 (49.3 %) *Missing:* 85 (54.5 %)	4 (40.0 %) *Missing:* 17 (63.0 %)
IDH1	14 (6.8 %) *Missing:* 87 (29.8 %)	6 (5.9 %) *Missing:* 35 (25.7 %)	8 (7.7 %) *Missing:* 52 (33.3 %)	0 *Missing:* 10 (37.0 %)
ATRX-lost	12 (10.0 %) *Missing:* 172 (58.9 %)	4 (6.9 %) *Missing:* 78 (57.4 %)	8 (12.9 %) *Missing:* 94 (60.3 %)	0 *Missing:* 19 /70.4 %)
MIB-1 (%)	22.7 (range 2–80) *Missing:* 105 (36.0 %)	22.7 (7–60) *Missing:* 52 (38.2 %)	22.6 (2–80) *Missing:* 53 (35.3 %)	19.2 (2–70) *Missing:* 4 (14.8 %)
Tumor progression observed	179 (61.3 %)	78 (57.4 %)	101 (64.7 %)	16 (59.3 %)
Progress free survival, Median in Months (IQR)	9 (6–15)	9 (6–14)	9.5 (6–16)	11 (6–18)
Overall survival, Median in Months (IQR)	13 (6–22)	13 (5–18)	14 (8–25)	10 (5–25)
Follow-Up, Median in Months (IQR)	13 (7–23)	12 (5–18)	14.5 (8–25)	11 (6–23)
Time Surgery-first seizure (days)	−2.5 (−250–1473)	2.5 (−227–1333)	−4.0 (−250–1473)	−6 (−226–1093)
Seizure Onset				
Preoperative	154 (52.7 %)	57 (41.9 %)	91 (58.3 %)	17 (63.0 %)
Early Postoperative	21 (7.2 %)	15 (11.0 %)	6 (3.8 %)	0
During RT	40 (13.7 %)	18 (13.2 %)	22 (14.1 %)	6 (22.2 %)
Posttherapeutic	76 (26.0 %)	40 (29.4 %)	36 (23.1 %)	4 (14.8 %)
Median time between first seizure/initiation ASM (IQR, range; in weeks)	0 (0–0, −271 – 203)	0 (0–0, −271 – 156)	0 (0–0, −98 – 203)	0 (0–0, −4 – 183)
Semiology				
Bilateral tonic-clonic	177 (60.6 %)	68 (50.0 %)	109 (69.9 %)	20 (74.1 %)
Status epilepticus (SE)	48 (16.4 %)	13 (9.6 %)	35 (22.4 %)	18 (66.7 %)
Semiology first seizure				
SE	18 (6.2 %)	11 (8.1 %)	7(4.5 %)	4 (22.2 %)
Bilateral tonic-clonic	150 (51.3 %)	66 (48.5 %)	84 (53.8 %)	15 (55.6 %)

Table 1 shows patients' characteristics for all PWE as well as for the subgroups PWE with a single seizure, PWE with recurrent seizures and PWE with drug-resistant epilepsy.

Abbreviations: ASM antiseizure medication, DRE drug-resistant epilepsy, MGMT O(6-methylguanine-DNA methyltransferase promoter methylation, IDH1 isocitrate dehydrogenase 1 mutation, IQR interquartile range, KPS Karnofsky performance scale, LEV levetiracetam, PWE patients with epilepsy, RT radiotherapy, TMZ temozolomide, SD standard deviation, SE Status epilepticus.

significant correlations from the univariate analyses in addition to potential confounders and parameters of primary oncologic therapy. We calculated another model using only significant correlations from the univariate analysis, which showed similar results (data not shown). We chose to include parameters of primary oncological therapy (surgery and radio-chemotherapy) because previous studies have found significant effects of radiation and chemotherapy on seizure freedom in low-grade glioma [14,35,36].

Complete removal of the epileptogenic lesion by gross tumor resection correlates with a lower risk of seizure recurrence and thus better seizure control than debulking. If tumor tissue remains in situ, factors such as increased intracranial pressure, edema, hypoperfusion, neoangiogenesis, and structural and functional changes in the peritumoral tissue may continue to induce glioblastoma-associated epileptogenesis [37]. Moreover, the inflammatory microenvironment in this region may also influence both epileptogenesis and tumor proliferation [38]. As the risk of postoperative intratumoral bleeding or reactive peritumoral edema may be increased in patients who undergo

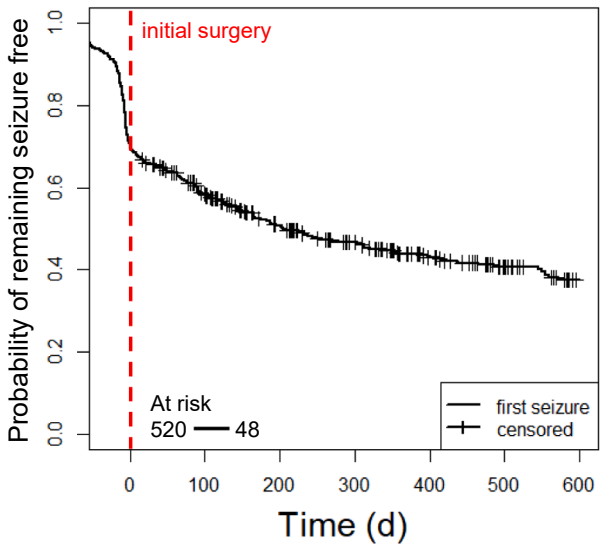

Fig. 2. Kaplan-Meier Curve for absence of epilepsy. The plot illustrates the probability for the absence of epilepsy for the entire cohort (N = 520). The x-axis represents the time elapsed between the first diagnosis (=initial surgery, red vertical line) and the occurrence of the first seizure. Patients were censored if they either reached end of follow-up or died without experiencing a seizure. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Initially vs. last documented antiseizure medication (ASM) in patients with epilepsy (PWE).

ASM	Initial ASM Number of PWE (%)	Last documented ASM Number of PWE (%)
Levetiracetam	245 (83.9 %)	242 (82.9 %)
Benzodiazepine	13 (4.5 %)	22 (7.5 %)
• Clobazam	5	9
• Clonazepam	0	1
• Diazepam	1	1
• Lorazepam	6	9
• Midazolam	1	1
• Unknown	0	1
Oxcarbazepine	12 (4.1 %)	10 (3.4 %)
Valproic acid	11 (3.8 %)	9 (3.1 %)
Lacosamide	6 (2.1 %)	18 (6.2 %)
Phenytoin	5 (1.7 %)	6 (2.1 %)
Lamotrigin	3 (1.0 %)	7 (2.4 %)
Topiramat	2 (0.7 %)	1 (0.3 %)
Pregabalin	2 (0.7 %)	6 (2.1 %)
None	13 (4.5 %)	26 (8.9 %)
1 ASM	256 (87.7 %)	222 (76.0 %)
2 ASM	19 (6.5 %)	36 (12.3 %)
> 2 ASM	4 (1.3 %)	8 (2.7 %)

debulking, this may explain our findings [39]. In light of recent evidence of synaptic connections between neurons and brain tumor cells, suggesting a vicious cycle between brain tumor growth and epilepsy, it may even be possible that debulking creates more surface area for tumor-immune-neuron interaction, thereby increasing seizure activity [40]. However, this is highly speculative. The non-significant effects for biopsy in this regard may well be explained by the small group sizes.

When the first seizure occurred early postoperatively, the risk of recurrence was significantly lower than when the epilepsy started at a different time. This further supports the view that early postoperative seizures may not be associated with an increased risk of epilepsy because they can be considered acute symptomatic seizures which was already

Table 3
Patients' characteristics influencing seizure recurrence.

Parameter	**Univariate Analysis OR N = 156/ 292 (53.4 %)**	**P-Value**	**Multivariate Analysis aOR**	**P-Value**
Age	0.997 (0.978–1.016)	0.722	1.012 (0.989–1.037)	0.313
Sex = Female	0.968 (0.606–1.545)	0.891	–	–
Tumor location				
Frontal lobe	1.463 (0.911–2.351)	0.116	–	–
Temporal lobe	0.796 (0.497–1.273)	0.341	–	–
Parietal lobe	0.970 (0.566–1.663)	0.913	–	–
Occipital lobe	0.517 (0.267–1.002)	**0.051**	0.714 (0.315–1.622)	0.421
Multifocal	0.540 (0.309–0.944)	**0.031**	0.526 (0.262–1.056)	0.071
Laterality				
Left vs Right	0.868 (0.546–1.379)	0.548	–	–
Initial tumor volume (cm^3)	0.995 (0.986–1.003)	0.235	–	–
KPS at admission < 70 %	0.727 (0.423–1.252)	0.25	–	–
MGMT methylated	1.361 (0.681–2.721)	0.383	–	–
IDH1-mutation	1.319 (0.441–3.947)	0.62	–	–
ATRX Lost	2.000 (0.568–7.037)	0.28	–	–
MIB-1 (%)	0.999 (0.976–1.023)	0.948	–	–
Resection extent				
Biopsy vs. Debulking	1.455 (0.763–2.772)	0.255	1.594 (0.745–3.413)	0.23
Biopsy vs. „Gross total“	1.075 (0.605–1.909)	0.806	0.800 (0.399–1.605)	0.53
'Gross total' vs. Debulking	1.354 (0.778–2.356)	0.284	1.993 (1.018–3.901)	**0.044**
Adjuvant RCT				
Discontinuation	1.007 (0.562–1.807)	0.98	0.721 (0.320–1.625)	0.43
RT single dose	1.029 (0.331–3.202)	0.96	1.128 (0.218–5.826)	0.886
RT total dose	0.995 (0.972–1.018)	0.654	0.989 (0.956–1.023)	0.529
TMZ 75 mg/m^2	0.826 (0.471–1.449)	0.504	0.723 (0.370–1.412)	0.342
Progress occurred	1.366 (0.851–2.191)	0.196	–	–
Follow-Up in months	1.021 (1.005–1.036)	**0.01**	1.030 (1.009–1.051)	**0.005**
Progress-free survival	1.024 (0.991–1.059)	0.156	–	–
Semiology first seizure				
Focal only	0.798 (0.498–1.279)	0.348	–	–
Status epilepticus	0.534 (0.201–1.418)	0.208	–	–
Seizure onset				
preoperative	1.622 (1.020–2.579)	**0.041**	1.273 (0.734–2.207)	0.391
early postoperative	0.323 (0.122–0.857)	**0.023**	0.324 (0.103–1.021)	**0.054**
during RT	1.076 (0.551–2.104)	0.83	–	–
Posttherapeutic	0.720 (0.426–1.216)	0.219	–	–
Time (in weeks) between first seizure/ initiation of ASM	1.011 (0.999–1.023)	0.075	1.020 (1.001–1.040)	**0.041**

Abbreviations: aOR adjusted odds ratio, ASM antiseizure medication, DRE drug-resistant epilepsy, MGMT O(6)-methylguanine-DNA methyltransferase promoter methylation, IDH1 isocitrate dehydrogenase 1 mutation, IQR

interquartile range, KPS Karnofsky performance scale, LEV levetiracetam, OR odds ratio, PWE patients with epilepsy, RT radiotherapy, TMZ temozolomide, SD standard deviation, SE Status epilepticus.

hypothesized in previous work [21,22].

Neither radiation nor chemotherapy had a significant effect on seizure control in our study. While beneficial effects of radiation on seizure control have been shown in low-grade gliomas [41], data in patients with glioblastoma are scarce. Climans et al. found a minimal effect of TMZ on seizure control in elderly patients with glioblastoma, which we did not reciprocate in our study [42].

The positive correlation between the length of follow-up and the likelihood of subsequent seizures is an expected finding, highlighting the importance of follow-up as a confounding factor in this type of investigation. In addition, our analysis revealed a statistically significant but small effect on seizure recurrence for patients with a longer interval between the first seizure and initiation of ASM treatment. Importantly, both associations had only small effect sizes (follow-up: OR 1.030, ASM initiation: OR 1.020).

Younger age and the occurrence status epilepticus (SE) as the first manifestation of epilepsy predicted drug-resistant tumor epilepsy (DRE). These results need cautious interpretation given the limited size of the study groups. However, SE was found to be a risk factor for drug-resistant epilepsy before [43]. It is left unclear from our results why younger age may be associated with DRE. Clearly, larger, prospective studies are needed to clarify this issue.

4.1. Limitations

Our study has several limitations, including its retrospective, monocentric design.

Accurate assessment of seizure frequency and semiology relied heavily on both patient and clinician reporting. Given the possibility that seizures may have been underreported or undocumented, there is a possibility that the achievement of seizure freedom may have been overestimated in our study. Because seizure frequency was inconsistently reported, especially in patients with frequent seizures (as opposed to first and second seizures), we focused on the analysis of patients with single versus multiple seizures. In particular, the incidence of drug-resistant epilepsy may have been underestimated due to inconsistent documentation. We therefore restrained from analyzing the exact total number of seizures as these numbers may have been subject to bias due to the retrospective design.

Our results must be interpreted with caution because of the small number of patients in certain subgroups, particularly those with drug-resistant epilepsy. Generalizability may be limited by the analysis of a monocentric convenience cohort. To address the potential bias caused by some patients receiving postoperative care at another hospital and being lost to follow-up, we included follow-up time as a covariate in each multivariate analysis.

Another major limitation of our study is the lack of missing neuropathological data. As MGMT promotor methylation analysis was not routinely performed in our hospital until recently, we lacked information on this important predictor of glioblastoma survival in >60 % of the cases. As many patients treated before 2021 were included, we relied on the initial diagnosis given to the patients at the time of their disease and did not re-diagnose them as this would have been impossible in most patients. The new WHO classification no longer classifies astrocytoma with IDH1-mutation as glioblastoma and includes additional molecular markers which were not determined in most of our patients [44]. In approximately 30 % of our cases, data on IDH1 status were missing. While previous studies in low-grade gliomas have found that seizures are associated with IDH mutations, the relationship in glioblastoma patients is less clear, with conflicting results from other studies [45]. In our study, IDH1 mutation was not a significant factor for seizure recurrence. Although we did not find significant differences in epilepsy between patients with missing and present IDH1 mutation data (data not shown), we cannot exclude the possibility of bias caused by missing data.

5. Conclusions

In this monocentric, retrospective study, around 50 % of the glioblastoma patients developed the epilepsy preoperatively and around 50 % experienced only one seizure throughout the disease course. Drug-resistant epilepsy was present in less than 10 % of cases. These findings demonstrate a generally good prognosis of tumor-related epilepsy which aligns with previous findings. Early postoperative seizures as first seizures and gross total resection were independently associated with a lower risk of further seizures.

Our findings may be valuable in clinical settings to assess the risk of seizure recurrence after the first seizure and identify patients at higher risk for such recurrences. Our results may aid in designing research that bridges the clinical course of tumor epilepsy and the intricate molecular patterns of the tumors involved.

6. Disclosure of conflicts of interest

H.M. Hamer has served on the scientific advisory boards of Arvelle, Bial, Corlieve, Eisai, GW, Novartis, Sandoz, UCB Pharma and Zogenix. He has served on the speakers' bureaus of or received unrestricted grants from Amgen, Ad-Tech, Alnylam, Bracco, Desitin, Eisai, GW, Nihon Kohden, Novartis, Pfizer, and UCB Pharma. The remaining authors have no conflicts of interest.

7. Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This study was approved by the ethics committee of FAU Erlangen-Nürnberg.

CRediT authorship contribution statement

Jenny Stritzelberger: Writing – original draft, Methodology, Data curation, Conceptualization. **Anna Gesmann:** Writing – review & editing, Investigation, Data curation. **Imke Fuhrmann:** Writing – review & editing, Investigation. **Martin Uhl:** Writing – review & editing, Investigation. **Sebastian Brandner:** Writing – review & editing, Investigation. **Tamara-M. Welte:** Writing – review & editing, Investigation. **Leah Schembs:** Writing – review & editing, Investigation. **Arnd Dörfler:** Writing – review & editing, Investigation. **Roland Coras:** Writing – review & editing, Investigation. **Werner Adler:** Writing – review & editing, Methodology, Conceptualization. **Stefan Schwab:** Writing – review & editing, Investigation. **Florian Putz:** Writing – review & editing, Investigation. **Rainer Fietkau:** Writing – review & editing, Investigation. **Luitpold Distel:** Writing – review & editing, Investigation. **Hajo Hamer:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The following work was performed in (partial) fulfilment of the requirements for obtaining the degree "Dr. med".

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.yebeh.2024.109919.

References

[1] van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 2007;6:421–30.
[2] Kerkhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. Epilepsia 2013;54(Suppl 9):12–7.
[3] Sokolov E, Dietrich J, Cole AJ. The complexities underlying epilepsy in people with glioblastoma. Lancet Neurol 2023;22:505–16.
[4] Armstrong TS, Grant R, Gilbert MR, Lee JW, Norden AD. Epilepsy in glioma patients: mechanisms, management, and impact of anticonvulsant therapy. Neuro Oncol 2016;18:779–89.
[5] Marku M, Rasmussen BK, Belmonte F, Andersen EAW, Johansen C, Bidstrup PE. Postoperative epilepsy and survival in glioma patients: a nationwide population-based cohort study from 2009 to 2018. J Neurooncol 2022;157:71–80.
[6] Marku M, Rasmussen BK, Belmonte F, Hansen S, Andersen EAW, Johansen C, et al. Prediagnosis epilepsy and survival in patients with glioma: A nationwide population-based cohort study from 2009 to 2018. J Neurol 2022;269:861–72.
[7] Ahmadipour Y, Rauschenbach L, Santos A, Darkwah Oppong M, Lazaridis L, Quesada CM, et al. Preoperative and early postoperative seizures in patients with glioblastoma-two sides of the same coin? Neurooncol Adv 2021;3:vdaa158.
[8] Chaichana KL, Parker SL, Olivi A, Quiñones-Hinojosa A. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clinical article. J Neurosurg 2009;111: 282-92.
[9] Berendsen S, Varkila M, Kroonen J, Seute T, Snijders TJ, Kauw F, et al. Prognostic relevance of epilepsy at presentation in glioblastoma patients. Neuro Oncol 2016;18:700–6.
[10] de Bruin ME, van der Meer PB, Dirven L, Taphoorn MJB, Koekkoek JAF. Efficacy of antiepileptic drugs in glioma patients with epilepsy: a systematic review. Neurooncol Pract 2021;8:501–17.
[11] Toledo M, Sarria-Estrada S, Quintana M, Maldonado X, Martinez-Ricarte F, Rodon J, et al. Epileptic features and survival in glioblastomas presenting with seizures. Epilepsy Res 2017;130:1–6.
[12] van Breemen MS, Rijsman RM, Taphoorn MJ, Walchenbach R, Zwinkels H, Vecht CJ. Efficacy of anti-epileptic drugs in patients with gliomas and seizures. J Neurol 2009;256:1519–26.
[13] Phan K, Ng W, Lu VM, McDonald KL, Fairhall J, Reddy R, et al. Association between IDH1 and IDH2 mutations and preoperative seizures in patients with low-grade versus high-grade glioma: A systematic review and meta-analysis. World Neurosurg 2018;111:e539–45.
[14] Rudà R, Bello L, Duffau H, Soffietti R. Seizures in low-grade gliomas: natural history, pathogenesis, and outcome after treatments. Neuro Oncol 2012;14 Suppl 4: iv55-64.
[15] Semah F, Picot MC, Adam C, Broglin D, Arzimanoglou A, Bazin B, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51:1256–62.
[16] Ius T, Pauletto G, Tomasino B, Maieron M, Budai R, Isola M, et al. Predictors of postoperative seizure outcome in low grade glioma: From volumetric analysis to molecular stratification. Cancers (Basel) 2020;12.
[17] Mazzucchi E, Vollono C, Pauletto G, Lettieri C, Budai R, Gigli GL, et al. The persistence of seizures after tumor resection negatively affects survival in low-grade glioma patients: A clinical retrospective study. J Neurol 2022;269:2627–33.
[18] Le Fèvre C, Sun R, Cebula H, Thiery A, Antoni D, Schott R, et al. Ellipsoid calculations versus manual tumor delineations for glioblastoma tumor volume evaluation. Sci Rep 2022;12:10502.
[19] Sreenivasan SA, Madhugiri VS, Sasidharan GM, Kumar RV. Measuring glioma volumes: A comparison of linear measurement based formulae with the manual image segmentation technique. J Cancer Res Ther 2016;12:161–8.
[20] Iliadis G, Selviaridis P, Kalogera-Fountzila A, Fragkoulidi A, Baltas D, Tselis N, et al. The importance of tumor volume in the prognosis of patients with glioblastoma: Comparison of computerized volumetry and geometric models. Strahlenther Onkol 2009;185:743–50.
[21] Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia 2010;51:671–5.
[22] Stritzelberger J, Gesmann A, Fuhrmann I, Brandner S, Welte TM, Balk S, et al. Time dependent risk factors for epileptic seizures in glioblastoma patients: A retrospective analysis of 520 cases. Epilepsia 2023.
[23] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51:1069–77.
[24] Stritzelberger J, Gesmann A, Fuhrmann I, Balk S, Reindl C, Madžar D, et al. Status epilepticus in patients with glioblastoma: Clinical characteristics, risk factors, and epileptological outcome. Seizure 2023;112:48–53.
[25] Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. Lancet 2021;397:1363–74.
[26] van der Meer PB, Maschio M, Dirven L, Taphoorn MJB, Koekkoek JAF. First-line levetiracetam versus enzyme-inducing antiseizure medication in glioma patients with epilepsy. Epilepsia 2023;64:162–9.
[27] van der Meer PB, Dirven L, Fiocco M, Vos MJ, Kouwenhoven MCM, van den Bent MJ, et al. First-line antiepileptic drug treatment in glioma patients with epilepsy: Levetiracetam vs valproic acid. Epilepsia 2021;62:1119–29.
[28] Kumar R, Vidaurre J, Gedela S. Valproic acid-induced coagulopathy. Pediatr Neurol 2019;98:25–30.
[29] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.
[30] Chen DY, Chen CC, Crawford JR, Wang SG. Tumor-related epilepsy: epidemiology, pathogenesis and management. J Neurooncol 2018;139:13–21.
[31] van Opijnen MP, Tesileanu CMS, Dirven L, van der Meer PB, Wijnenga MMJ, Vincent A, et al. IDH1/2 wildtype gliomas grade 2 and 3 with molecular glioblastoma-like profile have a distinct course of epilepsy compared to IDH1/2 wildtype glioblastomas. Neuro Oncol 2023;25:701–9.
[32] Xie M-G, Wang X-F, Qiao J, Zhou J, Guan Y-G, Liu C-Q, et al. The long-term surgical outcomes of low-grade epilepsy-associated neuroepithelial tumors. Epilepsia Open 2022;7:697–709.
[33] Yang I, Chang EF, Han SJ, Barry JJ, Fang S, Tihan T, et al. Early surgical intervention in adult patients with ganglioglioma is associated with improved clinical seizure outcomes. J Clin Neurosci 2011;18:29–33.
[34] Luyken C, Blümcke I, Fimmers R, Urbach H, Elger CE, Wiestler OD, et al. The spectrum of long-term epilepsy-associated tumors: long-term seizure and tumor outcome and neurosurgical aspects. Epilepsia 2003;44:822–30.
[35] Yue J, Yin C, Chen L, Xu R, Zhao D. Is there a role for temozolomide in glioma related seizures? A systematic review. Neurol India 2022;70:864–71.
[36] Rudà R, Magliola U, Bertero L, Trevisan E, Bosa C, Mantovani C, et al. Seizure control following radiotherapy in patients with diffuse gliomas: A retrospective study. Neuro Oncol 2013;15:1739–49.
[37] Pallud J, Capelle L, Huberfeld G. Tumoral epileptogenicity: How does it happen? Epilepsia 2013;54(Suppl 9):30–4.
[38] Radin DP, Tsirka SE. Interactions between tumor cells, neurons, and microglia in the glioma microenvironment. Int J Mol Sci 2020;21.
[39] Jackson C, Westphal M, Quiñones-Hinojosa A. Complications of glioma surgery. Handb Clin Neurol 2016;134:201–18.
[40] Venkataramani V, Tanev DI, Kuner T, Wick W, Winkler F. Synaptic input to brain tumors: Clinical implications. Neuro Oncol 2021;23:23–33.
[41] Koekkoek JA, Kerkhof M, Dirven L, Heimans JJ, Reijneveld JC, Taphoorn MJ. Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: A systematic review. Neuro Oncol 2015;17:924–34.
[42] Climans SA, Brandes AA, Cairncross JG, Ding K, Fay M, Laperriere N, et al. Temozolomide and seizure outcomes in a randomized clinical trial of elderly glioblastoma patients. J Neurooncol 2020;149:65–71.
[43] Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. Epilepsia 2018;59:2179–93.
[44] Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 2021;23:1231–51.
[45] !!! INVALID CITATION !!! [42-45].