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Status epilepticus in patients with glioblastoma: Clinical characteristics, risk factors, and epileptological outcome

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ABSTRACT

Purpose: Epilepsy is a common comorbidity in patients with glioblastoma, however, clinical data on status epilepticus (SE) in these patients is sparse. We aimed to investigate the risk factors associated with the occurrence and adverse outcomes of SE in glioblastoma patients.
Methods: We retrospectively analysed electronic medical records of patients with de-novo glioblastoma treated at our institution between 01/2006 and 01/2020 and collected data on patient, tumour, and SE characteristics.
Results: In the final cohort, 292/520 (56.2 %) patients developed seizures, with 48 (9.4 % of the entire cohort and 16.4 % of patients with epilepsy, PWE) experiencing SE at some point during the course of their disease. SE was the first symptom of the tumour in 6 cases (1.2 %) and the first manifestation of epilepsy in 18 PWE (6.2 %). Most SE episodes occurred postoperatively ($n = 37$, 77.1 %). SE occurrence in PWE was associated with postoperative seizures and drug-resistant epilepsy. Adverse outcome (in-house mortality or admission to palliative care, 10/48 patients, 20.8 %), was independently associated with higher status epilepticus severity score (STESS) and Charlson Comorbidity Index (CCI), but not tumour progression. 32/48 SE patients (66.7 %) were successfully treated with first- and second-line agents, while escalation to third-line agents was successful in 6 (12.5 %) cases.
Conclusion: Our data suggests a link between the occurrence of SE, postoperative seizures, and drug-resistant epilepsy. Despite the dismal oncological prognosis, SE was successfully treated in 79.2 % of the cases. Higher STESS and CCI were associated with adverse SE outcomes.

1. Introduction

Epileptic seizures are a common symptom in patients with glioblastoma. 50–70 % of all patients with glioblastoma will develop seizures during the course of their disease [1–3]. With an incidence of 7–16 %, status epilepticus (SE) represents a less frequent, but severe complication of epilepsy in glioblastoma patients [4–8].

While risk factors for seizures in glioblastoma patients have been extensively studied [9–12], and various factors such as tumour location, tumour size, and disease progression have been associated with seizure occurrence, it remains largely unclear whether there are specific, tumour-related triggers for SE in these patients [13–15]. The appearance of SE has been associated with tumour growth and may be a risk factor for unfavourable oncological prognosis [4,14,16]. However, the relationship remains unclear [17]. Despite the dismal oncological prognosis, tumour-related epilepsy seems to be associated with a relatively benign

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course which is unknown for SE in this situation. A few studies show good response to antiseizure medication (ASM) treatment in patients with tumour-associated SE [14,17–19]. However, these patient cohorts are usually small and often encompass tumours of various histologies.

In this retrospective study, we aim to elucidate incidence, clinical characteristics, risk factors for the occurrence, and epileptological outcome of SE in a consecutive single-centre cohort of glioblastoma patients.

2. Methods

2.1. Study population and clinical data

Patient information was retrospectively retrieved from electronic medical records of patients with newly diagnosed glioblastoma treated at our institution between January 2006 and January 2020. The exclusion criteria were: (a) paediatric cases (<18 years old), (b) previous history of epilepsy (unrelated to the glioblastoma disease), and (c) infratentorial or extracranial location. The study was approved by the Institutional Ethics Committee, Friedrich-Alexander Universität Erlangen-Nürnberg (No. 390_20Bc). Part of this data has been previously published [20].

The following measures were retrospectively assessed: age, sex, radiographic, histological, and molecular characteristics of the tumour, tumour volume as determined on presurgical MRI scans, oncological treatment, radiographic progression, seizure and SE occurrence and semiology, antiseizure medication (ASM) treatment, and the Status Epilepticus Severity Score (STESS), including its categories (patient age, history of previous seizures, seizure semiology, mental status at presentation [21]. Comorbidities were quantitatively assessed with the Charlson Comorbidity Index (CCI) for the medical condition pre-SE [22].

All glioblastoma cases were histologically confirmed via stereotactic biopsy or tumour resection. Adjuvant radio(chemo-)therapy (RCT) was initiated after surgery according to current guidelines. Patients with poor perioperative neurological condition and/or without willingness for further treatment, were referred to best supportive care.

2.2. Definition of seizures, SE, and adverse outcome

Epilepsy was diagnosed according to the ILAE criteria [23], counting both focal seizures and focal to bilateral tonic-clonic seizures. We classified seizures occurring before the first surgery (biopsy or tumour resection) as preoperative and seizures occurring at least 30 days after the surgery as postoperative. In this study, we aimed to separate acute symptomatic seizures after craniotomy (usually defined as seizures within 7 days after surgery [24]) from other seizures since acute symptomatic seizure did not go along with an increased risk of recurrence as shown in previous work [20]. However, we sometimes could not identify the exact date of a postoperative seizure in the physicians' notes. Therefore, we grouped together any seizure occurring within the hospital stay after surgery as "early postoperative seizures", leading to the definition of "postoperative seizures" as seizures occurring after 30 days after surgery for the purpose of this study (see Supplementary Fig. 1). Drug-resistant epilepsy was classified according to the ILAE-definition in patients with epilepsy (PWE) who were not seizure-free after administration of two ASM [25]. Due to the short time interval between first seizure and surgery, drug-resistant epilepsy was only observed postoperatively in our cohort.

Status epilepticus (SE) was defined as a seizure persisting for at least 5 min or a series of seizures between which patients did not recover clinically according to the ILAE criteria and German clinical guidelines [26,27],. This definition was chosen since patients were treated according to these guidelines.

For the purpose of this study, adverse outcome was defined as in-hospital mortality or direct admission to palliative care or hospice during the SE episode. This definition was chosen due to the dismal prognosis of the underlying oncological disease, which may intervene with SE prognosis and compromise functional or long-term outcome in these patients.

2.3. Statistical analysis

Statistical analyses were performed using SPSS (version 26, SPSS Inc., IBM). Patients' baseline characteristics were expressed as mean ± standard deviation (SD) or percentage of patients, as appropriate. For overall survival (OS) data, median values with interquartile range were reported. Since this was an exploratory study, significance level was set at $p < 0.05$ without correction for multiple testing.

All associations between the potential risk factors and SE occurrence [1] and adverse outcome [2] were first tested using univariate analysis. Significant correlations from the univariate analyses ($p < 0.05$) were then evaluated in a multivariate analysis along with age and mean follow-up duration as possible confounders.

3. Results

3.1. Patient characteristics

After the exclusion of 33 non-eligible cases (age < 18 years, $n = 13$; prior epilepsy, $n = 6$; extracerebral or infratentorial glioblastoma, $n = 14$), 520 individuals were included in the final analysis. Of these, 292 suffered from epilepsy (56.2 %). SE occurred in 48 (16.4 %) of all PWE. Table 1 shows clinical characteristics of all patients in the final cohort and PWE with vs. without SE.

3.2. Characteristics of SE

Amongst the 48 patients with SE, SE semiology was non-convulsive (NCSE) in 17 patients (35.4 %). Of the 28 patients with prominent motor symptoms, 15 had generalized convulsive SE (GCSE, 31.3 %).

SE was the first symptom of the tumour in 6 patients (1.2 % of the total cohort). The median time between first surgery and SE was 142 d (range −99 – 1896 d). The median time between first seizure and SE was 7 d (range 0–1896 d). SE was the first manifestation of tumour epilepsy in 18/292 PWE (6.2 %) and the majority of patients with SE (30/48, 62.5 %) had already had at least one seizure prior to the SE episode. Supplementary Table 1 and supplementary Fig. 1 show the occurrence during the course of the tumour disease.

3.3. Risk factors for SE

In the univariate analysis, the occurrence of SE was associated with lower radiotherapy dosage, later onset of epilepsy, drug-resistant epilepsy, and the occurrence of postoperative seizures. However, only drug-resistant epilepsy and the occurrence of postoperative seizures survived in the multivariate analysis (adjusted Odds Ratio (aOR) 4.09, $p = 0.01$ and aOR 3.56, $p = 0.02$, respectively, Table 2).

3.4. Treatment

In PWE, Levetiracetam was the most frequently used drug and was administered in 245/292 (83.9 %) patients (Table 1). Of the 30 patients with epilepsy before the SE episode, 29 (96.7 %) received ASM treatment before the SE. SE was treated with first line agents (benzodiazepines) in 6 patients (12.5 %), with first- and second-line agents (Levetiracetam, Valproic acid, Lacosamide, Phenytoin) in 30 patients (62.5 %), and with third line agents in 6 patients (12.5 %). In 4 patients, documentation on medical treatment was sparse but indicated they were treated with first- and second line agents, and in 2 patients who were referred to palliative care, ASM treatment remained unclear (data not shown).

Table 1
Characteristics of patients.

Parameter	Total Cohort ($N = 520$) N (%) or Mean (± SD)	PWE without SE ($N = 244$) N (%) or Mean (± SD)	PWE with SE ($N = 48$) N (%) or Mean (± SD)
Age (years)	61.7 ± 12.2	60.3 ± 12.3	61.2 ± 11.2
Sex (% female)	44.2 %	96 (39.3 %)	23 (47.9 %)
KPS at admission			
≥ 70 %	361 (70.8 %)	184 (75.4 %)	33 (68.8 %)
< 70 %	148 (29 %)	55 (22.5 %)	14 (29.2 %)
	Missing: 10 (1.9 %)	*Missing:* 5 (2.0 %)	*Missing:* 1 (2.1 %)
Tumour location			
Frontal	185 (35.6 %)	100 (41.0 %)	15 (31.3 %)
Parietal	127 (24.4 %)	57 (23.4 %)	13 (27.1 %)
Temporal	213 (41 %)	96 (39.3 %)	20 (41.7 %)
Occipital	79 (15.2 %)	36 (14.8 %)	7 (14.6 %)
Right	243 (46.7 %)	110 (45.1 %)	26 (54.2 %)
Left	228 (43.8 %)	114 (46.7 %)	17 (35.4 %)
Bilateral	49 (9.4 %)	20 (8.2 %)	5 (10.4 %)
Multifocal	125 (24 %)	57 (23.4 %)	8 (16.7 %)
Extent of resection (EOR)			
Biopsy	152 (29.3 %)	57 (23.4 %)	13 (27.1 %)
Partial	140 (27 %)	74 (30.3 %)	8 (16.7 %)
"Gross"	226 (43.6 %)	112 (45.9 %)	26 (54.2 %)
	Missing: 2 (0.4 %)	*Missing:* 1 (0.4 %)	*Missing:* 1 (2,1 %)
Tumour volume (cm^3)	29.8 (32.3)	26.8 ± 29.8	40.4 ± 43.9
	Missing: 49 (9.4 %)	*Missing:* 24 (9.8 %)	*Missing:* 5 (10.4 %)
Post-surgical treatment			
None	10 (1.9 %)	6 (2.4 %)	0 (0.0 %)
RT only	41 (7.9 %)	14 (5.7 %)	6 (12.5 %)
RT+TMZ	468 (90 %)	224 (91.8 %)	42 (87.5 %)
RT total dose (Gy)	55.7 ± 11.0	57.3 ± 8.7	54.1 ± 15.0
RT single dose (Gy)	2.1 ± 0.3	2.0 ± 0.2	2.0 ± 0.2
TMZ courses	6.5 ± 5.9	6.4 ± 5.5	6.0 ± 3.5
TTF	32 (6.2 %)	19 (7.8 %)	3 (6.3 %)
Therapy discontinuation	119 (22.9 %)	45 (18.4 %)	11 (22.9 %)
Time between surgery and RT-start (days)	31.6 ± 23.9	32. 4 ± 21.5	36.0 ± 22.8
Treatment with ASM, n (%) Initial drug	330 (63.5 %)	231 (94.7 %)	48 (100 %)
Levetiracetam	278 (53.5 %)	203 (83.2 %)	42 (87.5 %)
Valproic acid	11 (2.1 %)	8 (3.3 %)	3 (6.3%)
Lacosamide	6 (1.7 %)	4 (1.6 %)	2 (4.2 %)
Oxcarbazepin	14 (4.2 %)	9 (3.7 %)	3 (6.3 %)
Benzodiazepine	15 (2.9%)	8 (3.3 %)	5 (10.4 %)
Lamotrigin	3 (0.9 %)	3 (1.2 %)	0 (0.0 %)
Phenytoin	5 (1.5 %)	4 (1.6 %)	1 (2.1 %)
Topiramat	2 (0.6 %)	1 (0.4 %)	1 (2.1 %)
Pregabalin	3 (0.9 %)	2 (0.8 %)	0 (0.0 %)
None	–	12 (4.9 %)	1 (2.1 %)
Molecular status			
MGMT methylated	92 (41.6 %)	51 (47.2 %)	9 (39.1 %)
	Missing: 299 (57.5 %)	*Missing:* 136 (55.7 %)	Missing: 23 (47.9 %)
IDH1-mutation	26 (5 %)	11 (6.2 %)	3 (10.7 %)
	Missing: 150 (28.8 %)	*Missing:* 67 (27.5 %)	Missing: 20 (41.7 %)
ATRX lost	18 (8.1 %)	11 (10.7 %)	1 (5.9 %)
	Missing: 298 (57.3 %)	*Missing:* 141 (57.8 %)	Missing: 31 (64.6 %)
MIB-1 (%)	21.8 (range 2–80) *Missing:* 190 (36.5 %)	22.7 (range 6–80) *Missing:* 89 (36.5 %)	22.6 (range 2–70) Missing: 16 (33.3 %)
Tumour progression observed	279 (53.7 %)	150 (61.5 %)	29 (60.4 %)
Death observed	415 (78.8 %)	192 (78.7%)	43 (89.6 %)
Progression free survival, Median in Months (IQR)	9 (6–15)	9 (6–15)	10 (6.5–15)
Overall survival, Median in Months (IQR)	11 (4–18)	13.5 (7–22)	12 (5–123)
Follow-Up, Median in Months (IQR)	11 (4–19)	13 (7–22)	13 (5.25–13)
Time Surgery-first seizure (days, in PWE)	−2.5	−3.5	33
Time Surgery-SE (days, min-max)	–	–	142 d (−99 – 1896)
Seizure Occurrence			
Preoperative	154 (29.6 %)	133 (54.5 %)	21 (43.8 %)
Postoperative	189 (36.3 %)	147 (60.2 %)	42 (87.5 %)
No bilateral tonic-clonic seizures	328 (63.1 %)	88 (36.1 %)	12 (25.0 %)
Drug-resistant epilepsy	27 (5.2 %)	9 (3.7 %)	18 (37.5 %)
DRE before SE	17 (3.3 %)	9 (3.7 %)	8 (16.7 %)

The percentage values refer to the number of patients minus the missing cases, as indicated in the respective variable.
Abbreviations: Gy, Grey; IQR, interquartile range; MGMT, O(6)-methylguanine-DNA methyltransferase promoter methylation; IDH1, Isocitrate dehydrogenase 1 mutation; KPS, Karnofsky performance scale; PWE, patients with epilepsy; RT, radiotherapy; TMZ, temozolomide; TTF, tumour treating fields.

3.5. Adverse outcome

Adverse outcome was defined as in-hospital mortality or direct admission to palliative care or hospice during the SE episode and was observed in 10/48 (20.8 %) patients. Of the 38 patients with "favourable" SE outcome (79.2 %), 32 (66.7 %) were successfully treated with first- and/or second-line agents while escalation to third-line agents was successful in 6 (12.5 %) cases. On multivariate analysis, higher STESS and CCI scores were significantly associated with adverse outcome (aOR 1.91, $p = 0.026$ and aOR 1.75, $p = 0.040$, respectively; Table 3, Fig. 1), while this was not the case for radiographic progression in general and progression at the time of the SE episode (defined as tumour progression occurring between 30 days before and after SE, Table 3).

3.6. Influence of SE on oncological treatment

119 patients (22.9 %) of the total cohort and 56 (19.2 %) of the PWE did not complete the oncological adjuvant therapy as planned (radiotherapy or chemotherapy). In the SE cohort, 11 patients (22.4 %) withdrew from the adjuvant therapy. Of the 7 patients who suffered from SE during RCT, 4 (57.1 %) discontinued the therapy.

4. Discussion

This study sought to retrospectively analyse SE occurrence and epileptological outcome in a cohort of 520 consecutive glioblastoma patients treated at our institution. Around 60 % of the patients had epilepsy, with approximately 10 % glioblastoma patients (16 % of the PWE) experiencing status epilepticus (SE). SE was the first symptom of the tumour in only 1.2 % of all cases and less than 10 % of the patients experienced a SE as the first manifestation of the tumour epilepsy [4,6, 28–31],.

Previous studies found an incidence between 7–16 % of SE in patients with glioblastoma [4–8]. SE was rarely the first tumour manifestation with 0–4 % of all glioblastoma patients experiencing this complication at disease onset [4,29–31]. While some studies found an association between SE and tumour progression or the end of life [16, 18], other studies did not reciprocate these findings [17]. Still, SE responded well to first and second line treatment in these studies [14,17, 19].

While there are some tumour-related risk factors for seizures in glioblastoma patients, particularly at disease onset, such as tumour localization or size, or tumour progression later in the course of the disease [11,12], these did not predict the occurrence of SE in our study.

Table 2
Univariate and multivariate analyses of potential risk factors for SE in PWE.

Parameter	Univariate Analysis SE occurrence (OR, 95 % CI) $N = 48/292$ (16.4 %)	P-Value	Multivariate Analysis SE occurrence (aOR, 95 % CI) $N = 48/292$ (16.4 %)	P-Value
Age at diagnosis	1.008 (0.982–1.034)	0.546	1.010 (0.980–1.042)	0.505
Sex = Female	1.404 (0.754–2.613)	0.285	–	–
Tumour volume	0.990 (0.976–1.004)	0.173	–	–
KPS at admission <70 %	1.394 (0.697–2.788)	0.348	–	–
MGMT-methylated	0.718 (0.287–1.800)	0.481	–	–
IDH-Mutation	1.822 (0.475–6.986)	0.382	–	–
ATRX-Retention	0.523 (0.063–4.332)	0.548	–	–
MIB-1 (%)	0.999 (0.969–1.031)	0.963	–	–
Location				
Frontal lobe	0.659 (0.340–1.277)	0.217	–	–
Temporal lobe	1.109 (0.591–2.079)	0.748	–	–
Parietal lobe	1.198 (0.594–2.415)	0.614	–	–
Occipital lobe	0.991 (0.413–2.380)	0.984	–	–
Multifocal	0.660 (0.292–1.490)	0.317	–	–
Right vs. left	0.594 (0.302–1.167)	0.131	–	–
Bilateral	1.058 (0.363–3.081)	0.918	–	–
Resection extent				
	1.072 (0.491–2.146)	0.944	–	–
Biopsy vs. Debulking	0.489 (0.109–1.259)	0.138	–	–
Biopsy vs. „Gross“	0.476 (0.205–1.109)	0.085	–	–
Gross vs. Debulking				
Adjuvant Radiochemotherapy				
RT single dose (Gy)	1.452 (0.365–5.771)	0.596	–	–
RT total dose (Gy)	0.975 (0.951–1–000)	**0.048**	0.974 (0.946–1.003)	0.080
TMZ	0.690 (0.340–1.402)	0.305	–	–
Nr of TMZ-courses	0.985 (0.906–1.070)	0.714	–	–
TTF received	0.687 (0.424–1.113)	0.127	–	–
Therapy discontinuation	1.315 (0.623–2.774)	0.473	–	–
Progression occurred	0.916 (0.513–1.820)	0.916		
Epilepsy onset (days after glioblastoma diagnosis)	1.001 (1.000–1.002)	**0.005**	1.001 (1.000–1.003)	0.087
Seizure Occurrence				
Preoperative	0.649 (0.348–1.211)	0.174	**–**	**–**
Postoperative	4.619 (1.891–11.282)	**<0.001**	3.557 (1.281–9.873)	**0.015**
No bilateral tonic-clonic seizures	0.595 (0.294–1.202)	0.148	–	–
Drug-resistant epilepsy	4.477 (1.579–12.691)	**0.005**	4.090 (1.403–11.927)	**0.010**
Time to last follow-up In months	0.996 (0.978–1.013)	0.622	0.988 (0.962–1.014)	0.370

Statistically significant values ($p < 0.05$) are expressed in bold. Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; IDH1 Isocitrate dehydrogenase 1 mutation; MGMT O(6)-methylguanine-DNA methyltransferase promoter methylation; KPS, Karnofsky performance scale; OR, odds ratio; RT, radiotherapy; TMZ, temozolomide; TTF, tumour treating fields.

Table 3
Univariate and multivariate comparisons of patients with “favourable” vs adverse SE outcomes.

Variable	SE patients	Outcome		Univariate Analysis		Multivariate Analysis	
		Favourable	Adverse	OR (95 % CI)	P-Value	aOR (95 % CI)	P-Value
	$N = 48$	$N = 38$	$N = 10$				
STESS							
Total Score (per unit increase)	2 (1–3)	2 (1–3)	3 (2.75–4.25)	1.784 (1.076–2.958)	**0.025**	1.912 (1.079–3.388)	**0.026-**
Stuporous/Comatous	19 (39.6 %)	12 (31.6 %)	7 (70.0 %)	5.056 (1.111–23.014)	**0.036**	–	**–**
Age ≥ 65 years	20 (41.7 %)	14 (36.8 %)	6 (60.0 %)	2.571 (0.617–10.708)	0.194	–	**–**
NCSE in Coma	8 (16.7 %)	3 (7.9 %)	5 (50.0 %)	11.667 (2.108–64.556)	**0.005**	–	**–**
GCSE	15 (31.3 %)	13 (34.2 %)	2 (20.0 %)	0.481 (0.089–2.601)	0.395	–	**–**
SPSE or CPSE	25 (52.1 %)	22 (57.9 %)	3 (30.0 %)	0.312 (0.070–1.394)	0.127	–	**–**
History of Seizures	22 (45.8 %)	17 (44.7 %)	5 (50.0 %)	1.235 (0.306–4.983)	0.767	–	
Sex (Female)	23 (47.9 %)	18 (47.4 %)	5 (50.0 %)	1.111 (0.276–4.477)	0.882	–	–
CCI (per unit increase)	2 (2–3)	2 (2–3)	2 (2–7)	1.689 (1.041–2.741)	**0.034**	1.749 (1.026–2.982)	**0.040**
Progression	29 (60.4 %)	24 (63.2 %)	5 (50.0 %)	0.583 (0.143–2.375)	0.452	–	–
SE associated with progression (± 30 d)	5 (10.4 %)	4 (10.5 %)	1 (10.0 %)	0.944 (0.094–9.526)	0.961	–	–

Values are n (%) or median (25th–75th percentile). Adverse outcome was defined by inhouse-mortality or admission to palliative care. Statistically significant values ($p < 0.05$) are expressed in bold. Due to the small size of the patient groups, we included only the total STESS score, rather than the individual parameters of STESS, in the multivariate analysis.
Abbreviations: aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; CPSE, complex partial SE; GCSE, generalized convulsive SE; NCSE, nonconvulsive SE; OR, odds ratio; RSE, refractory SE; SE, status epilepticus; SPSE, simple partial SE; STESS, Status Epilepticus Severity Score.

SE was more frequently observed later during the course of the glioblastoma disease, confirming previous studies [19]. The occurrence of postoperative, but not preoperative seizures, and drug-resistant epilepsy were associated with an increased risk of SE. Marku et al. suggested that pre- and postoperative epilepsy may signify different subtypes of epilepsy with postoperative epilepsy emerging from a biologically more aggressive and invasive tumour [9]. While postoperative seizures and tumour progression are frequently linked [9,32], the relationship between SE and tumour progression remains controversially discussed with clinical data on this subject being sparse [4,16–18]. In

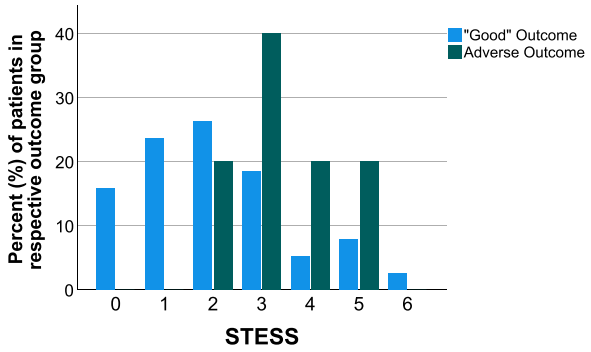

Fig. 1. Comparison of STESS scores between patients with adverse and "favourable" outcomes.

Fig. 1 illustrates the distribution of STESS (status epilepticus severity score) amongst patients with adverse outcomes, defined as in-hospital mortality or direct admission to palliative care or hospice, in comparison to patients with "favourable" outcomes.

this study, tumour progression was neither associated with an increased risk of SE nor adverse SE outcome. The potential link between postoperative seizures, SE, and tumour progression is particularly interesting when considering novel findings of synaptic connections between neurons and brain tumour cells, suggestive of a vicious cycle between brain tumour growth and epilepsy [33]. Our data cannot contribute to this ongoing discussion due to the uncontrolled retrospective design of the study relying heavily on physicians' notes. It remains open to further research to identify in which ways SE potentially contributes to tumour growth and invasion and how the correlation between drug-resistant epilepsy and SE can be connected to these findings.

We chose to define adverse outcome as in-house mortality during the admission for the SE episode or direct admission to palliative care or hospice. Due to the dismal prognosis of the underlying disease, parameters such as survival or functional outcome are biased and may not be meaningful regarding SE prognosis. We chose not to assess the influence of SE on overall survival in this study as data on MGMT promotor methylation status, an important prognostic biomarker [34], were missing in $>$ 60 % of all cases which would have made it impossible to adjust for this major confounding factor. This surely is a limitation of this study alongside missing data on IDH1-mutation status.

The STESS, a well-established score to assess the prognosis of SE in adults [21,35], along with the CCI, were the only parameters associated with adverse SE outcome [36–38]. Previous studies on SE in unselected cohorts found significant, but in comparison to other factors such as STESS and SE aetiology small effects of CCI on SE prognosis. In our cohort specifically focusing on SE in glioblastoma patients, we were able to confirm that the CCI had an impact on the SE prognosis. A limitation of the CCI and this study is that the CCI does not account for factors like the patient's clinical condition.

Still, SE was treated successfully in almost 80 % of the cases in our study, with many cases only requiring treatment with first- or second-line agents. These findings are consistent with previous studies demonstrating good response to ASM treatment compared to SE in unselected SE cohorts [14,17,19]. The good response to ASM in SE patients may further support the notion of a generally favourable prognosis for tumour-related epilepsy [39–41].

4.1. Limitations

Our study has several limitations, including the retrospective, single-centre design. We did not have precise information on seizure frequency which is why we only scored whether or not a patient had a seizure during the time periods under study (0 = no seizure, 1 = seizure) and if seizures were documented after administration of at least two ASM, defining DRE. Our study may have therefore underestimated the incidence of DRE. The limited sample size of patients with SE in this study may have led to the underestimation of potential associations, highlighting the need for careful interpretation of our findings. We did not have sufficient data on duration or neurophysiological monitoring of SE, since EEG monitoring has only recently been implemented on the neurological intensive care unit in our hospital. Since we adhered to the German guidelines recommending a pragmatic definition of all types of SE as a seizure activity lasting at least 5 min or a series of seizures without clinical recovery in between, our results might not be transferable to countries using different guidelines. The recent 2021 WHO classification for CNS tumours no longer categorises astrocytomas with an IDH1-mutation as glioblastoma and incorporates other molecular markers to define glioblastoma [42] which were not present in many cases. As this research was conducted before 2021, our results only apply to tumours diagnosed according to the old classification. Additionally, the negative associations found by this study between molecular markers and the occurrence and outcome of SE require cautious interpretation due to the substantial amount of missing data on molecular markers.

5. Conclusion

In this study, SE tended to manifest in the later stages rather than in the early stages of the glioblastoma disease. SE occurrence was associated to postoperative, but not preoperative seizures, and drug-resistant epilepsy. Although there are a few, tumour-related risk factors for epilepsy in glioblastoma patients, these did not affect the occurrence of SE. Despite the high disease burden and the dismal oncological prognosis of glioblastoma, SE could be controlled in more than three quarters of the patients. Higher STESS and CCI were independently associated with adverse outcome. Although SE occurs late during the disease and may be linked to the end of life, aggressive treatment of SE may still improve the quality of life even in palliative settings.

Data availability statement

Full access to data is possible upon reasonable request.

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.

CRediT authorship contribution statement

Jenny Stritzelberger: Conceptualization, Funding acquisition, Formal analysis, Data curation, Methodology, Writing – original draft. **Anna Gesmann:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Imke Fuhrmann:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Stefanie Balk:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Caroline Reindl:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Dominik Madžar:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Martin Uhl:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Tamara M. Welte:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Sebastian Brandner:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Felix Eisenhut:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Arnd Dörfler:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Roland Coras:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Werner Adler:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing, Methodology. **Stefan Schwab:** Funding acquisition, Formal analysis,

Data curation, Writing – review & editing. **Florian Putz:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Rainer Fietkau:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Luitpold Distel:** Funding acquisition, Formal analysis, Data curation, Writing – review & editing. **Hajo M. Hamer:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Outside of the work reported in this paper, H.M. Hamer has served on the scientific advisory boards of Arvelle, Bial, Corlieve, Eisai, GW, Novartis, Sandoz, UCB Pharma and Zogenix. He has been part of 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.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2023.09.014.

References

[1] 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(5):700–6.
[2] Chang SM, Parney IF, Huang W, Anderson Jr FA, Asher AL, Bernstein M, et al. Patterns of care for adults with newly diagnosed malignant glioma. JAMA 2005;293(5):557–64.
[3] van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 2007;6(5):421–30.
[4] Mastall M, Wolpert F, Gramatzki D, Imbach L, Becker D, Schmick A, et al. Survival of brain tumour patients with epilepsy. Brain A J Neurol 2021;144(11):3322–7.
[5] Kerkhof M, Vecht CJ. Seizure characteristics and prognostic factors of gliomas. Epilepsia 2013;54(9):12–7.
[6] Kauw F. P08.73 Prevalence and predictors of status epilepticus in patients with glioblastoma. Neuro-oncol 2016;18(4):iv58–iiv9.
[7] Fan X, Li Y, Shan X, You G, Wu Z, Li Z, et al. Seizures at presentation are correlated with better survival outcomes in adult diffuse glioma: a systematic review and meta-analysis. Seizure 2018;59:16–23.
[8] Michelucci R, Pasini E, Meletti S, Fallica E, Rizzi R, Florindo I, et al. Epilepsy in primary cerebral tumors: the characteristics of epilepsy at the onset (results from the PERNO study–Project of Emilia Romagna Region on Neuro-Oncology). Epilepsia 2013;54(7):86–91.
[9] 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(1):71–80.
[10] 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(2):861–72.
[11] Li L, Fang S, Li G, Zhang K, Huang R, Wang Y, et al. Glioma-related epilepsy in patients with diffuse high-grade glioma after the 2016 WHO update: seizure characteristics, risk factors, and clinical outcomes. J Neurosurg 2022;136(1):67–75.
[12] Yu Z, Zhang N, Hameed NUF, Qiu T, Zhuang D, Lu J, et al. The analysis of risk factors and survival outcome for Chinese patients with epilepsy with high-grade glioma. World Neurosurg 2019;125:e947–ee57.
[13] Wychowski T, Wang H, Buniak L, Henry JC, Mohile N. Considerations in prophylaxis for tumor-associated epilepsy: prevention of status epilepticus and tolerability of newer generation AEDs. Clin Neurol Neurosurg 2013;115(11):2365–9.
[14] Vilaseca-Jolonch A, Abraira L, Quintana M, Sueiras M, Thonon V, Toledo M, et al. Tumor-associated status epilepticus: a prospective cohort in a tertiary hospital. Epilepsy Behav 2020;111:107291.
[15] Moots PL, Maciunas RJ, Eisert DR, Parker RA, Laporte K, Abou-Khalil B. The course of seizure disorders in patients with malignant gliomas. Arch Neurol 1995;52(7):717–24.
[16] 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.
[17] Knudsen-Baas KM, Power KN, Engelsen BA, Hegrestad SE, Gilhus NE, Storstein AM. Status epilepticus secondary to glioma. Seizure 2016;40:76–80.
[18] Giovannini G, Pasini F, Orlandi N, Mirandola L, Meletti S. Tumor-associated status epilepticus in patients with glioma: clinical characteristics and outcomes. Epilepsy Behav 2019;101:106370.
[19] Goonawardena J, Marshman LAG, Drummond KJ. Brain tumour-associated status epilepticus. J Clin Neurosci 2015;22(1):29–34.
[20] 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;64(7):1853–61.
[21] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status epilepticus severity score (STESS): a tool to orient early treatment strategy. J Neurol 2008;255(10):1561–6.
[22] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43(11):1130–9.
[23] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475–82.
[24] 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(4):671–5.
[25] 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(6):1069–77.
[26] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus – report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56(10):1515–23.
[27] Rosenow F, Weber J. [S2k guidelines: status epilepticus in adulthood: guidelines of the German society for neurology]. Nervenarzt 2021;92(10):1002–30.
[28] Kerkhof M, Dielemans JC, van Breemen MS, Zwinkels H, Walchenbach R, Taphoorn MJ, et al. Effect of valproic acid on seizure control and on survival in patients with glioblastoma multiforme. Neuro Oncol 2013;15(7):961–7.
[29] Pesce A, Armocida D, Paglia F, Palmieri M, Frati A, D'Andrea G, et al. IDH wild-type glioblastoma presenting with seizure: clinical specificity, and oncologic and surgical outcomes. J Neurol Surg A Cent Eur Neurosurg 2022;83(4):351–60.
[30] Dobran M, Nasi D, Chiriatti S, Gladi M, Somma LD, Iacoangeli M, et al. Prognostic factors in glioblastoma: is there a role for epilepsy? Neurol Med Chir (Tokyo) 2018;58(3):110–5.
[31] 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(1):vdaa158.
[32] Chaichana KL, Parker SL, Olivi A. Quiñones-Hinojosa A. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clin Article J Neurosurg 2009;111(2):282–92.
[33] Venkataramani V, Tanev DI, Kuner T, Wick W, Winkler F. Synaptic input to brain tumors: clinical implications. Neuro Oncol 2021;23(1):23–33.
[34] Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997–1003.
[35] Rossetti AO, Logroscino G, Bromfield EB. A clinical score for prognosis of status epilepticus in adults. Neurology 2006;66(11):1736–8.
[36] Alvarez V, Januel JM, Burnand B, Rossetti AO. Role of comorbidities in outcome prediction after status epilepticus. Epilepsia 2012;53(5):e89–92.
[37] Ciurans J, Grau-López L, Jiménez M, Fumanal A, Misis M, Becerra JL. Refractory status epilepticus: impact of baseline comorbidity and usefulness of STESS and EMSE scoring systems in predicting mortality and functional outcome. Seizure 2018;56:98–103.
[38] Leitinger M, Höller Y, Kalss G, Rohracher A, Novak HF, Höfler J, et al. Epidemiology-Based Mortality Score in Status Epilepticus (EMSE). Neurocrit Care 2015;22(2):273–82.
[39] 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(5):1256–62.
[40] Borger V, Hamed M, Ilic I, Potthoff AL, Racz A, Schäfer N, et al. Seizure outcome in temporal glioblastoma surgery: lobectomy as a supratotal resection regime outclasses conventional gross-total resection. J Neurooncol 2021;152(2):339–46.
[41] 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.
[42] 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(8):1231–51.