IDH Wild-type Glioblastoma Presenting with Seizure: Clinical Specificity, and Oncologic and Surgical Outcomes.

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Abstract

Background Glioblastoma (GBM) is the most common and aggressive primary brain neoplasia in adults. Seizure is a common manifestation in GBM. Up to 25 to 60% of patients with GBM have seizures. We aim to summarize all the relevant clinical, surgical, radiologic, and molecular features of a cohort of patients suffering from GBM-related epilepsy and measure the outcome, to understand the possible existence of a clinical/phenotypical specificity of this subgroup of patients.

Methods We retrospectively analyzed a cohort of 177 patients affected by isocitrate dehydrogenase wild-type (IDH-WT) GBM; 49 patients presented seizure at onset (SaO) and 128 were seizure free (SF). We investigated the relationship between seizures and other prognostic factors of GBMs.

Results A statistically significant association between the location of the lesions in the parietal lobe and seizures was observed. The left side was more commonly affected. Interestingly, there was a statistical relationship between tumors involving the subventricular zone (SVZ) and SaO patients. The tumors were also smaller on average at diagnosis, and generalized SaOs were associated with longer overall survival.

Conclusions The typical patient with IDH-WT GBM with SaO is a young (<55 year) male without a history of headache. The lesion is typically small to medium in size and located in the temporoparietal dominant lobe, with a high tendency to involve the SVZ.

Keywords
- seizure
- glioblastoma
- EGFR
- p53
- survival
- brain tumor
- epilepsy

Introduction

Background

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain lesion in the adult population[1,2] representing between 12 and 15% of all intracranial neoplasms. This tumor can occur at any age, although the peak of incidence lies between ages 55 and 85 years.[1] Mass effect and peritumoral edema are marked, and increased vascularity and intratumoral hemorrhage are frequent[3] with malignancy's tendency to induce seizures, which negatively impact the quality of life.[1–4]

For many patients suffering from gliomas, seizures may represent both the initial and the disease's eventual

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symptoms. Tumor–related epilepsy may be seriously impairing and even completely drug resistant.[4–7] To our current knowledge, as many as 25 to 60% of patients with GBM have seizures[4–6]: a lower number than low-grade glioma patients.[8] Therefore, most of the available studies so far have concentrated on low-grade gliomas to understand the underlying mechanisms for tumor-associated seizures. The mechanisms triggering seizures in high-grade gliomas are not completely clarified, and in the studies taking into account GBM patients exclusively[9,10] it seems that the initial size of the lesion, the edema, and the necrosis represent notable factors associated with the occurrence of seizure at the onset. However, several anatomical and molecular features may facilitate the onset of seizures in GBM, including the temporoparietal and general and cortical localization. Although in low-grade gliomas, the tumor-defining isocitrate dehydrogenase 1 R132H (IDH1) mutation seems to play a major role in generating seizures, a plethora of different mechanisms could play a role in newly diagnosed IDH wild-type (IDH-WT) GBM. It is supposed that IDH-1-WT tumors express the branched-chain amino acid transaminase 1 (BCAT1), which is relevant for the synthesis glutamate in GBM.[9,11,12] Otherwise, there are currently few theories concerning the mechanisms generating epilepsy in IDH-WT GBMs. Such mechanisms could also account for the clinical heterogeneity of the seizure symptoms among the different tumor types, especially for IDH-WT GBMs.

Objectives

The aim of this article is to summarize and investigate all the clinical, surgical, radiologic, and molecular features of a cohort of patients suffering from IDH-WT GBM–related epilepsy and to study the oncologic and clinical outcomes, to disclose a possible clinical/phenotypic specificity of the subgroups of patients in regard to their seizure symptoms.

Materials and Methods

Participants and Eligibility

We performed an institutional retrospective review of a consecutive series of surgically treated patients suffering from histologically confirmed GBMs, operated on in the Department of Neurosurgery of Policlinico Umberto I of Rome (Università "La Sapienza"). Histologic diagnoses were performed according to the updated version of the WHO guidelines.[13] We included a cohort of IDH-WT GBMs.

We selected in total 177 patients affected by newly diagnosed GBM who underwent surgery, radiation, and chemotherapy in our institution between January 2014 and December 2016, out of a total cohort of 193 patients, 16 of which were excluded as specified in the flow diagram in ►**Fig. 1**. The inclusion criteria were the following:

- Patients were included in the study if their pre- and postoperative magnetic resonance (MR) imaging was either performed at our institution or available on the picture archiving and communication system (PACS) for review.

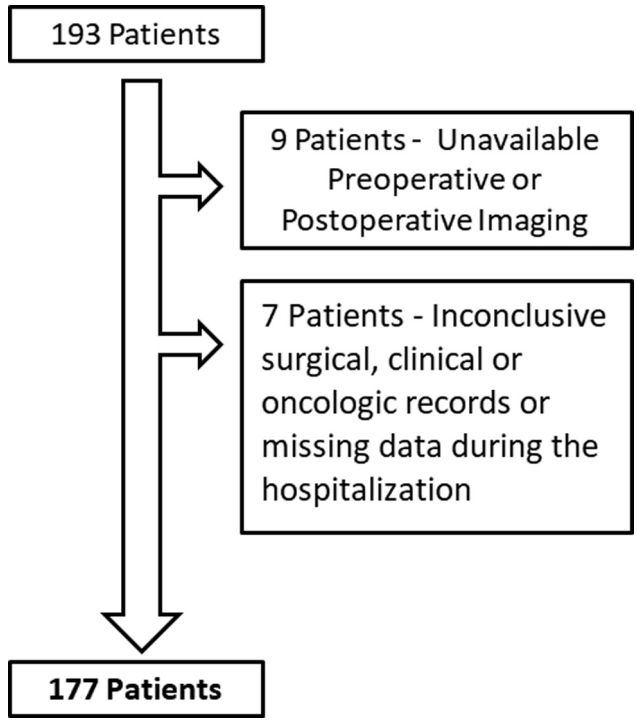

Fig. 1 A flow diagram summarizing the exclusion process.

- Patients were included if, in the postoperative period, they could undergo a standard Stupp protocol starting from 30 to 35 days after surgery.
- Patients were included if they received a standard conformational planning with a linear accelerator (LINAC), and no stereotactic radiosurgical treatment was performed.
- Once the progression of the disease was noticed, the patient and the relevant imaging were referred again to our attention, to evaluate the feasibility of a second surgery or to address the patient to a second line of adjuvant treatment.
- The estimated target of the surgical procedure was the total or subtotal resection of the lesions: no biopsies were included to obtain an analysis after complete removal of all epileptic foci; moreover, no survival analysis is feasible if biopsies are included in the final cohort.
- All the patients included in the study were newly diagnosed with GBMs at their first surgery.

All the patients who met the inclusion criteria were assigned on the ground of the preoperative imaging to the following subgroups:

- Patients classified as seizures at onset (SaO): patients whose clinical onset included, among the presenting symptoms, a seizure.
- Patients classified as seizure free (SF): patients whose clinical onset did not include seizures.

Patients who were SF received no antiepileptic prophylaxis, until the first seizure. Each patient presenting with seizure was treated with levetiracetam 2,000 mg/d at the onset of symptoms. An electroencephalogram (EEG), renal

functionality data, and eventually blood level guided the dose adjustment of levetiracetam. For patients whose seizures were unresponsive to levetiracetam 2,000 mg/d, the doses of such drugs were increased up to 3,000 mg/d. In case of failure, valproate up to a maximal dosage of 1,200mg/d was introduced. The third choice, in case of multidrug resistance, fell between phenytoin, carbamazepine, and lamotrigine, usually after an evaluation with a team of epileptologists. Interruption of the therapy and follow-up were performed according to the Italian League Against Epilepsy (LICE) recommendations.[14] Clinical results, from an epileptologic perspective were recorded by means of the Engel scale for the patients whose clinical course included seizures.

Special emphasis was given to recording and subsequently analyzing the different subtypes of seizures experienced by the patients. The epileptic symptoms were thus divided in four subgroups, following the International League Against Epilepsy (ILAE) definitions[15]: (1) generalized motor onset, (2) focal onset, (3) generalized nonmotor onset (also defined as atypical absence), and (4) unknown onset. The last subgroup encompassed all the patients whose clinical records included EEG-demonstrated epileptic abnormalities *and* seizure episodes like olfactory, visual, or auditory delusions and transient visceral or psychic manifestations.

None of the patients belonging to the SaO group presented with a *status epilepticus* as the first epileptic manifestation.

Data Sources and Quantitative Variables

For all the included patients, we recorded their age, sex, location, tumor volume, clinical onset, Ki67, p53, and epidermal growth factor receptor (EGFR) expression status.[16,17] Immunohistochemistry with ki67, EGFR, ATRX, and anti-IDH1 R132H antibody (DIA-H09; 1:50; Dianova, Rome, Italy) was routinely performed.

Overall survival (OS) was recorded in months; it was measured from the date of radiologic diagnosis to the date of death or the date of last contact if alive. Clinical information was obtained from the digital database of our institution, whereas OS data were obtained by telephonic interview. Special emphasis was given to the Karnofsky performance status (KPS) results: such parameter was considered, as previously observed,[18] associated with survival. In particular, it was recorded at three different moments: (1) before surgery, (2) at 30 days after surgery, and (3) at the end of the adjuvant treatment (the moment of the last outpatient evaluation).

Radiologic, Surgical, and Anesthesiology Protocol

All the patients underwent a preoperative 3T MR imaging-with the following sequences: T2-weighted (T2w), fluid attenuated inversion recovery (FLAIR), and isotropic volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) before and after intravenous administration of paramagnetic contrast agent; diffusion tensor imaging (DTI) with 3D tractography, and functional MRI (fMRI) completed our protocol in gliomas affecting eloquent locations.[19,20] The volume of the contrast-enhancing lesion was calculated drawing a region of interest (ROI) in a volumetric enhancing postcontrast T1-weighted study (a multivoxel study,[21] conforming to the margins of the contrast-enhancing lesion with software Osirix).[22]

All the procedures were performed with an infrared-based neuronavigator (Kick—Purely Navigation, Brainlab), in a standard neurosurgical theater, with a standard operative microscope. At the first postoperative day, the patients underwent volumetric brain CT scan to rule out early complications and a brain MRI scan as soon as possible, possibly within 24 to 48 hours, to evaluate the extent of resection (EOR).[23]

Patients whose lesions were located in eloquent areas (according fMRI and/or tractography) or who presented obvious preoperative speech and/or motor impairmentwere operated on with a full-awake surgery protocol, under light intravenous sedation and local anesthesia with the aid of intraoperative neuromonitoring realized with use of bi- and monopolar stimulating probes, respectively, for cortical and subcortical mapping, whenever the deficits did not prevent it. In general, it was intraoperatively judged necessary to stop tumor excision under the following conditions:

- When white matter appeared free of disease in any aspect of the surgical cavity.
- When despite a directly visualized or a navigation-proven remnant, neuromonitoring or intraoperative neuropsychologic testing outlined risk of postoperative motor morbidity.[24–26]

Statistical Methods

The sample was analyzed with SPSS version 18. Comparisons between nominal and dichotomous variables have been made with the chi-squared test. EOR, OS, and progression-free survival (PFS) means were compared with one way and multivariate analysis of variance (ANOVA) along with contrast analysis and post hoc tests. Kaplan–Meier and Cox's regression survival analyses assessed survival in a univariate fashion. Continuous variable correlations have been investigated with Pearson's bivariate correlation, whereas Spearman's method was used for ordinal variables. A $p < 0.05$ was considered statistically significant.

Potential Source of Bias and Study Size

We did not address any missing data since incomplete records were an exclusion criterion. A potential source of bias is expected from exiguity of the sample, which nevertheless, with regard to the endpoints selected, presents a reliable post hoc statistical estimated power ($1-\beta = 0.91$, with $\alpha = 0.05$ and an effect size of 0.5), thus providing extremely reliable conclusions in regard to strong statistical effects.

Informed consent was approved by the institutional review board of our institution. Before surgical procedure, all the patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed. This study is consistent with the Helsinki declaration of human medical research.

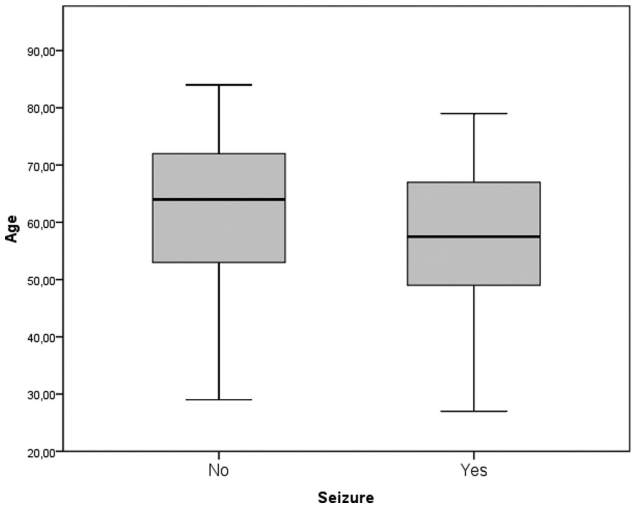

Fig. 2 The average age of the two subgroups (seizure at onset [SaO] and seizure free [SF]) was 57.3 ± 13.31 and 62.3 ± 12.31 ($p = -029$).

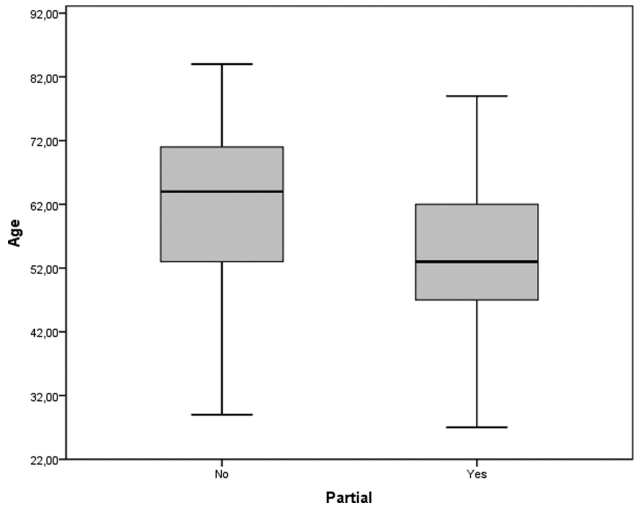

Fig. 3 Patients suffering partial seizure were significantly younger than the general cohort (52.95 versus 62.3 years, $p = 0.002$).

Results

Participants

In the period between January 2014 and December 2016, 177 patients, who met the inclusion criteria (►**Fig. 1**), suffering from GBM underwent surgery in our institution and were retrospectively evaluated for this study. Informed consent was obtained from all individual participants included in the study. The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Descriptive Data

The final cohort consisted of 177 patients, of which 49 presented seizures at clinical onset of the disease and 128 presented with other symptoms. The average age of the two subgroups was, respectively, 57.3 ± 13.31 and 62.3 ± 12.31 years in SaO and SF, with a statistically significant difference ($p = 0.029$; ►**Fig. 2**), with the SaO patients being younger than their SF counterparts on average. Partial seizures were significantly associated with a younger age at clinical onset with an average age of 52.95 versus 62.3 of the general cohort ($p = 0.002$; ►**Fig. 3**). No sex-related difference between the subgroups was identifiable. No significant differences in KPS with regard to the preoperative, early postoperative, and late postoperative period were observed (for details, see ►**Table 1**).

Patient-Related Features

There was a significant negative association between headache as presenting symptom for patients suffering from generalized seizures ($p = 0.038$), whereas there was no such a statistical association in patients with partial seizures ($p = 0.195$). Over all, seizures were absent in patients presenting with headache. The SaO patients were less likely to suffer from language disturbances, movement disorders, and general cognitive disturbance or behavioral impairment ($p = 0.004$, 0.001, and 0.006, respectively), with seizure often being the very first manifestation of the disease. There was no statistically significant association between SaO and disorders of the memory, visual function, balance, and gait.

Lesions: Anatomical Features and Molecular Patterns

When compared as dichotomous variables (parietal lobe involvement and presence of seizures: 0/1 = No/Yes), parietal lobe lesions demonstrated a statistically strong association with seizures (chi-squared analysis, $p = 0.027$; ►**Fig. 4**; odds ratio: 2.164; 95% confidence interval [CI]: 1.055–4.441); partial seizures demonstrated a nonstatistically significant trend toward an association with the frontal lobe ($p = 0.058$) and a statistically significant association with the parietal lobe ($p = 0.028$). The entire subventricular zone (SVZ), defined as the subependymal white matter proximal to the lateral ventricles, disclosed an obvious association with SaO patients ($p = 0.027$; ►**Fig. 5**), thus outlining the tendency of the SVZ lesions to trigger seizures at the onset of the disease. Lesions involving the left side had a strong statistical association with the SaO patients ($p = 0.049$), the left side being significantly associated with generalized seizures ($p = 0.007$). By performing a retrospective statistical ANOVA, we obtained a significant dichotomy at 22 cm^3 in the comparison between the two groups in relation to PFS and OS. The volume of the lesions played a statistically significant role in the association between the lesion and the epileptogenesis: lesions with a volume of $<22\ cm^3$ were more commonly associated with SaO ($p = 0.021$; ►**Fig. 6**). The two groups did not demonstrate differences in EGFR expression, ki67 index, and p53 mutation (66.6, 25, and 57.1%, respectively, in the SaO group vs. 71.6, 24.5, and 53.1%, respectively, in the SF group).

Follow-up and Survival

The possible associations of SaO with the EOR and survival parameters were investigated (►**Tables 2** and **3**). SaO patients did not experience per se a difference in terms of OS or PFS in respect to the SF patients ($p = 0.226$ and 0.928), although the subgroup of patients suffering from generalized SaO, had, in our cohort, a statistically significant longer OS

Table 1 Patient's demographics

IDH-WT GBM	$N = 177$ patients				p value
Subgroup	SaO = 49		SF = 128		–
Sex	Male, $N = 28$ (57.1%) Female, $N = 21$ (42.9%)		Male, $N = 69$ (53.9%) Female, $N = 69$ (46.1%)		0.475
Age (y)	57.3 ± 13.31		62.3 ± 12.31		0.029
KPS $\geq$ 80 at admission	37/49 (75.5%)		90/128 (70.31%)		0.544
KPS $<$ 80 at admission	12 (24.5%)		38 (29.69%)		0.544
Volume in cm^3	18.97 ± 16.6		22.85 ± 18.63		0.099
Ki67 (%)	25 ± 13.3		24.5 ± 14.95		0.375
EGFR: 155/177 patients	EGFR overexpressed: 28/42 (66.6%)		EGFR overexpressed: 78/113 (71.6%)		0.468
MGMT methylation: 50/177 patients	MGMT methylated: 11/18 (61.1%)		MGMT methylated: 14/32 (43.75%)		0.336
p53: 150/177 patients	Mutant p53: 24/42 (57.1%)		Mutant p53: 60/113 (53.1%)		0.323
EOR	GTR: 46/49 patients (93.8%) STR: 3/49 patients (6.2%)		GTR: 104/128 patients (81.25%) STR: 24/128 patients (18.75%)		0.026
KPS after surgery	KPS $\geq$ 80: 36/49 (73.5%) KPS $<$ 80: 13/49 (26.5%)		KPS $\geq$ 80: 90/128 (70.3%) KPS $<$ 80: 38/128 (29.7%)		0.456
KPS at last evaluation	KPS $\geq$ 80: 8/49 (16.33%) KPS $<$ 80: 41/49 (83.7%)		KPS $\geq$ 80: 21/128 (16.4%) KPS $<$ 80: 107/128 (83.6%)		0.200
Overall survival	19 ± 17.1 mo 8/49 LTS (16.32%) 2/49 still alive (4.1%)		16 ± 17 22/128 LTS (17.2%) 7/128 still alive (5.5%)		0.226 0.259
Location	Frontal	14 (28.6%)	Frontal	47 (36.7%)	0.207
	Temporal	20 (40.8%)	Temporal	48 (37.5%)	
	Occipital	4 (8.1%)	Occipital	8 (6.25%)	
	Parietal	9 (18.4%)	Parietal	23 (18.0%)	
	Corpus callosum	2 (4.1%)	Corpus callosum	2 (1.6%)	
Side	Left	26 (53.1%)	Left	53 (41.4%)	0.049
	Right	21 (42.9%)	Right	68 (53.1%)	
	Midline or bilateral	0 (0.0%)	Midline or bilateral	6 (4.7%)	
Symptoms	Generalized seizures	18 (10.2%)	No seizures	128 (72.3%)	–
	Partial seizures	21 (11.9%)			
	Atypical absence	4 (2.3%)			
	Unspecified	6 (3.4%)			

Abbreviations: EGFR, epidermal growth factor receptor; EOR, extent of resection; GBM, glioblastoma multiforme; GTR, gross total resection; IDH, Isocitrate dehydrogenase; KPS, Karnofsky performance status; LTS, long-term survivors; MGMT, O^6-methylguanine DNA methyltransferase; NTR/STR, near-total/subtotal resection; OS, overall survival; PFS, progression-free survival; SaO, seizure at onset; SF, seizure free; WT, wild type.

compared to other patients ($p = 0.050$; ►**Fig. 7**). A Kaplan–Meier survival estimation curve illustrates a similar survival association. A univariate Cox regression analysis disclosed a statistically significant association between a preoperative KPS score >80, the presence of seizures at clinical onset, and the survival parameters (both OS and PFS, respectively, $p = 0.001$ and 0.003; 95% CI for OS and PFS: 15.52–28.27 and 6.85–15.16, respectively; ►**Fig. 8**).

Clinical Outcomes: Seizures

Among the 128 patients presenting without seizures (SF subgroup), we recorded new postoperative seizures in a total of 3 (2.34%) patients (1 generalized and 2 partial motor).

In the SaO group, despite the surgical resection of the lesion and administration of antiepileptic drugs, four patients presented seizures. Of these, two (4.1%) patients experienced episodes of postoperative seizures (both generalized), whereas 2/49 (4.1%) patients presented with generalized seizures in the preoperative period and evolved in a structured epileptic syndrome graded as Engel class IV with respect to the effect of the surgery (no significant improvement).

The remaining 45/49 patients (SaO subgroup) demonstrated excellent seizure control with no seizure relapse after the first-line levetiracetam therapy, thus experiencing an Engel class I result. The subgroups of both SaO and SF patients

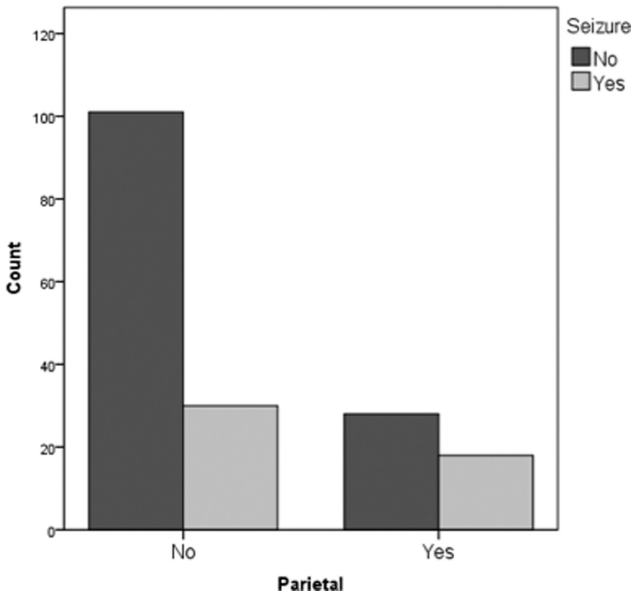

Fig. 4 The location of the lesions in the parietal lobes was found to be statistically strongly associated with seizures ($p = 0.027$).

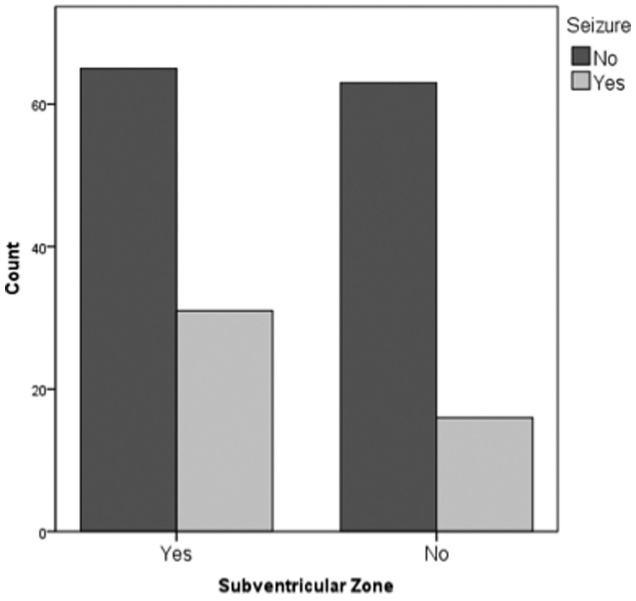

Fig. 5 The subventricular zone (SVZ) had an association with seizure at onset ($p = 0.027$).

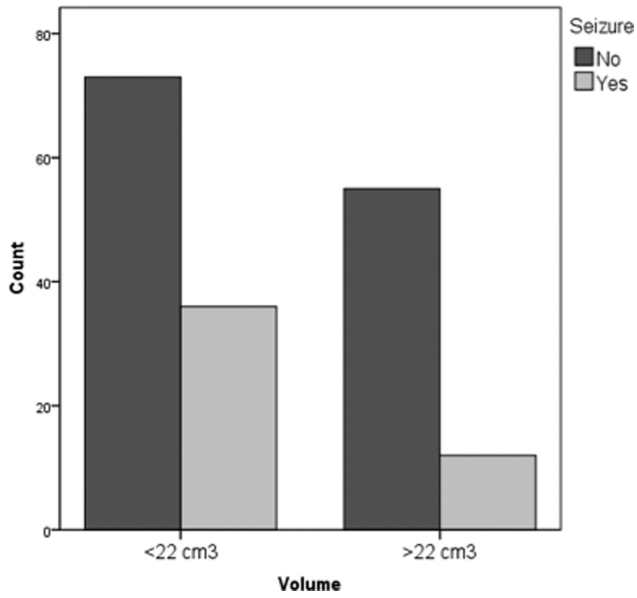

Fig. 6 A statistically significant association between lesion volume and epileptogenesis was found: lesions with volumes $<22\ cm^3$ were more commonly associated with seizures at onset ($p = 0.021$).

Table 2 Chi-squared analysis demonstrating the association between seizures and EOR

		EOR		Total	significance
		GTR	STR		
Seizures at onset	SaO	46	3	49	0.026
	SF	104	24	128	
Total		150	27	177	

Abbreviations: EOR, extent of resection; GTR, gross total resection; SaO, seizure at onset; SF, seizure free; STR, subtotal resection.

did not show a statistically significant association with a different EOR.

Moreover, neither the postoperative seizure in the SaO or SF subgroups nor the structured epileptic syndrome was associated with a statistically significant worse oncologic outcome.

Discussion

Seizure is the first symptom of glioma in 40 to 70% of patients. There is an abundant literature[4,6,27–29] supporting the association between tumor grade and histopathology glioma and glioma-related epilepsy.[29] Whereas there is a well-established relationship between low-grade glioma and SaO, the relationship is not evident for high-grade gliomas and IDH-WT GBM.[28]

In this study, we focused exclusively on a subpopulation of patients suffering from newly diagnosed IDH-WT GBM, based on data of recent investigations suggesting that epileptogenesis could be influenced by molecular genetic tumor markers.[11,30]

Clinically, we found a statistically significant difference between the two subgroups, with the SaO patients being, on average, younger than their SF counterparts. The occurrence of partial seizure was significantly associated with a younger age at clinical onset.[31]

In our sample, we found a higher frequency of onset of symptoms with epilepsy in males. Such a relationship has not yet reported in GBM patients; however, extensive data on the onset of epilepsy in adults showed sex differences in seizure semiology. The precise causes of this prevalence are unknown.[32]

It is confirmed that the location of the tumor influences the incidence of epilepsy. A cortical/subcortical location is

Table 3 Univariate ANOVA analysis demonstrating the nonsignificant association between seizures and survival parameters

			Statistic	Bootstrap				
				Bias	Sig	Std. error	95% confidence interval	
							Lower	Upper
PFS	SF	Mean	9.3509	−0.0145	0.928	1.2126	7.1379	12.0358
		Std. deviation	12.88203	−0.22936		2.05718	8.55213	16.58637
		Std. error	1.20651					
	SaO	Mean	9.7073	−0.0536		1.7379	6.5792	13.5309
		Std. deviation	10.83569	−0.63456		2.99147	4.86009	16.05783
		Std. error	1.69225					
OS	SF	Mean	16.44	−0.02	0.226	1.27	14.16	19.22
		Std. deviation	13.731	−0.220		2.004	9.597	17.434
		Std. error	1.286					
	SaO	Mean	20.20	−0.06		2.63	15.13	25.81
		Std. deviation	17.106	−0.508		3.066	10.173	22.356
		Std. error	2.671					

Abbreviations: ANOVA, analysis of variance; OS, overall survival; PFS, progression-free survival; SaO, seizure at onset; SF, seizure free.

considered one of the most important predictive factor for the development of preoperative seizure.[29,33,34] The entire deep SVZ had an association with SaO, thus outlining the tendency of the SVZ lesions to trigger seizures at the onset of the disease.[35,36] The SVZ is known to harbor pluripotent neural stem cells, thus increasing the propensity to generate aggressively proliferating tumors, which in turn can favor epileptogenesis.

In general, the supratentorial space is definitively more significantly associated with the development of seizures (in our series, this finding is confirmed regarding the parietal lobe)[37] than the infratentorial compartment.[34] We also confirmed an association between epilepsy and the dominant hemisphere.[38] Lesions involving the left hemisphere presented an overall strong statistical association with the SaO, with the left side of the lesion being significantly associated with generalized seizures.

Although the temporal lobe is the most epileptogenic area in pathologic conditions,[39] it is suspected that in the case of highly infiltrative pathologies such as GBM, the connections to other lobes (as in the case of the parietal lobe, especially the associative areas [inferior parietal lobule] of the dominant hemisphere), are more frequently activated. This could explain the parietal dominance in our group.

The lesions' volume plays a statistically significant role in the association between the lesion and epileptogenesis: lesions with a volume of $<22\,cm^3$ were more frequently associated with SaO. Besides, greater lesions are generally associated with increased intracranial pressure, in which headache is usually the first symptom.

Accumulating evidence also suggests that tumor growth stimulates seizures and that, conversely, seizures could encourage tumor growth, suggesting that the two conditions may share common and reciprocally influencing pathogenic mechanisms.[29] Some authors argue that peritumoral edema could play an important role in triggering seizures. Isoardo et al[33] suggest that reduced expression of Aquaporin-4 (AQP-4) indirectly reduces the risk of seizure allegedly by reducing the peritumoral vasogenic edema in patients affected by GBM. Such a finding could explain why large tumors could be associated with a clinical presentation with focal deficits rather than a seizure.

Further molecular evidence outlines possible connections between the epileptic behavior of gliomas and the expression of IDH9, MGMT,[30,40,41] BRAF,[42] D-2 hydroxyglutarate,[43,44] EGFR, and Ki67,[16,17,45,46] but, although often studied in low-grade gliomas, their role is not yet completely clarified in GBM. In the specific case of MGMT methylation, it was extensively discussed and peculiarly remains controversial.[47,48] Every molecular tumor marker promoting tumor proliferation might participate independently to the epileptogenesis, although, according to our results, a clear association with SaO cannot be found.

SaO patients did not experience per se a difference in terms of OS compared to the SF patients; however, the subgroup of patients suffering from generalized SaO had, in our cohort, a significantly longer OS compared to the other patients. However, this difference can be explained by the younger age, as young age in GBM is a well known positive prognostic factor.

We suppose that patients perceive seizure as a major warning of a serious health problem, demanding medical attention. These patients thus obtain an earlier diagnosis than patients experiencing a slowly worsening motor function, sensory deficit, or headache. Earlier diagnoses translate to better functional outcomes and earlier accessibility to adjuvant treatments,[31] resulting in longer OS.[49]

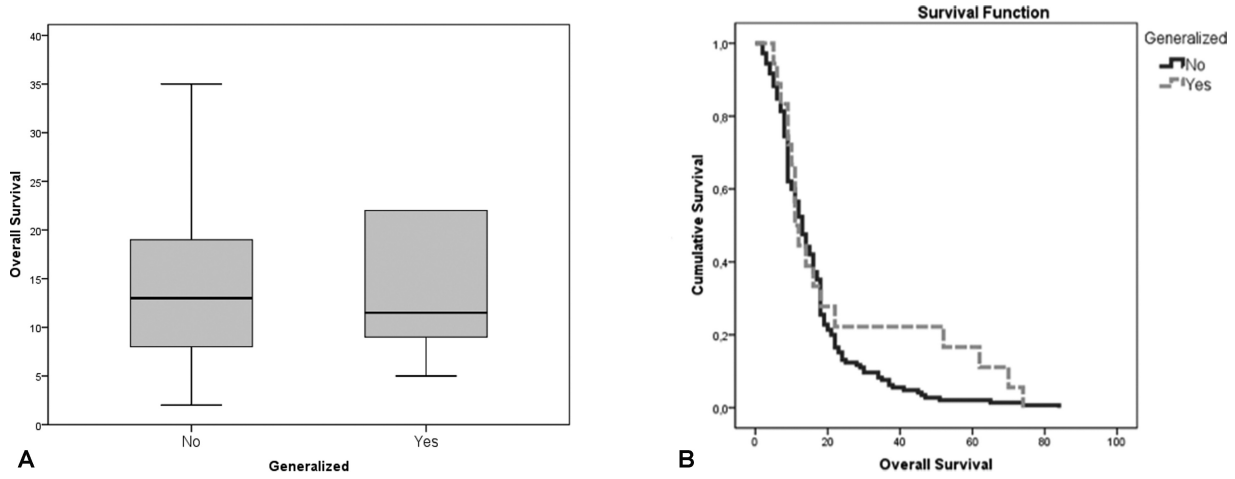

Fig. 7 (A,B) The subgroup of patients presenting with generalized seizures at onset had a longer overall survival (OS), than the remaining glioblastoma patients, almost reaching statistical signifcance ($p = 0.050$). A Kaplan–Meier survival estimation curve discloses the association between longer OS and generalized seizure at onset symptom.

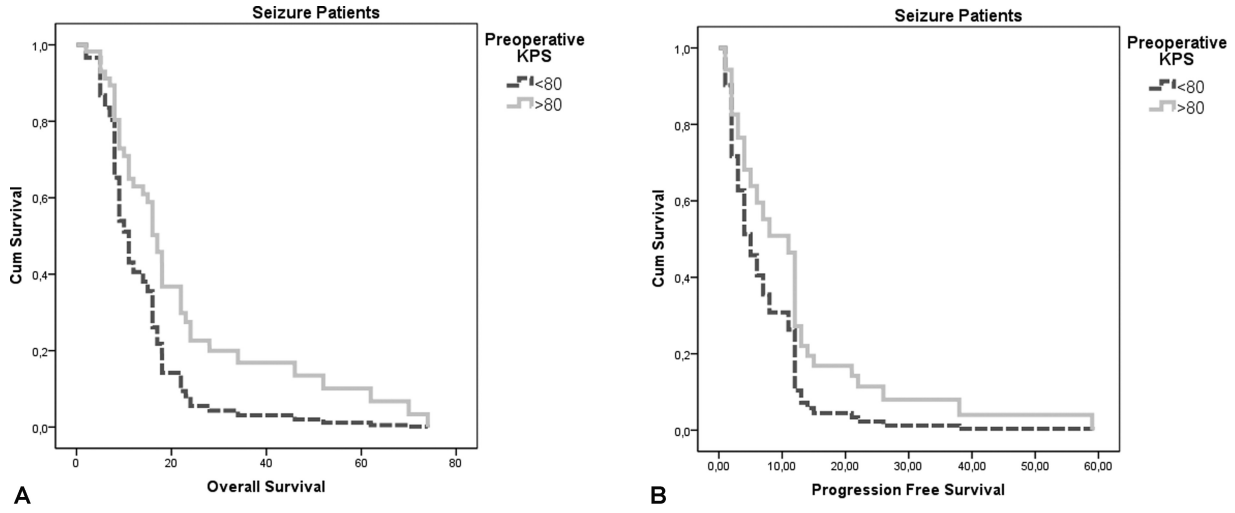

Fig. 8 (A,B) Cox regression analysis disclosing the effect of preoperative Karnofsky performance status (KPS) on the survival of patients of the seizure at onset (SaO) subgroup.

Limitations

Several limitations should be considered. First, the retrospective nature introduced significant selection and protopathic biases. Selection bias in the control group is difficult to consider since minor, subliminal, or even uncommon seizure symptoms (olfactory, visual, auditory delusions, or visceral manifestation) could be misevaluated or underestimated. This cohort may be biased since, to investigate survival parameters, we did not biopsy any of the patients. Diencephalon or brainstem gliomas are often addressed with biopsies; therefore, the seizure symptoms in this subgroup of patients could be theoretically different from those of patients with supratentorial lesions.

Furthermore, the SVZ was found to be a possible "trigger area" for epileptic symptoms. Excluding patients undergoing biopsy might have led to the exclusion of a large proportion of the SVZ-contacting tumors in our institution. Despite this, we prefer not to extend our cohort to biopsied patients to avoid a major confounding effect on EOR and survival parameters. Our immunohistochemistry-based molecular analysis is probably insufficient to draw definitive conclusions concerning the effects of EGFR amplification or mutation on SaO. Also, MGMT analyses were only performed in a minority of patients (50/177 patients). IDH mutation was only evaluated with immunohistochemistry, which misses 10% of IDH mutations.

Conclusion

In our cohort, SaO was associated with young age (<45 years), male, and a short-term history of headache. A generalized seizure is typically related to small to medium size lesion (average size = 22 cm^3) located in the dominant hemisphere, with a high tendency to involve the SVZ.

We identified some clinical and radiologic characteristics like a predominance of the dominant hemisphere and a smaller tumor volume in GBMs presenting with seizures.

Insight into the association between mechanisms of glioma growth and epileptogenesis could provide the opportunity to develop interventions targeting each of the dysregulated processes, thus further improving the clinical results.

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Conflict of Interest
None declared.

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